Dosage

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- Refers to the package or container which the drug is contained
- The ability to release the active ingredient over an extended period of time

Classification

It is according to the drug's physical properties

1. Gaseous
2. Liquid
3. Semi-solid
4. Solid

Gaseous

- Medicinal gases are used
- Are inhaled/volatile anaesthetics
- Aero dispersion of solid/liquid particles
- Composed of:
- Sprays
    i. Composed of various bases (alcohol/water)
    ii. Found in pump-type dispensers
- Inhalants
- Aerosols

Liquid

- Composed of:
    iii. **Solutions or drops**
        a) Have one homogenous phase
        b) Are prepared by mixing one or more solutes in a liquid/solvent
            § Syrups
            § Oils
        c) Can be admimnistered via all routes
    iv. **Syrups**
        a) Are sugar-based aqueous solutions
        b) Medications are dissolved in them
        c) Can be found with or without flavouring agents
            § Improve the taste of the drug
    v. **Elixirs**
        a) These are sweetened solutions containing dissolveed medicatin in an alcohol base
        b) The alcohol covers up the bad taste of the drug
        c) Avoid in children
    vi. **Tinctures**
        a) Are alcoholic/hydroalcoholic solutions
        b) Used for herbal extracts
    vii. **Emulsions**
        a) It is a dispersion system, consisting of two immiscible liquids
        b) Used wit han emulsifier (which binds the two liquids)
    viii. **Suspensions**
        a) It is a dispersion system where solid particles are dispersed in liquid state
        b) Not intended for systemic administration
        c) Comes with a 'shake well' sticker
    ix. **Enemas**
        a) Might be administered for retention or evacuation
        b) To deliver the medication to the body, bypass the stomach while being absorbed
        c) Used to evacuate the lower intestine for surgeries or for women in labour
    x. **Eye drops**
        a) Found in smaller volumes (10-20ml)
        b) Usually sterile
        c) Are isotonic to tears
        d) The vehicle is sterile water
    xi. **Ear drops**
        a) Usually isotonic
        b) Are non-irritating
        c) Are not necessarily sterile
        d) Are used for clearing up infections or cleaning out ear wax building
    xii. **Parenteral dosage forms**
        a) *Injectables*
            § For administration using a hypodermic needle (hollow-pointed needle)
            § Formulated as liquids/powders/lyophilisates for preparations of solutions
        b) *Injections (available as ampules and vials)*
            § Found as solutions, emulsions or suspensions
            § Are sterile, pyrogen-free and isotonic
        c) *Infusions (found in plastic bags)*
            § Administered via IV routes

§ Higher volumes used over longer times
§ Infusion pumps, tubing and flexible canules are needed for infusion

d) *IV injectons*
§ Are particle free
§ Iso-acidity is desirable
§ Irritating compounds can be used
§ Sterile water are vehicles for injections, co-solvents may be added
§ Slow administrations are employed to avoid problems with concentration waves

e) *Intramuscular and subcutaneous*
§ Isoacidity should be guaranteed
§ Are non-irritating
§ Suspension/emulsion injectables can be administered (depot forms).
§ Oil based vehicles can be used
§ Volumes administered = site of administered

Semi-solid doses

- Found in two states

xiii. **Unshaped**

a) *Gels*: systems in which a liquid phase is contained within a 3D cross-linked matrix
b) *Creams*: semi-solid emulsion systems containing more than 10% of water in them
c) *Ointments*: semi-solid dispersion system with an oleagenous, water soluble or emulsifying base
d) *Pastes*: semi-solid dispersion systems, where a solid particle (>25%) are dispersed in ointment.

xiv. **Shaped**

a) *Suppositories (for rectal administration)*
§ Solid dosage form under room temperature
§ Melts at body temperatures
§ Suppository bases
i. Oleagenous (cacao butter, *Adeps neutralis*)
ii. Aqueous (PEGs, glycerated gelatin)
§ Shaped like a torpedo

b) *Pessaries (vaginal suppositories)*
§ PEGs or glycerated base
§ Mainly used to treat vaginal infections

Solid Doses

- Unshaped
  - Powders
    - Contained in various packages
    - Adminisrered by all routes except parentarily
    - Contains inert ingredients
- Shaped
  - Tablets
    - Compressed product (API - excipients - e.g. fillers, desintegrants)
    - Conventional: can be divided (half/quarter)
    - Coated: usually not to be divided
    - Effervescent tablets: final dosage form is a solution (rapid absorption)
    - Sublingual tablets
    - Chewable tablets: usually if swallowing is difficult
    - Vaginal tablets
  - Lozenges
    - Not swallowed
    - Dissolve in the mouth
    - Release medication slowly
    - Similar to hard candy
    - Flat, larger than normal sized candy
    - Chalky consistency
  - Capsules
    - Substances enclosed in hard/soft water soluble container made of gelatin
      - → Hard
        - Consists of the capsule and the body
        - Filled with pellets, powders or granules
        - Can be pulled apart for medication to be sprinkled on foods
      - → Soft
        - Are made of one piece
        - Filled with paste
        - Can be squeezed to dissolve medication into food
  - Transdermal patches
    - Designed foe affixing on healthy and clean skin
    - Controlled drug delivery into systemic circulation over time
  - Implants
    - Parenteral route dosage form
    - Controlled drug delivery for a long period of time
    - Overcome problems with individual compliance
    - Mini-surgeries needed
    - Uneasy to discontinue therapy
    - Local reactions

Conventional (Unmodified) Release

- Spontaneous disintegration of dosage form and dissolution of active ingredient
- Absorption and distribution based on physico-chemical properties of ingredients

Controlled Release

- The release of active ingredient is under the control of the drug delivery system (temporal control)
- Avoidance of fluctuations of plasma drug control
- More economical
- Decreased frequency of drug administration
- Types include:
    - Sustained release (SR): release of the initial dose and further prolonged release
    - Controlled release (CR): properly controlled release of active ingredient
    - Pulsatile release

Log-Dose Responses

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- The relation between dose of a drug and the clinically observed response may be complex
- However, in carefully controlled in vitro systems, the relations between concentration of a drug and its effect can be described with mathematical precision
- This idealised relation underlies the more complex relations between dose and effect that occur when drugs are given to patients

Concentration-effect curves and receptor binding of agonists

- Responses to low doses of a drug usually increase in direct proportion to the dose
- As the dose increases however, the response increment diminishes
  - Finally, doses may be reached at which no further increase in response can be achieved
- In idealised or I vitro systems, the relation between drug concentration and effect is described by a hyperbolic curve
  - The hyperbolic curve is according to the following equation
    - $E = \frac{Emax \times C}{C + EC50}$
- Dose response data are often presented as a plot of the drug effect on the y-axis against the logarithm of the dose or concentration on the x-axis
- This mathematical manoeuvre transforms the hyperbolic curve into a sigmoid curve with a linear mid portion
- This expands the scale of the concentration axis at low concentrations (where the effect is changing rapidly) and compresses it at high concentration (where the effect is changing slowly)
  - However, this has no special biological or pharmacological significance

1. Potency
   - Drugs A and B are said to be more potent than other drugs C and D because of the relative positions of their dose response curves along the dose axis
   - Potency refers to the concentration (E_{50}) or dose (ED_{50}) of a drug required to produce 50% of that drug's maximal effect
   - Hence the pharmacological potency of drug A (in diagram) is less than drug B, a partial agonist because the EC50 of A (concentration required to produce 50% of drug A's maximal effect
   - Potency of a drugs depends
     - partly on the affinity of the receptors for binding on the drug
     - Partly on the efficiency with which drug-receptor interaction is coupled to response
   - There are some doses of drug A that produce larger effects than any dose of drug B despite drug B being pharmacologically more potent
     - This is because drug A has a larger maximal efficacy
   - For clinical use, it is important to distinguish between a drugs potency and efficacy
   - The clinical effectiveness of a drug depends no on its potency (EC50) but on.
     - Maximal efficacy
     - Ability to reach relevant receptors
       - Route of administration
       - Absorption which depends on:
       - Distribution through the body
       - Clearance from the blood or site of action
   - In deciding which of the 2 drugs to administer, the doctor should consider relative effectiveness rather than relative potency
   - Pharmacological potency can largely determine the administered dose of the chosen

drug
    - For therapeutic purposes, the potency of a drug should be stated in dosage units, usually in terms of a particular therapeutic end point e.g.
        - 50mg for mild sedation
        - 1mcg/kg/min for an increase in HR of 25 beats/min
    - Relative potency is the ratio of equi-effective doses (e.g. .2, 10 etc.)
        - May be used to compare one drug to another
2. Maximal efficacy
    - It reflects the limit of the dose-response relation on the response axis
    - Drug A, C as D (in the figure that I do not have) have equal maximal efficacy, while all have greater normal efficacy than drug B
    - The maximal efficacy of a drug is sometimes referred to simply as efficacy
        - It is crucial for making clinical decisions when a large response is required
    - May be determined by
        - The drug's mode of interaction with receptors
            - Partial agonist produce a lower response, at full receptor agonist than do full agonists
        - Characteristics of the receptor effector system involved
            - Diuretics that act o one portion of the nephron may produce much greater excretion of fluid and electrolytes than diuretics that act elsewhere
    - In addition, the practical efficacy of a drug for achieving a therapeutic end point e.g. increased cardiac contractility, may be limited by the drug's propensity to cause a toxic effect (e.g. fatal cardiac arrhythmia) even if the drug could otherwise produce a greater therapeutic effect
        - Digoxin

Shape of dose response curve

- Extremely steep dose response curves may have important clinical consequences if the upper portion of the curve represents an undesirable extent of response (e.g. coma caused by a sedative hypnotic)
- Steep dose-response curves in several patients can result from interactions of several actions of a drug (e.g. effects on the brain, heart and peripheral vessels, all contributing to lowering of BP)

Quantal dose-effect curves

- Graded dose-response curves as described above have certain limitations in their application to clinical decision making
- For example, such curves may be impossible to construct if the pharmacological response id either-or (quantal) event such as prevention of convulsions, arrhythmia or death
- In addition, the clinical relevance to a quantitative dose response relationship in a single patient, may be limited _
- Some of these difficulties may be avoided by determining the dose of a drug required to produce a specified magnitude of effect in a large no. of individual characters and especially animals and plotting the cumulative frequency (distance of respondence vs dose-response)
- The specific quantal effect may be chosen the basis of:
    - Clinical relevance (e.g. relief or headache)
    - For preservation of safety of experimental subjects (e.g. using low doses of a cardiac stimulant and specifying an increase in HR of 20 beats/min as the quantal effect)
    - It may be an inherently quantal event
- For most drugs, the doses required to produce a specified quantal effect in individuals are log-normally distributed
    - That is, a frequency distribution of such responses plotted against the log of the dose produces a Gaussian normal curve variation
- When these responses are summated, the resulting cumulative frequency distribution constitutes a quantal dose-effect curve (or dose-percentage curve) of the proportion or

percentage of individuals who exhibit the effect plotted as a function of log dose

- The quantal dose-effect curve is often characterised by stating the median effective dose (ED50) i.e. the dose where 50 exhibits the specified quantal effect
- The abbreviation ED50, has a different meaning in this context from its meaning in relation to graded dose-effect curves, described above
- Similarly, the dose required to produce a particular toxic effect in 50% of animals is called the median toxic _
- _
- Such values provide a convenient way of comparing the potencies of drugs in experimental and clinical setting
    - E.g. if the ED50
- Similarly, one can obtain a valuable index of the selectivity of a drug's action by comparing its ED50S for 2 different quantal effects in population (e.g. cough suppression verses sedation for opioid drugs
- Quantal dose-effect curves may also be used to generate information regarding the margin of safety to be expected for a certain drug used to generate_

Therapeutic index

- A measure, which relates the dose of a drug required to produce a desired effect to that which produces an undesired effect
- In animal studies, the therapeutic index is usually defined as the median toxic dose to the medial therapeutic dose for some therapeutically relevant effect
- _
- The TI of a drug in humans is almost never known with precision
    - However, drug trials and accumulated clinical experience often reveal a range of usually effective doses and a different _
    - The clinically acceptable risk of toxicity depends critically on the severity_
        - The dose range that provides relief from ordinary headache in the grate majority of patients, should be very much lower than the dose range that produces serious toxicity, even if the toxicity, even if the toxicity occurs on a small minority of patients
        - However, for treatment of lethal disease e.g. cancer, the acceptable difference between therapeutic and toxic doses may be smaller

GDEC vs QDRC

- The quantal dose-effect curve and the graded dose-response curve summarises somewhat the different sets of information
- _
- Critical information required 4 making rational therapeutic decisins can be obtained from each curve e.g.
    - Both curves provide information regarding potency and selectivity of drugs
    - GDRC indicates the maximal efficacy of a drug
    - The QDEC indicates the potential variability of responsiveness among individuals
- Maximal efficacy used in a therapeutic context, does not have exactly the same meaning the term denotes in the_
    - In an idealised in vitro system, efficacy denotes the relatively of agonists and partial agonists that via the same receptor
    - I therapeutics, efficacy denotes the extent or degree of an effect_
- Therefore, therapeutic efficacy may be affected by the characteristics of a particular drug-receptor interaction
    - However, it depends also, on other factors noted earlier

Adverse Drug Reactions

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Adverse Drug Reaction

- Definition:
    - It is an effect that is:
        - Nontoxic/toxic
        - Unintended
        - Occur at normal doses or overdose
        - May be due to a drug interaction
- ADR can involve every organ and system and may be mistaken for signs of disease
- Excipients may cause ADR – agents used in drug formulation
- Time course of ADR varies. It may be:
    - Closely related to time administration and/or discontinuation
    - Delayed
- Making a diagnosis of ADR may be a challenge.

ADR Classification

1. Type A – Augmented
2. Type B – Bizarre/idiosyncratic
3. Type C – Chronic – Continuous
4. Type D – Delayed
5. Type E – End of treatment effects

Type A ADR

- Due to exaggeration of the main/principle pharmacological action of drug
- Often dose-dependent and therefore can be Reversed by a decrease in dose
- Are predictable
- More common than type B
- Mild ones are called side effects
- Examples:
    - Hypoglycemia (insulin)
    - Bleeding/haemorrage (anticoagulants eg. Warfarin)

Type B ADR

- Unrelated to the main pharmacological action of the drug
- May be predictable
- Due to excessive dose
    - Aspirin - tinnitus
    - Aminoglycoside - ototoxicity
    - Paracetamol - hepatotoxicity
- During pregnancy -
    - Thalidomide - teratogenicity
- Due to predisposing disorder
    - Primaquine - haemolysis in G6PDH deficient patients
- May also be :
    - unpredictable
    - Independent of dose
    - cytotoxic reactions and immunologic mechanisms

    - Aplastic anaemia (chloramphenicol)
    - Anaphylaxis (penicillin)
- Frequently severe and associated with higher mortality

Type C

- Occur during prolonged treatment and not with single doses
    - Cushing's syndrome (prednisone)

Type D

- Occur long after treatment has stopped
    - Secondary cancers - alkylating agents
- Can occur in the next generation
    - Clear cell carcinoma of the vagina in daughters (mothers took diethylstilbestrol during pregnancy)

Type E - ADWE

- Occur when treatment has been suddenly stopped
- Adrenal insufficiency (prednisone)
- Withdrawal seizures (phenytoin)
- Severe hypertension (clonidine)

ADR may be unknown

- Therefore, ADR may only be known only after marketing
    - clinical research exposes few people to drugs
        - Fenfluramine (appetite suppressant) found to cause pulmonary hypertension and valvar heart disease after long term use
- Be cautious when prescribing new drugs
    - Rare and previously unrecognised adverse effects may occur
- These need to be reported
    - Pharmacy and Poisons Board

Risk Factors for ADR

1. Extremes of age (decreased liver and renal functions)
2. Women> men (p'kinetics change in puberty, pregnancy)
3. Past history of allergic reaction
4. Past history of ADR
5. Genetic factors
    a. Polymorphisms in drug metabolism
    b. G6P deficiency - Some drugs cause haemolysis eg Primaquine, sulfonamides

- Adverse effects may be exploited to develop a new indication for the drug
    - Minoxidil (for hypertension) causes unwanted hair growth
- Drug now used to promote hair growth

Cytotoxic ADR

- Usually caused by reactive metabolites
    - May form covalent bonds or non-covalent bonds with target molecules

Non-covalent interaction

- Lipid peroxidation
- Generation of toxic oxygen radicals
- Depletion of glutathione
- Modification of sulfhydryl groups

- Some of these effects are also produced by covalent reactions

Lipid Peroxidation

- Results in the formation of lipid peroxyradicals on the cell membrane
- These cause call damage and eventually death due to:
  - Altered membrane permeability
  - Reactions of the products of lipid peroxidation with proteins
- The body's defensive mechanisms against lipid peroxidation (eg. glutathione peroxidase and Vitamin E) may reduce cell damage

Generation of Toxic Oxygen Radicals

- These are generated by reactive metabolism
- They are cytotoxic both:
  - Directly
  - Through lipid peroxidation

Depletion of glutathione (GSH)

- GSH depletion can be caused by the action of toxic metabolism
- GSH depletion result in oxidative stress
- Therefore cellular defense against toxic oxidative compounds is impaired and cell death can result

Modification of sulfhydryl groups

- The sulfhydryl groups are involved in the catalytic activity of many enzymes
- Therefore, modification results in enzyme inactivation
- If enzymes involved in maintenance of cytoplasmic Calcium levels are involved, there is an increase in cellular calcium levels
- This can lead to death through
  - Activation of degradative enzymes and protein kinases
  - Mitochondrial damage

Covalent interactions

- The targets for these interactions include DNA, proteins, lipids and carbohydrates
- Covalent binding to:
  - A protein can produce an immunogen
  - DNA can cause carcinogenesis and teratogenesis
- Examples
  - Hepatotoxicity by paracetamol overdosage
- Normally, reactive metabolites are detoxified by combining with hepatic glutathione (GSH), When GSH is exhausted, they bind to hepatic protein and cause damage
- N-acetylcysteine or methionine increases GSH availability

Immunologic/allergic/hypersensitivity reactions

- Most drugs:
  - have low molecular weights (<2000 daltons) and thus are poor immunogens
- Generation of an immune response requires covalent linkage to proteins, CHO or nucleic acids
- Stimulation of antibody production may mediate tissue injury by several mechanisms

Type I hypersensitivity reactions

- Immediate type, anaphylactic or IgE -mediated
- Results from release of histamine, leukotrines, prostaglandins from basophils or mast cells
- May result in anaphylaxis, bronchospasms, urticaria

Anaphylaxis

- Penicillins cause 75% of anaphylactic deaths
- Is life-threatening
  - Death within minutes to hours
- The clinical picture vary in intensity
- The most dramatic
  - Sudden, severe hypotension and rapid death
- Other presentations
  - Respiratory distress due to bronchoconstriction or laryngeal oedema
  - Crampy abdominal pain, Nausea, Vomiting, Diarrhoea
  - Extreme weakness and fall in BP
  - Pruritus, urticaria with or without angioedema
- Treatment
  - Adrenaline (SC, IM, IV (Lifesaving))
  - Volume expanders - normal saline
  - Dopamine - if intractable(unmanageable) hypotension
  - Oxygen +/- albuterol (Beta2 adrenergic agonist- bronchodilation), aminophylline
  - Antihistamine
  - Corticosteroids (act late, prevent recurrence of symptoms)

Type II hypersensitivity

- Antibody-dependent cytotoxicity
- Complement - dependent cytotoxicity
- The antibody may attack the drug when the drug is covalently bound to the cell, and thereby destroy the cell
  - Penicillin induced haemolytic anaemia
- Antibody-drug-antigen complexes may be passivelyy adsorbed by a bystander cell
- This cell will then be destroyed by activation of complement
  - Quinine and quininidine - induced thrombocytopenia

Type III hypersensitivity

- Serum sickness
- Due to deposition of drug-antibody complexes on endothelial surfaces
- Complement activation occurs
- Chemotactic factors are generated locally and an inflammatory response develops
- Arthralgia, urticaria, cerebritis may occur
- Common causes:
  - Foreign proteins
    - Vaccines, streptokinase, therapeutic antibody
    - Antibiotics

Type IV hypersensitivity

- Cell mediated
- delayed in tuberculin
- Ab not involved
- Cf example

Drugs or their reactive metabolites may alter host tissue rendering it antigenic and eliciting auto Ab

- Hydralazine and procainamide
  - alter nuclear material
  - promote formation of antinuclear Ab
  - Cause lupus erythematosus (Autoimmune diseases)

Diseases of allergic reactions

- Clinical criteria (6 features)
- Occur only after prior exposure
- Reaction occur 8-9 days from first exposure suggesting a period of sensitisation is required
- Reaction appears to be
- Reaction are often accompanied by eosinophilia and fever
- Usually subside promptly after the drug is stopped unless drug-induced autoimmune response has been initiated
- On re-exposure with the drug the same pathologic reactions occur

Diagnosis

- Be familiar with ADR of a drug
- Identify a temporal relationship between drug administration and development of ADR
- Take drug history - ask about OTCs, herbal and prescription medicines
  - 30 days
  - Remember topical

Suspected ADR

- Discontinuation of a drug is followed by resolution of s/s
  - presumptive evidence
- Cautious drug reintroduction to see if ADR occurs – confirming evidence
- Confirming evidence is only useful if
  - The drug may be useful in future management and
  - Entails no undue risk
- If an ADR is thought to be allergic, re-administration of the drug may be hazardous since anaphylaxis may occur
- For concentration-dependent adverse effects
  - Lowering the dose may cause ADR to disappear
- Variable time needed
  - Time required for the concentration to fall below the range associated with the ADR
  - ADR of drugs with long half life take a considerable time to disappear
- If a patient is receiving many drugs when ADR is suspected
  - All drugs may be stopped at once
  - Discontinue one at a time, starting with the one most suspect and observe the patient for signs of recovery

Ototoxicity

- Aminoglycosides
- Vancomycin
- Erythromycin
- Diuretics
- Salicylates
- Quinine, quininidine, chloroquine
- Cisplatin

Nephrotoxicity

- NSAIDS
- Penicillins

- Cephalosporins
- Aminoglycosides
- AmphotericinsB
- Vancomycin
- Cisplatin
- Cyclosporine
- Radiocontrast agents

Hepatotoxicity

- Halothane
- Paracetamol
- Isoniazid
- Methotrexate
- Chlorpromazine
- Androgens

Mutagenesis and Carcinogenesis

- Mutation is a change in genotype that is passed on when a cell divides
- Chemical agents cause mutations by covalent modification of DNA
- Certain mutations cause carcinogenesis because the affected DNA codes for a protein that is involved in growth regulation
    - Oncogenes (they regulate cell growth)
    - Tumor suppressor genes (code for products that inhibit the transcription of oncogenes)
- Few therapeutic drugs are known to increase the risk of cancer
- The most important groups are those that act on DNA
    - Cytotoxic drugs
    - Immunosuppressant drugs
    - Sex hormones (eg. oestrogen increase the risk of endometrial cancer)

Teratogenesis

- Gross structural malformations during foetal development
- 70% of birth defects do not have a recognised cause (idiopathic)
- Drugs are thought to account for 1% of all foetal malformations

Known teratogens

- Thalidomide
    - Phocomelia, heart defects, gut atresia
- Valproate
    - Neural tube defects eg spina bifida

Frequency of ADR

- Very common >= 1/10
- Common (frequent) >= 1/100 and < 1/10
- Uncommon (infrequent) >= 1/1000 and < 1/100
- Rare >1/10000 and < 1/1000
- Very Rare <1/10000

ADRs

- Mild->moderate->severe->life threatening->death
- Grade 1-5
- Check DAIDS (Division of AIDS) tables (Nov 2014 version)

- Kenya HIV guidelines

Mild ADRs

- Continue drugs
- Can affect adherence
- Manage if bothersome
    - Eg. Mild rash-Antihistamine

Moderate and severe ADRs

- Substitute the offending drug

Life threatening toxicity

- Stop all drugs
- Manage ADRs
- After resolution
    - substitute offending drug with one that has a different toxicity profile
- Document and tell the patient

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Autonomic Nervous System

- Section of the nervous system not controlled by will power
- It controls:
  - The GIT
  - The exocrine system
  - The heart and vasculature
  - The respiratory system
  - The genitourinary system
- Impulses from the ANS only initiate the actions, the controlled systems do not stop functioning when the ANS is cut off
- There are two major divisions of the ANS
  - Sympathetic system for djustment to the environment
  - Parasympathetic system which tends to oppose the SS (strike a balance)

Functional Organisation of the Autonomic Activity

Both have preganglionic and postganglionic fibres and ganglia

Parasympathetic System

- Carries afferent and efferent impulses to and from the viscera which reflex and modify the ANS function
- Fibres supply the heart, smooth muscles, motor nerves, viscera
- Outflow is cranio-sacral
  - CN III, IV, IX, X
  - S2-4
- Some preganglionic parasympathetic fibres terminate in the ganglia located in the ganglia outside the innervated region
  - Ciliary ganglia
  - Otic ganglion
  - Pterygopalatine ganglion
  - Submandibular ganglion
  - Several pelvic ganglia
- Majority of preganglic fibres terminate on ganglion cells distributed diffusely or in the wall of the innervated organs

Sympathetic System

- Carries efferent impulses to the viscera that modify autonomic activity
- Fibres supply the heart, smooth muscles, glands, viscera and motor nerves
- Outflow is thoraco-lumbar
  - C8-L5

Ganglia Division

1. Paravertebral ganglia (main division):
    a. Comprises of two chains on either side of the spinal cord
    b. Monitor sweat glands,sphincter pupillae, nerves to skeletal muscles, sublingual and submandibular plexi, skin and blood vessels
2. Prevertebral:
    a. Lies infront of the vertebrae in the abdomen
    b. Includes coeliac ganglia, inferior and superior mesenteric ganglia.
    c. Suplies the viscera
3. Intermediate:
    a. Cardic plexus, pulmonary plexus and supply to the oesophagus
4. Terminal ganglia:
    a. In viscera and bladder, few in the rectum

- Pre-ganglionic fibres originate from nuclei in the brain (CNS)
- Large numbers of afferent run from the periphery to integrating centres including:
    - Enteric plexus
    - Autonomic ganglia
    - CNS – many of these terminate in the hypothalamus, medulla and evoke reflex moteor activity carried to the effector organs via efferent fibres
        - Some sensory fibres have peripheral motor functions

Enteric Nervous System

- Sometimes considered the third division of the ANS
- Large and highly organised collection of neurons found on the wall of the GIT
- It includes:
    - Myenteric plexus (plexus of Auerbach) – 2nd behind the circular layer of muscle
    - Submucous plexus (plexus of Meissner) – 1st
- The network receives preganglionic fibres
- From the parasympathetic system, and postganglionic sympathetic axons
- They receive sensory input from within the wall of the gut, the mucosa and stretch receptors to motor neurons in the plexi and to postganglionic neurons in the sympathetic ganglia to control peristalsis and secretory cells in the mucosa. These fibres only play a modulatory role.
- The two divisions and the endocrine and the endocrine system are intergrated with each other and with informatin from the higher CNS centres
- At a more subtle level of interactions in the brainstem, medulla, and spinal cord, there are important cooperative functions between sympathetic and parasympathetic systems. For example, sensory fibres in the parasympathetic system like those in the nerve IX form.
- The baro-receptors exert reflex control over motor outflow of the sympthetic system – sympathetic outflow from the VMC (vasomotor centres)

Neurotransmitter Chemistry of the ANS

Parasympathetic system (cholinergic)

5. Neurotramsmitter at the ganglia and neuroeffector junctions is acetylcholine.It is synthesised at the cytoplasm and stored in vesicles with co-transmiters - ATP, peptides and proteoglycans
6. A good number of parasympathetic postganglionic fibres use nitric oxide or peptides as neurotransmitters
7. Choline is transported into the presynaptic nerve terminals by a sodium dependent choline transporter (CHT). The transporter can be inhibited by hemicholinium
8. Acetylcholine is synthesised from choline and acetyl-coA by enzyme choline acetyl transferase (ChAT)
9. Synthesised Acetylcholine is trasnported into the storage vesicles by trasporter 2, vesicle associated transporter (VAT)
10. VAT can be inhibited by Vesamicol
11. Release of acetylcholine occures when voltage-sensitive calcium channels in the nerve terminals are opened allowing an influx of calcium. The increased calcium causes fusion of the storage vesicles with surface membrane and exocytotic expulsion of acetylcholine and co-transmitters into the junctional cleft. This can be blocked by botulinum toxin (releasd by clostrodium toxin [gram positive bacterium] and is known as one of the most powerful poisons in the world)
12. Vesicle associated membrane proteins (VAMPS) and synaptosome nerve associated proteins (SNAPS), regulate transmitter release. The proteins are coded for in the genes.
13. Released acetylcholine binds to receptors on the postsynaptic membrane modifying function of the cell.
14. Action of acetylcholine is terminated by acetylcholinesterase which breaks it down to acetate and choline. Enzyme also found in other tissues like RBCs.
15. Butyrylcholinesterase (pseudocholinesterase) is found in blood, liver, glia and other tissues, has a lower affinity and specificity for acetylcholine

Sympathetic System (adrenergic)

- Neurotransmitter at the ganglia is acetylcholine
- Neurotransmitter at the cardiac and smooth muscle, gland cells, NEJs and nerve terminals is NE
- Dopamine at renal vascular SM NEJ
- Acetylcholine at the sweat glands NEJ

16. Tyrosine taken in by carrier 1 linked to sodium uptake. Hydroxylated to DOPA and decarboxylated to dopamine in cytoplasm. The rate limiting step, tyrosine hydroxylation, inhibited by metyrosine
17. Dopamine taken into storage vesicles by carrier 2, vescicular monoamine transporter (VMAT). Can be inhibited by reserpine (used for treating depression and hypertension)
18. Norepinephrine transporter (NET) carries norepinephrine and similar molecules back into the cell cytoplasm from the synaptic cleft. Inhibited by cocaine, Tricycline Antidepresants (TCA)
19. Dopamine and serotonin reuptaken by DAT and SERT respectively into their neurons
20. Norepinephrine stored with ATP, dopamine beta hydroxylase (converts dopamine into norepinephrine) and peptides
21. Release mechanism similar to acetylcholine
22. Indirect acting sympathomimetics (eg. tyramine, amphetamines, ephedrine) capable of releasing norepinephrine from storage through calcium-independent mechanisms. Amphetamines also inhibit MAO. And other effects
23. Metabolism of catecholamines is by MAO and COMT. Metabolic products are VMAs

24. MAO metabolises norepinephrine in the cytoplasm, COMT norepinephrine in the synaptic cleft
25. Metabolic product of dopamine is HVA
26. Termination of catecholamine action is mainly through diffusion into the surrounding tissues and reuptake by NET, metabolism contributing less
27. Most ANS nerves also release co-transmitters beside the primary ones

Other neurotransmitters in ANS

- Other neurotransmitters are found in the ANS, ENS and the NANC neurons. They include:
  - ATP
    - Acts as a tramsmitter or co-transmitter at many ANS effector synapses
  - Calcitonin gene related peptide (CGRP)
    - Found with substance P in CV sensory nerve fibres, present in some secretomotor ENS neurons and interneurons.
    - A cardiac stimulant
  - Cholesystokinin (CCK)
    - May act as a co-transmitter in some excitatory neuromuscular ENS neurons
  - Dopamine
    - A modulatory neurotransmitter in some ganglia and the ENS.
    - A postganglionic sympathetic transmitter in the renal bed vessels
  - Enkephalin and related opioids
    - Present in some secretomotor and interneurons in the ENS.
    - Appears to inhibit acetylcholine release and peristalsis
    - May stimulate secretion
  - Galanin
    - In secretomotor neurons, involved in appetite and satiety mechanisms
  - GABA
    - May have pre-synaptic effects on excitatory ENS nerve terminals
    - Relaxant effect in the gut
  - Gastrin releasing hormone (GRP)
    - Extremely potent excitatory transmitter to gastrin cells
    - Also known as mammalian bombesin
  - Neuropeptide Y (NPY)
    - Found in many noradrenergic neurons
    - Present in secretomotor neurons in ENS and may inhibit water and electrolytes secretion in the gut.
    - Causes long-lasting vasoconstriction.
    - Also a co-transmitter in some parasympathetic postganglionic neurons
  - Nitric oxide
    - A co-transmitter at inhibitory ENS neuromuscular junctions.
    - May especially be important at the sphincters
  - Serotonin
    - Important transmitter and co-transmitter at excitatory neuron-to-neuron junctions in the ENS
  - Substance P
    - An important sensory transmitter in ENS and elsewhere
    - Vasodilator
  - Tachykinins
    - Thought to be excitatory co-transmitters with acetylcholine at ENS neuromuscular junctions
    - Found with CGRP in cardiovascular sensory neurons

- Vasoactive intestinal peptide (VIP)
  - Excitatory secretomotor transmitter in the ENS
  - May also be an inhibitory ENS neuromuscular co-transmitter in many cholinergic neurons.
  - A vasodilator and cardiac stimulant

Receptors

28. Cholinergic
    a. Muscarinic (M1-M5)
    b. Nicotinic (Nm [found in NMJ] and Nn [found in the ganglia and in the brain])
29. Adrenoceptors
    a. Alpha 1 and 2
    b. Beta 1, 2, 3
30. Dopamine – divided according to excitatory or inhibitory activity
    a. DA1
        i. (D1)
        ii. D5
    b. DA2
        i. (D2)
        ii. D3
        iii. D4

The NANC (non adrenagic, non cholinergic)

- NO, purines, CGRP, CCK, dynorphin, enkephalins, GRP, 5HT, neuropeptides, somatostatin, substance P, VIP

Receptor	Location	Effect
M1	Cns neurons,	formation of ip3 and DAG, increased intracellular calcium
M2	Myocardium, smooth muscles, in some presynaptic sites, some CNS neurons	Opening of K+ channels, inhibition of adenylyl cyclase
M3	In exocrine glands, in smooth muscles and endothelium of blood vessels	Increased DAG and IP3, increased intracelluar calcium
M4	CNS neurons, vagal nerve endings	Opening of potassium channels, inhibition of adenylyl cyclas
M5	Vascular endothelium	Inreased IP3 and DAG, increased intracellular calcium
Nn	Post ganglionic neurons, presynaptic cholinergic nerve terminals	Opening of sodium-potassium channels and depolarisation

Nm	Skeletal muscle, neuromuscular end plates	Opening of sodium-potassium channels and depolarisation
Alpha 1	Post synaptic effector cells esp smooth muscles	formation of ip3 and DAG, increased intracellular calcium (smooth muscle contraction
Alpha 2	Pre synaptic nerve terminals	inhibition of adenylyl cyclase (inhibit vasoconstriction)
Beta 1	Post synaptic effector cells esp heart, lymphocytes, brain, pre synaptic adrenagic and cholinergic end terminals, juxtaglomerular apparatus, ciliary bodies	Stimulation of adenylyl cyclase and increased cAMP
Beta 2	Post synaptic	Stimulation of adenylyl cyclase and cAMP Activate cardiac G_i-protein
Beta 3	Post synaptic effector cells esp lipocytes and heart	Stimulation of adenylyl cyclase and cAMP Release of FA
D1 and D5	Brain, effector tissues esp smooth muscle	Stimulation of adenylyl cyclase and increased cAMP
D2	Brain, effector tissues esp smooth muscle	Inhibition of adenylyl cyclase Decreased potassium
D3	Brain	Inhibition of adenylyl cyclase
D4	Brain, CVS	Inhibition of adenylyl cyclase

Organ	Effect of sympathetic activity	Receptor responsble for activity	Effect of parasympathetic activity	Receptor responsible for activity
Eye radial muscles	Contraction of radial muscles	Alpha 1		

Heart	Tachycardia	Beta 1 and 2	Bradycardia	M2
Myocardium	Increased contraction	Beta 1 and 2	Decreased atrial contraction	M2
Blood Vessels	Vasoconstriction Relaxation of skeletal blood vessels	Alpha Beta 2	Relaxation of skeletal BV Vasodilation	Muscarinic
Bronchiolar smooth muscle	Bronchodilation	Beta 2	Bronchoconstriction	M3
GIT smooth muscles	Relaxation (reduced peristalsis)	Alpha 1 and beta 2	Contraction (increased peristalsis)	M3
GIT sphincters	Contraction	Alpha 1	Relaxation	M3
GIT secretion			Increased secretion	M3
Bladder wall muscles	relaxation	Beta 2	Contraction	M3
Genitourinary Sphincter	relaxation	Alpha 1	contraction	M3
Pregnant uterus	Relaxation	Beta 2		M3
At term	contraction	Alpha 1		
Penis	ejaculation	Alpha	Erection	M
Pillomotor smooth muscle	Contract	alpha		
Sweat glands (eccrine)	Increase	M		
Sweat glands (Apocrine)	Increase	alpha		
Metabolic activity in liver	gluconeogenesis	Alpha and beta 2		
Renin release	Increased	Beta 1		

Drug Agonists and Antagonists

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Definitions

Receptors: chemicals that binds to drugs to exert a pharmacologic effect
D + R = Complex
Analogous to a switch ie on and off

Agonists, Partial Agonists and Inverse Agonists:

- Molecules that activate the receptors and bring about effect (both affinity and activity)
- Most drugs are agonist. E.g. dobutamine that mimics the effect of norepinephrine at receptors in the hearts to cause tachycardia
- Affinity: allows the agonist to bind to receptors
- Intrinsic activity: allows the bound agonist to activate or turn on receptor function
- Example: Cholinomimetic effects by acetylcholinesterase inhibitors
    - Amplify effects of physiologically released agonists. They are less toxic and more selective
- There are also agonists that inhibit the molecule responsible for terminating the effect of the endogenous agonist
    - Acetylcholinesterase inhibitors bind acetylcholinesterase, stopping the metabolism of ACh and prolonging its effect.
- **Theory Behind Agonism**:
    - The receptor is postulated to exist in the inactive, non-activated form R_i and the activated state, R_a.
    - Thermodynamic considerations state that some of the receptors must exist in the R_a state and produce the same physiologic agonist-induced activity even in the absence of any agonist. This is called **constitutive activity**.
    - Agonists have a higher affinity for the R_a form, stabilising it and causing a large fraction of the receptor to exist in the R_a-D(Drug) complex form and producing an effect.
    - **Full agonists**:
        - ◇ When administered at concentrations sufficient to saturate the receptor pool can activate their receptor systems to their maximum potential.
        - ◇ That is, they shift almost all of the receptor pool to the R_a-D pool
    - **Partial agonists**:
        - ◇ Bind to the same receptor but do not evoke maximum response no matter how high the concentration.
        - ◇ Do not stabilise the R_a form as fully so a large portion of the receptor pool still exists in the R_i form.
        - ◇ Have low intrinsic efficacy
        - ◇ Act as antagonist in presence of full agonist
    - **Inverse agonists**:
        - ◇ Have a stronger affinity for the R_i form than the R_a form and stabilises a large fraction of the R_i-D pool.
        - ◇ produce the opposite of the conventional agonist effect (reduces constitutive effect)
        - ◇ GABA is a good example

Antagonists

- Substance that does not evoke biological response
- blocks or reduces the agonist-mediated responses
- Have affinity but no efficacy
- Inhibit functions of full, partial and inverse agonist
- Binds to active site or allosteric sites on the receptors

- Reversible or irreversible nature of binding

Types of Antagonism

1. Chemical
2. Physiological
3. Pharmacological

1. Chemical

- Interaction of the drug (agonist) with another chemical (antagonist) outside of the receptor to form an inactive complex
- Substances combine in solution:
    i. Chelating agents (dimercaprol) bind heavy metals
    ii. Antacids bind gastric acids

2. Physiological

- Opposite effects of two drugs on same function
- Two agonists working in different receptors have antagonistic effects
    i. Histamine (H1 agonist) causes bronchoconstriction, adrenaline (beta2 agonist) causes bronchodilation
    ii. Insulin (insulin receptors) cause hypoglycemia, glucagon (glucagon receptors) cause hyperglycemia

3. Pharmacological

- Opposite effect of two drugs binding to the same receptor
- Receptor antagonism is specific
- Divided into:
    i. Competitive
        1. Equilibrium (reversible)
            - Binds to same receptor site as agonist
            - Inhibition overcome by increasing [agonist]
            - Dose-response curve shifts to the right (without change in slope of curve)
            - Maximal response occurs at higher [agonist]
            - Affects agonist potency
        2. Non-equilibrium (irreversible)
            - Binds to the same site as agonist
            - Form covalent bonds with the receptor (irreversible)
            - Inhibition not overcome by increasing [agonist]
            - Reduced maximal response
            - Dose response curve shifts to the right (reduced slope of curve)
            - Agonist potency may/not affected
            - Inhibition overcome by increasing number of receptors
    ii. Non competitive
        - Does not bind to the same receptor site as agonist
        - Ballistic inhibition
            Ø Binds to a distinctly separate binding site
            Ø Prevent conformational change after agonist binds
        - Inhibition does not overcome by increasing [agonist] - irreversible
        - Maximal response will be depressed
        - Dose curve shifts to the right (reduced curve slope)
        - Agonist potency may or may not be affected

Drug Disposition in Disease States

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Influence of disease states on drug disposition

- Course of actionn of drug is dependent upon the normal functioning of organs
- Combined effect of absorption, distribution, metabolism and excretion at characteristic rate changes
- Pathological conditions of these organs may be:
  a) Organs individual contribution to the course of drug action
  b) SEcondary effect to function of other organs eg heart failure that causes git oedema, congested liver and decreased renal perfusion

Disease states that influence drug disposition

- CV, GIT, Liver and KIdney disorder influence:
  a. Rate and extent of absorption
  b. Apparent volume of distribution
  c. Plasma protein binding
  d. Plasma half life
  e. Plasma and hepatic clearance
  f. Drug metabolising enzymes and transporters
- For a kidney pathology, the p'kinetic consequence is not necessarily the same for all drugs
- It is not always possible to predict the effect of a given disease on the effectiveness of therapy
- Plasma drug level monitoring if low therapeutic window

Disease states that influence drug kinetics

- GIT disease - absorption surfaces
- Hepatic - influence metabolism by enzyme systems found in the liver. Reduced synthesis of plasma protein resulting in altered drug distribution
- Renal disease - alter drug excretion
- Drug-drug interaction in patients on therapy
  - Ø p'kinetic interaction - ADME
  - Ø P'dynamic interaction - agonists/antagonists

Absorption

- Influenced by the factors that determine the rate of gastric emptying and absorption
  a. Food
  b. Hormones
  c. Posture
  d. Peritoneal irritation
  e. Pain
  f. Gastric ulcer

Drugs influencing the rate of gastric emptying and absoption

1. Alcohol
2. Anticholinergics
3. Harcotic analgesics

4. Adrenergic blocking drugs
5. Antacids
6. Metoclopramide - it's a prokinetic drug. used to stop vomiting (reflux) ie it is antiemetic

How do the rest affect absorption?

Gastric Emptying

- Increases the rate of some drug absorption
- Digoxin and riboflavin are exceptions and the rate of absorption is decreased with increasing GIT motility

Delayed absorption

- Altered motility of the intestines
- Decreasesd rate of abrortion
- Altered gastric emptying
- Therapeutic failure especially if the drug has a short half life

Abnormal absorption

- Lower GIT diease, Crohn's disease
- Physicochemical and p'kinetic properties of the drug and disease pathopathology will not predict pattern of absortion
- Variability in absortion from patient to patent with the same condition

Application

- Migrane reduces drug absorption by causing GIT stasis and reduce the rate of gastric emptying
- Use of prokinetic drug improves the analgesic effect of aspirin by enhancing absorption

Volume of Distribution

- Relates drug concentration to the plasma to the total amount of drug in the body

Changes induced by drugs influence therapeutic or toxic significance

- Plasma protein binding, weight and are important
- PPB lower in hepatic and renal disease, neonares and elderly individuals
- Heart, liver and kidney determine
    a. Volume of distribution
    b. Elimination of the drug
    c. Alteration of organ functions influences p'kinetics of drugs
- Drugs with high PPB,eg phenytoin, diazepam and warfarin demonstrate increased Vd in liver or kidney disease
- This is due to lower PPB
- Renal failure is associated with reduced vd of digoxin
- Monitor PP in hepatic, renal and cardiac diseases

Does reduced PPB have significance in reducing pharmacologic effect of drugs?
Should you correct drug dosage or level of PP?

Metabolism

- Hepatic
- Renal
- GIT

- Enzyme systems
    a. Mixed function Oxidasases
    b. CYP450
    c. Cytochrome reductase

List some common drugs that are CYP450 enzyme inducers/inhibitors
Notice the releance of these drugs in drug-drug interaction and influence on drug-dose adjustment

Thyroid Disease

- Affect the rate of metabolism and elimination
- Digoxin in thyroid disease
- Antipyrine ecreased in thyrotooxic patients
- Propylthiouracil disposition not changed in thyrotoxicosis unlike methimazole which is reduced

Cardiac Failure

1. Changes in CO, ANS Na+ and water Influence tissue perfusion
2. GIT motility - GIT oedema
3. Visceral congestion
4. Vd lignocaine
5. Hepatic function
6. Accumulation of metabolites and interaction

Nephroic Syndrome
Decrease in plasma albumin increases the fraction of unbound drug

Acute and Chronic Kidney Injury
Characterised by increase in urea and creatinine
Levels predict kidney function
Creatinine clearance and glomerular filtration rare can be worked out
Need to appreciate mode of drug disposition
Drug dosages adjusted on basis of eGFR
Drugs with hepatic disposition may not necessitate dose adjustmnt
Digoxin excreted via renal route
Digigoxin excreted via hepato-biliary rute

Does weight influence drug dosing?
Does changing weight necessitate dosage adjustment?

Drug Interaction

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- When one drug (A) alters the intensity of pharmacological effects of another drug (B) given concurrently.
    - A - Precipitant drug
    - B - Object drug

Why are drug interactions (DIs) important?

1. The incidence of clinical drug-drug interactions (DIs) range from:
    a. 3-5% in patients taking a few drugs to
    b. 20% of patients receiving 10-20 drugs
2. 3% of hospital admissions are related to drug interaction
3. The use of several drugs concurrently (polypharmacy) is essential to obtain a desired therapeutic effect or for treatment of coexisting diseases.
   Eg. treatment of:
    a. Hypertension
    b. heart diseases
    c. Cancer
    d. Certain infectious diseases eg TB
4. Patients often receive several prescribed drugs plus
    1. Proprietary over-the-counter drugs
    2. 'alternative' remedies
    3. Lifestyle drugs

- During polypharmacy, the doctor needs to know whether a specific combination in a given patient has the potential to result in an interaction and if so, how to
    1. Take advantage of the interaction if it leads to effective therapeutic effect
    2. How to avoid the consequences of the interaction

Clinical Significance of DIs

- Whether or not the DI occurs, depends on both the patient and drug specific factors
- Patient factors can include:
    1. Intrinsic drug clearance
    2. Genetics
    3. Gender
    4. Concurrent diseases
    5. Diet (eg grapefruit juice downregulates CYP3A4 in the gut)
- Drug specific factors include:
    1. Dose
    2. Route of administration
    3. Drug formulation
    4. Sequence of drug administration

For DI to be clinically important, it is necessary that the therapeutic range of drug B is narrow, ie, a small decrease in action in effect will lead to loss of efficacy, increase will lead to toxicity
For P'kinetics to be clinically important, it is also necessary that drug B has a steep dose-response curve
i.e a small change in concentration will result in a substantial effect

Several drugs have steep dose-response curves and serious dose-related toxicity
DI with such drugs are liable to cause harm
Special caution is necessary for concurrent therapy. They include:

1. Warfarin and other anticoagulants
2. Anticonvulsants
3. Cytotoxic (anti-cancer drugs)
4. ARV drugs
5. Immunosuppressants
6. Digoxin and other antiarrhythmic drugs
7. Oral hypoglycemic drugs
8. Xanthine alkaloids
9. MAO inhibitors

Mechanisms of DI

1. Pharmaceutical
2. Pharmacodynamic
3. Pharmacokinetic
4. Combined DIs

Pharmaceutical Mechanisms

These occur by chemical reaction or physical reaction when drugs are mixed eg

1. Thiopentane (IV anaesthetic agent) and succinylcholine (muscle relaxant)
2. Penicillin and hydrocortisone

Pharmacokinetic Mechanisms

Occur when one drug affects the p'kinetics of another (ie those that affect the ADME of a drug)

a) ABSORPTION

- The GIT absorption of drugs may be affected by concurrent use of other agents that
    i. Bind/adsorb/chelate
        1. Aluminium, Calcium and Magnesium ions contained in antacids form chelates with tetracycline antibiotics, quinolone or thyroxine leading to reduced GIT absorption of the latter drugs
        2. Cholestyramine (acid binding resin used to treat hypercholesterolemia) binds several drugs eg. warfarin and digoxin leading to their reduced absorption
    ii. Alter gastric pH
        1. Antacids increase gastric pH and hence reduce the absorption of Itraconazole (antifungal) which require acids to be absorption
    iii. Alter GIT motility
        1. Atropine and opioids slow absorption by inhibiting gastric emptying
        2. Metoclopramide (prokinetic drug) accelerates gastric emptying hence accelerates their absorption
    iv. Affect transport proteins such as p-glycoprotein and organic anion transporters
- Example of a DI at subcutaneous level
    i. Absorption from Sc sites can be slowed by vasoconstrictors given simultaneously
        1. Adrenaline causes vasoconstriction that slow absorption of lidocaine to prolong its anaesthetic effect

b) DISTRIBUTION

- The mechanisms
    a. Competition for PPB
    b. Displacement from tissue binding sites
    c. alteration in local tissue barriers eg. p-glycoprotein inhibition in bbb
- Examples
    a. sulphonamides displace the following from binding sites on albumin
        i. Warfarin increased prothrombin time – increased bleeding
        ii. Methotrexate
        iii. Phenytoin
        iv. Sulphonylureas
    b. The following drugs alter protein binding and reduce elimination of displaced drugs to cause clinically important DI
        i. Salicylates: displace methotrexate from albumin binding sites and also decrease its secretion into the nephron by competition with the organic anion transporter
        ii. Quinidine and other arrhythmic drugs displace digoxin from tissue binding sites and simultaneously reduce its renal excretion and as a result may cause severe arrhythmia through digoxin toxicity
    c. Changes in drug distribution can occur if one agent alters the size of the physical compartment in which another drug distributes
        i. Diuretics reduce total body water. They can therefore increase plasms lever of aminoglycosides or lithium to enhance their toxicities

c) METABOLISM

- Metabolism of drugs can be stimulated (induced) or inhibited by concurrent therapy of other drugs
    a. Enzyme induction (stimulation) of CYP450 isozymes. Enzyme induction leads to enhancement of drug metabolism. Maximal effects usually occur after7-10 days and require equal or longer time to disappear after enzyme inducer is stopped. Examples:
        1) Rifampicin when given for three or more days, induces the metabolism of the following:
            a) Warfarin
            b) Tolbutamide leading to hyperglycemia in diabetic patients on treatment
            c) Theophylline leading to reduced bronchodilation
        2) Phenytoin: induces hepatic microsomal drug metabolism of the following leading to their reduced serum concentrations and the following effects:
            a) Methadone (opioid) leading to withdrawal symptoms
            b) Theophylline leading to reduced bronchodilation in asthmatics on treatment
            c) Verapamil (calcium channel blocker) leading to reduced hypotensive effects
    b. Enzyme inhibition
        1) Inhibition of drug metabolising enzymes takes place faster than enzyme induction and leads to:
            a) Increase in plasma concentration of parent drug
            b) Reduction in concentration of the metabolite
        2) You get exaggerated and prolonged pharmacologic effect of parent drug and increased likelihood of toxicity.
        3) This changes are critical for drugs that are
            a) Extensively metabolised
            b) Narrow therapeutic index
        4) Examples
            a) Cimetidine: (H2 receptor antagonist used to treat peptic ulcers) inhibits hepatic microsomal drug-metabolising enzymes. Therefore inhibits metabolism of the drugs leading to toxicity
                i) Diazepam leads to increased sedation
                ii) Quinidine: arrhythmia
                iii) Theophylline: toxicity
                iv) Amiodarone: increased hypotension
                v) Pethidine: increased sedation and depression
            b) Erythromycin: inhibits the metabolism of the following to increase toxicity
                i) Quinidine
                ii) Sildenafil
                iii) Selective serotonin reuptake inhibitors
    c. Increase of drugs due to decreased drug clearance because of reduced hepatic blood flow
        1) Drugs that reduce hepatic blood flow may reduce clearance of other drugs metabolised in then liver especially flow limited drugs such as morphine and verapamil.

d) EXCRETION

- The main mechanisms how one drug can affect renal excretion of another are:
  a. Synergism is said to occur when the effect of 2 or more drugs used together are significantly greater than expected from their effects when used - Alteration of PPB hence filtration
    a. Inhibition of tubular secretion
      i. Probenecid inhibits tubular secretion
        1. Penicillin (beneficial DI)
        2. Zidovudine
      ii. Alteration of urine flow/pH
      i. Drugs that alter_
      ii.
      iii. This is clinically impo

Examples of additive PD DI

a) The additive depression of the CNS caused by concurrent administration of diazepam with Pethidine (opioid)
b) The concomitant use of several antihypertensive drugs with different mechanisms and sites of action to lower BP
   a. Enalapril (ACE inhibitor) and Chlorthalidone (Thiazide diuretic)

Interactions based on synergistic effects

Occurs when the effects of 2 or more drugs used together are significantly greater than their arithmetic sum from their expec ted effects when used separately

Examples

1. Trimethoprim and Sulfamethoxazole in Cotrimoxazole block two sequential steps in folic acid synthetic pathway, This results in a much more complete inhibition of bacterial growth (bactericidal effect) than what is achieved by other drug alone (bacterial static)
2. Penicillin and other inhibitors of cell wall synthesis increase uptake of aminoglycosides by a number of bacteria eg staphylococci, enterococci and streptococci

Interactions based on antagonistic action

The effect of two drugs used together is less than the sum of the responses to the same doses given separately (ie. one drug reduces the effect of the other drug)

E.g. a. Propanolol (beta-adrenoceptor antagonist) diminishes the bronchodilator effect of salbutamol (beta 2 agonist) if given concurrently = harmful competitive antagonism

b. Naloxone reverses respiratory depression caused by opioids by competing for the same receptor site = beneficial competitive antagonism

COMBINED TOXICITY

The combined use of 2 or more drugs which have the toxic effects on the same organs can increase the likelihood of organ damage

Example : : Concurrent administration of gentamycin (aminoglycoside AB) with vancomycin are both nephrotoxic, increases the likelihood of nephrotoxicity even though the dose of either drug alone may not be enough to cause nephrotoxicity

Drug Use in The Elderly

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Introduction

- Geriatric medicine is the branch of medicine that is concerned with the clinical, preventive, remedial and social aspects of illness in the elderly.
- unfitness could be as a result of disease, chronic alcoholism, social problems e.g. living alone
  - Aging, disease, social problems, unfitness

Special features of illness in old people

1. Multiple pathology
2. Effect of pre-existing disease processes - Altered presentation of an illness e.g. electrolyte disturbance, constipation and confusion
3. Adverse reactions to drugs
4. Prolonged recovery time
5. Adverse social problems
6. immobility - simple illness can immobilise the elderly - clinical problem
7. Mental confusion
    a. likely in already forgetful person
    b. by any of the commonly used drugs
    c. Severe infection eg pneumonia
    d. Metabolic problems
8. falls and hypotension
9. incontinence
10. Constipation

P'kinetics in Geriatrics

- Known physiological changes with age are likely to affect drug absorption and distribution
- Drug absorption and metabolism not affected with age with exception of some drugs subject to first pass effect where increased bioavailability may result
- distribution of water soluble drugs may decrease while that of lipid soluble drugs increases
- Plasma protein binding of acidic drugs may be decreased while binding of basic drugs may be increased
- Drugs metabolised by phase 1 enzyme mediated metabolic reactions often show a decreased clearance with aging while those by phase2 may be relatively unaffected
- Drugs whose excretion is predominantly renal show reduced renal clearance and dose adjustment may be necessary

Physiological Changes

- CO reduced - blood flow to the kidney and GIT reduced
- Increased tendency towards achlorhydia and reduction in the volume of gastric secretions
- Active transport of endogenous compounds may be diminished
- Increased GIT transit time, constipation and impaired bowel function - laxative abuse
- Changes in body composition with increasing age (25 - 70 years)
  - Fat 14 - 30%
  - Water 61 - 53%
  - Cell solids 25 -17%

- Decrease in albumin concentration and increase in alpha-1-acid glycoprotein
- Beyond 50 years, the liver mass declines as a percentage of BWt accompanied by decline in hepatic BF
- Age related changes in renal functions i.e declines in GFR, renal plasma flow, tubular secretion,

Absorption

- Elevated gastric pH may affect drug ionisation, dissolution, degradation and gastric emptying time
- Reduction in splanchnic BF might impair or delay drug absorption
- No major alteration in drug absorption but nutritional habits and slow gastric emptying may affect absorption of many
- drugs undergoing significant first pass metabolism due to decreased deficiency

Distribution

- Significant reduction in lean body mass --> loading dose of digoxin might need to be decreased
- For water soluble drugs, there might be significant decreased apparent Vd and increased lipid soluble Vd.
-

Metabolism

- Decreased liver mass and hepatic blood flow
- Slow metabolic inactivation of drug
- With few exceptions phase 1 processes are most adversely affected by age --> prolonged half life
- Phase 2 conjugation processes in particular are not affected.

Excretion

- Decline in the healthy with the absence of renal disease
- Both serum creatinine and its clearance may be used as indicators of impaired RF in the elderly
- The Cockcroft-Gault equation is widely used for dose adjustments of renally excreted drugs in older people --> applied in dosing of such drugs as gentamicin, digoxin, lithium
- CL of creatinine (ml/min) = [140 - age] x Wt (kg)/ 72 x serum creatinine (mg/dl)
- (x 0.85 for females)

P'dynamics

- Reponses may alter with age to produce either a lesser/greater effect than is anticipated in younger adults
- Drugs acting on the CNS produce an exaggerated response
- Sedatives and hypnotics may have a hangover effect and are more likely to depress respiration because vital capacity and max breathing capacity are reduced
- Response for beta adrenoceptor agonists and antagonists are blunted sue to a decrease in receptors
- Baroreceptor sensitivity is decreased leading to the potential of orthostatic hypotension with drugs that reduce BP
- >80 year olds are particularly intolerant to neuroleptics (confusion) and diuretics (ankle swelling that is postural and postural hypotension)

Guidelines to drug therapy in old age

- There is no drug to combat senescence

- Mere prolongation of life is not a valid aim
- The effects of prescription must be clearly better than no prescription e.g. use of warfarin in patients with atrial fibrillation
- On the other hand, do not deny medication
- Many diseases that the elderly suffer, do not respond to treatment
- Multiple pathology may require prioritisation of drugs eg benzodiazepines (BDZ) - Lorazepam, oxazepam instead of diazepam in treatment of insomnia
- Avoid some drugs eg chlopramide - long half life with the risk of hypoglycemia; anticholinergic - urinary incontinence
- Consider dosage forms - syrup, effervescent tablets compared to capsule etc
- Patient education - teach patient to understand the drugs prescribed for them
- Minimise number of drugs --> avoid polypharmacy (found in 20-40% of the old)
- You should have good knowledge of the pharmacology of the drugs you prescribe
- Review medication regularly and discontinue unnecessary drugs.
- Monitor patients especially the critically ill for therapeutic and adverse effects
- Select drugs whose metabolism isn't affected by age
- Start treatment at low doses then titrate upwards on the basis of response eg CNS doses should be 50% lower than for young adults
- Drugs should be clearly labelled in large prints and packed in readily opened containers --> avoid child proof containers
- Simple dose regimens
- Supervision or therapy may be necessary eg by relative, friend, neighbour etc

Mechanisms of Drug Action

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Signal Transduction Mechanisms

Drug Action

- Chemical interaction between drug and tissues
- Small quantity of chemical get close to one or more cell constituents
- Alter function of cell constituent
- Drugs may alter physiological function
- Molecules exert chemical influence on tissue to produce a pharmacological effect
- Targets are distributed heterogeneously in tissue

Receptors

- Sensing elements in the system of chemical communication that control cell function
- Specialised target macromolecules present on the surface of the cell or within the cell
- Chemical messengers (ligand) - hormones, transmitters and other mediators
- interaction of the drug and the receptor initiates signal transduction leading to a pharmacological effect
- Drug-receptor complex initiates a biochemical or biophysical change of the cell
- Usually inactive
- Active when bound by agonists
- Inactive state maintained by antagonists
- Partial agonists cause incomplete activation
- Drugs may act as agonists or antagonists for known endogenous mediators
- Drug binding on a receptor may cause direct action or act via channels, enzymes etc

Note:

- « Hormones are molecules prod by glands and tpt'd to distant tissues to prod a physiological effect
- « Neurotransmitters are produced by neurons
- « Autacoids are local hormones e.g. histamine, serotonin, bradykinin, angiotensin-II etc.

Receptor Isolation

- Extract and purify radio-labelled receptors
- Expressive cloning

Receptor Responses

Different responses i.e.

- Ø Rapid NT (ms) - ACh, NE
- Ø Long (hours): Hormones
- Ø Auto(a)coids (sec)

Signal Transduction

- Signal-drug(ligand)
- Signal detector is the receptor
- Second messenger effector molecules that cascade upon agonist-binding to cause a cellular response
- Magnitude of response proportional to the receptor occupancy
- Not all receptors have to be occupied for optimal response (spare receptors)

Protein targets for drug binding (R.I.C.E)

i. Receptors

ii. Ion Channels
iii. Carrier Molecules
iv. Enzymes
v. Structural Proteins - tubulin
vi. Cellular elements - DNA and cell wall constituents
vii. Plasma proteins
viii. Cytokines

Drug Specificity

- Selective on particular cells or tissue
- High degree of binding site specificity
- Specificity is reciprocal with classes of drugs binding on certain and targets and target recognizing on certain drug classes
- No drug is completely specific. Increasing dose will cause side effects

Receptor Classification

- Based on pharmacological responses e.g. histamine receptors
- Subtypes elucidated by molecular cloning e.g. drugs that cover receptors without effect are antagonists are thus formed through molecular cloning.

Interaction of a drug and receptor

- Occupation
- +/- activation
- Tissue response
- Agonist/antagonist
- **Affinity** - tendency to bind receptor
- **Efficacy** - tendency to activate a receptor
- **Potency** - maximal response

Ion Channels

- Local anaesthetics and voltage gated Na^+ channels
- Vasodilators that inhibit L-type Ca^{2+} channels
- Benzodiazepines and GABA receptor/chloride channel complex
  - Valium and Xanax
  - Used to treat insomnia, anxiety and seizures
  - Enhance response to inhibitory neuroceptor GABA by opening GABA-activated Cl- channels and allowing Cl- ions to enter the neuron and stop depolarisation (allow membrane potential to be more negative)
- Sulphonamides on ATP-sensitive K+ channels
- Diabetes mellitus patients are treated by oral agents called sulphonylureas agents

Transmembrane ligand gated ion channel

- Extracellular portion contains the ligand binding site
- Site regulates gating: shape of the pores through which the ions can flow across the cell membrane
- Channels closed until the receptor is activated
- Voltage gated ion channels may also possess ligand-binding site that regulate ion influx_
- _
- _

Enzymes

A drug molecule is a substrate analogue that is a competitive inhibitor of the enzyme eg Neostigmine and acetylcholinesterase, ASA and COX
Drugs act as false substrate forming abnormal metabolites that subverts the normal metabolic pathway e.g. fluorouracil, azido thymidine

Enzyme-linked Receptors

Proteins form dimers and

G-Coupled
All three

Questions

1. Give 2 examples of endogenous substances that cause diverse physiological effects when they bind to receptors
    a. Atropine
    b. propranolol
2. Indicate the drugs that act on the listed receptors to cause agonist and antagonist effects
3. What is an inverse agonist?
4. What is the mechanism of insulin secretion?
    a.
5. How do sulphonylureas agents act to enhance insulin secretion?
    a. They block ATP sensitive k+ channels hence cause depolarisation of the beta-cell membrane
    b. This will cause a rise in intracellular Ca2+ which stimulates exocytosis of insulin-containing secretory granules

G-Proteins and Second Messengers

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G-Proteins and Second Messengers

Receptors

They are

a) Regulatory proteins mediating the actions of endogenous chemical signals eg autacoids, hormones
    1. Enzymes
    2. Transport proteins
    3. Structural proteins

Endogenous protein receptor types

1. Transcellular receptors
2. Transmembrane receptors
3. Tyrosine kinase type receptors
    a. Simple type
    b. Cytokine type
4. Ion channel associated receptors
5. G-protein linked receptors

Intracellular Receptors

- Utilised by steroids, hormones, thyroid hormone, Vitamin D
- Three domains:
    1. Hormone binding domain
    2. DNA Binding domain
    3. Receptor regulatory activity

Protein Kinase Receptors

- Utilised by:
    - Tyrosine kinases - insulin, epidermal growth factor, platelet derived growth factor, certain lymphokines
        - Have three domains
            - Ligand binding domain
            - A hydrophobic amino acid chain crossing the cell membrane, connecting a and c
            - Intracellular tyrosine kinase catalytic domain
    - TGF (transforming growth factor)- beta
        - The receptors phosphorylate serine and threonine residues (because they have -OH groups)
    - Intracellular domain is guanylyl cyclase
        - Synthesis cGMP (increases
        - Used by atrial natriuretic peptide (ANP)
        - All receptors dimerise; in inactive states, they double stimulating activity

Cytokine Receptors

- Uses Janus kinase family proteins (JAKS) and signal transduction and activators of transcription proteins (STATS)
- Dimeration involved
- Used by GH, ERYTHROPOIETIN, INTERFERON AND OTHER REGULATORS

Ion Channel Associated

- Used by neurotransmitters, nicotinic cholinergic receptors, GABA alpha receptors, amino acid receptors - glutamate, aspartate and glycine
- Multi- sub unit protein spanning plasma membrane many times to form a channel

G-Protein Linked Receptors

- Receptor structure - heterotrimeric - alpha, beta, gamma
- Classification based on alpha sub unit
- Have 3 domains
  - Binding domain
  - Receptor
  - Regulatory
- Used by biogenic amines e.g. dopamine, serotonin, adrenaline/noradrenalin (beta receptors), glucagon, TSH
- They act by facilitating binding of GTP to certain proteins
- The G-protein regulates another effector molecule
- Effector molecule produces a second messenger
  (Resting state protein binds GDP. When catalytic end of receptor is activated, GTP replaces GDP. Results in activation of effector protein. Leads to formation of GTP-Protein complex)
- The receptors are hydrophobic molecules that span the membrane in seven alpha helical segments. Interacts with G-protein at the cytoplasmic end
- An individual cell may express 5 or more G-proteins, each of which may respond to several different receptors and regulate several different effectors with a characteristic pattern of selectivity
- Effectors include:
  - Adenylyl cyclase (converts AMP to cAMP), phospholipase C and A2
  - Ion channels
  - Certain transport molecules

  The g-protein effector system are complex networks of convergent and divergent interactions that permit extraordinarily versatile regulation of cell functions

Types of g-proteins

1. G_s
2. G_i
3. G_{olf}
4. G_o
5. G_q
6. G_t

Type of G-Protein	Receptor	Effector
G_s (stimulator)	beta adrenergic amines, glucagon, histamine, serotonin	Adenylyl cyclase (produce cAMP from ATP)
G_i (inhibitor) 3 types: 1, 2, 3 Inhibits adenylyl cyclase	alpha-2 adrenergic eceptors, muscarinnic receptors, opioids, some serotonin receptors	· Adenylyl cyclase (reduced cAMP) · Open K+ channels in heart (bradycardia) · Phospholipase C (stimulation causes increase in IP3 concentrations, increased cytoplasmic Ca^{2+})
G_{olf} (olfactory)	odourance receptors in olfactory epithelium	Adenylyl cyclase stimulation
G_o	Associated with certain neurotransmitters in the brain	function not clear
G_q	Associated with ACh receptors, muscarinic-1 receptors, bombesin receptors, some serotonin receptors (5HT1C)	Stimulae phospholipase C (increased IP3, DIACYLTGLYCEROL, cytoplasmic Ca
G_t (transduction) 2 types: 1 and 2	Associated with photon recetors (in retina)(rhodopsin and colour opsins in retinal rods and cones)	increase cGMP-diesterase - reduced cGMP

Second Messengers

1. cAMP

2. cGMP
3. Calcium
4. IP3
5. DAG

cAMP

- Functions include
    - Hormonal responses
    - Mobilisation stored energy - FFA, glycogen
    - Conservation of water
    - Calcium homeostasis
    - Rate and force of contraction of heart
    - Regulation of adrenal and sex steroids
    - Relaxation of smooth muscle
    - Many other endocrine and neural processes
- Acts through cAMP dependent protein kinases
- Specificity depends on the substrate on the substrate of the kinase expressed on the different cells
- Myosin light chain kinase - smooth muscle relaxation
- Liver glycogen phosphorylase - glycogen breakdown

Phosphoinositides/Ca

- Final step stimulation of phospholipase C
- Hydrolises phosphatidyl inositol 4,5 phosphate top DAG, inositol 1,4,5 triphosphate (IP3)
- IP3 - releases calcium from storage sites which regulates other ca- dependent protein kinases. Stopped by
- DAG (diacylglycerol is confined to the cell membrane) - activates a phospholipid and ca-sensitive protein kinase protein C
- 9 types of protein kinase C

cGMP

- Has roles a few cell types e.g. intestinal mucosa and vascular smooth muscle
- cGMP dependent protein kinases regulated
- cGMP stimulates relaxation of smooth muscles
- ANF stimulates guanylyl cyclase
- cGMP works through Nitric Oxide to relax smooth muscle
- Action terminated by cGMP breakdown
- cGMP-kinase dephosphorylates myosin light chain - muscle relaxation

Paediatric Clinical Pharmacology

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Premature neonate - <36 weeks
term neonate - >36 weeks
Neonate - birth - 1 month
Infant - >1 month -12 months
Child - >1 year - 11 years
Adolescent - 12 - 16 years

- Growth and development of 36 weekschildren is similar but the timing of maturation may vary
- physiological changes in infancy affect drug p'kinetics - developmental pharmacology

Drug absorption

- Most drugs are absorbed from the GIT by passive diffusiion
- The bioavailability of most orally administered drugs in infants is adequate
- When possible, oral route is preffered
- Is affected by the following:
  1. **Blood flow at the site of administration**
     - Affects absorption after IM or SC injections
     - peripheral perfusion may be reduced in sick infants
       - Absorption is irregular and may be slow
       - I f perfusion is suddenly improved, an increased amoutnt of drug my be be absorbed leading to toxicity
       - reduced splanchnic flow
         - Reduces the rate and axtent of absorption
     - IM injections may be delayed due to:
       - Reduced muscle size
       - Weaker muscular contractions
       - Immature vasculature resulting in erratic blood flow to and from the muscle
       - Advantageous for Vitamin K in newborns (depot - a single dose is effective for one month)
  2. **GI Function**
     - Gasteic acid production
       - Slower in preterms than fullterm infants
         - Highest gastric acid concentration in pre term by day 4 of life
       - Absorptio of acid liable drugs
         - Erythromycin
       - Absorption of weak acidic drugs
         - phenytoin
     - Delayed gastric emptying (upto 6-8 hours) during first day of life
       - may be delayed by disease
         - Respiratory distress syndrome
         - Congenital heart disease
         - IV preferred
       - If a drug is absorbed in the:
         - stomach then there is > absorption
         - small intestines then there is delayed absorption
     - peristalsis in the neonate is irregular and slow
       - Unpredictable amounts of drug may be absorbed
       - Slow peristalsis may increase absorption

- Rapid peristalsis may reduce absorption
    - May lead to inadequate serum levels
- Reduced pancreatic enzymes in infants < 4 months
- Neonates have low concenteations of bile acids and lipase
    - May reduce the absorption of lipid soluble drugs
    - May alter absorption of pH sensitive drugs

3. **Factors associated with the skin**
    - Directly related to the degree of hydration of the skin
    - Inversely related to the thickness of the stratum corneum
    - the preterm's skin is thinner than the fullterm new born
    - Skin has better hydration and perfusion
    - The skin SA to body weight is 3x > than an adulth
        - Thereforer, 3x the amount of drug absorbed for an identical percutaneous dose in an infant than in an adult
    - Systemic toxic effects
        - Adrenal suppression can occur in 2 weeks after excessive topical hydrocortisone use

Drug Distribution

- Affected by:
    - Organ size
    - Body water content
    - Fat stores
    - Plasma proteiin concentration
    - Acid-base balance
    - Cardiac output
    - tissue perfusion
- This affects voluume of distribution of drugs

Body Water

- Total body water of paediatric patient (% of body weight)
    - 85% preterm
    - 70-75% neonate
    - 60-65% at 1 year
    - 50-60% adult
- Extracelluler water
    - 4-45% neonate
    - 20-25% from 1 year to adult
- Intracellular water
    - Relatively sttabe iin all agge groups
- More body water leads to > distribution of water soluble drugs eg aminoglycosides

Fat Stores

- Total body fat
    - Preterm 1-2% of body weight
    - Term 10-15%
    - Infant 20-25%
- < accumulation of lipid soluble drugs
    - benzodiazepines
    - Digoxin
    - Amphotericin B
    - Amiodarone

- Effects of obesity not yet clear

Plasma Protein Concentrations

- Reduced plasma proteiins (they reach adult values by 10-12 months of age)
  - Reduced albumin
  - Reduced alpha1-acid glycoprotein
  - BInding affinity also reduced
- May be associated with more free druug concentrations and adverse effects initially
- If free drug concentration is increased then drug elimination is increased
- Patological rises in billirubin eg due to blood group incompatibility
- BIlirubin can displace a drug from albumin - > risk of blood toxicity
- Drugs may displace bilirubn from albumin - Kernictus
- Clinically significant protein displacement reactions occur when a drug:
  - is 80-90% protein bound
  - Has limited clearance
  - Has a small volume of distribuution (approximately 1.5 l/dl)

Tissue Perfusion

- BBB is immature. More permeable in childhood
  - Gentamicin used for meningitis in neonates but not older patients
- Brain
  - 2% of adult body weight
  - 10-12% of infant body weight
  - Has > blood flow than in adult
- Can lead to higher drug concentrationsin CNS
  - Risk of neurotoxicity

Drug Metabolism

- Most drugs are metabolised in the liver
- the activity of cyp450 MIXED FUNCTION OXIDASES AND CONJUGATING ENZYMES ARE 50-70% of adult values in early neonatall lif
  - Variable levels of different isoenzymes
- Gluucoronide level reach adult levells at 3-4 years
- Low glucoronide levels
  - Chloramphenicol causes grat baby syndrome
- Blood estereses activity is low
  - Delayed clearance of cocaine
- Drug doses should be adjusted to avoid toxicity
- Bioavailability of drugs may be increased
- If the mother was taking drugs that can induce foetal liver enzymes eg phenobarbital
- > ability to metabolise certain drugs than expected
- Therefore less therapeutic effect of drugs unless doses are adjusted

Drug Excretion

- Occurs mainly thriugh the kidneys
- GFR is much lower in newborns than older infants
- GFR compared to adult values
  - Newborn - 30-40%
  - 3 weeks - 50-60%
  - 6-12 months - 100%
- Therefore drugs are eliminated by GF are cleared slowly in the first weks of life eg

aminoglycoside, vancomycin)
- Other renal functions also decrease
  - Tubular secretion
    - penicillins
    - Cephalosporins
    - Furosemide
    - Digoxin
  - Reabsorption
- The clearance of penicillin
  - Preterms - 17%
    - Doses of ampicillin
      - <7 days- 50-100mg/kg/d at 12 hour intervals
      - > 7 days - 100-200mg/kd/d at 8 hour intervals
      - Adult 250-1000mg at 6 houur iintervals
- Note: renal functions may not improved at the predicted rate in a sick infant
- Therefore appropriate adjustments of doses may be difficult
- PLasma drug concentrations should be measured
- Toddlers may have shorter half life of drugs that other children or adults
- This is thought that they may have increased metabolism of drugs and renal elimination
- The mechanism for these developmental changes is porly understood

Adolescents

- P'kinetic changes
  - Increased body fat
  - Rapid increase in protein concentration
  - GFR may exceed adult values
    - Faster clearance of vancomycin, aminoglycosides
  - Changes in metabolic activity
    - The clearance of
    - Girls have reduced CYP3A4

PHARMACODYNAMIC FEATURES

- Patent ductuis arteriosus (PDA)
  - Indomethacin is used to close it
- Prostaglandin E1 keeps PDA open
  - This can be life-saving in some congenital heart diseases eg Transpositio of great arteries, Tetralogy of Fallot
  - Antral hyperplasia with gastric outlet obstrraction reported. dose dependent

P'dynamic effects

- Tetracyclines
  - Permanent staining of developing teeth
  - Dental hypoplasia
- Corticosteroids
  - Stunted linear growth
- Aspirin
  - Reye's syndrome
- Isoniazid and paracetamol
  - Hepatotoxicity in children < in adults
- Antihistamins and barbiturates
  - Cause sedation in adults

    - May cause hyperactivity in children
- Amphetamine
    - Sedation in hyperactive children

Paediatric dosage forms

- Elixirs - alcohol solutions in which the drug moleculesare dissolved and evenly distributed
    - No shaking required
- Suspensions - these contain undissolved drug particlles
    - shaking is needed to distribute these particles evenly
    - If not shaken, the first dose may contain < drug than the last
    - Intial reduced therapeutic effect and later toxicity is possible
    - Parents should be given proper instructions on drug use
- MOstt drugs ae administered to infants and young children in liquid formulations
    - The rate of absorption in liquid formulationns is higher
    - liquuid > suspensions
    - Capsule > tablet > sustained/delayed release
- Tablets difficult to swallow for < 5 years
- Metered dose inhalers (pressurised aerosols)
    - Use with spacer or face masks in children < 10 years

Compliance/adherence

- Factors affecting compliancce:
    - Taste
    - Smell
    - Colour
    - Consistency
    - Dosing fequency
    - Cost (use effective generic)
- A committed parent/caegiver needed
- Proper drug measurement
    - Use a callibrated medicine spoon or syringe
    - Teaspoon volumes vary (2.5-7.8 mls)
- Drug may spill
- Drug may be spitted out (taste, smell)
- proper drug frequency and duration
    - 6 hourly drugs require one to wake up the child
    - Drugs needed for long periods may be stopped when the child appears better
- Children should be given appropriate responsibility for taking medications
- Computerised pill containers which record each lid opening
- Random pill counts or measurement of serum drug concentrations may reveal non-compliance
- Promote adherance by
    - Providing onformationo to the parent
    - Why use the drug
    - How long to treat
    - Potential adverse effects
- Adverse effects
    - Cavities from chronic use of sucrose containing drugs
    - Hypersensitivity to dyes and flavours

Paediatric Drug Dosage

- Most drugs are tested in adults
- Studies in children provide efffective and safe doses
- Use doses recommemded by the manufacturer
- Information on drug use in children may be unavailable
- Paeditric doses are calculated
    - Dose errors possible
- There ois no reliable formula for calculating paediatric doses
- Doses are calculated on the basis of the age and weight and tend to underestimate doses
- Doses based on SA are more accurate
- The calculated doses should never exceed the adult dose

Use of new drugs

- If severe adverse effects from usual drugs
- Presciber takes responsibility
- Parents should be informed and consent taken

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Parasympathomimetics (Cholinomimetics)

- Drugs that produce pharmacological effects similar to those produced by parasympathetic stimulation

Classification according to the mode of action

1. Directly acting parasympathomimetics
    a. Choline esters
        i. Acetylcholine
        ii. Bethanechol
        iii. Methacholine
        iv. Carbachol
    b. Alkaloids
        i. Muscarine and nicotine
        ii. Pilocarpine
        iii. Lobeline
        iv. Oxytremorine
2. Indirectly acting
    a. Reversible
        i. Physostigmine
        ii. Neostigmine
        iii. Tacrine
        iv. Donepezil
    b. Irreversible
        i. Organophosphates

- Few cholinomimetics are highly selective for muscarinic and nicotinic receptors
- The choline esters have quaternary ammonium group rendering them relatively lipid insoluble
- Muscarinic receptors are strongly stereoselective ie (S)-bethanechol is almost x1000 more potent than (R)-bethanechol

P'Kinetics

- Choline esters are hydrophilic – poorly absorbed and poorly distributed into the CNS
- Less active by oral route – hydrolysed in the GIT
- Differ in their susceptibility to hydrolysis by Cholinesterase – acetylcholine rapidly hydrolysed ie large IV bolus produces an effect for 5-20 seconds
- Methacholine and carbamic acid esters (carbachol and bethenachol) more resistance have a longer duration of action
- The tertiary natural cholinomimetic alkaloids are well-absorbed from most sites of administration. Nicotine can be absorbed through the skin

- Muscarine, a quaternary amine is less completely absorbed from the GIT but is toxic when ingested – found in some mushrooms. Enters the brain.
- Lobeline is a plant derivative of nicotine (nicotine transdermal patches/polacrilex gum/polacrilex lozenges for smoking cessation)
- The amines are chiefly excreted by the kidneys – acidification of urine accelerates their clearance

Mechanism of action of parasympathomimetics

- Directly acting parasympathomimetics:
  - Bind to and directly stimulates the cholinergic receptors (M, Nm, Nn) in the effector organs
  - Prolonged receptor activation can cause depolarisation blockade (nicotinic) or receptor desensitisation hence muscle paralysis
- Indirect acting parasympathomimetics:
  - Inactivate cholinesterase leading to accumulation of acetylcholine at the cholinergic receptors

Pharmacological actions of parasypathomimetics

- Relatively predictable – effects of acetylcholine
- Acetylcholine has both muscarinic and nicotinic activity
- CVS
  - Heart (decrease in HR and CO – mimic effects of vagal stimulation)
    - SA node – negative chronotropy
    - Atria – negative inotropy. Decrease in refractory period
    - AV node – negative dromotropy. Increase in refractory period
    - Ventricles – small decrease in contractile response
  - Blood Vessels
    - Vasodilation – small dose produces transient drop in BP due to generalised VD.
      - Large dose induces lesser VD due to reflex increase in HR (symp. ++) so BP is not markedly lowered
- Glands:
  - Sweat (thermoregulatory), salivary , lacrimal nasopharyngeal secretion
- GIT
  - Increased peristalsis; relaxation of sphincters
  - Stimulation of secretions (gastric, salivary…)
- Lung
  - Bronchoconstriction
  - Bronchial gland stimulation – secretion
- Urinary Tract
  - Contracts the wall (detrusor muscle) and relaxation of trigone and the sphincters of the urinary bladder
  - Increased peristaltic waves of the ureters
  - Promote voiding of the urine
- Eye
  - Sphincter muscle of the iris – contraction (myosis)
  - Ciliary muscle – contraction for near vision
  - Decreased intraocular tension
  - Increased lacrimation
- Skeletal muscle
  - Contraction due to stimulation of nicotinic receptors on the motor end plate

- Peripheral Nervous System
  - Activation of the nicotinic receptors at the autonomic ganglia and initiate action potential in post ganglionic neurons
  - Nicotine itself has greater affinity for neuronal than for skeletal muscle nicotinic receptors but the same action on both para- and sympathetic ganglia
  - Unlike the other drugs, in the CVS, effects of nicotine are chiefly sympathomimetic (hypertension, tachycardia may alternate with bradycardia mediated by vagal discharge)
  - In the GIT and UT, effects are largely parasympathomimetic

Toxicity of parasympathomimetics

- Varies depending on absorption, access to the CNS and metabolism
- Muscarinic toxicity
  - When drugs given in overdose
  - Myosis, spasm of accommodation
  - Increased GIT smooth muscle activity and GU and NVD increased secretion urinary urgency, salivation, sweating, cutaneous vasodilation, bronchoconstriction – can be blocked competitively with atropine and its congeners
  - Bradycardia if injected as IV bolus and CNS ++
- Nicotinic toxicity
  - CNS stimulation – convulsions may progress to coma and respiratory arrest – treatment by parenteral anticonvulsants e.g. diazepam
  - Muscarinic effects resulting from parasympathetic ganglion stimulation can be controlled using atropine
  - Skeletal muscle and end plate depolarisation which may lead to depolarisation blockade and respiratory effect (fasciculation and paralysis)
  - Hypertension and cardiac arrhythmias

Contraindication of parasympathomimetics

3. CVS
   a. Bradycardia, heart blocks
   b. Heart failure
   c. Hypotension
4. Respiratory
   a. Bronchial asthma
5. GIT
   a. Peptic ulcer
   b. Organic obstruction
6. Endocrinal
   a. Hyperthyroidism as it was increases the atrial conduction in already sensitised heart – atrial fibrillation

Comparison between various choline esters*

Pilocarpine

Kinetics

- Not hydrolysed by cholinesterase
- Has a longer duration than acetylcholine

Effects

- Acts at muscarinic receptors to produce muscarinic effects similar to that of

acetylcholine

Uses

- Applied locally in the eye
- Used in glaucoma to increase aqueous drainage (due to myosis and opening of the canal of Schlemm and spaces of Fontana)
- To counteract the action of mydriatics eg homatropine
- In alternation with a mydriatic to cut adhesion between the iris and lens in iridocyclitis (inflammation of the iris and ciliary body) or between iris and cornea

Adverse Effects

- Can enter the brain and cause CNS disturbances.
- Stimulate sweat secretion
- Cevilamine is a new drug in this category, is long action and is used for Sjogren's syndrome

Indirect Acting Cholinomimetics

Direct acting

- Alkaloids
- Choline esters

Indirect acting

- Reversible
- Irreversible

Mode of Action

- Direct acting – bind to activate muscarinic or nicotinic receptors
- Indirect acting
  - Inhibit acetylcholinesterase. They also inhibit the pseudocholinesterase
  - Increase endogenous Ach
  - Excess Ach stimulates cholinoreceptors to evoke increased responses
- Some inhibit pseudocholinesterase – clinically insignificant
- Some have direct action – neostigmine activate Nm receptors in addition to AchE inhibition

Structure

- 3 chemical groups
  - Simple alcohol bearing a quaternary ammonium group
    - Edrophonium – myasthenia gravis
  - Carbamic acid esters of alcohols having quaternary or tertiary ammonium groups (carbamates)
    - Neostigmine (quaternary) – MG, Ileus (intestine not contracting)
    - Pyridostigmine (quaternary) - MG
    - Physostigmine (tertiary) - Glaucoma
    - Carbaril (lipid soluble insecticide)
  - Organic derivatives of phosphates (organophosphates)
    - Echothiophate (water soluble, rest highly lipid soluble) - Glaucoma
    - Soman (nerve gas)
    - Parathion (prodrug)
    - Malathion (prodrug)

ADME

- Quaternary Carbamates
  - Poor absorption – lipid soluble, large oral doses
  - Negligible CNS distribution
  - Stable in aqueous solution
  - Metabolised by non-specific esterases and cholinesterases
- Physostigmine (tertiary)
  - Well-absorbed

    - Distributed in CNS
    - More toxic
- Organophosphates
    - Well-absorbed
    - Highly effective insecticides
    - Less stable in aqueous solution
    - Well distributed in CNS
- Thiophosphate insecticides (Parathion, malathion)
    - Lipid soluble
    - Rapidly absorbed by all routes
    - Activated in the body to oxygen analogs (paraoxon, malaoxon)
    - Malathion is detoxified in the body unlike parathion

Mechanism of Action

- AchE is the primary target (molecular details vary)
- Quaternary alcohols
    - Reversibly bind electrostatically and by hydrogen bonds (2-10 minutes)
- Carbamate esters
    - Covalent bond of the carbamoylated enzyme is resistant (1-6 hours)
- Organophosphates
    - Result in phosphorylated active site
    - Covalent phosphorus-enzyme bond is extremely stable (100 hours)
    - Undergo aging (strengthening the phosphorus-enzyme bond)
    - Cholinesterase regenerators
        - Break the phosphorus enzyme bond
        - Given prior to aging
        - Include strong nucleophiles – pralidoxime

CNS Effects

- Lipid soluble AchE inhibitors:
    - Low concentrations
        - Diffuse activation on the EEG
        - Subjective alertness
    - High concentrations
        - Generalised convulsions
        - Coma and respiratory arrest

CVS Effects

- Increase activity of SNS and PNS (predominant)
- Heart
    - PNS predominate (mimic vagal nerve activation)
    - Negative chronotropic, dromotropic, inotropic effects
    - Cardiac output falls
        - Bradycardia
        - Decreased atrial contractility
        - Decreased ventricular contractility
    - Net effect (moderate doses)
        - Modest bradycardia
        - Fall in CO
        - Increased TPR (BP)
    - Toxic doses : marked bradycardia, significant decrease in CO, hypotension.

    - Other side effects include
        - Contraction of visceral smooth muscle
        - Myosis
        - Hypotension
        - Increase glandular and respiratory secretion
        - Cause bronchospasms
        - Bradycardia

Neuromuscular Junction

- Low (therapeutic) concentrations
    - Prolong and intensify Ach actions
    - Increase strength of contraction
- High (toxic) concentrations
    - Muscle fasciculation and fibrillation
    - Depolarising NM blockade followed by non depolarising blockade

Clinical Uses

- Eye
    - Glaucoma - Physiostigmine
    - Accommodative esotropia (accomodation issues)
- GIT and GUT
    - Postoperative atony
    - Neurogenic bladder
- NMJ
    - Myasthenia gravis
    - Curare-induced NM paralysis
- Alzheimer's disease
- Occasionally:
    - Treatment of atropine overdose
    - Therapy of certain atrial arrhythmias

Acute Toxicity

- Extensions of pharmacological actions
- Sources
    - Pesticides (major)
    - Chemical warfare agents (soman, sarin, VX)
- Dominant initial signs are of muscarinic excess
    - Miosis
    - Sweating
    - Vomiting
    - Salivation
    - Bronchial constriction
    - Diarrhoea
- CNS involvement with peripheral nicotinic effects
    - Cognitive disturbances
    - Convulsions
    - Coma
    - Depolarising NM blockade
- Therapy

- Air patent, Breathing, Circulation
- Decontamination
- Large doses of atropine
- Pralidoxime (AchE regeneration)
- Benzodiazepines (anticonvulsants)
-
-
-

Chronic Toxicity

- Delayed neuropathy
  - Associated with demyelination
  - Caused by triorthocresyl phosphate
  - _
- Intermediate syndrome
  - 1-4 days after exposure
  - Characterised by muscle weakness
  - Related to AchE inhibition

Pregnancy and Breastfeeding

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- Physiological changes may influence p'kineics and p'dynamics
  - GIT transit time is prolonged
  - Albumin concentration decreased
  - Alpha-acid glycoprotein increase
  - Body water and fat increases
    - Plasma volume goes up by 30-50%
  - Renal blood flow doubles by third trimester
    - Increased GFR
  - Liver blood flow does not change
  - Increased CO

eg. anticonvulsants

- Increased metabolic clearance
- Serum concentration
  - Became lower as pregnancy progresses
  - And increases by 6 weeks postpartum
- Increased seizures in pregnancy
- Drug monitoring recommended
- Drugs cross the placenta through passive diffusion

Factor affecting placental drug transfer

1. Physicochemical properties of the drug
   - Lipid soluble and unionised drugs cross readily
     - Eg thiopental used un C-sections
       - Sedation or apnea of the foetus
   - impermeability to polar compounds is relative rather than absolute
   - Low molecular weight drugs easily cross the placenta (250-500)
     - Heparin is a hugh weight and polar drug that does not cross the placenta
2. The rate at which the drug crosses the placenta and the amount of drug reaching the foetus
   - Placental p-glycoprotein pumps drugs back into maternal circulation eg protease inhibitors
   - Different transporters efflux glyburide
   - Drugs with > binding to maternal proteins than foetal proteins
     - Eg sulphonamides, barbiturates, phenyton and local anaesthetics
   - The placenta protects the foetus
     - Semipermeable membrane
     - Metabolises sopme drugs (not clinically significant)
     - Drugs that cross the placenta enter the umbilical vein to the foetal liver where metabolism occurs
3. The duration of exposure to the drugs
4. Distribution of the drug in the foetal tissue
5. the stage of foetal and placental development at time of drug exposure
6. The effects of drugs used in combination

Foetal Therapeutics

- Drugs given to the mother for foetal benefits
- Corticosteroids used to speed up lung maturation when a preterm birth is expected

- Maternal use of ARVs reduces foetal HIV infection (PMTCT)

Drugs in the first trimester

- From day 18-55 the human foetus undergoes organogenesis
- Drugs that cause structural abnormalities during this period - teratogens
- Teratogen - a substance that leads to the birth of a malformed baby

Identifying drug teratogens

- Animal studies have dubious vallue (species variation)
- Thalidomide (causes phocommelia) is ateratogen only in primates
- Lithium
  - In rats 200mg/kg no foetal abnormalities
  - In rats >300mg/kg causes cleft palate
  - In man <200mg/kg causes cardiac abnormalities
- The absence of teratogenic affect in an animal provides no assurance that a substance is safe for humans
- hUman studies needed (? ethical)
- Report congenital abnormalities in newborns

Note: there is a 2% chance of foetal malformation whether or not drugs are used

Teratogenic drugs

- kNow which drugs are teratogeniceg folate
  1. Warfarin
     - § chrondrodysplasia punctata (bone and cartilage abnormality)
     - § Facial abn
     - § CNS abn - microcephaly
     - § Asplenia
     - § Diaphragmatic hernia
  2. Cytotoxic drugs
  3. Ethanol eg folate antagonists
  4. Retinoids
     - § Used for treatment of acne and other chronic dermatosis
     - § Maximum risk of abn iis approximately 3 weeks after conception where the women might not realise they are pregnant
     - § THong half licontraception must be used long after the corse of Rx. in the case of isotretinoin, it is 2 years
  5. Angiotensin converting enzyme inhibitors
  6. Thalidomides
  7. Penicillamide
  8. Phenytoin
  9. Valproate
- congenital malformations > in epileptic mothers
  - Regardless of which antiepileptic drug
- Foetal hydantoin syndrome has been reported in one of dizygotic twins
- Cleft lip was found in the children of either an epileptic father or mother
- Anticonvulsants lower serum folate concentration
- Folate deficiency is associated with neural tube defects
- take folate before conception
- no epileptic drug is considered less teratogenic than the other
- Use the most effective drug
- Advise on possiblr teratogenicity

Drugs after the first trimester

- Warfarin
  - 2.6% - bleeding into the fortal brain even when the mother's anticoagulation profile is optimal
  - Due to difference in foetal p'kinetics

Antibiotics contraindicated in pregnancy

- M - metronidazole (hepatic failure)
- C - Chloramphenicol
- A - Aminoglycosides
- T - Tetracyclins
- Chloramphenicol
  - Not teratogenic
  - Associated with grey baby syndrome
- Aminoglycosides
  - Foetal ototoxicity
- tetracyclines
  - Tooth discolouration
  - Bone dysplasia

ACE-1

1. Oligohydramnios
2. Foetal renal failure
3. Neonatal hypotension
4. Patent ductus arteriosus
5. Respirartory distress syndrome
6. lung hypoplasia
7. Intruterine foetal death
8. Defects in skull ossification

Barbiturates or Phenytoin

- coagulation defects
- Bleeding in the first 24 hours of life
- Prevent with Vitamin K at birth
- The mother's coagulation profile amy be normal

Late morphhological effects

- Diethylstibestriol takken in early pregnancy
- Effects seen in late tteenage years
  - Vaginal carcinoma
  - Male infertility
- Ideally, rwsearch of drugs in pregnancy should follow offspring into later life
- Safety of drugs during pregnancy is usually unknown
- dEcide whether the pregnant patient needs the drugs
- Use the minimum effective dose
- UIse the minimum duration of Rx
- Avoid in early pregnancy as compared to later pregnancy

Use of new drugs

- Research of drugs on pregnancy is rare
- avoid use of new drugs
- When given, report their effects (both good and bad) so that data on their safety is collected

FDA categorisation of drugs in pregnancy (category A, B, C, D, X, N)

1. **Category A**
   - § Adequate and well-controlled studies have failed to demonstrate a risk to the foetus in the first trimester and there is no evidence of risk in later trimesters.
2. **Category B**
   - § Animal reproduction studies have afiled to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant wommen
3. **Category C**
   - § Animal reproduction studies have shown adverse effect on the foetus and there are no adequate or well-controlled studies in human but potential benefits may warrant its use on pregnant women despite the adverse effects
4. **Category D**
   - § There is positive evidence of human foetal risk based on adverse reaction data from investigational and marketinng experience or studies in humans, but potential benefits , may warrant use in pregnant women despite adverse effects
5. **Category X**
   - § Studies done in animals or humans have demonstrated foetal abnormalities and/or there is positive evidence of foetal risk based on the investigational and marketing experience. Risks involved outweigh the potential benefits to the pregnant mother.
6. **Category N**
   - § FDA has not classified the drug

Drugs and breastfeeding

- Most drugs may pass into breastmilk
- Quantity is small
  - < than the therapeutic dose
- Many women stop breastfeeding
- Formula feeding associated with morbidity and mortality
- Formula feeding
  - Inadequate feeds - malnutrition
  - Contaminated feeds - diarrhoea
    - § Water
    - § Bottle feeding'
    - § Storage
  - Lack protective factors found in breastmilk

General considerations

- Avoid drug therapy when possible
- Use topical therapy when possible
- Choose drugs that can be used in infants to treat the breast-feeding mother

Factors that affect the concentration of drug in the mother's blood

1. Drug dose, frequency, route and patient compliancce
2. Clearance rate
3. Plasma protein binding

Factor that affect drug transfer into the breast

1. Breast blood flow
2. Metabolism of the drug within the breast
3. Molecular weight of the drug (small > large
    a. Heparin does not enter breast milk
4. Solublity of the drugs in water and lipids (> for fat soluble and unionised)
5. Relative binding affinity to plasma andd milk protein
6. Difference between the pH of maternal plasma and milk
    a. Weak alkaline drugs accumulate in breastmilk more than acidic
    b. Breastmilk has a lower pH than serum

Factors that affect the drug concentration in the infant

1. Timing of feeds
    a. Avoid feeds during peak drug concentration
    b. 30-60 minutes before or 3-4 hours before breastfeeding
    c. Once daily medications are administered before the longest sleep interval for the baby
        i. Usually after bedtime feeding
    d. Most drugs should have been cleared from maternal drugs
2. Frequency and duration of feeds
3. Volume of milk consumed
4. Ability of the infant to metabolise the drug (immature half life in infants
5. few drugs are actively transported into breastmilk eg cimetidine

DRugs that reduce milk production

1. Bromocriptine
2. Cabergoline
3. Thiazide diuretics
4. The combined oral contraceptive pils (use progestin onoly pills)
5. Ergotamine
6. Levodopa
7. Trazodone

Drugs contraindicted during breastfeeding due to effects on the infant

1. Ergotamine
    a. Vomiting, diarrhoea,, convulsions
2. Laxatives
    a. Diarrhoea
3. chloramphenicol
    a. Bone marrow suppression
4. Ciproflaxacin
    a. Arthropathy
5. Diazepam, chloral hydrate
    a. Sedation
6. Androgens
    a. Androgenisation of infant
7. Radioactive drugs
    a. Destruction of thyroid
8. Cytotoxic drugs
    a. Cytotoxicity
9. Iodine containing compounds
    a. Effect on thyroid
10. Nicotine

    a. Vomiting, diarhhoea, restlessness
11. Drugs of abuse
    a. Addiction
12. Danazol
    a. Antiandrogenic effects

Sympathomimetics

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- The ANS originates from the CNS
- It as 3 divisions
  - Sympathetic
  - Parasympathetic
  - Enteric Nervous System
- The 'sympathetic' and parasympathetic' are anatomic designations
  - These terms do not automatically determine the type of neurotransmitter involved
- The autonomic efferent pathway consists of two neurons arranged in series
  - The pre and post ganglionic fibres
  - Except to the adrenal medulla (only preganglionic fibres)
- The sympathetic nerve fibres leave the spinal nerves as the thoracolumbar sympathetic outflow
- The sympathetic ganglia are found in:
  - Paravertebral chains that lie on either side of the spinal column
  - Prevertebral ganglia

Neurotransmitter

- All preganglionic nerves leaving the CNS release Ach
- All postganglionic SNS fibres release Norepinephrine, with may act on either & or ß – adrenoceptors
  - Except the sympathetic innervation of sweat glands where transmission is due to Ach acting on muscarinic receptors
- Sympathetic stimulation is mediated by:
  - NE from nerve terminals
  - NE and epinephrine from the adrenal medulla
  - Dopamine in the CNS mainly
- Sympathomimetics – Drugs that mimic NE, E and dopamine actions

Synthesis of NE and E

Tyrosine – L-DOPA – dopamine – NE - E

Mode of action

- Direct acting sympathomimetics
  - Interact directly and activate receptors
- Indirect acting
  - Dependent on endogenous catecholamines
- Mixed acting
  - Activate receptor and release NE

Indirect Acting Sympathomimetics

Mechanisms

- Displacement of stored catecholamines (e.g amphetamine, tyramine)
- Inhibition of catecholamine uptake (cocaine, tricyclic antidepressants)
- Block NE metabolising enzymes (MAO and COMT [catechol–O–methyl transferase])
- Tyramine, amphetamine and ephedrine and pseudoephedrine
  - Release stored transmitter by a calcium-independent process
  - These drugs bind to monoamine transporters
    - NET and VMAT
  - VMAT transports them to the vesicles, displacing NE which is subsequently expelled into the synaptic space by reverse transport via NET
- Amphetamines also inhibit MAO
- Their action does not require vesicle exocytosis

Adrenoceptors

- &-adrenceptors
  - &1
    - a,b,d
  - &2
    - a,b,c
- ß – adrenoceptors
  - ß1, ß2, ß3
- Dopamine receptors (precursor of NE and neurotransmitters in the brain)
  - D1-5
- Drugs can display selectivity for adrenoreceptors
- Selectivity is relative
  - Clonidine - &2>&1, .>>ß
    - &2-agonist
  - Albuterol – ß2>>ß1>>>>&
    - ß2 – agonist
- Adrenoceptors are G-protein coupled receptors
- G- proteins are classified according to the & subunit
  - G_s, G_i, G_o, G_q, G_{11}
- Gs
  - The stimulatory G protein of adenylyl cyclase
- Gi and o
  - The inhibitory G protein of adenylyl cyclase
- Gq and 11
  - The protein coupling & receptors to phospholipase C

&1 – adrenoceptors

- DAG activates protein kinase C
- Activate
  - Mitogen-activated protein kinase
  - Polyphosphoinositol 3 – kinase
- These modulate various signaling pathways

&2 – adrenoceptors

- Inhibit adenylyl cyclase – reduced cAMP
- Regulate ion channel activity
- Cause platelet aggregation

ß – adrenoceptors

- All activate adenylyl cyclase
- ATP leads to increased cAMP
- May activate voltage sensitive Ca2+ channels

Dopamine – adrenoceptors

- D1, D5
  - Stimulates adenylyl cyclase
- D2-4
  - Inhibit adenylyl cyclase
- D2
  - Open K+ channels
  - Decreased Ca2+ influx

Sympathomimetics

1. Catecholmines
   a. E
   b. NE
   c. Dopamine
   d. Isoprenaline, Dobutamine, Dopexamine
2. Non-selective ß – adrenergic agonists
   a. Isoproterenol
3. Selective ß1 adrenergic agonists
   a. Dobutamine
   b. Prenaterol
4. Selective ß2 – adrenergic agonists
   a. Terbutaline
   b. Albuterol (Salbutamol)
   c. Pirbuterol
   d. Biltoterol
   e. Fenoterol
   f. Formoterol
   g. Procaterol
   h. Salmeterol
   i. Metaproterenol
   j. Isoetherine
   k. Ritodrine
5. Non selective &-adrenergic agonists
   a. Phenylephrine
6. Selective &1 adrenergic agonists
   a. Methoxamine
   b. Midodrine
7. Selective &2 adrenergic agonists
   a. Clonidine
   b. Guanfacine
   c. Methyldopa
   d. Brimonidine
   e. Oxymetazoline
   f. Apraclonidine

g. Guanabenz
h. Tizanidine
i. Zylometazoline
j. Modafonil

8. Dopamine agonists
    a. Levadopa
    b. Fenoldopam (D1)
    c. Bromocriptine (D2)
    d. Quinagolidine (D2)
    e. Cabergolide (D2)
    f. Pergolide (D1,2)
    g. Pramipexole (D3)
    h. Ropinirole (D2)
    i. Rotigotine
9. Mixed acting adrenergic agonists
    a. Ephedrine
    b. Pseudoephedrine
    c. Phenylpropranolamine
10. Indirect acting adrenergic agonists
    a. Releasing agents
        i. Amphetamine
        ii. Methamphetamine
        iii. Phenmetrazine
        iv. Methylphenidate
        v. Modafinil
        vi. Tyramine
    b. Uptake inhibitors
        i. Cocaine
        ii. Atomoxetine
        iii. Reboxetine
        iv. Sibutramine
        v. Duloxetine
    c. MAO inhibitors
        i. Selegiline
    d. COMT inhibitors
        i. Entacapone

Organ system effects

- CVS
    - Blood vessels
        - &1, 2 – contraction (skin, skeletal muscle)
        - ß2 – relaxation (skeletal muscle)
        - D1 – relaxation of renal blood vessels
    - Heart
        - &1, ß1 – increased force of contraction
        - ß1 – increased rate of contraction
    - Increased BP by & agonists
- Eye
    - &- agonists
        - Contracts radial pupillary dilator muscle – mydriasis

        - Increased outflow of aqueous humor
    - ß – agonists
        - Relax ciliary muscles
- Respiratory system
    - ß2 – agonists –bronchial smooth muscle relaxation
- GIT
    - & and ß agonists – smooth muscle relaxation
    - &2 agonists – decreased salt and water flux into the lumen of the intestines
- GUT
    - &- agonists – promote urinary incontinence
    - & agonists – promote ejaculation
    - ß2 agonists – relax the bladder walls
    - ß – agonists – relax uterine smooth muscles
- Sweat glands – increased sweating
- Metabolic
    - ß3 agonists – increased lipolysis
    - & agonists – inhibit lipolysis
    - ß agonists – increased glycogenolysis
    - high doses of catecholamines cause metabolic acidosis
    - ß2 agonists – decreased K+ extracellularly
- Endocrine
    - ß agonists – increase insulin release
    - ß1 agonists – increased renin release
    - & agonists – decreased insulin release
    - &2 agonists – decreased renin release
- Blood
    - Leukocytosis
- CNS
    - D2 – modulate neurotransmitter release

P'kinetics of catecholamines

- Epinephrine
    - It is unstable in alkaline solutions
    - When exposed to light or air, it changes colour to pink and later brown
- SC, IM, IV, inhalation, topical
    - Absorption after SC admin is slow because of local vasoconstriction
    - IV used in emergencies

P'kinetics of Epinephrine

- Metabolised by the liver and kidney by MAO and COMT
    - MAO also found in the intestinal mucosa and nerve endings
- Catecholamines usually ineffective when given orally because of MAO (half life – 2 minutes)
- Excretion is through urine
- Note the concentrations
    - 1:100 is suitable for inhalation
    - 1:1000 is suitable for IV administration
    - If the 1:100 is used for IV administration, inadvertently, it can be fatal

Epinephrine – adverse effects

- Restlessness, throbbing headache, tremor and palpitations

- Cerebral haemorrhage
  - Large doses or rapid administration
- Arrhythmias
- May induce angina in patients with coronary artery disease

Epinephrine – contraindication

- Patients receiving nonselective betablockers
  - Unopposed &1-receptor stimulation may lead to severe hypertension and cerebral haemorrhage

Synthetic non-catecholamines

- Can be given orally
- More resistant to enzymatic degradation
- Longer half life
  - Salbutamol half life – 4 hours

Cocaine

- Local anaesthetic
- Inhibits reuptake of NE
- CNS – inhibits dopamine reuptake

Tyramine

- Found in cheese
- Metabolised by MAO
- Released stored NE
- Tyramine + MAO-A inhibitors leads to increased BP
- Avoid tyramine containing foods if on MAO inhibitors

Tyramine containing foods

- Chicken liver
- Fermented sausage (pepperoni, salami)
- Smoked or pickled fish
- Red wine
- Yeast

Therapeutic uses

- Hypotensive emergencies
  - NE
  - Phenylephrine
  - Methoxamine
- Chronic orthostatic (postural) hypotension
  - Ephedrine
  - Midodrine (prodrug)
- Cardiogenic shock
  - Dopamine
  - Dobutamine
- Reduction of blood flow
  - Epinephrine (nasal packs, gingival strings)
  - Cocaine
- Mucous membrane decongestion
  - Phenylepinephrine (topical, oral)
  - Ephedrine (oral)

- Local acting (topical)
  - _
  - _
- Cardiac arrest and complete heart block
  - Epinephrine
  - Isoproterenol
- Asthma
  - Salbutamol (albuterol)
  - Terbutaline
- Anaphylaxis
  - Epinephrine
- Ophthalmic uses
  - Mydriasis (phenylephrine)
  - Allergic hyperemia (phenylephrine)
  - Glaucoma
    - Apraclonidine
    - Brimonidine
- GUT
  - Suppress premature labour
    - Ritodrine
    - Terbutaline
  - Urinary incontinence
    - Ephedrine
    - Pseudoephedrine
- CNS
  - Narcolepsy
    - Modafinil
  - ADHD
    - Methylphenidate
    - Clonidine
      - Can also be used in Rx for
        - Hypertension
        - Diarrhoea in D. Mellitus
        - Reduced craving for abused substances
        - Postmenopausal hot flashes
  - Sedation in ICU - _

Adverse effects

- Can be deduced from physiologic effects
- Precipitate CCF and cardiac ischemia
- Tachycardia, arrhythmia
- Amphetamines – restlessness, paranoid state, etc
- Cocaine – convulsions, myocardial infarctions etc

Sympatholytic Agents

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Sympathetic NS stimulation

- Physical and metabolic responses mediated by catecholamines and cotransmitters
- Adrenal medulla produces epinephrine in response to stress and increase epinephrine into circulation
- Epinephrine dilates blood vessels in skeletal muscles and contract myocardium cf. constriction of blood vessels in skin, mucosa and kidneys by NE

Dopamine

- Basal ganglia of the CNS
- Dopaminergic nerve endings
- Specific ANS and periphery receptors

Terminology

Sympathomimetics – adrenergic receptor agonists
Sympatholytics – adrenergic receptor antagonists

Adrenergic Receptor agonists

- Useful in treatment of CVS diseases
- Reduce the amount of epinephrine released from SNS stimulation
- Suppress SNS outflow from the brain

Adrenergic Receptor antagonists

- Sympatholytic
- Inhibits interaction of NE, E and other sympathomimetics with adrenergic receptors
- Most are competitive antagonists by interacting with & and ß adrenergic receptors
- Except phenoxybenzamine that irreversibly interacts with &-adrenergic receptor by forming a covalent bond

Adrenergic receptors

- Structural receptors
- Variable affinities of drugs/endogenous amines for receptors
- Selective antagonism possible eg. Atenolol ß1 selective and no effect ß2 in the airway, &1 and 2

&-adrenergic receptor antagonists

- **Alkylating agents:** phenoxybenzamines, Tamsulosin
- **Imidazoles:** phentolamine, tolazoline
- **Piperazinyl quinazoline:** prazosin, terazosin, doxazosin
- **Indoles:** yohimbine, indoramine

ß-adrenergic receptor antagonists

- **Non-subtype selective:** propranolol, nadolol, timolol, pindolol, labetalol, carvedilol
- **Subtype ß1 selective:** metoprolol, atenolol, esmolol, acebutolol
- Pindolol and acebutolol have intrinsic sympathomimetic activity
- Carvedilol and labetalol: dual & and ß blockade

&-1 adrenergic receptors

- &-1 receptors mediates
  - Contraction of the arterial and venous smooth muscle

Receptor site and action

- &2 - vascular smooth muscle: agonists - constriction and increase in PVR - increased BP
  - Antagonists - vasodilation
  - Useful in treatment of hypertension
  - C.f with agonists used in treatment of shock (hypotension)
- &2 receptors are found post synaptic in many blood vessels (vasoconstrictor effect)
  - Adrenergic receptors in the BP control centres in the CNS (agonists suppress sympathetic outflow from the brain)
  - Agonists such as clonidine_

Other effects of &2 receptors activation

- Suppress sympathetic outflow
- Increase vagal tone - facilitate platelet aggregation

- Inhibit release of NE and ACh
- Regulate metabolic effects - decrease insulin decrease lipolysis
- Contraction of some arteries and veins

&-adrenergic receptor antagonists

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- **Indoles:** yohimbine, indoramine

ß1 receptors

- ß1 receptors - rate and force of the heart contraction (positive inotropic and chronotropic)
- Antagonist effect slow heart rate and contraction force

ß2 receptor site and action

- Airway agonist bronchial smooth muscle relaxation
- Antagonist bronchoconstriction

ß-adrenergic receptor antagonists

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- **Subtype ß1 selective:** metoprolol, atenolol, esmolol, acebutolol
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- Carvedilol and labetalol: dual & and ß blockade

Specificity of & adrenoceptor antagonists

- Heterogenous
- Different affinities of &1 and 2 eg prazosin &1 and Yohimbine &2
- Phentolamine 1=2
- Tamsulosin &1a > &1b

Pharmacological properties of & adrenergic antagonists

- &1 - inhibits vasoconstriction mediated by catecholamines; vasodilation in arteriole and venules, decreased PVR and BP
  - Greater BP drop in upright position (postural drop)
    - Postural hypotension/orthostatic hypertension
- Effect opposed by baroreceptor reflex that cause increased HR and CO and fluid retention
- Blockade of &1 also inhibit vasoconstriction and increased BP caused by catecholamine administration

ß adrenergic antagonists

- Slow the heart and decrease myocardial contractility
- Short term ß adrenergic antagonists
  - Decreased CO and increased PVR (unopposed & receptor) in proportion to maintain BP following blockade of vascular ß2 receptors and compensatory reflexes
- Long term PVR returns to normal or decrease on HT
- Dual blockade - labetalol and carvedilol; cardiac output maintained with a greater fall in PVR
  - Will reduce CO and PVR (more effective than using ß alone since PVR will rise to increase PVR)
- Reduction of sinus rate by ß antagonists
- Decrease spontaneous rate of ectopic depolarisation
- Slow conduction in atria and AV node
- Increased functional refractory period in AV node

Phenoxybenzamine and related compounds

- Haloalkylamine
- Block &1 and 2 adrenergic receptors irreversibly
- Slight selectivity to &1

Chemistry

- Haloalkylamine
- Related to nitrogen mustards used in cancer therapy
- Chemical reaction of alkyl groups _

Pharmacological properties

- Reduced PVR and increased CO due to reflex sympathetic nerve stimulation

- Tachycardia due to enhanced release of catecholamines NE due to &2 blockade by phenoxybenzamine
- Decreased inactivation of amines because of inhibition of neuronal and extra neuronal uptake mechanisms
- Pressor response to exogenously administered compounds impaired
- Hypotensive responses to epinephrine because of unopposed ß adrenergic receptor mediated vasodilation
- Little effect on supine BP in normotensive subjects, there is marked fall in BP on standing because of antagonism of compensatory vasoconstriction
- Ability to respond to hypovolaemia and anaesthetic induced vasodilation is impaired
- Inhibits uptake of catecholamines in both adrenergic nerve terminals and extra neuronal tissue
- Inhibits responses to serotonin, histamines and ACh at higher doses
- Half-life less than 24 hours but
- Duration of effect depends on synthesis of a new & adrenergic receptors may take days

Therapeutic uses

- Treatment of phaechromocytoma and associated hypertension
    - Tumor of adrenal medulla
- Drug used prior to surgery
- Metyrosine, a competitive inhibitor of Tyrosine hydroxylase which is required in the synthesis of catecholamines, is useful as an adjuvant in patients with malignant disease
- ß adrenergic receptor antagonists also used but only after administration of & adrenergic receptor antagonists
- Benign Prostatic Hypertrophy (BPH) blockade of & receptors in smooth muscles of the prostate and bladder (terazosin and related drugs safer)
- Control of autonomic hypereflexia in spinal cord transection

Adverse Effects

- Postural hypotension
- Reflex tachycardia and arrhythmias
- Reversible inhibition of ejaculation and aspermia
- Mutagenic in animal studies
- Nasal stuffiness

Phentolamine and Tolazoline

- Phentolamine is an imidazole derivative
- &-adrenergic antagonist
- Affinity for & receptor; &1 = &2
- Effects on CVS similar to phenoxybenzamine
- Can also block serotonin receptors
- Causes the release of histamine from mast cells
- Block K^+ channels

Tolazoline

- Less potent than phentolamine
- Like phentolamine, stimulate GIT smooth muscle. Atropine antagonises this effect
- Both Tolazoline and phentolamine enhance gastric and secretion
- Tolazoline stimulates salivary, lacrimal and sweat glands as well

Pharmacokinetics

- PK of phentolamine not well elucidated but drug extensively metabolised
- Tolazoline - well absorbed PO, excreted in urine

Therapeutic uses of Phentolamine

- Short term control of hypertension due to phaechromocytoma
- Administered as a slow infusion to avoid hypotension
- Relieves pseudo obstruction of the bowel in patients with phaechromocytoma (secondary to inhibitory effect of catecholamines on GIT smooth muscle)
- Locally used to prevent necrosis after extravasation of &2 agonists
- Hypertensive crises following withdrawal of clonidine, ingestion of tyramine-containing food, or non-selective MAOI
- Direct intracavernous injection into the male genitalia with papeverine in ED
- Risk of orthostatic hypotension and priapism reversible by phenylephrine, an & adrenergic agonist
- Also risks fibrotic reaction from repeated penile injection
- Tolazoline use in persistent pulmonary hypertension in newborns (replaced by PGs and NO)

- Diagnostic aid in visualising distal peripheral vessels in arteriography

Toxicity and adverse effects

- Hypotension
- Reflex tachycardia and cardiac arrhythmias, ischaemic events and MI
- GIT stimulation may cause abdominal pains, nausea and exacerbation of peptic ulcer disease (PUD)

Prazosin and related drugs

- Piperazinyl quinazoline nucleus
- Potent selective &1-adrenergic antagonist
- &1 > &2 x1000 fold
- Similar potency across 1A, 1B and 1D &1 receptor subtypes
- Potent inhibitor cyclic nucleotide phosphodiesterases

Pharmacological properties

- Blockade of &1 adrenergic receptors in arterioles and venules
- Decreased PVR and venous return
- No increase in HR unlike with other vasodilators
- Since little or no &2 - antagonistic effect which would cause NE release
- Decrease cardiac preload; little effect on CO
- Minimal effects on veins unlike hydralazine
- May suppress sympathetic outflow from the CNS
- Depress baroreceptor function in hypertensive patients
- Small favourable effects on serum lipids, decreased LDL and TGs and increased HDL
- May have effects on cell growth

Pharmacokinetics

- Well absorbed orally
- Bioavailability: 50-70%
- Peak concentration: 1-3 hours
- PPB: &1-acid glycoprotein
- 5% free drug in circulation
- Free fraction may change in diseases that modify the concentration of inflammatory proteins
- Extensively metabolised in the liver
- Little unchanged drug passes in urine
- Half life: 2-3 hours, increased to 6-8 hours in CCF
- Duration: 7-10 hours in the treatment of HT
- May be used TID. First dose at night

Terazosin

- Analogue of prazosin but less potent
- High specificity for &1 receptors
- No discrimination across 1A, 1B ad 1D, & receptor subtypes
- More soluble in water and more bioavailable cf. prazosin
- Half life: 12 hours
- Duration of action > 18 hours ----> use OD
- Used in BPH and more effective than Finasteride
- 10% excreted unchanged in urine

Doxazosin

- Analogue of prazosin also selective to &1
- Non selective among &1 receptor subtypes
- Half life: 20 hours
- Duration of action: 36 hours
- Metabolism cf, to prazosin with most metabolites lost in faeces
- Used in HT and BPH

Other &1-receptor antagonists

- Alfuzolin - used in BPH
- Tamsulosin - selectivity to 1A and 1D receptor subtypes thus effective for 1A prostatic receptor subtype in BPH
    - Little effect on 1B thus no hypotension

Adverse effects of &-adrenergic receptor antagonists

- First dose postural hypotension and syncope
- Start with small night time dose, increase dose slowly and carefully when introducing added agents
- Headache, dizziness and asthenia

Therapeutic indications

- Primary systemic hypertension
- Can be useful in hypertensive patients with potential dyslipidemias and glucose intolerance
- CCF vasodilators, however no survival benefits cf hydralazine and ACEI
- BPH - relaxation of smooth trigone muscle of the bladder and urethra
- Used for angina

Ergot Alkaloids - Vasoconstrictor and alleviates migraines

Other &-adrenergic antagonists

- Indoramin - &1 selective and H1 and SHT antagonists
- Labetalol blocks &1 and potent ß antagonists
- Kentasrin - SHT and &1 selective
- Urapididl - &1 selective
- Banazosin - &1 selective
- _

ß-adrenergic receptor antagonists

- Indicated in the treatment of
  - Congestive heart failure
  - _

ß-adrenoceptor antagonist prototype

- Propanolol competitive receptor antagonists is the prototype drug
- Non selective affinity for ß1=ß2
- _

Other ß- receptor drugs

- Metoprolol and atenolol ß1>ß2 selective
- Pindolol and acebutolol ISA that is, activate ß-receptor partially in the absence of catecholamines. Partial agonists
- Inverse agonists, decreased ß-receptor signaling by shifting to inactive state
- Carvedilol and labetalol dual & and ß blockade
- Celiprolol - ß1 antagonist and ß2 agonist

Pharmacologiccal properties

- _

Sending notes…do not get lazy :)

Cf. Propranolol

- How would an OD of ß adrenoceptor antagonist present?
- What are some of the drug interactions seen with ß adrenoceptor antagonists?
- Review the therapeutic uses of these drugs?

Drug Absorption

Monday, 4 January 2016 12:05 PM

- The ADME of drugs are the processes of pharmacokinerics

Absorption is the movement of a drug from its site of administration into the central compartment

Transfer of drugs across membranes

- In most cases, a drug must traverse plasma membranes of many cells to reach the site of action
- Characteristics of a drug that predicts its movement and availability at sites of action are:
  - Its molecular size and structural features
  - Degree of ionisation
  - Relative lipid solubility
  - Its binding to serum
- Drugs cross membranes by either passive or active processes
- In passive transfer, the drug molecule penetrates by diffusion along a concentration gradient by virtue of its solubility in the lipid bilayer
- Such transfer is directly proportional to:
  - Concentration gradient across the membrane
  - Lipid-water partition coefficient of the drug
  - The membrane surface area exposed to the drug

★ Because the cell membrane is lipoid, lipid-soluble drugs diffuse most rapidly. Small molecules tend to penetrate membranes more rapidly than larger ones.

Carrier-mediated membrane transport

- Active transport is mediated by:
  - Direct requirements for energy
  - Movement against an electrochemical gradient
  - Saturability
  - Selectability
  - Competitive inhibition by co-transported compounds

★ Na+, K+, ATPase are important examples of an active transport mechanism that is a therapeutic target of digoxin in the treatment of heart failure

Active transport is selective, requires energy expenditure, and may involve transport against a concentration gradient. Active transport seems to be limited to drugs structurally similar to endogenous substances (eg, ions, vitamins, sugars, amino acids). These drugs are usually absorbed from specific sites in the small intestine.

Facilitated Diffusion

- Facilitated diffusion is a carrier mediated transport process in which there is no input of energy
- Movement of the involved substance is down a chemical gradient
- May also be an efflux pump
- Limits oral absorption of transported drugs because it transports compounds back into the GI lumen after their absorption

Certain molecules with low lipid solubility (eg, glucose) penetrate membranes more rapidly than expected. One theory is facilitated passive diffusion: A carrier molecule in the membrane combines reversibly with the substrate molecule outside the cell membrane, and the carrier -substrate complex diffuses rapidly across the membrane, releasing the substrate at the interior surface. In such cases, the membrane transports only substrates with a relatively specific molecular configuration, and the availability of carriers limits the process. The process does not require energy expenditure, and transport against a concentration gradient cannot occur.

Absorption after oral drug administration

- Absorption from the GI tract is determined by:
  - Surface area for absorption
  - Blood flow to the site of action
  - Physical state of the drug
  - Water solubility
  - Drug concentration at site of absorption
- For drugs given in solid form, rate of dissolution may limit their absorption especially drugs of low aqueous solubility
- Since most drug absorption from the GIT occurs by passive diffusion, absorption is favoured when the drug is non-ionised and more lipophilic
- The stomach is lined with thick mucous and its surface area is small; by contrast, the villi of upper intestines provide a larger surface area
- Therefore, the rate of absorption of a drug from the intestine will be > than the stomach
- Any factor that accelerates gastric emptying, increases rate of absorption

Controlled Release Preparations

- Rate of absorption of a solid oral drug is partially dependent on its rate of dissolution in GI fluids
- This is the basis for contro lled release or sustained release preparations
- Produces slow, uniform absorption of the drug; ≥ 8hours

- Controlled-release forms are designed to reduce dosing frequency for drugs with a short elimination half-life and duration of effect.
- These forms also limit fluctuation in plasma drug concentration, providing a more uniform therapeutic effect while minimizing adverse effects.
- Absorption rate is slowed by coating drug particles with wax or other water-insoluble material, by embedding the drug in a matrix that releases it slowly during transit through the GI tract, or by complexing the drug with ion-exchange resins.
- Most absorption of these forms occurs in the large intestine.
- Crushing or otherwise disturbing a controlled-release tablet or capsule can often be dangerous.
- Transdermal controlled-release forms are designed to release the drug for extended periods, sometimes for several days.
- Drugs for transdermal delivery must have suitable skin penetration characteristics and high potency because the penetration rate and area of application are limited.
- Many non-IV parenteral forms are designed to sustain plasma drug concentrations.
- Absorption of antimicrobials can be extended by using their relatively insoluble salt form (eg, penicillin G benzathine) injected IM.
- For other drugs, suspensions or solutions in non-aqueous vehicles (eg, crystalline suspensions for insulin) are designed to delay absorption.

Sublingual Absorption

- Small surface area available for absorption
- Venous drainage from the mouth is to the superior vena cava, therefore bypassing portal circulation
  - Therefore protects the drug from first pass effect

- The un-ionized form is usually lipid soluble (lipophilic) and diffuses readily across cell membranes.
- The ionized form has low lipid solubility (but high water solubility—ie, hydrophilic) and high electrical resistance and thus cannot penetrate cell membranes easily.
- The proportion of the un-ionized form present (and thus the drug's ability to cross a membrane) is determined by the environmental pH and the drug's p K_a (acid dissociation constant).
- The p K_a is the pH at which concentrations of ionized and un-ionized forms are equal. When the pH is lower than the p K_a, the un-ionized form of a weak acid predominates, but the ionized form of a weak base predominates. Thus, in plasma (pH 7.4), the ratio of un-ionized to ionized forms for a weak acid (eg, with a p K_a of 4.4) is 1:1000; in gastric fluid (pH 1.4), the ratio is reversed (1000:1).
- Therefore, when a weak acid is given orally, most of the drug in the stomach is un-ionized, favouring diffusion through the gastric mucosa.
- For a weak base with a p K_a of 4.4, the outcome is reversed; most of the drug in the stomach is ionized.
- Theoretically, weakly acidic drugs (eg, aspirin) are more readily absorbed from an acid medium (stomach) than are weakly basic drugs (eg, quinidine).
- However, whether a drug is acidic or basic, most absorption occurs in the small intestine because the surface area is larger and membranes are more permeable

The oral mucosa has a thin epithelium and rich vascularity, which favor absorption; however, contact is usually too brief for substantial absorption. A drug placed between the gums and cheek (buccal administration) or under the tongue (sublingual administration) is retained longer, enhancing absorption.

The stomach has a relatively large epithelial surface, but its thick mucous layer and short transit time limit absorption. Because most absorption occurs in the small intestine, gastric emptying is often the rate-limiting step. Food, especially fatty food, slows gastric emptying (and rate of drug absorption), explaining why taking some drugs on an empty stomach speeds absorption. Drugs that affect gastric emptying (eg, parasympatholytic drugs) affect the absorption rate of other drugs. Food may enhance the extent of absorption for poorly soluble drugs (eg, griseofulvin), reduce it for drugs degraded in the stomach (eg, penicillin G), or have little or no effect.

The small intestine has the largest surface area for drug absorption in the GI tract, and its membranes are more permeable than those in the stomach. For these reasons, most drugs are absorbed primarily in the small intestine, and acids, despite their ability as un-ionized drugs to readily cross membranes, are absorbed faster in the intestine than in the stomach. The intraluminal pH is 4 to 5 in the duodenum but becomes progressively more alkaline, approaching 8 in the lower ileum. GI microflora may reduce absorption. Decreased blood flow (eg, in shock) may lower the concentration gradient across the intestinal mucosa and reduce absorption by passive diffusion.

Intestinal transit time can influence drug absorption, particularly for drugs that are absorbed by active transport (eg, B vitamins), that dissolve slowly (eg, griseofulvin), or that are polar (ie, with low lipid solubility; eg, many antibiotics).
To maximize adherence, clinicians should prescribe oral suspensions and chewable tablets for children < 8 yr. In adolescents and adults, most drugs are given orally as tablets or capsules primarily for convenience, economy, stability, and patient acceptance. Because solid drug forms must dissolve before absorption can occur, dissolution rate determines availability of the drug for absorption. Dissolution, if slower than absorption, becomes the rate-limiting step. Manipulating the formulation (ie, the drug's form as salt, crystal, or hydrate) can change the dissolution rate and thus control overall absorption.

Transdermal absorption

- Not all drugs penetrate intact skin
- Absorption of those that do, is dependent on:
  - Surface area over which they are applied
  - Lipid-solubility
- The dermis is freely permeable to many solutes. Systemic absorption is increased in:
  - Abraded, burned or denuded skin
  - Inflammation or other blood-flow increasing conditions
- Toxic effects are sometimes produced by absorption through skin of highly lipid substances e.g. lipid-soluble insecticides
- Absorption through the skin can be enhanced by suspending the drug in oily vehicles and rubbing the preparation onto skin
- Because hydrated skin is more permeable than dry skin, an occlusive dressing may be used to facilitate absorption
- Controlled-release topical patches include:
  - Nicotine for tobacco smoking withdrawal
  - Scopolamine for motion sickness
  - Various oestrogens and progestins for birth control
  - Fentanyl for pain relief

Rectal Administration

- ~50% of the drug that is absorbed from the rectum will bypass the liver; hepatic first-pass effect is therefore less than that of oral administration
- A major drug metabolism enzyme CYP-3A4 is present in the upper intestine but not in the lower
- However, rectal absorption can be irregular an incomplete and some drugs can irritate

Parenteral Absorption

- Absorption from subcutaneous and intramuscular sites occur by simple diffusion along a concentration gradient from the drug depot to the plasma
- Rate of absorption is limited by:
  - Area of absorbance of the capillary membranes
  - Solubility in interstitial fluid
- Relatively large aqueous channels in the endothelial membrane facilitate diffusion of the molecules regardless of their lipid solubility
- Larger molecules such as proteins, slowly gain access to the circulation

Intravenous Routes

- No need for absorption - 100% bioavailability
- Potentially immediate effects
- Suitable for large volumes of irritating mixtures and complex substances

Subcutaneous Route

- Only for non irritating drugs
- Constant and slow rate of absorption for sustained effect
- Can vary period over which the drug is absorbed
- A vasoconstrictor agent can be incorporated to be infected to reduce absorption
- Absorption of drugs implanted under the skin in a solid pellet form occurs after a long time

Intramuscular Route

- Drugs in aqueous state are absorbed quickly after intramuscular injection
- Depends on the rate of blood flow to the injection site
- May be increased by:
  - Local heating/hot bath
  - Massage
  - Exercise
- Increased rate of absorption when injection is made into the deltoid or vastus lateralis compared to the gluteus maximus
- Absorption rate is even slower for females after injection into gluteus maximus (more subcutaneous fat which is relatively poorly perfused)
- Absorption is abnormal in obese/emantiated patients
- Slow, constant absorption on oil based drugs, oil vehicles or drugs suspended in other repository (depot) vehicles

Intra-thecal route

- Blood-brain barrier and blood-CSF barrier often slow entrance of blood into the CNS
- Direct injection into the spinal subarachnoid space is used when local and rapid effects of drugs is needed in the CNS e.g
  - Spinal anaesthesia
  - Treatment of acute CNS infection
- Brain tumours may also be treated by direct intraventricular drug administration

Pulmonary Absorption

- Gaseous/volatile drugs may be inhaled and absorbed through the pulmonary epithelium
- Access to the circulation is rapid because the lungs' surface area is large
- Absorption is almost instantaneous
- Important route of entry of certain drugs of abuse and toxic environmental substances

Topical Absorption

Mucous Membranes

- Drugs are applied to mucous membranes of the conjuctiva, nasopharynx, oropharynx, vagina, colon, urethra, urinary bladder for local effect
- Sometimes, systemic absorption is the goal
- Absorption happens readily
- Because of rapid absorption, it may cause toxicity e.g. in the case of local anaesthetic

Eye

- Topically applied ophthalmic drugs are used primarily for their local effects
- Systemic absorption may result from drainage through the nasolacrimal canal
- Absorbed drug is not subject to first order elimination in the intestinal and hepatic metabolism thus unwanted systemic pharmacological effects may occur
- Local effects usually require absorption of the drug through the cornea; corneal infection or trauma may occur thus may result in more rapid absorption
- Ophthalmic suspensions and ointment may provide prolonged duration of action
- Ocular inserts e.g. for the treatment of glaucoma, provide continuous delivery of small amounts of drugs with minimal side effects

- Drugs given IV enter the systemic circulation directly. However, drugs injected IM or sc must cross one or more biologic membranes to reach the systemic circulation.
- If protein drugs with a molecular mass > 20,000 g/mol are injected IM or sc, movement across capillary membranes is so slow that most absorption occurs via the lymphatic system.
- In such cases, drug delivery to systemic circulation is slow and often incomplete because of first-pass metabolism (metabolism of a drug before it reaches systemic circulation) by proteolytic enzymes in the lymphatics.
- Perfusion (blood flow/gram of tissue) greatly affects capillary absorption of small molecules injected IM or sc. Thus, injection site can affect absorption rate.
- Absorption after IM or sc injection may be delayed or erratic for salts of poorly soluble bases and acids (eg, parenteral form of phenytoin) and in patients with poor peripheral perfusion (eg, during hypotension or shock).

Distribution of Drugs

Monday, 4 January 2016 4:45 PM

Distribution involves the delivery of drugs from systemic circulation, into the tissues

- The rate at which a drug penetrates the tissues and other body fluids depends on the following factors:
  - Perfusion rate
  - Extent of specific organ binding
  - Regional differences in pH
  - Transport mechanisms available
  - The permeability characteristics of specific tissue membranes
- Drug distribution occurs in 2 phases
  a. First phase
     - Initial distribution of the drugs into well perfused organs such as the liver, heart, kidney and brain
  b. Second phase
     - Distribution into the muscle, most viscera, skin and fat
     - It is slower
       - Minutes to hours before the concentration of the drug is in equilibrium in the tissue and in blood
     - Involves a larger fraction of body mass
     - Redistribution
     - May terminate drug effect of a highly-lipid soluble drug that acts on the brain or CVS when administered rapidly by IV or inhalation routes e.g.
       - IV anaesthetic thiopental
       - Highly lipid soluble
       - Rapidly distributed in the brain
       - Little binding to brain by the drug
       - Rapidly distributed to other organs/tissues
       - Onset of anaesthesia is rapid
       - Termination is also rapid
- Drugs diffuse rapidly into the interstitial fluid when:
  - Capillary endothelial membranes are highly permeable
  - Transfer of drugs is faster than the diffusion of drugs in other tissues
  - Junctions between cells serve as pores
    - Except in the CNS (tight junctions)
- Water-soluble drugs are carried through these junctions through bulk flow
- Small drug molecules are transported through these junctions
- Larger molecules are transported across capillary membranes by pinocytosis
- Highly lipid soluble drugs generally only require a single passage of blood through an organ to establish a blood-tissue equilibrium
- The rate of passage of drugs across capillary walls may be affected by:
  - Histamine: increases capillary permeability
  - Epinephrine: reduces blood flow (vasoconstrictor)
- Tissue distribution is determined by the partitioning of drugs between blood and a particular drug
- Blood-tissue partitioning is determined by:
  - Binding of a drug to plasma protein
  - Binding of a drug to tissue
  - Lipid solubility
  - Transmembrane pH gradients

        - Can cause ion trapping
        - This is a minor factor because the pH difference between tissue and blood (7.0 versus 7.4) is small
- Drugs circulate in the blood stream bound to plasma proteins
- The extent of binding influences drug distribution and elimination
- Only unbound drugs can diffuse through the capillary wall
    - To produce a systemic effect
    - To be metabolised and excreted
- As free drug leaves the circulation, the protein-drug complex begins to dissociate
- Protein binding retards the rate at which a drug reaches its site of action
    - Suramin is strongly bound to plasma proteins
        - A single IV dose produces a clinically effective plasma level
- Albumin is a major carrier for acidic drugs
- Basic drugs are bound by:
    - Albumin
    - &1 - acid glycoprotein
    - Lipoproteins
    - Beta-globulin
- Specific hormone carrier proteins_

Nitric Oxide

Monday, 11 January 2016 10:42 AM

- Diatomic free radical consisting of one atom of nitrogen and one atom of oxygen
- Gaseous signalling molecule
- First gas to act as a biological messenger
- Lipid soluble and very small for easy passage (diffusion) between cell membranes
- Many physiological functions such e.g. vasodilator, platelet inhibitor, immune regulator, neurotransmitter

Synthesis of Nitric Oxide

- Synthesis - by 3 closely related NO synthase (NOS) isozymes
    a. Neuronal NO synthase ~ nNOS or NOS-1
    b. Macrophage or inducable NO synthase - iNOS or NOS-2
    c. Endothelial NO synthase ~eNOS or NOS-3

- NOS isozymes generate NO form L-arginine in an oxygen and NADPH-dependent reaction
- The reaction involves enzyme bound cofactors including heme, tetrahydrobiopterin and FAD
- In case NOS-1 and 3, NO synthesis evoked by agents or processes that increase cytosolic calcium concentration while NOS-2 is not regulated calcium but is inducable

Properties of the 3 isoforms of NO synthase (diagram from Katzung)

Property	**NOS-1**	**NOS-2**	**NOS-3**
Other names	nNOS (neuronal NOS)	iNOS (macrophage NOS)	eNOS (endothelial NOS)
Tissue	Neuronal, epithelial cells	Macrophages, smooth muscle	Endothelial cells
Expression	Constitutive	Transcriptional induction	Constitutive
Calcium regulation	Yes	No	Yes
Chromosome	12	17	7

Signalling mechanisms

- NO mediates its effects by covalent modification of proteins
- The 3 major effector targets are:
    - Metalloproteins
    - Thiols
    - Tyrosine nitration

Metalloproteins

- NO interacts with metals especially iron in heme
- Heme contained in soluble guanyl cyclase (sGC)
- Binding of NO to the iron of heme activates sGC and elevates the levels of cGMP
- cGMP activates protein kinase G (PKG) which phosphorylates certain proteins

- Vasodilation exerted by NO is largely mediated by NO-dependent elevation in cGMP and PKG
- Several other metalloproteins are targets of NO
- Affinity for iron also has inhibitory effects e.g. inhibition of enzymes that contain iron-sulphur clusters such as tricarboxylic acid cycle enzyme, aconitase; inhibition of mitochondrial respiration by inhibiting cytochrome oxidase

Note: inhibition of CYP450 enzyme is the major pathogenic mechanism in inflammatory liver disease

Thiols

- NO reacts with compounds containing SH^- groups to form nitrosothiols ~ process catalysed either by metals or O_2
- Exposure of certain proteins to NO can lead to an accumulation of nitrothiols which can activate or inhibit the proteins
- NO can undergo both oxidative and reductive reactions resulting in the formation of a variety of oxides that can nitrosylate thiols, nitrate tyrosines to form stable oxidative products
- Nitrosylation activates H-ras (gene marker ~ regulator of cell proliferation) while glyceraldehyde - 3 - phosphate (metabolic enzyme) is inhibited
- Glutathione (-SH containing) interacts with NO under physiological conditions to form S-nitroglutathione ~ may serve as a long lived barrier of NO
- Vascular glutathione is decreased in diabetes mellitus and atherosclerosis ~my account for increased incident of CV complications in these conditions

Tyrosine Nitration

- NO reacts with superoxide to form peroxynitrate (ONOO-) ~powerful oxidant leading to DNA damage, irreversible nitration of tyrosine, oxidation of cysteine to disulphides or to various oxides
- Used as a marker for the presence of oxidative and nitrosactive stress

Inactivation

- NO is labile and rapidly reactive with metals and reactive oxygen species
- NO reacts with heme and hemoproteins including oxyHb ~ oxyHb catalyses NO oxidation to nitrate
- Reaction with haemoglobin may lead to partial S-nitrosylation of haemoglobin resulting in NO transport throughout the vasculature
- Superoxide also inactivates NO. Scavengers of superoxide anion such as superoxide dismutase may protect NO and enhance its potency and also prolong its duration of action

Pharmacological manipulation of NO

Inhibitors of NO synthesis

- Inhibitors of NO synthase are arginine analogs that bind to the NOS-arginine binding site
- Most are non-selective for NOS isoforms ~may impair its haemostatic signalling and also result in vasoconstriction and potent ischaemic damage
- It would be desirable to have nNOS-specific inhibitor for neurodegenerative conditions and iNOS-specific inhibitors for inflammatory disorder and sepsis

Some inhibitors of NO
(katzung)

NO donors

- Used to elicit smooth muscle relaxation

Organic nitrates

- Nitroglycerine - used in the management of angina ~ dilates veins and coronary arteries; metabolised to NO by mitochondrial aldehyde reductase
- Isosobide dinitrate - metabolised to NO-releasing species
    - Continuous administration of organic nitrates leads to loss of therapeutic effect ~ due to NO-mediated inhibition of mitochondrial aldehyde dehydrogenase

Organic Nitrites

- Are arterial vasodilators e.g. antoanginal isoamylnitrate (requires metabolic activation to elicit vasorelaxation) Do not exhibit rapid tolerance seen with the nitrates

Sodium nitroprusside

- Generates NO in response to light as well as chemical or enzymatic mechanisms in cell membranes.
- Rapid pressure reduction in arterial hypertension

Hybrid NO donors

- Involves incorporation of NO-donating molecules onto currently available CV drugs

NO gas inhalation

- Results in reduced pulmonary pressure and improves perfusion of ventilated areas of the lung

Alternative strategies

- Enhancement of downstream NO signalling pathways e.g. sildenafil (inhibitor of type 5 phosphodiesterase) causes prolongation of the duration of NO-induced cGMP elevations in a variety of tissues

Nitric Oxide in disease

- Vascular effects: NO has significant effect on vascular smooth muscle tone and blood pressure
    - Endothelium dependent vasodilators e.g. Ach and bradykinin act by increasing intracellular calcium levels which induces NO synthesis
    - Effect of vasopressor drugs increased by inhibition of NO synthase
    - Antithrombotic effect is also mediated by NO-dependent inhibition of platelet aggregation
        - Endothelial cells and platelets contain eNOS which acts to regulate thrombus formation
    - cGMP mediates the effects of NO in platelets
    - NO protects against thrombosis and atherosclerosis by e.g.
        - Inhibition of proliferation and migration of vascular smooth muscles
        - Reducing endothelial adhesion of monocytes and leukocytes
        - Acting as antioxidant blocking the oxidation of LDLs thus preventing/reducing formation of foam cells in the vascular wall reducing endothelial permeability to lipoproteins
    - Inadequate production of NO - atherogenesis, thrombosis
    - Atherogenesis risk factors e.g. smoking, hyperlipidemia, diabetes and hypertension are associated with decreased endothelial NO production
    - If NO synthesis inhibited, the BP skyrockets
    - If NO synthesis is in excess, there is hypotension due to vasodilation

Septic shock

- Lipopolysaccharide components form the bacterial cell wall induce synthesis of iNOS - results in exaggerated hypotension, shock and death ~ reverse the hypotension by administering inhibitors of NOS, compounds that prevent the action of NO e.g. methylene blue or scavengers of NO e.g. haemoglobin (haemoglobin is a vasoconstrictor, Fe scavenges NO)

Inflammation

- NO is an inflammatory mediator
- Cytokines such as TNF and IL-1, as well as bacterial-derived mediators induce transcription of iNOS in leukocytes, fibrinoblasts and other cell types thus there are enhanced levels of NO
- NO is a microbicide and may have a role in tissue adaptation to inflammation but overproduction may exacerbate tissue injury, both acute and chronic conditions
- NO produced during inflammation is involved in vasodilation associated with acute inflammation
- Elevated levels of NO and iNOS in psoriasis lesions, airway epithelium in asthma and inflammatory bowel lesions in humans
- Synovial fluids from patients with arthritis contains increased oxidation products of NO
- Been shown that NO stimulates the synthesis of inflammatory prostaglandins by activation COX-2 (cyclo-oxygenase 2)
- NO, however, appears to play a protective role in the body via immune cell function

NO in host defence

- Macrophage, neutrophils, leukocytes
    - Defence against viruses, bacteria, fungi, protozoa, parasites
- iNOS catalyses the synthesis of NO used in host defence reactions
    - Synthesis happens in most nucleated cells, particularly macrophages
    - NO is a potent inhibitor of viral replication
- NO is a bactericidal agent
    - NO is created from the nitrates extracted from food near the gums
    - NO kills bacteria in the mouth that may be harmful to the body

NO versus other neurotransmitters

- NO serves in the body as a neurotransmitter, but there are definite differences between other neurotransmitter commonly used in the body
    - NO is synthesised on demand vs constant synthesis
    - NO diffuses out of the cells making it vs storage in vesicles and release by exocytosis
    - NO does not bind to surface receptors but instead exits cytoplasm, enters target cell and binds with intracellular guanylyl cyclase

Similarities of NO to normal neurotransmitters

- Present in presynaptic terminals
- Natural removal from synaptic junctions

NO in the CNS

- NO proposed to have a major role as a neurotransmitter, as a neuromodulator of ligand-gated receptors, or both
- Long-term potentiation
- Plasticity (memory, appetite and nociception)
- Excess production leads to excito-toxicity e.g .ischaemic stroke, Huntington's disease and

AIDS dementia

NO in PNS

- Evidence than NO is a mediator of certain non-adrenergic, non-cholinergic (NANC) actions and that some NANC neurons release NO
- Penile erection is thought to be caused by the release of NO from NANC
- NO promotes relaxation of the smooth muscle in corpora cavernosa resulting in penile erection
- Inadequate production leads to erectile dysfunction

NO in digestive system

- NO is used in adaptive relaxation:
    - Role in gastric emptying
        - Promotes the stretching of the stomach in response to filling
        - When the stomach gets full, stretch receptors trigger smooth muscle relaxation through NO releasing neurons
        - Inadequate production leads to hypertrophic pyloric stenosis

Respiratory Disorders

- NO inhalation decreases pulmonary arterial pressure and improves blood oxygenation
- NO may have an additional role in relaxing airway smooth muscle and thus acts as a bronchodilator
- NO improves cardiopulmonary function in adult patients with pulmonary artery hypertension
- NO may be of benefit to newborns with pulmonary hypertension and acute respiratory distress syndrome

Autacoids

Tuesday, 23 February 2016 10:22 AM

- Auto means self
- Akos means remedy
- Autacoids may be defined as chemical substances produced within the body and help in the remedy of local injuries
- May be released by various stimuli
- When released, may bring about many physiological changes such as pain, itching, bronchospasm, reddening of the skin etc.
- These effects may be undesirable and may cause death
- To prevent undesirable effects, autacoid antagonists are used
- Usually have a very brief life time and act near the site of synthesis ~ local hormones

Classification

- Decarboxylated amino acids
  - Histamine
  - Serotonin
- Polypeptides
  - Angiotensin
  - Plasmakinins
  - Vasopressin
  - Substance P
  - Vasoactive intestinal peptide
  - Slow reacting substance anaphylaxis
- Eicosanoids
  - Leukotrienes
  - Thromboxanes
  - Prostaglandins etc.

- Some autacoids are also found in nervous tissues e.g. histamine, serotonin and prostaglandins where they act as neurotransmitters

Functions of Autacoids

- They take place in:
  - Inflammation
  - Allergic reactions
  - Neurotransmissions
  - Gastric acid secretion
  - Neuroendocrine regulation
  - Anaphylactic reactions

Difference between autacoids and hormones

- Autacoids are produced by virtually all cells while hormones are produced by specific cells
- Autacoids act mainly i.e. act near the site of synthesis while hormones are transported through the blood stream and act at distant target tissues

Histamine

Tuesday, 23 February 2016 10:32 AM

- An autacoid
- Amine formed by decarboxylation of L-histidine by histidine decarboxylase
- Decarboxylation can also be accomplished by bacterial decomposition
- Widely distributed in tissues of plants and animals including man
- Chemical messenger - mediates a wide range of cellular responses such as allergic and inflammatory reactions and gastric acids secretion
- Functions as a neurotransmitter in parts of the brain and also a neuromodulator
- Plays a role in chemotaxis of white blood cells
- Methacoline - histamine agonist used for diagnosis of asthma
- No clinical application but agents that interfere with its action have important therapeutic applications

Location

- Occurs in practically all tissues
- Large amounts in the lung, skin ---> sites where the outside of the body meets the inside
- High concentration in mast cells and basophils
- Component of venoms and in secretions of insect stings

- Synthesised in the same tissues in which it is stored i.e. mast cells, basophils, lungs, skin and GIT mucosa
- In mast cells, histamine is stored in granules as an inactive complex (composed of histamine and polysulphated anion, heparin, along with anionic protein)
- If not stored, it is rapidly inactivated by MAO

Stimuli causing release

- Allergy and anaphylaxis
- Destruction of cells - trauma, cold, bacterial toxins, bee sting venoms etc.
- Dissolution of cytoplasmic granules as a result of the action of radiation or surfactants
- Action of histamine liberators i.e. foreign proteins, drugs (curare, morphine etc.), dextran, radiograph contrast media

Receptors

- 4 subtypes H_{1-4}
- Located on the surfaces of cells
- Exert pharmacological effects by different secondary messenger pathways
- Binding of antagonists to H_1 stimulates that intracellular activity of the polyphosphotidylinositol cycle
- Stimulation of H_2 enhances the production of cAMP by adenylate cyclase
- H_3 receptors are G-protein coupled; present in the CNS and also peripherally; have multiple functions including roles in cognition, sleep-wake status, inflammation etc.

H1 receptor mediated effects

- Intestinal smooth muscle - powerful constriction resulting in intestinal cramps ad diarrhoea
- Bronchial smooth muscle - powerful constriction of bronchioles resulting in symptoms of asthma, decreased lung capacity

- Exocrine secretion - increased production of nasal and bronchial mucus, resulting in respiratory symptoms
- Sensory nerve endings - acts as LA resulting in decreased pain and itch
- H_2 receptors in the stomach - powerful stimulant pf gastric juice, HCl secretion
- H_1 and $_2$ receptors
    - Skin
        - Dilatation and increased permeability of the capillaries resulting in leakage of proteins and fluid into tissues (classical triple response)
    - CVS
        - Lowers systemic BP by reducing PR
        - Causes positive chronotropic mediated by H_2 receptors
        - Positive inotropic by both H_1 and $_2$ receptors

H_1 Receptor Antagonists

Tuesday, 2 February 2016 8:15 AM

Histamine Antagonists

- 3 types
  a. Physiologic antagonists
     i. Actions opposite to those of histamine via different receptors
     ii. Epinephrine
  b. Release inhibitors
     i. Reduce mast cell degranulation eg cromolyn
  c. Histamine receptor antagonists

H_1 receptor antagonists

- Competitively block histamine at H1 receptors
- Divided into
  - First generation
    - Strong sedative effects
      - Highly lipid soluble thus easily crosses the BBB
    - More likely to block autonomic receptors
  - Second generation
    - Less sedating (lower CNS penetration)

First Generation Antihistamines

Antihistamine	Anticholinergic activity	Sedative effect
Ethanolamine • Carbinoxamine • Dimenhydrinate • Diphenhydramine	 +++ +++ +++	 Slight to moderate Marked Marked
Piperazine derivatives • Hydroxyzine • Cyclizine • Meclizine	 - - -	 Marked Slight Slight
Alkylamines • Bromphiramine • Chlorpherinamine	 + +	 Slight Slight
Phenothiazine derivatives • Promethazine	 +++	 Marked
Miscellaneous • Cyproheptadine	 +	 Moderate

Second generation

Antihistamine	Examples
Piperadine	Fexofenadine Ebastine
Piperazine	Cetirizine Levocetirizine

Tricyclic	Dibenzoxepines
Alkylamines	Acrivastine
Phthalazinones	Azelastine

Pharmacokinetics

- Rapidly absorbed after oral administration
- Wide distribution
- First generation penetrate CNS readily (lipid soluble)
- Several second generation agents metabolised by CYP3A4
- Duration of action = 4 - 6 hours
- Meclizine and second generation agents have a longer duration (12 - 24 hours)

Active Metabolites

Parent drug	Active Metabolites
Hydroxyzine	Cetirizine
Terfenadine	Fexofenadine
Loratadine	Desloratadine

Pharmacodynamics

- Antagonists at H_1 receptors
- Negligible effect on H_2 receptors (acid secretion) or H_3 receptors (CNS)
- First generation agents have additional effects on:
    - Muscarinic cholinoceptors
    - &-adrenoceptors
        - May cause orthostatic hypotension
    - Serotonin
    - Local anaesthetic receptors sites

Effects of H_1 antagonists

1. Sedation
    - Caused by first generation agents
    - Intensity depends on the drug and the patients
    - Children may have excitation instead
    - At very high doses, may cause stimulation, agitation, convulsions and coma
2. Antinausea and antiemetic effects
    - Doxylamine was used to treat emesis gravidarum
    - Promethazine also has antiemetic actions
    - First generation agents also useful in prevention of motion sickness (Dimenhydrinate, Diphenhydramine, Cyclizine, Meclizine)
3. Anti-Parkinsonism effect
    - Diphenhydramine can be used to suppress extrapyramidal symptoms associated with antipsychotic drugs
4. Anticholiniceptor actions
    - First generation agents have antimuscarinic effects
    - May cause urinary retention and blurred vision
    - Examples
        - Ethanolamine and Ethylenediamine subgroups
5. Alpha adrenoceptor blocking effect
    - Especially seen with Promethazine
    - May cause orthostatic hypotension

6. Serotonin blocking action
    - Most notable with Cyproheptadine
7. Local anaesthetic effect
    - Diphenhydramine and Promethazine have potent local anaesthetic action
    - Block Na+ channels in excitable membranes

Clinical Uses

1. Allergic reactions
    - Used in prevention and treatment of allergic rhinitis and urticaria
    - Sedative effect of diphenhydramine useful in atopic dermatitis to reduce awareness of itching
    - Ineffective in bronchial asthma and angiodema
2. Motion sickness and Vestibular disturbances
    - Diphenhydramine and promethazine are the most effective
    - Methclizine and cyclizine may also be used

Toxicity

- Includes:
    - Sedation
    - Antimuscarinic effects
    - Excitation and convulsions in children
    - Orthostatic hypotension
    - Drug allergy: allergy dermatitis, drug fever, photosensitization
    - Cardiac arrhythmias with high doses of astermizole or terfenadine
- Other adverse effects include:
    - Dizziness
    - Tinnitus
    - Fatigue
    - Blurred vision
    - Nervousness
    - Tremors

Use in pregnancy and lactation

- Use with caution as they cross the placenta
- Azelastine, fexofenadine and hydroxyzine have teratogenic effects
- Chlorpheniramine, diphenhydramine, cetirizine and loratadine - non-teratogenic
- Are excreted in small amounts in breast milk
- First generation agents may cause irritability, drowsiness or depression in the nursing infant

Drug Interactions

- CYP3A4 inhibitors (ketoconazole, itraconazole, macrrolides) cause significant increase in antihistamine levels especially astemizole and terfenedine
    - Can lead to lethal ventricular arrhythmias
- Additive sedative effects when combined with other CNS depressants
- Additive autonomic blocking effects when combined with muscarinic and alpha-blocking drugs

Ergot Alkaloids

Thursday, 15 June 2017 5:30 AM

Ergot Alkaloids

- Partial agonists of serotonin
- Affects also &-adrenoceptors and dopamine receptors
- From claviceps purpurea - fungus
  - Causes serotonin syndrome
  - May cause hepatotoxicity and possibly death
- Chemistry
  - 2 families known:
    - Amine alkaloids: 6-methyl ergoline, Lysergic acid, LSD, ergonovine (ergometrine), methylsergide, carbegoline, pergolide
    - Peptide alkaloids: ergotamide, a-ergocryptine, bromocryptine

Mechanism of Action

- Actions include:
  - Agonist
  - Partial agonist
  - Antagonist at &-adrenoceptors, serotonin receptors
  - Agonists at CNS dopaminergic receptors

+				
Ergotamine	--/PA	0	+/PA	+
Ergot alkaloid	AA	DR	SR	USMS
bromocryptine	Inhibitory No action on uterine smooth muscle	+++	-	0
Ergonovine	+	+	-/PA	++++
LSD	0	+++	---	++
Methysergide	+/0	+/0	---	0

Pharmacological Actions

1. CNS
   - LSD - is a powerful hallucinogen
     - Habituated but not addictive
   - Bromocryptine - suppresses prolactin secretion (By releasing dopamine)
     - Competitive antagonist of dopamine and other dopamine agonists e.g. apomorphine at receptors
2. Vascular smooth muscles
   - Ergotamine constricts most blood vessels. Has both & blockade and stimulation action
   - Ergotamine, ergonovine and methysergide all partial agonists at $5HT_2$ vascular receptors.
     - All used in migraine
     - OD causes severe and prolonged vasospasm
3. Uterine smooth muscles
   - Stimulates muscle contraction
   - Seems to combine & agonist, serotonin and other effects
   - Pregnant uterus is more sensitive and most at term
   - Ergonovine, the most selective

4. Other smooth muscle organs
    - GIT
        - Sensitivity varies
        - Nausea, vomiting, diarrhoea, induced by varying doses of each

Pharmacokinetics

- They are variably absorbed from the GIT
- Oral dose of ergotamine is x10 the IM dose
- Oral absorption is improved by caffeine
- The amine alkaloids are also absorbed by rectal, buccal cavity routes and as aerosol inhaler
- IM absorption is slow but reliable
- Bromocryptine and amine alkaloid carbegoline are well absorbed from the GIT
- Extensively metabolised in the body
- Metabolites
    - Hydroxylated at A-ring
    - Peptides also modified at peptide moiety
    - Methysergide excretory products de-methylated at N1 position
- Excretion in the urine

Clinical uses

- Migraine
    - Ergotamine tartrate for oral, sublingual, rectal suppository and inhaler use
        - Often combined with caffeine
        - 100mg caffeine/1mg ergotamine tartrate
        - Maximum 6mg oral dose per attack and 10mg/week
        - Severe attacks - 0.25-0.5mg IV or IM
    - Dihydroergotamine - 0.5-1mg IV or IM
    - Ergonovine - 0.2-0.4mg TDS for prophylaxis
    - Methysergide maleate - 4-8mg/d for prophylaxis.
        - Give drug holidays of 3-4 weeks to reduce incidences of retroperitoneal fibrosis and subendocardial fibrosis
- Hyperprolactinaemia
    - Bromocryptine mesylate - 2.5mg 2-3 times daily
        - Also used to suppress physiologic lactation
    - Carbegoline more potent
- Post partum haemorrhage
    - Ergonovine maleate - 0.2mg IM at placenta delivery
- Diagnosis of variant angina
    - Ergonovine
        - Cause spasticity of coronary vessels
- Parkinson's disease
    - Bromocryptine
    - Pergolide

Toxicity

- The most common are GIT effects
    - Nausea, vomiting, diarrhoea limits methysergide especially
- Prolonged vasospasm
    - Ergotamine. Ergonovine
        - May cause gangrene
- Fibroblastic changes with prolonged methysergide use
    - Pleural, retroperitoneal, endocardial

- Drowsiness
    - Methysergide
        - Occasionally central stimulation and hallucinations

Contraindications

- Obstructive vascular disorders
- Collagen diseases

Serotonin Agonists and Antagonists

Monday, 18 January 2016 10:11 AM

Serotonin (5-hydroxytriptamin [5-HT])

Introduction

- Is a biologically active amine
- Widely distributed in nature
- Found in
  - Plant and animal tissue
  - Venom
  - Stings
- It has complex physiological and pathological effects through multiple receptor subtypes
- It functions both as:
  - A neurotransmitter in the brain and periphery
  - A local hormone in the peripheral vascular system

Pharmacokinetics

Biosynthesis

- The mechanisms of synthesis, storage, release and reuptake of endogenous 5-HT are very similar to those which generate noradrenaline
- However, the precursor amino acid for 5-HT is dietary tryptophan instead of tyrosine
- Tryptophan is converted into 5-hydroxytryptophan (in chromaffin cells and neurons, not in platelets) by the action of tryptophan hydroxylase
  - Confined to 5-HT producing cells
- It is then decarboxylated to 5-HT by L-aromatic decarboxylase
  - Enzyme also used in synthesis of catecholamines and histamine
- 5-HT transported into cells by specific transport system

Uptake

- Platelets and neurons have a high affinity 5-HT uptake mechanism
  - Platelets become loaded with 5-HT as they pass through the intestinal circulation where the local concentration is relatively high
  - They concentrate 5-HT by means of an active serotonin transporter mechanism (SERT) similar to that in the membrane of serotonergic nerve endings

Storage

- Once transported into the platelet or nerve endings, 5-HT is concentrated in vesicles by a vesicle associated transporter (VAT) that is blocked by Reserpine
- Is often stored in neurons and chromaffin cells as a co-transmitter together with various peptide hormones such as
  - Somatostatin
  - Substance P
  - Vasoactive intestinal peptides (VIP)
- 5-HT is also found in the raphe nuclei of the brain stem which contains the cell bodies of serotonergic neurons that synthesis, store and release serotonin as a transmitter
- Stored serotonin can be depleted by reserpine in the same manner the drug depletes catecholamines in the vesicles in adrenergic nerve and the adrenal medulla

Distribution

- Occurs in the highest concentration in 3 organs in the body:
  - In the wall of the intestine
    - >90% of the total amount of 5-HT in the body is present in the enterochromaffin cells in the gut
    - These are cells derived from the neural crest which resemble those of the adrenal medulla
    - Found mainly in the stomach and small intestine

        - Interspersed with mucosal cells
        - Enterochromaffin cells synthesis serotonin and store it as a complex with ATP and other substances in granules
        - Release serotonin in response to mechanical and neuronal stimuli
        - Some 5-HT also occurs in nerve cells on the myenteric plexus
    - In blood
        - Found in high concentration in platelets
        - They accumulate it from the plasma by an active transport system and release it when they aggregate at sites of tissue damage
    - In the CNS
        - Is a transmitter in the CNS and is present in high concentration in localised regions of the midbrain
        - Although 5-HT is present in the diet, most of it is metabolised before entering circulation

Degradation

- Occurs through oxidative deamination, catalysed by MAO to 5-hydroxyindoleacetylaldehyde
- Further oxidised by aldehyde dehydrogenase to 5-hydroxyindoleacetic acid (5-HIAA)

Excretion

- 5-HIAA is excreted in the urine
- In people consuming a normal, diet, the excretion is a measure of serotonin synthesis in the body
- The 24-hour excretion of 5-HIAA can therefore be used as a diagnostic test for tumours that synthesise excessive quantities of serotonin especially carcinoid tumours
- A few foods, e.g. bananas, contain large amounts of serotonin and its precursors and must be prohibited during such diagnostic tests

Pharmacodynamics of 5-HT

Mode of Action

- Currently, there are ≥ 14 known 5-HT receptor subtypes
- There are subdivided into 7 classes [families (5-HT 1-7)]
- All are g-protein coupled receptors (GPCRs), except 5-HT_3 which is a ligand gated cation channel
- The 6 GPCR families are further divided into 13 receptor subtypes based on their sequence and pharmacodynamics
- The most common second messenger is cAMP produced by activation of adenylate cyclase
    - However, the 5-HT_2 subtype activates phospholipase C (PLC) to generate phospholipid-derived second messengers
- With the exception of 5-HT_3 - selective agents, 5-HT receptor agonists and antagonists are relatively non-selective for different receptor subtypes
- 5-HT_1 receptors are further subdivided into subtypes A, B, D, E, F and P
- 5-HT_2 receptors are further subdivided into subtypes A-C
- Little is known about the function as pharmacology of 5-HT_{5-7} receptors
- All are present in the CNS as well as other tissues

Tissue and Organ Systems Effect

1. GIT
    - 5-HT has complex and important roles I the regulation of GIT function
    - Most 5-HT receptor subtypes are present in the gut with exception of the 5-$HT_{5/6}$ families
    - Only ~10% of 5-HT in the intestine is located in neurons, where it acts as a neurotransmitter
    - The reminder is located in the enterochromaffin cells, which acts as sensors to transduce information about the state of the gut
    - The 5-HT is released from these cells into the lamina propria, where it stimulates receptors located in the enteric neurons
    - 5-HT receptors are present on most neuronal components of the ENS as well as in smooth muscles, secretory and other cells
    - Main function is to regulate:
        - Peristalsis
        - Intestinal motility

        - Secretion
        - Visceral sensitivity
    - 5-HT is a powerful stimulant of GIT smooth muscle
        - It increases tone and facilitates peristalsis
    - This action is caused by the direct action of 5-HT on 5-HT to smooth muscle receptors plus a stimulating action on ganglion cells located on the ENS
    - 5-HT_{1A} and 5-HT_7 receptors may also be involved
    - Stimulation of 5-HT_3 receptors slows motility and mediates the neurotransmission involved in sensory perception of the gut by the CNS
    - Activation of 5-HT_4 receptors in the ENS causes increased Ach release and mediates a motility-enhancing/pro-kinetic tract
    - Overproduction of 5-HT (and other substances) in a carcinoid tumour is associated with severe diarrhoea
    - 5-HT has little effect on GIT secretion
    - The importance of 5-HT in the gut is indicated by the widespread distribution of SERT
        - SERT rapidly and efficiently removes released 5-HT, limiting its action
    - Back up transporters have also been identified
2. Smooth muscles
    - SM e.g. in the uterus and bronchial tree is to minor extent contracted by 5-HT
    - Smooth muscle of respiratory tree
        - Serotonin has a small direct stimulant effect on bronchiolar SM In normal humans probably by 5-HT_{2A} receptors
        - 5-HT also appears to facilitate Ach release from bronchial vagal nerve ending
        - In patients with carcinoid syndrome, episodes of bronchoconstriction occur in response to elevated 5-HT or peptides released from the tumour
        - May also cause hyperventilation as a result of chemoreceptor reflex or stimulation of bronchial sensory nerve endings
3. CVS
    a. Blood vessels
        - The effect of 5-HT on blood vessels depends on various factors including:
            - Size of the vessel
            - Species
            - Prevailing sympathetic activity
        - In humans, 5-HT is a powerful vasoconstrictor except n skeletal muscle and the heart where it dilates blood vessels
        - Large vessel, both arteries and veins, are usually constricted by 5-HT
        - This is a direct action on vascular smooth muscles cells, mediates though 5-HT_{2A} receptors
        - Activation of 5-HT_1 receptors causes constriction of large intracranial vessels, dilatation of which contributes to migraines
        - 5-HT can also cause vasodilation:
            - Partly by acting on endothelial cells to release nitric oxide
            - Partly by inhibiting sympathetic nerve terminals
        - When the endothelium is damaged, coronary blood vessels are constricted by 5-HT
        - A tri-phasic BP response is often seen following IV injection of 5-HT in experimental animals
            - Initially, there is a decrease in CO,HR and BP caused by the chemoreceptor response
            - BP then increases as a result of constriction of large vessels
            - The third phase is again decreased BP attributed to vasodilation in blood vessels supplying skeletal muscles
        - In contrast, pulmonary and renal vessels seen very sensitive to the vasoconstrictor action of 5-HT
            - 5-HT may play a role in pulmonary hypertension
            - Preliminary studies suggests that 5-HT2B antagonist can prevent development pulmonary hypertension in animal models
        - 5-HT also constricts veins
            - Venoconstriction with increased capillary filling appears to be responsible for the flush that is observed after 5-HT administration or release from carcinoid tumours
    b. Heart
        - 5-HT has small direct positive chronotropic and inotropic effects on the heart
        - Prolonged elevation of the blood levels of 5-HT as observed in carcinoid syndrome is

associated with pathologic alterations in the endocardium (sub-endocardial fibroplasia)
        - May result in valvular malfunctions
    c. Platelets
        - Causes platelet aggregation by action on 5-HT2A receptors
        - The platelets that collect in the vessel release further 5-HT
            - If the endothelium is intact, 5-HT release from adherent platelets causes vasodilation which helps to sustain blood flow
            - However, if it is damaged, as in atherosclerosis it causes constriction and impair blood flow further
        - These effects of platelet-derived 5-HT are thought to be important in vascular disease
4. Nerve endings
    - 5-HT stimulates nociceptive (pain and itch mediating) sensory nerve endings
        - This is mediated mainly by 5-HT3 receptors
    - If injected into the skin, 5-HT causes pain
    - When given systematically, it elicits a variety of autonomic reflexes through stimulation of afferent fibres in the heart and lungs
    - 5-HT also inhibits transmitter release from adrenergic neurons in the periphery
    - 5-HT is also a powerful activator of chemo-sensitive endings located in the coronary vascular bed
    - Activation of 5-HT3 receptors on these afferent vagal nerve ending is associated with the chemo-receptor reflex
    - The reflex response consists of marked bradycardia and hypotension
    - The bradycardia is mediated by vagal outflow to the heart and can be blocked Atropine
    - The hypotension is the consequence in the decrease in CO that results from bradycardia
5. CNS
    - 5-HT is present in various sites I the brain
    - Its functions as a neurotransmitter
    - It excites some neurons and inhibits others
    - It may also act to inhibit transmitter release from nerve endings
    - 5-HT3 receptors in the GIT and vomiting centre in the medulla, participates in the vomiting reflex
        - They are particularly important in vomiting caused by chemical trigger such as cancer chemotherapy drugs
        - ENS functions
    - Serotonin is also a precursor of melatonin in the pineal glands
6. Skeletal muscle and the eye
    - 5-HT2 receptors are present on skeletal muscle membranes
    - Serotonin syndrome is associated with skeletal muscle contractions
    - It is precipitated when MAOIs are given with serotonin agonists, especially antidepressants of the selective serotonin reuptake inhibitors (SSRIs)
    - The hyperthermia of serotonin syndrome results from excessive muscle contraction
        - However, serotonin syndrome is probably caused by the CNS effect of these drugs

Clinical Pharmacology of Serotonin

- Because of its broad and largely undesirable effects, serotonin has no clinical application in the treatment of disease
    - However ,compounds that selectively activate certain of its receptor subtypes or selectively antagonise its actions are of considerable clinical usefulness
- The ergot alkaloids have partial agonist activity at serotonin receptors

1. 5-HT1 receptors/agonists and antagonists

- Subdivided into subtypes a,b d e f p
- Occur mainly in brain
    - CNS
    - Blood vessels - HT_{1D}
- The receptors function mainly as inhibitory presynaptic receptors
- They mediate synaptic inhibition via increased potassium conductance
- They are linked to the decrease of adenylate cyclase and G_i
- Effects, mediated through inhibition of adenylate cyclase are
    - Neural inhibition

    - Vasoconstriction
- The 5-HT1A subtype is particularly important in the brain
    - Feeding
    - Mood
    - Sleep
    - Thermoregulation
    - Anxiety
- The 5-HT1D and 1B are expressed in cerebral blood vessels
    - Believed to be important in migraine
    - They are the target for triptans. Such as sumatriptan used in treatment of acute migraines
- The 5-HT1D receptor is also present in the vasculature of the heart and elsewhere
    - Responsible of the unwanted effects associated with triptan therapy
- Vasoconstriction in the cerebral vessels is mediated by 5-HT1 receptors
- In most other vessels, mediated by 5-HT2 receptors

a. Agonists at 5-HT1 receptors
    - Selective 5-HT1A agonists such as 8-hydroxy-2- di-n-propylaminotertralin (8-OH DPAT); potent hypotensive effect
    - Busipirone:
        - Partial agonist of 5-HT1A
        - Used as an anxiolyte (inhibits anxiety)
    - Repinotan:
        - Partial agonist at 5-HT1A
        - Currently at clinical trials
        - Appears to have anti-nociceptive action at higher doses
        - Reverses opioid induced respiratory depression
    - Sumatriptan and other triptans
        - $5\text{-HT}_{1D/1B}$ agonists used almost exclusively to the treatment of acute attacks of migraine
    - Eletriptan
        - Partial agonist at 5-HT_{1D}
    - 5-hydroxyindalpine
        - Partial agonist 5-HT_{1P}

5-HT1D/1B agonists and treatment or migraines headaches
- Classic migraine
    - Characterised by an aura of variable duration that may involve nausea, vomiting, visual scotomas or even hemianopsia, and speech abnormalities
    - The aura is followed by a severe throbbing unilateral headache that lasts for a few hours and can persist for about 2 days
    - Aura
        - A subjective sensation experienced before an effect of migraine or epilepsy
    - Scotoma
        - A blind or dark spot in the visual field
    - Hemianopsia
        - Blindness involving half of the visual field
- Common migraine
    - Lacks the aura phase but the headache is similar
    - Pathophysiology of migraine
        - Migraine involves the trigeminal nerve distribution of intracranial and possibly extra-cranial arteries
        - These nerves release peptide neurotransmitters, especially calcitonin gene related peptide (CGRP), an extremely powerful vasodilator
            - Substance P and neurokinin A may be involved
        - Extravasation of plasma proteins into the perivascular space appears to be a common feature in migraine patients
            - Probably reflects the action of the peptides on the blood vessels
        - The mechanical stretching caused by this perivascular oedema may be the immediate cause of activation of pain nerve ending in the dura
        - The inset of the headache is sometimes associated with a marked increase in amplitudes of temporal artery pulsations
        - Relief of pain by administration of effective therapy is sometimes accompanied by the

reduction of arterial pulsations
    - The MoA of drugs used in migraines are poorly understood, partly include a wide variety groups and actions
- Drugs used for Rx
    - The triptans
    - Ergot alkaloids
    - NSAIDs
    - ß-adrenoceptor blockers
    - Calcium channel blockers
    - TCAs and SSRIs
    - Several anti-seizure agents
    - Some of these drug groups are only for effective for prophylaxis and not acute attacks

MoA of drugs used for Rx of migraines

- 2 primary hypotheses have been proposed to explain the actions of these drugs

a. The triptans, ergot alkaloids and antidepressants may activate 5-HT1D/1B receptors on presynaptic trigeminal nerve endings to inhibit release of vasodilating peptides
    - Anti-seizure agents may suppress excessive firing of these nerve endings

b. The vasoconstrictor actions of direct 5-HT agonist (triptans and ergots) may prevent vasodilation and stretching in pain endings
    1) It is possible that both mechanisms contribute to the case of most drugs

- Sumatriptan and other triptans are selective agonists of 5-HT1D/1B receptors
- 5-HT1D/1B receptor types are found in cerebral and meningeal vessels
    - Also found on neurons and probably function as presynaptic inhibitory receptors

Clinical use of the triptans

- Sumatriptan and its analogs are currently the first line treatment for acute severe migraine attacks in most patients
- The efficacies of all the triptan 5-HT1 agonists in migraine are equal
- Their efficacies are also equivalent to or greater than that of other acute drug treatments e.g. parenteral, oral and rectal ergot alkaloids

Pharmacokinetics

- The pharmacokinetics of the triptans differ significantly
- They are active orally
- Zolmitriptan is also available for nasal administration
- Sumatriptan is available for SC, nasal and rectal admin
- It has an onset of action of 12 minutes following SC administration
- After oral administration, rizatriptan and sumatriptan have the fastest onset of action (1 - 2.5 hrs and 1.5 hours respectively)
- The latter 2 also have the shortest half lives of 2 hours
- Frovatriptan has 27 hours

Adverse effects

- Most are mild
- They include
    - Altered sensation (tingling feeling and warmth)
    - Dizziness
    - Muscle weakness
    - Neck pain
    - Injection site reaction (Sumatriptan parenteral injection)
- Chest discomfort occur in 1-5% of patients
- It has been reported probably because of the ability of the triptan to cause coronary vasospasms
    - They are therefore contraindicated in patients at risk of coronary heart disease and patients with angina

Challenges with the use of triptans

a. Duration of effect especially in the following drugs is often shorter than the duration of the headache
    - Sumatriptan and Rizatriptan - 2 hours
    - Zolmitriptan - 2.8 hours

- Almotriptan - 3.3 hours
- Therefore, several doses may be required during a prolonged migraine attack
  - However, their adverse effects limit the maximum safe daily dosage

b. The brand name triptans are very expensive
Therefore, generic sumatriptan should be used whenever possible

Contraindication and caution with triptan use

- Naratriptan and Eletriptan are contraindicated with patients with severe hepatic or renal impairment or peripheral vascular syndromes
- Frovatriptan is contraindicated in patients with peripheral vascular disease
- Zolmitriptan in patients with Wolff-Parkinson-White syndrome (Cardiac conduction dx)

Note:

- The following drug groups are effective only for prophylaxis and not acute attacks
  - Propranolol - ß-adrenoceptor blocker
  - TCAs e.g. amitrityline and SSRIs
  - Several antiseizure agents e.g. Valproate
  - Some calcium channel blockers

Use of the other calcium channel blockers

- Verapamil has mild to moderate efficacy as prophylaxis against migraines
- Flunarizine is useful in both prophylaxis and treatment of acute attack

5-HT2 receptors/agonists and antagonists

- Neuronal and smooth muscle effects are excitatory
- The effects of 5-HT on smooth muscle and platelets are mediated by the 5-HT2A receptors
- It also mediates some of the behavioural effects of agents such as lysergic acid diethylamide (LSD)
- Some blood vessels dilates as a result of NO release from endothelial cells
- 5-HT2 receptors being link to PLC and hence they stimulate IP3 formation
- The 5-HT2A subtype is functionally the most important
- The role of 5-HT2 receptor in normal physiological processes is minor
  - However, it is more prominent in pathological conditions e.g. asthma and vascular thrombosis

Agonists

- LSD is a relatively non-selective 5-HT2a/b/c/7 agonist or partial agonist in CNS and periphery
  - Acts centrally as a potent hallucinations

Antagonists

- Phenoxybenzamine
  - Has a long lasting blocking action

5-HT2A antagonists

- Ketanserin
  - Competitively blocks 5-HT2 receptors on smooth muscle and other tissues
  - It has little or no reported antagonist activity at other 5-HT or H1 receptor
    - Potently block vascular &1 receptors
  - Blocks 5-HT2 receptors on platelets and antagonises platelet aggregation promoted by serotonin
  - It has a hypotensive action probably mediated via &1 adrenoceptor blockade more than 5-HT2 receptor blockade
  - It is used for the treatment of hypertension and vasospastic conditions
  - May be useful in the treatment of carcinoid tumour
- Ritanserin
  - Is a 5-HT2 antagonist with little or no &-blocking action
  - Hs been reported to alter bleeding time and to reduce thromboxane formation and probably altering platelet platelet formation

- Ketotifen
- Pizotifen (NS)
- Methysergide
  - Ergot alkaloid
- Cyproheptadine
  - Resembles the phenothiazine antihistamine drugs in chemical structure
  - Has potent h1 - receptor - blocking actions as well as 5-HT2 blocking action
  - Effects
    - Prevents the smooth muscle effects of both amines
      - Has no effect on gastric secretion stimulated by histamine
    - Has significant anti-muscarinic effects and causes sedation
  - Major clinical applications
    - The treatment of the smooth muscle manifestation of carcinoid tumour
    - Treatment of cold induced urticaria
    - Of some value in the treatment of serotonin syndrome
  - Available only in oral from
    - Must be administered by NGT in unconscious patients
- Dihydroergotamine
  - ergot alkaloids

5-HT2C receptors

- Appetite suppression appears to be associated with agonist action at 5-HT2C receptors in the CNS
- Dexfenfluramine was widely used as an appetite stimulant
  - Withdrawn because of cardiac valve toxicity
- Lorcaserin has been recently FDA approved

5-HT3 receptors

- Occur mainly in the PNS particularly at the following sites where 5-HT exerts a strong excitatory effect:
  - Nociceptive sensory neurons
  - Autonomic and enteric receptors
- Also occur in the brain particularly with; _
- 5-HT3 receptors are exceptional in being directly linked to membrane ion channels
  - Directly involved in excitation without using second messengers
- Selective 5-HT3 antagonists
  - Ondansetron
    - The pro-typical 5-HT3 antagonists
    - With its analogs, are used mainly as anti-emetics
    - Important in prevention of nausea and vomiting associated with surgery and cancer chemotherapy
  - Dolesatron
  - Granisetron

5-HT4 receptors

- Occur in the brain and peripheral organs such as the GIT, bladder and heart
- Their main physiological role appears to be in the GIT where they produce neuronal excitation and mediate the effect of 5-HT in stimulating peristalsis and hence causing increased GIT motility
- Agonists include:
  - Metochlopromide
    - Stimulates coordinated peristaltic activity - pro-kinetic action
    - Affects dopamine receptors
    - Used to stimulate gastric emptying
  - Tergaserod
    - Partial agonist in the colon
    - Used for treatment of irritable bowel syndrome with constipation
      - Because of CVS toxicity, its use is now restricted
  - Cisapride
    - Used in the treatment of gastro-oesophegeal reflux and motility disorders
      - Not used because of CV toxicity

Carcinoid tumour

Other 5-HT receptors

- 5-HT important NT in CNS
- Several important antipsychotic and antidepressant drugs have actions on these pathways

Serotonin Syndrome

- Due to excessive synaptic serotonin levels
- Serious, potential fatal syndrome
- Diagnosed on the basis
    - The h/o administration of a setonergic drugs within several weeks
    - The physical findings
- Occurs when OD with a single drug or concurrent use of several drugs, results in excess serotonergic activity in CNS
- Predictable and not idiosyncratic

Precipitating drugs

- SSRIs
- Second generation antidepressants
- MAOIS
- Linezolid (AB)
- Tramadol
- Opioids: Meperidine, fentanyl
- Ondansetron
- Sumatriptan
- LSD
- Herbals: St. John's Warts, Ginseng

Clinical presentation

- Onset within hours
    - Hyperthermia
    - Hyper-reflexia, tremor, clonus, agitation
    - Hypertension
    - Hyperactive bowel sounds, diarrhoea
    - Mydriasis
    - Coma

Treatment

- Sedation with benzodiazepines
- Paralysis
- Intubation and ventilation
- Consider 5-HT2 block with cyproheptadine or chlorpromazine
    - Many of the SS signs can be reversed by 5-HT2 blockers

Other 5-HT agonists and antagonists of clinical significance

- Selective serotonin reuptake inhibitors (SSRIs) - agonists
    - E.g Fluoxetine are serotonin agonists
    - Block 5-HT reuptake by inhibiting SERT
    - Used for the management of depression
    - SSRIs may exaggerate the action of 5-HT in the gut: one common side effect is diarrhoea
- Atypical antipsychotic drugs
    - E.g. clozapine is the prototype
    - Have a greater ability to block 5-HT2A receptors than D2 receptors
    - In most cases, they act as partial agonists at the 5-HT1A receptors and this produces synergistic effects with 5-HT2A receptor antagonism
    - In addition, most are either 5-HT6/7 receptor antagonists
- Melatonin agonists and antagonist
    - Melatonin is N-acetyl-5-methoxytryptamine
        - Is a product of serotonin found in the pineal gland

        - Produced and released primarily at night
        - Promoted commercially as a sleep aid by the food supplement industry
        - Used to reduce jet lag
        - Usually administered orally at bedtime
    - Ramelteon
        - Selective MT1 and 2 that is used for medical treatment of insomnia
        - No addition liability and is therefore not a controlled substance
        - Appears to ne more efficacious than melatonin
    - Agomelatine
        - MT1 and 2 agonist and 5-HT2C antagonist
        - Approved in treatment of major depressive disorders

- LSD

Summary
Important actions and functions of 5-HT

- Increased GIT motility
    - Direct excitation of smooth muscle and indirect action of via enteric neurons
- Contraction of other smooth muscles
    - Bronchi
    - Uterus
- Mixture of vascular constriction Direct and via sympathetic innervation and dilation (endothelial)
- Platelet aggregation
- Stimulation of peripheral nociceptive nerve endings
- Excitation/inhibition of CNS neurons

Postulated physiological and pathophysiological roles

- In periphery
    - Peristalsis
    - Vomiting
    - Platelet aggregation and haemostasis
    - Inflammatory mediator
    - Sensitisation of nociceptor
    - Microvascular control
- In CNS
    - Control of appetite, sleep, mood, hallucination
    - Stereotyped behaviour
    - Pain perception
    - Vomiting

Clinical conditions associated with disturbed 5-HT function

- Migraine
- Carcinoid syndrome
- Mood disorders
- Anxiety

Eicosanoids

26 September 2016 09:22

- Include:
  - Prostaglandins
  - Thromboxanes
  - Leukotrienes
  - Related compounds e.g. PAF
- Prostaglandins, leukotrienes and thromboxanes are derived from membrane phospholipids

Biosynthesis

- Formed from 20-carbon essential fatty acids that contain 3, 4 or 5 double bonds
  - 8, 11, 14-eicosatrienoic acid (dihomo-gamma-linoleic acid)
  - 5, 8, 11, 14 eicotetraenoic acid (arachidonic acid)
  - 5, 8, 11, 14, 17 eicosapentaenoic acid
- Other eicosanoids like PAF are derived from modifies phospholipids

Eicosanoids

- Extremely prevalent
  - Present in almost every tissue and fluid of the body
- Are autacoids
  - Synthesised and exert their biological action in the same tissue
- Also found in a variety of plants
- Family of highly potent compounds with extraordinary wide spectrum biologic activity
- Bind to receptors on target cell plasma membranes of various tissues to stimulate or inhibit the synthesis of other messengers e.g. cAMP
- Have physiological and pathological effects on the CV, pulmonary, reproductive and digestive systems

Arachidonates

- Is the most abundant precursor and is derived either from dietary linoleic acid (9, 12 - octadecdienoic acid) or ingested as a dietary constituents
- Esterified to the phospholipids of cell membranes or other complex lipids
- Concentration low so the biosynthesis of eicosanoids is mainly from cellular stores of lipids by the action of acyl hydroxylases

Arachidonic acid

- Rapidly oxygenated by 4 distinct enzyme systems (separate routes)
  - Cyclooxygenase (COX) pathway to yield prostaglandins and thromboxane
  - Lipoxygenase pathway to yield H(P) ETES (hydroxyl[peroxy] ecosatetraenoic acid) leukotrienes and lipoxins
  - CYP P450 pathway to yield epoxides
  - Isoprostane pathway to yield isoprostanes

- Eicosanoids have biologic activity
  - Their specific receptor and enzyme inhibitors
  - Their plant and fish oil precursors have therapeutic potential
- Eicosanoids have a short half-life (seconds to minutes)
  - For clinical use, need special delivery systems or synthetic stable analogs

Prostaglandins

Thursday, 15 June 2017 5:32 AM

Prostaglandins

- Phospholipase A2 hydrolyses the ester bond to mobilise arachidonic acid from membrane phospholipids
- Arachidonic acid oxygenated and cyclised by prostaglandin endoperoxide synthesases (COX) to form the cyclic endoperoxide PGG2 and then converts it to PGH_2
- PGH_2 transformed enzymatically by synthesising to TXA, PGI_2, PGEs, PGF and PGD
- Interconversion of PGE_2 and $PGF_{2\alpha}$, catalysed by a 9-keto reductase in some tissues

synthesis of PGs and leukotrienes flow chart

Prostacyclin <-----PGH_2 --------> PGD_2
l ----------> PGE_2
l ----------(dypyridomole) -------> Thromboxane
l ----------> $PGF_{2\alpha}$

- PGs are analogs of prostanoic acid
- Unsaturated fatty acid derivatives containing 20 carbons and cyclic ring structure
- Prostacyclin. (PGI_2) has a double ring structure - in addition to a cyclopropane, a second ring is formed by an oxygen bridge between C6 and 9
- Thromboxane contain a 6 member oxane ring instead of a cyclopentane ring

Cyclooxygenases (PG endoperoxide syntheses)

- 2 isozymes
  - COX-1
  - COX-2
- COX important
  - NSAIDS exert their therapeutic effects at this step
- COX-1
  - Widely distributed
  - Has functions like gastric cytoprotection
- COX-2
  - Inducible and its expression varies markedly depending on the stimulus
  - Immediate early response gene product in inflammation and immune cells
  - Involved in normal renal development and prostacyclin production

Structural properties of PGs

- Diagram
  - PGE and D series are hydroxy ketones
  - F$_{2\alpha}$ are 1,3-diols
  - PGA, B and C unsaturated ketones
- Letter after PG such as A, B, G, H, F refers to. the substituents on the cyclopentane ring
- Most common conformations are E and F
- Subscript shows he number of double bonds in the side chain

table of characteristics of prostaglandins

Roles of prostaglandins on reproductive processes

- Effect on smooth muscle
  - $PGF_{2\alpha}$ contracts the uterine smooth muscle
  - PGEs effects depend on species and hormonal state I.e. human non-pregnant

myometrium is relaxed while PGE_2 contracts pregnant human uterus
    - Can be used for abortion
- Corpus luteum
    - In sheep and other sub-primate species $PGF_{2\alpha}$ has lutealytic effect (inhibit production and release of progesterone y the corpus luteum of the ovary)
    - $PGF_{2\alpha}$ and analogs for synchronising ovulation in animals (not true for humans)
- Menses
    - Dysmenorrhoea is attributed to increased endometrial synthesis of PGE_2 and $PGF_{2\alpha}$ during menses
    - Cause contraction of the uterus leading to ischaemic paint
    - PGs may play a part in involution of the corpus luteum in the post-menstrual period
- Parturition
    - Initiating factor is probably the release of prostaglandins from the foetal and maternal placenta
    - $PGF_{2\alpha}$ inhibits progesterone synthesis and stimulates oestrogen synthesis which further stimulates $PGF_{2\alpha}$ synthesis
    - Uterine contraction induced by $PGF_{2\alpha}$ and reinforced by oxytocin from maternal pituitary, resulting in expulsion of the foetus
    - PGE_2 is 5X more potent than $PGF_{2\alpha}$ for induction of labour at term
- Abortion
    - PGE_2 and $PGF_{2\alpha}$ have potent oxytocic effects and are used clinically (IV or vaginal tabs)
        - To promote uterine contraction at any stage I.e. after 12 weeks of pregnancy (surgical techniques have serious disadvantages)and for ripening the cervix before abortion
        - As post coital contraceptives
    - Dinoprostone, a synthetic analogue of PGE_2 administration vaginally; carboprost tromethamine (15-methyl derivative of $PGF_{2\alpha}$) intra-amniotic injection for second trimester abortion
        - May cause CV collapse.
        - Can be given IM

NB:
15-methyl analogues of $PGF_{2\alpha}$ and PGE_2 more potent than parent compounds (not substrates of PG-15-dehydrogenase)

- Main side effects of PGs used therapeutically
    - NVD is more severe with PGE_2 and $PGF_{2\alpha}$
    - Irritation of the vein at the site of injection
- PGs in semen
    - May play a role in the transport of sperm in the female and male genital tracts during and after coitus
    - May assist in the nutrition of sperm by producing vasodilation in genital mucous membranes
    - Absorbed through the genital mucosa to affect motility of the fallopian tubes
        - Facilitate transport of sperms to ovum
          NB:
          PGE content of seminal fluid of infertile males is low
- PGE_1
    - May be used in the treatment of impotence
    - Intracavernous injection or urethral suppository of PGE1 (alprostadil) causes partial or complete erection in impotent patient
        - Erection lasts 1 - 3 hours
    - Adverse effects
        - Penile pain
            - May be related to algestic effects of PGE derivatives
        - Prolonged erection and priapism (<4%)

- Minimise by careful titration to the minimum effective dose

PGs and the gut

- Gut wall contains manly PGE and F series
- Large amount of PGs liberated from GIT tissue during peristaltic activity than at rest
- PGs cause intestinal cramps and diarrhoea
- PGs of A and E series inhibit gastric acid secretion induced by histamine and pentagastrin without a decrease in mucosal blood flow
- PGE compounds and heir analogues protect against ulcers produced either by steroids or NSAIDS e.g.
    - Misoprostol (oral synthetic PGE_1 analogue) and Enprostil are cytoprotective at low doses and inhibit gastric secretion at high doses
- Their adverse effects
    - Dose related
    - Abdominal discomfort
    - Occasional diarrhoea

NB:

- GIT side effects of NSAIDS can be reduced by giving COX-2 selective inhibitors that spare COX-1 so that the local PGE_2, the natural protector, is not disturbed

PGs and respiratory tract

- Lungs contain $PGF_{2\alpha}$, mainly in the parenchyma and PGE_2 in the bronchial walls
- PGEs relax the bronchial smooth muscles
    - Counteract bronchoconstriction in response to histamine, serotonin and other bronchospasmogens
    - Causes irritation
        - Coughing and soreness of respiratory tree when given by an aerosol
- $PGE_{2\alpha}$ produce contraction of bronchial smooth muscle and bronchospasm in vivo, counteracting the bronchodilator effects of PGE2 and isoprenaline
    - Which PE can be used to induce labour in an asthmatic pregnant mother?
- Bronchospasm in asthma may be due to imbalance between the effects of PGE_2 and $PGF_{2\alpha}$

- Prostacycline (PGI_2)
    - Predominantly from vascular epithelium acts on IP receptors
    - Lowers peripheral and coronary resistance and is used in treatment of primary and secondary pulmonary hypertension (sometimes occurs after mitral valve surgery
    - Epoprostinol, a commercial preparation of prostacyclin has a very short half-life in plasma and given by continuous IV infusion for treatment of pulmonary hypertension
    - Treprostinil is given by continuous SC infusion

PGs - CV actions

- PGEs call a fall in BP due to decrease in PR as a result of relaxation of arteriolar smooth muscle
- ON molar basis PGE_1 and PGE_2 are approximately equal in depressor potency and more potent than Acetylcholine and histamine
- There is little or no CV response to PGs administered to induce abortion or labour
- PGI_2 causes vasodilation
- CV response to PGF series are more complex

CV uses of PGs

- PGE and PGI_2 compounds may be used in Raynaud's phenomenon and vascular atherosclerosis
- PGE1 (alprostadil) may be used in certain types of congenital heart disease to maintain the patency of the neonates ductus arteriosus before surgery

NB:

In delayed closure of ductus arteriosus, COX inhibitors such as indomethacin are used

- PGI_2 (epoprostinol) inhibits platelets aggregation
    - Given during haemodialysis if heparin is contraindicated

PGs - Renal action

- PGs are released from the renal medulla by noradrenaline and angiotensin II and sympathetic nerve stimulation but the stimulation is inhibited by indomethacin (NSAIDS)
- PGE_2 and A_2 have diuretic and natriuretic actions when PGA_1 stimulates the release of aldosterone leading to Na^+ retention
- PGs are concerned with autoregulation in the kidney so that the renal blood flow remains relatively constant despite the changes in blood pressure

Eye

- PGE and PGF derivatives lower the intraocular pressure by probably increasing outflow of aqueous humour from the anterior chamber via uveoscleral pathway
- Latonoprost, a $PGF_{2\square}$ derivative is stable and long acting and is applied topically for glaucoma
- Bimatoplast, travaprost and unoprostone also have ocular hypotensive effects

PGs and Bone metabolism

- Skeletal tissue, PGs are produced by osteoblasts and the adjacent haematopoietic tissues
- PGs especially PGE_2 acting on EP_4 receptors stimulate bone resorption and formation
- PGs may play a role in some of the changes that occur in bone inflammation and in the bone loss occurring at menopause

PGs and Lipolysis

- PGs, particularly PGE_2 antagonises the lipolytic actions of CAs endocrine hormones (ACTH, TSH, glucagon)
- Effect of lipolytics result s in elevation of plasma levels of FFAs
- Lipolytics act be stimulation of cAMP but PGs inhibit adenylate cyclase of adipose tissue

PGs and body temperature

- Endotoxins induce the synthesis and release of PGs (especially PGE_1) which acts on the temperature controlling centres to produce fever
    - The antipyretic NSAIDs owe their action to the inhibition of PG synthesis

PGs and inflammatory reactions

- PGs E_1, E_2, $F_{1\square}$ and $F_{2\square}$ are released together with other pharmacologically active substances in various inflammatory and hyper sensitivity reactions
- Venoms from bee and other snakes also release PGs from tissues
    - The released PGs mediate some manifestation of inflammation
- Phospholipase A2 also present in many venoms
- Bronchoconstrictions occurring in hypersensitivity reactions of lungs could be due to the release of $PGF_{2\square}$
- Leucocyte migration into inflammatory sites is simulated by PGE_1
- Synthesis of PGs in inflammation could be secondary to release the precursor of FA from membrane lipid complexes by the action of lysosomal enzymes particularly phospholipase A2

- While corticosteroids stabilise the lysosomal membrane, the NSAIDS with anti-inflammatory and analgesic properties that inhibit the synthesis of PGs implying that the PGs are involved in inflammatory reactions and production of pain
- PGs do not act directly to stimulate sensory receptors subserving pain but they lower the threshold to stimulatory substances such as bradykinin and thereby produce hyperalgesia

Metabolism of PGs

- Pharmacological activity of PGE and Fs is almost entirely destroyed in their passage though the lung circulation by PG-15-degydrogenase (also present in kidney and liver)
- The enzyme acts on the 15-OH group to convert it to a corresponding keto
- Metabolism may occur at C20 to a dicarboxylic acid. Also removal of 2 or more carbon units
    - Many metabolic routes I.e. isomerases converting one compound to another with low or no activity e.g. PGA_1-PGB_1, PGA_2-PGC_2 etc.
    - Reduction of double bonds may also occur

Leukotrienes

Tuesday, 16 February 2016 9:48 AM

Arachidonic acid esterifired in the membrane in the phospholipids
Follows 2 pathways
- LOX (lipooxygenases)
- COX (cyclooxygenases)

Synthesis
- Arachidonic acids is metabolised by 5, 12, 15 lipooxygenases to hydroxyeicosatetraenoic acids (HPETEs)
- Converted to HETE and leukotrienes
- Produces by leukocytes, mast cells and dendritic cells
- 5 types
  - LTA_4
  - LTB_4
  - LTC_4
  - LTD_4
  - LTE_4
- LTC4, D4, E_4 are cysteinyl leukotrienes
- LTC4 and LTD_4 are potent Bronchoconstrictions
  - Component of the slow-reacting substance of anaphylaxis (SRS-A)
- Act on G-protein coupled receptors

Biodegradation
- LTA_4 converted by 12-lipooxygenase to lipotoxins
  - LXA_4
  - LXB_4

Mechanism of Action
- 2 receptor isoforms
  - LTB_4, BLT1,BLT2
  - Cysteinyl: cysLT1, cysLT2
- BLT1--->IP3----> activation, degranulation, superoxide generation in PMNS
- cysLT1----> Gq----> in creased intracellular Ca2+ levels

Effects
- Blood cells and inflammation
  - Potent chemoattractant (LTB4, cysteinyl)
  - Promote eosinophil adherence
  - Cytokine release
  - Oxygen radical formation
  - Increase endothelial permeability
  - Stimulate T cell clonal expansion
  - Promote IFN-gamma, IL-1, IL-2 release
- CVS
  - Reduce myocardial contractility and coronary blood flow (LTC4, D4)
- Airways
  - Potent bronchoconstrictors (LTC4, LTD4)
  - Increased microvascular permeability, plasma exudation and mucus secretion

Inhibition of Leukotrine Synthesis
- 5 lipooxygenase inhibitor - Zileuton
  - Hepatotoxicity (5%)
  - Drug interactions - warfarin, theophylline, propanolol
  - Associated with Churg Strauss Syndrome
    - Autoimmune asthma-like disease
- Leukotriene receptor antagonist
  - Zafirlukast
  - Montelukast
  - Pranlukast
- NSAIDs - enhance leukotriene formation by diverting arachidonic acid to the LOX pathway

Clinical Pharmacology

- Asthma/allergic rhinitis
  - Adjunctive
  - Leukotriene receptor inhibitors (montelukast, zafirlukast)
  - Useful in
    - Moderate - severe asthma
    - Aspirin induced
    - Exercise induced

Thromboxane

Tuesday, 16 February 2016 10:06 AM

Synthesis

- Synthsised from arachidonic acid via the COX pathway
- Derived from PGH2 (thromboxane synthases)
- Rapid metabolism by hydration

Mechanism of action

- Acts as autocrine or paracrines - short half life
- 2 receptor isoforms
  - &
  - ß
- G-protein coupled receptor
- Activates phosphatidylinositol metabolism ----> IP3----> increase intracellular Ca2+

Effects

- Vascular
  - Potent vasoconstrictor
  - Mitogen
- Airways
  - Bronchoconstriction
- Platelets
  - Enhances platelet aggregation
  - Amplifies the effects of thrombin
- Kidney
  - Intrarenal vasoconstriction (decline in renal function)
- Female reproductive organs
  - Uterine muscle contraction
- Inflammation and immunity
  - Increase platelet leukocyte interactions
  - Stimulate T cell clonal expansion

Inhibition of thromboxane formation

- Corticosteroids - block all pathways of eicosanoid synthesis
- NSAIDs - reversibly inhibit COX activity
- Aspirin - irreversible COX inhibitor (extended inhibition)

Clinical Pharmacology

- Chronic administration of low dose aspirin reduces risk of MI, stroke

Platelet Activating Factor

Monday, 22 February 2016 9:55 AM

- _
- Synthesised in response to stimulation by enzymes - phospholipase A2, lyso-PAF-acetyl transferase in the presence of
- Not stored
- Metabolised by PAF acetyl hydrolase in plasma and cells, and acetyl transferase. Metabolite 1-O-alkyle-2-acylglycerophosphocholine
- Regulated by the levels of calcium in blood

Physiologic Action

1. CVS
    - Potent vasodilator
    - Increases coronary blood flow, higher doses reduce flow by platelet aggregates and TXA2 formation
    - Pulmonary vasculature is constricted
    - Intradermal injection causes first constriction, then wheal and flare
    - Increase vascular permeability and exudation
    - PAF x1000 more potent as histamine and bradykinin in increasing permeability by contraction of venular endothelium
2. Platelets
    - Potent aggregator with release of TXA2 and granular contents
3. Leukocytes
    - PAF causes polymorphonuclear leukocytes (PMNL) to aggregate, release leukotrienes and release lysosomal enzymes to release super-oxides
    - Causes monocyte aggregation and eosinophil degranulation
    - Chemotactic factor for neutrophils, monocytes
    - Stimulates adherence or neutrophils and diapedesis
    - Causes thrombocytopenia
4. Smooth muscles
    a. PAF contracts the uterine, GIT and pulmonary SMs except trachea. NSAIDs inhibit these actions. increases airway bronchoconstriction and bronchial responsiveness
    b. Mucus secretion and permeability of pulmonary microvasculature increases
5. Stomach
    a. Constricts the fundus and is ulcerogenic
6. Kidneys
    a. Decrease renal blood flow
7. GUI
    a. PAF involved in ovulation, implantation and parturition

Receptor antagonists

- Triazolobenzodiazepiones - aloprazolam, triazolam
- Apafant
- Natural products - terpenes from Gingko biloba are potent and selective

Polypeptides

- Used by a variety of tissues for cell to cell communication
- Play important roles in the CNS and PNS
- Some have important direct effects on vascular and other smooth muscles
- Vasoconstrictors
    - Angiotensin II
    - Vasopressin
    - Endothelins

    - Neuropeptide Y
- Vasodilators
    - Bradykinin and other kinins
    - Natriuretic peptides
    - Vasoactive intestinal peptide
    - Calcitonin gene related peptide
    - Substance P
    - Neurotensin

Natriuretic Peptides

- The family consists of
    - Atrial natriuretic peptide (ANP)
    - Brain natriuretic peptide (BNP)
    - C-type natriuretic peptides (CNP)
- Structures ae similar but have different biological effects
- Have natriuretic, diuretic, vaso-relaxant and other properties

ANP

- Derived from carbonyl terminal of a common precursor called preproANP (has 151 amino acids)
- The ANP circulates as a 28 amino acid peptide with a single di-sulphide bridge
- Synthesis
    - Mainly in the atriocytes but small quantities synthesised in ventricles
    - Other areas includes CNS, peripheral neurons and the lungs
- Release is caused by
    - Atrial stretch by mechaniosensitive ion channels
    - Blood volume expansion
    - Head out water immersion
    - Changing from standing to supine position (on back)
    - Exercise
    - Sympathetic stimulation
        - Glucocorticoids
        - Endothelins
        - Vasopressin
- Clinical states
    - Congestive heart failure
    - In primary aldosteronism
    - Chronic renal failure
    - In syndrome of inappropriate ADH secretion
- Receptors
    - 3 types
        - ANP-A
            - Mainly acted on/used by ANP and BNP
        - ANP-B
            - Mainly used by CNP
        - ANP-C
            - Used equally by all types od natriuretic peptides

Pharmacokinetics

- Metabolised in kidneys, liver and lungs
- Short half-life
- The metabolic enzyme is neutral endopeptidase

Pharmacological effects

- ANP causes a prompt and marked increase in sodium excretion and urine flow
    - The GFR increases with little or no change in renal flow
    - The natriuresis is due to increased GFR and decreased PRT reabsorption

- ANP inhibits secretion of renin, aldosterone and vasopressin
- ANP decreases arterial blood pressure due to vasodilation
- ANP decreased sympathetic tone to peripheral vasculature and antagonises the effect of angiotensin II and other vasoconstrictors

Other natriuretic peptides

- BNP is primarily synthesised in brain and heart
- Similar functions with ANP in blood levels are low
- CNP consists of 22 amino acids
- Mainly produced in CNS but also found in vasculature endothelium in kidneys and intestines
- Has less natriuretic and diuretic effect but it is a potent vasodilator

Pathophysiology

- Reduce salt-water retention
- Decrease heart failure

Endothelins

- Potent vasoconstrictors
- 3 isoforms exist
    - ET1-3
- Receptors Etb, Ets
- Bosentan - receptor blocker given IV and orally
- Phosphoramidon - endothelin converting enzyme blocker

- Produced in preproforms
- Each of the isoforms is a 21 amino acid peptide with 2 disulphide bridges
- Widely distributed in bodies
- ET1 is the predominant form produced in endothelium. Also produced by neurons, astrocytes of CNS, endometrium, renal mesangial cells, sertoli cells, breast epithelium and other cells
- ET2 mainly produced in kidneys and intestines
- ET3 - highest concentration in brain but smaller quantities in GIT, kidneys and lungs

Production

- ET1 stimulated by:
    - Growth factors
    - TGF-ß
    - IL-1
    - Vasoactive substances
    - Angiotensin II
    - Vasopressin
    - Mechanical stress

Actions of endothelins

- Widespread actions
    - A dose dependent vasoconstriction in most vascular beds
    - A positive inotropic and chronotropic action
    - Potent coronary vasoconstrictors
    - In the kidneys, they decrease GFR and decrese water and sodium excretion
    - In respiratory system
        - Brochoconstrictor
        - Trachial constriction
    - Endocrine system
        - Increase RAAS, vasopressin and ANP
    - CNS, PNS, GIT, Liver, Urinary tract, reproductive system, eye, skeletal muscle and skin
    - Potent mitogens for vascular smooth muscles, myocytes and glomerular mesangial cells

inhibitors and stimulators

- Potential candidates for treatment of cardiac hypertrophy and chronic hypertension with fluid retention states

- Synthesis inhibited by NO, prostacyclin and ANP

VIP

- Distributed in
- Neurotransmitter and modulator
- Causes the following physiologic action
    - Dilation in most vascular beds including CNS, renal, coronary , splanchnic and pulmonary vascular beds
        - Acts directly on vascular smooth muscle
            - Decreased BP
            - Decreased CO
        - Bronchodilation and GIT smooth muscle relaxation
        - Stimulate water and electrolyte secretion
        - Increased glycogenolysis
        - Neuronal excitation
        - Increases
            - GH
            - Prolactin
            - Renin

Substance P

- Belongs to the tachykinin family
- Other family members include neurokinin A and B
- Neurotransmitter in CNS and GIT
- A local hormone
- Has a role in behaviour, anxiety, depression, nausea and vomiting
- Potent vasodilator

Effects

- Contraction of venous, intestinal and bronchial smooth muscle
- Salivary gland secretion stimulation
- Diuretic and natriuretic effect in kidney
- Through 3 receptors
    - NK1-3
        - NK-1 mainly used, in brain and peripheral nerves
- Antagonists
    - Depression and drug induced emesis

Neurotensin

- Tri-decapeptide found in brain, GIT and circulation
- Neurotransmitter and neuromodulator in CNS and a local hormone peripherally
- Receptor
    - NTS1-3
- Antagonists
    - Treatment of hypothermia and analgesia

CGRP

- Most potent vasodilator
- Largest concentration in C-cells of thyroid gland
- Also found in CNS, PNS, GIT, GUT
- Found with substance P and acetylcholine
- Centrally given
    - Suppression of feeding
    - Hyper tension
- Peripherally given
    - Hypotension
    - Tachycardia

Neuropeptide Y

- A member of family including peptide YY and pancreatic polypeptide
- Most abundant neuropeptides in CNS and PNS
- Receptors
    - Y1-6
        1- Vasoconstrictor and neurotransmitter
- Inositol antagonises vasoconstrictor effect
- In CNS
    - Increases feeding
    - Hypotension
    - Hypothermia
    - Respiratory depression

Kinins

Tuesday, 16 February 2016 9:44 AM

- Formed from kininogens by action of kallikrein

Kallikrein
- Serine proteases
- Found in
  - Plasma (plasma kallikreins)
    - Activated by factor XII
  - Tissues (tissue kallikrein)
    - Kidneys
    - Intestines
    - Salivary glands
    - Pancreas
    - Sweat glands

Kininogens
- Substrates for kallikreins
- Precursors for kinins
- Present in lymph, interstitial fluid, plasma
- LMW kininogens
  - _ to the capillary walls
  - Substrate for tissue kallikreins
- HMW kininogens
  - Confined to bloodstream
  - Substrate for plasma kallikrein

Metabolism
- 2 major kinins
  a. Bradykinin
     - From HMW kininogen by plasma kallikrein
  b. Lys-bradykinin
     - From LMW kininogen by tissue kallikrein
     - Converted to bradykinin by arginine aminopeptidase
- Present in plasma (bradykinin), urine (kallidin)
- Metabolised rapidly by kininases
  - Kininase I
    - Synthesised in the liver
  - Kininase II
    - In plasma endothelial cells
    - Identical to ACE
- Half-life is 15 seconds
- Completely hydrolysed during a single passage through the pulmonary vascular bed

Organ Effects
1. CVS
   - Marked arteriolar dilation in the heart, skeletal muscle, kidney, liver, intestine
     - X10 more potent than histamine
     - Direct inhibitory effect on endothelial cells
     - Release of NO, PGE2, PGI2
   - Venous constriction
     - Direct stimulation of venous smooth muscle

        - Release of PGF2&
        - Contraction of visceral smooth muscle
    - Through IV
        - Rapid but brief fall in BP
        - Reflex tachycardia
        - Due to arteriolar vasodilation action
    - Efflux of fluid from blood into tissues (oedema)
        - Increased_
        - Increased capillary permeability
        - Contraction of endothelial cells
        - Widening of intracellular junctions
        - Increased venous pressure secondary to constriction of veins
2. Glands
    - Regulate GIT motility
    - Regulate transport of water, electrolytes, glucose, amino acids in GIT kidneys
    - Activation of prohormones (proinsulin, prorenin)

Pain and inflammation

- Produce classic symptoms of inflammation
    - Insert symptoms
        - Redness
        - Tempeprature
        - Swelling
        - Pain
        - Loss of function
- Rapidly produced after tissue injury
- Impaired role of development; maintenance of inflammation
- Potent pain producing substance
- Stimulate nociceptive afferents in skin, viscera

Hereditary angioedema

- Rare
- Autosomal dominant disorder
- Deficiency of Cl esterase inhibitor (Cl-INH)
    - Activation of kallikrein
    - Increased formation of bradykinin
    - Increased vascular permeability
- Recurrent episodes in airways, GIT, extremities, genitalia

Kinin receptors

- 2 types:
    - B1
    - B2: B2A, B2B
- GPCRs
- Bradykinin has highest affinity for B2 receptors
- B1 receptors
    - Inflammatory response
    - Collagen synthesis
    - Cell multiplication

Signal transduction

- Calcium mobilisation

- Chloride transport
- Formation of NO
- Activation of PLC, PLA2, AC

Drugs affecting kinins
Icatibant
- Second generation B2 receptor antagonist
- Decapeptide
- Treatment of
    - Hereditary angioedema
    - Thermal injury
    - Pancreatitis

Kinin Synthesis inhibitors
- Include
    - Angiotensin
    - Aproteinin
        - Prophylaxis and treatment of hereditary angioedema

Ecallantide
- Recombinant kallikrein inhibitor
- More potent
- Given SC
- Prophylaxis, treatment of hereditary angioedema

Other drugs
- NSAIDs (aspirin)
    - Prostaglandin synthesis inhibitor
    - Inhibit actions of kinin mediated by prostaglandins
- Angiotensin Converting enzyme inhibitor (Enalaprin)
    - Enhance effects of kinin
    - Block kinin degradation
    - Additive antihypertensive effect

Pharmacogenetics

Tuesday, 12 January 2016 8:15 AM

- Variability in drug responses between individuals:
  - Genetics
  - Environment
- Variability can be in pharmacokinetics or pharmacodynamics

Pharmacogenetics: study of variation of a drug responses under hereditary control

Single nucleotide polymorphism

- Mutation results in change in DNA nucleotide sequence
- SNPs are very common:
  - Change function of the protein
  - Change level of expression of protein

Why it is a good approach: Personlised medicine

- Drugs can be dangerous
- Drugs are expensive (to take and make)
- Genetics provide a priori information
  - Genetics don't change (except in cancer)
  - Genetics can point to the cause and not just the symptoms

Genetic influences on drug metabolism

(diagram: CYP2D6: consequences of genotype for systemic drug exposure)

CYP2D6

- Found on chromosome 22
- Deficient in 7 - 10% of caucasians
  - PM: 7-10%
  - Im + EM: 85-90%
  - UM: 1-2% (30% of Egyptians) - require larger doses
- Increased susceptibility
  - Nortriptylinie (headache, confusion)
  - Codeine (weak analgesia)
  - Phenformin (lactic acidosis)

CYP2C9

- Found on chromosome 10
- Deficient in 1-3% of caucasians
- Reduced enzyme activity
  - S-warfarin
  - Losartan
  - Celecoxib
  - Sulphonylureas

CYP2C19

- Found on chromosome 10
- Deficient (PM):
  - 3-5% of caucasians
  - 15-20% of asians
- Reduced enzyme activity:
  - Proton pump inhibitors
  - Phenytoin
  - Phenobarbitone

Acetylator status (N-acetyltransferase 2)

- Acetylator status (measuring ratio of monoacetyldapsone to dapsone):
  - Rapid:
    - 40-45% caucasians

        - 95% Japanese, Eskimos
        - 20% Jews
    - Slow
        - 50-60% caucasians
- Inherited in the simple Mendelian manner
    - Autosomal dominant (rapid acetylators)
- Rapid acetylators:
    - Slower response, relapse of TB for Isoniazid
    - Isoniazid induced hepatotoxicity
- Slow acetylators
    - Isoniazid induced peripheral neuropathy
    - Phenytoin toxicity when given with isoniazid (inhibits phenytoin metabolism)
    - Procainamide induces lupus erythromatosus
    - Lower doses of hydralazine for BP control
    - Hydralazine induced lupus erythromatosus

Sulphation
- Reduced activity
    - Oestrgens
    - Progesterones
    - Catecholamines

Suxamethonium sensitivity
- Usual response
    - Muscular paralysis for 5 minutes
    - Hydrolysed by plasma pseudocholinesterase
- Prolonged response (2 hours)
    - Presence of aberrant plasma cholinesterase
    - 1 in 2500
    - Autosomal recessive
    - Heterozygotes (4%) - unaffected carriers

Thiopurine methyltransferase
- Deficiency leads to toxicity due to azathiopurine
    - Prodrug of 6-mercaptopurine
    - Inactivates 6-MP
- Caucasians deficient:
    - 0.3% homozygotes
    - 11% heterozygotes

Metabolisers, dosing, effects
Various diseases that can predispose drug action especially G6P-DH deficiency

Genetic influences on drug action
Receptor polymorphism
- Many polymorphic variants
- Produce altered receptor expression

Warfarin susceptibility
- Warfarin inhibits Vitamin K epoxide complex 1 (VKORC1)
- Sensitivity associated with:
    - Reduced metabolism of CYP2C9
    - Reduced activity of VKORC1

Inherited diseases that predispose to drug toxicity
Glucose-6-phosphate dehydrogenase deficiency
- Maintains glutathione in its reduced form
- Located on the X-chromosome (sex-linked)
- Common in the Mediterranean people, Africans and Indians
- Reduced enzyme activity:
    - Methaemoglobinaemia
    - RBC haemolysis when exposed to oxidising agents
- Precipitant drugs
    - Analgesics - aspirin
    - Antimalarials - primaquine, quinacrine, quinine
    - Antibacterials - sulphonamides, sulphones, nitrofurantoin, ciproflaxacin
    - Miscellaneous - quinidine, probenecid

Methaemoglobinaemia
- Drugs that convert Hb to metHb
    - Nitrates
    - Sulphonamides
    - Local anaesthetics

Malignant hyperthermia
- Fatal complication of GA:
    - Inhalational anaesthetic (halothane, isoflurane)
    - Suxamethonium
- Rapid rise in temperature
- Mendelian dominant
    - Variant ryanodine R1 receptor
    - Controls intracellular calcium flux
    - 1:20,000

Acute porphyrias
- Acute illness precipitated by drugs (enzyme inducers)
- Inherited enzyme deficiencies in haem biosynthesis
- Single dose can precipitate an acute episode
- Precipitanr drugs:
    - Phenytoin
    - Ethanol
    - Sulphonamides
    - Methyldopa
    - Theophylline
    - Sex hormones
    - Rifampicin
    - Sulphonylureas

Gilbert disease
- Benign unconjugated hyperbilirubinaemia
- Reduced activity uridine phosphoglucoronyl transferase (UGT1A1)
- Precipitated by oestrogens (impair bilirubin uptake)
- Increases irinotecan toxicity (metabolised by (UGT1A1)

Gene Therapy
- Experimental technique for correction of defective genes:
    - Gene transplantation (to patient with gene deletion)
    - Gene correction (to revert specific mutation in the gene of interest)
    - Gene augmentation (to enhance expression of gene of interest)

History and Development of Gene Therapy
- 1960: Concepts of gene therapy introduced
- 1970: first attempt to perform gene therapy
- 1990: first approved gene therapy case
    - 4 year old girl with SCID
- 2006: gene therapy effective in treating cancer
- 2007: ongoing research

Disease Targeted
- SCID
- Cystic fibrosis
- Parkinson's Disease
- AIDS
- Haemophilia
- Cancer
- Alzheimer's disease
- Hepatitis B

Types of gene therapy
- Germ line therapy

- Somatic gene therapy

Germ line

- Results in permanent change
- Potential for offering a permanent therapeutic effect to the offspring
- Possibility of eliminating disease from a particular family
- Controversy
    - Unnatural therapy ("playing God")

Cleaning genes

One way germ line therapy may be done to ensure a man with a genetic disease doesn't pass it to his child

1. Doctors remove the man's sperm producing cells, which contain a defective gene
2. A healthy gene is added to each cell to replace the defective one
3. The cells are put in a mouse testis
4. They mature inside the mouse and start to produce sperm
5. Those sperms, once tested, are used to fertilise a woman's egg in a lab dish
6. The resulting embryos are placed in the woman's womb
7. She gives birth to a child that is free from the father's disease

Somatic gene therapy

- Affects only the somatic (targeted) cells
- Not passed to future generations
- Short-lived (cells die and replaced)
- Problem with transporting gene to target cells
- Appropriate and acceptable

Types of somatic GT

- Ex vivo
    - Cells are modified outside the body
    - Transplanted in again
- In vivo
    - Gene is transferred to cells inside patient's body

Ex vivo

1. Cells are removed from the patient
2. In the lab, a virus is altered such that it cannot reproduce
3. A gene is inserted into the virus
4. The altered virus is mixed with cells from the patient
5. The cells from the patient become genetically altered
6. The altered cells are injected into the patient
7. The genetically altered cells produced the desired protein or hormone

Ideal vector

- Adequate carrying capacity
- Undetectable by the IS
- Non-inflammatory
- Safe
- Efficient
- Long duration of expression

Types of vectors

- Viral vectors
    - Retroviruses
    - Adenoviruses
    - Adeno-associated viruses
    - Herpes simplex virus
- Non-viral vectors
    - Liposomes
    - DNA polymer conjugate
    - Naked DNA

Viral vectors

- Introduce genetic material into host cell
- Plausible strategy
    - Remove viral DNA

    - Use the virus as a vehicle to deliver therapeutic gene

Non-viral vector

- Physical (carrier-free gene delivery)
- Chemical (synthetic vector based gene delivery)

Physical method

- Employs a physical force that permeates the cell membrane, facilitating intracellular gene transfer
    - Needle injection
    - Electroporation
    - Gene gun
    - Ultrasound

Chemical method

- Lipoplexes
    - DNA covered with lipids (micelles)
    - Protects DNA
- Polyplexes
    - Complexes polymers with DNA

Vector	**Advantage**	**Disadvantage**
Liposomes	Virus-free Cheap to produce	• Low efficiency • Cytotoxic
DNA cassettes	Virus free	• Low efficiency • Temporary expression
Herpes simplex virus 1	• Highly effective • Persistent expression	• No integration with the host DNA • Cytotoxic • Difficult to handle
Adenovirus	Highly effective	• Immunogenic • Transient • Requires re-administration
Adeno-associated virus	Stable	• Low-capacity
Retrovirus	Efficient, permanent	• Must integrate with host DNA • Requires dividing cells

Problems

- Viral vectors
    - Acquire virulence
    - Immunogenic
    - Elicit inflammatory response
    - Damage host genome - may cause changes in cell cycle
- Require repeated administration

Applications

- Curing genetic diseases
- Correcting cancer cells
- Inducing cancerous cells to make toxins to kill themselves
- Blocking viral genes
- Creating stem cells from somatic cells

Gene therapy

- Restore protective proteins (P53)
- Inactivation of oncogenes
- Rendering malignant cells sensitive to drugs
- Protecting healthy cells from chemotherapy
- Making cancer cells more immunogenic

Ethical problems

- Gene therapy for serious genetic diseases OK but for other health problems
- Somatic cell treatment stays with the individual, germ cell treatment passes down the germ line (becomes immortal)
- Very costly. Who pays? Who is eligible?

Anti-Microbials

Monday, 29 February 2016 9:32 AM

Classification

1. Compounds that inhibit cell wall synthesis
    - ß-lactam antibiotics
        - Penicillins
        - Cephalosporins
        - Carbapenems
            - Imepenem
        - Monobactams
            - Aztreonam
    - Vancomycin
    - Bacitracin
    - Cycloserine
2. Protein synthesis inhibitors
    - 30S subunit
        - Aminoglycosides
        - Tetracyclines
    - 50S subunit
        - Chloramphenicol
        - Macrolides
        - Lincomycin
        - Clindamycin
3. Altering cell membrane permeability (affect/alter active transport)
    - Polymyxins
    - Polyenes
    - Azoles
    - Amphotericin B
4. Inhibit nucleic acids synthesis
    - Quinolones
        - Inhibit DNA gyrase and topoisomerases
    - Anti-folates - inhibit folic acid synthesis
        - Sulphonamides
        - Sulphones
        - Biperidines
            - Dihydroperidines
    - Rifampicin
        - Alkylates DNA helix - cannot unwind

- Can be:
  Bactericidal - kill dividing cells
    - Cell wall inhibitors
    - Aminoglycosides in high doses
    - Quinolones
    - Rifampicin
    - Bacteriostatic - inhibits cellular metabolic activities of divided cells
        - Antifolates

How bacteria respond to antibiotics

- Depends on the class and structure

Gram negative bacteria, pseudomonas , are the most difficult to treat

Resistance

- 3 mechanisms
    - Impaired intracellular accumulation due to either impaired influx or increased efflux by an active proton pump
    - Impaired ribosome binding due to a protein produced
    - Enzyme inactivation
- The most important is plasmid mediated efflux pump mechanism

Mechanisms of Resistance

- Non-genetic mechanisms
    - Dormancy
    - Loss of specific targets
        - Lack of cell walls
- Genetic mechanisms
    - Chromosomal
        - Transduction

        - Resistance is through bacterial viruses
    - Spontaneous mutations
    - Transformation
    - Conjugation
    - Transposition
  - Extra-chromosomal
    - Involve plasmids
    - Include

Quinolones

- Drugs:
  - Norfloxacin
  - Ciprofloxacin
  - Ofloxacin
  - Levofloxacin - respiratory Quinolones
  - Moxifloxacin
- Mechanism of action
  - Inhibit bacterial DNA synthesis by inhibiting DNA gyrase and topoisomerase IV - rapid cell death
  - Gram positive and negative bacteria
  - Post antibiotic effect: lasts 1 to 2 hours, increases with increasing concentration
- Mechanism of resistance
  - Chromosomal
    - Alter target enzymes: DNA gyrase and topoisomerase IV
    - Decreased drug penetration
  - Plasmid: seen in some K. pneumoniae and E. coli
  - Mutations in both the target enzymes are needed to produce significant resistance

Carbapenems

Tuesday, 1 March 2016 9:24 AM

ß-lactam antibiotics

- Contain a ß-lactam ring in their structure
- Classification
  - Penicillin
  - Cephalosporins
  - Cephamycins
  - Carbapenems
  - Monobactams

Carbapenems

- Are ß-lactams that contain a fused ß-lactam ring and a five member ring system
- Differ from the penicillin because of the 5 member ring system contains a carbon atom instead of sulphur
- Have a broader spectrum of activity than other ß-lactam antibiotics
- Examples
  - Imipenem
  - Meropenem
  - Doripenem
  - Ertapenem

Imipenem

- Derived from a compound produced by Streptomyces cattleya
- Is marketed in combination with cilastatin, a drug that inhibits the degradation of imipenem by renal tubular dehydropeptidase

MoA

- Binds to penicillin-binding proteins, disrupts cell wall synthesis and causes death of susceptible microorganisms
  Is bactericidal
  It is very resistant to hydrolysis by most ß-lactamases

Antimicrobial activity

- Is excellent for gram negative rods, gram positive organisms and anaerobes
- Susceptible organisms
  - Streptococci
    - Including penicillin-resistant *S. pneumoniae*
  - Enterococci
    - Excluding *E. faecium*
  - Staphylococci
    - Including penicillinase-producing strains
  - Listeria
  - Pseudomonas
  - Acinetobacter
  - Anaerobes
    - *B. fragilis* are highly susceptible

Resistant organisms

- *Enterococcus faecium*
- *MRSA*

- *Clostridium difficile*
- *Burkholderia cepacia*
- *Strenotrophominas maltophilia*

Pharmacokinetics
- Not absorbed orally
    - Available as a parenteral solution
- Hydrolysed rapidly by dehydropeptidase found in the brush border of p.tubule
- Cilastatin is a dehydropeptidase inhibitor
- Both imipenem and cilastatin have a half life of ~1 hour
- When administered concurrently with cilostatin, ~70% is recovered in urine as active drug
- Dosage should be modified in patients with renal insufficiency

Adverse effects
- Nausea and vomiting
- Seizures (1.5% of patients) - especially when high doses are given to patients with CNS lesions and those with renal insufficiency
- Patients who are allergic to other ß-lactam antibiotics may have hypersensitivity reactions when given imipenem

Therapeutic uses
- UTI
- Lower respiratory tract infection
- Intra-abdominal and gynaecological infections
- Skin, soft tissue, bone and joint infections
- Useful for empirical treatment of serious infections in hospitalised patients who have received other ß-lactam antibiotics (have an increased risk of infection with cephalosporin and/or penicillin-resistant bacteria)

Caution
- Imipenem should not be used as monotherapy for infections due to P. aeruginosa because of the risk of resistance developing during therapy

Dosage
- 250 - 500 mg after 6 - 8 hours
- given via the IV route

Meropenem
- Is a dimethylcarbamoyl pyrolidinyl derivative of thiaenamycin
- It does not require co-administration with cilastatin because it is not sensitive to dehydropeptidase
- Toxicity similar to imipenem except that it may less likely cause seizures (0.5% for meropenem)

Antimicrobial activity
- Similar to that of imipenem, with slightly against gram-negative aerobes but less activity against gram-positive cocci
- Clinical experience with meropenem demonstrates therapeutic equivalence with imipenem

Meropenem
- Penetrates well into many tissues and body fluids including CSF
- Given IV
- Dose must be adjusted in renal insufficiency

Uses

- Febrile neutropenia
- Complicated skin infection
- Complicated intra-abdominal infections
- Bacterial meningitis
- Dose
    - 0.5 to 1g every 8 hours

Doripenem

- Has a spectrum of activity similar to meropenem and imipenem with greater against some resistant isolates of pseudomonas
- Dosage
    - 0.5g administered as a 4-hour infusion every 8 hours

Ertapenem

- Differs from imipenem and meropenem by having a long half life that allows once daily dosing
- Has inferior activity against P. aeruginosa and Acinetobacter spp.

Clinical uses

- Useful in intra-abdominal and pelvic infections due to its spectrum of activity against gram-positive organisms, enterobacteriaceae, and anaerobes

Dosage

- 1g IV or IM once daily
- IM ertapenem is irritating thus given with 1% lidocaine

Monobactams

Tuesday, 1 March 2016 9:41 AM

Aztreonam

- Is a monocyclic ß-lactam compound (a monobactam) isolated from chromobacterium violacium

MoA

- Aztreonam prevents bacterial cell wall synthesis by binding to and inhibiting cell wall transpeptidases
- Bactericidal
- Is resistant to many of the ß-lactamases that are elaborated by most gram negative bacteria

Antimicrobial activity

- Differs from those of the other ß-lactam antibiotics and more closely resembles that of an aminoglycosides
- Has activity only against gram negative bacteria; it has no activity against gram-positive bacteria and anaerobic organisms
- Has excellent activity against:
    - Enterobacterioceae
    - P.aeruginosa
    - H.influenzae
    - Gonococci

Pharmocokinetics

- Given either IM or IV
- The halflife is 1.7hours
- Most of the drug is recovered unaltered in the urine
- The half life is prolonged to ~6 hours in anephric patients

Adverse effects

- Is generally well tolerated
- Patients allergic to penicillins or cephalosporins appear not to react to aztreonam (except those allergic to ceftazidime which is structurally similar)

Dosage

- The usual dose of aztreonam for severe infections is 2g every 6-8 hours
- Should be reduced in patients with renal insufficiency

Other examples of monobactams

- Tigemonam
- Nocardicin A
- Tabtoxin

Penicillins

Monday, 7 March 2016 9:15 AM

- They are ß-lactam antibiotics because they have a ß-lactam ring in their structure
- ß-lactam antibiotics have a common mechanism of action
    - Inhibit synthesis of peptidoglycan cell wall

Basic Penicillin Structure

- Have a thiazolidine ring connected to the ß-lactam ring to which a side chains attached
- Side chain determines the antibacterial and pharmacological characteristics of a specific type of penicillin
- Penicillin G is the only natural penicillin
- Others are semi-synthetic

Classification

- Based on their spectra of activity
    - Narrow spectrum penicillins
        - Penicillin G
        - Penicillin V
    - Penicillinase resistant penicillin (anti-staphylococcal Penicillins)
        - The isoxazolyl P
            - Cloxacillin
            - Flucloxacillin
            - Oxacillin
            - Dicloxacillin
        - Nafcillin
        - Methicillin (not used)
    - Broad spectrum Penicillins (Extended spectrum Penicillins)
        - Aminopenicillin
            - Amoxicillin
            - Ampicillin
                - Bacampicillin
                - Pivampicillin
                - Talampicillin
                - Epicillin
        - Anti-pseudomonal Penicillins
            - Carboxycillins
                - Carbenicillin
                - Ticarcillin
            - Ureidopenicillin
                - Piperacillin
                - Mezlocillin
                - Azlocillin

Broad Spectrum Penicillins

- Gram positive
- Gram negative
- Hydrolysed by penicillinases

- Extends the spectrum penicillin to include:
  - *Enterobacteriaceae*
  - *Haemophilus influenzae*
  - *Escherichia coli*
  - *Proteus mirabilis*
  - *Salmonella*
  - *Shigella*
  - *Helicobacter pylori*
- Superior to Penicillin G and V for
  - *Listeria monocytogenes*
  - Sensitive enterococci
- Amoxicillin is the most active of all oral ß-lactams against penicillin resistant *Streptococcus pneumoniae*

Anti-Pseudomonal Penicillins

- Extends spectrum of aminopenicillins to include
  - *Pseudomonas aeruginosa*
  - *Enterobacteriaceae*
  - *Bacteroides spp.*
- All these agents except piperacillin have < activity than ampicillin against gram positive and *Listeria monocytogenes*
- None of the penicillins are active against
  - Amoebae
  - Plasmodia
  - Rickettsia
  - Fungi
  - Viruses

Mechanism of Action

- Inhibit the first step in bacterial cell wall synthesis
  - Interfere with the transpeptidation reaction
- Cell walls
  - Essential for normal bacterial growth
  - Rigid and prevents cell lysis due to high osmotic pressure
  - Contains peptidoglycan which is composed of polysaccharides and polypeptides
- A peptide is attached to the polysaccharides
- This peptide terminates in D-alanyl-D-alanine
- Penicillin binding proteins (PBP) catalyse a transpeptidase reaction that removes the terminal alanine to form a cross-link with a nearby peptide
- This cross linking gives the cell wall its rigidity
- ß-lactam antibiotics are structural analogs of D-ala-D-ala
- Penicillins covalently bind to PBPs and inhibit the transpeptidation reaction
- Therefore, cross linking of peptidoglycans does not occur
- The bacteria is unable to synthesise a stable cell wall and is eventually lysed
- Penicillin is only active if cells are growing and synthesising cell walls

Mechanisms of Resistance

1. Altered structure of PBP
   - Reduced affinity for ß-lactam antibiotics
2. Inability of penicillins to penetrate site of action.
   - Transpeptidase is bound to the cell membrane. Gram negatives have an outer

membrane that contains pores. Antibiotics have to diffuse through the pores to reach the transpeptidase and act on them. Broad spectrum penicillins penetrate more rapidly than Penicillin G
    - Absence or reduced production of porins
3. Bacteria produce ß-lactamases or penicillinases. These enzymes hydrolyse the ß-lactam ring
    - ß-lactamases have higher affinity for the antibiotic than the antibiotic for its target
    - ß-lactamases can be of different types
        - If the substrate is low, they are described as penicillinases or cephalosporinases
        - Others are more broad spectrum - they hydrolyse a variety of ß-lactam antibiotics
        - Gram positive secrete this enzyme extracellular
        - Gram negatives secrete it into the periplasmic space between the inner and outer sell membrane
        - Encoded in plasmids or chromosomes
    - Types of ß-lactamases
        - Over 340 different enzymes
        - Extended spectrum ß-lactamases (ESBLs)
            - Hydrolyse penicillins, third and fourth generation cephalosporins
            - Do not affect cephamycins (second generations), carbapenems, ß-lactamases
            - Also hydrolyse aztreonam
        - AmpC
            - Are not inhibited by ß-lactamase inhibitors
            - Sensitive to fourth generation cephalosporins
        - Carbapenemases
            - Resistance to penicillins and carbapenems
            - May be sensitive to aztreonam
4. Presence of efflux pump (gram negative)
    - Removes the antibiotic from its site of action before it can activate.

General Statements

- Bactericidal
- Generally have greater affinity for gram-positive bacteria
- Oral route if stable in gastric acid e.g. Penicillin V, cloxacillin, amoxicillin
- Widely distributed with therapeutic levels in most tissues
- Low concentration in the brain, eye, prostate and phagocytic cells
- Higher concentration in CSF if meninges are inflamed (5% vs 1%)
- Penicillins are secreted rapidly from the CSF into the blood stream by an active transport process
- Eliminated by
    - Glomerular filtration (10%)
    - Tubular secretion (90%)

Adverse Effects of Penicillins

- Hypersensitivity reactions (by penicillinoic acid)
    - Most common
    - Manifestation
        - Rash (mild-severe e.g. Steven Johnson syndrome)
        - Fever
        - Anaphylaxis
        - Angioedema

        - Serum sickness
        - Bronchospasm
        - Vasculitis
        - Interstitial nephritis
            - _
    - Occur at any dose, via any route of administration
    - Cross hypersensitivity between Penicillins and cephalosporins
    - Can occur in the absence of previous known exposure
    - Take history of allergy
    - Skin test
    - Desensitisation
        - Small dose administered SC/ID
        - Watch out for anaphylaxis
- Other AE
    - Bone marrow suppression
        - Neutropenia (nafcillin)
    - Hepatitis
        - Exacillin, nafcillin
    - Bleeding
        - Impaired platelet aggregation
    - Pain
        - IM and IV
    - NVD
    - High dose
        - Lethargy, confusion, twitching, seizure
        - Penicillin G potassium - hyperkalemia
    - Intrathecal ---> arachnoiditis encephalopathy ---> convulsions
- Carbenicillin indanyl sodium
    - CCF - due to excessive sodium
    - Hypokalaemia - drug causes its excretion through the kidneys
    - Abnormal platelet aggregation
- High doses of procaine penicillin
    - Immediate effects due to procaine liberation
        - Dizziness
        - Tinnitus
        - Headache
        - Hallucinations
        - Seizures
- Superinfections
    - Clostridium difficile toxin causes pseudomembranous colitis
    - Fungal infections e.g. *Candida albicans*

Drug Interactions

- Probenicid increases plasma and CSF penicillin levels
    - By decreasing tubular secretions
    - Competitively inhibiting active transport from the CSF
- Penicillins can be hydrolysed by ß-lactamases
- ß-lactamases avidly bind the inactivating enzymes, preventing its attack on antibiotic
- They do not bind all ß-lactamases
    - E.g. *Enterobacter*
- Examples
    - Clavulanic acid
    - Sulbactam
    - Tazobactam

- They are combined

Clavulanic acid

- Has poor antimicrobial activity
- It is a 'suicide' inhibitor (or irreversible inhibitor) of ß-lacatamses
- Oral and parenteral route
- Adjust dose in renal failure

Sulbactum

Tazobactum

- Piperacillin + Tazobactam
- This combination does not increase the activity of piperacillin against *Pseudomonas aeruginosa*
    - Resistance may be due to:
        - Chromosomal ß-lactamases
        - Decreased permeability in the periplasmic space

Drugs Used in Combination

- Amoxicillin + clavulanic acid
    - Augumentin
- Ticarcillin + clavulanic acid
- Ampicillin + sulbactam
- Pipercillin + tazobactum

Narrow Spectrum Penicillins (Penicillin G and V)

Tuesday, 13 June 2017 9:21 AM

Narrow Spectrum Penicillins

- Gram positive organisms
- Gram negative cocci
- Non ß-lactamase producing anaerobes
  - *Bacteroides fragilis* produces ß-lactamase
- Little activity against gram-negative rods
  - Hydrolysed by penicillinases
  - Ineffective against most strains of *Staphylococcus aureus*

Specific examples

- *Streptococcus species*
- *Enterococci*
- *Listeria meningitidis*
- *Spirochetes*
- *Actinomyces*
- *Pasteurella multocida*

Penicillin G

- A.k.a Benzyl penicillin
- Active against gram positive and negative organisms and is the DOC for:
  - Most streptococci
  - Non-beta-lactamase producing staphylococci and gram-negative anaerobic bacteria
  - *Neisseria meningitidis*
  - *Bacillus anthracis*
  - *Clostridium spp.*
  - *Listeria monocytogenes*
  - *Treponema pallidum*
- Gastric acid destroys it
  - Therefore given IV
  - Benzathine salts of Penicillin G can be given IM
- Peak concentration are reached in plasma within 15-30 minutes
- Half-life - 30 minutes
- Widely distributed
- 60% bound to plasma proteins
- 10-40% metabolised to penicillinoic acid
  - Allergy to penicillinoic acid
- Eliminated mainly through the kidneys, little through bile
- Acute renal failure half-life increases from .5 - 10 hours
- In renal failure, 7-10% of the antibiotic may inactivated each hour by the liver
- Modified forms prolong Penicillin G action
  - They release Penicillin G slowly from the area where they are injected and produce persistent concentrations of the antibiotic in blood
  - Penicillin G procaine
  - Penicillin G benzathine

- If large doses of procaine Penicillin, are given, procaine may reach toxic levels in plasma
- Procaine and benzathine have local anaesthetic effects - the injections are virtually painless
- Benzathine Penicillin has the longest duration of antimicrobial activity in plasma - 26 days
- Therapeutic uses
    - Pneumonia
    - Meningitis
        - Caused by *Neisseria meningitidis* if the isolate is proven to be susceptible
    - Pharyngitis
    - Infective endocarditis
        - Left sided endocarditis cased by *Streptococcus viridans* and *Streptococcus bovis*
    - Clostridial infections (tetanus, gas gangrene)
    - Anthrax
    - Gonorrhoea
    - Syphilis
        - In secondary syphilis - Jarisch Herxheimer reaction occurs
            - It is a reaction to endotoxin-like products released by the death of harmful micro-organisms within the body during anti-biotic treatment
            - Efficacious anti-microbial therapy results in lysis of bacterial cell membranes, and in the consequent release into the blood stream of bacterial toxins, resulting in a systemic inflammatory response
                - Hours after the first injection of penicillin
                - Chills, fever, headache, myalgias and arthralgias
                - Syphilitic cutaneous lesions may become oedematous and brilliant colours
                - Symptoms persist for a few hours
                - The rash begins to fade within 48 hours
                - It does not recur with the second or subsequent doses of Penicillin therefore, therapy should not be discontinued
                - This is thought to be due to release of spirochetal antigens and host reactions
            - Give anti-inflammatory agents
                - Aspirin or Ibuprofen every four hours for a day
                - PO or IV Prednisone as adjunctive treatment with the above

- Prophylactic uses
    - Recurrences of Rheumatic fever
    - Intrapartum for Group B Streptococci (*Streptococcus agalactiae*)
    - Gonorrhoea
    - Syphilis - for contacts
    - Surgical procedures in patients with valvular heart disease
        - Dental extraction
        - Tonsillectomy
        - GUT and GIT procedures

Penicillin V

- Oral route
- More stable in acid
- Distribution and excretion similar to Penicillin G
- Is indicated only for minor infections due to
    - Its poor bioavailability
    - 4 times a day dosing
    - Narrow spectrum of activity

- Clinical use
  - Group A streptococcal pharyngitis
  - Rheumatic fever

Adverse Effects

- IgE mediated (Type I) hypersensitivity reactions
  - Note, cross-reactivity with Cephalosporins
- Drug induced autoimmune haemolytic anaemia
  - Gives a positive direct Coombs test
  - This is due to antibodies formed against penicillin, binding to the surface of RBCs
- Drug induced interstitial nephritis
  - Caused by mononuclear cells that enter the interstitium of the kidney

Anti-Staphylococcal Penicillins

Tuesday, 13 June 2017 9:24 AM

Anti-Staphylococcal Penicillins/Penicillinase Resistant Penicillins

- Effective against penicillinase producing *Staphylococcus aureus* and *Staphylococcus epidermidis*
  - Resistant to staphylococcal penicillinases
    - They contain R-groups that prevent beta-lactamase binding
  - Therefore used for staphylococcal infections
- Streptococci
- Less potent against other gram positive organisms (than narrow spectrum Penicillins) [Less active than Penicillin G against other microorganisms and should not be used as substitutes]
- No activity against
  - Enterococci
  - Anaerobic bacteria
  - Gram negative cocci and rods
  - Methicillin resistant *Staphylococcus aureus*
- Note:
  - MRSA and *Staphylococcus epidermidis* are resistant to:
    - Penicillinase resistant Penicillins
    - Cephalosporins
    - Usually resistant to:
      - Aminoglycosides
      - Tetracyclines
      - Erythromycin
      - Clindamycin
  - MRSA and epidermidis
    - It has a PBP with low affinity for these drugs
    - Vancomycin is the drug of choice
    - +/- rifampicin if there is a foreign body or a life-threatening infection
  - Methicillin is no longer used due to high rates of adverse effects

The Isoxazolyl P

- Include:
  - Cloxacillin
  - Flucloxacillin
  - Oxacillin
  - Dicloxacillin
- Stable in acidic medium
- Oral (30-80% absorbed)
- Better absorbed on an empty stomach
  - 1 hour before meals/2 hours after meals
- Intestinal absorption is variable
- The oral route is not a substitute for the parenteral routes in a serious infection
- Plasma protein binding is 90-95%
- Half-life = 30 to 60 minutes
- Not removed significantly by haemodialysis

- Excreted via kidneys and bile

Nafcillin

- Inactivated to a variable degree in acidic medium
- Absorption is irregular even on an empty stomach, IM preferred
- 90% plasma bound protein
- Peak concentrations in bile > in plasma
- CSF concentration adequate for staphylococcal meningitis therapy

Clinical Use

- When given orally, anti-staphylococcal penicillins are suitable for treating mild to moderate localised staphylococcal infections e.g.
    - They are empirically to treat skin and soft tissue infections like folliculitis and abscesses, for which *Staphylococcus aureas* is common
- When given IV, anti-staphylococcal penicillins can be used to treat serious systemic infections e.g.
    - *Staphylococcal epidermidis* endocarditis
    - Staphylococcal osteomyelitis

Adverse Effects

- Similar profile to that of penicillins in general
    - Hypersensitivity reactions
    - Interstitial nephritis
- Nafcilin is asscosiated with neutropenia
- Oxacillin can cause hepatitis

Broad Spectrum Penicillins

- Gram positive
- Gram negative
- Hydrolysed by penicillinases
- Extends the spectrum penicillin to include:
  - *Enterobacteriaceae*
  - *Haemophilus influenzae*
  - *Escherichia coli*
  - *Proteus mirabilis*
  - *Salmonella*
  - *Shigella*
  - *Helicobacter pylori*
- Superior to Penicillin G and V for
  - *Listeria monocytogenes*
  - Sensitive enterococci
- Amoxicillin is the most active of all oral ß-lactams against Penicillin Resistant *Streptococcus pneumoniae*

Aminopenicillins

- Amoxicillin and ampicillin have similar antibacterial activity
  - Amoxicillin is less effective than ampicillin for shigellosis
- They are all affected by ß-lactamases

Ampicillin

- Prototype of aminopenicillins
  - Improved activity against gram-negative bacteria because of its enhanced ability to penetrate the outer membrane - broad spectrum activity
- Spectrum of activity
  - Anaerobes e.g.
    - Aspiration pneumonia
  - Enterococci
    - Common for UTIs and infective endocarditis
    - However, there are some resistant strains due to production of beta-lactamases
  - Listeria
    - Causes meningitis in paediatrics and geriatrics
  - GIT and GUT gram negative rods e.g.
    - E.coli
    - However, Ampicillin is not first line
- Because Ampicillin is susceptible to beta-lactamases produced by some bacteria, it is paired with Sulbactam, a beta-lactamase inhibitor
- PK
  - Stable in gastric acid therefore oral. Also IM and IV
    - Amoxicillin is better absorbed orally
    - IV administration of Ampicillin is preferred because its useful in treating serious infections caused by anaerobes
  - Food reduces absorption (binds to food proteins)
  - Half life is 80 minutes

- 20% plasma protein bound
- Widely distributed
- EnteroHepatic Circulation - excreted in faeces
- Excreted in urine
- Not removed by peritoneal dialysis
- Haemodialysis removes 40% of the drug in 7 hours
- Adjust the dose in renal failure

Amoxicillin

- PK
  - Stable in gastric acid therefore oral
    - Also IM/IV
  - Food does not interfere with absorption
  - More rapidly and completely absorbed than Ampicillin
  - Less diarrhoea
  - Half life is 80 minutes
  - Effective concentrations are found in plasma for twice as long as with Ampicillin because of the more complete absorption
  - 20% protein bound
  - Most is excreted as active drug in urine

Adverse Effects

- SJS
- Drug induced liver injury
- Can precipitate rash in viral infections e.g. EBV
- Ampicillin has been associated with Pseudomembranous colitis
- Secondary infection such as candidiasis

Therapeutic Indication for Aminopenicillins

- Respiratory tract infections (sinusitis, otitis media, pneumonia)
- UTI
- Prophylaxis against encapsulated bacteria (Streptococcus pneumoniae and Haemophilus influenzae) in asplenic patients, esp. the younger patients
- Used to treat streptococcal pharyngitis in children
- Meningitis in paediatrics and geriatrics, caused by *Listeria monocytogenes*
- *Helicobactor pylori* treatment
- Ampicillin may prolong the carrier state caused by Salmonella
- Prophylaxis of endocarditis before dental procedures in patients with heart disease

Anti-Pseudomonal Penicillins

- Ureidopenicillins more active against pseudomonas than Carboxypenicillins
  - Because of the propensity of *Pseudomonas aeruginosa* to develop resistance during treatment, an anti-pseudomonal penicillin is sometimes used in combination with a fluoroquinolone or aminoglycoside for pseudomonal infections outside the urinary tract
- Can be destroyed by ß-lactamases
- Ureidopenicillins (Piperacillin, Mezclocillin and Azlocillin) are also active against selected gram-negative bacilli, such as *Klebsiella pneumoniae*

Carbenicillin Inadyl Sodium

- Acid stable- oral

- Converted into Carbenicillin in plasma by hydrolysis of ester linkage
- Low concentrations in plasma
- Excreted rapidly in urine
- UTI only - proteus, pseudomonas
- No loner used in the USA because there are more active, better tolerated alternatives

Ticarcillin

- Parenteral
- Similar to Carbenicillin
- More active than Carbenicillin on Pseudomonas

Piperacillin

- Piperacillin + Tazobactam = broadest spectrum
- Tazobactam is a ß-lactamase inhibitor
- Useful in serious infections caused by gram-negative bacteria
- Not absorbed from GIT
- IV
- Half-life = 1 hour but prolonged in neonates, hepatic impairment and renal failure
- 20% plasma protein binding
- Distribution - Ampicillin
- ~60% excreted unchanged in urine mainly, 20% in faces
- Adverse effects like in carbenicillin

Cephalosporins

Monday, 14 March 2016 9:16 AM

- Antibiotics
- Antimicrobials
- Interfere with bacterial cell wall - peptidoglycan
- Synthesis of the polymer of glucans and peptide bonds i.e. transpeptidation (cross linkage) is reduced leading to cell lysis
- Bactericidal - growing organisms
- Source
  - Fungus cephalosporium acremonium
- 7-aminocephalosporanic acid nucleus
- Side chain addition in synthetic cephalosporin

Chemistry

- ß-lactam antibiotic
- 7 aminocephalosporanic acid relatively stable to dilute and resistant to penicillinase
- Modification influence to its kinetics, activity spectra and disposition
- Cephamycins similar to cephalosporins but have a methoxy group at position 7 of the ß-lactam ring
  - Cephalosporins
  - Cephamycin
  - Cephalosporum
  - Streptomycin

MoA

- Inhibit cell wall synthesis in a manner similar to penicillin i.e.
  - Transpeptidation
  - Binding on PBP
  - Inhibiting autolysins ineffective
    - Modulated peptidoglycan remodelling

Classification

- Chemical structure
- Clinical pharmacology
- Resistance to ß-lactamases
- Antimicrobial spectrum
- Generation
  - First
    - active against gram + and poor activity against gram -
    - Exception of enterococci, MRSA and S. epidermidis
    - Oral cavity organisms are suscetible except B. fragilis
    - ! Good activity against Moraxella catarrhalis, K. pneumoniae, E. coli and proteus mirabilis (produce extended spectrum ß-lactamases)
      - Cephalothin
      - Cefazolin
      - Cephalexin
      - Cefadroxil
  - Second
    - Increased activity against gram- but still less than 3rd generation
    - Cefoxitin, cefotetan and cefometazole are active against Bacteroides fragilis (anaerobe)
    - Generally less active against gram+ (cf. 1st generation)
    - Active against **enterobacteriaceae** including beta lactamase producing ones (but not ESBLs-extended spectrum beta lactamases)
      - Cefamandole
      - Cefoxitin
      - Cefaclor
      - Loracarbef
      - Cefinicid
      - Cefotetan
      - Cefuroxime, Cefuroxime axetil
  - Third generation
    - More activity against gram -, < on gram +
    - Enterobacteriaceae; psudomonas aeruginosa. Serratia, neisseria gonorrhoeae
    - Staph. Aureus, strep. Pneumoniae efficacy similar to first generation

        - Activity against B. fragilis is inferior to cefoxotin and
            - Cefotaxime
            - Cefpodoxime proxetil
            - Ceftizoxime
            - Ceftriaxone
            - Cefoperazone
            - Ceftazimide
    - Fourth generation
        - Comparable to third generation but more resistant to ß-lactamases
            - Cefepime
    - Fifth generation
            - Cetfobiprole
            - Ceftoriline

Pathogens resistant to cephalosporins

- Enterococci
- Listeria monocytogens
- Legionella spp.
- MRSA
- Xanthomonas maltophilia
- Acinetobacter spp.

1. PBP's or other binding site alterations
2. ß-lactamases
3. Porin mediated
4. Other enzymatic
5. Efflux pumps

Mechanism of bacterial resistance

- Inability to reach site of action
- Alteration in PBP
- ß-lactamases - most prevalent

Orally available cephalosporins

- Cephalexin -1st. Gen
- Cephadrine (Duracef) - 1st gen
- Cephaclor - 2nd gen
- Loracarbef - 2nd gen (carbacephem)
- Cefprozil - 2nd gen
- Cefixime - 3rd gen
- Cefpodoxime proxetil - 3rd gen
- Ceftibuten - 3rd gen
- Cefuroxime axetil (Zinnat) - 2nd gen

- Cephalothin and cephalopirin cause pain when given as IM injection and thus used only IV
- Other agents given IM/IV

General features

- Excreted primary by kidney and doses should be adjusted in kidney disease
- Probenecid slows the tubular secretion of most cephalosporins.
- Probenecid is mainly used for uric acidemia.
- Cefpiramide and cefoperazone are exceptions because they are eliminated via the hepatobiliary route
    - Given to patients with end-stage renal disease
- Cephalothin, cephapirin and cefotaxime are deacetylated and metabolites have less antimicrobial activity.
- Most cephalosporins are lost unchanged - no appreciable metabolism
- Cefuroxime, cefotaxime, ceftriaxone, cefepime, ceftizoxime cross BBB
    - Treatment of meningitis.

Disufirum-like effect characteristics

? Write notes on the relative importance on and indications of each generation of cephalosporins

- What are the mechanisms of bacteria antimicrobial resistance?
- What are the similarities and differences between penicillins and cephalosporins?

First Generation Cephalosporins

Thursday, 15 June 2017 7:01 AM

- Active against gram-positive and poor activity against gram-negative
- Exception of enterococci, MRSA and *Streptococcus epidermidis*
- Oral cavity organisms are susceptible except *Bacteroides fragilis*
- Good activity against
  - *Moraxella catarrhalis*
  - *Klebsiella pneumoniae*
  - *Escherichia coli*
  - *Proteus mirabilis* (produce extended spectrum ß-lactamases)
- Include:
  - Cephalothin
  - Cefazolin
    - Cefazolin used in surgery prophylaxis
    - We do not give multiple prophylaxis for risk of super infections
  - Cephalexin
  - Cefadroxil
- Oral drugs are given for staphylococcal and streptococcal infections e.g.
  - Cellulitis
  - Soft tissue abscesses
  - Streptococcal pharyngitis caused by *Steptococcus pyogenes* as a second-line agent

Cephalothin

- Cephalothin - IV, poor BA and painful IM
- Useful in staphylococcus endocarditis
- Cefazolin more active against E. coli and klebsiella species and more sensitive to staph ß-lactamase than cephalothin
- Cephalothin tolerable IM and IV
- Cefazolin has lower renal clearance, has ling half-life and PPB of 85% and thus more frequently used

Cefalexin

- Given orally
- Antibacterial spectrum like the other first generation drugs
- Less active against penicillinase producing staphylococci
- Not metabolised
- 70 - 100% lost in urine

Cephadrine

- Similar to cephalexin in structure and activity
- Not metabolised and lost through the kidneys unchanged
- IM, IV, orally
- Well absorbed

Cefadroxil

- Analogue of cephalexin with higher concentration in plasma and urine
- Used in UTI

Second Generation Cephalosporins

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- More active against gram negatives
- Cefamandole contains methyl tetrathiazole (MTT) group which has disufiram-like effect and causes hypoprothrombinaemia and inhibition of vitamin K activation
- Broader spectrum than first generation
- Activity against enterobacter species,indole positive proteus and klebsiella species
- Strains of ß-lactamase producing H. influenzae are resistant to cefamandole
- Many gram positives are sensitive
- Excreted unchanged in urine
- High concentration in plasma after IM dose

Cefoxitin

- Cephamycin from strotomyces lactamdurans
- Resistant to some ß-lactamase produced by gram negative rods
- More active than cephalothin against some gram negative bacteria and more active than first and second generation cephalosporins (except cefotetan) against anaerobes especially B. fragilis
- Used in anaerobic and mixed aerobic-anaerobic infections

Other second generation antibiotics

- Cefaclor
  - orally given
  - Higher concentration in plasma in relation to cephalexin and more active against H. influenzae and M. catarrhalis
- Loracarbef
  - Orally given
  - More stable against ß-lactamase
- Cefuroxime
  - Similar to cefamandole in structure and antibacterial spectrum
  - More resistant to ß-lactamases and has no MTT group thus devoid of toxicities
  - Half-life is longer than cefamandole
  - CSF 10% of plasma but inferior to third generation in the treatment of meningitis
  - Cefuroxime axetil (Prodrug) ester is given orally with 30 - 50% being absorbed and the drug then being hydrolysed to cefuroxime

Cefotetan

- Cephamycin
- Activity against B. fragilis in relation to cefoxitin
- More active than cefoxitin against gram negative aerobes
- Has MTT and may cause bleeding preventable with administration of vitamin K

Third Generation Cephalosporins

Thursday, 15 June 2017 7:04 AM

Cefotaxime

- Cefotaxime - highly resistant to many but not ESBLs
- What are ESBLs?
  - Extended spectrum ß-lactamases
- Activity against many gram positive and negative aerobes
- Activity against B. fragilis is poor in relation to clindamycin and metronidazole
- Used in meningitis

Ceftizoxime

- Similar to cefotaxime in spectrum of activity
- Less active against Strep. Pneumoniae
- Not metabolised and 90% lost in urine unchanged

Ceftriaxone

- Similar spectrum
- Half life of 8 hours thus given OD or BD
- Meningitis treatment
- Eliminated by renal and hepatobiliary route
- Urethral, cervical, rectal or pharyngeal gonorrhoea

Cefixime

- Oral
- Less active against gram positives and active against gram negative in relation to the second generation agents
- Activity against enterobacteriaceae, ß-lactamase producing H. influenzae, M. ctarrhalis, N. gonorrhoeae and poor activity against staph. aureus

Cefpodoxime proxetil

- Oral
- More active against staph. Aureus

Third generation cephalosporins with antipseudomonal activity

- Cefoparazone - hepatobiliary loss and has MTT
- Ceftazidime

Fourth Generation

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- Include:
  - Cefaxime and cefpirome
- Stable to hydrolysis by many of the previously identified plasmid encoded ß-lactamases
- Active against gram negatives P. aeruginosa, MSSA
- No activity against MRSA
- Renal excretion 100% and good CSF penetration

Adverse Reactions

- Hypersensitivity reactions anaphylaxis, bronchospasms and rash
- Cross-reactivity with penicillin 20% immunologically but only 1% clinically
- Rarely bone marrow suppression
- Positive coombs test
- Nephrotoxicity renal tubular necrosis with cephaloridine
- Cephalothin high doses produce ATN
- Diarrhoea
- MTT and bleeding - cephamandole, cefotetan, cefoperazone and moxalactam

Aminocyclitol

Monday, 21 March 2016 10:01 AM

Spectinomycin
Antimicrobial activity

- Treatment of gonorrhoea
  - Resistant of first line drugs
- Selectively inhibits protein synthesis(30S)
- Bacteriostatic
- Resistance
  - Ribosomal resistance
  - Modification of drug by adenylytransferase

Pharmacokinetics

- Rapidly absorbed after IM
- Not bound to plasma proteins
- Secreted unchanged in urine
- Safe in pregnancy

Adverse effects

- Urticaria
- Chills
- Fever
- Dizziness
- Nausea
- Insomnia
- Pain at injection site

Streptogramins

Monday, 21 March 2016 10:05 AM

- Quinupristin aka Streptogramin B
- Dalfopristine aka Streptogramin A
- Both combined Q/D at 30:70 ratio
- Semisynthetic derivatives of pristinamycins
    - More soluble derivatives
    - Suitable for IV

Antimicrobial activity

- Active against gram + cocci
    - ß, &-haemolytic strains of streptococci
    - E.faecium
    - Coagulase +, negative strains of staph
- Bactericidal against strep, staph
- Bacteriostatic against E. faecium
- Inactive against gram - except:
    - Moraxella catarrhalis
    - Neisseria spp.
- Active against:
    - M. pneumoniae
    - Legionella spp
    - Chlamydia pneumoniae
    - Cause atypical pneumonia

MoA

- Protein synthesis inhibitors (50S)
- Quinupristine binds to the same site as macrolides
    - Inhibition of polypeptide elongation
    - Early termination of protein synthesis
- Dalfopristin binds at site nearby:
    - Synergistically enhancing binding of quinupristine at site
    - Interferes with polypeptide chain formation

Pharmacokinetics

- Used as combination
- Given IV - incompatible with saline, heparin
- Half-life is 50 minutes
- Volume of distribution is 0.8L/kg
- Metabolised in the liver
- Eliminated by biliary excretion (80%)

Clinical use

- Vancomycin resistant strains of E. faecium
- Complicated skin infections by methicillin-susceptible strains of S. aureus, S. pyogenes
- Nosocomial pneumonia, infections by MRSA

Adverse effects

- Infusion related (given through a central line)
    - Pain
    - Phlebitis
- Arthralgia, myalgia
    - More with hepatic insufficiency
    - Accumulation of metabolites
    - Reduce infusion frequency

Drug interactions

- Is a CYP3A4 inhibitor
    - Antihistamines (azelastine, clemastine)
    - Macrolide antibiotics
    - Ketoconazole
    - Antidepressants (fluoxetine, imipramine)
    - Tacrolimus
    - doxepin

Oxazolidinones

Monday, 21 March 2016 10:17 AM

Linezolid

- Active against gram +
  - Bacteriostatic: enterococci, staph
  - Bactericidal: strep
- Poor activity against gram -
- Moderate activity against mycobacterium tuberculosis

MoA

- Inhibits protein synthesis
- Binding to the P site of 50S ribosomal subunit
  - Prevents initiation of protein synthesis
- Active against other resistant strains
  - Penicillin resistant strains of S. pneumoniae
  - MRSA, VRSA
  - Vancomycin resistant enterococci

Pharmacokinetics

- Well absorbed orally
- 100% bioavailability
- Half-life is 4 - 6 hours
- 30% protein bound
- Distributes widely to well perfused tissues (0.6-0.7L/kg)
- Metabolised to aminoethoxyacetic acid, hydroxyethyl glycine derivatives
- 80% excreted in urine
  - 30% as active compound
  - 50% as 2 primary metabolites
- 10% excreted in faeces
- Eliminated by dialysis (give after haemodialysis)

Clinical use

- Vancomycin resistant E. faecium
- Nosocomial pneumonia by MSSA, MRSA
- Community acquired pneumonia by S. pneumoniae
- Complicated skin infections
- Should be reserved as alternative agent for multi-drug resistant strains

Adverse effects

- Well tolerated
- Myelosuppression
  - Anaemia
  - Pancytopenia
  - Leukopenia
  - Thrombocytopenia
- GIT complaints,Headache (Serotonin syndrome due to slight MAO inhibition)
- Rash
- Long term treatment (>8 weeks)

    - Peripheral neuropathy
    - Optic neuritis
    - Lactic acidosis
    - All are irreversible

Drug interactions

- Weak inhibitors of MAO
    - Avoid SSRIs, tyramine containing foods (chocolate, cheese)
    - Precipitate serotonin syndrome

Aminoglycosides

Tuesday, 22 March 2016 9:17 AM

Include
- streptomycin
- Neomycin
- Kanamycin
- Amikacin
- Gentamycin
- Tobramycin
- Sisomycin
- Netimicin

- Widely used for:
  - Gram negative enteric bacteria
  - Endocarditis (synergistic with vancomycin)
  - TB - first and second line

Physical and Chemical Properties
- Have a hexose ring
  - Streptidine (streptomycin)
  - 2-deoxystremptamine
- Water soluble
- Active in alkaline pH

MoA
- Irreversible inhibitors of protein synthesis
  - Interference with peptide initiation complex
  - Misreading of mRNA (non-functional protein)
  - Break up of polysomes
- Binds to specific 30S subunit ribosomal proteins

Mechanisms of resistance
- Production of transferase enzyme (main)
- Impaired aminoglycoside entry (mutation of a porin protein)
- Altered receptor on 30S subunit

Pharmacokinetics
- Poorly absorbed orally
- Well absorbed IM or IV
- Peak concentration in 60 minutes
- Given IV as an infusion
- Once daily dose
- Concentration dependent killing:
  - Higher the concentration, higher the proportion of the bacteria killed
- Significant post-antibiotic effect
  - Antibacterial activity persists beyond measurable drug
- Toxicity is both time and concentration dependent

    - Unlikely until certain concentration threshold achieved
    - Time above this threshold is critical
- Toxicity more with multiple smaller doses
- Highly polar (don't enter the CNS)
    - In meningitis, the concentration is 20% in CSF
- Concentration high in renal cortex, bile (30%)
- Half life is 2 hours
    - Increase to 48 hours in renal impairment
- Extensively cleared by the kidney
- Partially removed by haemodialysis
- Dosage adjustment in renal failure

Adverse effects

Ototoxicity

- Risk factors
    - Therapy for >5 days
    - Higher doses
    - Elderly
    - Renal insufficiency
- Auditory damage
    - Tinnitus, high-frequency hearing loss
    - Neomycin, kanamycin, amikacin are most ototoxic
- Vestibular damage
    - Vertigo, ataxia, loss of balance
    - Streptomycin and gentamycin are most vestibulotoxic

Nephrotoxicity

- Risk factors
    - As ototoxicity
    - Concurrent use
        - Loop diuretics
        - Nephrotoxic, antimicrobial agents (vancomycin, amphotericin B
        - neomycin, tobramycin and gentamycin

Others

- Curare like effect with neuromuscular blockade
    - Respiratory paralysis
    - Reversible by calcium gluconate, neostigmine
- Infrequent hypersensitivity

Clinical uses

- Gram negative enteric bacteria
- Combined with ß-lactam
    - To extend coverage (gram +)
    - Synergism
    - Enterococcal endocarditis
    - Shorten duration of therapy for infective endocarditis

Streptomycin

- Clinical Use
    - Used in mycobacterial infection - relapsed TB
    - Plague, tularaemia, brucellosis
    - Penicillin plus streptomycin for enterococcal endocarditis
- Adverse effects
    - Hypersensitivity

        - Prolonged course
        - Desensitisation is successful
    - Pain in the injection site
    - Vestibular dysfunction
    - Neonatal deafness (contraindicated in pregnancy)

Gentamycin
- Clinical uses
    - IM/IV
        - Severe gram negative infection (in combination)
    - Topical
        - Infected wounds
        - Prevention of IV catheter infections
        - Ocular infections (sub-conjuctival)
- Adverse effects
    - Reversible nephrotoxicity
    - Irreversible ototoxicity - vestibular dysfunction and hearing loss
    - Hypersensitivity (uncommon)

Tobramycin
- Pharmacology is similar to gentamycin
- Ototoxic and nephrotoxic
- Inhalation treatment of pseudomonas pneumonia in cystic fibrosis

Amikacin
- Semi-synthetic derivative of kanamycin
- Resistant to enzymes that inactivate gentamycin and tobramycin
    - Used for drug resistant organisms
- Used in multi-drug resistant - TB
- Cross resistant with kanamycin
- Nephrotoxic, ototoxic

Netilmycin
- Similar characteristics to gentamycin, tobramycin
- Active against resistant bacteria
- Interchangeable with gentamicin and tobramycin

Neomycin, kanamycin, paromomycin
- Similar properties
- Antimicrobial properties
    - Active against gram +, gram -, some mycobacteria
    - Resistant to pseudomonas, streptococci
    - Cross resistance with kanamycin, neomycin
- Pharmacokinetics
    - Poorly absorbed
    - Intestinal flora when taken orally, are suppressed
    - Excreted in faeces
    - Not given parenterally because of high toxic profile
- Clinical uses (topical, oral)
    - Infected skin lesion
    - Injected into joints, pleural cavity, abscess
    - Preparation for elective bowel surgery (oral)
    - Hepatic coma (suppresses normal flora, reducing ammonia production)
        - Occurs in patients with liver failure because they cannot detoxify molecules in the blood…increased plasma concentration (ammonia) and may get into the

brain and cause coma
    - Intestinal amoebiasis (paromomycins)
- Adverse effects
    - Nephrotoxicity
    - Ototoxicty
    - Curare like neuromuscular blockade
    - Allergic reactions (prolonged application)

Sulphonamides and Related Compounds

Monday, 4 April 2016 9:29 AM

- Inhibit bacterial folate synthesis
- Inhibit
  - Both gram + and - bacteria
  - Norcardia
  - Chlamydia trachomitis
- Are bacteriostatic
- Soluble in alkaline solutions

MoA
- Are PABA (p-aminobenzoic acid) analogues
- Inhibits dihydropteroate synthase
- Mammalian cells depend on exogenous sources of folate (not affected)

Resistance
- Lack enzymes for folate synthesis
- Overproduction of PABA
- Low affinity for sulphonamides
- Impaired sulphonamide permeability

Classification
- Oral absorbable
- Oral non-absorbable
- Topical

1. Oral absorbable
   - Examples
     - Sulphacytine
     - Sulphisoxazole
     - Sulphamethizole
     - Sulphamethoxazole
     - Sulphapyridine
     - Sulphadiazine
     - Sulphadoxine
   - Pharmacokinetics
     - Widely distributed (CNS, placenta, foetus)
     - 20 - 90% plasma protein bound
     - Metabolised by acetylation, glucoronidation
     - Excreted in urine (dose adjustment)
   - Clinical uses
     - UTIs
     - Acute toxoplasmosis (sulphadiazine + pyrimethamine)
     - Malaria (sulphadoxine + pyrimethamine)
     - Sulphamethoxazole + trimethoprim (Cotrimoxazole):
       - Pneumocystis jirovecii pneumonia
       - Toxoplasmosis
       - Nocardiosis
2. Oral non-absorbable
   - Include sulphasalazine
   - Used in inflammatory bowel disease

        - Ulcerative colitis
        - Enteritis
3. Topical
    - Examples
        - Sodium sulphacetamide
            - Bacterial conjuctivitis
            - Trachoma
        - Mafenide acetate
            - Burns
            - Absorbed from site (metabolic acidosis)
        - Silver sulphadiazine
            - Less toxic
            - Prevent infection of burn wounds

Adverse effects

- Fever
- Exfoliative dermatitis, photosensitivity, urticaria
- Nausea, vomiting and diarrhoea
- Stevens-Johnson's syndrome
- Urinary tract - precipitate in acid pH (crystalluria) - urinary alkalinisation
- Haemolytic anaemia, bone marrow suppression

Pregnancy

- Kernicterus in new-born
    - Used in last trimester
    - Displacement of bilirubin from plasma protein
    - Free bilirubin enters into the CNS
    - Presents with jaundice and neurological problems such as flaccidity and convulsions

Trimethoprim, Pyrimethamine

MoA

- Anti-folate agents
- Inhibit bacterial and protozoal dihydrofolate reductase
    - TMP is x50,000 less efficient
- Synergistic action when combined with sulphonamides (bactericidal)

P'kinetics

- TMP given orally alone
- TMP-SMX combination - oral, IV
- Well absorbed
- TMP is more lipid soluble than SMX (larger volume of distribution)
- 50% excreted in urine
- TMP concentrates in prostatic and vaginal fluid
    - High antibacterial activity

Resistance

- Reduced of cell permeability
- Overproduction of dihydrofolate reductase
- Altered reductase with reduced drug binding

Clinical uses

- Oral TMP
  - UTI
- Oral TMP-SMX
  - UTI
  - URTI
  - Otitis media
  - PCP pneumonia
  - Prostatitis
- IV TMP-SMX
  - Severe PCP pneumonia
  - Gram - bacterial sepsis
  - UTI
- Oral pyrimethamine and Sulphadiazine
  - Leishamaniasis
  - Toxoxplasmosis
- Pyrimethamine and sulphadoxine
  - Malaria

Adverse effects
- Similar to sulphonamides

Folinic Acid
- Prevention of bone marrow toxicity with high doses of TMP, pyrimetamine
- Converted to tetrahydrofolate in cells
- Does not require action of dihydrofolate reductase

Other Antibiotics

Tuesday, 5 April 2016 9:41 AM

They include:

- Bacitracin
- Polymixins
- Vancomycin
- Fosfomycin

Bacitracin

- A cyclic peptide mixture, first extracted from a tracy strain of bacillus subtilis in 1943
- Antibacterial action
- Active against gram + bacteria
-

MoA

- Inhibits cell wall synthesis by interfering with dephosphorylation of bactoprenol.
- That transfers peptidoglycan subunits to the growing cell wall
- No cross resistance with other antibiotics

P'kinetics and Clinical use

- It I poorly absorbed and highly nephrotoxic when given systemically. Only used topically
- Action topically is local, no systemic toxicity
- Given as an ointment, 5000 units per gram. Often combined with polymixin or neomycin
- Indicated for mixed infections on the skin, wounds or mucous membranes
- Solutions containing 100 - 200 units per ml in saline used to irrigate joints, wounds, pleural cavity

Vancomycin

- Produced by streptococcus orientalis
- Active only against gram + bacteria especially staphylococcus and flavobacterium

Chemistry

- A glycopeptide, MW 1500 is water soluble and stable

MoA

- Inhibits cell wall synthesis by binding to the D-ala-D-ala terminus of newly formed pentapeptide. This inhibits the transglycosylase, preventing further elongation of peptidoglycan and cross-linking. The peptidoglycan becomes weak, cell becomes easily lysed. The cell membrane is damaged.

Resistance

- Enterococci and resistant S. aureus have modification of the D-ala-D-ala binding site of the peptidoglycan building block. Terminal D-ala replaced by D-lactate

Antibacterial activity

- Bactericidal for gram +, ß-lactamase producers and those resistant to nafcillin and methicillin. Kills slowly and only dividing cells
- Synergistic with gentamycin and streptomycin against Enterococcus faecium and E.

faecalis

P'kinetics

- Poorly absorbed orally, only given IV.
- Half life is 1 - 2 hours
- Widely distributed in the body. CSF has 7 - 30% serum concentrations in meningitis
- 90% excreted by glomerular filtration, Half-life in anephric patients, 6 - 10 days. Not removed by dialysis

clinical uses

- Vancomycin for methicillin resistant staphylococci in endocarditis and in sepsis
- Combined with gentamycin, an alternative to treatment of enterococcal endocarditis in those with penicillin allergy
- In combination with cefotaxime, ceftriaxone or rifampicin in meningitis caused by highly penicillin resistant pneumococcus
- Usual dose 30mg/kg/d in 2 - 3 divided doses
- For most infections, typical dose is 1gm BD. In children, 40mg/kg/d in 3 - 4 divided doses
- Anephric patients 1gm once weekly
- Oral vancomycin 0.125 - 0.25gm 6 hourly for pseudomembranous colitis. In these cases metronidazole is the first choice, vancomycin is the second choice

Adverse reactions

- Seen in 10%. Most are minor
- Irritation to the tissues, may cause phlebitis
- Ototoxicity and nephrotoxity are rare. Mixing with other ototoxic or nephrotoxic drugs increases chances
- Redman or red neck syndrome

Teicoplanin

- A glycopeptide antibiotic very similar to vancomycin in MoA and antibacterial spectrum
- Given both IV and IM
- Half-life is 45 - 70 hours
- Has less toxicity but not commonly used

Daptomycin

- A cyclopolypeptide fermentation product of streptomyces roseosporus
- Spectrum of activity is similar to vancomycin only that it is more rapidly bactericidal and is active against vancomycin resistant enterococci and S. aureus
- MoA not clear
- Doses 4mg/kg for skin and soft tissue infections and 6mg/kg for bacterimia and endocarditis OD in normal renal patients, but alternate days in RF
- Excreted renally
- Adverse effects
    - Myopathy.
    - Surfactants destroys its actions

Fosfomycin

- Comes as fosfomycin trometamol, a stable salt
- An analogue of phosphoenol pyruvate.
- Inhibits the enzyme enolpyruvate transferase by binding to its cysteine residues blocking addition of phosphoenol pyruvate to UDP-N-acetylglucosamine. This is the first step in

formation of N-acetyl muramic acid
- Transported into cells by glycerophosphate or glucose-6-phosphate transport systems
- Resistance due to failure of the pumps
- Active against both gram positive and negative
- Synergistic with beta-lactams, aminoglycosides and fluoroquinolones
- Oral bioavailability 40%. Dose 2 - 4g OD
- Half-life is 4hours
- Excretion is urinary
- For UTI as 3gm dose
- Safe in pregnancy

Cycloserine
- Produced by streptomyces orchidaceus. Water soluble, very unstable in acid pH
- Inhibits many gram + and - organisms, but is almost exclusively used as second line in the treatment of TB, when there is failure of the first line of drugs
- Structural analogue of D-alanine, inhibits the cell wall synthesis by inhibiting alanine racemase and D-alanyl-D-alanine ligase
- 250mg gives blood levels of 20 - 30mcg/ml. this is enough to inhibit TB and may gram negatives. Widely distributed in tissues
- Most of it is excreted in urine unchanged
- Causes serious dose related CNS adverse effects including headaches, tremors, acute psychosis and convulsions
- Adverse effects minimal at total doses below 750mg/d
- Usual anti-TB doses 0.5g/d in 2 - 3 doses

Polymyxins
- A group of basic peptides active against gram - organisms
- Include polymyxin B, polymyxin E (colistin)
- Act like cationic detergents. Attach to and disrupt bacterial cell membranes. Also bind and inactivate endotoxins
- Gram +, proteus and neisseria are resistant
- Largely restricted to topical use because of systemic toxicity. Commonly, preps are mixed with neomycin, bacitracin as creams, polymyxin B 0.5mg/g for skin infections
- Colistin is a parenteral prep for salvage treatments of resistant strains of acinetobacter, pseudomonas

Anti-TB Drugs

Tuesday, 3 May 2016 10:12 AM

- TB is a chronic multisystem disease which kills untreated.
- Problem now is Multi-Drug Resistance (MDR)
- Drugs divided into first and second line
  - First-line:
    - Are very effective and have less adverse adverse effects.
    - Treatment is with combination therapy of 6 - 24 months
      - INH
      - Rifampicin
      - Pyrazinamide
      - Ethambutol
      - Streptomycin

Isoniazid (INH)

- Introduced in 1952 and is the most active anti-TB drug
- Included in all regimens
- Isonicotinic Acid Hydrazide. A small simple molecule freely water soluble.
- Structurally similar to pyridoxine

Antibacterial activity

- Mic 0.2mcg/ml
- Bactericidal for actively growing bacilli
- Kills both intracellular and extracellular organisms
- Less effective against atypical mycobacteria except M. kansasii

MoA

- Thought to involve inhibition of mycolic acid, interfering with bacteria cell wall
- Addition of pyridoxine prevents neuritis but does not influence antibacterial activity

P'Kinetics

- Readily absorbed in the gut
- Peak plasma levels within 1 - 2 hours
- Readily diffuses into all body fluids and tissues.
- CNS and CSF concentrations are 20% to 100% on that in plasma
- Intracellular and extracellular concentrations are the same
- Metabolised in the liver by acetylation followed by conjugation and excretion in the urine.
- A small quantity is passed in the urine unchanged
- In renal failure give normal doses. In liver failure, give less doses
- Acetylation under genetic control
- Half-life in fast acetylators is 1.5 hours, while in slow acetylators, 3 hours
- Fast acetylators are prone to hepatotoxicity and slow acetylators to peripheral neuropathy

Clinical Use

- Usual dose is 5mg/kg, maximum in adults is 300mg/day, children 10mg/kg/day
- Prophylactic pyridoxine - 10mg/100mg INH
- Prophylaxis
  - Persons converting from negative to positive skin tests - 5 - 10mg/kg for 1 year
  - Household and very close people to new cases
  - Skin positives undergoing immunosuppressive therapy

Adverse Effects

- Incidence and severity is dose related
- Allergic reactions - fever, skin rashes, hepatitis
- The most common toxic effects, 10% - 20% are in the CNS and peripheral nervous system - peripheral neuritis, insomnia, restlessness, fasciculation, psychotic episodes, convulsions
- Hepatotoxicity
  - 1% clinical, 10% subclinical
  - Abnormal LFTs, jaundice, multi-lobular necrosis
  - Some fatal
  - Rarely <20years, 1 - 5% in 20 - 50 years, 2.5% in >50 years
  - Higher risk in alcoholics
  - Haemolysis in G6Pdeficients
  - INH may reduce phenytoin metabolism

Signs of TB infection

- Chronic cough for more than 2 weeks with blood in the sputum (haemoptysis)
- Night sweats and fevers
- Weight loss of more than 10% of total body weight within 1 month

Diagnosis

- Microscopy of the sputum
  - Alcohol fast bacteria
  - Use Ziehl-Nielson
- Culture of bacteria in pulmonary or pericardial effusion
- Gene expert test of the sputum

Treatment

Rifampicin

- Is a large complex semisynthetic derivative of rifamycin, an antibiotic produce by the fungus streptomyces mediterranai

MoA

- Binds strongly to DNA dependent RNA polymerase, inhibiting DNA synthesis in bacteria and chlamidiae
- The human DNA is unaffected
- It also blocks the late stage of assembly of pox viruses and interfering with envelope formations

Antimycobacterial activity

- Active in vitro against:
  - Some gram+ and -ve cocci
  - Some enteric bacteria
  - Mycobacters
  - Chlamidiae
  - Pox viruses
- Many meningococci and mycobacteria are inhibited by 1mcg/ml. highly resistant mutants occur in all bacterial populations at a rate of $1:10^7$ or more
- There is no cross resistance with other antimycobacteria
- Rifampicin is bactericidal for mycobacteria and tends to sterilise infected tissues, cavities or sputum when given with INH
- It penetrates phagocytes well and kills both intracellular and extracellular bacteria

P'Kinetics

- Well absorbed orally
- Widely distributed in tissues and body fluids
- Excreted mainly through the liver in bile and faeces
- Small amounts are excreted in the urine
- It undergoes enterohepatic circulation
- Usual doses give serum levels of 5 - 7 mcg/ml
- CSF levels 10 - 40% of serum levels

Clinical Uses

- In TB, whichever form
- Usual dose 600mg/d (10 - 20 mg/kg/d) orally.
- Given together with INH, ethambutol or other anti-TB drugs. some regimens given twice weekly 600mg
- In atypical mycobacterial infections, same regimen
- Leprosy
  - Effective when given with a sulphones
- Meningococcal carriers
  - Eliminates majority of meninigococcal bacterial from carriers 600mgb.d X2/7. Up to 10% may be resistant
- Prophylaxis in contacts of children with H. influenzae type B disease
- Staphylococci carriage in nasopharynx. Rifampin combined with trimethoprim-sulphamethoxazole, may eradicate staphylococci in nasopharynx

Adverse effects

- Occasionally rashes, thrombocytopenia, nephritis, impaired liver function
- Commonly causes light chain proteinuria and may impair antibody response
- Flu-like syndrome and anaemia
- Harmless orange colouration of urine, saliva, sweat, tears, contact lenses

Interactions

- Induces microsomal enzymes
- Increases elimination of anticoagulants and contraceptives
- Significant lower serum levels of ketoconazole, cyclosporine, chloramphenicol when given with rifampicin concomitantly
- Methodone - rifampicin increases urinary excretion. Lowers plasma concentration and may cause methadone withdrawal signs

Ethambutol

- A synthetic, water soluble, heat stable compound.
- Preparations are those of the d-isomer as the dihydrochloride salt

MoA

- Inhibits mycobacterial arabinosyl transferases
  - The transferases catalyse the polymerisation of arabinoglycan, an essential

component of mycobacterial cell walls

Antimycobacterial Activity

- Many strains of M. tuberculosis and other mycobacteria are inhibited in vitro by 1 - 5 mcg/ml concentrations

P'Kinetics

- Well absorbed from the gut
- After 25 mg/kg, peak blood levels of 2 - 5 mcg/ml is reached in 2 - 4 hours
- In meningitis, CSF levels are 10 - 40% serum levels
- 20% is excreted in faeces and 50% excreted in unchanged form. Excretion is delayed in renal failure

Clinical Use

- It is given in combination with other anti-TB drugs
- Dose - 15mg/kg o.d, max up to 25mg/kg/d

Adverse Effects

- Hypersensitivity - rare
- Visual disturbances
  - The most important and commonest adverse effect
  - Reduction in visual acuity
  - Optic neuritis
  - Retinal damage in some patients receiving 25mg/kg/day for several months
- It is reversible when the drug is discontinued
- Rare with $\leq$ 15 mg/kg/d

Pyrazinamide

- Structurally similar to nicotinamide.
- Is stable, slightly soluble in water
- Quite expensive
- It is converted into pyrazinoic acid, the active metabolite by pyrazinamidases of mycobacteria

Mechanism of Action

- Unknown

Antibacterial Activity

- At pH 5, it strongly inhibits the growth of M. tuberculosis and some other mycobacteria at concentrations of 15 mcg/ml
- This is achieved by daily oral doses of 1.5 - 2g (20 - 30 mg/kg/d)
- It maybe given as:
  - 0.75g twice daily
  - 1.5 - 2g once daily
  - 50 - 70mg/kg thrice weekly

Pharmacokinetics

- Well absorbed from the gut
- Widely distributed in body tissues
- Resistance develops fairly readily, but no cross resistance with INH other anti-mycobacterial drugs

Adverse Effects

- Hepatotoxicity in 1- 5%
- Nausea and vomiting
- Drug fever
- Hyperuricemia

Streptomycin

- Isolated from the streptomyces griseus by Waksman and Associated in 1944
- It is water soluble, stable in solution, more active at alkaline than acidic pH
- May form complexes with ß-lactam drugs in vitro, losing some activity

MoA

- Binds to the 30S subunit of bacterial ribosomes irreversibly, inhibiting protein synthesis in 3 ways:
  - Interfering with the initiation complex of peptide formation
  - Induces misreading of the code on mRNA template
  - Breaks down polysomes into non-functional monosomes
- It is bactericidal for susceptible organisms

Mechanisms of Resistance

- Alteration in cell surface
- Receptor proteins on 30S may be deleted or altered by chromosomal mutation
- Production of enzymes that inactivate the aminoglycoside by adenylation, acetylation, phosphorylation. This is the main mechanism and is plasmid controlled

Antibacterial Activity

- Resistance present in most bacterial species, except tularaemia, brucellosis, gram- aerobic bacteria
- Emergence of resistance is rapid. Therefore, if used alone, limit to 5 days use

Pharmacokinetics

- Little is absorbed or not at all in the gut, but may be absorbed if there are ulcers present
- IM
    - Well absorbed, giving each peak concentration in the blood within 30 - 90 minutes.
    - Occasionally given IV.
    - Only 10% plasma protein bound
- Being highly polar, it does not enter cells readily.
- Doesn't normally reach the CNS,
- When inflammation is present in meningitis, CSF levels may reach 20% _
- Concentration in the renal cortex is high
- Concentrations in most secretions are modest - bile, 30% of the blood level
- Synovial and pleural fluids - 50 - 90% in prolonged treatment
- There is no significant metabolic breakdown
- Half life is _
- _

Clinical uses

- Therapeutic plasma levels is 10mcg/ml
- Usual dose is 30mg/kg in adults and 15mg/kg in children
    1. Mycobacterial infections
        - Usually used here as the initial therapy in re-treatment cases, non-compliance and is a severe disease in combination with other anti-TB drugs
        - 1gm/d IM for the first 60 days, those <45kg 750mcg, small patients 500 mg. Cumulative dose should normally not exceed 100g
    2. Non-tuberculous infections
        - Plague, tularaemia, brucellosis
        - 1g/d IM (1.5mg/kg/d in children)
    3. Combination treatment
        - In infective endocarditis, caused by the faecal streptococci (enterococci) or viridans streptococci and bacteraemia with some gram- aerobic bacteria e.g, pseudomonas spp. Especially in immunodeficient patients
        - Combined with penicillins, they are bactericidal

Adverse effects

- Allergy
    - Fever skin rash, hyoersensitivity
        - Hypersensitivity due to body contact or prolonged use
        - Desensistise
- Toxicity
    - Pain at injection site
    - Vestibular disturbance
        - There is vertigo which is dose dependent
        - Partial recovery occurs on withdrawal
        - Nerve deafness
        - The phosphate preparetion causes cochlear toxicity while the sulphate preparation causes vestibular toxicity
        - In pregnancy, it causes deafness in the newborn
        - GIT nausea nad vomiting
        - Headache
        - Nystagmus and ataxia
        - Renal toxicity
        - Respiratory paralysis in myasthenia gravis

Second-line Anti-TB Drugs

Capreomycin
- Dose - 1gm IM/d (20mg/kg/d)
- Causes kidney toxicity, 8th nerve damage
- There is less toxicity if schedule is 1g 2 - 3times weekly

Cycloserine
- It is produced by strep orchidaceus
- It is an analogue of D-serine and acts by inhibiting alanine racemase
- Theraeutic leels 5 - 20mcg/ml
- Dose - 250 - 500mg BD, max 1gm/d
- For UTI - 15 - 20mg.kg.d
- It causes CNS toxicity and psychotic reaction

Ethionamide
- It is closely related to INH
- Initially give 250mg b.d, then increase to 15 - 20mg/kg/d
- High doses are not well tolerated. It causes:
  - Gastric irritation
  - Neueologic symptoms
- Resistance to it develops rapidly

P-aminosalicyclic acid (PAS)
- It is a derivative of salicyclic acid an benzoic acid and is closely related to pPABA and sulphonamides
- Atypical mycobacteia are resistant to it
- Doses
  - 8 - 12 g/
  - _
- It is absorbed readily
- Orally given
- Wiely distributed within the body tissues and fluids except for CSF
- Half-life is 1 hour
- It is rapidly excreted in urine as acetylated and other metabolites.
- A small portion is excreted unchanged
- High concentrations are reached in the urine

Adverse effects
- GIT
  - Anorexia
  - NVD
  - Epigastric pains and burning
  - Given with meals or antiacids to reduce this
  - Peptic alceration and haemorrhage may occur
- Kidney or liver damage, thyroid gland inury, metabolic acidosis are rare
- Drug fever, joint pains, skin rashes, granulocytopaenia and a variety of neurologic symptoms often occur at 3-8 weeks. Stop treatment for there

Violycin
- Given as 2g IM twice weekly
- Resistance emerges rapidly
- It has cross resistance with streptomycin, kanamycin, capreomycin
- Adverse effects
  - Kidney damage
  - 8th nerve damage

Ansamycin
- Derived from Rifamycin
- Is slightly active against - M. avium, M. intracellulare, M. fortutium
- Usual dose - 0.15 - 0.5g/d

Kanamycin/amikacin

Fluoroquinolones
- Ciprofloxacin 750mg BD
- Levofloxacin 500 - 750 OD, orthofloxacin
- Gatifloxacin, moxifloxacin 400mg OD
  - Inhibits some strain of M. tuberculosis at concentrations of less than 2mcg/ml.
  - Moxifloxacin is the most active against M. tuberculosis
- Levofloxacin more than ciprofloxacin against M. tuberculosis but ciprofloxacin more active on atypical mycobacteria. Used with at least 2 or more other active agents

Linezolid

Rifabutin/Rifapentin

Others are active against atypical mycobacteria aew doxycycline, clarithromycin, micocycline, macrolides

Combination Regimens
2RHZE/4RHE
2RHZE/7HE - most commonly used
2SRHZE/7HE - severe disease and non-compliance

Manyatta regimes
Drugs active against atypical mycobacteria

- Determined by culture studies
- Clofazimine and Kanamycin have been effective at times
- Ethambutol, INH, erythromycin, ethionamide, minocycline, rifampin, streptomycin, cycloserine, capromycin, tetracyclines

R- rifampicin
H - isoniazid
Z - pyrazinamide
E - ethambutol
S - streptomycin

Leprosy and its Treatment

Tuesday, 10 May 2016 9:42 AM

- Also known as Hansen's disease
- It is very contagious
- Starts with flat macular lesions that are discoloured. The discolouration spreads and nodules form
- Caused by Mycobacterium leprae
  - It is an acid alcohol fast bacteria
- Definitive diagnosis is both clinical and microbiological mechanisms
  - Skin biopsy and stains are made
- No culture media for M. leprae
  - Injected into armadillo foot pads and false colonies grow for analysis
- Patients have enlarged and hardened peripheral nerves
  - Patients suffer from numerous neuropathies
    - Loss of sensation leading to traumatic injury
- Untreated, patient dies from wounds and other infections
- 4 major drugs used for treatment
  - Sulphone - dapsone (diaminodiphenylsulphone)
    - Cornerstone drug
  - Rifampicin
  - Clorfazimine
  - Amithiozone

Dapsone

- Structure closely related to that of sulphonamides
- MoA is also the same
- Folate synthesis inhibitor
  - Competitively inhibits dihydropteroate synthase

Antimycobacterial Activity

- Catalyses the reaction between PABA and pteridine to form pteroic acid
- Residues of glutamate are added to pteroic acid to form folic acid
- Very effective M. leprae
  - Inhibits folic acid and therefore DNA and RNA are not formed and the organisms cannot replicate, transcribe and produce proteins (metabolically immobilised)
- Given alone, there is always a colony of bacteria that resistance will emerge rapidly especially in low doses
- Effective against P.C.P in AIDS patients
- Also has antimalarial action

Pharmacokinetics

- Well absorbed from the gut and widely distributed in the body tissue s and fluids
- Half-life is 1 - 2 days
- Tends to be retained in the skin, muscle, liver and kidneys
- Excreted in the bile and undergoes enterohepatic circulation
  - Long half-life
- Excretion in urine is variable, most is excreted acetylated. Dose may be adjusted in renal failure

Clinical Use

- Leprosy
  - Dose - 25 - 50 mg/week initially increasing one tablet weekly until full dose of 100mg once daily is reached
  - Initial treatment is in combination with rifampicin - 600mg/month and with clorfazimine - 300mg/month and 50mg/day
  - Treatment up to 12 months with lepromatous leprosy
- P.C.P
  - Treatment and prophylaxis
- Combined with pyrimethamine
  - Maloprim is the product

Adverse reaction

- Haemolysis
  - Especially in G6PD deficiency
  - Methaemoglobinaemia
  - GIT intolerance
  - Fever
  - Pruritus
  - Rashes
  - Erythrema nodosum leprosum often occur during lepromatous leprosy treatment.
    - May be suppressed by steroids or thalidomide (no pregnant women)

- Lepromatous leprosy
  - Patient has lowered immunity and the lesions are macular and also nodular
  - Concentration/density of bacteria is very high
  - Treated for 12 months
- Tuberculoid/tuberculous leprosy
  - Found in patients with good immunity
  - Lots of nodules but lesions are mainly macular
  - Biopsy reveals low density of bacteria
  - Treated for 6 months
- Borderline leprosy
  - Borderline lepromatous leprosy
    - Rx for 6 months
  - Borderline tuberculoid leprosy
    - Rx for 12 months

Acedapsone

- acedapsone (4, 4 diacetamidodiphenyl sulphonate) is a repository form of dapsone
- Single IM injection of 300mg can maintain inhibitory levels up to 3 months
- Several other sulphones have also been used
- When tolrance develops, it is all to sulphones

Rifampicin

- 600mg/daily used in LL
- 600g/month in combination therapy

Clofazimine

- A phenazine dye that can be used as an alternative to dapsone
- MoA is unknown
- Thought to bind to DNA

Pharmacokinetics

- Orally given
- GIT absorption is variable
- Major portion is excreted in the faeces
- Much of the drug is stored widely in the RES and skin.
- Its crystals can be seen from inside phagocytic RES cells.
- It is slowly released from these deposits
- Serum half-life is about 2 months
- Only a small portion is excreted into urine and bile

Clinical use

- Sulphone resistant leprosy or intolerance, doses 100 - 300mg/d orally
- In combination therapy
    - 50 - 100mg/d
- In combination therapy to treat for atypical mycobacteria M. avium - intracellular infection in AIDS

Adverse Effects

- Mainly skin discolou□rations, ranging from red brown to nearly black
- GIT intolerance occasionally

Amithiozone

- A thiosemicarbazone employed as a substitute in dapsone intolerant patients.
- It is more effective in TL patients
- Dose is 150mg/d or 450mg/weekly
- Resistance may develop if given alone

Adverse effects

- GIT intolerance frequent
- Hepatic damage

for atypical mycobacteria□

Antifungal Agents

Monday, 16 May 2016 9:17 AM

Classification

- Systemic antifungal agents
  - Systemic infections
    - Amphotericin B
    - Flucytosine
    - Azole antifungals
    - Pneumocandins
  - Mucocutaneous infections
    - Griseofulvin
    - Terbinafine
- Topical antifungal agents
  - Azole antifungals
  - Cyclopirox olamine
  - Haloprogin
  - Allylamines
  - Polyene antifungals
- Miscellaneous
  - Undecylenic acid (fungistatic)
  - Whitefields's ointment = benzoic acid + salicylic acid
  - Proprionic acid + caprylic acid
  - Potassium iodide
    - Cutaneous sporotrichosis
  - Gentian violet

Amphotericin B

- Polyene, macrolide antibiotic
- Formulations
  - Amphotericin B - deoxycholate complex (DOC)
  - Lipid formulations
- Lipid formulations vs DOC
  - Less nephrotoxic
  - More expensive
- Broadest spectrum of antifungal activity
  - Candida spp
  - Cryptococcus neoformans
  - Blastomyces dermatitis
  - Histoplasma capsulatum
  - Aspergillus
  - Coccidiodes immitis
  - Paracoccidiodes braziliensis
- Limited antiprotozoal activity
  - Leishmania braziliensis
  - Naegleria fowleri
- No antibacterial activity
- MoA
  - Fungicidal
  - Binds on ergosterol on fungal cell membranes
  - Leads to formation of pores
  - Increased permeability of the cell membranes
  - Leakage of molecules
  - Cell death
- Mechanism of resistance
  - Failure to penetrate fungal cell wall
  - Reduced binding
    - Ergosterol replaced with precursor sterols
    - Decreased membrane concentration of ergosterol
- PK
  - Can be administered Iv, IT, Intraocular
  - Can be used through Bladder irrigation

    - Oral - For fungal infections in the GIT
    - 90% bound to beta lipoproteins
    - Widely distributed
        - Penetrates CSF = 2-3% of plasma levels
    - Half life is 15 days
    - Excreted through urine
    - Metabolised in the liver
        - Dose not altered in liver and renal disease
- Drug of choice for any life-threatening mycotic infection
    - Rapidly progressive
    - Immunosuppressed individuals are susceptible
    - Worst when it involves CNS
- Adverse effects
    - Infusion related toxicity
        - Immediate reaction (~30 - 40 minutes)
        - Fevers and chills
        - Hyperpnoea, hypotension, vomiting, headache
        - Muscle spasms
        - Rare - bronchospasms and anaphylaxis
        - Caution - cardiac and pulmonary disease
        - Test dose
        - To avoid infusion related toxicity:
            - Give premedication
                - Antipyretics - NSAIDS
                    - Acetaminophen/paracetamol
                - Meperidine
                - Hydrocortisone
                - Antihistamines
            - Slowing infusion rate
            - Decreased therapeutic dose
    - Slower toxicity
        - Azotaemia (80% of patient) - dose dependent and transient
            - Acute renal failure (reversible)
                - Reduced renal perfusion
                - Administer 1L of normal saline before administration of Amphotericin B
            - Renal tubular injury (irreversible)
                - >3 - 4g in adults
        - Hypochromic normocytic anaemia
            - Inadequate erythropoietin production
        - Others
            - Chemical arachnoditis
            - Fever and headache
        - Thrombocytopoenia
        - Malaise
        - Weight loss
        - Phlebitis
        - Abnormal liver tests

Flucytosine

- Fluorinated pyrimidine analog
- Narrower spectrum of activity than amphotericin B
    - Cryptococcus neoformans
    - Candida spp
    - Agents of chromoblastomycosis
- It is transported into fungal cells by cytosine permease

- Metabolism

Fluorocytosine
↓→ cytosine deaminase
5-fluorouracil (5FU)
↓→ UPRTase or UMP Pyrophosphorylase
5-fUMP (fluorouracil monophosphate) or 5-FdUMP (5-fluorodeoxyuracil Monophosphate)

    - 5-fUMP is diphosphorylated to 5-fUTP and incorporated into RNA
        - Disrupts protein synthesis
    - 5-FdUMP is a Thymidylate synthase inhibitor

        - Inhibits DNA synthesis
- Resistance
    - Secondary resistance - monotherapy
    - Reduced activity of cytosine deaminase
    - Reduced activity/deficiency of UMP pyrophosphorylase
    - Loss of the cytosine permease necessary for flucytosine transport
- PK
    - Administered orally
    - Rapidly absorbed in GIT (90%)
    - Well distributed in body fluid including CSF (65 - 90% of plasma concentration)
    - Very little is bound to plasma proteins
    - 80% of the drug excreted unchanged
    - Half-life is 3 - 6 hours
        - Increased up to 200hrs in renal failure
- Indications
    - Cryptococcal meningitis
        - With amphotericin B
        - Synergistic effect (Amphotericin B causes formation of pores)
    - Chromoblastomycosis
        - With itraconazole
        - Synergistic effect
- Adverse effects
    - Bone marrow suppression (most common)
        - Anaemia
        - Leukopoenia
        - Thrombocytopoenia
        - When patient
            - has underlying disease that causes bone marrow suppression
            - In radiation therapy
            - When taking drugs that suppresses bone marrow
    - Rash
    - NVD, severe enterocolitis
    - Increased liver enzymes
- Narrow therapeutic window
    - Plasma concentration especially if combined

Mammalian cells do not convert

Azole antifungals

- Imidazoles
    - Clotrimazole
    - Micornazole
    - Ketocornazole*
        - Only used systemically
        - The rest are topical
    - Econazole
    - Butoconazole
    - Oxiconazole
    - Sulconazole
- Triazole - all used systemically
    - Itraconazole
    - Terconazole
        - Not systemically used
        - The rest are
    - Fluconazole
    - Voriconazole
    - Posaconazole
- Antifungal activity
    - Candida spp
    - H.capsulatum
    - Coccidiodes immitis
    - P.braziliensis
    - Dermatophytes (ring worm fungi)
    - Aspergillosis spp
- Resistance
    - Candida krusei
    - Agents of mucormycosis
    - Bacteria

    - Parasites (except Leishmania major)
- MoA
    - Inhibit sterol 14-α-demethylase
        - Impair synthesis of ergosterol
    - Increases 14-a-demethylase
        - Decreased enzyme function and inhibit fungal growth
    - Inhibit CYP450 in fungal cells > human cells
        - Imidazoles less selective than triazoles >drug interactions and AE
- Mechanisms of Resistance
    - Mutations of gene for 14-α-demethylase
        - Cross resistance to all azoles
    - Increased production of 14-α-demethylase
    - Decreased azole influx by:
        - ATP-binding cassette (ABC) transporters
        - Major facilitator superfamily (MFS) transporters
- Most common AE for azoles
    - Minor GIT upset
- All azoles cause
    - Altered liver enzymes
    - Very rarely, clinical hepatitis

Ketoconazole

- Has > propensity to inhibit human CYP450 than itraconazole or fluconazole
- Drug interactions are common
- Inhibits adrenal and gonadal steroid synthesis
- PK
    - Oral
    - Acidic environment needed for dissolution (PUD treatment, didanosine)
    - 84% bound - plasma proteins
    - 15% bound - RBC
    - 1% free
    - Half-life increases with dose
        - Up to 7 - 8 hours
    - Little excreted through urine
- Drug interaction
    - Ketoconazole + rifampicin/isoniazid/phenytoin
        - Reduce ketaconazole by >50%
    - Ketoconazole + cyclosporin/midazolam/triazolam/warfarin
        - Increased concentration of these other drugs
- Adverse effects
    - Anorexia, nausea and vomiting
        - Most common - 20%
    - Rash, pruritus hair loss
    - Increased liver enzymes, hepatitis
    - Endocrine
        - Menstrual irregularities
        - Gynaecomastia
        - Decreased libido
        - Reversible azoospermia
        - Transient reduction in:
            - Testosterone
            - Estradiol
            - Cortisol
        - Increase in
            - Deoxycorticosterone
            - Corticosterone
            - 11-deoxycortisone
            - Hypertension and fluid retention
- Caution
    - Pregnancy
        - Syndactyly in rats
    - Nursing mothers
        - Secreted in breast milk
    - Major surgery, trauma, severe burns

Itraconazole

- Capsules with food
- Solutions - IV, oral (fasted state)
- Absorption increased by low gastric pH
- Oral formulations not bioequivalent (don't interchange)
    - Peak concentration of the solution is 150% more than capsule
- Little into CSF
- Metabolised by CYP3A4
- Active metabolite
    - Together with drug >99% protein bound
- Half-life: 30 - 40hrs
- Steady state levels
    - Itraconazole - 4 days
    - Hydroxyitraconazole - 7 days
    - Loading dose administered
- Excipient in solution is hydroxypropyl-ß-cyclodextrin
    - IV + azotaemia - excipient accumulation
- It does not affect mammalian steroid synthesis
- Contraindicated in renal failure and pregnancy
- Interactions
    - Increases the plasma levels of
        - Allentanil
        - Cyclosporine
        - Digoxin
        - Phenytoin
        - Calcium channel blockers
        - Sulphonylureas
        - Protease inhibitors
    - Itraconazole levels reduced by:
        - Drugs that reduce gastric acid acidity
        - Isoniazid
        - Nevirapine
        - Phenobarbital
        - Rifamycins (rifampin, rifabutin, rifapentine)
    - Concentration increased by:
        - Clarithromycin
        - Indanavir
        - Ritonavir
- Adverse effects
    - NVD, abdominal cramps
    - Hyper_

Fluconazole

- Oral, IV
- Bioavailability not altered by food or gastric acidity
- CSF - 50- 90% plasma levels
- 11 - 12% protein bound
- Half-life: 25 - 30 hours
- It has the least effect of all azoles on CYP450 ∴ < drug interactions
- AE
    - NVD, abdominal pain
    - Headache
    - Skin rash
    - Reversible alopecia
    - Hepatotoxic
    - Teratogenic
- Treatment of choice
    - Cryptococcal menningitis
    - Coccidioidal meningitis
- No activity
    - Aspergillosis
    - Mucormycosis
- Avoid in pregnancy

Voriconazole

- IV, oral
- Bioavailability > 90%
- Liver metabolism
- Inhibition of CYP450 - check for drug interaction
- Reversible visual disturbances (30% of patients)
    - Blurring and changes in colour vision
    - Occurs immediately after a dose is administered and resolve within 30 minutes
- Photosensitivity
- Active against fluconazole-resistant candida

Posaconazole

- Broadest spectrum of all azoles
- Absorption is improved when taken with meals high in fat
- Rapidly distributed to the tissues
    - High tissue but low blood levels
    - Measure concentration - serious invasive fungal infection
- Drug interactions occur

Pnuemocandins

- Echinocandins
    - Caspofungin
    - Micafungins
    - Anidulafungin
- _

MoA

- Inhibits ß-glucan synthase
- ∴ inhibits formation of ß-D-glucans in the fungal cell wall

Mech of Resistance

- Mutation of the gene coding for ß-glucans synthase
- Azole resistant candida are susceptible to caspofungins
- Active against
    - C.albicans
    - Aspergilus fumigatus
    - P.carinii
    - H.capsulatum
- No activity
    - Cyrptococcus neoformans
        - Common cause of meningitis in HIV patients

Griseofulvin

- Fungistatic
- Spectrum of activity
    - Dermatophytes only
        - Microsporum
        - Epidermophyton
        - Trichophyton
        - No effect on other bacteria or fungi

MoA

- Interacts with tubulin and disrupts the mitotic spindle
- ∴ it inhibits fungal mitosis and produces multinucleate cells

Pharmacokinetics

- Oral route
- Half-life of 1 day
- Fatty meals increase absorption
- Deposited in keratin precursor cells

- Minimal amounts in body tissues and fluids
- Excreted in urine

Indications

- Mycotic disease of the skin, hair and nails caused by dermatophytes
- Treatment continued until infected tissue is replaced by normal cells
    - Scalp - 1 month
    - Fingernails - 6-9 weeks
    - Toe nails - 1 year
    - Skin and hair infection - 2-6 weeks
- High doses are carcinogenic and teratogenic
    - ∴ not for infections that respond to topical agents

Adverse Effects

- Minor headaches (15%)
- CNS
    - Blurred vision
    - Syncope
- GIT
    - NVD
    - Heart burn
    - flatulence
- Blood
    - Leucopoenia
    - Neutropoenia
- Renal
    - No renal failure
- Skin
    - rashes
- Others
    - Angioedema
    - Hepatitis
- Induces hepatic microsomal enzymes
- Increased warfarin and oral contraceptive metabolism

Terbinafine

- An alylamine
- Fungicidal
- Keratophilic

MoA

- Inhibits fungal squalene epoxidase
- ∴ blocks ergosterol synthesis
- Accumulation of squalene is toxic to the fungi

Pharmacokinetics

- Oral
- Bioavailability - 40%
- Protein binding - 99%
- Accumulates in skin, nails and fat
- Half-life is 12 hours initially
- Caution
    - Renal and liver disease

Interactions

- Rifampicin
- Cimetidine

Adverse effects

- Severe neutropoenia
- Headache

- Mild to severe rashes
- Hepatotoxicity - rare

Topical Antifungal Agents

Tuesday, 17 May 2016 9:41 AM

- For superficial fungal infections
  - Stratum corneum
  - Squamous mucosa
  - Cornea
- Not useful
  - Onychomycosis (nails)
  - Tenia capitis (hair)
  - Subcutaneous mycosis
- Hyperkeratotic lesions - poor penetration
  - Whitefield's ointment
- Creams or solutions
- Ointments
- Powders

Topical Azole antifungals

- Indications
  - Ringworms
  - Tenia versicolor
  - Mucocutaneous candidiasis
- Formulations
  - _
- Adverse effects
  - Vagina - Irritation, itching burning
  - Skin - Redness, Desquamation, Pruritus
  - Oral - GIT irritation

- Clotrimazole - Fungicidal conc for 3 days in vaginal application
- Econazole - Derivative of miconazole
- Miconazole - Persists in stratum corneum for more than 4 days
  - Lotion recommended for intertriginous areas
- Ketaconazole and shampoos are used for seborrhoeic dermatitis and pityriasis versicolor
- Ciclopirox Olamine
  - Fungicidal
  - PK
    - Penetrates dermis, hair, sebaceous glands to treat deeper infections
- Haloprogin
  - A halogenated phenolic ether and is fungicidal against dermatophytes and candida sp.
- Tolnaftate
  - Thiocarbamate that is ineffective against candida and has no adverse effects
- Naftifine
  - An allylamine
  - C.f Terbinafine
  - Inhibits squalene epoxidase
- Nystatin
  - A polyene antifungal - Amphotericin B
  - Not absorbed from any site
  - Useful against candida (oral) only

    - Has a bitter taste
    - Rare nausea and allergic reactions
- Topical Amphotericin B
    - Candidiasis
    - Fungal ulcers and Keratitis

Miscellaneous agents

- Undecylenic acid (Fungistatic)
- Whitefield's ointment = Benzoic acid (Fungistatic action) + salicylate acid (exfoliative function)
- Proprionic acid + Caprylic acid
    - Expensive and low efficient
- Potassium iodide
    - Cutaneous sporotrichosis
    - Bitter.
    - Start at a low dose - dilute with water
    - Increase salivation
    - Acne like rash on chest..
- Gentian Violet
    - Antiseptic Dye
    - Against staph
    - Also against stuff
    - Ineffective against acid-fast bacteria and bacterial spores
    - Mark skin prior to surgery.
    - It is carcinogenic to animal so avoid application to broken skin
    - Irritation and ulceration of mucous membranes
    - Esophagitis, NVD

Macrolides

Tuesday, 24 May 2016 10:03 AM

- All have a macrocyclic lactone ring (14 - 16 atoms) to which deoxy-sugars are attached
- Examples:
    - Erythromycin (prototype)
    - Clarithromycin
    - Azithromycin
    - Ketolides
        - Telithromycin
- Erythromycin (Streptomyces erythreus)
- The others are semisynthetic derivatives of erythromycin
- Weak bases
- Activity enhanced at alkaline pH - cross cell membranes well
- Bacteriostatic
- May also be bactericidal in high concentrations to susceptible microorganisms

Spectrum of Activity

- Gram + and some Gram- aerobes
- Also includes:
    - Legionella pneumophilia
    - Mycoplasma pneumoniae
    - Rickettsia
    - Chlamydia
    - Atypical mycobacteria
    - H.pylori
- Azithromycin and clarithromycin have > activity than erythromycin
    - Mycobacteria avium intracellulare
    - Protozoa
        - Toxoplasma gondii
        - Plasmodium
        - Cryptosporidium
    - If an organism is resistant to penicillin
        - High chance of macrolide resistant
    - No effect on:
        - Fungi
        - Viruses
        - Yeasts

Mechanism of Action

- Inhibit protein synthesis by binding reversibly to the 50S ribosomal subunit

Mechanism of resistance

- Mediated through plasmids
- Decreased permeability of the cell membrane or active efflux
- Production of esterases (enterobacteriaceae)
- Modification of the ribosome binding site (ribosomal protection) by
    - Chromosomal mutations
    - Methylase
- Cross resistance occurs between macrolides

    - Except ketolide group
- Macrolide resistant strains may be susceptible to ketolides
    - Ketolides are poor substrates for efflux pump mediated resistance
    - They bind to ribosomes with higher affinity than macrolides
- Resistance by methylase production also occurs for other drugs which share the same ribosomal binding site i.e. MLS_B resistance
    - Macrolide - lincosamide - streptogramin B resistance

Erythromycin (E)

Pharmakokinetics

- Base is destroyed by gastric acid
- Administer orally as
    - Enteric coated formulation
    - Esters (E. stearate, E ethyl succinate, E estolate)
    - IV preparations
        - E lactobionate
        - E gluceptate
    - These formulations are more acid resistant
- Food interferes with absorption
- E estolate - best absorption
- Absorption site
    - Upper small intestine
- Widely distributed
- Poor concentration in CSF
- Crosses the placenta
- Enters breast milk
- Half-life of 1.5 hours (administered 4 times a day after 6 hours)
    - 5 hours in anuric patients
- Excretion is mainly through bile. 5% excreted through urine
- Dose adjustment in renal failure is ∴ unnecessary
- It is not removed through haemodialysis or peritoneal dialysis

Adverse effects

- GIT (most frequent and dose dependent)
    - ANVD, abdominal pain
    - E acts on motilin receptors to stimulate GIT motility
- Acute cholestatic hepatitis
    - Especially the estolate
    - May be a hypersensitivity reaction
- Arrhythmias
    - Macrolides prolong the QT interval
    - In patients on drugs that prolong the QT interval e.g. Cisapride
    - Other risk factors like hypokalaemia
- Reversible hearing loss
- Allergic reactions
    - Rash (mild to severe) - rare
    - Anaphylaxis, fever, eosinophilia
- Overgrowth of nonsusceptible micro organisms
    - Bacteria eg clostridium difficile
    - Fungi

Drug interactions

- E inhibits CYP450 (14-atom lactone)
- It therefore increases the concentration of drug such as
    - Theophylline
    - Oral anticoagulants
    - Cyclosporin
- E + digoxin
    - Digoxin is metabolised by intestinal microflora
    - Digoxin bio-availability is increased

Contraindications

- Known hypersensitivity to E

Precautions

- Impaired liver function
- Pregnancy and lactation
- Myasthenia gravis
    - E reported to aggravate muscle weakness

Therapeutic use

- Drug of choice
    - Chlamydial infections
    - Corynebacterial infections e.g. diphtheria
- Community acquired pneumonia
- Pre-operative preparation of the bowel
    - E + neomycin (or kanamycin)
- Prophylaxis against endocarditis during dental procedures (penicillin allergic patients)
    - Clindamycin - less GIT effects

Clarithromycin

P'kinetics

- Oral - better absorbed than E
- More acid stable than E
- Bioavailability 50 - 55% (first-pass effect)
- Metabolised in the liver to active metabolite
- Half-life is 6 hours (bi-daily dose)
- Tissue penetration good
- Eliminated in the liver and kidney
- Adjust dose in renal failure
- Dialysis is ineffective

Adverse effects

- Like E
- CNS
    - Anxiety
    - Dizziness
    - Insomnia
    - Nightmares
    - Confusion

Contraindications
- Known hypersensitivity to macrolides
- Combination with cisapride

Drug interactions
- Like E because it also has 14-aton lactone ring

Azithromycin

P'kinetics
- 15 - atom lactone macrolide
    - Does not inactivate CYP450
    - None of the drug interactions like E
- Food decreases its bioavailability
    - Give 1 hour before meals or
    - 2 hours after meals
- Tissue concentrations are higher (10 - 100 fold) than those in serum
- Half-life is 3 days

Adverse effects
- Like E
- Others
    - Chest pain, palpitations
    - Meleana
    - Headache
    - Vertigo
    - Somnolence
    - Fatigue
    - Nephritis

Telithromycin

P'kinetics
- Oral
- Bioavailability - 57%
- Good tissue penetration
- Liver metabolism
- Excretion - bile and urine
- Inhibits CYP450 (14-atom lactone ring)
    - Drug interactions like E

Adverse effects
- Rare
- Hepatitis
- Liver failure

Contraindications
- Myasthenia gravis
    - Exacerbates condition

Other indications

- URTI
- LRTI
- Pertussis
- H.pylori infections
    - Patients with PUD
- Skin infections
- Gonorrhoea
- syphillis

Antiviral Chemotherapy (Anti-Herpes, Hepatitis and Influenza Drugs)

Monday, 19 September 2016 9:13 AM

Introduction

- Viruses are simple microorganisms
  - Double or single stranded DNA,RNA
  - Enclosed in a capsid
  - Host derived lipid envelope
  - Obligate intracellular parasites
- Most antiviruses try to alter the
  - Attachment to host membrane
  - Intracellular uptake
  - Integration into the nucleus
  - Disrupt protein synthesis
  - Inhibit release of virions to prevent infection of other cells

Anti-Herpes Drugs

- Most drugs are antimetabolites
- Bio-activated via viral or host cell kinases
- Inhibit viral DNA polymerases

Name of Drug	Notes and MoA	Pharmacokinetics	Clinical Use	Toxicity
Acylovir (Acycloguanosine - prototype drug of anti-herpes drug)	• Guanosine analog • Active against HSV-1,2 VZV • Activated to monophosphate form by viral thymidine kinase • Activated to acyclovir diphosphate then triphosphate by host thymidine kinase • Interferes with viral synthesis ○ Competitive substrate for DNA polymerase ○ If it binds to the DNA template there will be chain termination • Mimics guanosine • Cross resistant to famciclovir, valacyclovir, gancicyclovir • Mimics guanosine	• Administered by topical, oral, IV • Short half-life (2.5-3hrs in normal patients, 20hrs in anuric patients) ○ Multiple doses • F - 15-20% • CSF - 20-50% of serum levels • Excreted mainly through the kidneys ○ Dose adjust	• Oral ○ Mucocutaneous, genital herpes lesions ○ Prophylaxis in AIDS, organ transplantation • IV (severe) ○ Encephalitis ○ Neonatal HSV infection ○ VZV • Topical ○ Herpes Labialis Rx	• Oral ○ GIT distress ○ Headache • IV ○ Delirium ○ Seizures ○ Tremors ○ Hypotension ○ Nephrotoxicity • Do not use with probenecid and cimetidine • Somnolence and lethargy occurs in patients receiving acyclovir and AZT at the same time
Valacyclovir	• Prodrug • Converted to acyclovir via hepatic metabolism ○ Acyclovir has lower bioavailability • Higher plasma levels	• Administered orally • F - 54-70% • CSF - 50% of serum levels • Excreted renally • Dose adjustment • Half-life is 2.5 - 3.3 hours • Well tolerated	• First or recurrent genital herpes and VZV infection • 1-day treatment for orolabial herpes • Genital herpes suppression	• NVD • Rash • High doses • Confusion • Hallucinations • seizures
Penciclovir	• Activation by viral thymidine kinase • Triphosphate inhibits DNA polymerase			Uncommon
Famciclovir	• Prodrug • Converted to penciclovir by first-pass metabolism • Well tolerated	• F - 70% • $T^{0.5}$ - 7-20 hours • Mainly excreted in urine	• Used for genital herpes and herpes zoster	• NV • Headache
Docosonol	• Inhibits fusion between HSV envelope and plasma • Prevents viral entry • Used topically • Shortens healing time			
Ganciclovir	• Guanine derivative • Triphosphorylated • Inhibits DNA polymerases of CMV, HSV • First phosphorylation is catalysed by virus specific enzymes	• Given IV, intraocular implants (CMV retinitis) • Penetrates well into the tissues (eye, CNS) • Undergoes renal elimination • Bioavailability is 10% • Valganciclovir ○ Prodrug ○ High oral bioavailability ○ Increases the half-life of Ganciclovir	• Prophylaxis • Treatment of CMV retinitis • Infections in immunocompromised patients	• Leukopoenia • Thrombocytopoenia • Mucositis • Hepatic dysfunction • Seizures • Severe neutropoenia when combined with zidovudine
Cidofovir	• Activated by host cell kinases • Inhibits DNA polymerases of HSV, CMV, Adenovirus, HPV • Does not require viral kinase ○ Active against acyclovir, ganciclovir resistant strains	• Given IV • Renal elimination (dose adjustment)	• CMV retinitis • Mucocutaneous HSV • Genital warts	• Nephrotoxicity ○ Major dose limiting drug ○ Additive with other nephrotoxic drugs
Foscarnet	• Phosphonoformate derivative • Does not require phosphorylation • Inhibits ○ RNA polymerase ○ DNA polymerase	• Given IV • Penetrates well into tissues (CNS) • Undergoes renal elimination	• Used as an alternative for prophylaxis and treatment of CMV infections • Supress resistant herpertic infections in AIDS	• Nephrotoxicity (30%) • Hypocalcaemia • Genitourinary ulceration • CNS (headaches, hallucinations, seizures)

	○ HIV reverse transcriptase • Not used in HIV treatment		AIDS	
Vidarabine	• Adenine analog • Active against HSV, VZV, CMV • Rapid metabolic inactivation		• Used topically for herpes keratitis (infection of the cornea)	• Toxic effects ○ GI irritation ○ Tremors ○ Hepatic dysfunction ○ Paraesthesia ○ Convulsions
Idoxuridine, Trifluridine	• Pyrimidine analogs	• Topically in HSV-1 keratitis		• Toxic for systemic use
Formivirsen	• Oligonucleotide • Binds to mRNA of CMV (inhibit protein synthesis)	• Injected intra-vitreally for CMV retinitis		○ Iritis ○ Vitritis ○ Increased intraocular pressure

Anti-Influenza Agents

- Drugs used in the management of influenza
- More cost effective to be vaccinated against influenza
- Given to people who are allergic to influenza vaccine and those exposed to the virus
  - Reduces the symptoms by a day or 2 if taken within 24 hours

Name	Notes and MoA	Pharmacokinetics	Clinical Use	Toxicity
Amantidine, Rimantidine	• Prevent viral 'uncoating' by binding and inhibiting M2 protein • M2 protein activates viral RNA transcriptase • Effective only for influenza A	Rimantadine • Longer half-life • No dose adjustment in renal failure	• Prophylactic against influenza A infection • Reduce duration of symptoms if given within 48 hours	• GIT irritation • Dizziness • Ataxia, slurred speech
Oseltamivir, Zanamivir	• Inhibitors of neuraminidases (influenza A, B) ○ Cleavage of viral proteins ○ Promote virion release ○ Prevent clumping of newly released virions • Impede viral spread	• Oseltamivir ○ Prodrug ○ Given orally ○ Activated in the gut, liver • Zanamivir ○ Given intranasally	• Alleviate influenza symptoms (within 24 hours) • Prophylaxis against influenza	• Oseltamivir ○ GIT distress • Zanamivir ○ Cough ○ Throat discomfort ○ Bronchospasms in asthmatics

Drugs for Viral Hepatitis

Drugs for Hepatitis C

- Interferon
- Ribavirin
- Protease inhibitors
  - Boceprevir
  - Telaprivir
  - Simeprivir
- Polymerase inhibitor
  - Sofobuvir

Drugs for Hepatitis B

- Adefovir
- Entecavir
- Lamivudine
- Telbivudine
- Tenofovir
- Interferon &
- Emtricitabine

Name	Notes and MoA	Pharmacokinetics	Clinical Use	Toxicity	Contraindications
Interferon &	• Cytokine • Increases the activity of JAKS ○ Formation of antiviral proteins • Antiviral action ○ Activation of ribonuclease (degrade viral mRNA) ○ Promotes formation of natural killer cells (destroy infected liver cells)	• Slow absorption from IM and SC • Eliminated by proteolytic hydrolysis in the kidney • Conventional forms ○ Given three times a week • PEGylated forms ○ Conjugated to polythylene glycol ○ Given once a week	• Chronic HBV (monotherapy/combined with other HBV agents) • Chronic HCV (combined with Ribavirin) • All the drugs are not effective in acute infection • Kaposi's sarcoma • Papillomatosis • Genital warts (topical) • Prevent dissemination of herpes zoster in cancer patients • Reduce CMV shedding after renal transplantation	• GIT irritation • Flulike symptoms • Neutropoenia • Profound fatigue • Myalgia • Alopecia • Reversible hearing loss • Thyroid dysfunction • Confusion • Severe depression	• Autoimmune disease • History of cardiac arrhythmias • Pregnancy
Adefovir Dipivoxir	• Prodrug of adefovir • Undergoes phosphorylation • Competitively inhibits HBV DNA polymerase	• Good oral bioavailability • Eliminated renally • Half-life: 5 - 18 hours	• Suppresses HBV replication • Improves liver histology, fibrosis • Activity against lamivudine resistant HBV	• Nephrotoxicity • Lactic acidosis • Severe hepatomegaly with steatosis	
Entecavir	• Guanosine nucleoside • Inhibits HBV DNA nucleoside	• Given orally • Half-life - 12 hours • Renal elimination	• Clinical efficacy similar to lamivudine (cross resistant)	○ Headache ○ Dizziness ○ Fatigue ○ Nausea	
Lamivudine	• Nucleoside inhibitor • Active in chronic HBV infection (lower doses)	• Long intracellular half-life • Used as monotherapy • High rates of resistance		• Non-toxic ○ Pancreatitis (co-infection with HIV)	

Ribavirin	• Inhibits replication of a wide range of viruses • Inhibit GTP formation • Prevents capping of viral mRNA • Blocks RNA dependent RNA polymerases	• Given orally (avoid antacids prevent absorption), IV, aerosols • Eliminated by kidney (dose adjustment)	• Chronic HCV (with Interferons) • Viral haemorrhagic fevers	• Haemolytic anaemia • Conjuctival, bronchial irritation (aerosol) • Contraindicated in pregnancy	
Telbivudine	• Nucleoside analog • Phosphorylated to a triphosphate • Inhibits HBV DNA polymerase	• High resistant rate	• Used for chronic HBV	• Lactic acidosis • Steatosis • Hepatomegaly	
Tenofovir	Antiretroviral drug		• Active against lamivudine, entacavir resistant strains • Approved for chronic HBV		

A

Flow chart of acyclovir

Antiretroviral Drugs

Tuesday, 20 September 2016 9:11 AM

HIV Life cycle

- Binding
  - GP120 binds to the CD4 receptors and co-receptor (CCR5/CXCR4)
- Fusion and Entry
  - Fusion of the viral and host cell membrane
    - Mediated by gp41
  - Allows entry of virus core into host cytoplasm
  - Core protein dissolved by host enzymes releasing viral RNA and enzymes
- Transcription and integration
  - Reverse transcriptase converts the viral RNA into DNA
  - The dsDNA enters the host cell nucleus
  - Integrase integrates viral DNA into the host cell's DNA to for provirus
- Replication
  - Integrated viral DNA causes synthesis of viral mRNA
  - mRNA leaves the nucleus and enters the cytoplasm (ER) where it produces viral proteins
- Budding and Maturation
  - Viral proteins and the viral RNA are cleaved by protease enzyme and assemble to form immature viruses
  - Immature viruses bud off the cell and enter the blood stream
  - Newly assembled virions undergo polypeptide cleavage to form the mature virus
  - Maturation involves the protease enzyme

Classification

- Nucleoside reverse transcriptase inhibitor (NRTIs)
  - Thymidine analogues
    - Zidovudine (ZDV, AZT)
    - Stavudine (d4T)
  - Cytidine analogues
    - Lamivudine (3TC)
    - Emtricitabine (FTC)
    - Zalcitabine (ddC)
  - Guanosine analogues
    - Abacavir (ABC)
  - Adenosine analogues
    - Didanocine (ddI)
- Nucleotide reverse transcriptase inhibitors (NtRTIs)
  - Adenosine analogues
    - Tenofovir (TDF)
- Non NRTIs (NNRTIs)
  - Nevirapine (NVP)
  - Efavirenz (EFV)
  - Delavidine (DLV)
  - Etravirine (ETR)
  - Rilpivirine (RPV)
- Protease inhibitors (PIs)
  - Lopinavir (LPV)
  - Ritonavir (RTV)
  - Saquinavir (SQV)
  - Indinavir (ICV)
  - Nelfinavir (NFV)
  - Amprenavir (APV)
  - Darunavir (DRV)
- Entry inhibitors
  - Enfuvirtide (T-20)
  - Maraviroc (MVC) - CCR5 antagonist
    - Vicriviroc is similar
- Integrase strand transfer inhibitors (INSTIs)
  - Raltegravir (RAL)
  - Elvitegravir (EVG)
  - Dolutegravir

All antiretroviral drugs

- Prevent infection of susceptible cells
- Do not eradicate the virus from infected cells
- Uses
  - Antiretroviral treatment (ART)
  - Prevention of mother to child transmission (vertical transmission) (PMTCT)
  - Post exposure prophylaxis (PEP)
  - Pre-exposure prophylaxis (eg serodiscordant couple trying to conceive) (PrEP)

Examples of drug combinations in Kenya

- First line therapy for adults
  - TDF + 3TC + EFV
- First line for children < 3 years
  - ABC + 3TC + LPV/r

- Reverse transcriptase = RNA dependent DNA polymerase
- It is inhibited by NRTIs, NtRTIs and NNRTIs

NRTIs and NtRTIs

- Phosphorylated in cells

    - Substrates for reverse transcriptase
- Blocks replication of the virus genome
    - Competitively inhibits incorporation of native nucleotides
    - Terminates elongation of pro-viral DNA because they lack a 3-hydroxyl group
- NRTIs
    - Converted into monophosphates then diphosphates and then finally triphosphates
- NtRTIs
    - Converted to monophosphates then diphosphates
- Inhibit both HIV-1 and 2
- FTC, 3TC and TDF - Hepatitis B virus
- TDF - herpes viruses
- ZDV - human T-cell lymphotrophic virus I and II
- Some inhibit DNA polymerase gamma found in mitochondria hence toxicity
    - Anaemia
    - Granulocytopoenia
    - Myopathy
    - Peripheral neuropathy
    - Pancreatitis
- AZT, D4T and DDI rarely cause
    - Lactic acidosis +/- hepatomegaly
    - Hepatic steatosis
    - These are also due to mitochondrial toxicity
- FTC, 3TC, TDF
    - Low affinity for DNA polymerase gamma, therefore, devoid of mitochondrial toxicity
- Most are eliminated by the kidney
- ZDV and ABC cleared mainly by hepatic glucoronidation
- Half-life of parent drug is 1-10 hours except TDF (14 - 17 hours)
- Half-life of nucleoside TP and nucleotide DP is 2 - 50 hours
- No clinically significant drug interactions
    - No not inhibit or induce cytochrome enzymes
- Drug interactions for TDF and PIs
    - Inhibition of drug transporters
- High level resistance occurs rapidly with 3TC and FTC
- Cross resistance between agents of NRTIs and NtRTIs

Drug	MoA	MoR	Pharmacokinetics	Adverse Effects	Drug Interactions	Precautions
Zidovudine • More active in lymphocytes • S-phase specific ○ Active in actively dividing cells, not resting cells ○ That enzyme that activates the drug (thymidine kinase) is present	ZDV ----thymidine kinase----> ZDV-MP ----thymidylate kinase----> ZDV-DP ------ nucleoside diphosphate kinase -----> ZDV-TP (a nucleotide anabolite)	• Many mutations of reverse transcriptase codons can occur • Referred to as TAMs (thymine analog mutations) • TAMs promote excision of nucleotide anabolites through pyrophosphorolysis • Cross resistance varies according to mutations	• Given orally but can be IV (PMTCT) • Rapidly absorbed food slows down absorption but can be administered with food • Half-life of ZDV half an hour ○ ZDV-TP is 3 - 4 hours • Undergoes first-pass metabolism ○ Bioavailability - 64 • Crosses placenta ○ Plasma concentration in foetus is similar in mother • Crosses BBB ○ Concentration is CSF is 60% that of plasma • Detected in breast milk, semen and foetal tissues • PPB is 30 -40%	• Common ones that resolve within the first few weeks ○ Fatigue ○ Malaise ○ Myalgia ○ Anorexia ○ Nausea ○ Headache ○ Insomnia • Bone marrow suppression • Anaemia • Granulocytopoenia • Macrocytosis • Hyperpigmentation • Mitochondrial toxicity	• D4t + AZT are antagonistic	• Anaemic patients • Caution in patients taking other bone marrow suppression drugs
Stavudine • Phosphorylated like AZT • S-phase specific • Lower affinity that AZT		• TAMs		• Causes lipodystrophy ○ Thin cheeks and wide waist • Peripheral neuropathy ○ Common ○ More likely if the patient is on other drugs that cause neuropathy • Mitochondrial toxicity	• Ethambutol, Isoniazid, Phenytoin, Vincristine, ddI (peripheral neuropathy • ddI + d4T (pancreatitis) • AZT + d4T (antagonistic)	• Ethambutol, Isoniazid, Phenytoin, Vincristine, ddI (peripheral neuropathy) • ddI + d4T (pancreatitis) • AZT + d4T (antagonistic)
Lamivudine (3TC)	• Similar to AZT ○ Different enzymes be cause it is a cytidine analogue • Activated in resting cells • Decreased affinity than DNA polymerases	• Single amino acid substitution ○ M184V • Cross resistance to FTC and ABC • Restores ZDV and TDF sensitivity ○ Virus has less replicating capacity and less fit	• Given orally • Renal elimination (dose adjustment) • Does not bind significantly to plasma protein • Crosses placenta and BBB	• High doses ○ Neutropoenia ○ Headache ○ Nausea • Discontinuation ○ Rebound HBV replication ○ Hepatitis B fatal	• Becomes more active when combined with NRTIs and NtRTIs except FTC because of similar MoA	
Abacavir (ABC)	ABC ----> ABC-MP-----> CBV-	• K65R associated	• Given orally	• Hypersensitivity	• No clinically	

	MP (carbovir monophosphate) ----> CBV-DP -----> CBV-TP	with resistance to all NRTIs except AZT	• Metabolism by alcohol dehydrogenase and glucoronidation • Enters CSF	syndrome (onset is 11 days after start of treatment and subside after 6 weeks) ○ Fever ○ Malaise ○ Abdominal pain and other GIT symptoms ○ Mild papilloma rash ○ Respiratory symptoms ▪ Dyspnea, cough, difficulty in breathing • Discontinue the drug if symptoms persist and never restart the drug (anaphylactic shock) • Occurs in people with HLA-B*5701 in their genetic make up	significant ones • Do not take with large doses of alcohol ○ Increase ABC levels because both drugs are competing for alcohol dehydrogenase	
Tenofovir (TDF)	• Poor oral availbility • Formulation used is TDF-disoproxil • TDF-disoproxil ----> TDF -----> TDF-MP ------> TDF-DP (active metabolite) • Low affinity for DNA polymerase gamma ○ No mitochondrial toxicity	• K65R	• Oral route • Excreted in kidneys through glomerular filtration and tubular secretion • 70 - 80% is unchanged in urine	• Flatulence • Rare ○ Acute renal failure ○ Fanconi's Syndrome • Discontinuation and HBV infection, HBV replicates leading to fatal hepatitis		

MoR
- Many mutations of reverse transcriptase codons can occur
- Referred to as TAMs (thymine analog mutations)
- TAMs promote excision of nucleotide anabolites through pyrophosphorolysis
- Cross resistance varies according to mutations

Drug interactions
- D4T + AZT are antagonistic

Stavudine
- Phosphorylated like AZT
- S-phase specific
- Lower affinity than AZT

Adverse effects
- Causes lipodystrophy
  - Thin cheeks and wide waist
- Peripheral neuropathy
  - Common
  - More likely if the patient is on other drugs that cause neuropathy
- Mitochondrial toxicity

Interactions

Interactions
- Becomes more active when combined with NRTIs and NtRTIs except FTC because of similar MoA

NNRTIs
- Bind to a hydrophobic pocket in the p66 subunit of reverse transcriptase
- Induce conformational change and reduce enzyme activity
- Do not require intracellular phosphorylation
- HIV-1 only
- No activity on host DNA polymerases
  - No mitochondrial toxicity
- All metabolised by CYP450 enzymes including CYP3A4
- EFV, ETV and NVP induce CYP3A4
- Delavudine inhibite CYP3A4

MoR
- If you are resistant to one you are resistant to all except ETV

Adverse effects
- Skin rashes
  - In mucosa
- Fat accumulation
- Altered liver function - hepatic toxicity, hepatitis
- Occur with in first 4 weeks of treatment

Drug	Pharmacokinetics	Adverse Effects	Drug Interactions
Nevarapine (NVP) • Cross resistant with EFV, DLV	• Orally • Induces and metabolism by CYP3A4 • Half-life is 45 hours to 25 - 30 hours (due to autoinduction) • 200mg once daily for 2 weeks • Then 200mg twice daily	• Occur rarely • Steven-Johnson's Syndrome • Care to be taken if patient who has a high CD4 cell count ○ Female - 250 cells/mm3 ○ Male - ? • Causes hepatotoxicity	• CYP3A4 in • Increases the metabolism of oestrogen in all contraceptives ○ Use of dual-contraceptives • No use of Rifampicin with NVP ○ Causes NVP resistance

Efavirenz (EFV) • Cross resistance = NVP + DLV	• Taken at bedtime to reduce CNS adverse effects • Patients with genetic polymorphisms of CYP2B6 metabolise the drug slower	• 53% of patients experience CNS effects and resolve within the first 4 weeks of therapy ○ Dizziness ○ Impaired concentration ○ Dysphoria ○ Nightmares ○ Insomnia • Rashes • Found to be teratogenic in primates	• Inducer of CYPs especially CYP3A4 • Also inhibits CYPs • EFV reduces concentration of ○ Phenobarbital, phenytoin, carbamezepine, rifabutin • Does not change Rifampicin concentration • Still active when there is resistance to ○ Resistance requires multiple mutations

P'Kinetics
- Orally
- Induces and metabolism by CYP3A4
- Half-life is 45 hours to 25 - 30 hours (due to autoinduction)
- 200mg once daily for 2 weeks
- Then 200mg twice daily

Protease Inhibitors

- HIV-1 and 2
- Competitively inhibit viral protease
- Prevent proteolytic cleavage of HIV gag and pol precursor polypeptides e.g
  - Essential structural proteins (p17, p24, p9, p7)
  - Enzymes
- Prevents HIV maturation
- It is the mature virus that is infectious
- Most inhibit CYP3A4
- RTV most potent CYP inhibitor
- Most are p-glycoprotein efflux pump so they have limited CSF infiltration

Adverse Effects
- NVD
- Anorexia
- Abdominal pain
- Insulin resistance
- Hyperglycaemia
- Lipodystrophy
- Hyperlipidaemia
  - Increased triglyceride and cholesterol levels

Drug	Pharmacokinetics	Adverse Effects	Drug Interactions
RTV • Pharmacokinetic enhancer • No known resistance to low doses • Combined with another Pi ○ Prevents the metabolism of the other PI (boots the other PI)	• Oral route • Faecal elimination • Bound to &1-acid glycoprotein		• Should not be combined with dug with low therapeutic indices • Rifampicin increases its metabolism • RTV increases the metabolism of oestrogen in contraceptives • Use dual contraception
LPV • Formulation is LPV/r (ritonavir) • Multiple mutations for resistance to occur	• Oral route • Ratio of LPV to r is 4:1 • But when in plasma it changes to 20:1 • Bound to &1 acid glycoprotein • Low CSF and semen penetration • Placenta distribution ?		• Rifampicin increases its metabolism • Liquid formulation contains alcohol (42% alcohol) so should not be combined with Metronidazole
ATV	• Oral • Absorption is pH dependent • Proton pump inhibitors • Hydrogen receptor blockers	• Unconjugated hyperbilirubinaemia • Also caused by indanavir • Less like to increase cholesterol and triglycerides • Not known to cause glucose intolerance	
Darunavir • Contains a sulphur moiety like fosamprenavir		• Skin rashes	

Entry inhibitors

Drug	MoR	P'Kinetics	Adverse Effects	Drug Interactions
Maraviroc • A chemokine receptor antagonist • Binds to CCR5 receptor antagonist and blocks binding of gp120 • Targets host protein • Not active against CXCR4 tropic or mixed/dual tropism	• Shift of tropisms of the virus • Mutation of gp120		• Little significant toxicity	• Substrate of CYP3A4 • CYP3A4 inhibitor: 150mg bd • CYP3A4 inducer: 600mg bd • If none of the above: 300mg bd
Enfuvirtide • Binds gp41 and inhibits fusion of the HIV virus to the cell • Not active against HIV-1	• Mutation of gp41	• SC route • Unknown route of elimination	• Injection site • Pain • Oedema • Induration	• No significant ones

Integrase Inhibitors

Drug	MoR	Pharmacokinetics	Adverse Effects	Drug Interactions

Raltegravir
• Active against HIV-1 and 2
• Prevent covalent bond formation between host and viral DNA
	• Mutation of the gene that codes for the integrase enzyme	• Oral route	• Not common
			• Common are mild
			  • Headache
			  • Asthenea
			  • Fatigue
				• Rifampicin reduces Raltegravin levels

- Structure of HIV
- Lifecycle of HIV
  - Binds to CD4 receptor and a chemokine receptor
  - Fuses with CD4 cell membrane and uncoated
  - Reverse transcriptase converts ssRNA to dsDNA
  - Enters nucleus of cell and integrated into the host DNA
  - Transcribed to messenger RNA to structural protein
  - Protease enzyme prevents maturation of the virus

Topical Antimicrobials

Wednesday, 21 September 2016 11:38 AM

Clinical indications of topical antibacterial preparations

- Early treatment of superficial cutaneous infections (pyoderma) and wounds
- To reduce colonisation of the nostrils by staphylococci
- Axillary deodorisation
- Management of acne vulgaris
- Preventing infection of burns

Systemic antibiotics are commonly prescribed for acne and deeper bacterial infections

- Numerous topical antibacterial preparations contain corticosteroids as well
- Antibiotic (AB) - corticosteroid combinants may be useful in treatment of
    - Diaper dermatitis
    - Impetiginised eczema
- The selection of a particular antibiotic depends on the diagnosis and when possible, in vitro culture sensitivity studies of clinical samples
- The pathogens isolated from most infected dermatoses are
    - Group A ß-haemolytic streptococci (strep. pyogenes)
    - Staph aureus
    - A combination of the two
- Skin infections with Gram + bacilli are rare however they can occur in
    - Diabetics
    - Immunosuppressed patients
    - Parenteral antibiotics are required
- Pre packaged topical antibiotics preparations that contain multiple antibiotics are found in fixed dosages
- These formulations have the following advantages
    - Efficacy in mixed infections
    - Broader coverage for infections due to undetermined pathogens
    - Delayed microbial resistance to any single component of the antibiotics

Specific antimicrobials

- Bacitracin
- Polymixins
- Gramicidin
- Mupirocin
- Neomycin and gentamycin
- Retapamulin
- Topical antibiotics in acne

Bacitracin

- A cyclic polypeptide AB
- Active against a wide variety of gram + organisms including ß-lactamase producing staphylococci
- Also effective against
    - Most anaerobic cocci

- Neisseria
- Tetanus bacilli
- Diphtheria bacilli

MoA

- Is bactericidal
- Inhibits cell wall synthesis

P'Kinetics and P'Dynamics

- Is markedly nephrotoxic if administered systematically
- May produce proteinuria, haematuria and nitrogen retention
  - Its use is therefore limited to topical applications
- Poorly absorbed through the skin
- Topical application results in local antibacterial activity without significant systemic toxicity
- The small amounts of bacitracin that is absorbed is excreted by glomerular filtration

Adverse effects

- Allergic contact dermatitis occurs frequently
- Immunologic allergic contact urticaria syndrome including anaphylaxis occurs rarely

Preparations available and clinical use

- Bacitracin is compounded in an ointment base alone or combined with neomycin, polymixin B or both
  - Used for the suppression of mixed bacterial flora in surface lesions of the skin, on wounds or on mucous membranes e.g. the nose
- Solutions of bacitracin in saline can be used for irrigation of joints, wounds or the pleural cavity

MoR

- Not defined
- Resistance may develop following prolonged use
  - However, there is no cross resistance between bacitracin and other antimicrobial drugs

Polymixins

Chemistry

- Basic peptide AB
- Include
  - Polymixin B
  - Polymixin E (colistin)

Antimicrobial spectrum

- Many gram - bacilli including P. aeruginosa, E. coli, enterobacter and Klebsiella
- Most strains of proteus, neisseria and serratia are resistant
- All gram + are resistant

MoA

- Bactericidal
- They disrupt the permeability of both the outer and cytoplasmic membranes of bacteria

- They also bind and inactivate endotoxin
- In susceptible bacterial populations, resistant mutants are rare

Adverse Effects

- Local reactions and hypersensitivity to topical administration are rare
- Neurotoxicity and nephrotoxicity may be serious if the drugs are administered systemically
- Very high doses applied to open wounds may cause nephro- and neurotoxicity

Clinical use

- Polymixins are largely restricted to topical use because of
    - Poor tissue distribution
    - Substantial nephro- and neurotoxicity
- Topical preparations may be compounded in either a solution or ointment base
- Numerous pre-packaged AB combinants containing polymixins B in mixtures with Bacitracin, Neomycin or both are commonly applied to infected superficial skin lesions
- Detectable serum concentrations are rarely achieve from topical applications
- Are used for
    - Gut sterilisation
    - Topical treatment of eye, ear or skin infections caused by susceptible organisms

Gramicidin

- Is a peptide AB with a spectrum similar to that of Bacitracin
- Systemic toxicity limits the drug to topical use
- Its is available with other AB such as neomycin, polymixin, bacitracin and nystatin
- The incidence of sensitisation following topical application_

Mupirocin

- Natural substance produced by the bacteria P. fluorescens
- For topical use only

MoA

- Mupirocin is bactericidal
- Inhibits bacterial protein synthesis by reversible binding and inhibition of isoleucyl t-RNA synthetase

Antibacterial Spectrum

- Effective against most gram + aerobic bacteria, including MRSA

P'Kinetics

- Following topical application to intact skin, Mupirocin is rapidly inactivated after absorption and systemic levels are undetected

Clinical use

- Available as
    - a cream and ointment for dermatological use in treatment of
        - Traumatic skin lesions
        - Minor skin infections such as impetigo secondarily infected with Staph aureus and group A ß-haemolytic strep.
    - An ointment for intranasal use

- Highly effective against S. aureus nasal carriage which often precedes infection

MoR

- No cross resistance with other classes of AB
- 2 types of resistances occur
  - Low-level which is not clinically significant
    - Observed after prolonged use
    - Due to point mutation in the host gene encoding isoleucyl t-RNA synthetase
  - High-level resistance due to the presence of a second isoleucyl-t-RNA synthetase gene which is plasmid encoded
    - Results in complete loss of activity to Mupirocin
    - May result in nosocomial outbreaks of staph infection and colonisation

> 95% od staphylococcal isolates are still susceptible to Mupirocin

Adverse effects

- May cause irritation and sensitisation at the site of application
- Contact with the eyes should be avoided because it causes tearing, burning and irritation that may take several days to resolve
- Systemic reactions to mupirocin occur rarely
- Intranasal use may be associated with irritation of mucous membranes caused by absorption of the polyethylene glycol (PEG) vehicle from damaged skin
- Application of the ointment to large surface areas should be avoided in patients with moderate to severe renal failure to avoid accumulation of PEG

Topical medications usually consists od active ingredients incorporated in a vehicle that facilitates cutaneous applications
Depending upon the vehicle, dermatological formulations ,ay be classified as wet dressings, tinctures, lotions, gels, creams, ointments, powders, pates, aerosols

Aminoglycoside ABs

- Gentamycin and neomycin are active against gram - organisms including proteus, E. coli, Klebsiella nd enterobacter
- Gentamicin shows more activity against P. aeruginosa, staphylococci and group A ß-haemolytic strep., than neomycin

Clinical Use

- Neomycin is available in numerous topical formulation, alone or in combination with polymixins, bacitracin etc.
- Also available as a sterile powder for topical use
- Gentamycin is available as an ointment or cream

P'Kinetics

- Topical application f Neomycin rarely results in detectable serum concentrations
- However, gentamycin can result in significant serum concentrations if it is applied in a water miscible preparation to large areas of lacerated skin, e.g. burns
- Both drugs are excreted primarily in the urine and may accumulate in renal failure with a possibility of nephrotoxicity , neurotoxicity and ototoxicity

Adverse effects

- Neomycin frequently causes sensitisation particularly if applied to eczematous dermatoses

or if compounded in an ointment vehicle
- When sensitisation occurs, cross sensitisation_

Retapamulin

Chemistry

- Semisynthetic pleromutilin derivative

PK and PD

- Effective on the treatment of uncomplicated superficial_

Clinical use

- Available as 1% ointment
- Indicated in the treatment of impetigo in adults and children ≥ 9 months
- Administered by twice daily application f 5 days

AE

- Well tolerated
- Occasional irritation

Antibiotics used in acne
Introduction

- Acne vulgaris is the most common dermatological disorder treated with either topical or systemic Abs
- The anaerobe Propionibacterium acnes is a component of normal skin flora
- It proliferates in the obstructed, lipid rich lumen of the pilosebaceous unit where oxygen yenison is low
- P.acnes generates free fatty acids that are irritants and may lead to microcomedo formation_
- Suppression of P. acnes with antibiotic therapy is correlated with clinical improvement in acne
- AB treatment in acne may be
    - Topical
    - Systemic

Topical AB

- Commonly used topical AB used in acne include
    - Clindamycin phosphate
    - Erythromycin base
    - Antibiotic-benzoyl peroxide combinations
    - Benzoyl peroxide
- Other that can be used include
    - Sulfacetamide
    - Sulfacetamide/sulphur combinations
    - Metronidazole
    - Azelaic acide
    - Dapsone
- A topical AB is less effective than systemic administration of the same AB
- Topical therapy is therefore generally suitable only in mild to moderate cases of inflammatory acne

Systemic AB in acne

- Indicated in patients with
    - More extensive acne
    - Acne that is resistant to topical therapy
- Effective agents
    - The tetracyclines: tetracycline, doxycycline and minocycline
    - Trimethroprim - _

Specific topical AB
Clindamycin

- Has in vitro activity against P. acnes, the causative organisms for acne vulgaris
- ~10% of the applied dose is absorbed
    - Rare cases of bloody diarrhoea and peusdomembranous colitis have been reported_
- The hydroalcoholic vehicle and foam formulation may cause drying and irritation of the skin with complaints of burning and stinging
- The water based gel and lotion formulations are well tolerated and less likely to cause irritation
- Allergic contact dermatitis is uncommon and clindamycin is also available in a fixed combination topical gel with benzoyl- peroxide and tretinoin

Erythromycin

- In topical preparations, the base or erythromycin rather than a salt, is used to facilitate penetration
  The MoA of topical erythromycin in inflammatory acne vulgaris is presumed to be due to its inhibitory effects on P. acnes
- If erythromycin resistant strains develop during topical therapy, it should be discontinued and appropriate systemic AB therapy started
- Adverse local reactions include
    - Burning sensation at time of application
    - Drying/irritation of the skin
- The topical water based gel is less drying and may be better tolerated
- Allergic hypersensitivity appears to be uncommon
- Also available in a fixed combination preparation in treatment of acne vulgaris

Metronidazole

- Topical metronidazole is more effective in the Rx of acne rosecea
- MoA mat relate to its inhibitory effects on Demodex brivus
- Alternatively, it may act as an anti-inflammatory_
- Oral metronidazole has ben shown to be carcinogenic in susceptible rodent species
- Topical use not recommended
    - During pregnancy
    - Breastfeeding mothers
    - In children
- AE of the water based gel formulation include dryness, burning and stinging
- Less drying creams or lotion formulations may be better tolerated
- Caution is required when applying metronidazole near the eyes to avoid excessive tearing

Sodium Sulfacetamide

- Topical sulfacetamide is available as a 10% lotion and 10% wash
- Also available in several preparations in combinations with sulphur in acne vulgaris rosacea
- The MoA is thought to be inhibition of P. acnes by competitive inhibition of PABA utilisation
- ~4% of topically applied sulfacetamide is absorbed percutaneously
    - Its use is therefore contraindicated in patients with a known hypersensitivity to sulphonamides

Dapsone

- Topical dapsone is available as a 5% gel for the treatment of acne vulgaris
- Its MoA is unknown

AE

- The serious AE associated with oral dapsone use have not been reported with topical use
- Adverse local side effects include mild dryness, redness, oiliness and skin peeling
- Application of dapsone gel, followed by benzoyl peroxide may result in the a temporary yellow discolouration of skin and hair

Protozoa

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Amoebiasis

- Mild to moderate colitis with recurrent diarrhoea
- Severe colitis including bloody diarrhoea, fever and abdominal pain
- Hepatic abscess with fever, hepatomegaly and abdominal pain
- Drugs for the treatment of extra-intestinal form of amoebiasis e.g. amoebic liver abscess
- Tissue amoebiasis PLUS luminal agents
- Drugs of choice
  - Nitroimidazoles
    - Metronidazole, tinidazole, ornidazole, secnidazole
    - For amoebic colitis add a luminal agent
    - Levels may not be therapeutic in colon
    - Less active on cysts
- Alternative agents
  - Nitazoxanide
  - Emetine
  - Dehydroemetine
  - Tetracycline
  - Erythromycin
- Luminal agents
  - Can be used alone for asymptomatic intestinal infection
  - All are drugs of choice
    - Paromomycin
    - Iodoquinol
    - Diloxanide

Giardiasis

- Chronic diarrhoea
- Acute diarrhoea
- Abdominal cramps, distention, flatulence, malaise
- Metronidazole (drug of choice)
- Tinidazole (drug of choice)
- Paromomycin (pregnant women - to avoid mutagenesis)
- Nitazoxanide = N- (nitrothiazolyl) salicyclamide
- Furazolidone
- Albendazole

Trichomoniasis

- Copious vaginal discharge in women
- Non-gonococcal urethritis in men
- Drugs of choice
  - Metronidazole
  - Tinidazole

Toxoplasmosis

- Primary infection
  - Fever, malaise, headache, sore throat, lymphadenopathy
- Congenital infection
  - CNS abnormalities and retinochoroiditis
- Infection in immunocompromised patients
  - Reactivation leads to encephalitis, retinochoroiditis, pneumonitis, myocarditis
- Toxoplasmic encephalitis
  - Pyrimethamine + Sulfadiazine + folinic acid
  - Clindamycin + pyriethamine +folinic acid
- Other alternative combinations
  - Azithromycin, clarithromycin, atovaquone or dapsone
  - Plus
  - Trimethoprim - sulfamethoxazole or pyrimethamine
  - Plus
  - Folinic acid
- Acute toxoplasmosis in pregnancy to prevent transmission to the foetus
  - Spiramycin

African Trypanosomiasis

- Exposure to tsetse flies
  - chancre at bite site
- Haemolymphatic disease

    - Irregular fever, headache, joint pain, rash, oedema, lymphadenopathy
- Meningoencephalic disease
    - Somnolescence, severe headache, progressing to coma

Disease	Stage	First line Rx	Alternative Rx
East African T	Early	Suramin	Pentamidine
	CNS involvement	Melarsoprol	
West African T	Early	Pentamidine	Suramin, Eflonithine
	CNS involvement	Eflonitnine	Melasoprol, Nifurtimox

Melarsoprol is a derivative of arsenic (20% arsenic), melts plastic tubes, causes caustic burns, is extremely painful at injection and kills 5-10% patients.

American trypanosomiasis, or Chagas' diseasse

- Nifurtimox (DOC)
- Benzinidazole (DOC)

Leishmaniasis

- Sand fly bite in an endemic area
- Visceral leishmaniasis
    - Irregular fever, progressive hepatosplenomegaly, pancytopenia, wasting
- Cutaneous leishmaniasis
    - Chronic, painless, moist ulcers or dry nodules
- Mucocutaneous leishmaniasis
    - Destructive nasopharyngeal lesions
- Mucosal, visceral and cutaneous leishmaniasis
    - Pentavalent antimony (=sodium antimony gluconate = stibogluconate
- DOC
    - Amphotericin
    - Pentamidine
    - Meglumine antimoniate
    - Miltefosine (visceral and cutaneous L)
    - Paromomycin (visceral leishmaniasis
- Additional drugs for cutaneous leishmaniasis
    - Fluconaole
    - Ketoconazole
    - Itraconazole

Babesiosis

- History of tick bite or exposure to ticks
- Fever, flu-like symptoms, anaemia
- DOC
    - Clindamycin + quinine for severe disease
- Alternatives
    - Azithromycin or atovaquone for mild or moderate infections

Balantidiosis

- DOC
    - Tetracycline
- Alternative agent
    - Metronidazole
- Coccidiosis and /microsporidiosis
- Acute diarrhoea
- Prolonged diarrhoea in immuno-compromised persons

Cryptosporidia

- Cryptosporidiosis in AIDS patients
- Restoration of their immune function is most effective
- Highly active antiretroviral therapy (HAART)
    - This is a combination of 3 antiretroviral drugs
- Paromomycin (DOC)
- Azithromycin
- Nitazoxanide
- Pyrimethamine

Isospora belli

- Self-limiting diarrhoea except in immunocompromised persons
- Trimethroprin-sulfamethoxazole (DOC)
- Pyrimethamine + folinic acid

Microsporidia

- Albendazole (DOC)

- Fumagilin

Free living amoeba

- Acute meningocephalitis
- Chronic granulomatus encephalitis after contact with fresh warm water
- Keratitis, particularly in contact lens users

Naegleria

- Amphotericin B
- Rifampicin

Acanthamoeba

- Pentamidine
- Trimethoprim-sulfamethoxazole
- Fluconazole

Cyclosporiasis

- Trimethoprim-sulfamethoxazole

Pneumocystis carinii

- Fungus
  - Previously protozoa due to morphology an drug sensitivity
- DOC
  - Trimethoprim-sulfamethoxazole
- Alternative Rx
  - Pentamidine
  - Trimethroprim +dapsone
  - Clindamycin + primaquine
  - Atovaquone

Malaria

- Treatment of uncomplicated malaria
  - Artemether - lumefantrine
- Treatment of severe malaria
  - Parenteral artemisins (artesunate, artemether) OR parenteral quinine

Treatment of Malaria

27 September 2016 09:10

Introduction

- Infects 500 million people
- Causes 2.5Mdeaths/year
- Highest risk are children under 5, pregnant women and non-immune
- Mosquito is the vector
- Challenges to therapy due to chloroquine resistance
- Vaccine is elusive
- 4 major species
- P. falciparum is responsible for nearly all serious complications and death

Drugs used in treatment

- Acting against asexual erythrocytic form
  - Chloroquine
  - Quinine
  - Quinidine
  - Nefloquine
  - Atovoquone
  - Artemisinin compounds
- Slower acting
  - Proguanil
  - Pyrimethamine
  - Sulphonamides
  - Sulphones
- Antibiotic
  - Tetracyclines
- Tissue form active agents
  - Primaquine

Biology of infection

- Obligate intracellular protozoa
  - Plasmodium
- Transmission
  - Injection of sporozoites
  - Blood transfusion
- Only erythrocytic parasite causes clinical illness

Considerations of therapy

- Reinfection
- Recrudescence
- Relapse
- Resistance
- Resurgence

Classification of antimalarial drugs

- Causal prophylaxis
  - Act on primary tissue forms
    - Proguanil
    - Primaquine
- Prevent relapse
  - Terminal prophylaxis, radical cure
    - Primaquine
- Blood schizonticides
  - Rapidly acting
    - Chloroquine
    - Quinine
    - Mefloquine
    - Quinidine
    - Artemisin
    - Atovoquine
  - Slower acting
    - Antifolates
    - Antibiotics
- Gametocytocides
  - Act against sexual erythrocytes
    - Chloroquine and Quinine (against ovale, malariae)

        - Primaquine - P.falciparum
- Sporotocides
    - Inhibit formation of malarial oocytes and sporozoites

Classification

- 4-aminoquinolines
    - Chloroquine (CG)
    - Amodiaquine
- Quinoline methanols
    - Quinine
    - Quinidine
    - Mefloquine
- 8-aminoquinolines
    - Primaquine
    - Etaquine
    - Tafenoquine
- Folate antagonists/combination
    - Sulphadoxine-pyrimethamine (Fansidar)
- Tetracycline
    - Doxycycline
- Phenantherene methanol
    - Halofantrine
    - Lumefantrine
- Folate antagonists
    - Proguanil
- Sesquiterpene lactone endoperoxides
    - Artemisinins
- (Hydroxynaphtho)Quinone
    - Folate antagonist combination
    - Atovaquone-proguanil (Malarone)

Artemisinin Derivatives

- Sesquiterpene lactone endoperoxides
- Source
    - Qing Hao (Artemisis annua) a
- Qinghaosu
- Synthesised derivatives
    - Dihydroartemisinin: H_20 soluble ∴, PO
        - Artemether: H20 stable ∴, IV, IM, PO, PR
        - Artesunate: Lipid soluble ∴, IM, PO, PR
        - Artenilate
        - Artether

Activity

- Endoperoxide moiety is vital for activity
- Act rapidly on the asexual erythrocytic stage
- Gametocidal
- No tissue effects unlike primaquine
- Not useful for chemoprophylaxis due to short half-life

MoA

- Intraparasitic heme iron of infected erythrocyte catalyses cleavage of endoperoxide bridge
- This forms a carbon-centred radical
- Damage of malarial protein and lipids
- Also causes alkylation of heme and prevention of conversion of hematin to hemazoin causing toxicity in plasmodium
- Also, some anti-leishmania and anti-toxoplasmosis effects

P'Kinetics

- Variable disposition
- Artemether and artesunate both converted to dihydroartemisinin
- Variable PPB
- Hydrolysed to its active component
- Metabolised into inactive components
- Half-life is 45 minutes
- Little in urine

- CYP2C19 activation but devoid of interactions

Indications
- Severe malaria
  - Severe malaria
- Multi-Drug Resistant strains
  - Used in their presence
- Not used for chemoprophylaxis
- Sequential and combination therapy

Toxicity and C/I
- First degree heart block
- Dose related reversible decrease in reticulocyte and neutrophil count
- Temporary rise AST (aspartate aminotransferase)
- Fever
- Neurotoxic in high doses
- QT prolongation
- BM suppression
- Foetal malformation

4-aminoquinoline
- Chloroquine
  - Resistance concern
- Amodiaquine
  - Agranulocytosis
  - Reintroduced (CQ resistance)

Chloroquine
- Potent blood schizonticide, synthetic
- Effective against erythrocytic forms of all 4 species of malaria
- No effect on sporozoites, hypnozoites or gametocytes

MoA
- Unchanged at neutral pH this readily diffuses into the parasite lysosome and at the acid pH of the lysosome protonated, trapped inside the parasite
- Concentrates in parasite food vacuole preventing polymerisation of haemoglobin breakdown products, heme and hemozoin and thus parasite toxicity
- Drug of first choice in SENSITIVE P.falciparum

Resistance
- Global P. falciparum and now growing problem for P. vivax
- Human-MDR-transporter gene codes for P-glycoprotein efflux pump
- Efflux of drug from the parasite vesicles

Actions
- Antimalarial
- Disease modifying anti-rheumatic agent
- Quinidine-like action on the heart

P'Kinetics
- Given orally, loading dose
- Completely absorbed
- Extensively distributed in tissue and concentrated in parasitised RBCs
- IM, SC, small doses by continuous IV infusion
- Large volume of distribution, released slowly from the tissue and metabolised in the liver
- Excreted in urine 70% as unchanged and 30% as metabolites
- Slow elimination
- Major phase half-life 50 hours and residue persists for weeks or months

Adverse Drug Reactions
- NV, dizziness and blurring of vision
- Pruritus
  - Common in Africans
- Headache and urticaria
- Retinopathies following large doses
- Hypotension and dysrhythmias with IV bolus due to prolonged QT
- Safe in pregnancy unlike artemisinins

Indications
- Treatment of drug responsive malaria
- Chemoprophylaxis of malaria due to tissue reservoirs that allow for a long half life

- Hydroxychloroquine is a better drug as a DMARD

8-aminoquinolines

- Primaquine and its more active and slowly metabolised analogues
  - Etaquine
  - Telaquine
- Act on the tissue forms

MoA

- Not known
- Act on liver hypnozoites to cause radical cure I.e P. vivax and ovale
- No effects on sporozoites and little effect on erythrocytic stage of the parasite
- Gametocidal like Artemisinins and most effective in preventing transmission of malaria
- Used invariably in combination.

Resistance

- Resistance is rare
- Decreased sensitivity in some strains of p. vivax

P'Kinetics

- Well absorbed PO
- Rapid disposition following metabolism
- Half-life of 3-6 hours
- Tafenoquine broken down more slowly and can be given weekly

Adverse reaction

- Dose related GI symptoms
- Large doses cause methaemoglobinaemia
- Haemolysis in patients with *G6PD deficiency*
- CI in pregnancy

Phenanthrene Methanol

- Halofantrine
- Lumefantrine

Drug	Pharmacokinetics	Adverse Drug Reaction	Drug Interactions
Halofantrine • Schizonticidal • Active against some strains of P. falciparum resistant to chloroquine(4-aminoqunoline), pyrimethamine (antifolate) and quinine (quinoline methanol) • Effective against the erythrocytic forms of P. vivax • No effects on hypnozoites • Cross resistant with mefloquine (quinoline methanol)	• Slow regular absorption ○ Erratic absorption (increased during intake with a fatty meal) • Peak plasma levels in 4 -6 hours • Half-life is 1 -2 days • Active metabolite with equal potency has half-life of 3 -5 days • Absorption increased by a fatty meal • Elimination in faeces	• Abdominal pains • GIT disturbance • Headache • Pruritus • QT prolongation • Haemolytic anaemia	
Lumefantrine • Aryl alcohol • Used as a fixed drug combination with artemether • Coartem primary agent in the treatment of malaria • Sesquiterpene derivative	• Absorption increased with food		

Atovaquone

- Synthetic hydroxynaphthoquinones
- Good responses but high relapse rates in patients with uncomplicated P. falciparum
- Good cure rate when used with proguanil (Malarone). Few relapses and minimal toxicity
- Activity against PJP and Toxoplasma gondil, Babesia, Plasmodia and P. jerivocii
- Lipophilic
- Interferes with mitochondrial electron transport and pyrimidine synthesis
- Cause membrane collapse

P'Kinetics

- Low water solubility
- Microfine suspension improves absorption
  - Also give with a fatty meal
- Erratic PO absorption (increased with fatty meals)

- PPB 99%, CSF concentration <1%
- Enterohepatic circulation with plasma peaks at 1 -8 hours and 1 - 4 days after a single dose
- Not metabolised significantly and is lost by biliary excretion and 94% recovered in stool

Therapeutic uses

- Malarone - atovaquone and proguanil
- P. carinii
- T. gondii
- Babesia

Toxicity and C/I

- Rash, fever, vomiting, headache
- Dose related maculopapular rash
- Abnormalities of serum transaminases like artemisinins

Antibacterial agents in Malaria therapy

- Sulphonamides
  - Sulphadoxine used with pyrimethamine and with quinine in CQ resistant malaria
- Sulphones
  - Dapsone
  - Sulphonamides and dapsone are active against erythrocytic forms of P. falciparum but less active on P.vivax
- Tetracyclines
  - Slow acting schizonticides used alone as short-term prophylaxis and with quinine for MDR P. falciparum

Sulphonamides and Sulphones

- Sulphadiazine + Pyrimethamine + quinine
- Sulphadoxine + Pyrimethamine (Fansidar)
- Dapsone +Chlorproguanil
- Possible combination with artemisinin
- Resistance to agent by P. falciparum develops rapidly

Terms to note in drugs used in combination
- Have no physico-chemical interaction
- Must have different MoA

Sulphonamides

- Inhibitors of parasite folate synthesis
- Used in combination in treatment of malaria
- Sequential inhibition of dihydropteroate synthase (sulphonamide) and dihdrofolate reductase (pyrimethamine)
- Slow acting schizonticides
- Activity on P. falciparum >P. vivax
- PABA analogue competes with dihydrofolate reductase inhibitors
  - E,g. Sulphadoxine - pyrimethamine (Fansidar)

Quinoline Methanols

- Examples
  - Quinine
  - Quinidine
  - Mefloquine
- Quinine and quinidine are also cinchona alkaloids derived from the bark of the cinchona tree
- Both have the same structure but differ in the configuration of a secondary alcohol group
- Quinidine is more potent and toxic than quinine

Quinine

Pharmacological effects

- Antimalarial actions
  - Blood schizontocide (rapid acting)
    - All malaria spp
  - Gametocidal (p. vivax and malariae)
- Action on skeletal muscle
  - Decreases the excitability of the motor end plate region so the responses to repetitive nerve stimulation and to acetylcholine are reduced

MoA

- Unknown
- May be similar to chloroquine ?
- Inhibition of the conversion of the toxic heme to hemozoin (non-toxic) ??

MoR

- Unknown

- Thought to be a p. falciparum multi drug resistance 1 (pfmdr1) gene, that confers resistance of p. falciparum to mefloquine, halofantrine and quinine in vitro. May differ in vivo i.e. sensitive to mefloquine and vice versa

Pharmacokinetics

- Oral, IM, IV
- Oral rapid absorption (80%)
  - Even in patients with diarrhoea
- Peak plasma levels in 3 - 8 hours
- Loading dose
  - Peak concentration reached faster
- Volume of distribution
  - 1.5 litres/kg
- Half life
  - 11 hours
- Concentration of quinine plasma concentration
  - in RBCs: 33 - 40%
  - In CSF 2- 5%
- Crosses placenta and found in breast milk
- Metabolised by CYP3A4 mainly and other isoforms e.g. CYP2D6
- 3-hydroxyquinine is a less active metabolite
- Only 20% of dose excreted unchanged in urine
- Renal excretion more rapid in acidic urine
- P'kinetics change with the severity of malaria
  - Decreased volume of distribution
  - Reduced systemic clearance (malaria impairs hepatic functions)
  - Half life increases from 11 hours to 18 hours
  - Peak plasma levels = 15 - 20 mg/l
    - Levels > 10 mg/l are toxic in self poisoning
  - Increased levels of &1-glycoprotein
  - Free fraction of quinine reduced from 15% to 5 - 10% of the total plasma concentration
  - Therefore, no toxicity - increased protein binding

Therapeutic uses

- Treatment of severe malaria
  - Also drug resistant malaria
- Babesiosis

Toxicity

- Triad of related toxicities (therapeutic and excessive doses)
  - Cinchonism (frequent)
  - Hypoglycaemia (common)
  - Hypotension (rare)

Cinchonism

- Tinnitus, high tone deafness, vertigo (8th cranial nerve neurotoxicity)
- Headache, dysphoria
- Postural hypotension, seating
- NV
- Visual disturbances
  - Blurred vision
  - Disturbed colour perception
  - Photophobia
  - Diplopia
  - Mydriasis
  - Blindness
- Severe cinchonism
  - NV and abdominal pain
  - Deafness, blindness
  - Disturbance of cardiac rhythm and conductance

Hypoglycaemia

- Quinine stimulates pancreatic ß cell leading to hyperinsulinaemia
- Life-threatening
  - 10% dextrose solution given IV

Hypotension

- Usually due to rapid IV infusions

Other AE

- Skin
  - Sweating
  - Rashes

    - Angioedema
- CVS
    - Hypotension (rapid IV)
    - Cardiac arrhythmias overdose)
        - Prolongs QT interval
    - Quinidine is more cardiotoxic than quinine
- GIT
    - NVD
    - Abdominal pain
- Hypersensitivity reactions (toxic manifestations in small doses)
    - Cutaneous flushing and pruritus (common)
        - Urticaria
        - Steven-Johnson Syndrome (SJS)
        - Toxic epidermal necrolysis (TEN)
    - Cinchonism
    - Bronchospasm
    - Blackwater fever (rare): Haemoglobin in urine
        - Triad of massive haemolysis, haemoglobinaemia and haemoglobinuria
            - Leads to anuria and renal failure
                - Death can occur
    - Mild haemolysis in G6PD deficiency
    - Thrombocytopoenic purpura
    - Anaphylactic shock
    - Angioedema
    - Stop Quinine if hypersensitivity reaction occurs
- Other toxic effects
    - Hypoprothrombinaemia
    - Leukopenia
    - Agranulocytosis
    - Can stimulate the uterus (doses higher than therapeutic)
    - Foetal abnormalities ???
        - Optic nerve hypoplasia
    - Concentrated solutions can cause abscesses IM or thromophlebitis IV
    - Irritates tissues therefore, not given SC

Contraindications

- Patients who are hypersensitive to drug
- History of hypersensitivity to quinine, quinidine and mefloquine (cross sensitivity)
- Prolonged QT intervals
- Stop if haemolyses, severe cinchonism or hypersensitivity
- Optic neuritis
- Concurrent use of quinine and mefloquine
- G6PD deficiency
- Myasthenia gravis

Effects due to action on skeletal muscle

- Quinine
    - Can antagonise the effects of physostigmine on skeletal muscle
    - May cause respiratory distress and dysphagia in patients with myasthenia gravis
    - May cause symptomatic relief of myotonia congenita

Drug interactions

- Antacids delay absorption of Q
- Quinine and quinidine delay absorption and elevate plasma level of digoxin and related cardiac glycosides
- Quinine increases plasma levels of warfarin
- The renal clearance of quinine
    - Decreased by cimetidine
    - Increased by acidification of the urine and by rifampicin

Quinidine

- Also used as an antiarrhythmic agent
- Blocks Na+ and K+ currents
- α-adrenoceptor blockade and vagal inhibition
    - IV can cause hypotension and sinus tachycardia

Adverse effect

- Cardiac
    - Prolonged QT interval and torsades de pointes
    - Ventricular tachycardia (high doses)
    - Exacerbate heart failure or conduction system disease in some patients
- Non-cardiac
    - Diarrhoea (30 - 50%) of patients

    - Immunological reactions
        - Thrombocytopoenia
        - Hepatitis
        - Bone marrow suppression
        - Lupus syndrome
    - Cinchonism

Drug interactions

- Quinidine is an inhibitor of CYP2D6
    - Quinidine + codeine
    - Quinidine + propafenone
- Quinidine + digoxin / digitoxin
    - Increased digoxin
- Quinidine + phenobarbitone / phenytoine
    - Reduced quinidine
- Quindine + cimetidine / verapamil

Mefloquine

Antimalarial action

- Blood schizontocide
- Possible sporontocide

MoA

- Unknown ??
- Like chloroquine
- May be similar to chloroquine ?
- Inhibition of the conversion of the toxic heme to hemozoin (non-toxic) ??

MoR

- See quinine

Pharmacokinetics

- No parenteral preparations
    - Severe local reactions
- Oral only
    - Well absorbed
- Food increases absorption
- Widely distributed
    - Crosses placenta and found in breastmilk
- 98% PPB
- Metabolised by the liver
- Slowly eliminated
    - Half life = 20 days
- Faecal excretion

Therapeutic use

- Prophylaxis of malaria
    - Non-immune travellers
        - Brief periods of travel
        - In areas where there is chloroquine resistance
    - Treatment of malaria
    - Active against drug resistant strains

Toxicity

- Frequent
    - NVD
    - Abdominal pain
    - Altered mood
    - CNS (~0.5%)
        - Dizziness, ataxia, headaches
        - Altered motor functions and level of consciousness
        - Visual or auditory disturbances
        - Reverse when treatment is stopped
- Alter cardiac conduction
    - Arrhythmias, bradycardia
- Rare CNS
    - Severe neuropsychiatric reactions (stop mefloquine)
        - Disorientation, confusion
        - Seizures
        - Encephalopathy
        - Psychosis, depression
        - Paranoia, hallucination

Contraindications
- Patients with a history of
  - Seizures
  - Severe neuropsychiatric disturbance (schizophrenia, depression)
  - Arrhythmias or cardiac conduction effects
  - Adverse reactions to quinine, quinidine, mefloquine, halofantrine and chloroquine
  - Do not co-administer with quinine, quinidine, halofantrine, ketoconazole
    - ECG changes
- Mefloquine can be administered 12 hours after last dose of quinine, quinidine and chloroquine treatment

Drug interactions
- Mefloquine + sodium valproate
  - Increased risk of seizures
- Mefloquine and live typhoid vaccine
  - Not good immunological response to live typhoid vaccine
- Mefloquine + drugs that affects cardiac conduction

Anti-folate anti-malarials

Pyrimethamines
- A 2,4 - diaminopyridine related to trimethoprim
- Used in fixed combinations with sulphones and sulphonamides
- Acts by inhibiting dihydrofolate reductase, preventing folate use in parasites
- A blood schizonticide but acts slowly, therefore, only used in prophylaxis
- Resistance noted with P. falciparum and vivax
- Has cross resistance with chloroquine
- When combined with sulphonamides and sulphones may be effective
- No effects on the host at normal doses but at high doses e.g. toxoplasmosis, causes macrocytic anaemia

P'kinetics
- Slowly but adequately absorbed orally
- Peak plasma levels at 4 - 6 hours
- Extensively metabolised in the liver
- Renal elimination
- Half-life of 3.5 days

Clinical uses
- Treatment of acute malaria, Fansidar (pyrimethamine-sulphadoxine, 25:500, 2-3 tabs stat)
- Toxoplasmosis
  - 75mg stat then 25mg/day with sulphadiazine 1-1.5g qid for 3-4 wks
- Give with folininc acid 10-20mg/day to prevent megaloblastic anaemia and bone marrow suppression

Adverse effects
- Well tolerated in therapeutic doses
  - GIT AE
  - Allergic reactions

Proguanil
- A biguanide derivative

MoA
- Metabolite cycloguanil has high affinity for dihydrofolate reductase, inhibits its actions

Antimalarial actions
- Blood schizonticide acts slowly
  - Prophylactic
- Has marked effect on the primary tissue stages of P. falciparum
  - A casual prophylactic

Resistance
- P.vivax and ovale known
- Cross resistance with chloroquine

PK
- Slow, adequate absorption, PO
- Peak levels after 5 hrs
- Half-life of 16 hours
- Metabolised to a triazine, cycloguanil which is the active form

Clinical use
- Prophylaxis
  - 100mg/d
- May be given with chloroquine

    - 500mg/7
- With Atovaquone
    - Malarone
        - Acute and prophylaxis of malaria

Adverse effects
- GIT symptoms
- Allergic reactions

Sulphonamides and Sulphones
- Sulphadiazine + pyrimethamine
    - For toxoplasmosis
- Sulphadoxine + pyrimethamine
    - Fansidar
- Dapsone + pyrimethamine
    - Maloprim
- Sulphamethoxazole + trimethroprim
    - Septrin/ cotrimoxizole
- Sulphametopyrazine + pyrimethamine
    - Metakelfin

Actions
- Sulphonamides and sulphones are blood schizonticides effective on falciparum
- Only a weak action on vivax
- No effect on gametocyte or hypnozoites
- Inhibit dihydropteroate synthase
- Synergistic with pyrimethamine and trimethoprim
- Slow acting with numerous side effects

PK
- Fansidar
    - Well absorbed orally
    - Peaks at 2 - 8hours
- Sulphadoxine
    - Half-life 170hrs
- Pyrimethamine
    - Halflife 80-110hrs

Clinical uses
- Acute malaria treatment
- Prophylaxis
    - 2 -3 tabs stat
- Maloprim
    - Prophylaxis
        - 2 tabs/7
- Metakelfin
    - Acute malaria treatment
        - 2 - 3 tabs stat

Adverse effects
- Rare at therapeutic doses
- Mainly the sulphonamides
    - Allergy
    - Haematologic effects
        - Anaemia
        - Leukopenia
    - GIT
        - NV
    - CNS
        - Confusion
        - Seizures
    - Renal
        - Renal stones
    - Dermatologic
        - Erythema marginatum (EM)
        - TEN
        - SJS
- Dapsone
    - Haemolytic anaemia
    - Methaemoglobinaemia
    - Agranulocytosis
    - Bone marrow depression with RBC aplasia

- Cross sensitivity with sulphonamides

Antiprotozoals

Tuesday, 4 October 2016 9:14 AM

Amoebiasis

- AKA amoebic dysentery
- Infection of the intestinal tract caused by the protozoan parasite, Entamoeba histolytica
- Usually transmitted from person to person through faecal contamination of food or by sexual contact in homosexuals
- Infective forms are cysts
    - After ingestion release trophozoites which lodge in the caecum and ascending colon where they multiply and form other cysts
- Over 5M people worldwide may harbour these parasites and several thousands die due to fulminating colitis and liver abscesses
- Amoebic dysentery occurs when the parasite invades the intestinal wall and abscesses may form in the live, lung or brain as a result of haematogenous spread. Sin lesions may also occur
- Malnourished, immunocompromised individuals as well as pregnant women are most vulnerable

Therapeutic strategies

- Adhere to good hygienic standards
- Aimed at acutely ill as well as those who are asymptomatic carriers
- Elimination of intestinal flora which is amoeba's food source, hence, the use of antibiotics in combination with other drugs

Classification

- Luminal amoebicides
    - Dichloroacetamides
        - Diloxanide furoate (commonly used)
        - Clefamide
        - Etofamide
        - Teclozan
    - Antibiotics
        - Tetracycline
        - Paromomycin
        - Erythromycin
    - Halogenated 8-hydroxyquinolines
        - Iodoquinol (di-iodohydroxyquin)
        - Clioquinol
        - Act on parasites in the lumen of the bowel
- Systemic amoebicides (effective against amoeba in the intestines and the liver)
    - Emetine
    - Dehydroemetine
    - Chloroquine
- Mixed amoebicides (5-nitroimidazoles, effective against both luminal and systemic forms of amebiasis
    - Metronidazole

Diloxanide Furoate (Furamide, entamizole)

- An ester
- Hydrolysed to diloxanide and furoic acid in lumen of mucosa of the intestine
- 90% absorbed, conjugated with glucoronic acid, excreted in urine

- It is unabsorbed diloxanide which is antiamoebic (affect amoeba before encystment)
- 60 - 90% of an oral dose excreted in urine within 48 hrs with more than half appearing in 6 hours
- 4 - 9% is excreted in faeces
- Peak plasma concentration of glucoronide an hour
- Administer oral 500mg tabs for 10 days
    - Children 20mg/kg/day in divided doses for 10 days
- Drug of choice in the treatment of asymptomatic passers of cysts
- Indicated for the treatment of non-invasive intestinal amoebiasis
- Also used for eradication of residual amoeba in the colonic lumen following treatment of invasive diseases with antiamoebic drugs
- Both diloxanide and diloxanide furoate are effective
- MoA not well documented
- AE
    - Mild GIT symptoms particularly flatulence
    - Pruritus and urticaria may also occur
- Should not be used in pregnancy and in children < 2 years

Halogenated Hydroxyquinolones

- Believed to inactivate the enzymes or halogenate the proteins of amoebae
- Alternative drugs for the therapy of mild or asymptomatic infestations
- Commonly used with metronidazole to treat amoebic infections
- Effective alone or with tetracycline in the treatment of dientamoeba fragilis infections
- May treat some cases of G. lambilia and B. coli infections
- 90% not absorbed
- Half-life is 11 - 14 hours
- Excreted in urine as glucuronides
- Effective against organisms in the bowel lumen but not against trophozoites in the intestinal wall or extra intestinal tissues
- Should be taken with meals to limit GIT toxicity
- Contraindicated in persons intolerant to iodine
- Side effects
    - NVD
    - Skin rashes
    - Anal pruritus
    - Sub-acute myelo-optic neuropathy
    - Iodine sensitivity

Antibiotics

- May be used in conjunction with metronidazole to treat severe forms of intestinal amoebiasis
- Reduce the population of the intestinal food source for proliferation of pathogenic amoeba

Paromomycin

- An amoebicidal aminoglycoside
- Not significantly absorbed from the GIT
- The small amount absorbed is excreted slowly, mainly by GF in those with renal impairment
- Use in caution in those with GIT ulcerations
- Exerts anti-amoebic effect in 2 ways
    - Reduces population of intestinal flora
    - Directly amoebicidal, probably by acting on cell membrane of amoeba to cause leakage

- Erythromycin and older tetracyclines (oxytetracycline, chlortetracycline and tetracycline itself) are frequently used because a large proportion of dose administered escapes absorption in the bowel

Systemic Amoebicides

- Ementine is the main alkaloid obtained from Cephaelis ipecacuanha (Brazil Root)
- Oral ipecac is used as an expectorant and emetic
- Dehydroemetine is a close structural analogue (synthetic) of emetine and is claimed by some authors to be the most effective tissue amoebicide
- Dehydroemetine has similar pharmacological properties as emetine
- Dehydroemetine and emetine:
    - Are alternative treatment for amoebiasis
    - Use limited by their toxicities
    - Both have been largely replaced by mixed amoebicides of nitroimidazole class because they are effective but far safer
    - Given with anti-emetic

Uses

- Amoebic dysentery
    - As an alternative to parenteral 5-nitroimidazoles in severely ill and cannot take drugs orally
    - Following inadequate response to 5-imidazoles
    - Given supplementary treatment with tetracycline to reduce the risk of bacterial superinfection
- Amoebic abscess
    - Dehydroemetine effective when used alone, but is usually necessary to give a second course 6 weeks later inpatients with extensive liver abscesses
    - Supplement treatment with chloroquine which concentrates in the liver
        - Give concurrently or immediately after
- NB: All patients must take diloxanide orally to eliminate surviving organisms in the colon

Disadvantages

- Given parenterally (IM, SC) therefore local reactions ranging from pain to abscesses
- After prolonged administration systemic toxic reactions some of which may be serious or fatal. Adverse effects mainly involve CVS, CNS and GIT
- Cannot be used alone for curative purposes
- Close medical supervision is required
- Contraindicated in:
    - Pregnancy
    - Cardiac, renal or NM disease

Chloroquine

- Used in conjunction with metronidazole and diloxanide furoate to treat and prevent amoebic liver abscesses
- Eliminates trophozoites in liver abscesses but is not useful in treatment of luminal amoebiasis
- Extra details in antimalarials

Mixed Amoebicides

- Metronidazole
- Tinidazole - good amoebicide
- Nimorazole, Secnidazole, Ornidazole - poor results for treatment of amoebiasis

Metronidazole

- Has antimicrobial activity against anaerobic bacteria and some protozoa including E. histolytica
- Used for treatment of invasive amoebiasis
    - Eradicates amoebic tissue infections (liver abscesses, intestinal wall and extraintestinal infections
- Kills trophozoites but no the cysts of E. histolytica
- Patients should receive luminal amoebicides to eliminate surviving organisms in the colon

5-nitroimidazoles
- Damage to the DNA of the trophozoites by toxic oxygen products generated from the drug by the parasites

Drug interactions
- Potentiates anticoagulant effects of coumarin anticoagulants
- Elimination accelerated by phenytoin and phenobarbitone
- Cimetidine decreases clearance of metronidazole

P'kinetics
- Rapidly and completely absorbed from the GIT
    - Peak plasma concentration on 1 - 3 hours
    - May fail to reach the large intestines in therapeutic concentrations therefore poorly effective in luminal but excellent in tissue amoebiasis
- Half-life of about 7 hours
    - Less than 20% plasma protein bound
- Rapidly distributes throughout the body tissues and CSF
- Eliminated through the kidneys as unchanged drug, glucuronides or in form of oxidation products (urine may become dark in colour)
- Tinidazole and nimorazole similar with metronidazole
    - Tinidazole half-life - 12 - 14 hours

AE of metronidazole
- GIT
    - NVD
    - Anorexia
    - Metallic taste in the mouth
    - Epigastric distress and abdominal crumpling
- CNS
    - Dizziness
    - Headache
    - Sensory neuropathies
    - Disulphirum-like effect (abdominal distress, vomiting, flushing or headache
        - Metronidazole interferes with alcohol metabolism, by inhibiting both alcohol and aldehyde dehydrogenases
            - Avoid alcohol
- Proven to be carcinogenic in animals and mutagenic in bacteria
    - Potentially dangerous to man

Trichomoniasis
- Caused by trichomonas vaginalis
- Most common STI
- Estimated that more than 200M people infected annually
- In females causes
    - Vaginal discharge
    - Dysuria
    - Vulvovaginal pruritus

    - Signs also occur in female infants born of an infected mother
- Men
    - Carriers and may not cause symptoms of infections, although urethritis can occur
- Control
    - Treat all sex contacts whether they have symptoms or not

Trichomonacides
- 5-nitroimidazoles
    - Metronidazole
    - Tinidazole
    - Nimorazole
    - Ornidazole
- Metronidazole contraindicated in early pregnancy
    - Relieve the symptoms of trichomoniasis by clotrimazole pessaries 100mg OD daily for a week
    - In lactating mothers, breast-feeding should be interrupted until 24 hours of cessation of treatment
    - Infection in neonates resolve simultaneously within a few weeks
        - If signs are still evident after 4 weeks of birth, give 20mg/kg/day 5/7
    - Treatment of patients with identified infection and their sexual partners
        - Dose 2gm stat; 200 - 250mg tabs 7/7
            - Infants 20mg/kg daily 5/7

Contraindications
- Known HS
- Early pregnancy
- Chronic alcohol dependence

Giardiasis
- Caused by Giardia intestinalis which freely coexists with E. histolytica and is transmitted the same way
- Common cause of both acute and persistent diarrhoea in children in developing countries
- Ingested cysts release the trophozoites that attach firmly to the mucosa of the jejunum where they multiply and eventually form another generation of cysts that are passed in the faeces
- Many carriers are asymptomatic but others lose weight and complain of diarrhoea and GIT discomfort
- Severe symptoms are more likely to occur in malnourished, hypochlorhydric and immunocompromised individuals
- Treatment
    - 5 - nitroimidazoles
    - Mepacrine
        - 100mg tabs 5/7, child 2mg/kg 8 hourly

Pneumocystosis
- Trimethroprim - sulphamethoxazole
- Clindamycin + primaquin

Toxoplasmosis
- Pyrimethamine + Sulphadiazine
- Pyrimethamine + clindamycin

Trypanosomiasis

- Melasoprol
- Nifurtimox *
- Suramin
- Pentamidine

Leishmaniasis
- Sodium stibogluconate
- Miltefosine
- Pentamidine

Babesia
- Clindamycin
- Quinine

Pentamidine
MoA
- Unknown
    - Thought to interfere with protozoal nuclear metabolism by inhibition of DNA, RNA and protein synthesis

PK
- Given parenterally
- Initial elimination half-life 6 hours, bound to tissues avidly then eliminated gradually, half-life 12 days
- Does not cross into CNS
- Alternative DOC in pneumocytosis, African trypanosomiasis, Leishmaniasis

Side Effects
- Significant in 50% of patients
    - Pain at IM injection site and formation of sterile abscess
    - Severe hypotension
    - Tachycardia
    - Dyspnea after IV admin
    - Pancreatitis
    - Hypoglycaemia
    - Hallucinations
    - Cardiac arrhythmias

Sodium Stibogluconate
- Pentavelent antimonial
- First-line drug in treatment of visceral and cutaneous leishmaniasis

MoA
- Unknown

PK
- IV, IM or intralesional administration

Side Effects
- Chest pain
- Dyspnoea
- Thrombophlebitis
- Pancreatitis
- NV

- Metallic taste

Melarsoprol
- Trivalent arsenical
- Used as first-line treatment of east African trypanosomiasis with CNS involvement

PK
- IV
- Rapid excretion but accumulates in CNS

Side Effects
- Vomiting
- Hypotension
- Fever
- Renal disease
- Cardiac disease
- Reactive encephalopathy that may result in seizures, coma and death

Suramin
- Used in treatment of trypanosomiasis but not effective against CNS form or advanced disease
- Can be used for prophylaxis against trypanosomiasis
- Less effective against West African Trypanosomiasis

PK
- Highly protein bound
- Short initial half-life but terminal half-life ~ 50 days

MoA
- Unknown

Anti-Helminthic Drugs

Wednesday, 5 October 2016 11:22 AM

- There are 2 clinically important types of helminthic infections
  - Those which the worm lives in the hosts 'GIT
    - Tapeworms
    - T. saginata
    - Intestinal round worms
      - Ascaris lumbricoides
      - Trichuris trichuria
  - Those which live in other tissues in the host body
    - Trematodes
      - Schistosoma haematobium
      - S.mansoni
    - Tissue roundworms
      - Trichinella spiralis
      - Filarial worms
    - Hydatid tapeworms
      - Echinococcus granulosus

General MoA of AHD

- Act by the following 3 mechanisms
  - Causing paralysis of the worm
  - Damaging the cuticle of the worm
    - This leads to partial digestion of the worm or rejection by immune mechanisms
  - Interfering with the metabolism of the worm
- In addition, AHD may either act
  - Locally to expel worms from the GIT
  - Systemically to eradicate adult/immature worms that invade organs and tissues

Roundworms (nematodes)

- The medically important intestinal nematodes responsive to drug therapy include
  - Enterobius vermicularis
  - Trichuris thrichiuria
  - Ascaris lumbricoides
  - Ancyclostoma and Necator spp
  - Strongyloides stercoralis
- Tissue nematodes responsive to drug treatment
  - Ancyclostoma spp that cause cutaneous larvae migrans
  - Dracunculus
  - Onchocerca
  - Toxocara
  - Filarial spp
    - W.bancrofti
    - B.malayi
    - Loa loa

Drugs for treatment of nematodes

- Benzimidazoles
- Pyrantel pamoate
- Piperazine
- Ivermectin

- DEC
- Doxycycline

Benzimidazole

- Include
    - Thiabendazole
    - Mebendazole
    - Albendazole

MoA

- Inhibit microtubule synthesis in susceptible helminths
    - As a result they interfere with microtubule dependent functions such as glucose uptake in helminths

Albendazole

- Its additional AH action
    - Larvicidal effect in hydatid disease, cysticercosis, ascariasis and hookworm infection
    - Ovicidal effects in asariasis, ancyclostomiasis and trichiuriasis
- PK
    - Erratically absorbed after PO
    - Absorption increases with fatty meal
    - Rapidly undergoes first-pass metabolism in the liver to an active metabolite, albendazole sulphoxide
    - It reaches maximum plasma concentration after 3 hours
    - Plasma half-life is 8 - 12 hours
    - The sulphoxide is mostly protein bound, well distributed into tissues and enters bile, CSF and hydatid cysts
    - Its metabolites are excreted in urine
- AE
    - When used for 3 days, it is free from major adverse effects
    - Mild and transient AE
        - Epigastric discomfort
        - ND
        - Headache
        - Dizziness
        - Insomnia
    - Long term use for hydatid disease can cause
        - Abdominal discomfort, headaches, fever, fatigue, alopecia, increased liver enzymes and pancytopoenia
            - Blood counts and LFTs should be monitored with long term use
- CI
    - Hypersensitivity to other benzimidazoles
    - In liver cirrhosis
    - Caution
        - Safety in pregnancy and in children <2 years old, is not yet established
- CU
    - Albendazole is a broad spectrum, oral, AH
        - It is the DOC for
            - Ascaris lumbricoides
            - Hookworm
            - Cutaneous and viceral larva migrans
            - Angiostrongylus cantonensis
            - Capillaria phillipinensis (intestinal capillariasis)
            - Hydatid disease (Echinococcus spp)

        - Cysticercosis (pork tapeworm larval stage)
    - Alternative DOC
        - Strongyloides stercoralis
        - Enterobius vermicularis
        - Trichostrongylus spp
        - Clonorchis sinesis (liver fluke)
        - Opistorchis spp

Albendazole should be taken on an empty stomach when used against intraluminal parasites but with a fatty meal when treating tissue parasites

Mebendazole

- Additional AH action
    - Parent drug appears to be active form
    - Ovicidal to hookworm, ascaris and trichuris

PK

- <10% of PO is absorbed
- Increased absorption if ingested with fatty meal
- Absorbed drug is >90% protein bound rapidly converted to inactive metabolites primarily during first-pass in the liver
- Half-life 2 - 6 h
- Excretion is mostly in urine, mainly as decarboxylated derivatives within 24 - 48 hours
- Small amounts excreted in bile

AE

- Low incidence of AE
- Nearly no AE with short term treatment
- Rare Aes
    - GI symptoms
- Rare reaction with high dose treatment
    - HS reactions (rash , urticaria)
    - Agranulosis
    - Alopecia
    - Elevated liver enzymes

CU

- Wide spectrum on AH activity
- DOC for
    - Ascaris
    - Hookworms
    - Trichuris triciuria
    - Enterobius vermicularis
    - Trichinella spiralis
    - Trichostrongylus spp
    - Angiostrongylus cantonensis
- Alternative drug for
    - Visceral larvae migrans
    - Dracunculus medinensis
    - Capillaria phillipinensis
    - Taenia saginata

CI

- Teratogenic in animals and contraindicated in pregnancy

Caution

- Children <2 years because of limited experience and rare reports of convulsions in this age group
- Patients with liver cirrhosis

DI

- Mebendazole's plasma levels are
  - Reduced with concomitant use of carbamazapine or phenytoin
  - Increased with cimetidine use

Thiabendazole

- Additional MoA
  - Ovicidal effects against some parasites

PK

- Rapidly absorbed after ingestion
- Peak plasma concentration in 1 - 2h
- Half-life of 1.2h
- Almost completely metabolised in the liver to 5-hydrothiabendazole
- 90% excreted in urine in 48h as glucuronide or sulphonate conjugate
- It can also be absorbed from the skin

CU

- Alternative drug
  - Strongyloides stercoralis
  - Cutaneous larvae migrans
    - Used topically
  - Dracucunlus medinensis

AE

- It is much more toxic than other benzimidzoles
- Also more toxic than ivermectin and therefore, other drugs are now preferred for most indications
- Common AE include
  - Dizziness
  - Anorexia
  - NV
- Less common AE
  - Epigastric pain
  - Abdominal cramps
  - Diarrhoea
  - Pruritus
  - Headache
  - Drowsiness
  - Neuropsychiatric symptoms
  - Irreversible liver damage and fatal SJS have been reported

Caution

- Limited data on safety in children weighing less than 15kg

CI

- Pregnancy
- Hepatic or renal disease

Pyrantel Pamoate

Chemistry

- It is a tetrahydropyrimidine derivative

MoA

- Neuromuscular blocking agent
- Causes release of acetylcholine and inhibition of cholinesterase
- This results in paralysis of worms followed by expulsion

PK

- Poorly absorbed from the GIT
- Peak plasma levels are reached in 1 - 3 hours
- >50% of the administered dose is recovered unchanged in the stool

AE

- Minor
- Include
    - GIT discomfort
    - Headache
    - Dizziness
    - Drowsiness
    - Insomnia
    - Rash
    - Fever
    - Weakness

CU

- Wide activity against nematodes
- Active mainly against luminal organisms
- Effective against adult and immature forms of susceptible helminths within the intestinal tract
- However, it is not active against migratory stages I the tissues or against ova
- It is the DOC for treatment of
    - Ascaris
    - Enterobius vermicularis
    - Hookworm
    - Trichostrongylus spp
- It has no action on flukes and tapeworms

Caution

- Use pyrantel pamoate with caution in patients with hepatic dysfunction
    - It has caused transient aminotransferase elevations
- Experience of the drug in pregnant women and children <2 years is limited

Piperazine

MoA

- Paralyses ascaris by blocking acetylcholine at NM junction
    - Paralysed live worms are expelled by normal peristalsis

PK

- Rapidly absorbed
- Maximum plasma levels reached in 2 - 4 hours

- Most of the drug is excreted unchanged in the urine in 2 - 6 hours and excretion is complete with in 24 hours

CU
- Alternative drug for ascariasis treatment
- Not recommended for other helminth infections

AE
- Mild GIT irritation, dizziness and headache, are the most common
- Neurotoxicity and allergic reactions are rare

CI
- Piperazine should not be used in
    - Pregnancy
    - Patients with hepatic or renal dysfunction
    - History of epilepsy or chronic neurologic disease

Ivermectin
Chemistry
- Its is a semisynthetic macrocyclic lactone

MoA
- Intensifies GABA-mediated neurotransmission in peripheral nerves of nematodes to cause immobilisation of parasites
- Facilitates removal through the reticuloendothelial system
- In onchocerciasis, it is microfilarial
- Does no effectively kill adult worms but blocks the release of microfilaria for some months after treatment

PK
- Available only for PO
- Rapidly absorbed
- Reaches maximum plasma concentration, 4 hours after a 12mg dose
- Wide tissue distribution
- Volume of distribution is ~50L
- Half-life - 16 hours
- Excretion of the drug and its metabolites is almost exclusively in the stool

CU
- Is the DOC for
    - Onchocerciasis
    - Cutaneous larva migrans
    - Strongylodiasis
    - Some forms of filariasis

AE
- Single dose PO treatment in onchocerciasis results in reactions to the dying worms including
    - Fever
    - Headache
    - Rashes
    - Pruritus
    - Tachycardia hypotension
    - Pain in joints, muscles and lymph glands
- These symptoms are usually short duration and most can be controlled with

antihistamines and NSAIDS

CI and caution
- Avoid drugs that enhance GABA activity
- Should not be used in pregnancy

DEC (Diethylcarbamazine)
Chemistry
- Synthetic piperazine derivative

PK
- Rapidly absorbed from the GIT
- Should be taken after meal
- Peak plasma levels reached within 1 - 2 hours
- Plasma half-life 2 - 3 hours in presence of acidic urine and 10 hours in alkaline urine
- Rapidly equilibrates with all tissues except fat
- Excreted principally in urine as unchanged drug and the N-oxide metabolite
- Dosage should be reduced in persistent urinary alkalosis or renal impairment

MoA
- Immobilises microfilaria and alters their surface structures
- The microfilariae get displaced from tissues and become more susceptible to destruction by host defence mechanisms
- Microfilariae are killed rapidly however, adult parasites are killed more slowly and often require several courses of treatment

CU
- DOC for parasites
    - W.bancrofti
    - B.malayi
    - B.timori
    - Loa Loa

AE
- Generally mild and transient and include headache, anorexia, vomiting, dizziness
- AE also occur from release of proteins from dying Microfilariae and adult worms
- They include
    - Fever
    - Papular rash
    - Headache
    - GI symptoms
    - Cough
    - Chest pain
    - Muscle and joint pains
    - Leukocytosis
    - Proteinuria
    - Eosinophilia may increase with treatment
    - Retinal haemorrhages and rarely encephalopathy, may occur

Doxycycline
- Is is a tetracycline
- Significant microfilarial activity against W. bancrofti suggesting better activity than any other drug, against adult worms
- Also has activity against onchocerciasis

MoA

- Acts indirectly by killing wolbachia, an intracellular bacterial symbiont of filarial parasites
- Hoped to be important in active treatment of both active filariasis and mass chemotherapy campaigns

Trematodes or Flukes

- The medically important trematodes include
  - Schistosoma spp (blood flukes)
  - Clonorchis sinensis (liver fluke)
  - Paragonimus westermani (lung fluke)
- S.haematobium, S.mansoni and S. japonicum are the main spp that cause human schistosomiases
- The spp in Africa
  - S.mansoni and haematobium
- Schistosomal disease primarily affects the liver, spleen or GIT (mansoni and japonicum) or Genitourinary tract (haematobium)

Drugs for treatment of trematodes

- Praziquantel
- Bithionel
- Metrifonate
- Oxamniquibe
- Triclabendazole
- Niclosamide

Praziquantel

Chemistry

- Synthetic isoquinoline-pyrazine derivative

PK

- Rapidly absorbed
- Bioavailability is 80% after PO
- Peak plasma concentration with in 1 - 3 hours
- CSF concentration are 14 - 20% of the plasma concertation
- ~80% PPB
- Extensive first pass metabolism
- Most of the drug is metabolised to inactive hydroxylated and conjugated products
- Plasma half-life is 0.8 - 2 hours
  - May be prolonged in patients with severe liver disease including those with hepatosplenic schistosomiasis
- 60% - 80% renal excretion, 15 - 35% bile excretion

MoA

- Appears to increase the cell membrane permeability of the helminth to calcium
  - Results in contraction of the musculature and eventually, paralysis, dislodgement and death of the worm
- Effective against the adult and immature schistosomes
- Also has prophylactic effect against cercarial infections

CU

- Praziquantel tabs taken with liquid after a meal
- Should be swallowed without chewing because of the bitter taste that can induce retching

and vomiting

NB: with few exceptions, fluke _

- DOC
  - All flukes (trematodes) except fasciola hepatica
  - All tapeworms except cycticercosis (pork tapeworm larval stage)
- AD for cycticercosis

AE
- Common include
  - Headache
  - Drowsiness
  - Dizziness
  - Malaise
- Less frequent
  - GI irritation
  - Skin rash
  - Fever
- Neurologic effects can occur in the treatment of neural cycticercosis including intracranial hypertension and seizures
- Corticosteroid therapy reduces the risk of the more serious reactions

CI and caution
- CI in intraocular cysticercosis because host response to parasite destruction may cause irreversible destruction to eye
- Shortly after taking drug, patient should avoid driving, operating machinery and other tasks that demand mental alertness (causes dizziness and drowsiness)
- Should be preferably avoided during pregnancy because high doses increase abortion rates in rats
- Patients should be cautioned against chewing the bitter tasting drug because the retching and vomiting that results can cause regurgitation of segments during the treatment of T. solium infection which can lead to cysticercosis

DI
- Plasma concentrations of praziquantel increase when taken with a high carbohydrate meal of cimetideine (hepatic CYP inhibitor)
- Bioavailability is markedly reduced with some antiepileptic like phenytoin or carbamezepine or corticosteroids

Mtrofonate
- Organophosphate prodrug, converted by the body to cholinesterase inhibitor dichlorvos
- Active metabolite exclusively against S, haematobium
- AE occur from excess cholinergic stimulation
- The drug id CI in pregnancy

Oxamniquine
Chemistry
- Synthetoc tetrahydroquinoline

MoA
- Causes paralysis of the worms however precise MoA unknown

CU
- Effective exclusively in mansoni infections

- Acts on male immature forms and adult schistosomes

AE
- Dizziness is common
- Headache, GIT irritation and pruritus may occur
- Reaction to dying parasites include eosinophilia, urticaria, and pulmonary infiltrates

CI and caution
- Not advisable in pregnancy or patient with history of seizure disorder
- Patients should not drive within 25 hour use

Bithionol
- DOC for Rx of fasciola hepatic
- AD in Rx of pulmonary paragonimiasis

PK
- Peak blood levels 4 - 5 hours after ingestion
- Excretion mainly renal

MOA
- Unknown

AE
- Occur in up to 40% of patients and generally mild and transient
- Common AE
    - GIT distress
    - Dizziness
    - Rah
    - Phototoxicity
- Less frequent
    - Pyrexia
    - Tinnitus
    - Proteinurua
    - Leukopenia
- Skin rashes may occur after a week or more of treatment suggesting a reaction to antigens released from dying worms

CI and Caution
- Should be used in kids <8 years because there is limited experience in its use in this age group

Cestodes
- Medically important
    - Taenia saginata
    - T.solium
        - Can cause cysticerci in brain and eyes
    - Diphyllobothrium latum (fish tapeworm)
    - Hymenolepsis nana (dwarf tapeworm)
- Human being are definitive host for above
- Others
    - E,granulosus
        - Can cause hydatid cysts in liver, lungs and brain

Drugs

- Main
    - Praziquantel
    - Niclosamide
- Others
    - Albendazole
    - Mebendazole

Niclosamide
Chemistry
- Salicylamide derivative

PK
- Minimally absorbed in GIT
    - Because neither drug or metabolites have been recovered form the blood or urine

MoA
- Presumably inhibits (uncouples) oxidative phosphorylation of ADP by parasitic mitochondria
- May also stimulate ATPase activity
    - Leads to rapid adult killing but not larvae or ova

CU
- DOC for
    - Fasciolopsis buski (large intestinal fluke)
    - Heterophyes heterophyes
    - Metagonimun yokogawai
    - T.saginata
    - T.solium
    - D.latum
- AD for treatment of H. nana
    - Should be given in the morning on an empty stomach or after a light meal
    - Tabs must be chewed thoroughly and swallowed with water
- Not effective in
    - Cysticercosis
        - Albendazole or praziquantel used
    - Hydatid disease
        - Albendazole used
    - Scoleces and cestode segments killed, not ova

AE
- Usually infrequent, mild and transient
- Include
    - GIT AE
    - Headache
    - Skin rash
    - Urticaria
    - Pruritus ani
    - Vertigo
    - Fever

CI and caution
- Avoid consumption of alcohol on the day of treatment 1/7 afterwards
- Safety not established in pregnancy of kids <2 years of age

Analgesics and Anti-Inflammatory Drugs

Friday, 7 October 2016 8:03 AM

Pain

- Inflammatory
  - Mediated by autacoids e.g. Prostaglandins
  - Swelling, redness and temperature
  - Prostaglandins
    - Stimulate nerve ending to pain
    - Enhance vessel dilation
      - Oedema
    - Work on CNS to cause readjustment to temperature
- Neuropathic
  - Nerve transduction
  - No swelling
  - Use drugs that stop Na+ channels from opening so that there is no nerve transduction e.g. Lidocaine
- Visceral
  - Cramps, abdominal colics
  - Use a drug that stops the spasms
- Psychogenic
- Can be mild, moderate and severe

Analgesia

- Opioid analgesia through action at regions in the CNS
- Non-opioid
  - NSAIDS
  - Membrane stabilisers e.g. Lidocaine /anticonvulsants

Inflammation

- Noxious stimuli cause elaboration of inflammatory mediators such as prostaglandins, histamines and other local hormone
- COX-2 is induced in the setting of inflammation
  - In response to injury
  - Is the one inhibited by analgesics
- COX-1 is constitutive and important in maintaining normal physiology
- Pain, fever and swelling in response to injury
- A non-selective drug that inhibits both COX-1 and 2 will interfere with normal body functions
  - E.g. Aspirin
    - Will stop pain but will interfere with blood clotting mechanisms, GIT injury
- Stimuli
  - Infection, ischaemia, Antigen-antibody complexes, thermal and physical
- Response to inflammatory mediators
  - Pain, swelling, redness, heat and loss of function

Indications of NSAIDS

- Analgesics
  - Pain
- Anti-inflammatory
  - Inflammation
- Antipyretics
  - Fever
  - Prostaglandins interfere with temperature regulation in the brain
- Antiplatelets
  - Platelet aggregation e.g. aspirin

Cyclooxygenase (COX) enzyme

- Constitutive
  - COX-1
- Inducible
  - COX-2
- Cerebral?
  - COX-3??
- Selectivity

COX Inhibitors

- Aspirin is the prototype drug in this class
- Aspirin is non-selective by binding irreversibly and acetylating cyclo-oxygenase
  - Form covalent bonds
- Selectively to binding determine effects and adverse effect profile

Classification of NSAIDS

- Non-selective COX inhibitors
- Selective COX inhibitors

Non selective COX inhibitors

- Salicylic acid derivatives
  - Aspirin
  - Sodium salicylate
  - Salsalate diflunisal
  - Sulphasalazine
  - Olsalazine
- Para-aminophenol derivatives*
  - Inhibit centrally and may work on COX-3????*
  - Acetaminophen
- Indole and indene acetic acid derivatives
  - Indomethcin
  - Sulindac
  - Etodilac
- Heteroaryl acetic acid derivatives
  - Tolmetin
  - Diclofenac
  - Ketorolac
- Arylpropionic acids
  - Ibuprofen
  - Naproxen
  - Flubiprofen
  - Ketoprofen

- Inhibit formation of phospholipids to arachidonic acid
- Inhibit COX enzymes from changing arachidonic acid to prostaglandins

    - Fenoprofen
    - Oxaprosin
- Anthranilic acids (fenamates)
    - Mefenamic acid
    - Meclofenamic acid
- Enolic acid (Oxicams)
    - Piroxicam
    - Meloxicam
    - Tenoxicam
    - Pyrazolidinediones
        - Phenylbutazone
- Alkanones
    - Nebumetone
- Sulphanilides
    - Nimesulid
- Diaryl substituted pyrazoles
    - Celecoxib
    - Paracoxib
- Diaryl substituted furanone
    - Rofecoxib
    - etoricoxib

Selective COX-2 inhibitors

- Diaryl-substituted furanones
    - Rofecoxib
- Diaryl-substituted pyrazoles
    - Celecoxib
- Indole acetic acid
    - Etodolac
- Sulphonalinides
    - Nimesulide

Effects

- Therapeutic indications
    - Pain
    - Swelling
    - Platelet aggregation inhibition
    - Inflammation
    - Fever
- Adverse effects
    - GIT irritation
    - Formation of leukotrienes leading to asthma

Salicylates

- Antipyretic, analgesic and anti-inflammatory
    - Aspirin (ASA)
    - Sodium salicylate
    - Benorylate
    - Aloxipirin
- Used only externally
    - Choline salicylate
    - Methyl salicylate
    - Salicylic acid
        - Has keratolytic and antiseptic properties

NSAIDS

- Suppress the signs and symptoms of inflammation
- Have antipyretic and analgesic effects
- Effective in
    - Rheumatoid arthritis
    - Seronegative spondyloarthopathies
    - Osteoarthritis
- ASA is the original NSAID and because of its AE, many NSAIDS have been develop in an attempt to improve upon its efficacy and decrease its toxicity
- NSAIDS fall into several chemical classifications and have a broad range to PK profiles
- All except Nabumetone are weak organic acids
- Nabumetone is a ketone pro-drug, biotransformed to the acid active drug

Aspirin

- Analgesic
- Anti-inflammatory
    - Replaced by other drugs due to ADR
        - Diclofenac
- Anti-platelet in vascular events
- Anti-pyretic
- Over the counter the drug

MoA

- Non-selective COX inhibitor and hence inhibits the synthesis of prostaglandins
    - Prostaglandins are thought to be mediators of inflammation, pain and pyrexia
- Mild analgesic effect i.e. less than that of codeine and is due to central and peripheral effect
- Reduces renal tubular absorption of uric acid
    - More uricosuric in alkaline urine
    - Antagonises uricosuric agents
- May induce CHF or pulmonary oedema even in therapeutic doses in those with rheumatic fever with active carditis
- GIT effects
    - Heartburn
    - Epigastric distress
    - Vomiting
    - GIT bleeding that may lead to anaemia
        - ASA acts as a local chemical irritant

P'Kinetics

- Organic acid
- Rapidly absorbed in the stomach and upper intestine
- Peak levels in 1 - 2 hours
- Hydrolysed to acetic acid and salicylate by esterases
- PPB
- Binding saturable
- Alkalinisation of urine increases the rate of salicylate urine excretion

PK of Salicylates

- Salicylates are weak acids
- Salicylic acid is a simple organic acid with a pKa of 3.0 while ASA has a pKa of 3.5
- Well absorbed in the stomach (acid pH)
  - Because of the small surface area and short residence time, most absorption takes place from the ilium (extensive surface area in the microvilli)
- C_{max} within 1 - 2 hours
- ASA is hydrolysed by esterases in plasma and the tissues, particularly in the liver to yield salicylate
- Salicylate is bound to plasma albumin but the binding is saturable
  - Unbound fraction increases as total concentration increases (first order and saturation kinetics)
- As dose of ASA increases, salicylate elimination half-life increases from 3 - 5 hours (for 600mg/day dosage) to 12 - 16 hours (dose >3.6gm/day)
- Salicylate undergoes oxidation (25%), SO_4 and glucuronide conjugation prior to urinary excretion
- 25% of salicylate excreted unchanged

NB:
Alkalisation of urine increases the rate of excretion of free salicylate and its water soluble conjugates

ASA - Carbohydrate metabolism

- Can lower blood sugar by increasing peripheral utilisation of glucose
- With heavy doses, hyperglycaemia may occur due to
  - Depression of aerobic glycolysis
  - Increased hepatic glycogenolysis
  - Increased adrenal cortical activity
- Serum cholesterol is reduced by high doses taken at least for 2 weeks

Antiplatelet Effect

- ASA irreversibly inhibits platelet COX. Effects last the life of the platelet (8 - 10 days)
  - Prolonged bleeding time.
    - Property made use of in the management of myocardial infarction or thromboembolic disorders

Adverse Effects

- Salicylates may produce local and systemic toxic effects
- Local
  - At the usual dose ASA's main effects are gastritis, focal erosions and bleeding
    - Due to inhibition of mucosal COX with consequent loss of the mucosal protecting action of prostaglandins
  - Inhibitory effect on platelet COX decreases platelet aggregation contributing to bleeding
  - 3 or more millilitres of blood is lost in the stool per day depending on the doses taken
    - Presence of occult blood in stool is common
- Systemic
  - In addition to the common adverse effects of NSAIDS, repeated ingestion of large doses of salicylates can cause salicylism, vertigo, decreased hearing and sometimes also NV
  - Other effects include
    - Hyperpnoea
    - Headache
    - Sweating
    - Restlessness
    - Mental confusion
  - With big overdose, these symptoms may be followed by
    - Mania
    - Hyperpyrexia
    - Convulsions
    - Coma with severe dehydration and ketosis
  - ASA worsens asthma in sensitive patients

NB:
Patients allergic to aspirin are seldom allergic to Sodium salicylate
- ASA intake is associated with a rare disorder in children called Reye's Syndrome that can follow a viral illness and has a 20 - 40% mortality
  - Avoid in children with viral infection

Write short notes on the sequence of events that occur in the acid-base balance and electrolyte balance following salicylate overdose

Management of Salicylate Poisoning

- Measure the plasma pCO_2, plasma HCO_3 and blood pH
- If alkalosis or mixed alkalosis/acidosis with normal pH, NO therapy directed to changing the acid-base balance
- If mixed alkalosis/acidosis with acid blood pH, small doses of $NaHCO_3$ may be given
- In emergency, without lab measurements, a patient thought to be acidotic may be given IV infusion of Na Lactate compound injection BP (Ringer's Lactate) or a similar solution containing an amount of HCO_3, equivalent to the lactate
- A patient thought to be alkalotic may be given NaCl and dextrose injection BP
- Correction of dehydration (can be severe due to sweating, vomiting and over breathing) is of primary importance and so is reduction of hyperpyrexia by sponging
- No attempt should be made to stop hyperventilation
- Dextrose may be given, despite hyperglycaemia for starvation contributes to ketosis
- Removal of salicylate by diuresis also successful
- Peritoneal dialysis, haemodialysis or exchange transfusion for severe cases may be done in well equipped centres
- When ASA is taken, the site of blood loss is predominantly the stomach
- To reduce blood loss
  - Buffered ASA tabs with a lot of fluid
  - Rapidly dispersing tablets
  - Enteric coated tabs but absorption is delayed
    - Not suitable for occasional analgesia - well suited for long-term medication e.g. rheumatoid arthritis (use higher doses of ASA)

NB:
- Alcohol increases gastric haemorrhage from ordinary ASA but negligibly with buffered ASA

- Commercial preparations of ASA
  - Plain tablets
  - Buffered tabs
  - Soluble tabs
  - Effervescent
  - Enteric coated

Uses

- Mild and moderate pain
- Combined with opioid in cancer pain
- Rheumatic fever in high doses
- Rheumatoid arthritis
- Transient ischaemic attack (TIA), Coronary Artery Disease (CAD) and AMI
  - Small doses of aspirin will only inhibit thromboxane A_2 as opposed to large doses that will also inhibit prostaglandins
    - Stopping platelet aggregation and vasoconstriction
- Long term use reduce colon cancer incidence

Non-Acetylated Salicylates

- Include
  - Mg choline salicylate
  - Na salicylate
  - Salicyl salicylate
  - Diflunisal
  - Methyl salicylate
- Effective anti-inflammatory drugs
- May be less effective analgesics than ASA
- Less effective than ASA as COX inhibitors therefore preferred in conditions when COX inhibition is undesirable e.g. those with
  - Asthma
  - Bleeding tendencies
  - Renal dysfunction
- Administered in the same doses as ASA
- Can be monitored by serum salicylate measurements

Selective COX-2 Inhibitors

- Rofecoxib
- Celecoxib
- Valdecoxib
- Etericoxib
- Meloxicum
- etodolac

Introduction

- The anti-inflammatory, analgesic and antipyretic effects of NSAIDS are primarily due to inhibition of arachidonate COX and thus to inhibition of prostaglandins
- Bind to and block the active site of COX2 isoenzyme much more effectively than that of Cox 1
- Do not affect the action of the constitutively active housekeeping Cox 1 isoenzymes found in the kidneys, platelets and GIT
- _
- Use: Osteoarthritis, rhemautoid arthritis, polyposis, dysmenorrhea, acute gouty arthritis
- NB: the anti inflammatory action of the NSAIDS is mainly related to inhibition of Cox2 and when used as an inflammatory agents, their unwanted effects are largely due to inhibition of COX1
- Unlike ASA, don't affect platelet function at usual doses
- Efficacy equals that of older non-selective Cox inhibitors but GIT safety is improved.
- NB: Toxic effects of highly selective COX2 inhibitors are attributed to inhibition of PG production in the kidney, oedema and HT
- Should be avoided in those in high risk of CV dx.

Rofecoxib

- Fumarose derivatives

PK

- Given orally, well absorbed.
- T1/2 is 17h
- High PPB
- Metabolism primarily by cytosolic reductases producing dihydro derivatives.
- Most of the drug excreted in urine as metabolites; 14% in faeces as unchanged drug.
- There seems to a saturable metabolism at therapeutic doses
- Significant metabolism with rifampin, methotrexate and warfarin
- NB : not recommended for use in those with advanced renal dx

Toxic effects

- Increased risk of myocardial infarction at doses conventionally used for tx of arthritis
- Rofecoxib and to a lesser extent increase BP in hypertensive patients and produce fluid retention that can result in decompensation in Heart failure
- Other toxicities are similar to other coxibs

Celecoxib

- Sulphonamide-may cause rashes in case of sensitivity
- Highly selective Cox 2 inhibitor- about 10-20 times more than Cox 1.

PK

- Rapidly absorbed after oral admin
- Half-life of 11 hours
- Extensively PPB
- Little drug eliminated unchanged. Most excreted as carboxylic as and glucuronide metabolites in urine and faeces
- Plasma concentration increase 40-130% in those with hepatic issues

DI

- Significant interactions with fluconazole and lithium but not ketoconazole or methotrexate
- Sometimes warfarin
- Metabolised by CYP2c9

Etoricoxib

- Bipyridine derivative with structural similarity to diclofenac
- 2nd gen COX2 inhibitor with highest selectivity ratio
- T1/2=22h
- Metabolised by CYP450 and renally excreted.
- Given orally at various dosages.
- NB: Increased risk of thrombotic events like diclofenac

Valdecoxib

- Diaryl-substituted isoxazole and is highly cox 2 inhibitor
- T1/2=8-11h
- Primary dysmenorrhea
- May cause reactions in those with sulphonamide sensitivity
- CV risk and SJS

Meloxicum

- Enolcarboxamide related to piroxicum
- Don't decrease platelet function

Etodolac

- Racemic acetic acid derivative
- Cox2:Cox1 ratio= 10

Other NSAIDS - Nimesulide and Apazone (Azapropazone)

Apazone:

- Antiinflammatory, analgesic and antipyretic.
- Less potent than other NSAIDS
- Potent uricosuric agent used in Tx of acute gout.
- Inhibits neutrophil migration, degranulation and superoxide production which may contribute to ints anti inflammatory effect

PK

- Rapidly and almost completely absorbed form the gut . T_{max} is about 4hrs
- Extensively PPB>95%
- Biological T1/2=20-24h
- Penetrates slowly into synovial fluid
- About 65% of dose excreted in urine unchanged and _
- Undergoes EHC
- Uses: Tx of RA,OA and gout
- NB: Reduce dose for the elderly
- Aes: Mild GIT effects, Skin rashes in 3%, CNS effects

Nimesulide

- Relatively cox2 selective
- Rapidly and extensively absorbed after oral admin. C_{max}= 1-4h, Elimination=3h
- Oral and Rectal, F=70%
- Highly PPB =95%
- SE: Serious liver damage so no paediatric use.

Ketorolac

- Systemic use as an analgesic
- Replace morphine as an analgesic
- IM/IV/PO
- Reduce opioid dose

Piroxicam

- Feledine is equivalent to aspirin and indomethazine, for long term treatment of rheumatoid arthritis
- Better tolerated than aspirin and indomethazine
- Equipotent to indomethazine in its inhibition of prostaglandin synthesis and anti-inflammatory process
- Inhibits neutrophil activation even in the presence of COX products
- It is analgesic, antipyretic and prolongs bleeding time

PK

- Completely absorbed after PO
- Peak concentration 2 - 4 hours
- Undergoes enterohepatic circulation
- Half-life 35 - 60 hours (50 hours)
- 99% protein bound
- Plasma and synovial fluid concentration are the same
- Mainly metabolised by CYP 450 system by hydroxylation followed by conjugation
- excretion in urine and small portion in faeces
- 5% excreted unchanged un urine

CU

- Rheumatoid arthritis
- Osteoarthritis
- Ankylosing spondylitis
- Musculoskeletal disorders
- Effective in dysmenorrhoea
- Post-operative pain
- Gout

Start dose 40mg on one day, maintenance dose once a day
IM forms and topical inflammation for local inflammation

Toxicity

- 20% incidence rate
- Up to 5% of patients stop drug use due to AE
- GI effects with peptic ulcers

DI

- reduce lithium excretion leading to lithium toxicity

Meloxicam

- COX-2 selective NSAID

Sualdose 15 - 17 mg once a day

Para-aminophenol Derivatives

- Paracetamol is a active metabolite of phenacetine and is responsible for its analgesic effect
- Phenacetine is more toxic than acetaminophen and has no rational indications
- It is N-acetyl-P-aminophenol

MoA

- Is a weak COX-1 and 2 inhibitor in peripheral tissues
- Selectively inhibits COX-3 isoforms in the CNS
- Has analgesic and antipyretic effect

PK

- PO/IV/Rectal
- Oral absorption is related to the rate of gastric emptying
- Peak blood concentrations are usually reached in 30 - 60 minutes
- Poorly bound to plasma proteins
- Partially metabolised by hepatic microsomal enzymes and is converted to acetaminophen sulphate and glucuronide which are pharmacologically inactive
- Less than 5% is excreted unchanged
- The half-life of acetaminophen is 2 - 3 hours and is relatively unaffected by renal function however, with toxic doses or liver disease, the half-life may be increased two-fold or more
- Toxicity occurs when normal conjugation reactions are saturated and the drug is alternatively metabolised by mixed function oxidases. This results in a toxic metabolite N-acetyl-P-benzoquinone imine, which is normally inactivated by conjugation with glutathione
- However, when glutathione is depleted, the toxic intermediate accumulates in the liver and the kidney tubules to cause necrosis

Clinical indications

- Acetaminophen is equivalent to aspirin as an analgesic and an antipyretic agent
- However, unlike NSAIDS, Paracetamol
    - Lacks anti-inflammatory effects
    - Lacks platelet-inhibiting properties

    - Lacks the tendency to cause gastric ulceration and bleeding
    - Unlike aspirin, it does not affect uric acid levels
- Acetaminophen is useful in the management of mild to moderate pain when an anti-inflammatory effect is not necessary e.g.
    - Headache
    - Myalgia
    - Post-partum pain
    - Other circumstance in which aspirin is an effective analgesic
- Acetaminophen alone is inadequate treatment for inflammatory conditions such as rheumatoid arthritis although it may be used as analgesic adjunct (add-on treatment) to an anti-inflammatory treatment
- For mild analgesia, acetaminophen is the preferred drug in patients allergic to aspirin or when salicylates are poorly tolerated
- Preferable to aspirin in patients with
    - Haemophilia
    - History of PUD
    - Those in whom bronchospasms is precipitated by aspirin
    - In children with viral infections (Reye's syndrome w/ aspirin)
- Does not antagonise the effects of uricosuric agents
    - It may therefore be used concurrently with probenecid in the treatment of gout

Dosage
- Acute pain and fever may be effectively treatment with 325 - 500 mg/dose QID for adults and 10 - 15 mg/kg/dose for children
- Doses more than 4 -6 gm/day are not recommended in adults (or >60mg/kg/day in children)
    - >4g/_

AE
- At therapeutic doses, AE are few and uncommon
- Allergic skin reactions may occur rarely
- A mild increase in hepatic enzymes may occasionally occur in the absence of jaundice
    - This is reversible when the drug is withdrawn
- In larger doses, dizziness, excitement and disorientation may occur

Paracetamol poisoning
- Ingestion of large amounts of paracetamol is a common method of suicide
- Ingestion of 10 - 15 g may be fatal
    - Death is caused by severe hepatotoxicity with_
- Early symptoms of hepatic damage include NVD and abdominal pain
- Cases of renal damage without hepatic damage have occurred even after usual doses of acetaminophen
- Haemolytic anaemia and methaemoglobinaemia are very rare
- Caution in patients with interstitial nephritis

Treatment of Paracetamol Toxicity
- This is much less satisfactory that for aspirin overdose
- Involves
    - Supportive therapy
    - Administration of acetylcysteine IV or methionine PO
        - Antidotes for paracetamol toxicity
        - They provides sulfhydryl groups and increase their glutathione formation in the liver
        - Hence neutralise toxic metabolites
    - If >12 hours have passed since the ingestion of a large dose, the antidotes are less likely to be useful
        - In addition these antidotes can cause AE e.g. nausea and allergic reactions

NB:
- Interstitial nephritis and papillary necrosis are serious effects of active form
    - Not seen in Para

Indole - acetic acids
Indomethacin
MoA
- Greater potent COX inhibitor that aspirin
- It may also
    - Inhibit phospholipase A and C
    - Reduce neutrophil migration
    - Decrease T and B cell proliferation
    - Depresses the biosynthesis of mucopolysaccharides
    - Have a direct, COX-independent vasoconstrictor effect

PK
- Oral indomethacin has excellent bioavailability
- Peak concentrations occur 1 - 2 hours after dosing
- Its concentration in synovial fluid is equal to that in plasma within 5 hours of administration
    - However, its concentration in CSF is low
- There is enterohepatic cycling of the indomethacin metabolites and probably indomethacin itself
- Its average plasma half-life is 2.5 hours
    - This is variable probably because of enterohepatic cycling

Clinical Indications of Indomethacin
- ~20X more potent than aspirin
    - Toxicity and availability of safer alternatives have limited its long term use
- Indicated in the treatment of
    - Moderate to severe rheumatoid arthritis
    - Osteoarthritis
    - Acute gouty arthritis
    - Ankylosing spondylitis
- An injectable form is used to accelerate closure of patent ductus arteriosus in premature infants
- Treatment with indomethcin may also decrease the incidence and severity of intraventricular haemorrhage in low birth weight neonates
- An ophthalmic preparation is efficacious for
    - Conjunctival inflammation
    - To reduce pain after traumatic corneal abrasion
- Indomethacin oral rinse may be used to reduce gingival inflammation
- Epidural injections produce a degree of pain relief similar to that achieved with methylprednisolone in post laminectomy syndrome

AE
- 35 - 50% of patients receiving usual therapeutic doses of indomethacin experience side effects and 20% must discontinue use
- Most common SE in NSAIDS t therapeutic doses
- Headache ins the mot common SE
    - Occurs in 15 - 25% of patients who take the drug for long periods
    - May be associated with dizziness, vertigo, light-headedness, confusion and depression
- The GIT AE are common and can be fatal especially in geriatrics and include
    - Diarrhoea which is sometimes associated with ulcerative lesions of the bowel
    - Acute pancreatitis has been reported
    - Rare, but potentially fatal, cases of hepatitis have occurred

- Haematopoietic reactions include
  - Neutropenia
  - Thrombocytopenia
  - Rare aplastic anaemia
- The following AE have also been reported
  - Seizures
  - Psychosis
  - Hallucinations
  - Suicide
  - Renal papillary necrosis

Caution
- Advised when administering indomethacin to the following because they are at greater risk of developing serious CNS Aes
  - Geriatrics
  - Patients with underlying epilepsy, psychiatric disorders or Parkinson's disease

Contraindications To the use in neonates
- Renal failure
- Endocolitis
- Thrombocytopenia
- Hyperbilirubinemia

DI
- Total plasma concentration of indomethacin plus its inactive metabolites, is increased by concurrent administration of probenecid
  - Indomethacin does not interfere with uricosuric effect of probenecid
- Antagonises the natriuretic and antihypertensive effects of furosemide and thiazide diuretics
- Reduces the antihypertensive effects of
  - ß-receptor antagonists
  - AT1-receptor antagonists
  - ACE inhibitors

Heteroaryl Acetic Acid Derivatives
- Examples
  - Tolmetin
  - Ketorolac

Tolmetin
- Oral, rapid and complete absorption
- Food reduces bioavailability and peak plasma concentration
- Half-life is 5 hours
- Accumulates in synovial fluid
- 99% PPB
- Partially metabolised in the liver
- Excreted as unchanged drug and metabolites in the urine

Toxic Effects
- Occur in 25 - 40% of patients
- GIT (most common)
  - Epigastric pain
  - Dyspepsia
  - NV
  - Ulcers
  - Therefore, give with food, milk or antacid
- Prolongs bleeding time
- Allergic thrombocytopoenic purpura (rare)
- CNS
  - Anxiety
  - Insomnia
  - Visual disturbances
  - Tinnitus
  - Deafness
  - Vertigo

Use
- Osteoarthritis
- Rheumatoid arthritis
- Ankylosing spondylitis

Ketorolac
- Oral, IV, IM, topical (eye)
- Excreted mainly through the kidneys (10% unchanged)
- Rate of elimination decreases
  - Elderly
  - Renal failure

Toxic Effects
- Blood
  - Inhibits platelet aggregation
- CNS
  - Somnolence
  - Dizziness
  - Headache
- GIT
  - Nausea
  - Ulcers
  - Dyspepsia
- Pain at injection site

Use
- Used for short term analgesia
  - Not more than 5 days
  - Due to high risk of adverse effects
  - Potent analgesic (severe pain), moderate anti-inflammatory effects
- Postoperative pain
- Inflammatory eye conditions
- K + opioid (opioid dose reduced by 25 - 50%)

Diclofenac

- Phenylacetic acid derivative
- Bromfenac (not used, irreversible liver injury)
- Nepafenac
- Lumiracoxib
  - A selective inhibitor of COX-2
  - Is an analogue of diclofenac
  - Not used due to liver toxicity

MoA

- Inhibits COX
- Reduces intracellular concentration of free arachdonate in WBCs

P'Kinetics

- Oral (tablets, mouthwash), ophthalmic solution, topical gel, topical patch, rectal, IM
- Rapid absorption
- 50% bioavailability due to FPE
- 99% PPB
- Half-life of 1- 2 hours
- Accumulates in synovial fluid therefore, longer duration of action
- Metabolised in the liver
- Excreted in urine (65%) and (35%) in the faeces

Toxic Effects

- GIT (most common)
  - Ulcers
- Liver
  - Increased aminotransferases (reversible)
  - Monitor in first 8 weeks of treatment
  - Stop drug if abnormal values persists of other signs and symptoms
- Skin rashes
- Allergic reactions
- Fluid retention and oedema
- Renal toxicity is rare

Contraindications

- Not recommended in
  - Children
  - Pregnant women
  - Nursing mothers

Use

- Osteoarthritis
- Rheumatoid arthritis
- Ankylosing spondylitis
- Acute musculoskeletal injury
- Postoperative pain
- Dysmenorrhoea
- Postoperative inflammation after cataract surgery
- Migraine

Interactions

- Preparations
- Diclofenac and misoprostol
  - Decreases upper gastrointestinal ulceration
  - May cause diarrhoea
- Diclofenac and omeprazole
  - Prevention of recurrent bleeding

Propionic Acid Derivatives

- = aryl propionic acid derivatives
- Examples
  - Ibuprofen
  - Flurbiprofen
  - Ketoprofen
  - Fenprofen
  - Pirbrufen
- All prolong bleeding time
- Highly protein bound
  - But don't affect oral hypoglycaemic agents and warfarin effects
  - Warfarin dose may be adjusted
    - Impaired platelet function
    - GIT ulcers

Ibuprofen

P'kinetics

- Oral, topical cream, gel, IV
- Rapid absorption
- Half-life - 2 hours
- 99% PPB
- Accumulates in synovial fluid
- Cross placenta
- Excreted as metabolites in urine

Toxicity

- Epigastric pain, N, heartburn
- Thrombocytopoenia
- Agranulocytosis, aplastic anaemia (rare)
- Skin rash
- Headache
- Dizziness
- Blurred vision, toxic amblyopia (stop treatment)
- Fluid retention, oedema
- Aseptic meningitis (especially in patients with systemic lupus erythematosus)

Indication

- Patent ductus arteriosus closure in pre-terms

- Can be used occasionally in
  - Pregnancy
  - Breastfeeding
- Lower doses 9<2400mg/day) - analgesia
- High doses
  - Anti-inflammatory
- Interaction with anticoagulants e.g. warfarin, are uncommon
- Antagonises the effect of aspirin effect on platelets

Naproxen

- Inhibits leukocyte function

P'Kinetics

- Oral absorption
  - Speed reduced by food
  - Accelerated by sodium bicarbonate
  - Reduces AlOH, and magnesium oxide
- Also rectal, ophthalmic, topical
- Crosses placenta and breastmilk

Toxicity

- GIT
- CNS
  - Drowsiness
  - Headache
  - Sweating
  - Depression
  - Ototoxicity
- Skin rashes, pruritus
- Rare
  - Agranulocytosis
  - Thrombocytopoenia
  - Allergic pneumonitis
  - Vasculitis
  - Jaundice
  - Impaired renal function
  - Angioedema

Fenprofen

P'Kinetics

- Oral
- Incomplete absorption (85%)
- Absorption reduced by food but not antacids
- GIT side effects most frequent
- NSAIDS most associated with interstitial nephritis

MoA

- COX inhibitor
- Inhibits LOX
- Stabilises lysosomal membranes
- ? Antagonises bradykinin actions

Interactions

- Food reduces absorption
- Probenecid increases K levels
- GIT toxic effects reduced by milk, food and antacids

Toxicity

- Fluid retention and increased creatinine
  - >60 year olds and patients on diuretics
  - Monitor renal function in these patients

Flurbiprofen

- Oral, transcutaneous patch (soft tissue injury), ophthalmic, IV, lozenge
- Causes
  - Cogwheel rigidity
  - Ataxia
  - Tremours
  - Myoclonus (rare)

Oxaprozin

- No EHC
- Half-life
  - 40 - 60 hours
  - Increases with age
  - Therefore, once daily dosing
- Adjust dose every 5 days
- Mildly uricosuric
- Indicated in
  - Osteoarthritis
  - Rheumatoid arthritis
  - Ankylosing spondylitis
  - Acute gouty arthritis
  - Acute bursitis and tendinitis
  - Dysmenorrhoea
  - Migraine

Opioid Analgesics

- Drugs derived from opium
- Can also be synthetic
- Opium is obtained from poppy
  - Papaver somniferum
  - Papaver album
- The poppy seed pod exudes a whites substance that turns into a brown gum (crude opium)
- Opium contains many alkaloids
  - The principle one is morphine
  - Morphine is named after Morpheus
    - The Greek god of dreams

- Morphine is the prototype of opioid agonists

Definitions

- Opiates
  - These are drugs derived from opium
    - Morphine, codeine
- Opioid
  - These are drugs with morphine like activity
  - Includes opiates
  - Also synthetic opioid peptides
  - All compounds that work on opioid receptors
- Endorphins
  - Endogenous opioid peptides
  - Enkephalins
  - Dynorphins
  - Endorphins
- Narcotics
  - Wide range of abused substances
  - Sleep-inducing agents
  - From the Greek word for "stupor"

Endogenous opioid peptides

- Produced during stressful conditions
  - Pain
  - Anticipation of pain
- Reduce sensation to noxious stimuli
- They are derived from precursors
- Proenkephalin
  - Met-enkephalin
  - Distribution
    - Areas of the brain related to pain perception, modulation of affective behaviour
    - Adrenal medulla
    - Exocrine glands of the stomach and intestines
- Prodynorphin
  - Leucine-enkephalin
  - Dynorphin A
  - Dynorphin B
  - Alpha and Beta Neoendorphins
  - Widely distributed in CNS
- Pro-opiomelanocortin (POMC)
  - Beta endorphins
  - Distribution
    - Areas in the brain where electrical stimulation can relieve pain
    - Pituitary
    - Pancreatic Islet cells
- Function
  - Not clear
  - ???neurotransmitters
  - ??? Modulators of neurotransmission
  - ??? Neuro-hormones

Opioid Receptors

- They are G-protein coupled receptors
  - μ receptors (1 and 2)
  - receptors (1-3)
  - δ receptors (1-2)
- Anatomic sites
  - μ1 - supra-spinal,
  - μ2- spinal, dorsal horn
  - 1 - dorsal horn of spinal cord
  - 2 - undefined
  - 3 - supra-spinal
  - Delta1 and 2 - both spinal cord and supra-spinally

Receptor-effector mechanisms

- Inhibition of adenylyl cyclase activity
- Activate (open) of receptor operated K+ current
- Suppression (close) of voltage gated Ca2+ channels
  - Reduce release of glutamate, acetylcholine, substance P, serotonin

General pharmacological effect

- μ
  - Analgesia
  - Respiratory depression
  - Miosis
  - Reduced GIT motility
  - Euphoria (feeling of well-being, feeling intense excitement and happiness)
  - Physical dependence properties
  - Sedation
  - Modulation of hormone and neurotransmitter release
-
  - Analgesia
  - Less intense miosis and respiratory depression
  - Slowed GIT transit
  - Dysphoric psychomimetic effects
    - Uncontrollable/racing weird thought
    - Anxiety
    - Nightmares
    - Hallucination
    - Dysphoria (a state of unease and a general dissatisfaction with life)
-
  - Effects are not clear
  - Analgesia
  - Modulation of hormone and neurotransmitter release

Strong Agonists

- Phenanthrenes
  - Morphine
  - Hydromorphone
  - Oxymorphone
  - Heroine
- Phenylheptylamines

    - Methadone
    - Levomethadyl acetate
- Phenylpiperidines
    - Meperidine
    - Fentanyl
    - Alfentanil
    - Sulfentanil
    - Remifentanil
- Morphinans
    - Levopharnol

Mild-moderate agonists

- Phenantherenes
    - Codeine
    - Dihydrocodeine
    - Oxycodone
    - Hydrocodone
- Phenylheptylamines
    - Propoxyphene
- Phenypiperidines (antidiarrhoeals)
    - Diphenoxylate
    - Difenoxin
    - Loperamide

Opioids with mixed receptor actions

- Phenanthrenes
    - Nalbuphine
    - Buprenorphine
- Morphinans
    - Butorphanol
- Benzomorphans
    - Pentazocine
    - Dezocine

Miscellaneous

- Tramadol
    - Weak μ agonist
    - Inhibit reuptake of serotonin and norepinephrine
- Antitussives (inhibit reuptake of serotonin)
    - Dextromethorphan
    - Levopropoxyphene

Opioid Antagonists

- Naloxone
- Naltrexone
- Nalmefene

Selectivity for receptors

	μ	□	□**1**	**κ2**
Morphine	+++		+	+
Etorphine	++++	++++	++++	++++
Buprenorphine	Partial agonist		--	
Naloxone	---	-	--	--
Pentazocine	Partial agonist		++	+

Strong agonists

- Morphine and codeine isolated from opium poppy
    - Relieve pain and are essential in current treatment of major diseases, trauma and surgery
- Morphine I the major analgesic drug contained in crude opium and is the prototype
- Codeine is present in lower concentrations and is less potent
- Widespread availability has led to drug abuse
- Opioid agonists have similar actions

Morphine and congeners

- Morphine
- Codeine
- Hydrocodone
- Hydromorphone
- Oxymorphone
- Heroin
- Hydromorphone, oxymorphone, hydromorphone and oxycodone are made by modifying the morphine molecule
- Codeine is methylmorphine
- Hydromorphone and oxymorphone more potent that morphine
- Hydromorphone and morphine also available as suppositories

Heroine - Diacetylmorphine

- Most important opioid that is abused
- Rapidly hydrolysed to 6-monoacetylmorpheine (6-MAM) and then to morphine
- More lipid soluble than morphine and readily enters the brain
- 6-MAM and morphine are responsible for the pharmacological actions of heroine
- Excretion in urine as free and conjugated morphine
- Opioids exert major effects by interacting with opioid receptors in the CNS and GIT

Actions

- Relieves pain by enhancing pain threshold at the spinal cord and by altering the brain's interpretation of pain
    - Patients still aware of pain but increased pain tolerance i.e. the sensation is not unpleasant
- Change in mood
    - Produces a powerful sense of contentment and wellbeing - euphoria

NB:

Not all opiates produce euphoria but they all produce the clouded state

- Respiratory depression
    - Reduce sensitivity of respiratory centres to carbon dioxide. Dose related effect
        - Causes the most death due to acute overdose
- Depression of cough reflex
    - Morphine and codeine have antitussive effects
- Miosis
    - Pin point pupil characteristic of morphine
        - Important diagnostically because most other cases of coma and respiratory depression produce dilation of the pupil
- Emesis

    - Stimulates vomiting centre in the CNS to cause emesis but the emesis does not produce unpleasant sensation
- GIT
    - Decrease GIT muscle motility and increases tone
        - Relieves diarrhoea and dysentery - produces constipation
- CNS
    - Increase in CSF pressure
        - Morphine is contraindicated with severe brain damage
- Histamine release
    - Releases histamine from mast cells, causing urticaria, sweating and vasodilation
- Hormonal actions
    - Inhibits the release of GnRH and CRH and decrease concentration of LH, FSH and ACTH and ß-endorphin. Testosterone and cortisol level increase
    - Increase in prolactin and growth hormone release by diminishing dopaminergic inhibition

Therapeutic Uses of Morphine

- Relief of moderate to severe acute or chronic pain, particularly of visceral origin
- Repeated administration may cause dependence and tolerance
    - Not deterrent in terminal illness pain control
- Opioid of choice in treatment of severe pain and palliative pain
- Used in acute pulmonary oedema and as peri-operative analgesia
- Opioid adjunct during general anaesthesia

Morphine Pharmacokinetics

- PO
    - Absorption is slow and erratic
    - Codeine in contrast, is well absorbed PO
- Significant first-pass metabolism in liver
    - Parenteral injections produce greater response
- Rapidly enters all body tissues and crosses the placenta and affects the foetus
    - Infants born of addicted mothers show physical dependence on opiates and exhibit withdrawal symptoms if opioids are not administered
- Less lipophilic
    - Small percentage crosses the BBB
- Metabolites excreted in urine and bile
- Duration of action
    - 4 - 6 hours
- Given regularly (twice or once daily as modified release preparations)
- Contraindicated in
    - Respiratory depression
    - Acute alcoholism
    - Raised intracranial pressure
    - Head injury
    - Comatose patients
    - When there is risk of paralytic ileus
    - Heart failure secondary to chronic lung disease
    - Delayed gastric emptying
    - Phaeochromocytoma

Morphine Side Effects

- NV, constipation and drowsiness
- Larger doses
    - Respiratory depression
    - Hypotension
- Difficulty in micturition, dry mouth, sweating, headache, dysphoria, mood changes, dependence, miosis, decreased libido or potency, rashes, urticaria, pruritus

NB:
Withdrawal produces responses that incapacitates the individual and causes serious, almost unbearable symptoms

Drug Interactions

- Depressant actions of morphine are enhanced by monoamineopioid inhibitors and tricyclineantidepressants (TCAs) and benzothiazenes

Tolerance and physical dependence

- Repeated use produces tolerance to the respiratory depressant , analgesic, euphoric and sedating effects of morphine

Methadone

- A phenylheptylamine
- Racemic mixture of D and L - isomers
- Long lasting μ receptor agonists
- Pharmacological properties qualitatively similar to those of morphine
- Administered PO/IV/SC/Rectally
- Has a longer bioavailability of morphine
- Blocks NMDA (N-methyl-D-aspartate) receptor and monoaminergic reuptake
    - Probably contributes to its ability to relieve difficult to treat pain (neuropathic, cancer pain) when morphine has failed

Uses

- Treatment of opioid abuse
    - Opioid abstinence syndromes and treatment of heroine addicts
        - Tolerance and physical dependence develop more slowly than with morphine
        - Withdrawal signs and symptoms after abrupt withdrawal are milder (but may be more prolonged) than with morphine
        - These make the drug useful for detoxification and maintenance of the relapsing heroin addict
            - Upon discontinuation , addict experienced mild but endurable withdrawal syndrome
                - Useful in psychiatric and rehabilitative therapy
- Relief of chronic pain (μ-receptor agonist)
- Suppression of cough in terminal disease

P'kinetics

- Long half-life (15 - 40 hours)
    - Given 8 hourly
- Variable PK
- T_{max} - 4 hours
- 90% plasma protein bound
    - Also in proteins in various tissues
- Peak concentration in brain is achieved in 1 - 2 hours after SC/IM administration
- Can be absorbed from buccal mucosa
- Metabolised in the liver and unchanged drug excreted in urine and bile
- Cumulative effects after repeated doses
- Analgesia
    - Onset is 10-20minutes following parenteral administration
    - 30 - 60 minutes after oral administration
- Side effects, toxicity and their management as for morphine
- Long term administration
    - Excessive sweating, lymphocytosis, increased concentrations of prolactin, albumin and globulins ins plasma

DI
- Rifampicin and phenytoin increased the metabolism of methadone

Levomethadyl Acetate
- Methadone congener
- D-isomer methadyl acetate is inactive
- Slow onset and log duration of action
- Used in the treatment of heroine addicts

Propoxyphene
- Structurally related to methadone
- D-propoxyphene (dextropropoxyphene) has analgesic effect while levopropoxyphene has some antitussive effect
- Analgesic effect 1/3 to 2/3 that of codeine
- Higher levels of analgesia given with other analgesics e.g. ASA, paracetamol etc.

Levophanol (L-dromoran)
- Only commercially available opioid agonist of morphinan series
- The D-isomer, dextromethorphan is relatively devoid of analgesic effect but may have inhibitory effects at the NMDA receptors
- Pharmacological actions closely parallel those of morphine but may produce les nausea and vomiting
- Less active given orally but the oral-parenteral potency ration comparable to that of codeine and oxycodone
- Duration of analgesia is longer than that of morphine
- Biotransformed less rapidly
  - Half-life 12 - 16 hours

Phenyl Piperidines
- Pethidine, alphaprodine, fentanyl and fentanyl sub-group (sulfentanyl, alfentanyl, remifentanyl)

Pethidine
- Synthetic opioid
- Can be given orally but less effective than when given parenterally
- Uses
  - Moderate to severe pain relief
  - Obstetric and peri-operative analgesia
- Produces prompt but short duration of analgesia than morphine
- Less constipating and less potent than morphine
- Not suitable for severe continuing pain
- Not clinically useful in treatment of cough and diarrhoea
- Less respiratory depression than other opioid analgesics
  - Use for analgesia in labour
- Causes dilation of pupil because of an atropine-like activity
- Well absorbed in the GIT compared with morphine but most often given IM
- Duration of action (2 - 4 hours) shorter than that of morphine (4 - 6 hours)
- Addictive and substituted for morphine or heroine in use by addicts
- Contracts smooth muscles to a less extent than morphine
- Impedes GIT motility
  - Constipation on chronic use

Adverse Events
- Large doses may cause tremors, twitches and rarely convulsions
- Use with major neuroleptics greatly enhances depression

Fentanyl and Congeners
- Strong opioid agonists
- Phenyl piperidines like pethidine
- Include
  -

	μ	Kappa	Delta
Sulfentanyl	+++	+	+
Alfentanyl			
Remifentanyl			
Fentanyl	+++	+	+

- Are μ-receptor agonists

Fentanyl and Sulfentanyl
- Similar analgesic effect as morphine
- Fentanyl is about 100X more potent than morphine as analgesic
- Sulfentanyl 1000X more potent than morphine as analgesic
- Most commonly administered IV
- May be administered epidurally and intra-thecally for acute postoperative and chronic pain management
- More lipid soluble than morphine
  - Risk of delayed respiratory depression is reduced
- After IV administration, time to peak analgesic effect is about 5 minutes (for morphine and pethidine is 15 minutes)
- Recovery from analgesic effect occurs more quickly
- Duration of effect prolonged by giving large doses or as prolonged infusions

CVS effects
- Fentanyl and its derivatives decrease HR and can mildly decrease BP

NB:
- They do not release histamine and in general, provide a marked degree of CV stability
- Because of the above properties, high doses of Fentanyl and Sulfentanyl are commonly used as the primary anaesthetic for patients undergoing CV surgery and for patients with poor cardiac function

Therapeutic Uses
- Popular anaesthetic adjuvants
- Given IV, epidurally or intra-thecally
- Epidurally of postoperative and labour analgesia
- Management of chronic malignant or non-malignant pain
- Transdermal patches available that release the drugs over 48 hours or more
- Sublingual formulation of fentanyl available

Alfentanyl and Remifentanyl
- Remifentanyl is approximately as potent as fentanyl and 20 - 30X more potent than alfentanyl
- Pharmacological properties similar to those of fentanyl and sulfentanyl
- Similar incidences of NV and dose dependent muscle rigidity
- Intracranial pressure changes are minimal when ventilation is controlled

P'Kinetics
- More rapid onset of analgesia effect than fentanyl
  - 1 - 1.5 minutes
- Duration of action of alfentanyl depends on dose and length of administration
- Alfentanyl is metabolised in the liver and has elimination half-life of 1 - 2 hours
- Remifentanyl is metabolised by plasma esterases and has elimination half-life of 8 - 20 minutes

Therapeutic Uses
- Useful for short and painful procedures that require intense analgesia and blunting of pain responses
- Remifentanyl is ideal for short surgical procedures where rapid recovery is an issue and for longer neurological procedures where rapid emergence from anaesthesia is important
  - Usually given by continuous IV infusion because of short duration of action
- Alfentanyl may be administered intra-spinally for pain control

Phenyl Piperidines (mild to moderate agonists)
- Diphenoxylate and its metabolite difenoxin
  - Not used as analgesics
  - Used in combination with atropine for treatment of diarrhoea
- Loperamide
  - Used to control diarrhoea

Opioid Toxicity
- Analgesic
- Abuse

? What are the clinical indications of opioids?

Chemistry
- Opium - Alkaline
- Content
  - Alkaloids
    - Morphine
    - Codeine
    - Thebaine
    - Paparverine
      - Vasodilator of Ca channel
- Properties
  - Agonist
  - Partial agonists
  - Antagonists

Receptors
- Agent may have varied levels of effect on different receptor subtypes
- Partial/weaker agonist responses can be used to mitigate full agonist responses
- Antagonists bind on receptors without effect
- Tolerance, physical dependence and abstinence syndrome (withdrawal)

Tolerance
- Analgesia, euphoria, sedation, respiratory depression, anti-diuresis, nausea and vomiting, cough suppression
- Miosis, constipation, convulsions
- Moderate
  - Bradycardia

Manifestations of toxicity
- Nausea, vomiting, constipation, respiratory depression
- Increased intracranial pressure
- Hypotension/hypovolaemia
- Urine retention
- Urticaria

Toxicity
- Extension of pharmacologic effect
- Idiosyncratic
- Hypersensitivity

Diagnosis
- Addiction
- Needle marks
- Miosis
- Companions
- ?comatose
  - Dramatic reversal with IV naloxone

Treatment
- ABC
- Respiratory support
- Naloxone

Mixed Agonist-Antagonist drugs
Analgesic Antagonists
- The analgesic activity of mixed agonist-antagonists varies with the individual drug
  - However it is less than that of full strong agonists like morphine
- Buprenorphine, butorphanol and nalbuphine have greater analgesia than pentazocine, which is similar to codeine in analgesic activity

Receptor Effects
- Butorphanol, nalbuphine and pentazocine are κ agonists with weak μ receptor antagonist activity
- Butorphanol may act as a partial agonist or antagonist at the μ-receptor
- Buprenorphine is a μ-receptor partial agonist with weak antagonist effects at κ and δ receptors

Phenanthrenes
Nalbuphine
PK
- Given parenterally

MoA
- It is a strong κ-receptor agonist and a partial μ-receptor antagonist
- At higher doses, there seems to be a definite ceiling to its respiratory depressant effects (which does not occur with morphine)
  - Unfortunately when respiratory depression occurs. It may be relatively resistant to naloxone reversal

CU
- Naloxone is included in some of its formulations to discourage abuse

Buprenorphine

PK
- Partial μ-receptor agonist with weak antagonist effects at the κ and δ receptors
  - This can lead to decreased analgesia, or even precipitate withdrawal symptoms, when it is used in patients taking more potent μ-receptor agonists such as morphine
- It has a long duration of action because it binds strongly to μ-receptors and slowly dissociates from them
  - This property makes Buprenorphine's effects resistant to naloxone reversal because of the antagonist short half-life
- It is inactive when given orally because of FPE
  - Administration is by the sublingual route is therefore referred to avoid significant FPE
- It has slow onset of action
- Half life is approximately 12 hours
- May also be given by intrathecal injection

CU
- Treatment of acute and chronic pain
  - It is potent and produces strong analgesia
  - Useful in chronic pain with patient-controlled injection systems
- Management of opioid dependence
  - Because of its antagonistic actions, it can produce mild_
  - Is as effective as methadone for management of opioid withdrawal and maintenance of opioid abusers
  - In contrast to methadone, high dose administration of buprenorphine results in a μ-opioid antagonist action
    - This limits its properties of analgesia and respiratory depression
  - Marketed as a sublingual preparation, combined with naloxone, for the management of opioid dependence
    - Helps prevent its diversion for illicit intravenous abuse
  - When administered sublingually, the naloxone is not absorbed and does not influence the effect of buprenorphine
    - However, if it is administered parenterally, the effects of the buprenorphine are reduced by the naloxone and that discourages such abuse
  - A slow release transdermal patch preparation that releases the drug over a one week period is also available

AE
- As for morphine but are less pronounced
- Induces less respiratory depression than other opioids
- Its respiratory depression is not reversed by naloxone
  - Therefore, it is not suitable for obstetric use
- May precipitate opioid withdrawal, due to its partial agonist effect

Morphinans

Butorphanol

PD
- Predominantly a K agonist
  - However, it may also act as a partial agonist or antagonist at the μ-receptor

CU
- It produces analgesia equivalent to nalbuphine and buphenirphine
  - However it appears to induce_

Benzomorphans

Pentazocine

- It is the oldest mixed agent available

PK
- It may be given orally or parenterally
  - However, because of its irritant properties, its subcutaneous injection is not recommended
- Half-life is 2 - 4 hours

PD
- Is a K-agonist with weak μ antagonist or partial agonist properties

CU
- Mainly used for treatment of acute pain

AE
- Irritation at injection site
- May precipitate withdrawal due to its μ antagonist effects when given to patient dependent on morphine or other μ-opioid receptor agonists
- Psychotomimetic effects at higher doses
  - It causes marked dysphoria with nightmares and hallucinations, rather than euphoria

General AE of mixed agonist-antagonists

- Often cause sedation at analgesic doses
- Dizziness, sweating and nausea may also occur
- K agonist tend to cause dysphoria rather than euphoria
- Psychotomimetic effects
  - Anxiety, hallucinations and nightmares are possible AE
- Respiratory depression may be less intense than with pure agonists
  - However, it is not predictably reversed by naloxone
- Tolerance develops with chronic use
  - However, it is less than that which develops to the pure agonists, and there is minimal cross-tolerance
- Physical dependence occurs
  - However, the abuse liability of mixed agonist-antagonist drugs is less than that of the full agonists

Antiseptics / Disinfectants / Sterilants

Monday, 10 October 2016 9:18 AM

- Disinfectant
  - A strong chemical or physical agent that inhibits or kills micro-organisms but not spores on inanimate objects
- Antiseptic
  - A disinfectant with sufficiently low toxicity to be used on skin, mucous membranes or wounds
- Sterilants
  - Kills both vegetative organisms and spores when applied for appropriate times and temperatures

- Disinfection process prevents infections by reducing the number of potentially infective organisms by either:
  - Killing
  - Removing
  - Diluting

Agents used

- Chemical agents
- Physical agents as ionising radiation, dry or moist heat or superheated steam (autoclave 120 degrees)
- Combinations can be used
  - Water and moderate heat over time (pasteurisation)
  - Ethylene oxide and moist heat (sterilant)
  - Addition of a disinfectant to agent
- Other methods of preventing infections
  - Washing of hands
    - Warm water and soap is the best
  - Barriers
    - Gloves, condom, masks, respirators, covers
  - Isolation
  - Vaccinations
  - Proper ventilation

Factors that Determine Efficacy

- Intrinsic resistance of micro-organisms
- Number of micro-organisms present
- Mixed population of micro-organisms
- Amount of organic material present e.g. blood, faeces, tissues
- Concentration and stability of disinfectant/sterilant
- Temperature and time of exposure
- pH
- Hydration
- Binding of agent to surfaces
- Toxicity to humans must be evaluated for both long and short terms

Disadvantages of disinfectants

- General biocidal activity
- May accumulates in the body of the patient and caregiver or environment

- May be contaminated with resistant organisms spores e.g. pseudomonas spp, and transmit infections
- Most antiseptics interfere with would healing. Topical antibiotics preferred

Alcohols

- The most commonly used as antiseptics and disinfectants are
    - Ethanol
    - Isopropyl alcohol (isopropanol)
- Rapidly active killing

Indications

- Vegetative bacteria
- M.tuberculosis
- Many fungi
- Inactivates lipophilic viruses

MoA

- Thought to act by denaturation of proteins
- Optimal bactericidal concentration is 60 - 90% by volume of water
- Used in situations where there is no running tap water
- The skin drying effect is alleviated by addition of emollients to formulation

Disadvantages

- They are not sporicidal
- Do not penetrate protein containing organic material
- May not be active against hydrophilic viruses
- Lack residual action as they evaporate completely
- Are flammable
    - Keep in cool, well ventilated areas
- Must be allowed to evaporate before use of cautery, electro-surgery or laser surgery
- Damaging if applied to cornea directly
- Allow alcohol to evaporate from instruments or rinse with sterile water before use

Chlorhexidine

- A cationic biguanide with very low water solubility.
- Chlorhexidine digluconate is, however, soluble and is used as an antiseptic
- Common names
    - Hibitane
    - Hibistat
    - Hibidens

MoA

- It strongly adsorbs to bacterial membranes causing leakage of small molecules and precipitation of cytoplasmic proteins
- Active at pH 5.5 - 7.0
- Slower than alcohols in action but has a residual effect when used repeatedly producing bactericidal activity equivalent to them
- It is active against vegetative bacteria and mycobacteria and has moderate activity against fungi and viruses
- It is most active against gram positive cocci and less active against gram positive and negative rods

- Spore germination is inhibited

Advantages

- Resistant to inactivation by blood and organic materials
- Has very low skin sensitising or skin irritating capacity
- Oral toxicity is low because it is poorly absorbed in the GIT

Disadvantages

- Anionic and non-anionic agents in moisturisers, neutral soaps and surfactants may neutralise action
- Can't be used in middle ear surgery as it causes sensorineural deafness
- Neural toxicity is observed in neurosurgery

Halogens

- Iodine
- Iodophores
- Chlorine

Iodine

- Available as Iodine and Povidone
- 1:20,000 solution of iodine
- Tincture of iodine
    - 2% iodine + 24% sodium iodide in alcohol
- It is the most active antiseptic for intact skin

MoA

- Gram positive and negative organisms are highly sensitive
- Kills lipophilic viruses
- Kills spores at high temperatures
- Kills amoebic cysts
- Hydrophilic viruses and prions are resistant

Disadvantages

- Serious HS reactions
- Stains clothes and dressings

Iodophors

- Are complexes of Polyvinyl pyrrolidine (PVP, POVIDONE, Betadine)
- They retain iodine activities, killing
    - Vegetative bacteria
    - Mycobacteria
    - Fungi
    - Lipid containing viruses may be sporicidal prologed exposure
- They can be used as antiseptics or disinfectants
- Disinfectants contain more iodine

Advantages

- Act rapidly as chlorhexidine
- Have a broader spectrum of activity but lack the persistent action of chlorhexidine
- Less irritating and cause less HS

Chlorine

- Is a strong oxidising agent and a universal disinfectant
- Commonly supplied as a 5.25% sodium hypochlorite solution
- At 1.10 dilution of household bleach provides 5000PPM of available chlorine. This concentration is recommended for disinfecting blood spills
- Undissociated hypochlorous acid (HOCL) is the active biocidal agent
- When pH is increased, the less active hypochlorite ion OCL- is formed
- When hypochlorite solutions contact formaldehyde, the carcinogen (bis-chloromethyl) is formed.
- Rapid evolution of irritating chlorine gs occurs when hypochlorite solutions are mixed with acid or urine

Activity

- Less than 5 PPM kills vegetative bacteria, they are highly sensitive
- Up to 5000 PPM is necessary to kill spores (pH 7.6)
- 1000 - 10,000 PPM is tuberculocidal (moderately sensitive)
- 100 PPM kills vegetative fungi in 1 hour but fungal spores require 500 PPM to kill
- Viruses are inactivated by 200 - 500 PPM
- Prions are moderately sensitive
- Dilution of 5.25% sodium hypochlorite are made up to pH 7.5 - 8 tap water
    - Retain their activity for months when kept in tightly closed opaque containers
- Alternative chlorine releasing compounds are
    - Chlorine dioxide
    - Chloramine
- They retain chlorine longer and have a prolonged bactericidal action

Disadvantages

- Chlorine is inactivated by blood, serum, faeces and protein containing materials. Clean surfaces
- Chlorine solutions are corrosive to aluminium, silver and stainless steel

Phenolics

- Phenol itself, the oldest surgical antiseptics, is no longer used even as a disinfectant because
    - It is corrosive to tissue
    - Toxic on absorption
    - Carcinogenic
- Derivatives in which a functional group replaces a hydrogen action in the aromatic ring have less adverse effects.
- The most commonly used are
    - O-phenylphenol
    - O-benzyl-p-chlorophenol
    - P-tertiaryamyphenol
    - Lysol
        - Methylated phenyl
    - Chloroxylenol (Dettol)
- Mixture of phenolic derivatives are often used.
- Skin absorption still occurs and care is needed
- Detergents are often added to formulations to clean and remove organic material that may decrease their activity

MoA

- They disrupt cell walls and membranes

- Precipitating proteins
- Inactivate enzymes

Spectrum of Activity
- Are
    - Bactericidal both to gram positive and negatives
    - Bactericidal to mycobacteria
    - Fungicidal
    - Capable of inactivating lipophilic viruses
- Spores, hydrophilic viruses and prions are resistant
- They are recommended for disinfecting hard surfaces in hospitals and labs e.g. floors, beds, counters, bench tops
- They are contraindicated in nurseries, incubators
    - May cause hyperbilirubinemia

Hexachloriphine (Phizohex)
- A skin disinfectant effective only on gram + bacteria
- Has caused cerebral oedema and convulsions in premature infants and occasionally in adults

Quaternary Ammonium Compounds (Quarts) e.g. Cetrimide
- Are cationic surface active detergents

MoA
- The active action has at least one long water repellent hydrocarbon chain, which causes the molecules to concentrate in an oriented layer on the surface of solutions and colloidal or suspended particles
- The charged nitrogen portion of the cation has a high affinity for water and prevent separation out of solution
- The bactericidal action is attributed to
    - Inactivation of energy producing enzymes
    - Denaturing of proteins
    - Disruption of the cell membrane
- They are bacteriostatic, fungistatic and also inhibits algae

Activity
- Bactericidal for both gram + and moderately active against gram - bacteria
- Lipophilic viruses are inactivated
- They are not tuberculocidal or sporicidal and ineffective on hydrophilic viruses

Clinical indication
- Used for sanitation of non-critical surfaces e.g. floors, bench tops
- Can be used as a preservative in food because of low toxicity

Disadvantages
- Bind to the colloidal surface of proteins in blood, in serum, milk and fibres in cotton, mops, clothes and paper towels
- Are inactivated by anionic detergents e.g. soaps
    - Many anionic detergents, calcium, magnesium, ferric iron and aluminium ions
- Several outbreaks have occurred due to pseudomonas and other gram - feed on the Quarts

Aldehydes
- Formaldehyde and Gluteraldehyde

- Used for disinfection and sterilisation of instruments
- Fibreoptic endoscopes, respiratory therapy equipment, haemodialysers, dental handpieces, which can't stand the high temperatures of steam sterilisers
- They have a broad spectrum of action against microorganisms and viruses

MoA
- They act by alkylation of chemical groups in proteins and nucleic acids

Activity and use
- Formaldehyde
  - available as a 40% solution in water (100% formalin)
  - 8% formaldehyde solution in water has a broad spectrum of activity against bacteria, viruses and fungi. Sporicidal activity may take up to 18 hours. Rapidity of action is enhanced by solution in 70% isopropanol
  - Used in high level of haemodialysers, preparation of vaccines and embalming of tissues
  - 4% formaldehyde (10% formalin) solution used for fixation of tissues and embalming
  - May not not be mycobacterial
- Gluteraldehyde
  - Is a dialdehyde (1,5 - pentanedial, cidex)
  - Most commonly used is 2% gluteraldehyde. The solution is alkalinised to pH of 7.4 - 8.5 for activation
  - Activated solutions are bactericidal, sporicidal, fungicidal and virucidal for both hydrophilic and lipophilic viruses
  - It has greater sporicidal activity than formaldehyde, but tuberculocidal activity might be less and may require prolonged exposure
  - Once activated, shelf life is 14 days

Advantages
- Non-corrosive to metal, plastic, rubber
- Highly effective
- Most common reason for loss of activity is dilution and exposure to organic material

Disadvantages
- Formaldehyde
  - Has a characteristic pungent odour and is highly irritating to respiratory mucous membranes and eyes at concentrations od 2 - 5 ppm
  - Carcinogenic. Employee exposure standard limit is 8 hours to 0.75 ppm
  - At concentrations of >0.2ppm protection measures and gears should be used e.g. goggles, gloves, respirators

Ortho-phthaldehyde (OPA)*

Perioxygen Compounds

- Hydrogen peroxide and Periacetic acid
- Have a high killing activity and broad spectrum of action against bacteria, spores, fungi and viruses in appropriate concentrations.
- They are powerful oxidisers used primarily as disinfectants and sterilants
- Degradation products are non-toxics

Hydrogen Peroxide (H_2O_2)
- Very effective disinfectant on inanimate objects or materials with low organic content
- Organisms producing catalase and peroxidase rapidly degenerate it
- Degradation products are water and oxygen
- Concentrated solutions of 90% are prepared electrochemically
- When diluted in high quality de-iodised water to 6 and 3% and put in clean containers, it

remains stable
- Used for disinfecting respirators, acrylic resin implants, plastic eating utensils, soft contact lenses, cartons for milk or juice products
- Concentrations up to 25% will be sporicidal
- Vapour phase hydrogen peroxide is a cold gaseous sterilant, which can replace the toxic and carcinogenic ethylene oxide and formaldehyde

Disadvantages
- Incompatible with liquids and cellulose products
- Penetrates the surface of some plastics

Periacetic aAcid (CH3COOOH)
- Prepared commercially from 90% hydrogen peroxide,acetic acid and sulphuric acid as a catalyst
- Usually used in a dilute solution and transported in containers with vented caps
- More effective than hydrogen peroxide
- as a bactericidal and sporicidal agent
- Concentrations of 250 -500ppm are effective against many bacteria in 5 minutes at pH 7, at 20 degrees
- Bacterial spores are inactivated by 500 - 30,000ppm periacetic acid
- Presence of organic matter requires slightly increased concentrations.
- Viruses require variable exposures. Enteroviruses require 2000ppm for 15 - 30 minutes for inactivation

Uses
- Automated machines for sterilisation of medical, surgical and dental instruments, use buffered solutions of 0.1 - 0.5%
- Haemodialysers
- In food processing and beverage industries

Disadvantages
- Peracetic acid is a tumour promoter but a weak carcinogen

Heavy Metals
- Mercury and Silver
- Now rarely used as disinfectats
- Mercury is an environmental hazard and there is resistance to it
- Hypersensitivity to thimerosal is high, about 40%. The compounds are absorbed from solution by rubber or plastic
- Thimerosal still used as a preservative for vaccines, antitoxins and immune sera at 0.001 - 0.004%
- Inorganic silver salts are strongly bactericidal. Silver nitrate 1:1000 has been used as preventive for gonococcal ophthalmitis in new-borns
- Silver sulphadiazine slowly releases silver and is used to suppress bacterial growth in burn wounds

Sterilants
- Pressurised steam (autoclaving) at 120 degrees for 30 minutes for sterilising instruments and decontaminating materials
- Ethylene oxide
    - Diluted either with flurocarbon or carbon dioxide
    - Used at 440 - 1200mg/ml at 45- 60 degrees with 30 - 60% relative humidity.
    - The higher concentrations are used to increase their penetration
    - Is mutagenic and a carcinogen
    - Used for lensed instruments and materials containing plastic and rubber

- Alternative sterilants
    - Vapour phase hydrogen peroxide
    - Peracetic acid
    - Ozone
    - Gas plasma
    - Chlorine dioxide
    - Formaldehyde
    - Propylene oxide
    - Automated peracetic acid systems

Preservatives

- Disinfectants used as preservatives to prevent overgrowth of bacteria and fungi in
    - Pharmaceutical products
    - Laboratory sera and reagents
    - Contact lenses
    - Multiuse vials re-entered through rubber diaphragm
    - Eye and ear drops
- They are mainly organic acids including
    - Benzoic acid and salts
    - The parabens (alkyl esters of p-hydroxybenzoic acid)
    - Sorbic acid and salts
    - Phenolic compoiuns
    - Sodium nitrite and nitrate
    - Sulphites
    - Alcohols
    - Butirates
    - Merculial compounds like thimerosal
    - Benzoates salts (juices and drinks)

Disease Modifying Anti-Rheumatic Drugs (DMARDS)

Monday, 17 October 2016 9:22 AM

Introduction

- Arthritis means inflammation of a joint or joints
- DMARDS suppress the disease process in rheumatoid arthritis
- Also known as second line drugs
- Unlike the NSAIDS, most of them do not produce an immediate therapeutic response but require 4 - 6 months of treatment for a full response
- If no objective (response) benefit within 6 months, the drug should be discontinued
- Used in rheumatoid arthritis where treatment with NSAIDS alone provides inadequate control
- Should be initiated if severe symptoms persist
- Improve symptoms of and signs of inflammatory joint disease and extra articular manifestations such as vasculitis
- Reduce the erythrocyte sedimentation rate and sometimes the titre of rheumatoid factor

DMARDS

- Gold compounds
  - Gold sodium thiomalate
    - Water soluble and IM
  - Aurothioglucose injection
    - IM and water soluble
  - Auranofin
    - Oral administration
- Penicillamine
- Antimalarial drugs
  - Chloroquine
  - Hydroxychloroquine
- Sulphasalazine
- Immunosuppressants
  - Methotrexate
  - Alkylating agents
    - Chlorambucil
    - Cyclophosphamides
  - Cyclosporin
  - Azathioprine
  - Mycophenolate mofetil
- Anti TNF-α drugs
  - Infliximab
  - Etarnercept
  - Adalimumab
- Leflunomide
- Glucocorticoid drugs
  - Dexamethasone
  - HC
  - Prednisolone
  - Methylprednisolone
  - Triamcinolone

Gold Compounds

- Administered in the form of organic complexes
- Sodium aurothiomalate and auranofin are the two most common preparations
- The effect of gold compounds develop slowly over 3 - 4 months
    - Pain and joint swelling subsides and the progression of bone and joint damage diminishes

MoA

- Not clear
- Auranofin is thought to inhibit induction of IL-1 And TNF-α

P'Kinetics

- Sodium aurothiomalate is given by deep IM injections
- Initially given weekly then at monthly intervals

AE

- Seen in about 1/3 of patients treated and serious toxic effects in about 1 patient in 10
- Skin and mucous membranes
    - Erythema
    - Glossitis
    - Exfoliative dermatitis
- Kidneys
    - Proteinuria
    - Membranous glomerulonephritis
- Blood
    - Thrombocytopenia
    - Leukopenia
    - Agranulocytosis
    - Aplastic anaemia

Penicillamine

- A metabolite of penicillin and is the analogue of cystine
- D isomer and has been used in rheumatoid arthritis
- Rarely used due to its toxicity

Chloroquine and Hydroxychloroquine

Proposed mechanisms of anti-inflammatory action

- Suppression of T lymphocyte responses to mitogens
- Decreased leukocyte chemotaxis
- Stabilisation of lysosomal enzymes
- Inhibition of DNA and RNA synthesis
- The trapping of free radicals

P'Kinetics

Ref. Antimalarials

Indications

- Rheumatoid arthritis that has been unresponsive to NSAIDS
- Treatment if rheumatoid arthritis of moderate inflammatory activity
- Can also be used with NSAIDS, allowing for low doses of chloroquine or hydroxychloroquine to be administered
- Have been shown to slow the progression of erosive bone lesions and may induce remission
- Need 12 - 24 weeks for their action to be apparent
- Also effective for mild systemic lupus erythematosus, particularly involving cutaneous and joint manifestations
- Better tolerated than gold or penicillamine
- Relatively safe in pregnancy

NB:

Should not be used for psoriatic arthritis

AE

- Ocular toxicity which rarely occurs at higher doses used for rheumatoid arthritis
- Ophthalmologic monitoring 6 - 12 months is advised
- In elderly, difficult to distinguish drug-induced retinopathy from ageing changes
- Dyspepsia, NV, rashes and nightmares
- Less frequent
    - EC changes
    - Convulsions
    - Keratopathy
    - Ototoxicity
    - Hair depigmentation
    - Hair loss
    - Discolouration of skin, nails and mucous membranes
- Rare SE
    - Blood disorders
    - Mental changes
    - Myopathy
    - Acute generalised exanthemata's pustulosis
    - Exfoliative dermatitis
    - SJS
    - Hepatic damage

Cautions

- In hepatic impairment and in renal impairment
- The drugs secreted in breast milk and breastfeeding should be avoided when they are used to treat rheumatoid arthritis

NB:

- Chloroquine can, however, be used for treatment of malaria during pregnancy and breastfeeding
- In neurological disorders e.g. severe GIT disorders G6PD deficiency, porphyria and in the elderly, may exacerbate psoriasis and aggravate myasthenia gravis
- Avoid concurrent use with hepatotoxic drugs

Glucocorticoids

- Include:
    - Dexamethasone
    - Prednisolone
    - Methylprednisolone

    - Hydrocortisone
    - Triamcinolone
- Reserved for specific indications i.e. when other anti-inflammatory drugs are unsuccessful
- May be administered by many routes depending on the condition being managed
- In rheumatoid arthritis, the drugs are given by intra-articular injection to relieve pain, increase mobility and reduce deformity
- Effect is prompt and dramatic
- Drugs slow appearance of new bone lesions
- Used for non-specific treatment of inflammatory and allergic conditions
    - They decrease the capillary and leukocyte response to local injury
    - Inhibit secretion of proteolytic and lipolytic enzymes
    - Inhibition of fibroblast growth and inhibition of scar formation
- In rheumatoid arthritis
    - Reduce acute inflammation and scar deformity
    - Effects are prompt and palliative
    - Prompt symptomatic relief with diminution of joint swelling, effusion and pain but symptoms return on cessation of treatment and joint rapidly deteriorate due to over dosage
    - Cartilage and bone destruction are not arrested

MoA for anti-inflammatory and immunosuppression

- Inhibition of transcription of the genes for COX-2, cytokines (e.g. the ILs), cell adhesion molecules and the inducible form of NOS
- Block of Vitamin D_3 mediated induction of the osteocalcin gene in osteoblasts and the modification of transcription of the collagenase genes

Side Effects

- Numerous including infections, osteoporosis, fractures, cataracts
- In predisposed patients
    - Diabetes mellitus
    - Hypertension
    - Accelerated atherosclerotic heart disease
- With intra-articular injections
    - Flushing
    - Charcot-like arthropathies also reported
- Hyaline cartilage may be affected and each joint should not be treated more than 3 times a year

Azathioprine

- A prodrug of 6-mecarptopurine
    - Both are purine anti-metabolites
- Appears to be more effective as an immunosuppressant than 6-MP and this may be due to
    - Differences in drug uptake into target cells
        - Local conversion of azathioprine to 6-MP in target cells responsible for immune effects
    - Pharmacokinetic differences in handling azathioprine and 6-MP
- More widely used than 6-MP as an immunosuppressant in humans

MoA

- Nucleophiles such a glutathione cleave azathioprine to 6-MP
- 6-MP is converted to its nucleotides, leading to inhibition of purine synthesis or anabolism

to thio-IMP
- Thio-IMP ----> Thio-GMP -----> Thio-GTP
- Intercalation of thio-GTP into the DNA backbone damages the DNA
- Destroy simulated lymphoid cells
- Kill proliferative cells and appear to work at the same level in the immune system
- Can block cellular immunity as well as primary and secondary serum antibody responses
- Acts through its metabolite 6-thioguanine to suppress
    - Inosinic acid synthesis
    - B and T cell function
    - Immunoglobulin production and IL-2 secretion

PK

- Administered IV, PO
- Well absorbed orally
    - C_{max} 1 - 2 hours
- Serum half-life <2 hours, however, the active metabolite, 6-thioguanine (6-TG) nucleotides are concentrated in cells resulting in prolonged half-life

NB:

- The prolonged kinetics of 6-TG nucleotides results in a median delay of 17 weeks before onset of therapeutic effect for oral azathioprine and 6-MP
    - Observation made in those with obstructive bowel syndrome
- Metabolism is bimodal
- Rapid metabolisers clear the drug 4X more rapidly than slow metabolisers
- Production of 6-TG is dependent on thiopurine methyl transferase (TPMT)
- Patients with low or absent TPMT activity (0.3% of population) are at particularly high risk of severe myelosuppression by excess concentration of azathioprine
    - Avoid use if possible or reduce the dose (to a tenth of normal or less)
- Xanthine oxidase (XO) metabolises 6-MP to 6-thiouric acid, which is excreted in urine
- Small amounts of azathioprine and mecaptopurine are also excreted by the kidneys
- Increased toxicity occurs in anephric or anuric patients
    - Reduce dose of azathioprine to one fourth to one third the usual amount to prevent excessive toxicity if allopurinol is being used to control hyperuricaemia

Therapeutic uses

- Prevention of transplant rejection
    - May be used combined with cyclosporine and/or prednisone
    - May be given to patients who do not respond to cyclosporine and prednisone
    - Prophylactic therapy with azathioprine is started 1 or 2 days before renal transplantation or on the day of operation
    - Maintenance doses are lower than initial dose
- Treatment of autoimmune diseases
    - E.g. Severe RA, Crohn's dx and imultiple sclerosis
    - Mx of acute glomerulonephritis and in the renal component of SLE; psoriatic arthritis, polyreactive arthritis, polymyositis
    - Some case of prednisone-resistant Ab-mediated idiopathic thrombocytopenia_
- Autoimmune dx of dermatology
    - May be used as steroid sparing agent for pemphigoids, lupus and dermatomyositis.
    - Decreases antibody production and has anti-inflammatory properties
    - Maintenance does are lower than initial doses
    - Doses vary widely depending on dx

Drug interactions

- Allopurinol
    - XO inhibitor

    - Reduces the metabolism of AZA
    - Increased risk of toxicity
    - Avoid combination
    - Reduce AZA to 1/4-1/3 of the original dose
- 5-aminosalicylates
    - Used for treating inflammatory bowel dx by inhibiting ThioPurineMethylTransferase activity
    - May increase bone marrow toxicity of AZA (May be less likely with balsalazide)
- Ribavirin
    - Inhibits Inosine MP Dehydrogenase
    - Reduce AZA metabolism
    - Increasing AZA metabolites causing toxicity
    - May result in pancytopenia.
    - Avoid combination
- Warfarin
    - Oral anticoagulant
    - AZA may decrease INR, reducing warfarin's therapeutic effect,
    - May require an increase in warfarin dose
- Drugs that affect leucocyte production (e.g. co-trimoxazole) may lead to exaggerated leukopenia, esp. in renal transplant patients.

AE

- Cytotoxic drug therefore can rapidly affect growing cells, including bone marrow and GIT cells
- Bone marrow suppression can lead to leucopoenia, macrocytosis, anaemia or thrombocytopenia
- Hepatic dysfunction.
    - High serum alkaline phosphatase levels and mild jaundice occurs occasionally particularly in patients with pre-existing hepatic dysfunction
- Hypersensitivity reactions in about 5% of patients
- GIT symptoms mainly at higher doses
- Alopecia
- Routine lab monitoring with complete blood count and LFTs required
- Leucopoenia or elevation in liver enzymes may respond to dose reduction
- AZA may predispose to infections
- Leucopoenia may respond to Rx with GSF
- Risk of lymphomas in transplant patients in long term therapy
- Avoid in pregnancy. Crosses placenta- cause teratogenicity, mutagenicity and possible carcinogenicity

CI

- Should be avoided in
    - Women of child bearing potential
    - Pregnant women
    - Lactating mothers
    - Hypersensitivity to drug

Sulfasalazine, Leflunomide and Others

- Divided into:
    - Biologic
    - Nonbiologic
        - Leflunomide

        - Mycophenolate mofetil
        - Sulfasalazine
        - Minocycline
        - Older agents
            - Gold salts
            - Penicillamine
                - No longer recommended because
                    - Significant toxicities
                    - Slight efficacies

Biologics

- Mainly antibodies or binding proteins
- T cell modulating biologic
    - Abatacept
- B cell cytotoxic agent
    - Rituximab
- Anti-IL-6 receptor antagonist
    - Toliximab
- TNF-a blocking agents
    - Etanercept
    - Infliximab
    - Adalimumab
    - Golimumab
    - Certolizumab
- Anti-IL-1 antagonist
    - Anakinra

Drugs

- NSAIDS
    - Usually ASA
    - Other NSAIDS are not more effective
    - Other NSAIDS have less GIT effects esp. coxibs
    - Provide symptomatic relief (anti-inflammatory)
    - _
- DMARDS or SARDS
    - Have minimal direct analgesic or anti-inflammatory effect so NSAIDS are needed
    - Effects take weeks to months to appear
    - Retard the development of bone erosions and facilitate their healing

Sulfasalazine

- It is a sulphonamide

P'kinetics

- Poorly absorbed (10 - 20%) from the GIT
- Undergoes EHC
- Not metabolised by liver enzymes
- 90% excreted through bile and 10% through urine
- 70% enters the colon
    - Broken down by intestinal bacterial enzymes to sulphapyridine + 5-aminosalicylate (=mesalamine)
- Highly lipid soluble
- Sulphapyridine is an active metabolite
    - Absorbed and metabolised by various pathways including acetylation
    - Rapid acetylators have lower levels of the drug and less adverse effects

- Excreted in urine
- Sulphapyridine is responsible for most toxicity
- 5-aminosalicylate
    - Not absorbed
- Reaches high levels in the faeces
- Sulphapyridine is thought to be the active moiety for RA
- 5-aminosalicylate is for inflammatory bowel disease

Effects
- Reduced rheumatoid factor
- Suppression of T cell responses
- Inhibition of B cell proliferation
- Reduced rate of bone damage

MoA
- Unknown

Toxic Effects
- common
    - NVD
    - epigastric pain
    - Malaise
    - Headache rash
- Megaloblastic anaemia
- Haemolytic anaemia
- Neutropoenia
- Methaemoglobinaemia
- Reversible infertility in males
- Not teratogenic
    - Safe for use in pregnancy but folate supplementation necessary

Leflunomide
- Prodrug
- Immunosuppressant

MoA
- Rapidly converted into active metabolite which inhibits dihydroorotate dehydrogenase
- This leads to reduced ribonucleotide synthesis and arrest of the stimulated cells in the G1 phase of cell growth
- This causes
    - Inhibition of T cell function
    - Inhibits production of antibodies from B cells
    - It inhibits bony damage

P'Kinetics
- Oral
- Completely absorbed
- Half-life of 19 days
- Half-life of active metabolite is several weeks
- Active metabolite undergoes EHC
- Cholestyramine can enhance leflunomide excretion by 50%

Adverse effects
- D (25% of patients)

- Elevated liver enzymes
- Mild alopecia
- Weight gain
- Hypertension
- Leukopenia (rare)
- Thrombocytopenia (rare)

Contraindications
- In pregnancy

Methotrexate
MoA
- Inhibits
    - Aminoimidazolecarboxamide ribonucleotide (AICAR) transformylase
    - Thymidylate synthase
    - This affects PMN chemotaxis
- Affects dihydrofolate reductase
    - This affects lymphocyte and macrophage function
- Directly inhibits proliferation and stimulates apoptosis in immune inflammatory cells
- Inhibition of proinflammatory cytokines, linked to rheumatoid synovitis

Adverse Effects
- Most common
    - Nausea
    - Mucosal ulcers
    - Elevation of liver enzymes
    - GIT and liver effects can be reduced by using leucovorin or folic acid
- Rare
    - Liver cirrhosis (do liver biopsy every 5 years)
    - Hypersensitivity lung reaction (acute shortness of breath)

Chlorambucil
MoA
- It crosslinks DNA and this prevents cell replication

Adverse Effects
- Bone marrow suppression
- Infertility
- Risk of secondary cancer

Cyclophosphamide
MoA
- Crosslinks DNA to prevent cell replication
- Suppresses T and B cell function
- Active against RA only when given orally but not IV

Adverse Effects
- Bone marrow secretion
- Infertility
- Alopecia
- Haemorrhagic cystitis
- Rarely bladder carcinoma

Cycloserine
See calcineurin inhibitors in immunopharmacology

Mycophenolate mofetil
- Converted to the active drug mycophenolic acid
- It inhibits cytosine monophosphate dehydrogenase
- This interferes with
    - T cell proliferation
    - It interferes with leucocyte adhesion

AE
- GIT
    - NVD
    - Abdominal pain
- Headache
- Bone marrow suppression
- Hypertension
- Hepatotoxic

TNF-alpha blocking drugs
- All are IgG anti-TNF MAbs
    - They complex with TNF-alpha
    - Results in downregulation of macrophage and T cell function
- Adverse effect for al these agents
    - Risk of opportunistic disease e.g. TB. Screening for TB is recommended

Adalimumab
PK
- SC
- Half-life
    - 10 - 20 days
    - Methotraxate reduces clearance and production of antibodies against this compound

AE
- Rare
    - Leukopenias
    - Vasculitis

Infliximab
See Immunopharmacology

Eternacept
See Immunopharmacology

Abatacept
- Inhibits T cells
- Ab formation against the drug does not change clinical outcome

AE
- Risk of URTIs
- Lymphomas
- Rarely causes anaphylaxis

- Don’t combine with other anti-TNF drugs due to infection risk

Rituximab

- A MAb that targets CD20 B lymphocytes

MoA

- Rapidly depletes B lymphocytes
- This reduces inflammation by
    - Decreasing the presentation of antigens to T lymphocytes
    - Inhibiting the secretion of pro-inflammatory cytokines

PK

- IV infusion
- Pre-treatment with
    - Acetaminophen
    - Antihistamine
    - Glucocorticoids (usually IV methylprednisolone)
- Given 30 minutes prior to infusion
- Decreases infusion reactions

AE

- Rash
- Immunoglobulins (IgG and M) may decrease
- Serious bacterial, fungal and viral infections are reported for up to one year of the last dose of rituximab
- Patients who have severe active infections should not receive rituximab
- Associated with reactivation of HBV
- Not associated with
    - Activation of TB
    - Lymphomas or other tumours
- Fatal mucocutaneous reactions
- Cytopoenias
    - Complete blood counts every 2 - 4 months

Tocilizumab

MoA

- Binds and inhibits IL-6 receptors
- IL-6 pro-inflammatory cytokine produced by different cell types

PK

- IL-6 suppresses several CYP450 isoenzymes
- It
    - May increase CYP450 activity
    - Dose adjustment for drugs with marrow therapeutic window e.g. cyclosporine and warfarin

AE

- Most common
    - URTIs
    - Headache
    - Hypertension

    - Elevated liver enzymes
- Infections
    - TB
    - Fungal
    - Viral
    - Other opportunistic infections
    - Screen for TB before use
- Rare
    - Neutropoenia
    - Thrombocytopoenia
    - GI perforation
    - Demyelinating disorders
        - Multiple sclerosis
    - Anaphylaxis

Anakinra

- A recombinant IL-1RA (receptor antagonist)

MoA

- Blocks the effect of IL-1alpha and 1ß of IL-1 receptors hence decreasing the response in inflammatory diseases

PK

- SC admin.
- Dose adjustment in renal insufficiency

Immunopharmacology

Tuesday, 18 October 2016 9:20 AM

The Immune Response
Innate IS (Non-specific)

- Physical barriers
- Biochemical- complement, lysosomes, interferons
- Cellular - macrophages, neutrophils, monocytes, natural killer and cytotoxic T- cells (NKTCs)

Complement System

- C1-9
- Enhance macrophage and neutrophil phagocytosis by acting as opsonins (C3b) and chemo attractants (C3a, C5a)
- Membrane attack complex (C5b, C6, C7, C8, C9) break cells
- In inflammation, cellular influx mediated by chemoattractant cytokines (IL-8, macrophage chemotactic protein-1 and macrophage inflammatory protein-1 from endothelial cells and immune cells at the site
- If successful, invading pathogen is ingested, degraded, and eliminated and disease is either prevented or duration shortened
- NK cells and cytotoxic-T cells secrete Interferon-gamma, which activates resident tissue macrophages and dendritic cells
- NK cells are able to recognise and attack virus infected normal cells and tumour cells without prior exposure
- Activity regulated by killer cell immunoglobulin-like receptors (KIRs) on NK cell surface specific fro MHC-1 proteins
- MHC-1 proteins produced by all nucleated cells. Their signals prevent self-killing
- They release cytotoxic granules that induce programmed cell death
- CTKC express T-cell receptors as well as KIRs. They recognise microbial lipids antigens by MHC like molecules, CD-1. implicated in host defence against microbes, autoimmune diseases and tumours

Adaptive IS (Specific)

- Responds to a variety of antigens
- Discriminates between self and foreign antigens
- Responds to previously encountered pathogens rapidly by a vigorous memory response
- Antibodies produced (humoral response)
- Activation of T-lymphocytes (CMI)
- Antigen presenting cells
    - Macrophages, dendritic cells, Langerhans cells, B-lymphocytes
    - Phagocytose and process protein antigens, digest them to generate peptides which are then loaded onto MHC I and II proteins and presented to the cell surface T-cell receptor
    - CD-8 T-cells recognise MHC-I peptide complexes
    - CD4 T-cells recognise the MHC II peptide complexes
    - Two signals required
    - Co-stimulatory signals CD40 and CD80 and CD86
    - Ligands CD40L for CD40, CD28 for CD80 or CD86 on APCs
    - Negative feedback T-cell associated antigen 4 (CTLA4)
- TH1 and TH2
    - TH1
        - Interferon-gamma, IL-2 and TNF-ß
        - Induces cell mediated immunity by activating macrophages, CTC and NK cells

    - TH2
        - IL-4, 5, 6 and 10 and sometimes 3 which induce B lymphocyte proliferation and differentiation to antibody secreting plasma cells
    - IL-10 produced by TH2 inhibits cytokine production by TH1 cells by down regulating MHC expression by the APCs
    - IF-gamma produced by TH1 cells inhibits TH2 proliferation
    - Extracellular bacteria typically cause production of TH2 cytokines resulting in production of neutralising opsonic antibodies
    - Intracellular organisms e.g. Mycobacteria, cause production of TH1 cytokines, resulting in activation of effector cells like macrophages
- TH3 subset of t-cells, produces transforming growth factor-ß (TGF-ß), whose functions include down-regulation of proliferation and differentiation of T lymphocytes
- CD8 T lymphocytes are able to recognise endogenously processed peptides presented by virus infected cells and tumour cells loaded on MHC I
- CD4 recognise proteins from extracellular pathogens loaded onto MHC II
- Sometimes, cross -penetration can occur
- CD8 induce target cell death by lytic granule enzymes (granzymes), perforin and Fas-ligand apoptosis pathways
- B cells undergo selection in the bone marrow
- On meeting an antigen, a mature B cell binds, internalises it. It presents its peptide bound to MHC II to CD4 helper cells, CD4 helper cells produce IL 4 and 5 which stimulate B cell proliferation and differentiation into memory B and plasma cells
- The primary response is IgM antibodies. Subsequent stimulation causes a vigorous booster response accompanied by class switching to IgG, IgA and IgE antibodies. Affinity maturation takes place allowing more efficient antigen binding
- Antibodies act as opsonins to enhance phagocytosis and cellular cytotoxicity and by activating complement system to elicit an inflammatory response and induce bacterial lysis

Abnormal Immune Response

- Hypersensitivity reactions
    - Immediate
        - Type I
        - Type II
        - Type III
    - Delayed
        - Type IV
            - Cell mediated, 2 - 3 days after exposure
- Auto immunity
    - Systemic lupus erythematosus
    - Rheumatic arthritis
    - GPS
- Immunodeficiency
    - SCID
        - ADA deficiency
    - DiGeorge Syndrome
        - Failed thymus
        - Poor T cells
        - _

Immunomodulators

Immunosuppressants

- Glucocorticoids
- Cyclosporins
- Tacrolimus/sirolimus
- Interferons

- Mycophenolate mofetil
- 15-deaxyspergualin
- Glatimerer

Cytotoxic Agents

- Azathioprine
- Leflunamide
- Cyclophosphamide
- Vincistine, methotrexate, cytarabine, viblastine, methoxsalen

Antibodies

- Anti-thymocyte globulin (ATG)
- Anti-lymphocyte (ALG)
- Immunoglobulin intravenous (IGIV)
- Rhesus (D) immunoglobulin microdose
- Hyperimmune globulin
- Monoclonal antibodies
    - Tratuzumab, rituximab, daclizumab, basiliximab, abciximab, palivizumab, infliximab, eternacept

Immunostimulants

- Cytokines
    - IL1 and 4
    - TNF-alpha and beta
    - G-CSF
    - GM-CSF
    - M-CSF
    - Erythropoietin
    - Thrombopoietin
- Levamisole
- Inosiplex (iosprimosine), cyanoaziridines - azimexin, ciamexon, imexon
- BCG
- Diethyl dithiocarbamates
- Thymosin

Immunosuppressant

Calcineurin Inhibitors

- Cyclosporine
- Tacrolimus (FK 506)
- Sirolimus

Mode of action

- Cyclosporine and tacrolimus form complexes with cytoplasmic immunophilins which block the action of calcineurin in activated T cells
- This prevents production of Il-2 and other cytokines, which normally stimulate T cell proliferation and differentiation

Cyclosporine

- Peptide antibiotic

MOA

- Inhibit

    - IL-1,2 receptor production
    - Macrophage T cell interaction
    - T cell responsiveness.
    - Prevents T cell dependent B cell function

PK

- Absorption is incomplete and erratic although may be enhanced due to
    - Micro emulsion preparation (20 - 30%)
    - Grapefruit juice (62%)
    - Metabolised by CYP3 enzyme and is therefore prone to a large number of drug interactions

Indications

- Prevention and treatment of transplant rejection
    - Concentration monitoring recommended)
- Nephrotic syndrome
- Rheumatic arthritis
- Psoriasis or atopic dermatitis
- Systemic Lupus erythematosus
- Polymyositis, dermatomyositis, Wegener's granulomatosus
- Juvenile chronic arthritis

AE

- Nephrotoxicity, which may be increased by drug interactions
    - With diltiazem and K+ sparing drugs
- Hypertension, hyperkalaemia, hyperglycaemia
- Hepatotoxicity
- Altered mental status, seizures and hirsutism
- Gingival hyperplasia (more common in children and adolescents)

Tacrolimus

- Also known as FK-506
- Immunosuppressant macrolide antibiotic
- Not chemically related to cyclosporine but similar MoA
- 10 - 100X more potent than cyclosporine in inhibiting immune responses
- Indications - as of cyclosporine

AE

- Common
    - Alopecia
- Rare
    - Hirsutism
    - Gingival hyperplasia
    - Ventricular hypertrophy
    - Cardiomyopathy
    - Torsades des pointes
    - Pure and red cell aplasia

Sirolimus (Rapamycin)

- Binds immunophilins and inhibits calcineurin as do cyclosporine and tacrolimus, however, does not block IL production by activated T cells but instead blocks the response of T cells to cytokines
- Potent inhibitor of B cell proliferation and immunoglobulin production

Indications
- Alone or in combination with other immunosuppressants to prevent rejection of solid organ allografts

Toxicities
- Myelosuppression
- Hepatotoxicity
- Diarrhoea
- Hypertriglyceridemia
- Headache

Antiproliferatives and Antimetabolites

Proliferation Signal Inhibitors (PSIs)
- They include
    - Sirolimus (Rapamycin)
    - Its analogs (called rapalogs) such as everolimus and etemsirolimus

Chemistry
- Sirolimus is an immunosuppressant macrolide antibiotic
- It is structurally similar to tacrolimus

MoA
- Inhibits T-lymphocyte activation and proliferation downstream of the eIL-2 and other T cell growth factor receptors
- Sirolimus binds to the circulating immunophilin FK506-binding protein 12 (FK506-BP12)
- The sirolimus FK506-BP-12 complex binds to and inhibits a protein kinase called mammalian target of rapamycin (mTOR)
- mTOR is a key enzyme in cell cycle progression
- It is involved in cellular processes such as
    - Cell growth and proliferation
    - Angiogenesis
    - Metabolism
- Inhibition of mTOR can ultimately lead to
    - Inhibition of interleukin-driven T cell proliferation
    - Blockage of cell cycle progression at the G1S phase transition
- Sirolimus also seems to inhibit B cell proliferation and antibody production

PK
- Is available only as an oral drug
- After oral administration, it is rapidly absorbed
- Systemic availability is 15%
- It reaches peak blood concentration within 1 hour after a single dose in healthy subjects and within 2 hours after multiple oral doses in renal transplant patients
- Blood concentration are proportional to doses given
- A high fat meal decreases peak blood concentration by 34%
    - Sirolimus should be taken consistently either with or without food and blood level should be monitored closely
    - Half-life 60 hours
        - The blood half-life after multiple doses in stable renal transplant patients is 62 hours
- ~40% of sirolimus in plasma is protein bound especially to albumin
- It partitions into formed elements of blood, with a blood to plasma ratio of 38 in renal transplant patients

- Sirolimus is extensively metabolised by CYP3A4 and is transported by P-glycoprotein
- Several metabolites have been identified in whole blood
- Metabolites have also been detected in stool and urine
- Its is mainly excreted in stool
- Some of its metabolites are active
    - Sirolimus itself is the major active component in whole blood
    - It contributes >90% of the immunosuppressive effect
    - A loading dose of 3X the maintenance dose provides nearly steady state concentrations within one day in most patients
    - The daily maintenance dose should be reduced by ~1/3 in patients with hepatic impairment

Drug interactions

- Concurrent use with cyclosporine can increase the plasma levels of both sirolimus and everolimus
    - Drug levels need to be monitored and their administration should be separated by time
- Dose abjustment may be required when sirolimus is co-administered with diltiazen or rifampin
- Dose adjustment is apparently not required when sirolimus is co-administered with acyclovir, digoxin, glyburide, nifedipine, norgestrel/ethinyl estradiol, prednisolone or cotrimoxazole

Clinical Use

- Sirolimus is used effectively alone, and in combination with other immunosuppressants (corticosteroids, syclosporine, tacrolimus and mycophenolate mofetil) to prevent rejection of solid organ allografts
    - Nephrotoxicity is a major concern when administering calcineurin inhibitors, therefore, sirolimus is frequently use as first-line immunosuppressant therapy in both solid organ and stem cell transplantation because it does not usually cause renal toxicity
    - Inpatients experiencing or at a high risk of calcineurin inhibitor associated nephrotoxicity, sirolimus has been used by glucocorticoids and mycophenolate to avoid permanent renal damage
- It is used as prophylaxis and as therapy for steroid-refractory acute graft-vs-host disease in haematopoietic stem cell transplant recipient
- Topical sirolimus is also used in
    - Some dermatologic disorders
    - In combination with cyclosporine in the management of uveoretinitis
- Sirolimus-eluting coronary stents reduce restenosis and other adverse cardiac events in patients with severe coronary artery disease
    - These benefits appear to be due to its anti-proliferative effects

Adverse Effects

- Include
    - Profound myelosuppression (esp. thrombocytopenia)
    - Hepatotoxicity
    - Diarrhoea
    - Pneumonitis
    - Headache
    - Dose-dependent increase in serum cholesterol and triglycerides that may require treatment
    - Mouth ulcers
    - Hypokalaemia
    - Proteinuria
    - Lymphocele, is a known surgical complication associated with renal transplantation

        - It is increased in a dose-dependent manner by sirolimus and requires close postoperative follow-up
    - Delayed wound healing with sirolimus
    - As with other immunosuppressive agents, there is an increased risk of
        - Neoplasms esp. lymphomas
        - Infections
    - Sirolimus by itself is not nephrotoxic
        - Patients treated with cyclosporine and sirolimus, have impaired renal function as compared to patients treated with cyclosporine and either azathioprine or placebo
    - May also prolong delayed graft function in deceased donor kidney transplants, presumably because of its anti-proliferative action
        - Renal function must therefore be monitored closely in such patients
    - Increased use of sirolimus in stem cell transplantation regimens as GVHD prophylaxis, particularly when combined with tacrolimus, has been associated with an increased incidence of haemolytic-uraemic syndrome

Contraindication and caution

- Sirolimus is not recommended in liver and lung transplants due to the risk of hepatic artery thrombosis and bronchial anastomosis dehiscence, respectively

Everolimus

Chemistry and PK

- It is closely related chemically and clinically to sirolimus
- It has a distinct PK
    - Absorbed rapidly after oral administration
    - Has a better bioavailability than sirolimus
    - The main difference is its shorter half-life of ~43 hours
        - Shorter time to reach steady state concentration

Clinical use

- Dosage on mg/kg basis is similar to sirolimus
- Clinical efficacy appears to be similar to that of sirolimus in solid organ transplant recipients
- It is under investigation as an additional therapeutic agent for the treatment of chronic cardiac allograft vasculopathy

Toxicity and DI

- As with sirolimus, the combination of a calineurin inhibitor and a PSI mTOR inhbitor worsens renal function at one than does calcineurin therapy alone
- This suggests a DI between the mTOR and calcineurin inhibitors that enhances toxicity and reduces rejection
- The toxicity of everolimus ad the DI reported to date, seem to be the same as with Sirolimus

Temsirolimus

- It is not currently used ad an immunosuppressant
- Both temsirolimus and everolimus are used and being investigated as targeted therapy for various cancers

Cytotoxic agents

- Azathioprine
- Cyclophosphamide

- Pyrimidine synthesis inhibitors
    - Leflunomide
    - Teriflunomide
- Hydroxychloroquine
- Methotrexate
- Mycophenolate mofetil
- Immunomodulatory derivatives or thalidomide (IMiDs)
    - Thalidomide
    - Lenalidomide
    - Pomalidonide
- Vincristine
- Cytarabine
- Pentostatin
- Chlorambucil
- Dactinomycin

Vinca Alkaloids

- Vincristine appears to be quite useful in idiopathic thrombocytopenic purpura (ITP) refractory to prednisolone
- Vinblastine
    - It prevents mast cell degranulation in vitro by binding to microtubule units within the cells to prevent release of histamine and other vasoactive compounds

- Methotrexate has been used extensively in the treatment of
    - Rheumatoid arthritis
    - GVHD
    - Immunosuppression in patients with idiosyncratic reactions to purine antagonists
    - Psoriasis
    - Some cancers
- Dactinomycin
    - An anti-tumour antibiotic that has been used with some success at the time of impending renal transplant rejection
- Cytarabine
    - Has immunosuppressive properties
- Pentostatin
    - Is an adenosine deaminase inhibitor
    - Clinical use
        - Primarily used as an anti-neoplastic agent for lymphoid malignancies
            - Produced profound lymphopoenia
        - Also frequently used for steroid resistant GVHD after allogeneic stem cell transplantation
        - In preparative regimens prior to these transplants to provide severe immunosuppression to prevent allograft rejection

Antibodies

- Polyclonal and monoclonal against lymphocyte cell-surface antigens
- Prevention and treatment of organ transplant rejection

Polyclonal Antisera

- Obtained by repeated injection of human thymocyte in animals to form:
    - Antithymocyte Globulin (ATG) or
    - Lymphocyte antilymphocyte Globulin (ALG)
- Sources of purified serum to generate Igs
    - Horse, Rabbit, Sheep, Goat

- Vary in efficacy and toxicity from batch to batch
- Highly effective immunosuppressive
- Variability of efficacy and toxicity overcome by hybridoma technology that produce monoclonal antibodies
- Monoclonal Abs are more limited in target specificity

ATG

- Thymoglobulins
- Purified gamma globulin from serum of rabbit immunised with human thymocytes
- Sterile freeze-dried product for IV us after reconstitution with water.

MoA

- Contain cytotoxic antibodies that bind to CD2, 3, 4, 8, 11a, 18, 25, 44, 45 and HLA class 1 and 11 molecules on the surface of human T lymphocytes
- The Abs deplete circulating lymphocytes by direct cytotoxicity (Complement and cell-mediated)
- Block lymphocyte fx by binding to cell surface molecules involved in the regulation of cell functions

Therapeutic uses

- Inductuion of immunosupression in Rx of acute renal transplant rejection in combination with other immunosupressive agents
- Calcinuerin sparing in delayed graft function
- Acute rejection of other graft organ transplant

Monoclonal Abs

- AntiCD3 monoclonal antibodies are directed towards CD3 antigen on the surface of human T cell.
- Used in human transplantation
    - Effective
- Useful in corticosteroid resistance
    - Mouse source IgG_2a antihuman CD3 Monoclonal antibody, muromonab-CD3 (OKT3)

MoA

- Binds to CD3 found in Tcell
- Involved in antigen recognition, cell signalling and proliferation
- Prevents antigen recognition
- Depletes Tcells rapidly from blood and peripheral lymphoid organs
- Reduction in fx of Tcells as a result of lack of IL-2 production and decrease of cytokines

Therapeutic use and toxicity

- Rx of acute organ rejection
- May cause cytokine release syndrome thus use corticosteroid to prevent this first dose effect
- Present with anaphylactic manifestation

New generation of anti-CD3 Abs

- Genetically altered and humanised
- Reduced toxicity
- Efficacy under evaluation

Anti IL2 receptor Abs

- Anti CD25
- Daclizumab- humanised murine complementarity-determining region
- Basiliximab- murine human chimeric monoclonal Abs

MoA

- Bind to receptor on Il2 present on surface of activated Tcells and blocks IL2 mediated Tcell activation events

Uses

- Prophylaxis of acute organ rejection in Adykts as part of combination therapy with calcineurin-inhibitors, AZA, glucocorticoids
- No cytokine release syndrome observed
- Anaphylactic rxns can occur

Infliximab

- Chimeric anti-TNF-alpha monoclonal Ab - TNF-& RA, CD
- Human constant region and murine variable region
- Binds with high affinity to TNF- & and prevents cytokines from bind to its receptor
- High level of TNF-& seen in RA and Crohn's dx thus used with or w/o methotrexate in Rx of these conditions

ADRs

- Infusion reactions
- Infections - URTI, UTI
- Positive AntiNuclearAb and SLE

CI in multiple sclerosis due to reports of demyelinating effect

Etanercept

- Fusion protein
- Ligand binding portion of TNF &
- Used in refractory rheumatoid arthritis
- Combination with methotrexate
- Infection, injection site reaction are common
- SC administration
- Half-life of 4.5 days

Questions

- Review the indications and uses of Abs and immunosuppressant drugs
- When and why do we use combination therapy?
- What are the common side effects and adverse reactions of antibodies
- What is tolerance

General Anaesthetics (GA)

Monday, 7 November 2016 11:15 AM

Anaesthetic Agents

- Local
  - Peripheral effects
- General
  - Effect on the CNS

Indications

- Adjunct to surgical procedures
- Render patient unaware and unresponsive to pain
- Systemic
- Effect on the CNS

Classification

- IV
- Inhalation

General Anaesthesia should give (although no single agent can do all the following):

- Analgesia
- Amnesia
- Loss of consciousness
- Inhibition of sensory and autonomic reflexes
- Skeletal muscle relaxation

Quality of anaesthetic agent

- Readily controllable
- Rapid induction and recovery
- Level of anaesthesia can be adjusted intraoperatively (controlled anaesthesia)
- Induction - usually IV
- Inhalational
  - Main maintenance modality

MoA

- Lipid theory
- Effect on ion channel

Lipid Theory

- Potency ← lipid solubility
- Minimal alveolar concentration is inversely proportional to potency
- MAC (Minimal alveolar concentration) required to produce lack of response to pain stimulation
- Expressed as oil/water partition coefficient for inhalational agents

Effect on Ion channels

- Bind to proteins and lipids
- Binds to ligand gated ion channels
- Inhibit the function of excitatory receptors
  - Ionotropic glutamate
  - Acetylcholine
  - Serotonin
- Enhance the function of inhibitory receptors
  - GABA
  - Glycine

Effects of Anaesthesia

- Inhibit synaptic transmission - presynaptic
- Reduction of neurotransmitter release - presynaptic
- Inhibition of NT action
- Reduction of excitability of postsynaptic cell

Site of Action

- Thalamus
  - Sensory relay nucleus
- Deep layer of the cortex where the nuclei project

Effect

- Short term amnesia (hippocampus function)
- Increased concentration affects
    - Motor control
    - Reflex activity
    - Respiration
    - Autonomic regulation

Surgery

- Pre-anaesthetic medication
- Anaesthetic agents
- +/- muscle relaxants

Induction, Stages of Anaesthesia and Pre-Anaesthetic Medication

Induction of general anaesthesia (GA)

- Occurs when a conscious or otherwise responsive being is rendered unconscious by the CNS effects of GA
- Classic anaesthesia described for diethyl ether (Ether)
- Diethyl ether is a volatile liquid
- Less often used today
- It is relatively soluble in blood and tissues so it is rapidly taken up by muscle and fat tissue and results in a moderate increase in blood and brain concentration
- Because of this, the stages of anaesthesia during induction and emergence can be described
- Ether is a complete anaesthetic agent which means it can be used without additional drugs
    - Complete because it produces the following effects at concentrations that permit adequate oxygenation
        - Unconsciousness
        - Amnesia
        - Analgesia
        - Muscle relaxation
- Modern anaesthetics act more rapidly than ether and their stages are more difficult to observe
- 4 stages of GA
    - Signs and stages of anaesthesia
    - Describe the stage of anaesthesia
- Were described by Guedel

Stage I - Analgesia

- Begins with the administration of the GA
- Lasts until consciousness is lost
- Note that for ether
    - Analgesia persists postoperatively because ether is lipid soluble and is slowly released from the tissue stores
    - If muscle relaxants are used, surgery can be done at this stage
    - Also major operations requiring minimal muscle relaxation can be done

Stage II - Delirium and Excitement

- Begins with loss of consciousness
- Ends with the beginning of rhythmical respiration
- Signs
    - Patients may be able to move, vocalise, salivate, cough, retch and vomit
    - Jaw becomes set
    - Skeletal muscle tone increases
    - Irregular respiration
    - Incontinence of urine and faeces may occur
    - Pupils may dilate
    - Hypertension and tachycardia may be marked
    - Modern drugs allow patients to pass through this stage rapidly and thus less hazards

Stage III - Surgical Anaesthesia

- Begins with rhythmic respiration
- Ends with apnoea
- It is divided into 4 planes (increasing depth of anaesthesia)
    - Plane 1
        - Begins with reappearance of regular respiration
        - Loss of automatic eye closure

        - Loss of reflex closure of eyelids on conjunctival stimulation
        - Most muscular and airway reflexes are obtunded
        - Ends with cessation of eye movement
    - Plane 2
        - Begins with cessation of eye movement
        - Ends with the beginning of paralysis of the respiratory muscles of the respiratory muscles (except the diaphragm)
    - Plane 3
        - Begins with increased abdominal excursions
            - Due to beginning of paralysis of intercostal and other respiratory muscles
            - Diaphragmatic respiration dominates
        - Ends with paralysis of all respiratory muscles except the diaphragm
    - Plane 4
        - Begins with the cessation of intercostal muscle movement
        - Ends with paralysis of the diaphragm

Stages	Resp. rhythm	Resp. volume	Pupil size	Pupil position	Reflex depression
I	Irregular	Small	Small	Divergent	Nil
II	Irregular	Large	Large	Divergent	Eyelash, eyelid
III	Regular plane 1-3 Irregular plane 4	Varies with plane	Varies with plane	Varies with plane	Varies with plane
IV	Apnoea		Fully dilated	Fixed centrally	

Planes	Resp. rhythm	Resp. volume	Pupil size	Pupil position	Reflex depression
1	Regular	Large	Small	Divergent	Conjunctival Pharyngeal
2	Regular	Medium	1/2 dilated	Fixed centrally	Corneal
3	Regular Pause after expiration	Small	3/4 dilated	Fixed centrally	Laryngeal Peritoneal
4	Jerky Irregular Quick inspiration Prolonged expiration	Small	Fully dilated	Fixed centrally	Anal sphincter Carinal

Stage IV - Medullary depression/Apnoea

- Begins with complete respiratory paralysis
- Ends with circulatory failure

- These signs and stages
    - Are partly recognised if you use other GA
    - Can be obscured by
        - Neuromuscular blocking agents
            - They cause paralysis
            - This eliminates eyeball movement, changes in respiration, tightness of the jaw, ability to phonate, swallow, move or close the glottis
        - Controlled ventilation
        - Opioid analgesics
            - Miosis
        - Thiopental
            - Cause rapid induction of anaesthesia with virtually eliminates the stage of excitement (Stage II)
    - Are not related to the concentration to the anaesthetic agent
    - Practical evaluation of the depth of the GA
    - Surgical anaesthesia has not been reached if
        - Eyelids blink when eyelashes are stroked
        - If respiration is irregular in rate and depth
    - Surgical anaesthesia
        - Loss of eyelash reflex
        - Regular respiration
    - In 'light' anaesthesia skin incision causes
        - Increased RR and BP
        - Jaw muscles may become tight
        - If the mouth can be opened an oral airway may not be tolerated
            - It causes gagging, coughing, vomiting or laryngospasm
        - Tears
        - Resistance to inflation of lungs

        - Apnoea following peritoneal stimulation
    - As GA deepens
        - These responses are reduced or abolished
        - Progressive reduction in tidal volume
        - Accessory muscles of respiration are used
            - Tracheal tugging
            - Lower chest wall indrawing
            - Diaphragmatic activity becomes jerky or snappy in character
        - Halogenated GA
            - BP varies with dosage
            - Hypotension can be used as an index of dosage
    - Severe respiratory depression or cessation of breathing and marked hypotension or asystole may also be due to
        - Muscle relaxant
        - Blood loss
        - Hypoxia
        - Vagal reflexes
    - The EEG as an index of depth of anaesthesia is not reliable

Pre-Anaesthetic medication

- Used to decrease anxiety without producing excessive drowsiness
    - Information/reassurance also reduces anxiety
- Provide amnesia for the perioperative period while maintaining co-operation prior to loss of consciousness
- Relieve pre-post operative pain
- Minimise undesired effects of some GA
    - Salivation
    - Cough
    - Bradycardia
    - Vomiting
- Usually achieved by using 2 or 3 drugs
- Agents used
    - Sedative - hypnotics
    - Antianxiety agents
    - Opioids
    - Antiemetics
    - Anticholinergics
    - Drugs that reduce gastric acid and volume

Sedative - hypnotics and antianxiety agents

- Drowsiness does not imply loss of anxiety
    - Benzodiazepines (BZP)
    - Barbiturates
    - Antihistamines
    - Phenothiazines
    - Butyrophenones
- When BZP and butyrophenones are given with opioids, there is reduction of catecholamine release in response to surgical stimulation

Benzodiazepines

- Include
    - Diazepam
    - Lorazepam
    - Midazolam
- Cause sedation/tranquillity
- Amnesia in 60% of patients at sedation doses
- Diazepam
    - PO, IM (less predictable)
    - Little effect on respiration at premedication doses
    - Does not potentiate respiratory depression caused by opioids

Barbiturates

- Include
    - Pentobarbital
    - Secobarbital
- PO or IM
- Provide sedation, relieve anxiety
- Minimal depression of respiration and circulation
- NV are rare

Antihistamines

- Include
  - Hydroxyzine
  - Diphenylhydramine
- Sedation is a desired effect
- Hydroxyzine effects
  - Bronchodilation
  - Antisialogogue
    - Drugs that reduce the production of saliva
  - Antiemetic
  - Antiarrhythmic
  - Ataractic
    - Drug that has a tranquilising effect
  - Minimal depression of respiration and circulation
  - Does not prolong anaesthesia

Phenothiazines

- Include
  - Promethazine
  - Propriomazine
- Both IM
- Sedative
- Antiarrhythmic
- Antihistamine
- Antiemetic
- Prolong post-anaesthetic sleep
- May cause respiratory depression or hypotension

Butyrophenones

- Includes
  - Droperidol
- Antiemetic
- Blocks alpha adrenoceptors partially so CVS effects are not significant
- Can cause restlessness and extrapyramidal dyskinesia
  - Especially in children
  - Reverse with atropine

Opioids

- Reduce amount of GA needed by 10-20%
- Act synergistically with sedatives to produce tranquil state
- Morphine
  - IM if there is severe preoperative pain
  - Pain relief minimizes restlessness and excitement during emergence from anaesthesia
  - Depresses cough reflex
  - Undesirable effects
    - Prolongs awakening from GA. Effects last 4-6hrs
- Meperidine
  - Respiratory depression lasts 2-3h
  - Like morphine
  - May cause tachycardia
- Fentanyl
  - Duration of action is 1-2h
  - Doesn't cause hypotension unlike morphine

Antiemetics

- Droperidol
- Hydroxyzine
- Benzquinamide
  - Has mild vasopressor effects
- Scopolamine
- Cyclizine
- Trymethobenzamide
- Phenothiazines

Anticholinergic drugs

- Ether-induced secretions
- Secretion is less likely with newer GA
- Used in surgery where reduced secretions is necessary
- Used to counteract vagal effects (hypotension and bradycardia) during GA

- Atropine
  - IM,IV
  - Oral dryness and blurred vision within 10-15 minutes
  - Not C/I in glaucoma (doses don't increase intraocular pressure)
  - May be used in asthmatics
    - Drying of resp. secretions is not a problem in asthma
  - Not used in febrile patients
    - Depresses sweating
- Scopolamine, IM
- Glycopyrrolate

Drugs that reduce gastric acid

- Used to increase gastric ph above 2.5
- Also reduce volume of gastric content
- Reduces risk of aspiration
- Less damage to lungs in case of aspiration
  - H_2 receptors antagonists
  - Antacids
  - Prokinetic agents

IV Anaesthetics

- Used to facilitate rapid induction of anaesthesia in most settings, except paediatrics
- Once induced, anaesthesia may be maintained with an inhalational agent
- May be used as a single agent for short procedures
- May be administered as an infusion to help maintain anaesthesia during linger cases
- In lower doses; for sedation during monitored anaesthesia cases and ICU setting
- For inhalational agents; currently available IV anaesthetic drugs are not ideal i.e. none produces all the five desired effects of GA (analgesia, amnesia, loss of consciousness, smooth muscle relaxation, inhibition of sensory and autonomic reflexes)

Induction

- After entering the blood, a percentage of the drugs binds to plasma proteins and the rest remains unbound
- The degree of protein binding depends on the physical characteristics of the drug
  - Degree if lipid solubility and _
- The drug is carried by venous blood to the right side of the heart through the pulmonary circulation and via the left heart into the systemic circulation
- The majority of CO flows to the brain, liver and kidney (vessel-rich organs)
- Therefore, a high proportion of initial drug bolus is delivered to the cerebral circulation and then passes along a concentration gradient from blood into the brain
- The rate of this transfer is dependent on
  - The arterial concentration of the unbound drug
  - The lipid solubility of the drug
  - The degree of ionisation
- Unbound lipid soluble, non-ionised molecules cross into the brain most quickly
- Once the drug has penetrated the CNS, it exerts its effects
- The IV anaesthetics used for induction of GA are lipophilic and preferentially partition into highly perfused lipophilic tissues
  - This accounts for their rapid onset of action

Recovery

- Regardless of the extent and speed of their metabolism, termination of the effect of a single bolus (recovery from a single bolus of IV anaesthetic) is determined by redistribution of the drug from the sites on the CNS into less perfused and inactive tissues such as the skeletal muscle and fat
- With secondary tissue uptake, predominantly by skeletal muscle, plasma concentration of the drug falls
- This allows the drug to diffuse out of the CNS, down the resulting reverse concentration gradient
- The initial redistribution of drug into other tissues leads to the rapid recovery seen after a single IV dose of induction agent
- Therefore, all drugs used for induction of anaesthesia, have a similar duration of action when administered as a single bolus dose despite significant differences in their metabolism
- Metabolism and plasma clearance become important only following infusions and repeat doses of a drug
- Adipose tissue makes little contribution to the early redistribution of free drug following a bolus, due to its poor blood supply
- However, following repeat doses of infusions, equilibration with fat tissue forms a drug reservoir, often leading to delayed recovery

Effect of reduced CO on IV anaesthetics

- When CO is reduced (e.g. in shock, the elderly or cardiac disease) the body compensates by diverting more CO to the cerebral circulation
    - Therefore, a greater proportion of the IV anaesthetic enters the cerebral circulation and the dose of the drug must be reduced
- In addition, decreased CO causes prolonged circulation time
- As global CO is reduced, it takes a longer time for an induction drug to reach the brain and exert its effects
- Therefore, slow titration of a reduced dose of an IV anaesthesia is important for safe induction in patient with reduced CO

Specific IV anaesthetics

1. Alkyl phenols
2. Barbiturates
3. Benzodiazepines
4. Ketamine
5. Etomidate
6. Dexmedetomidine
7. Opioids

Alkyl Phenols

- Propofol
- Fospropofol

Propofol

MoA

- Presumed to potentiate chloride current mediated through the $GABA_A$ receptor complex

PK

- Poorly soluble in water and is therefore formulated as an oil-in-water formulation which contains soybean oil, glycerol and lecithin, the major component of the egg yolk phospholipid
    - Susceptible patients may therefore experience allergic reactions
- The emulsion frequently causes transient pain at the injection site and supports microbial growth
- The solution appears milky white and slightly viscous and has a pH of ~7 and a propofol concentration of 1% (10mg/ml)
- A 2% formulation is also available
- Retardants of bacterial growth are also added to the formulations
    - However, solution should be used as soon as possible (≤8 hours after opening the vial) and proper sterile technique is also essential
- One of its formulations contains metabisulphate
    - Has raised concern regarding its use in patients with reactive airway disease (asthma)
- Has a rapid onset of action (30 - 40 sec)
- Rapid rate of distribution
- Half-life of 2 - 4 mins (Short acting)
- Rapid liver metabolism through first order kinetics (in contrast to thiopental)
- Resulting water soluble compounds appear to be inactive and excreted through the kidneys
- High plasma clearance and exceeds hepatic blood flow
- This indicates the importance of extra hepatic metabolism which presumably occurs in the lungs and may account for the elimination of up to 30% of a bolus dose of the drug
- The recovery from propofol is complete with less hangover than in thiopental
- Likely to its high plasma clearance
- However, as with other IV drugs, transfer of propofol from the plasma (central) compartment and the associated termination of drug effect after a single dose are mainly the result of redistribution from highly perfused (brain)_
- The redistribution curves for bolus administration of other IV anaesthetics are similar
- Note that the time axis is not linear
- As with other IV agents, awakening after an induction dose of propofol usually occurs after 8 - 10 mins
- The PK of propofol and other IV anaesthetics after a single bolus dose or continuous infusion, are best described by means of a three compartment model
- The context-sensitive half-time of a drug, describes the elimination half-time after discontinuation of a continuous infusion as a function of the duration of the infusion
- It is an important factor in the suitability of a drug for use as maintenance anaesthetic
- The context-sensitive half-life of propofol is brief even after a prolonged infusion and therefore recovery occurs relatively promptly
- Even after a prolonged infusion, the half-time of propofol is relatively short
- This makes it the preferred choice for IV anaesthesia
- Ketamine and Etomidate have similar characteristics but their use is limited by other effects

Organ System Effects

CNS Effects

- Acts as a hypnotic but does not have analgesic effects
- Leads to general suppression of CNS activity
    - However, excitatory effects such as twitching or spontaneous movements are observed during induction of anaesthesia
- Presumed to have an anticonvulsant effect
- May be safely administered to patients with seizure disorders
- Decreases cerebral blood flow and the cerebral metabolic rate for oxygen ($CMRO_2$)
- This decreases ICP and intraocular pressure
- The magnitude of these changes is comparable to that of thiopental
- Propofol can produced a desired decrease in ICP
- However, the combination of reduced cerebral blood flow and reduced mean arterial pressure (MAP) due to peripheral vasodilation, can critically decrease cerebral perfusion pressure
- When given in large doses, propofol produces burst suppression of the EEG
- This end point has been used when administering IV anaesthetics for neuroprotection during neurosurgical procedures
- Its neuroprotective effects during focal ischaemia are similar to those of thiopental and isoflurane

CVS Effects

- It has a CVS depressant effect that may lead to hypotension and bradycardia
- Compared to other induction drugs, propofol produces the most pronounced decrease in systemic BP
- This is as a result of profound vasodilation in both arterial and venous circulation leading to reduction in preload and afterload
- This effect on systemic BP is more pronounced
    - With increased age
    - In patients with reduced intravascular fluid volume
    - Rapid injection
- The hypotensive effects are further increased by the inhibition of the normal baroreflex response
- Therefore , the vasodilation only leads to a small increase in HR
- Profound bradycardia and asystole after its administration have been described in healthy adults despite prophylactic anticholinergic drugs

Respiratory Effects

- Is a potent respiratory depressant
- Generally produces apnoea after induction dose
- A maintenance infusion reduces minute ventilation through reduction in tidal volumes and respiratory rate with the effect on tidal volume being more pronounced
- In addition, the ventilatory response to hypoxia and hypercapnoea is reduced
- Propofol, causes a greater reduction in upper airway reflexes, than thiopental
    - This makes it more suitable for instrumentation of the airway, e.g. placement of a laryngeal mask airway

Other Effects

- Unlike other volatile anaesthetics, does not augment NM block
    - They are good intubation conditions after propofol induction without the use of Nm blocking agents
- Unexpected tachycardia occurring during propofol anaesthesia, should prompt lab evaluation for possible propofol infusion syndrome
- This syndrome occurs in ~1 in 300 patients when propofol has been given for a prolonged period to maintain sedation, particularly to sick patients esp. children, in whom it is contraindicated in ICUs
- This is characterised by
    - Severe metabolic acidosis
    - Skeletal muscle necrosis (rhabdomyolysis)
    - Hyperkalaemia
    - Lipaemia
    - Hepatomegaly
    - RF
    - Arrhythmias
    - Cardiovascular collapse
- Propofol has antiemetic effects
- Pain on injection site is common. Can be reduced by
    - Premedication with an opioid
    - Co-administration with lidocaine
    - Dilution of propofol
    - Use of larger veins for injection

Clinical Use

- Propofol is the most common IV administered drug for induction of GA by bolus injection
    - The following reduce the required induction dose

        - Increasing age
        - Reduced CVS reserve
        - Premedication with benzodiazepines or opioids
    - Children require higher doses/kg body weight than adults
    - Generally, titration of the induction dose helps to prevent severe haemodynamic changes
- May also be given as a continuous infusion during maintenance of anaesthesia either
    - As part of a balanced anaesthesia regimen with
        - Volatile anaesthetics
        - N_2O
        - Sedative hypnotics
        - Opioids
    - Part of total anaesthetic technique, usually in combination with opioids
    - Particularly useful for day-case surgery esp. because it causes less NV than inhalational anaesthetics
- Used for
    - Sedation of mechanically ventilated patients in the ICU
    - Conscious sedation during procedures
    - Short duration GA outside the operating room (e.g. in interventional radiology suites, emergency dept.)
    - Because of its pronounced resp. depressant effect and narrow therapeutic window, it should be administered only by individuals trained in airway management
- Used to treat NV in sub-anaesthetic doses

Fospropofol

- Water soluble prodrug of propofol
- Rapidly metabolised by alkaline phosphatase to produce propofol phosphate and formaldehyde
- Formaldehyde metabolised by aldehyde DH in liver and RBCs
- Available formulations _
- Causes less injection pain during administration and has less of the disadvantages associated with the lipid emulsion of propofol

Barbiturates

- Thiopental
- Methohexital

MoA

- Anaesthetic effect appears to involve a combination of
    - Enhancement of inhibitory neurotransmission
    - Inhibition of excitatory neurotransmission
- The effects of inhibitory transmission probably result from activation of the kappa A receptor complex
    - However, the effects on excitatory transmission are less well understood
- Thiopental
    - Ultrashort acting barbiturate
    - Potent anaesthetic but weak analgesic
- Barbiturates require supplementary analgesic administration during anaesthesia

Organ system Effects of thiopental
CVS

- Has minor effects on the normal CVS
- It may contribute to severe hypotension in patients with hypovolaemia or shock
- It depresses the cerebral blood flow and can also decrease intracranial pressure

Resp. system

- All barbiturates can cause
    - Apnoea
    - Coughing
    - Chest wall spasm
    - Laryngospasm
    - Bronchospasms (concern in asthmatics)
- Thiopental can cause profound resp. depression

PK

- The free acid of thiopental is insoluble in water
    - Therefore given as sodium salt
- Thiopental is ~85% bound to plasma albumin
- The bound fraction is less in cases of malnutrition, liver disease or renal disease
    - Can significantly reduce the dose required for induction of anaesthesia
- Thiopental and methohexital have high lipid solubility

- When given IV, both quickly enter the CNS and result in surgical anaesthesia in one circulation time (≤1 min)
- Anaesthetic effect lasts for 5 - 10 mins
- Anaesthetic effects are terminated by redistribution from the brain to other highly perfused tissue
    - Hepatic metabolism is required for their elimination from the body
- These drugs may remain in the body for relatively long periods because only ~15% of the dose entering the circulation is metabolised by the liver, per hour
    - Therefore, metabolism of thiopental is much slower than its redistribution
    - Thiopental metabolism shows saturation kinetics
    - Consequently, thiopental produces a long-lasting hangover

AE
- If thiopental - strongly alkaline solution - is accidentally injected round rather than into a vein, or an artery, this can cause
    - Pain
    - Local tissue necrosis or ulceration
    - Severe arterial spasm that can result in gangrene
- Because of its long aftereffect, associated with a slowly declining plasma concentration, drowsiness and some degree of resp. depression persists for some hours

CU
- Thiopental and methohexital are used for
    - Induction of anaesthesia
    - Short surgical procedures
        - Both drugs have largely been replaced by propofol
    - Thiopental is used to terminate status epilepticus
    - To lower ICP in patients with a secured airway

Benzodiazepines
- Most commonly used is midazolam
- Diazepam and lorazepam

MoA
- They enhance the inhibitory effects of various NTs particularly GABA
- All three facilitate amnesia while causing sedation

Organ System Effect
- They cause minimal CVS depressant effects
- All are potential resp. depressant esp. when administered IV

PK
- Onset of Midazolam's CNS effects is slower than that of thiopental
- However, it has a loner duration of action
- The benzodiazepines are metabolised by the liver with variable elimination half-lives

Dis
- Erythromycin may prolong their effects

AE
- Benzodiazepines can induce a temporary form of anterograde amnesia in which the patient retains memories of past events but new information is not transferred into long term memory
    - Important treatment information should be repeated to the patient after the effects of the drugs have worn off

CU
- Used in conjunction with anaesthetics for sedation
- Midazolam is widely used adjunctively with inhaled anaesthetics and IV opioids

Etomidate
PK
- Poor water solubility
    - Formulated in propylene glycol soultuib
- Rapid induction
- Drug short acting
- _

Organ System Effects
- Little to no effects on the heart and circulation
- Causes less hypotension than propofol or thiopental

AE

- Etomidate suppresses the production of adrenal steroids and therefore leads to reduced plasma cortisol and aldosterone levels, that can persist up to 8 hours
- Should not be infused for an extended time because prolonged suppression of these hormones is dangerous
- Has been associated with increased mortality in
- It causes post-op NV
- Injection site reaction and involuntary skeletal muscle movements are common
    - Later managed by admin of benzodiazepines and opioids

CU

- It is an hypnotic agent used to induce anaesthesia
    - Lacks analgesic effect
- Usually only used for patients with coronary artery disease or CVS dysfunction
- Preferred to thiopental in patients at risk of circulatory failure because of the larger margin between the anaesthetic dose and the dose needed to reach CVS depression

Caution
Avoided in patients at risk of having adrenal insufficiency e.g. sepsis

Ketamine

- Closely resembles phencyclidine both chemically and pharmacologically

PK

- Short acting
- Lipophilic
    - Brain
- Like barbiturates, it redistributes to other tissues and organs

MoA

- Block activation of NMDA receptor
- Induces a dissociation state in which the patient is unconscious but may appear to be awake and does not feel pain
- This dissociative anaesthesia provides sedation, amnesia and immobility
- Both ketamine and phencyclidine produce a similar anaesthesia like effect and profound analgesia but ketamine produces less euphoria and sensory distortion than phencyclidine

Organ System Effects

- Stimulates central sympathetic outflow
    - Stimulates the heart
        - Increased BP and CO
- Increased cerebral blood flow and may induce hallucination particularly in young adults
    - Not widely used for this reason
- Potent bronchodilator
    - Beneficial in patients with hypovolaemic and cardiogenic shock and asthmatics

CU

- Mainly used by children and geriatrics for short procedures
- Used in lower doses as analgesic
- Used as acute treatment for depression

Contraindication and Caution

- In hypertensive/stroke patients
- May be used illicitly because it causes a dream-like state and hallucinations similar to phencyclidine

Dexmedetomidine
MoA

- Like clonidine, it is an &2 receptor agonist in certain parts of the brain

Organ System Effects

- Has sedative, analgesic, sympatholytic and anxiolytic effect that blunt many cardiovascular responses
- It is relatively unique in its ability to reduce volatile anaesthetic, sedative and analgesic requirements without causing significant resp. depression

CU

- Sedative used in ICU and during surgery

Inhalational Anaesthetics

- Gases and volatile Liquids
- Diethyl ether was the first used
- Diverse_
- Low safety margins
- Therapeutic indices (LD50/ED50) between 2 and 4
- Toxicity is an extension of the side effect
- Due to the unique side effect profiles, selection of an agent is dependent on the disease pathophysiology
- Varying physical properties influence kinetics of the drug
- AE is usually due to
    - Metabolites
    - Extension of the PK effects/actions
    - Hypersensitivity reactions
        - Hepatic injury
        - Exanthema
        - Increased ALT/AST
        - Jaundice
    - Idiosyncratic

Pharmacological Effects

- Cerebral blood flow
- Cerebral metabolic rate for O2
- ICP
- MAP
- HR
- CO
- RR
- Minute ventilation

PK Principles

- Gases uptake and distribution from those of liquid
- Distribute between tissue or between blood and gas and equilibrium achieved when the partial pressure of the two tissues is equal
- Partial pressure of anaesthesia in tissue is equal to the inspired gas after sufficient inhalation
- While the partial pressure of the anaesthetic may be equal in all tissues, the concentrations are not
- Thus, the partition co-efficient is the ratio of anaesthesia concentration in two tissues when partial pressures in the two tissues are equal
    - Blood : gas
    - Blood : brain
    - Blood : fat
- The above show that inhalation anaesthesia ae more soluble in some tissue
- Equilibrium is clinically achieved when partial pressure in inspired air is equal to the partial pressure in end-tidal (alveolar) gas
- Equilibrium is achieved quickly in agents that are not soluble in blood or tissue
- If agent is soluble in tissue such as fat, equilibrium takes longer as fat is a reservoir for anaesthesia
- Anaesthesia induction requires that brain partial pressure to be equal to mean alveolar concentration
- Due to good brain perfusion, anaesthetic partial pressure in the brain becomes equal to partial pressure in the alveolar gas and in the blood in a few minutes
- Rate of rise in partial pressure is slower for anaesthesia that are soluble in blood and other tissues

Elimination

- Reverse process of intake
- Recovery mirrors induction for agents with reduced blood + tissue concentration

Halothane

- Volatile liquid at room temperature
- Stored in sealed containers
- Light unstable
    - Amber bottles with thymol as a preservatives
- Mixture with O2 or air are neither flammable nor explosive

PK

- High blood : gas partition coefficient and high blood : fat partition
- Induction is therefore slow and alveolar concentration of halothane is lower than inspired halothane concentration
- Accumulates due to its fat solubility if administered over prolonged period
- Recovery lengthened as a function of duration of administration

- 60 - 80% eliminated unchanged via the lungs in the first 24h
- Substantial amount biotransformed by cytochrome P450 in the liver
- Trifluoroacetic acid is the major metabolite
- Trifluoroacetylchloride, an intermediate metabolite, covalently binds several proteins in the liver to cause hepatitis if there is an immune reaction to these altered proteins
    - Common complication after use is jaundice

Clinical Use
- Maintenance anaesthesia
- Used reduced by availability of better profile drugs
- Use in children is simple
- Low cost

Side Effects
- CVS
    - Dose dependent reduction in arterial BP
    - MAP reduces by 20 - 25% at MAC
    - Reduction of BP due to depression of myocardium
    - Hypotension coupled with bradycardia or normal HR
- Respiratory
    - Bronchodilation and relaxation of bronchial smooth muscle
    - Effective in patients with asthma
- CNS
    - Dilates the cerebral vasculature
    - Increases cerebral blood flow
    - ICP increased in patients with SOL, brain oedema or patients with benign intracranial HT
- Muscle
    - Relaxation of smooth muscle
- Kidney
    - _
- Liver and GIT
    - Reduces hepatic and splanchnic blood flow
    - Fulminant hepatitis _

Enflurane
- Clear, colourless, non-flammable liquid
- Mild, sweet odour, stable
- Does not attack aluminium, tin, brass, iron or copper
- Soluble in rubber

Pharmacological properties
- Smooth induction
- Used with short acting barbiturates to render the patient unconscious
- Induction with 4% takes 4 minutes. Maintenance with 1.5 - 3%
- Mild stimulation of salivation and tracheo-bronchial secretions
- Laryngeal and pharyngeal reflexes are obtunded early and excitement during induction seldom
- Pupil smal and eye movements don’t occur
- Ventilation support is needed due to respiratory depression
- CVS
    - Decrease BP with increased doses
- Respiratory
    - Increase respiratory depression
    - Tachypnoea less common than with halothane
    - Bronchodilation
- CNS
    - Tonic clonic spasms
    - Frank seizures
    - Doesn't aggravate seizures in epileptic patients
    - Reduces cerebral oxygen consumption
    - Vasodilation and increased cerebral blood flow and increased ICP
- Muscle
    - Relaxation increases with depth of anaesthesia
    - Better than halothane anx s rhays abdominal surgery
    - Malignant hyperthermia
    - Uterine muscle relaxed
- Kidney
    - Reduces urine outflow and GFR and RBF

Biotransformation

- 80% recovered unchanged
- 2-10%metabolised in the liver
- Leaves fatty tissue rapidly and is available for metabolism
- BT increased by enzyme inducers
- Deep anaesthesia is associated with resp. and CV depression\
- High concentration may cause seizures particularly in presence of hypocarbia
- Uterine relaxation CI in Labour

Nitrous oxide
- Colourless, odourless, tasteless
- Inorganic gas anaesthetic, steel cylinder of colourless liquid
- Heavier than air, not flammable but support combustion like O2

Pharmacological properties
- Adjuvant in surgical procedures
- Anaesthesia when administered in hyperbaric condition i.e. 85% in oxygen
- Analgesic=morphine
- Sole agent
- Induction of sleep by thiopental, skeletal muscle relaxation by NM blocking agent, hyperventilation to reduce CO2
- Minimal depression of organ function and rapid recovery
- Recall may occur thus potentiate with opioid or benzodiazepines
- Can be combined with smaller doses of halogenated hydrocarbons to reduce respiratory and circulatory depression
- Little effect in respiration
- No effects on CNS
- Skeletal muscle doesn't relax unlike halogenated compounds
- Liver, kidney, GIT no effects
- NV seen in a few patients post op.
- Supplementation with halothane to reduce its dose
- No alteration in the depth of anaesthesia
- Pupil dilate
- Norepinephrine circulation increases
- BP, PVR, Co rise
- Increase cerebral blood flow and decrease renal and splanchnic visceral flow by halothane
- Depression of myocardial contractility by N2O but increase responsiveness of vascular smooth muscle to epinephrine
- Net effect is reduction of halothane and required to maintain anaesthesia and thus less hypotension can be co-administered with other halogenated agents
- Peripheral neuropathy of Vit B12 deficiency type

List of drugs that cause Vit B12 deficiency
Biotransformation

–

Disadvantage
- Weak agent with no muscle relaxant activity
- Hypoxia if used as sole agents
- Air pockets in closed spaces may expand in abdomen, chest and skull

Advantages
- Non flammable
- Non irritant
- Analgesic
- Rapid onset and recovery, low toxicity

Review
- Pre-anaesthetic medication
- GA
- Analgesia
- Muscle relaxant
- Anaesthesia circuits and equipment
- Observe where each fits in practice

Local Anaesthetics (LA)

Tuesday, 15 November 2016 11:21 AM

- LA is the loss of sensation in a body part
  - Without loss of consciousness
  - Without impairment of central control of vital organs
- Are weak bases with slight solubility
- Are marketed as water soluble salts usually hydrochlorides
  - HCl salts are mildly acids
  - Solubility and stability increases

Classification

- Ester LA
  - Cocaine
    - Intermediate/medium acting: 60 - 120 min
  - Chloroprocaine
    - Rapid/short
  - Procaine
    - Rapid - 25 - 40 min
  - Tetracaine
  - Benzocaine
- Amide
  - Lidocaine
    - Intermediate acting: 60 - 120 min
  - Mepivacaine
    - Intermediate acting
  - Prilocaine
    - Intermediate acting
  - Articaine
    - Rapid
  - Bupivacaine
    - Long: 400 - 450 min
  - Etidocaine
    - Long
- Ethers
  - Pramoxine
- Ketones
  - Dyclonine
- Phenetidine derivatives
  - Phenacaine
- All above agents can be used parenterally

MoA

- LA block voltage-gated Na+ channels
  - Depolarisation occurs due to inward movement of Na+ when membranes are stimulated
- Therefore prevents the generation and the conduction of nerve impulses
- During excitation, the Na+ channels open
  - Na+ moves inwards to depolarise the membrane
- Depolarisation causes the Na+ channels to close (inactivate) and K+ channels to open
  - K+ flows outwards and repolarises the membranes

- The degree of block produced by LA depends on their
  - Frequency of nerve stimulation
  - pKa and pH
  - Lipid solubility
  - Molecular size
  - Size of the nerve fibre
- A resting nerve is much more sensitive to LA than that is repetitively stimulated
- Higher frequency of stimulation and more positive membrane potential cause a greater degree of anaesthetic block
- The LA in its changes form gains access to its binding site only when the Na+ channel is open
- The LA binds more tightly to and stabilises the inactivated state of the Na+ channel

pKa

- Its is the pH at which half of the drug is in its ionised form
- Determines the proportion of the LA in uncharged or cation form at tissue pH
- Uncharged drug crosses the membrane
- The cation is the most active at the receptor site because it cannot readily exit from closed channels
- A high frequency of stimulation is required for rapidly dissociating drugs so that drug binding during the action potential exceeds drug dissociation between action potentials
  - Dissociation of smaller and more hydrophobic drugs is more rapid
- In general
  - Autonomic fibres, small unmyelinated fibres and small myelinated fibres are blocked before the larger myelinated fibres

Sensitivity of nerve fibres of LA

- Pain sensation disappears first
- Followed by loss of sensation of
  - Temperature
  - Touch
  - Deep pressure
  - Motor function

Duration of action of an LA

- It is proportional to the time of contrast with nerve
- Cocaine inhibits the neuronal membrane transporters for catecholamine
  - NE accumulates at adrenergic receptors causing vasoconstriction
- Ropivacaine and bupivacaine also cause vasoconstriction
- A vasoconstrictor can be added to LA e.g. epinephrine, phenylephrine
  - Usually LA with short or intermediate duration of action
  - It reduces the rate of absorption
- Localises the anaesthetic at the desired site
- Vasoconstrictors reduce the rate of LA absorption
  - This reduces its systemic toxicity since absorption and metabolic rates balance
  - Note: NE may cause vasodilation in skeletal muscle (via ß2 receptors) may increase toxicity if LA is injected IM
- Epinephrine in spinal anaesthesia
  - It prolongs the LA effects by acting on α_2-adrenoceptors, which inhibit release of substance P (neurokinin-1) and reduce sensory firing
- Clonidine and dexmedetomidine are also used in spinal anaesthesia
  - Similar MoA

PK

- Systemic absorption is determined by several factors
  - Dosage
  - Site of injection
  - Drug-tissue binding
  - Local blood flow
  - Use of vasoconstrictors
  - The physicochemical properties of the drug
  - Tissue vascularity
- More rapid absorption in highly vascular area
  - Tracheal mucosa or the tissue surrounding intercostal nerves
- Less absorption in poorly perfused tissue
  - Tendon, dermis or SC fat

Distribution

- Amide LA are widely distributed after IV bolus
  - An initial rapid distribution phase into highly perfused organs
    - Brain, liver, kidneys and heart
  - Then a slower distribution phase into moderately well-perfused tissues
    - Muscles fat and GIT
- The tissue distribution of LA has not been extensively studied
  - Extremely short half-lives (<1 min)

Metabolism

- Ester LA
  - Inactivated primarily by a plasma esterases
    - Pseudocholinesterase
  - CSF contains little or no esterase
    - Effects of intrathecal injection will persist until the LA has been absorbed into circulation
- Amide LA
  - Hepatic cytochrome enzymes
  - Initial reactions involving dealkylation and subsequent hydrolysis
  - Exception
    - Prilocaine, the initial step is hydrolytic, forming o-toluidine metabolites
  - Caution
    - In severe hepatic disease
    - Decreased hepatic blood flow
      - Volatile GA reduce hepatic BF
      - Reduced CO
  - 55-95% bound to □2 - acid glycoprotein
  - a_1-acid glycoprotein levels
    - Reduced by oral contraceptives, neonates
    - Reduced levels associated with greater systemic toxicity
  - Metabolism produces more water soluble metabolites
    - Excreted in urine
  - Unchanged form reabsorbed through lipid membranes
    - Little or no urinary excretion
  - Acidification or urine promotes ionisation
    - More water soluble

Adverse Effects

- LA also interfere with the function of all organs in which conduction/transmission of impulses occur
- Risk of adverse effects is directly proportional to the concentration of the LA in circulation
    - CNS - AE
        - CNS Stimulation
            - Restlessness, tremours, clonic convulsions
                - Selective depression of inhibitory neurons
            - IV benzodiazepines or barbiturates are DOC for both prevention and treatment of convulsions
        - CNS Stimulation is followed by CNS depression
            - Death usually is caused by respiratory failure
            - Ventilatory support
        - Rapid systemic administration of LA may produce death with little or no transient signs of CNS stimulation
            - The concentration of LA probably rises so rapidly that all neurons are depressed simultaneously
        - Drowsiness is most frequent
        - Lidocaine may produce dysphoria or euphoria and muscle twitching
        - Cocaine has a prominent effect on mood and behaviour
            - Potential for abuse
    - CVS - AE
        - The primary site of action is the myocardium
            - Reduced electrical excitability
            - Reduced conduction rate
            - Reduced force of contraction
        - Arteriolar dilation
        - Rare ventricular tachycardia and fibrillation
            - Except bupivacaine
        - Due to high systemic concentration
            - E.g. inadvertent IV administration
        - Usually follows CNS effects
    - Smooth Muscle -AE
        - Relaxes the vascular and bronchial smooth muscle
        - Reduced intestinal contraction
        - Uterine contractions seldom depressed during intrapartum regional anaesthesia
    - NMJ and Ganglionic Synapse
        - Procaine can block the response of skeletal muscle to direct electrical stimulation
        - Due to the block of ion channel of the acetylcholine receptor by increased concentration of procaine
    - Hypersensitivity to LA
        - Rare
        - Allergic dermatitis
        - Asthmatic attack
        - More frequent in ester LA
            - Cross HS with clinically related LA
            - Metabolised to a common metabolite
        - Allergy may be due to preservatives
            - Amide LA may contain methylparaben
            - LA + vasoconstrictor may contain a sulphite
    - Vasoconstrictor AE
        - Delayed wound healing
        - Tissue oedema
        - Necrosis
            - Sympathomimetics increase the oxygen consumption of the tissue

        - Vasoconstriction also leads to hypoxia
    - Vasoconstrictors are contraindicated for anatomical regions with limited contralateral circulation
        - Tissue necrosis/gangrene

Cocaine

- Toxicity due to reduced catecholamine uptake
    - Euphoria due to inhibition of dopamine uptake in the CNS
    - Mydriasis
    - Corneal sloughing if used topically

Lidocaine

- Prototype amide LA
- Rapid absorption after parenteral, GIT and resp. tract administration
    - Epinephrine reduces the rate of absorption

Clinical Use

- Solution of lidocaine + epinephrine
    - For dermal procedures, depth of anaesthesia = 10mm
- Transdermal patch
    - Used for relief of pain associated with post herpetic neuralgia
- Lidocaine + prilocaine in an occlusive dressing
    - Used prior to venepuncture, skin graft harvesting
- An antiarrhythmic drug

Bupivacaine

- Long DoA
- Provides more sensory than motor block
- Used for prolonged anaesthesia during
    - Labour
    - Post-op period

Adverse Effects

- More cardiotoxic because it dissociates much more slowly from the Na channel
    - Severe ventricular arrhythmias and myocardial depression after inadvertent IV administration of large doses

Articaine

- Parenteral
- Rapid onset (1 - 6 min)
- DoA - ~1hr
- For dental/periodontal procedures

Chloroprocaine

- Rapid onset of action
- Short DoA
- Rapid metabolism
- Plasma half-life ~ 25sec
- Prolonged sensory and motor block after epidural or subarachnoid administration of large doses
    - This neurotoxicity associated with low pH and the use of Sodium metabisulphite as a preservative

    - No neurotoxicity when Calcium EDTA is the preservative
- Muscular back pain following epidural anaesthesia
    - ? Due to tetany of the paraspinus muscles
    - May be a consequence of Ca2+ binding by EDTA

Etidocaine

- It produces preferential motor blockade
    - Useful for surgery requiring intense skeletal muscle relaxation
- Cardiotoxicity similar to bupivacaine

Prilocaine

- Causes little vasodilation
    - Can be used without a vasoconstrictor
- Its increased volume of distribution reduces its CNS toxicity
- Metabolised to o-toluidine
    - Methaemoglobinaemia
    - In healthy persons, methaemoglobinaemia is not a problem
    - If necessary, treat using methylene blue
- Not used in obstetrical anaesthesia
    - Methaemoglobinaemia complicates evaluation of the new-born

Procaine

- Slow onset of action
- Hydrolysed to produce para-amino benzoic acid (PABA) which inhibits the action of sulphonamides
    - Large doses should not be administered to patients taking sulphonamide drugs

Dyclonine HCl

- Rapid onset of action
- Used as a solution for topical anaesthesia
    - During endoscopy
    - For oral mucositis pain
- Dyclonine is an active ingredient in
    - Sore throat lozenges
    - Gels for_

Benzocaine

- Poorly soluble in water
    - ∴ too slowly absorbed to be toxic
    - Applied to surface wounds and ulcerated surfaces
- Ester of $PABA_A$
- Can cause methaemoglobinaemia

LA for ophthalmic use

- Proparacaine
- Tetracaine
- Others are too irritating for the eye
- AE due to long term administration
    - Retarded healing
    - Sloughing off of the corneal epithelium
    - Predisposition of the eye to inadvertent injury

LA for mucosal membranes and skin

- Those primarily used by this route
  - Dibucaine
  - Dycylonine
  - Paramoxine
- Others are usually too irritating or ineffective on the eye
- Used for sympathetic relief of
  - Anal and vaginal pruritus
  - Poison ivy rashes
- Preparations may also contain glucocorticoids or antihistamines

Methods of administration of LA

- Topical anaesthesia
  - Transdermal
  - Transmucosal
- Infiltration anaesthesia
  - Injection of LA directly into tissue without taking into consideration, the course of cutaneous nerves
- Field block anaesthesia
  - SC injection of LA in order to anaesthetise a region distal to the injury e.g.
    - SC infiltration of proximal portion of volar (flexor) surface of the forearm results in an extensive area of anaesthesia that starts 2 - 3 cm from the site of injection
- Nerve block anaesthesia
  - Injection of LA into or about a nerve
- IV regional anaesthesia (Bier's Block)
  - A proximally located tourniquet is inflated to 100-150mmHg above the systemic BP
  - The LA is injected into a distal vein
  - Tourniquet must remain inflated for at least 15 - 30 min to prevent toxic levels of LA from entering the systemic circulation
  - Tourniquet used for < 2hrs
    - Risk of ischaemic nerve injury
  - Adrenaline should not be used
  - Used for short surgical procedures
    - < 60 minutes
    - Surgery of the forearm and hand
    - Distal leg and foot
- Spinal anaesthesia
  - Injection of LA into CSF in lumber space
- Epidural anaesthesia
  - Injection of the LA into epidural space

Muscle Relaxants

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- Fall into 2 categories
  - Peripheral muscle relaxants
  - Central muscle relaxants

Peripheral Muscle Relaxants

- They can be divided into 2 main types
  - Those with action on the CNS principally used in relieving painful muscle spasms or spasticity occurring in NM disorders e.g.
    - Diazepam
    - Tizanidin
    - Baclofen
    - Dantrolene
  - The NMJ blockers affecting NM transmission and are used as adjuvants in anaesthesia, particularly to cause muscle relaxation to be achieved with light anaesthesia

Neuromuscular Blocking Drugs

- Block cholinergic transmission between motor nerve endings and the nicotinic receptors on the NM endplate of skeletal muscles
- Are structural analogs of acetylcholine
- Act as either antagonists (non-depolarising types) and the agonists (depolarising types) at the nicotinic receptors on the NMJ of skeletal muscle
- Enable light levels of anaesthesia to be employed with adequate relaxation of the muscles of the abdomen and diaphragm
- Also relax the vocal cords and allow the passage of a tracheal tube
- Patients who have received a muscle relaxant should always have their respiration assisted or controlled until the drug has been inactivated/antagonised

Non-depolarising (Competitive) Neuromuscular Blockers

- Steroid derivatives
  - Pancuronium
  - Pipecuronium
  - Vecuronium
  - Rocuronium
- Isoquinoline derivatives
  - Atracurium
  - Cisatracurium
  - Gallamine
  - Mivacurium
  - Doxacurium
  - Metocurine
  - Tubocurarine
- These drugs are quaternary ammonium compounds and so are poorly absorbed and rapidly excreted
- Can be classified according to their duration of action
  - Short acting - 15 - 30 minutes
  - Intermediate acting: 30 - 40 minutes

    - Long acting: 60 - 120 minutes
- NB:
    - Duration of action is dose dependent
    - Drugs with a short or intermediate duration of action e.g. atracurium and vecuronium are widely employed than those with a longer duration of action such as pancuronium

Note:

- Non-depolarising muscle relaxants have no sedative or analgesic effects
- Allergic cross-reactivity between NMJ blockers reported
    - Caution in cases of hypersensitivity
- Activity prolonged in those with myasthenia gravis and in hypothermia
    - Give lower doses
- Resistance may develop in patients with burns
    - May require high doses.
    - Low plasma cholinesterase activity requires dose titration of mivacurium

Mechanism of Action

- Combine with the nicotinic receptors and prevent the binding of acetylcholine and hence prevent the depolarisation of the muscle cell membrane causing muscle relaxation
- Used therapeutically as adjuvant drugs in surgical anaesthesia
- Compete with acetylcholine at the receptor and hence are called competitive blockers
- Action can be overcome by increasing the concentration of acetylcholine in the synaptic gap e.g. by administering ChEl e.g. neostigmine or edrophonium
- These drugs at high doses the ion channels at the end-plate which further weakens NM transmission and reduces the ability of AChEIs to reverse their actions

Pharmacology

- Given parenterally by injection
    - Oral absorption is poor
- Penetrates membranes poorly, do not enter cells or pass through BBB
- Many are not metabolised and are eliminated through the urine unchanged
- Most have duration of action ranging from 10mins to 1 - 2 hours

Drug Interactions

- Action overcome by anticholinesterases e.g. neostigmine, edrophonium, physostigmine but increased dosages of the CHEIs may cause a depolarising block as a result of enhanced Ach concentrations
- NM blockade enhanced by halogenated hydrocarbon anaesthetics (e.g. halothane) which exert a stabilising action at the NMJ
- Aminoglycoside antibiotics inhibit acetylcholine release from cholinergic nerves by competing with calcium and therefore synergises with competitive blockers to enhance the block
- Ca2+ channel blockers increase the neuromuscular block of both competitive and depolarising blockers

Tubocurarine

- Curare was the first skeletal NMJ blocker and was first used by the natives of Amazon in S. America to paralyse game during hunting expeditions.
- The low absorption contributed to its safety to humans
- Tubocurarine was introduced into clinical practice in the early 1940s
- Increased the safety of anaesthesia since less anaesthetic required to produce muscle relaxation
- Sequence of muscle paralysis by competitive NMJ blockers

    - Small rapidly contracting muscles of the face and eye are paralysed first followed by the fingers then
    - The limbs, the neck and trunk muscles, then
    - The intercostal muscles and lastly the diaphragm muscles
- NM blockade lasts 20 minutes to as long as 1 - 2 hours after a single administration depending on the dosage

Other Effects of Tubocurarine

- An produce a small degree of ganglionic blockade by blocking nicotinic receptors at the autonomic ganglia
- Adrenal medulla may also be blocked
- Fall in B
    - Releases histamine from mast cells
    - Histamine release may be in sufficient amounts to produce bronchospasm and skin wheals

Gallamine

- First synthetic successor of tubocurarine but has been superseded by compounds with fewer side effects
- Onset of action and duration of action as for Tubocurarine
- 100% renal excretion
    - Avoid in renal impairment
- Does not cause histamine release or fall in BP
- Blocks cardiac Vagus at the muscarinic site causing sinus tachycardia

Pancuronium

- Steroid based compound
- Similar MoA as tubocurarine
- Intermediate (1.5 - 2.5 mins) onset of effect
    - Similar duration of action as tubocurarine but 5X more potent and has largely replaced it
- Long duration of action and often used in patients receiving long-tern mechanical ventilation in ICUs
- Does not release histamine
    - Has little ability to lower BP
- Prolonged action in severe renal or hepatic impairment
- Better side effect profile than tubocurarine
- Pipecuronium has a similar profile

Vecuronium

- Steroid based
- Intermediate onset of effect and intermediate (30 - 40 minutes) duration of action
- Widely used
- May cause prolonged paralysis, probably owing due to active metabolite
- Prolonged action in severe renal or hepatic impairment
- Rocuronium is similar, with faster onset of effect (1 minute) and may facilitate intubation
- Intermediate DoA
- Few side effects

Atracurium

- Widely used
- Intermediate onset of effect and intermediate (<30 minutes) duration of effect

- Transient hypotension due to histamine release
- Mechanism of elimination
    - Spontaneous non-enzymatic chemical degradation independent on liver or KF. Degradation slowed by acidosis
- May be used in patients with renal or hepatic impairment
- No effect on heart rate
- Doxacurium is chemically similar but stable in plasma, giving it a long DoA
- Cisatracurium is the pure isomeric constituent of atracurium, similar but with less histamine release

Mivacurium

- Chemically similar to atracurium but rapidly inactivated by plasma cholinesterase
    - Longer acting in patients with liver disease or cholinesterase deficiency
- Fast (~2min) speed of onset and short (~15 minutes) duration of effect
- Transient hypotension because of histamine release
- No effect on heart rate

Depolarising NM blocking Drugs

- Succinylcholine
- Decamethonium

- The only drug of this class in clinical use is succinylcholine (suxamethonium)
- Used for brief procedures e.g. tracheal intubation, electroconvulsive shock therapy
- Fast speed of onset (~2 mins) and short DoA (~10min)
- Rocuronium has similar speed of onset and recovery with fewer unwanted side effects

MoA

- Attach to the nicotinic receptors and act like acetylcholine to depolarise the junction (nicotinic agonist effect)
- Unlike acetylcholine which is instantly destroyed by AChE, the depolarising agents persist at high concentration in the synaptic cleft providing constant stimulation of the receptor
- Succinylcholine initially produces muscle fasciculations, followed within a few minutes by paralysis
    - Phase I
        - The drugs cause the Na+ channel associated with the nicotinic receptors to open resulting in depolarisation of the receptor. This causes transient twitching of the muscle (fasciculations)
        - Continued binding of the depolarising agent renders the receptor incapable of transmitting further impulses
    - With time, the continuous depolarisation gives way to gradual repolarisation (but receptor is desensitised to effect of acetylcholine) as the Na+ channel closes or is blocked. This causes resistance to depolarisation (phase II) and flaccid paralysis
- Sequence of paralysis may be slightly different but as with competitive blockers, the respiratory muscles are paralysed last
- Does not produce ganglionic block, except in high doses
- Has weak histamine - releasing action
- DoA extremely short since drug rapidly hydrolysed by plasma cholinesterase. Given by continuous infusion
- Prolonged paralysis in patients with liver disease or genetic deficiency of plasma cholinesterase
    - Assist ventilation until muscle function is restored
- Action cannot be blocked and recovery is spontaneous
    - Anticholinesterases potentiate NM block
- Prolonged paralysis may occur in dual block (development of a non-depolarising block)

with high or repeated doses of succinylcholine
- Individuals with myasthenia gravis are resistant to succinylcholine but can develop dual block resulting in delayed recovery

Adverse Effects

- More adverse effects than the competitive blockers but has the advantage of short DoA and rapid onset of effect
- Administration with the anaesthetic, halothane, may cause malignant hyperthermia (with muscle rigidity ad hyperpyrexia) in genetically susceptible people
    - Treat with rapid cooling and by administration of dantrolene (blocks release of Ca2+ from the sarcoplasmic reticulum of muscle cells and hence reduced heat production and muscle tone)
- Bradycardia
    - Due to muscarinic agonist effect - can be prevented by atropine
- Cardiac dysrhythmias
    - Increase in cation permeability of motor end-plates causes a net loss of K+ from muscle and a small rise in plasma K+ concentration, therefore, avoid I patients with burns or severe trauma
- The resulting hyperkalaemia may cause ventricular dysrhythmias or even cardiac arrest
- Raised intraocular pressure
    - Nicotinic agonist effect on extraocular muscles
- Increased ICP and intragastric pressures
- Post operative muscle pains

(duration of suxamethonium may be prolonged by anticholinesterase drugs e.g. organophosphates used to treat glaucoma)

Contraindications

- Personal or family history of malignant hyperthermia
- Low or abnormal plasma cholinesterase, family history of suxamethonium apnoea
- Phaeochromocytoma
- Muscular dystrophies
- Hyperkalaemia
    - Risk of arrhythmias and heart block

Central Muscle Relaxants

- Also called spasmolytics
- Spasticity is characterised by an increase in tonic stretch reflexes and flexor muscle spasm together with muscle weakness

    - Drugs acting on the higher centres and brainstem
        - Benzodiazepines
            - Diazepams
        - Meprobamate
        - Barbiturates
            - Phenobarbital
    - Drugs acting in the basal ganglia used in Parkinson's disease
        - L-DOPA
    - Drugs acting on the spinal cord
        - Mephenesin
        - Carisoprodal
        - Methocarbamol
        - Datroleeme

        - Baclofen
    - Others
        - Progabide
        - Glycine
        - Idrocilmide
        - Tizanidine

Diazepam
Chemistry
- Weakly basic
- Mostly absorbed in the duodenum
- Has slow onset of action

MoA
- Facilitates the actions of GABA in the CNS by increasing frequency of chloride channel opening
- Acts centrally and also in the spinal cord

P'Kinetics
- Given orally and IV
- Lipid soluble
- Well absorbed orally
- Well distributed in the brain then peripherally to the skeletal muscle tissue
- PPB - 80 - 90%
- Metabolised in he liver
    - There is N-dealkylation, aliphatic hydroxylation then conjugation with glucuronic acids and excretion in the urine
- Half-life: 50 - 150 hours

Pharmacological Actions
- Relaxes muscle spasms of any cause
- A sedative/hypnotic
- Anaesthesia at high doses
- Anticonvulsant effect
- Resp. depressant at high doses
- Hypnotic doses may cause CV dysfunction with hypertension and collapse in those with heart disease

Usual doses: 4 - 60mg/day

Adverse Effects
- It is a well tolerated drug
- May cause psychologic and physical dependence

Mephenesin
- Glycerol ether
- The first muscle relaxant
- Relaxes both spastic and non-spastic muscles
- Depresses a number of polysynaptic reflexes
- Has mild sedative action
- Large doses may cause hypotension due to depression of the vasomotor centre
- Causes resp. paralysis
- Has local anaesthetic action equivalent to that of procaine

P'Kinetics

- PO and IV
- Muscle irritant ∴ not given IM
- Well absorbed orally with peak plasma levels at 1 - 3 hours
- Well distributed throughout the body
- Metabolised in the liver
- Excreted renally

Adverse Effects

- CNS
  - Nystagmus
  - Diplopia
  - Blurred vision
  - Drowsiness
  - Lethargy
- Git upsets
- IV administration may cause resp. depression and syncope
- More than 2% concentration may cause thrombophlebitis and gangrene
- Lightening of hair colour

Baclofen

- P-chlorophenyl-GABA
- An orally active GABAmimetic agent

MoA

- Acts as GABA agonist at $GABA_b$ receptors
- Activation of receptors causes hyperpolarisation by increased K+ conductance
- Calcium influx is inhibited
- There is decreased release of excitatory NT both in the brain and spinal cord
- May reduce pain probably by inhibiting release of substance P in the spinal cord

P'Kinetics

- Rapidly and completely absorbed after oral administration
- Half-life is 3 - 4 hours

Pharmacological Actions

- As effective as diazepam in reducing spasm with much less sedation
- Does not reduce muscle strength as dantrolene
- Intra-thecally, may reduce pain and spasticity resistant to other treatment
- Doses
  - Start at doses of 15mg BD, increase effective dose gradually, max 100mg/d

Adverse Effects

- Drowsiness
  - Tolerance occurs
- Increased seizures in epileptics
- Resp. depression and even coma have been reported
- Toxicity is treated conservatively

Dantrolene

- A hydantoin derivative

MoA

- Reduces muscle strength by interfering with the excitation-contraction coupling in the muscle fibre
- It interferes with calcium release from the sarcoplasmic reticulum

P'Kinetics
- Absorption in the GIT is slow and erratic, only 1/3 absorbed
- Usually given IV
- Metabolised in the liver
- Excreted in the urine
- Half-life: 8 hours

Clinical Use
- Muscle relaxation
- Treatment of malignant hyperthermia

IV 1mg/kg, repeating as necessary to a maximum of 10mg/kg

Adverse Effects
- Generalised muscle weakness
- Sedation
- Euphoria
- Dizziness, fatigue
- GIT
    - Diarrhoea
    - Occasional hepatitis

Tizanidine (Zanaflex)
- Indicated for spasticity f multiple sclerosis, cord injury or disease
- Al alpha2-adrenoceptor agonist
- Dose
    - 2mg OD to 24mg in 3 divided doses
    - Max 36mg/d

Adverse Effects
- Drowsiness
- Fatigue
- Dizziness
- Dry mouth
- N and other GIT disturbances
- Hypotension
- Rarer
    - Bradycardia
    - Insomnia
    - Hallucinations
    - Acute hepatitis
    - Increased liver enzymes

Contraindications
- Severe liver disease

Cautions
- Drugs which prolong QT interval
- Geriatrics
- Renal Failure (RF)

- Pregnancy and lactation

Carisoprodal (carisoma)
- Indicated for short term relief of muscle spasm
- Dose
  - 350mg tds
  - Give half the adult dose in geriatrics
- Causes drowsiness

Methocarbamol (Robaxin)
- Indicated for short term relief of muscle spasm
- Dose
  - 750 - 1500mg TDS - QID

Adverse Effects
- Lassitude
- Light-headedness
- Dizziness
- Restlessness
- Anxiety
- Confusion
- Drowsiness
- Nausea
- Allergy and angioedema
- Convulsions

Contraindications
- Coma
- Brain injury
- Epilepsy
- Myasthenia gravis

Fluid Therapy

Monday, 28 November 2016 12:03 PM

Normal Physiology

- In an average adult of weight 70kgs, makes 70% which is 42%
- In the lean = 70%, in obese = 50%, in babies up to 78%
- Intracellular - 50% - 30 litres
- Extracellular - 20%
    - Interstitial - 8% - 4.8litres
    - Intravascular - 12% - 7.2 litres
- Transcellular - 1 - 3%
    - Respiratory System
    - GIT
    - Renal System
    - Glands
    - Eye

Normal Body Ions (mEq/L)

- Variations occur in various body fluid compositions

Ions	**Intercellular**	**Extracellular**
Sodium	10	140
Potassium	150	4
Calcium	-	2.5
Magnesium	40	2
Chloride	-	102
Bicarbonate	10	26
Phosphate, Sulphate	150	3
Organic ions	-	5
Proteins	40	15

Normal Body Fluid Requirements

Molecule	**Requirement**
Water	2 - 3 litres/day
Sodium	4 gms/day (75mmols)
Potassium	80- 150 mEq/day
Calcium	-
Chloride	75 mmols/day
Water as fluid	1200mls
Water as food	1000mls, metabolism 300mls
Nitrogen	13gms
Non-volatile acid	70mEq/day
Volatile acids	14000mEg/day

Losses

- Water
    - Urine - 1500mls/day
    - Faeces - 1000mls/day
    - Insensible - 600-900mls/day
- Nitrogen

    - Urine - 12gms
    - Faeces - 1gm
- NaCl
    - Urine - 74mmol
    - Faeces - 0.5mmol
    - Insensible - 0.5mmol
- Potassium
    - Urine - 4.5mmol
    - Faeces - 5mmol
- Volatile acid
    - Insensible - 14000mEq
- Non-volatile
    - Urine - 70mEq

In dehydration

- Water loss
    - Mild - 5% body weight
    - Moderate - 5-10%
    - Severe - >10%
- In severe dehydration - diabetic ketoacidosis, diarrhoea
- Vomiting - losses 6-8 litres

Therapeutic Fluids

Solution	**Sodium**	**Potassium**	**Bicarbonate**	**Chloride**	**Calcium**	**Ammonium**	**Phosphate**
Normal Saline	150	-	-	150	-	-	-
Hartmann's Solution	131	5	29	111	2	-	-
Ringer's Lactate	147	4	-	155	4	-	-
Darrow's	121	35	53	103	-	-	-
Hypertonic Saline (5%)	855	-	-	855	-	-	-
Sodium Lactate	167	-	-	167	-	-	-
D/Sal (0.18,4%)	30	-	-	30	-	-	-
Potassium Chloride in 5% dextrose	-	40	-	40	-	-	-
Sodium bicarbonate 1.2%	150		150	-	-	-	-
Sodium Bicarbonate 8.4%	1000	-	1000	-	-	-	-
Ammonium Chloride 0.9%	-	-	-	170	-	170	-
Calcium Gluc 10%, 10ml	-	-	4.5	-	4.5	-	-
Potassium phosphate 20ml (Dil to 1L)	-	40	-	-	-	-	40

- Current total body water = 0.6 X current body weight (kgs)
- Desired total body water = $\frac{\text{measured serum sodium x current total body water}}{\text{normal serum sodium}}$
- Therefore, the desired water deficit = desired total body water - current total body water
- Rehydration
    - In first half hour, give 1L
    - In next one hour, give 1L
    - In the next 2hrs, give 1L
    - Calculate the balance over six hours and calculate _
    - In mild dehydration
        - 3 L in 24hrs
- Drip

    - Every 1ml of fluid, give 15 drops in the standard drip
    - 32 drops per minute
    - In microdrip, 1ml is 60 drops

Other Solutions

- FFP - 4.5%
- Albumin - 5%, 20%
- Plasma substitutes
    - Give only 1 - 2 litres acute
- Dextrans - 40, 70, 110% in 5% Dextrose or normal saline
- Gelatins (Haemocoel)
    - 3.5 - 4% solutions
- Starches
    - Hetastarch
    - Hydroxyethyl starch
    - Pentastarch

Renal Pharmacology

Friday, 18 November 2016 8:23 AM

- Normal GFR 125ml/min
- Urine formation 1ml/min
- Over 99% of filtrate and sodium is reabsorbed
- Urine formation a two stage process
    - Ultrafiltration of plasma in glomerulus
    - Reabsorption of water and electrolytes in the renal tubules
- Diuretics increase urine production

- In the PCT 85% of sodium bicarbonate is reabsorbed and up to 40% of the NaCl is reabsorbed
- Glucose, AA and other organic solutes are preferentially reabsorbed by specific transporters
- As a result the water left in the tubules, is isosmotic
- Some of the selective transporters include
    - Na-H exchanger in the PCT
        - Pumps hydrogen from the tubule cells to the lumen
        - For every H atom pumped out, a sodium atom is absorbed
    - Na- K-ATPase pump
        - Pumps reabsorbed sodium into the interstitial fluid
        - The hydrogen pumped into the lumen combines with bicarbonate to form carbonic acid
        - The carbonic acid is converted to carbon dioxide and water. They are small molecules and easily diffuse back into the cell
        - Back in the cell, the carbon dioxide recombines with water to form carbonic acid. The carbonic acid in the cell then dissociates into hydrogen and bicarbonate
        - On the basolateral side, a pump is present that pumps bicarbonate, back into the blood
        - The hydrogen left in the cell is ready for the Na-H pump to pick it up and exchange it with a sodium atom
        - All these reaction are mediated by carbonic acid anhydrase
- After the PCT hydrogen is not coupled to the Na-H exchanger and the pH in the rest of the fluid falls
- In the loop of Henle, the interstitial area is more osmotic as it has more Sodium than in the tubes therefore, water is absorbed osmotically from the lumen to the blood
- In the thick ascending loop, there is a special process that takes place. There is a Na-K-Cl symporter. It is impermeable to water.
- Na, K and Cl are actively reabsorbed by the symporter.
- Up of 35% of the filtered sodium is reabsorbed
- Reabsorbed Na is pumped in to the blood by the Na-K-ATPase pump
- The cell has high levels of K this its positivity is increased,
- . As a result, some of the K back-diffuses into the lumen to maintain ionic balance.
- The positive charge in the lumen is increased, therefore some of the positive ions (mostly divalent ions) are pushed into the cell and into blood
- The fluid moves to the DCT
    - Up to 10% of the sodium chloride is reabsorbed in the distal tubules that is relatively impermeable to water
    - Luminal fluid if further diluted
    - Ca2+ is actively reabsorbed a apical Ca2+ channel .A basolateral Na-Ca exchanger. This is regulated by PTH.

- In the collecting ducts
  - Further exchange takes place
  - Up to 2 - 5% of NaCl is reabsorbed and is the main determinant of sodium concentration in the urine
  - There are principle cells that
    - Are the site of NA, K and water transport
  - The intercalated cells
    - Site of H+ secretion
  - For every NA reabsorbed, a molecule of K is secreted. The more sodium reabsorbed, the more potassium is excreted. This activity is regulated by aldosterone
  - Water reabsorption is by another mechanism, mediated by ADH. Then ADH is absent, the membranes are impermeable to water and dilute urine is produced and vice versa
  - ADH secretion is regulated by the serum osmolality and blood-volume states
  - ADH
    - RAAS
  - Organic acid pumps are located in the middle 1/3 of the collecting ducts
    - Are responsible for pumping uric acid, diuretics, antibiotics and PAH acid
  - Organic base bumps are found in the proximal and middle 1/3s
    - Molecules handled include creatinine and choline

Diuretics

- Increase the excretion of sodium and water
- Act on the kidney
- Decrease reabsorption of Na^+ and Cl^- from filtrate
- Consequent increase in water loss

Classification of Diuretics

- Osmotic diuretics
  - Mannitol
  - Urea
  - Sucrose
  - Glucose
  - Glycerol
  - Isosorbide
- Mercurial compounds
  - Mercury chloride
- Acidifying agents
  - Ammonium chloride
- Xanthine alkaloids
  - Caffeine
  - Theophylline
- Thiazides
  - Hydrochlorthiazide
- Loop diuretics
  - Frusemide
  - Bumetamide
  - Ethacrynic acid
  - Torsemide
- Potassium sparing diuretics
  - Spironolactone
  - Triameterene
  - Amiloride
- Carbonic acid anhydrase inhibitors
  - Acetazolamide
  - Dorzolamide
  - Brinzolamide

Mechanism

- Direct action on the cells of the nephron
  - Ascending loop of Henle
  - The early DCT
  - The collecting tubule and duct
- Indirectly modifying the content of the filtrate

Loop Diuretics

- Most powerful

- Excretes up to 15 - 25% of the Na^+
- High ceiling diuretics
- Examples
    - Furosemide
    - Bumetanide
    - Pirentanide
    - Torsemide
    - Ethcrynic acid

MoA

- Act on the thick segment of the ascending loop of Henle
- Inhibit transport of NaCl out of the tubule into the interstitial fluid by
    - Inhibition of $Na^+/K^+/2Cl^-$ carrier in the luminal membrane
    - Furosemide, bumetanide and torsemide have direct inhibiting effect on the carrier acting on the Cl- binding site
- Water not to be reabsorbed into the interstitial fluid
- More solute is delivered to the distal nephron
- Osmotic pressure further reduces water reabsorption
- Normal water loss of 1% ↑ to 25%
- Profuse diuresis

Other Effects of Loop Diuretics

- Venodilatory through the release of a renal factor
- Vascular effect in CCF seen before the onset of diuresis
- ↑ Na^+ reaching the DCT results in the ↑ of H^+ and K^+ loss
- Leads to hypokalaemia and metabolic acidosis
- ↑ excretion of Ca^{2+} and Mg^{2+}
- ↓ excretion of uric acid
- Torsemide causes less loss of Na^+ and K^+

Pharmacokinetics

- Readily absorbed PO
- Can be given as an injection
- PPB, thus, not filtered
- Reach site of action the luminal membrane of the cells of the thick ascending loop by being secreted in the PCT by organic acid transport mechanism
- The fraction secreted will pass through urine
- The fraction not secreted is metabolised in the liver
    - Bumetanide and torsemide by CYP450 and Furosemide is glucoronidated
- PO, act in 1 hour
- IV peak effect in 30 minutes
- Plasma half-life: 90 minutes, ↑ in renal failure
- DoA: 3-6 hours
    - Torsemide longer half-life and DoA

Indication

- Acute pulmonary oedema
- Chronic heart failure
- Cirrhosis of the liver complicated by ascites
- Nephrotic syndrome
- Renal failure
- Complicated hypertension
    - Traditionally, thiazide diuretics are used - for uncomplicated hypertension

- Acute treatment of hypercalcaemia after IV replacement of isotonic NaCl solution

ADR/SE

- Hypokalaemia
- Metabolic alkalosis
- Hyponatraemia and hypomagnesaemia
- N, allergic reaction, deafness

DCT Acting Diuretics

- Thiazides and thiazide related drugs
- Thiazides:
  - Bendroflumethiade
  - Hydrocyclopentathiazide
  - Cyclopentathiazide
- Thiazide related:
  - Chlorthamidone
  - Indipamide
  - Xipamide
  - Metolazone
- Moderately powerful diuretics
- Reduce reabsorption of Na^+ and Cl^-
- MoA
  - Bind on the Cl^- site of the electroneutral Na^+/Cl^- co-transport system and inhibiting its action
  - No action on thick ascending limb of Henle
- K^+ loss is significant
- Uric acid and Na+ excretion is reduced and Mg^{2+} loss increased
- Hypochloraemic alkalosis can occur
- Vasodilation
- Hyperglycaemia
  - Inhibit insulin secretion from the pancreatic islets
  - Opening of ATP-sensitive potassium channels
- Initial ↓ BP due to diuresis but later vasodilation
- Diazoxide: non-thiazide, powerful vasodilator and ↑ blood sugar
- Indapamide
  - Lower BP at sub-diuretic doses and has lower metabolic effects

PK

- PO
- Excreted in urine
- Mainly by tubular secretion
- Competes with uric acid for secretion
- Chlorthalidone has longer half-life

Indications

- Hypertension
- Mild heart failure
- Severe resistant oedema, Metolazone particularly used with loop diuretic
- Prevent recurrent stone formation in idiopathic hypercalcaemic nephrogenic diabetes insipidus

ADR/SE

- Hypokalaemia

- Metabolic alkalosis
- Uric acid ↑
- Hyperglycaemia
- Hypercholestrolaemia
- Impotence
- Hypersensitivity

Potassium Sparing Diuretics

- Inhibitors of renal epithelial sodium channels
  - Triamterene
  - Amiloride
- Antagonists of mineralocorticoid receptors
  - Spironolactone
  - Eplerenone

Renal Epithelial Na+ channel Inhibitors

- Small increase in Na^+Cl^- excretion but also anti-kaliuretic
- Both are organic bases and are transported by the organic base secretory mechanism in the proximal tubules

MoA

- The reduction in Na^+ loss due to channel inhibition reduces the concurrent potassium secretion in the tubule (late distal and collecting duct)
- Renal Na^+ channels are different from the voltage dependent channels found in other tissues

Effects

- Late CT and CD have limited capacity for reabsorption of solutes
- Blockade of Na^+ channels causes mild increase in Na+ excretion
- This hyperpolarises the luminal membrane, reducing the luminal negative transepithelial voltage, which normally facilitates cation secretion, consequently decreasing K^+, H^+, Ca^{2+}, Mg^{2+} loss
- Volume contraction increases uric acid levels
- Little on renal haemodynamics
- Amiloride in high doses also block Na^+-H^+, Na^+-Ca^{2+} antiporter and inhibit the Na^+ pump

PK

- Amiloride
  - Relatively more potent than triamterene
  - 15 - 25% oral absorption
  - Half-life of 21 hours
  - Renal route of elimination
- Triamterene
  - PO absorption of 30 - 70%
  - Half-life: 4 hours
  - Metabolised prior renal loss
  - Toxicity enhanced by renal and hepatic disease

Adverse Effects

- Hyperkalaemia
  - Avoid in renal failure and patients in other potassium sparing diuretics and patients on ACEI and K+ supplements
  - Care with NSAIDS
- Cirrhosis patients prone to megaloblastosis that is worsened by weak folate antagonist

such as triamterene
- Triamterene
  - Reduce glucose tolerance
  - Photosensitisation
  - Interstitial nephritis and renal stones
  - NV, leg cramps and dizziness
- Amiloride
  - Headache
  - NVD

Indications

- In combination with other diuretics
- In hypokalaemic alkalosis
- Oedema - as an afjuct
- Hypertension - as an adjunct
- Hyperaldosteronism
- CCF - as an adjunct
- Cystic fibrosis
  - Aerolised amiloride improves mucociliary function
- Lithium induced nephrogenic diabetes insipidus
  - Amiloride blocks lithium transport in the collecting tubules and ducts

Contraindication
Renal impairment
Anuria
DM
Hepatic function impairment
Metabolic or respiratory acidosis
Hyprruricaemia or gout
Nephroliathis

Thiazide diuretics

- Inhibit NaCl transport predominantly in the DCT
- Some have predominant CAI activity
- Hydrochlorthiazide

Chemistry and PK

- Unsubstituted sulphonamide group
- PO
- Metabolism varied
- Chlorthiazide not lipid soluble thus large doses needed
- Only thiazide available IV
- Chlothalidone slowly absorbed, long DoA
- Indapamide lost by hepatobiliary route but enough lost in the kidney to act at the DCT
- All thiazides are secreted by the organic acid secretory system in the PCT
- Compete with uric acid for secretion

PD

- Inhibit NaCl reabsorption from the luminal side of the epithelial cell of the DCT
- Blocks Na/Cl transporter
- Enhance Ca^{2+} absorption at the thick ascending limb of the LOH unlike loop diuretics
- Used in the treatment of Ca^{2+} base kidney stones
- NSAIDS interfere with action of thiazides

Indications
- HT
- CHF
- Nephrolithiasis
- Idiopathic hypercalciuria
- Nephrogenic diabetes insipidus

Toxicity
- Hypokalaemic metabolic alkalosis
- Hyperuricaemia
- Hyperglycaemia
    - Impaired release of insulin and poor utilisation
- Hyperlipidermia
- Hyponatraemia
- Allergic reactions
- Weakness, fatigue, parasthaesia, impotence

Contraindications
- Borderline renal failure
- Hepatic cirrhosis
- CCF - congestive heart failure

Osmotic Diuretics
- Pharmacologically inert
- Example
    - Mannitol
- Filtered but incompletely, but not reabsorbed
- Reduced passive reabsorption of water
- Reduce Na^+ reabsorption
- Useful in conditions associated with Na^+ retention
- Used in
    - ↑ ICP and intraocular pressure
    - Prevention of acute renal failure

ADR/SE
- Transient expansion of ECF volume
- Hyponatraemia
- Pulmonary oedema
- Headache
- NV

Carbonic Anhydrase Inhibitors
- Direct acting on PCT
- Excretion of HCO_3, Na^+, K^+ and water
- Increase in flow of alkaline urine and mild metabolic acidosis
- Useful in treatment of glaucoma to ↓ formation of aqueous humour
- Antiepileptic
    - Acetazolamide

Agents Affecting Renal Water Conservation

28 March 2017 22:29

Vasopressin

- Aka. ADH, AVP (arginine vasopressin)
- Secreted by the hypothalamus and stored in the posterior_
- Receptors
  - They are G protein coupled receptors
    - V1
      - V1a - vascular smooth muscle
        - Mediate vasoconstriction
      - V1b - adenohypophysis
        - Mediate V induced ACTH release
    - V2
      - Renal collecting duct system
        - Mediates antidiuretic responses
- V and oxytocin has similar structures
- V agonists and antagonists may bind on oxytocin receptors at high doses

V1 receptor - effector coupling

- V1 receptor binding activates membrane bound phospholipases
- Phospholipase C and D
  - DAG + IP3 produced
  - IP3 causes intracellular release of Ca2+
  - Ca2+ activates intracellular proteins which mediate subsequent cellular response
- DAG activates protein kinase C
  - Phosphorylation of proteins which contribute to biological response
- Phospholipase A
  - Phospholipids → arachidonic acid → PGs
  - PGs mediate some of the effects of V

V2 receptor - effector coupling

- V2 receptor binding → stimulation of adenylyl cyclase → ↑cAMP
- cAMP stimulates protein kinase → protein phosphorylation → ↑ aquaporins on the cell membrane
- Aquaporins are proteins that allow water to cross biological membranes
- ↑ urea permeability in the medullary collecting duct
- Large amount of urea needed for maximum urine concentration
- ↑ NaCl transport in the thick ascending limb through stimulation of the Na+-K+-2Cl- symporter

Renal Actions of V

- V1
  - Reduction of inner medullary blood flow
  - Production of PGE2 which inhibits adenylyl cyclase in the collecting duct ∴ prevents V2 mediated anti-diuresis
- V2
  - ↑ water permeability of the collecting duct
  - ↑ urea transport in the inner medullary collecting duct
  - ↑ NaCl transport in the thick ascending limb
  - The latter two contribute to the urine concentration ability of the kidney

Non-renal Actions of V

- CVS
  - Potent vasoconstrictor in high doses (V1)
  - This is also associated with reduced cardiac output and heart rate
  - In some blood vessels V2 receptors cause vasodilation via release of nitric oxide
- CNS (V1)
  - Regulates temperature - antipyretic
  - Enhances ACTH release
- Blood coagulation (V2)
  - ↑ secretion of factor VIII and Von Willebrands factor
- Others
  - High doses stimulate uterine contraction (oxytocin receptors) and GIT contractions (V1)
  - Promotes platelet aggregation (V1)
  - Stimulate glycogenolysis in the hepatocytes

Antidiuretic peptides for clinical use

- If oral administration, quick inactivation by trypsin
- Further inactivation by peptidases in the liver and kidney mainly
- Vasopressin (SC, IV, IM, intranasal)
- Half-life: 17 - 35 minutes
- Desmopressin acetate (oral, SC, IV, intranasal)
  - Nasal bioavailability is 3 - 4%
  - Oral bioavailability is <1%
  - Less effective in nasal congestion
- Desmopressin acetate
  - Half-life: 1.5 - 2.5 hours
  - DoA: 6 - 20 hors
  - Minimal V1 activity
  - Greater antidiuretic activity than V
- Lypressin (intranasal)
  - DoA: 4 - 6 hours
- Terlipressin (IV)
  - Prodrug
  - Converted to lypressin
- Vasotocin (V1 agonist)
- Felypressin
  - Short acting

Therapeutic Applications

- V1 receptor mediated - Use V
  - Postoperative ileus
  - Dispel intestinal gas before abdominal x-rays
  - Vasoconstriction of the splanchnic arterial vessels reduces blood flow to the portal vessels and reduces oesophageal bleeding (also terlipressin and felypressin)
  - Reduces bleeding in
    - Acute haemorrhagic gastritis
    - Abdominal surgery in patients with portal hypertension
    - Colonic diverticular bleeding
  - Felypressin
    - A short acting vasoconstrictor
    - It is injected with local anaesthetic s such as prilocaine to prolong their actions
- V2 receptor mediated - use desmopressin

    - Central diabetes insipidus (inadequate ADH secretion)
        - Use lypressin and felypressin
    - Von Willebrands disease
    - Haemophilia A
    - Primary nocturnal enuresis
    - Post lumbar puncture headache (causes water retention and facilitates rapid fluid equilibration in the CNS)

Adverse effects

- V1 mediated mainly (less for desmopressin than other agents)
    - Facial pallor (cutaneous vasoconstriction)
    - VD, belching, cramps and tenesmus (urge to defecate)
    - Gangrene (high V doses)
    - Systemic V
        - Hypertension, myocardial infarction or ischaemia, mesenteric infarction
- V2 mediated
    - Water intoxication (Hypernatraemia, pulmonary oedema)
    - Seizures (hyponatraemia)
- Others
    - Allergic reaction(urticaria to anaphylaxis)
    - Local effects in the nasal passages
        - Oedema, scarring, rhinorrhoea, congestion, pruritus, ulceration, headache, agitation

Drug Interaction

- NSAIDS (esp. Indomethacin) + V
    - ↑ the anti_
- Lithium inhibits V
    - Lithium induced polyuria
    - It reduces V2 mediated stimulation of adenylyl cyclase
    - Lithium also ↑ plasma levels of PTH
    - PTH is a partial antagonist of PTH
- Demeclocycline reduces V effects by ↓ cAMP

Caution

- Patients with vascular diseases especially coronary vessels
- Diseases where rapid increase of water may impose risks
    - Angina, hypertension, heart failure

Contraindication

- Acute renal failure
- Primary of psychogenic polydipsia (risk of severe hypotonic hyponatremia)

Conviptan

- V1a and V2 antagonist
- IV route
- Half-life: 5 - 10 years
- Metabolised via CYP3A4 (drug interaction)
- Excreted renally
- Caution in hepatic, renal disease and elderly
- Most common A/E
    - Infusion site reaction

- For hyponatraemia and CHF

Tolvaptan

- V2 antagonist
- Oral
- Half-life: 12- 24 hours
- For hyponatraemia
- Adjunct to diuretic therapy CHF
- Contraindicated in patients receiving drugs that inhibit CYP3A4

Mozavaptan

- V2 receptor antagonist
- V2 > V1
- Dry mouth, abnormal LFT
- Treatment of SIADH

Other oral V2 receptor antagonist

- Lixivaptan
- Satavactan

Other non-selective ADH antagonist

- Demeclocycline
- Lithium

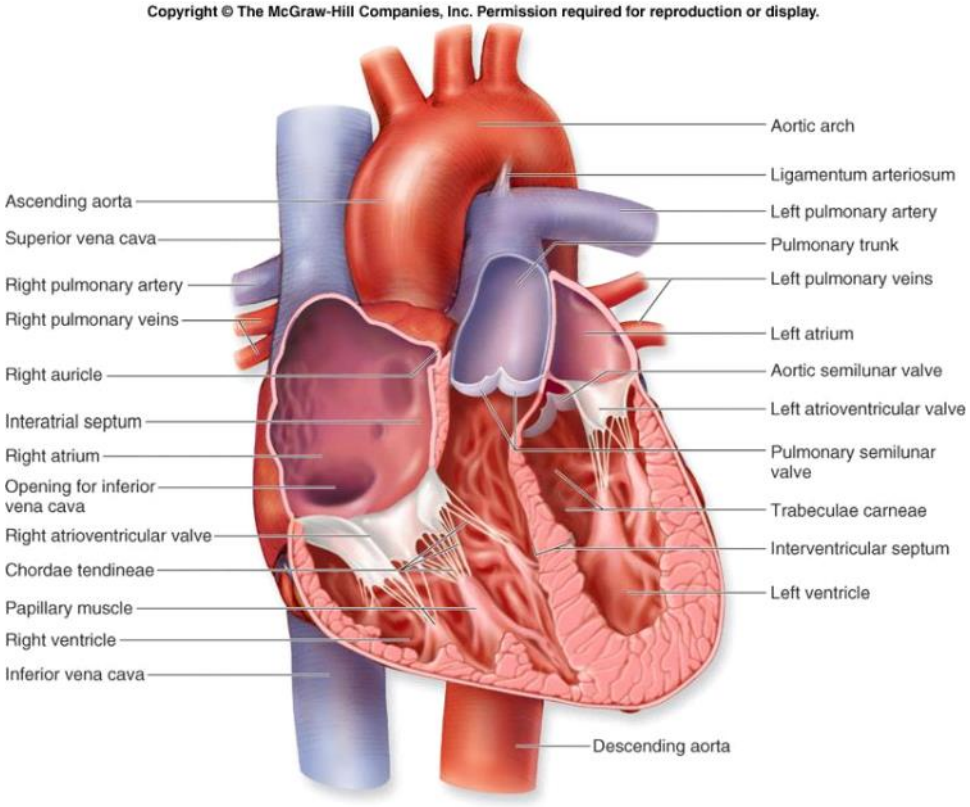
AE of ADH antagonists

- Nephrogenic D. Insipidus
- Renal AE
    - Lithium and democlocyline cause acute RF
    - Lithium may cause chronic interstitial nephritis
- Other
    - Dry mouth and thirst are common
    - Hypotension (tolvaptan)
- Avoid demeclocyline
    - In patients with liver diseases
    - In children < 12 years
    - Pregnancy

Cardiac Pharmacology

15 December 2016 11:37

Review of Cardiac Physiology
ANATOMY



- The Heart is a double, self-adjusting suction and pressure pump, the parts of which work in unison to propel blood to all parts of the body.
- Ithas four chambers: right and left atria and right and left ventricles. The atria are receiving chambers that pump blood into the ventricles (the discharging chambers).
- The synchronous pumping actions of the heart's two atrioventricular (AV) pumps (right and left chambers) constitute the cardiac cycle.
- The cycle begins with a period of ventricular elongation and filling(diastole) and ends with a period of ventricular shortening and emptying (systole).
- The wall of each heart chamber consists of three layers, from deep to superfirical:
    1. Endocardium, a thin internal layer (endothelium and sub endothelial connective tissue) or lining membrane of
       the heart that also covers its valves.
    2. Myocardium, a thick, helical middle layer composed of cardiac muscle.
    3. Epicardium, a thin external layer (mesothelium) formed by the visceral layer of serous pericardium.
- The walls of the heart consist mostly of myocardium, especially in the ventricles.
- Externally, the atria are demarcated from the ventricles by the coronary sulcus (atrioventricular groove), and the right and left ventricles are demarcated from each other by anterior and posterior interventricular (IV) sulci.

The **apex** of the heart:

- Is formed by the inferolateral part of the left ventricle.

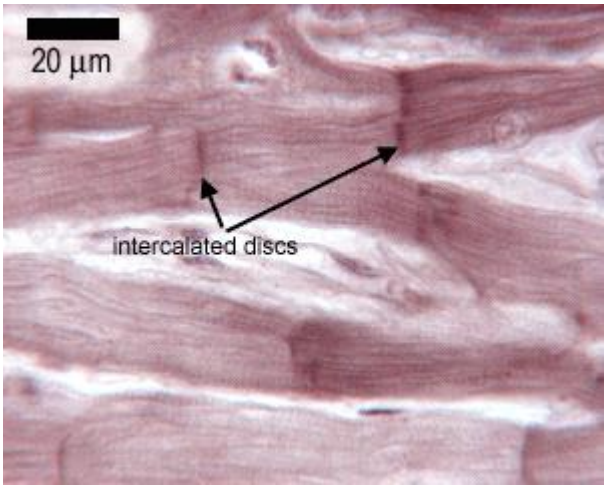
- Lies posterior to the left 5th intercostal space in adults, usually approximately 9 cm (a hand's breadth) from the median plane.
- Remains motionless throughout the cardiac cycle.
- Is where the sounds of mitral valve closure are maximal (apex beat); the apex underlies the site where the heartbeat may be auscultated on the thoracic wall.

The **base** of the heart:

- Is the heart's posterior aspect (opposite the apex).
- Is formed mainly by the left atrium, with a lesser contribution by the right atrium.
- Faces posteriorly toward the bodies of vertebrae T6–T9 and is separated from them by the pericardium, oblique pericardial sinus, oesophagus, and aorta.
- Extends superiorly to the bifurcation of the pulmonary trunk and inferiorly to the coronary sulcus.
- Receives the pulmonary veins on the right and left sides of its left atrial portion, and the superior and inferior venae cavae at the superior and inferior ends of its right atrial portion.

PHYSIOLOGIC ANATOMY OF CARDIAC MUSCLE

- Cardiac muscle is striated in the same manner as in skeletal muscle.
- Further, cardiac muscle has typical myofibrils that contain actin and myosin filaments almost identical to those found in skeletal muscle; these filaments lie side by side and slide during contraction in the same manner as occurs in skeletal muscle.
- The dark areas crossing the cardiac muscle fibres are called **intercalated discs**; they are actually cell membranes that separate
- individual cardiac muscle cells from one another. That is, cardiac muscle fibres are made up of many individual cells connected in series and in parallel with one another.
- The heart is composed of three major types of cardiac muscle: atrial muscle, ventricular muscle, and **specialized excitatory and conductive muscle fibre**s:
    1. The atrial and ventricular types of muscle contract in much the same way as skeletal muscle, except that the duration of contraction is much longer.
    2. The specialized excitatory and conductive fibres contain few contractile fibrils; instead they exhibit either automatic rhythmical electrical discharge in the form of action potentials or conduction of the action potentials through the heart.



- At each intercalated disc the cell membranes fuse with one another to form permeable "communicating" junctions (gap junctions).
- This allows ions move with ease (rapid diffusion) in the intracellular fluid along the longitudinal axes of the cardiac muscle fibres so that action potentials travel easily from one cardiac muscle cell to the next, past the intercalated discs.
- Therefore, cardiac muscle is a **syncytium.** Specifically, two syncytium's: the **atrial syncytium**

and the **ventricular syncytium**.

PHYSIOLOGY

ACTION POTENTIALS IN CARDIAC MUSCLE

- The action potential recorder in ventricular cardiac muscle averages 105 millivolt, rising from -85 millivolts between beats to the slightly positive +20 millivolts, during each beat.
- The membrane remains depolarized for about 0.2 second, i.e. a **plateau**, which causes ventricular contraction to last about 15 times longer than skeletal muscle contraction.
- Skeletal muscle action potential is caused primarily by the opening of "fast" sodium channels **(because they remain open for only a few thousandths of a second and then abruptly close).**
- Cardiac muscle action potential is caused by the opening of two types of channels:
    1. the same voltage activated fast sodium channels as those in skeletal muscle and;
    2. **L-type calcium channels** (slow calcium channels), which are also called calcium-sodium channels which are slower to open and **remain open for several tenths of a second.**
- The large quantity of sodium and calcium flowing through these channels maintains a prolonged action potential, causing the plateau.
- Further, these calcium ions are the ones that initiate the contractile process unlike skeletal muscle which is initiated by calcium from intracellular sarcoplasmic reticulum.
- Another difference between cardiac and skeletal muscle: immediately after the onset of an action potential, the permeability of cardiac muscle to **potassium** ions *decreases fivefold* (perhaps due to the calcium influx):
    1. This decreases the rate of outflux of potassium ions preventing early return to resting levels.
    2. When the calcium channels close, the membrane permeability for potassium ions rapidly increases, outflux occurs and the resting membrane potential is reached (about -90 millivolts).
- This ends the action potential.

Refractory Period:

1. period during which a normal cardiac impulse cannot re-excite an already excited area of cardiac muscle.
2. Lasts about 0.25 to 0.30 second (like the plateau)

- *There is an additional relative refractory period of about 0.05 second during which the muscle is more difficult to excite than normal but nevertheless can be excited by a very strong excitatory signal.*
- *The refractory period of atrial muscle is much shorter than that for the ventricles (about 0.15 second for the atria compared with 0.25 to 0.30 second for the ventricles).*

EFFECT OF POTASSIUM AND CALCIUM IONS ON HEART FUNCTION

- **Excess potassium** (2-3 times the normal levels) in the extracellular fluids causes the heart to become dilated and flaccid and also slows the heart rate - severe weakness of the heart abnormal rhythm and death.
- Large quantities of potassium also can block conduction of the cardiac impulse from the atria to the ventricles through the A-V bundle.
- This is partially because:
    1. High extracellular fluid potassium concentration partially depolarizes the cell membrane, causing the membrane potential to be less negative.
    2. As the membrane potential decreases, the intensity of the action potential also decreases, which makes contraction of the heart progressively weaker.
- **Excess calcium** ions cause effects almost exactly opposite to those of potassium ions, causing the heart to move toward spastic contraction.
- This effect is caused by a direct effect of calcium ions to initiate the cardiac contractile process.

- **Low calcium** causes the same effect as high potassium

Duration of Contraction.

- Cardiac muscle begins to contract a few milliseconds after the action potential begins and continues to contract until a few milliseconds after the action potential ends.
- Therefore, the duration of contraction of cardiac muscle is mainly a function of the duration of the action potential, including the plateau-about 0.2 second in atrial muscle and 0.3 second in ventricular muscle.

SPECIALIZED EXCITATORY AND CONDUCTIVE SYSTEM OF THE HEART

SA Node

- A small, flattened, ellipsoid strip of specialized cardiac muscle located in the superior posterolateral wall of the right atrium immediately below and slightly lateral to the opening of the superior vena cava.
- The fibres of this node have almost no contractile muscle filaments.
- However, the sinus nodal fibres connect directly with the atrial muscle fibres so that any action potential that begins in the sinus node spreads immediately into the atrial muscle wall.
- Called the pacemaker of the heart. This is because discharge rate of the sinus node is considerably faster than the natural self-excitatory discharge rate of either the A-V node or the Purkinje fibres so it spreads its discharge to them.

Self-Excitation of the SA Node.

- The “resting membrane potential” of the sinus nodal fibre between discharges has a negativity of about −55 to −60 millivolts, in comparison with −85 to −90 millivolts for the ventricular muscle fiber.
- The cause of this lesser negativity is that the cell membranes of the sinus fibres are naturally leaky to sodium and calcium ions, and positive charges of the entering sodium and calcium ions neutralize some of the intracellular negativity.
- When the potential reaches a threshold voltage of about −40 millivolts, the L-type calcium channels become “activated,” thus causing the action potential. Therefore, basically, the inherent leakiness of the sinus nodal fibers to sodium and calcium ions causes their self-excitation.
    1. The SA Node is not depolarized all the time because:
    2. the L-type calcium channels become inactivated (i.e., they close) within about 100 to 150 milliseconds after opening, and second, at about the same time, greatly increased numbers of potassium channels open.
- Both of these effects reduce the intracellular potential back to its negative resting level and therefore terminate the action potential.
- Potassium channels stay open for a little longer, causing hyperpolarization but due to the inherent leakiness of the SA node, the resting membrane potential returns to normal.

INTERNODAL AND INTERATRIAL PATHWAYS TRANSMIT CARDIAC IMPULSES THROUGH THE ATRIA

- The ends of the sinus nodal fibres connect directly with surrounding atrial muscle fibres.
- Therefore, action potentials originating in the sinus node travel outward into these atrial muscle fibres.
- In this way, the action potential spreads through the entire atrial muscle mass and, eventually, to the A-V node.
- The velocity of conduction in most atrial muscle is about 0.3 m/sec, but conduction is more rapid, about 1 m/sec, in several small bands of atrial fibres.
- One of these bands, called the anterior interatrial band, passes through the anterior walls of the atria to the left atrium.

- In addition, three other small bands curve through the anterior, lateral, and posterior atrial walls and terminate in the A-V node.

THE ATRIOVENTRICULAR NODE DELAYS IMPULSE CONDUCTION FROM THE ATRIA TO THE VENTRICLES

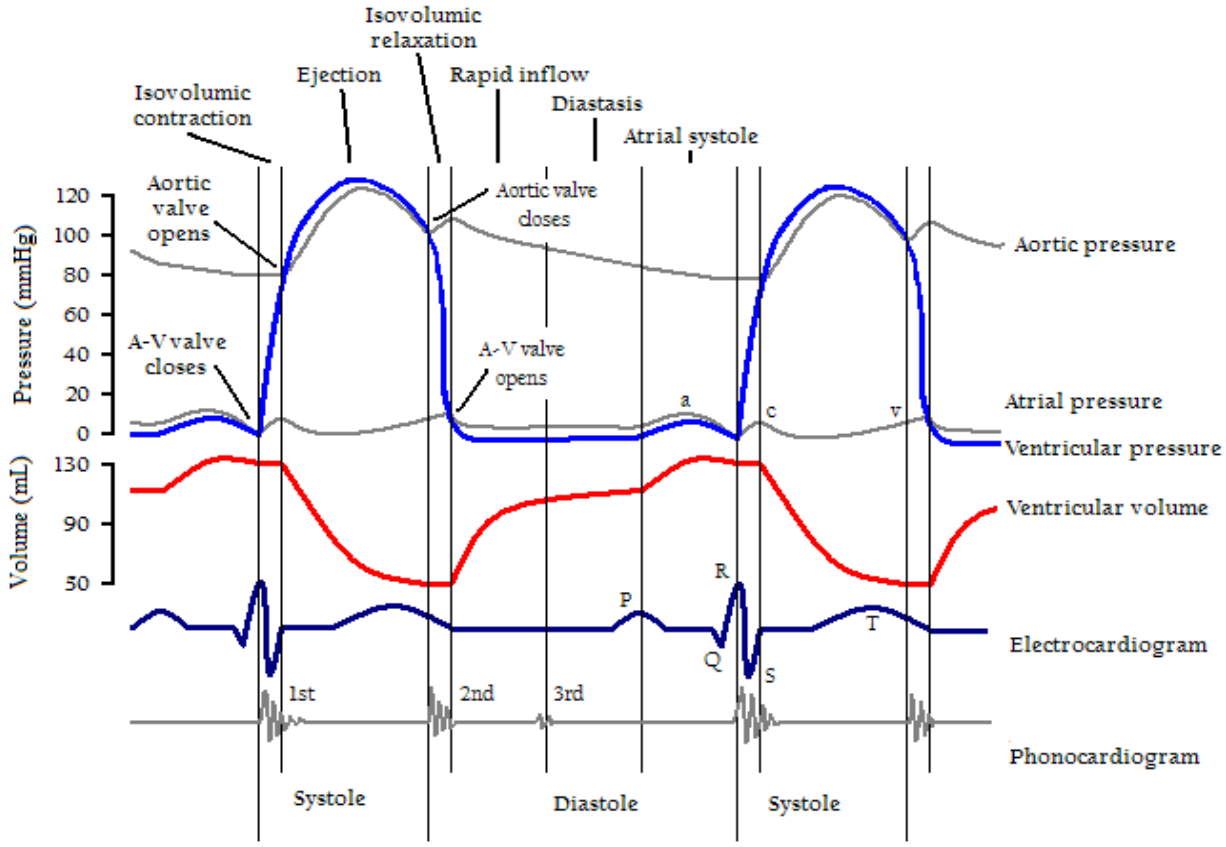
- The A-V node is located in the posterior wall of the right atrium immediately behind the tricuspid valve
- The AV Node and its connective tissue allows a delay so that the atria can fill the ventricles before they contract.
- The impulse, after traveling through the inter-nodal pathways, reaches the A-V node about 0.03 second after its origin in the sinus node.
- Then there is a delay of another 0.09 second in the A-V node itself before the impulse enters the penetrating portion of the A-V bundle, where it passes into the ventricles.
- A final delay of another 0.04 second occurs mainly in this penetrating A-V bundle, which is composed of multiple small fascicles passing through the fibrous tissue separating the atria from the ventricles.
- The slow conduction in the transitional, nodal, and penetrating A-V bundle fibres is caused mainly by diminished numbers of gap junctions between successive cells in the conducting pathways, so there is great resistance to conduction of excitatory ions from one conducting fibre to the next.

Ventricular Purkinje System

- Special Purkinje fibres lead from the A-V node through the A-V bundle into the ventricles.
- They are very large fibres, even larger than the normal ventricular muscle fibres, and they transmit action potentials at a velocity of 1.5 to 4.0 m/s.
- Once the cardiac impulse enters the ventricular Purkinje conductive system, it spreads almost immediately to the entire ventricular muscle mass.

CARDIAC CYCLE

- The cardiac events that occur from the beginning of one heartbeat to the beginning of the next are called the cardiac cycle.
- Each cycle is initiated by spontaneous generation of an action potential in the sinus node located in the superior lateral wall of the right atrium near the opening of the superior vena cava, and the action potential travels from here rapidly through both atria and then through the A-V bundle into the ventricles..
- Due to this arrangement of the conducting system there is a delay of 0.1sec for the action potential to pass from the atria to the ventricles. This allows the atria to contract ahead of ventricular contraction, thereby pumping blood into the ventricles before the strong ventricular contraction begins.



REGULATION OF HEART PUMPING

Parasympathetic (Vagal) Stimulation Slows the Cardiac Rhythm and Conduction.

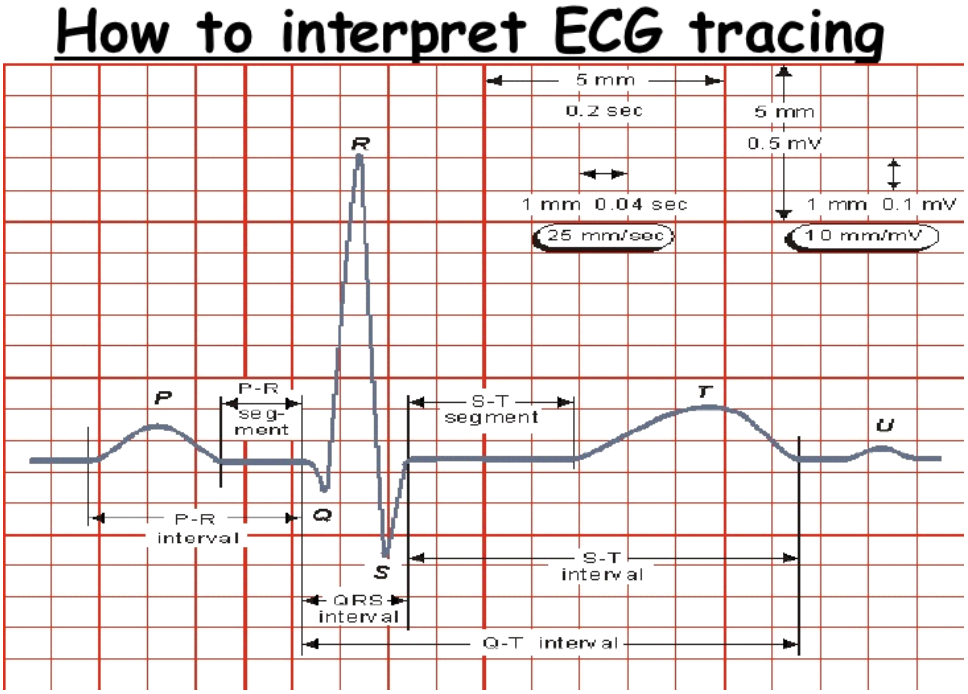
- Stimulation of the parasympathetic nerves to the heart (the vagi) causes the hormone acetylcholine to be released at the vagal endings.
- This hormone has two major effects on the heart:
  1. it decreases the rate of rhythm of the sinus node.
  2. it decreases the excitability of the A-V junctional fibres between the atrial musculature and the A-V node, thereby slowing transmission of the cardiac impulse into the ventricles.
- The acetylcholine released at the vagal nerve endings greatly increases the permeability of the fibre membranes to potassium ions, which allows rapid leakage of potassium out of the conductive fibres.
- This increases the negativity inside the fibre, *hyperpolarisation*, which makes this tissue much less excitable.
- In the sinus node, hyperpolarisation makes the resting membrane potential more negative, -65 to -75mV than the usual -55 to -60mV.
- Therefore, the initial rise of the sinus nodal membrane potential caused by inward sodium and calcium leakage requires much longer to reach the threshold potential for excitation. This requirement greatly slows the rate of rhythmicity of these nodal fibres.
- In the A-V node, a state of hyperpolarization caused by vagal stimulation makes it difficult for the small atrial fibres entering the node to generate enough electricity to excite the nodal fibres.

Sympathetic Stimulation Increases the Cardiac Rhythm and Conduction.

1. it increases the rate of sinus nodal discharge.
2. it increases the rate of conduction, as well as the level of excitability in all portions of the heart.
3. it increases greatly the force of contraction of all the cardiac musculature, both atrial and ventricular.

- Sympathetic nerve stimulation causes release of *norepinephrine* which activates the *beta-1 adrenergic receptors.*
- It is believed that this increases the permeability of the fibre membrane to sodium and calcium ions.
- In the sinus node, an increase of sodium-calcium permeability causes a more positive resting potential and also causes an increased rate of upward drift of the diastolic membrane potential toward the threshold level for self-excitation, thus accelerating self-excitation and, therefore, increasing the heart rate.
- In the A-V node and A-V bundles, increased sodium-calcium permeability makes it easier for the action potential to excite each succeeding portion of the conducting fibre bundles, thereby decreasing the conduction time from the atria to the ventricles.

The Normal Electrocardiogram



CHARACTERISTICS OF THE NORMAL ELECTROCARDIOGRAM

Consists of a P wave, a QRS complex, and a T wave. The QRS complex is often, but not always, three separate waves: the Q wave, the R wave, and the S wave:

1. The P wave is caused by electrical potentials generated when the atria depolarize before atrial contraction begins.
2. The QRS complex is caused by potentials generated when the ventricles depolarize before contraction, that is, as the depolarization wave spreads through the ventricles. Therefore, both the P wave and the components of the QRS complex are ***depolarization waves***.
3. The T wave is caused by potentials generated as the ventricles recover from the state of depolarization. This process normally occurs in ventricular muscle 0.25 to 0.35 second after depolarization. The T wave is known as a ***repolarization wave***.

Note:

1. **The atria repolarize about 0.15 to 0.20 second after termination of the P wave, which is also approximately when the QRS complex is being recorded in the ECG. Therefore, the atrial repolarization wave, known as the atrial T wave, is usually obscured by the much larger QRS complex. For this reason, an *atrial T wave* seldom**

is observed on the ECG.

2. ***Q-T Interval.*** **Contraction of the ventricle lasts almost from the beginning of the Q wave (or R wave, if the Q wave is absent) to the end of the T wave. This interval is called the Q-T interval and ordinarily is about 0.35 second.**

Renin-angiotensin-aldosterone system.

The renin-angiotensin- aldosterone system is activated in response to decreased arterial pressure (i.e., decreased renal perfusion pressure).
Angiotensin II:
stimulate the synthesis and secretion of aldosterone. Aldosterone then acts on the principal cells of the renal distal tubule and collecting duct to increase Na+ reabsorption and, thereby, to increase ECF volume and blood volume.
stimulates Na^+-H^+ exchange in the renal proximal tubule and increases the reabsorption of Na^+ and $HCO3^-$.
acts on the hypothalamus to increase thirst and water intake.

Lipid Lowering Drugs

14 June 2017 20:30

Lipids, Lipoproteins and Atherosclerosis

- High LDL and Low HDLs are associated with CVD because they promote atheroma (plaque) formation in arteries (atherosclerosis)
- Atherosclerosis leads to MI, stroke and peripheral vascular disease
- LDL (bad cholesterol) is linked to atheroma formation
  - Transports cholesterol from the liver to the body parts
  - LDL + Protein A = Lipoprotein A*
    - By disulfide bridge
- HDL (good cholesterol) has protective roles in mediating hepatic cholesterol excretion by reverse transport of cholesterol from the periphery and reverse atheroma formation
- Cholesterol is deposited in atheromatous lesions derived from LDL and enters the lesion at a rate dependent upon the plasma concentrations
- Atherogenicity of triglyceride rich lipoprotein is less clear but there is epidemiological association with ischaemic heart disease and peripheral vascular disease
- Plaques can form anywhere
  - Carotid artery - Carotid artery disease
  - Coronary artery - Coronary artery disease
  - May lead to angina
- If plaque breaks open, it can form a clot, and if the clot lodges in an artery and completely chokes off the blood supply, the cells may die due to lack of oxygen - stoke and heart attack
- VLDLs are synthesised in the liver and represent endogenous triglyceride synthesis
  - Apoprotein E + Apoprotein C = VLDL
  - VLDL will be acted upon by lipoprotein lipase to form a VLDL remnants of which on of them is LDLs
    - LDL is a VLDL without the triglycerides
- HDLs are produced in the liver and intestine and contain 20 - 50% of circulating cholesterol
  - Transport cholesterol from the body to the liver

HDL Level	Men mg/dL	Women mg/dL
Danger	<40	<50
Too Low	40-49	50-59
Acceptable	60	60
Very Good	>60	>60

- Normal is 130
- Person at risk, the drugs should aim to lower the cholesterol level beyond the normal

Hyperlipidaemia

- High cholesterol, hypercholesterolemia or hypertriglyceridemia
  - Hyperlipidaemia is high levels of triglycerides
  - Hyperlipaemia is high levels of everything else
- Commonly associated with diets high in saturated fats, sedentary lifestyle, obesity, diabetes
- Familial hyperlipidaemia is an inherited genetic disorder
- Has no symptoms and is a hidden risk factor of CV disease

Secondary Causes if Raised Cholesterol and Triglyceride

- Raised Cholesterol
  - Diet
    - Eating too much saturated fats, trans fat and cholesterol
  - Hypothyroidism
    - Decreased metabolism
  - Liver disease
    - Cholesterol is stored in the liver. Damage may cause release of cholesterol to the bloodstream
  - Nephrotic syndrome
  - Porphyria
- Raised Triglyceride
  - Obesity
  - Poorly controlled diabetes
  - Alcohol in excess
    - Cirrhosis
    - Alcohol contains sucrose and other sugars
  - High carbohydrate diet
  - Renal failure
  - Oestrogen therapy

General Principles in Management of Hyperlipidaemias

- Maintenance of lean body weight
- Low fat diet
- Avoidance of alcohol
- Avoid oestrogens and thiazides

- Avoid smoking
- Treatment of diabetes and hypertension if present
- Moderate exercise

1. Rationale for Drug Use
    - Reduce progression of atherosclerosis
    - Improve survival
    - Reduce risk of myocardial infarction and stroke in patients with established CV disease
    - Reduce premature CV morbidity and mortality in people with high risk of CV events
    - Prevent pancreatitis due to hypertriglyceridemia

Lipid Lowering Agents

- These may be effective in one of three ways
    - Reduce synthesis of VLDLs and LDLs
        - Nicotinic acid
    - Enhance VLDL clearance
        - Fibrates
    - Enhance catabolism
        - Cholestyramine

Classification

- Competitive inhibitors of HMG-CoA (3-hydroxyl-3-methylglutaryl-coenzyme A) reductase
    - Lovastatin
    - Atorvastatin
    - Fluvastatin
    - Pravastatin
    - Sinvastatin
    - Rosuvastatin
    - Cerivastatin
- Niacin (nicotinic acid)
- Fibric Acid Derivatives (fibrates)
    - Gemfibrizol
    - Fenofibrate
- Bile acid-binding resins
    - Colestipol
    - Cholestyramine
- Inhibitors of intestinal Sterol Absorption
    - Ezetimibe

Competitive Inhibitors of HMG-CoA Reductase (Statins)

- Structural analogue of HMG-CoA

MoA

- Competitively inhibit HMG-CoA reductase, a rate limiting step in cholesterol synthesis
    - Acetyl-CoA+ Acetyl-CoA -------Thiolase-------> Acetoacetyl-CoA
    - Acetoacetyl-CoA + Acetyl-CoA--------HMG-CoA Synthase--------> HMG-CoA
    - HMG-CoA ----------HMG-CoA reductase ----------> Mevalonic Acid (where Statins work)
- Also works by increasing the affinity of LDL receptors on the hepatocytes where they will take up more LDLs in the blood to be lysed by lysosomes
- Increase hepatic cholesterol uptake from the blood
- Reduce concentration of total cholesterol, LDL and triglyceride (modest)
- Produce small increase in HDL concentrations

Pharmacokinetics

- Lovastatin and Simvastatin are inactive lactone prodrugs and are hydrolysed in the GIT to the active beta-hydroxyl derivative
- Provastatin has an open lactone ring
- Atorvastatin, Fluvastatin and Rosuvastatin are fluorine containing active congeners
- Oral absorption: 40 - 70% with the exception of Fluvastatin (~100%)
- High FPE by the liver
- Most of absorbed drug excreted in bile: 5 - 20% in urine
- Half-life: 1- 3 hours except for Atorvastatin (14 hours) and Rosuvastatin (19 hours), Pitavastatin (12 hours)
- Should be given at night (between 12am to 2am) since that is the time cholesterol is formed

Clinical Manifestations

- Most effective LDL lowering agents
- Hypercholesterolaemia
- Mised hyperlipidemia
- High risk individuals of coronary heart disease, with or without hypercholesterolidemia
- LDL lowering effect
    - Atovastatin, Rosuvastatin and Simvastatin are more potent than Fluvastatin or Pravastatin
        - Order of potency
            - Rosuvastatin

- Atovastatin
- Simvastatin
- Lovastatin

Adverse Effects

Common	Rare
• Myalgia • Mild, transient GI symptoms • Headache • Insomnia • Dizziness • Elevated aminotransferase concentrations (occur in 0.5 - 2% of patients and is dose dependent):.'	• Myopathy (with or without creatinine kinase elevation) and rhabdomyolysis is dose dependent • RF • Hepatitis • Liver failure • Pancreatitis • Alopecia • Paresthsia • Amnesia • Nighmares • Peripheral neuropathy • Impotence • Anaphylaxis • Angioedema • Epidermal necrolysis • Intestitial lung disease

Drug Interactions

- Risk of statin-induced myopathy increases with increasing plasma concentrations
- Most statins metabolised by CYP450 isoenzymes and risk of adverse effects increase with treatment with other drugs
- There are fewer interactions with Fluvastatin, Pravastatin and Rosuvastatin, than with Atorvastatin or Simvastatin
- Those that inhibit or competitively inhibit CYP3A4 isoenzyme, resulting in increasing concentration of Lovastatin, Simvastatin and Atorvastatin
  - Macrolide antibiotics, cyclosporine, ketoconazole (and its congeners), HIV protease inhibitors, Tacrolimus, Nefazodone, Fibrates, Grape Fruit Juice
- Inducers of CYP3A4
  - Phenytoin
  - Griseofulvin
  - Barbiturate
  - Rifampin
  - Thazolidinones
- Amidarone or Verapimil causes an increased risk of myopathy
- Biotranformation and Fluvastatin and Rosuvastatin mediated by CYP2C9 isoenzyme and is inhibited by Ketoconazole (and congeners), Metronidazole, Sulfinpyrazone, Amiodarone and Cimetidine
- Pravastatin is catabolised through other pathways
  - Can be used with the drugs that interact with other statins

Niacin (Nicotinic Acid)

- Vitamin B_3 is converted in the body, to the amide which is incorporated into niacinamide adenine dinucleotide (NAD)
- Eliminated in the urine as parent and several metabolites

MoA

- Niacin inhibits lipolysis in adipose tissue (the primary producer of circulation FFAs)
- Liver utilises circulating FFAs as a major precursor for triglyceride synthesis
  - Niacin causes a decrease in liver triglyceride synthesis
- Triglycerides required for VLDLs
- LDL (the cholesterol rich lipoprotein) is derived from VLDLs in the plasma
  - Reduction of VLDL concentration in a decreased plasma LDL concentration, thus lowering both plasma triglycerides (in VLDL) and cholesterol (in VLDL and LDL)
- Increases HDL and uniquely lowers potentially atherogenic lipoproteins

- Acts on niacin receptors 1 and2 (NIACR1 and NIACR2) - are G-protein coupled receptors that reduce lipolytic and atherogenic activity (which when activated, cause vasodilation which is responsible for the niacin-related flushing)
  - ↓ lipolysis in adipose tissues → ↓ FA production → ↓ TAG and VLDL production in the liver
- Also increases expression of apoA-I which leads to an increase in HDL
  - By reducing the fractional clearance of apoA-I in the HDL
- Increasing the activity of LPL (lipoprotein lipase)
  - In the endothelial cells
  - Breakdown of LDLs
- Catabolic rate of HDL is reduced by niacin
- Also reduces the hepatic uptake of HDL so it circulates longer in blood
- Lowers LDL by 20-30%
- Lowers TG by 35-45%
- Lowers lipoprotein A

Pharmacokinetics

Chylomicrons

- A lipoprotein particle that consists of
  - Triglycerides (85-92%)
  - Phospholipids (6-12%)
  - Cholesterol (1-3%)
  - Proteins (1-2%)
- The transport dietary lipids from the intestines to other locations in the body

- Absorption is almost complete
- Peak plasma levels in 30-60 minutes
- Half-life is 1hr
- Excreted in urine
- At lower doses, nicotinuric acid is the metabolite
    - Higher doses metabolite is nicotinic acid
        - Its excreted unchanged
- Given in two doses
    - Extended release
        - Over a period of 6-8 hour
    - Immediate release
        - Crystalline
        - PO

Therapeutic Indications

- Given in combination with a fibrate or HMG-CoA reductase inhibitor for management of
    - Hypercholesterolemia
    - Mixed hyperlipidemia
    - Severe hypertriglyceridemia

Adverse Effects

- Most are dose-related

Common	Infrequent	Rare
• Vasodilation • Face and neck flushing • Hypotension • Dyspepsia • NVD • Hyperpigmentation	• Itching • Rash • Blurred vision • Abdominal pain • Jaundice • Impaired liver function • Hyperglycaemia • Hyperuricemia • Nervousness	• Hepatic failure • Myopathy • Increased creatinine kinase • Gout • Macular oedema causing reversible visual loss

- Reduced levels of LDL by ≥50% = Niacin toxicity which may lead to liver toxicity
    - Indicated by:
        - Altered transaminases
        - Hyperglycaemia
        - Flu-like fatigue
        - Weakness

Fibric Acid Derivatives (Fibrates)

- Include
    - Gemfibrozil
    - Fenofibrate
- Usually given together w/ Statins (Fibrate of choice to use is Fenofibrate)

MoA

- Activate peroxisome proliferator-activated nuclear receptors and modulate lipoprotein synthesis and catabolism
    - They activate peroxisome proliferated activator receptor alpha (PPAR-a)
        - Found in the cell nucleus in the regulation of carbs and Fas
            - When stimulated, the drug bind the receptor and the receptor moves into the nucleus. The PPARa binds another receptor, the retinoid X receptor (RXR), and the complex binds DNA on the peroxisome proliferator hormone response element sequence. They are responsible for the expression of proteins that increase the metabolism of Fas e.g.:
                - ↑ expression of lipoprotein lipase (LPL)
                    - ↑ TAG metabolism
                - ↑ expression of apoA-I and apoA-II
                    - ↑ HDL
- Increase lipolysis of lipoprotein triglyceride via LPL
    - Reduce plasma triglyceride
- Intracellular lipolysis in adipose tissue is decreased
- Levels of VLDLs decrease
- Moderately increase HDL and have a variable effect on LDL concentrations

Therapeutic Indications

- Severe hypertriglyceridemia with risk of pancreatitis
- Mixed hyperlipidaemia and dyslipidaemia associated with diabetes
- Dysproteinemia
- Dysbetalipoproteinuria
- Hypercholesterolaemia

Pharmacokinetics

- Gemfibrozil
    - almost totally absorbed from the GIT (also Niacin and Fluvostatin)
    - tightly bound to plasma proteins
    - Undergoes enterohepatic circulation

    - Readily crosses the placenta
    - Plasma half-life: 1.5 hours
    - 70% renal elimination
    - Some of the drug is biotransformed in the liver
- Fenofibrate
    - Is an ester and is hydrolysed in the intestine
    - Plasma half-life: 20 hours
    - 65% eliminated renally as glucoronide and about 25% in faeces

Adverse Effects

Common	Infrequent	Rare
• GIT disturbances (e.g. dyspepsia and abdominal pain) • Reversible elevation of creatinine	• Photosensitivity (may be rare with Gemfibrozil)	• Cholestatic jaundice • Gallstones • Anaemia • Leukopenia • Myopathy • Rhabdomyolysis • Hypersensitivity reactions (e.g. angioedema, anaphylaxis, exfoliative dermatitis)

Bile Acid-Binding Resins

- Include
    - Colestipol
    - Cholestyramine
    - Colesevelam
- Large polymeric cationic exchange resins
- Insoluble in water
- Bind bile acids in the intestinal lumen and prevent their absorption
- The resin itself is not absorbed
    - They are excreted along w/ any bile acids bound to the drug via the faeces

MoA

- Bind bile acids in intestinal lumen, preventing reabsorption and increasing bile acid excretion in faeces
- Increased demand for cholesterol for bile acid synthesis results in an increase in a LDL uptake and removal from plasma
- Bile acid sequestrants exchange anions such as chloride ions for bile acids,. By doing so, they bind to bile acids and sequester them from the enterohepatic circulation. The liver then produces more bile acids to replace those that have been lost. Because the body uses cholesterol to make bile acids (through 7α-hydroxylation, which is controlled by negative feedback by the bile acids), this reduces the amount of LDL cholesterol circulating in the blood
    - This negative feedback is through the farnesoid X receptor (FXR)
        - One of its primary functions is to suppress cholesterol 7α-hydroxylase (the rate limiting enzyme in bile acid synthesis from cholesterol)
            - Induces expression of a small heterodimer partner (SHP) which functions to inhibit transcription of 7α-hydroxylase
                - Negative feedback

Therapeutic Indications

- Hypercholesterolaemia
- Mixed hyperlipidaemia
    - May cause an increase in VLDLs and may need to be used in combination w/ another agent like niacin
- Itch associated with partial biliary tract obstruction
- Digitalis toxicity
    - They also bind digitalis glycosides
- Diahrroea following ileal resection or disease

Precautions

- Resins may exacerbate hypertriglyceridaemia
    - Because of the FXR regulation of hepatic triglycerides
        - Decreased activation of the FXR receptor by bile acids may result in a modest increase in the plasma triglycerides
- Malbsorption of Vitamin K and Folinic Acid (both are rare)
    - Prothrombin times need to be frequently measured
- Ineffective in complete biliary obstruction
- Absorption of drugs may be impaired
    - Additional medicine should be administered ~1 hour before the resin, or ~2 hours after the resin
- May worsen constipation
    - High fluid and high fibre diet, stool softener or laxative may be required
- May worsen diverticular disease, severe haemorrhoids
- Increases risk of constipation in the elderly
- Avoid breast feeding

Adverse Effects

- Dose-related
  - Minimise by starting with low dose and increasing gradually

Common	Infrequent	Rare
• Constipation • Abdominal pain • Dyspepsia • Flatulence • NVD • Anorexia	• Increased triglycerides	• Faecal compaction • Aggravation of haemorrhoids • Steatorrhoea • Decreased absorption of fat soluble vitamins • Increased bleeding tendency • Hyperchloraemic acidosis

Drug Interactions

- May impair absorption of anions, cationic or neutral drugs e.g. thiazides, digitalis glycosides, warfarin, tetracycline thyroxin, iron salts, Pravastatin, Fluvastatin, Ascorbic Acid, ASA, Phenylbutazone etc.
  - Avoid by giving the drugs, 1 hour before or 2 hours after the resin
- Malabsorption of Vitamin K may occur, lading to hyperprothrombinaemia

Inhibitors of Intestinal Sterol Absorption

Ezetemibe

MoA

- Reduces absorption of dietary and biliary cholesterol by inhibiting its transport across the intestinal wall
  - The NPC1L1 receptor is found in the GIT epithelial cell. The drug binds to the receptor and inhibits the absorption of cholesterol, which increases the body's demand for cholesterol, which leads to increased removal of LDLs from plasma to synthesis more cholesterol
    - NPC1L1 is an accessory receptor for Hepatitis C i.e. Hepatitis C can bind here and Ezetemibe can be used as a therapeutic strategy
- This leads to an increased demand for cholesterol, an increase in LDL uptake and its removal from plasma

Pharmacokinetics

- OP
  - Tablets
- Half-life
  - 19-30 hours
- Metabolism mostly in intestinal wall and liver
- Undergoes enterohepatic circulation
- Excretion
  - 78% in faeces
  - Rest, renally
- 90% PPB
- Bioavailability: 35-65%

Indications

- Hypercholesterolemia
- Homozygous sitosterolaemia (phytosterolaemia)
- Combination with Simvastatin for treatment of hypercholesterolemia when statin alone is not effective

Adverse Effects

Common	Infrequent	Rare
• Headache • Diarrhoea	• Myalgia • Raised ALT/AST > 3X ULN	• Allergic reactions (angioedema, rash) • Pancreatitis • Cholelithiasis • Myopathy • Raised creatinine kinase

Omega-3 Acid Ethyl Esters

Indications

- Secondary prevention after MI (with standard treatment)
- Hypertriglyceridemia in adults
- NB:
  - Not indicated for exogenous hypertriglyceridemia (type 1 hyperchylomicronaemia)

MoA

- Possibly inhibits acyl-CoA and 1,2-diacylglycerol acyltransferase
- Increase peroxisomal beta-oxidation in the liver
- May decrease hepatic triglyceride synthesis
- Plasma protein lipase activity may increase

Mixed Hyperlipidaemia - increased LDL and TG and low

HDL

- Initial choice of drug guided by predominant disorder
  - Raised cholesterol, start with statin
  - Raised triglyceride, generally choose a fibrate, however, consider a statin first, if the patient has CVD (more data for their efficacy)
- NB:
  - Nicotinic Acid lowers both cholesterol and triglyceride concentrations but is often poorly tolerated

Combination Treatment

- May be appropriate if a single agent is inadequate
  - E.g. adding fish oil to lower triglyceride or adding Exetemibe or a bile acid binding resin to reduce cholesterol concentration
- Combined use of a statin and a fibrate, is often effective in improving dyslipidaemia but may increase risk of serious adverse effects

Anti-Arrhythmic Drugs

14 June 2017 20:41

- Arrhythmias
  - Tachyarrhythmia: VR - 100bpm
  - Bradyarrhythmia

Aetiology

- Disorder or impulse conduction - most of tachyarrhythmia
  - Re-entry - conduction of the electrical activation retrograde to region that was initially refractory to antegrade conduction of waveform
  - Differential refractoriness of myocardial tissue
  - Ventricular tachycardia
- Disorder of impulse formation - enhanced automaticity
  - Accelerated junctional or AV rhythm

- Emergency by pacing and cardioversion
- Drugs proposed by Vaughan and Williams - 1970

Class	Basic Mechanism	Comments
I	Sodium-channel blockade	Reduce phase 0 slope and peak of action potential.
IA	Moderate	Moderate reduction in phase 0 slope; increase APD; increase ERP.
IB	Weak	Small reduction in phase 0 slope; reduce APD; decrease ERP.
IC	Strong	Pronounced reduction in phase 0 slope; no effect on APD or ERP.
II	Beta-blockade	Block sympathetic activity; reduce rate and conduction.
III	Potassium-channel blockade	Delay repolarization (phase 3) and thereby increase action potential duration and effective refractory period
IV	Calcium-channel blockade	Block L-type calcium-channels; most effective at SA and AV nodes; reduce rate and conduction.

Classification

- Class 1
  - Voltage sensitive Na^+ channel blocking drugs
- Class 2
  - ß-adrenoceptor blocking drugs
- Class 3
  - Prolong the cardiac action potential (potassium channel blockers)
- Class 4
  - Ca^{2+} antagonists
- Unclassified
  - Adenosine
  - Adrenaline
  - Digoxin

Class 1

- Class 1a
  - Na^+ channel blocking (intermediate dissociation)
    - Disopyramide
    - Quinidine
    - Procainamide
- Class 1b
  - Na^+ channel blocking (fast dissociation)
    - Lidocaine
    - Phenytoin
- Class 1c
  - Na^+ channel blocking (slow dissociation)
    - Flecainide
    - Encainide

Class 2

- ß-adrenoceptor blocking
  - Propranolol

Class 3

- Potassium channel blocking drugs
  - Amiodarone
  - Sotalol

Class 4

- Calcium channel blocking drugs
  - Verapimil

Wolff–Parkinson–White syndrome *(**WPW**) is one of several disorders of the electrical system of the heart that are commonly referred to as pre-excitation syndromes.*
WPW is caused by the presence of an abnormal accessory electrical conduction pathway between the atria and the ventricles. Electrical signals traveling down this abnormal pathway (known as the bundle of Kent) may stimulate the ventricles to contract prematurely, resulting in a unique type of supraventricular tachycardia referred to as an atrioventricular re-entrant tachycardia. Individuals with WPW have an accessory pathway that communicates between the atria and the ventricles, in addition to the AV node. This accessory pathway is known as the bundle of Kent. This accessory pathway does not share the rate-slowing properties of the AV node, and may conduct electrical activity at a significantly higher rate than the AV node.
Extremely rapid heart rates such as this may result in hemodynamic instability or cardiogenic shock. In some cases, the combination of an accessory pathway and abnormal heart rhythms can trigger ventricular fibrillation, a leading cause of sudden cardiac death.

Drug Interactions
*Many commonly used drugs interact with digitalis compounds. The Class IA antiarrhythmic, **quinidine**, competes with digoxin for binding sites and depresses renal clearance of digoxin. These effects increase digoxin levels and can produce toxicity. Similar interactions occur with **calcium-channel blockers** and **nonsteroidal anti-inflammatory drugs**. Other drugs that interact with digitalis compounds are **amiodarone** (Class III antiarrhythmic) and **beta-blockers**.*
***Diuretics** can indirectly interact with digoxin because of their potential for decreasing plasma potassium levels (i.e., producing hypokalaemia).*
***Hypokalaemia** results in increased digoxin binding to the Na^+/K^+-ATPase (possibly through increased phosphorylation of the enzyme) and thereby enhances digoxin's therapeutic and toxic effects.*
***Hypercalcemia** enhances digitalis-induced increases in intracellular calcium, which can lead to calcium overload and increased susceptibility to digitalis-induced arrhythmias.*
***Hypomagnesemia** also sensitizes the heart to digitalis-induced arrhythmias.*

Pharmacology of Phosphodiesterase Inhibitors
Intracellular concentrations of cAMP play an important second messenger role in regulating cardiac muscle contraction. Activation of the sympathetic nervous system releases the neurotransmitter norepinephrine and increases circulating catecholamines (epinephrine and norepinephrine). These catecholamines bind primarily to $beta_1$-adrenoceptors in the heart that are coupled to G_s-proteins. This activates adenylyl cyclase to form cAMP from ATP. Increased cAMP, through its coupling with other intracellular

- Diltiazem

Unclassified

- Atropine
  - Sinus bradycardia
- Adrenaline
  - Cardiac arrest
- Isoprenaline
  - Heart block
- Digoxin
  - Rapid atrial fibrillation
- Adenosine
  - Supraventricular tachycardia
- Calcium chloride
  - Ventricular tachycardia due to hyperkalaemia
- Magnesium chloride
  - Ventricular fibrillation
  - Digoxin toxicity

*messengers, increases contractility (inotropy), heart rate (chronotropy) and conduction velocity (dromotropy). Cyclic-AMP is broken down by an enzyme called **cAMP-dependent phosphodiesterase (PDE)**. The isoform of this enzyme that is targeted by currently used clinical drugs is the type 3 form (PDE3). Inhibition of this enzyme prevents cAMP breakdown and thereby increases its intracellular concentration. This increases cardiac inotropy, chronotropy and dromotropy. PDE3 inhibitors can be thought of as a backdoor approach to cardiac stimulation, whereas β-agonists go through the front door to produce the same cardiac effects.*

Glucagon exerts positive inotropic and chronotropic effects on the heart. This is done via stimulation of adenylyl cyclase stimulation (and subsequent phosphorylation of L-type Ca^{2+} channels).

Phosphodiesterase inhibitors enhance this effect as detailed above.

Mechanisms of Action of:

Class 1 Drugs

- Block Na+ channels
- Binds to sites in α -subunit
- Inhibits action potential in excitable cells ('membrane stabiliser')
- Reduce the maximum rate of depolarisation during phase 0
- Na+ channels
  - Resting
  - Open
  - Refractory
- Change from resting to open following depolarisation (activation)
- Inactivation
  - Refractory
- Repolarisation
- Drug acts on open or refractory i.e. use dependent
- Class 1b
  - Fast dissociation
    - Binds to open channel during phase 0 and dissociates in time for the next action potential
  - Selective binding to refractory channels
- Class 1c
  - Slower association and dissociation

Class 2 Drugs

- ß-adrenoceptor blocking drugs
- Use in ventricular fibrillation following myocardial infarction due to ↑ sympathetic activity
- Paroxysmal attacks of atrial fibrillation

Class 3 Drugs

- Prolong cardiac action potential
- Amiodarone and Sotalol
- Block some K channels in cardia repolarisation
- Increase refractory period
- Interrupts re-entrant and suppress ectopic activity

Class 4 Drugs

- Act on slow L-type Ca2+ channels
- Include
  - Verapimil
  - Diltiazem
- Sow conduction in AV and SA node
- Slow heart and terminate SVT by causing partial AV block

Pharmacokinetics of:

Class 1a

- Quinidine and procainamide
  - Similar and rarely used
- Disopyramide
  - Antiarrhythmic
  - Marked atropine like effects, thus blurred vision, dry mouth, constipation and urine retention
    - More negatively inotropic than quinidine
    - Less likely to cause hypersensitivity reaction
- Procainamide
  - MoA
    - Blocks open and inactivated Na^+ channels in the cell membrane('use-dependent' action) to reduce the rate of phase 0 depolarisation, thus causing an increase in the effective refractory

period and slowed AV conduction
        - Also produces some slowing of action potential repolarisation (class III action)
    - Abs/Distrib/Elim:
        - PO and IV
        - Half-life: 5-10 hours
        - Half is excreted unchanged by the kidney, half is metabolised by the liver
    - Clinical Use
        - Supraventricular and more usually, ventricular dysrhythmia

Class 1b

Lignocaine

- IV
- Treatment and prevention of ventricular arrhythmias immediately post MI
- Almost completely extracted from the portal circulation by hepatic first-pass metabolism
- Half-life in plasma is 2 hours
- Elimination slower if hepatic blood flow is reduced e.g. ↓ CO post MI and by ß-adrenoceptors
- Clearance has been used to measure hepatic blood flow cf. PAH clearance to measure renal blood flow
- ADR
    - Drowsiness
    - Disorientation
    - Convulsion

Phenytoin

- Anticonvulsant in seizure disorders
- No longer routinely used in arrhythmias

Class 1c

Flecainide and Encainide

- Suppress ventricular ectopic beats
- PO, long acting
- Sudden death post MI ↑ due to ventricular fibrillation.
    - Avoid post MI
- Used in prophylaxis against paroxysmal atrial fibrillation

Class 2 - ß-adrenoceptor Blockers

- Block ß-receptors
- Has some class 1 action
- May precipitate bronchospasms, negative inotropy and fatigue
- $ß_1$ - selective
    - Atenelol and Metroprolol, less bronchospasms

Class 3

Amiodarone and Sotalol

- Amiodarone used in Wolff-Parkinson-White syndrome
- SVTs and VTs
- Sotalol
    - Paroxysmal supraventricular dysrhythmias and suppress ventricular ectopics

Amiodarone

- Extensively found in tissues
- Long half-life: 10 - 100 days
- Action takes days to weeks to develop
- Loading dose for life threatening dysrhythmias
- IV central vein
- ADRs
    - Photosensitive skin rash
    - Hypo and hyperthyroidism due to high iodine content
    - Pulmonary fibrosis
    - Corneal deposits
    - Neuro. and GIT abnormalities

Sotalol

- Non-selective ß-adrenoceptor antagonist
- L-isomer active
- Prolong cardiac action potential, unlike other ß-antagonists and Q-T by delaying slow outward K+ current
- Like amiodarone can cause torsades des pointes ("twisting of the points", is a specific type of abnormal heart rhythm that can lead to sudden cardiac death. It is a polymorphic ventricular tachycardia that exhibits distinct characteristics on the electrocardiogram (ECG). Prolongation of the QT interval can increase a person's risk of developing this abnormal heart rhythm.

Class 4

Verapamil and Diltiazem

- Verapamil PO/IV

- Plasma half-life 6-8 hours
- Extensive first pass metabolism
- Care with digoxin due to displacement of digoxin from tissue binding and reduced renal elimination
- Contraindicated in Wolff-Parkinson-White syndrome
- Diltiazem has more smooth muscle relaxant effect but produces less bradycardia

Unclassified

Adenosine

- Endogenous chemical mediator
- Effects on breathing, cardiac muscle, afferent nerves and platelets
- Safer than Verapamil and short duration of action
- Effect blocked by theophyline but enhanced by dipyridamole

MoA

- Adenosine can bind to purinergic receptors in different cell types where it can produce a number of different physiological actions.
- One important action is vascular smooth muscle relaxation, which leads to vasodilation.
- This is a particularly important mechanism for matching coronary blood flow to the metabolic needs of the heart:
    a. In coronary vascular smooth muscle, adenosine binds to adenosine type 2A (A_{2A}) receptors, which are coupled to the Gs-protein.
    b. Activation of this G-protein stimulates adenylyl cyclase, increases cAMP and causes protein kinase activation.
    c. This stimulates K_{ATP} channels, which hyperpolarizes the smooth muscle, causing relaxation.
    d. Increased cAMP also causes smooth muscle relaxation by inhibiting myosin light chain kinase, which leads to decreased myosin phosphorylation and a decrease in contractile force.
    e. There is also evidence that adenosine inhibits calcium entry into the cell through L-type calcium channels. Since calcium regulates smooth muscle contraction, reduced intracellular calcium causes relaxation.

- In cardiac tissue,:
  Adenosine binds to type 1 (A_1) receptors, which are coupled to Gi-proteins.
    a. Activation of this pathway opens potassium channels, which hyperpolarizes the cell. Activation of the G_i-protein also decreases cAMP, which inhibits L-type calcium channels and therefore calcium entry into the cell.
    b. In cardiac pacemaker cells located in the sinoatrial node, adenosine acting through A_1 receptors inhibits the pacemaker current (I_f), which decreases the slope of phase 4 of the pacemaker action potential thereby decreasing its spontaneous firing rate (negative chronotropy).
    c. Inhibition of L-type calcium channels also decreases conduction velocity (negative dromotropic effect) particularly at the atrioventricular (AV) nodes.

- Finally, adenosine by acting on presynaptic purinergic receptors located on sympathetic nerve terminals inhibits the release of norepinephrine.
- In terms of its electrical effects in the heart, adenosine decreases heart rate and reduces conduction velocity, especially at the AV node, which can produce atrioventricular block
- Note, however, that when adenosine is infused into humans, heart rate increases because of baroreceptor reflexes caused by systemic vasodilation and hypotension.

Cardiac Glycosides

- Increase myocardial contractility
- Source
    - Foxglove (Digitalis spp.)

History and Chemistry

- Steroid nucleus containing unsaturated lactone
- And one or more glycosidic residue digoxin is the most important
- Plants and toads as protective venom against predators

History and Source

- William Withering 1785 in CCF
- Source:
    - Digitalis purpurea - foxglove
    - Digitalis lanata - digoxon and Digitoxin
    - Oubain - seed of straphanthus grat

Actions

- Cardiac slowing and reduced rate of conduction through the AV node
- Increase the force of contraction
- Adverse Effects
    - Block AV conduction
    - Increase ectopic pacemaker activity
- Other common AE
    - NVD
    - Confusion

MoA

- Inhibition of Na^+, K^+-ATPase
- All are potent and highly selective inhibitors of transport od Na+ and K+ across the cell membranes by

binding on the enzyme
- Increased vagal activity

Rate and Rhythm
- Slow AV conduction by increasing vagal activity via CNS action
- Useful in atrial fibrillation
- Improve ventricular filling and pumping efficiency
- Can terminate supraventricular tachycardias
- Larger doses can cause AV block, ectopic beats and bigeminy

Force of Contraction
- Inhibit Na^+/K^+ pump
- Increase Na^+ slow the extrusion of Ca^{2+} via Na^+/Ca^{2+} exchange transporter
- Increased Ca^{2+} stored in the sarcoplasmic reticulum increase Ca^{2+} released by each action potential

Pharmacokinetics
- Oubain
  - Low lipid solubility
  - Poorly BA orally
  - Short half-life of 21 hours
  - It is not bound to plasma protein and not metabolised
  - The volume of distribution is 18L/kg
- Digoxin
  - Most common prescription glycoside
  - Medium lipid solubility
  - PO BA of 75%
  - Half-life of 40 hours
  - PPB - 20 - 40%
  - <40% is metabolised
  - Volume of distribution is 6L/kg
- Digitoxin
  - Highly lipid soluble
  - >90% BA
  - Long half-life: 168hours
  - >90% PPB
  - Largely metabolised - >80%
  - Volume of distribution - 0.6L/kg

Digoxin
Kinetics
- 10% of individuals have enteric bacteria that inactivate digoxin in the gut and use of antibiotics can suddenly increase absorption
- Narrow therapeutic index
- All are widely distributed in tissue including CNS
- Volume of distribution decreases with increase in PPB

Metabolism and Excretion
- Almost $^2/_3$ digoxin is excreted unchanged
- Renal clearance proportional to Cr clearance
- Digitoxin is metabolised in the liver and excreted via the hepato-biliary route, with metabolites including digoxin going through entero-hepatic circulation
- Oubain is given parenterally and lost unchanged

Pharmacodynamics
- Direct, indirect and toxic effects
- Inhibit Na+ pump by binding on the α subunit of the enzyme
- _

Cardiac Effect
- Increase cardiac contractility by increasing intracellular Na+ and calcium
- Electrical effects on heart contraction
- Autonomic action
  - Lower doses predominantly parasympathetic with atropine like blockade particularly in the geriatrics
- Toxic levels increase sympathetic outflow

Effect On Other Organs
- Excite all excitable tissues including smooth muscle and CNS
- GIT
  - Anorexia
  - NVD
- Direct and via action on the CTZ
- Disorientation and hallucination, aberrations of colour perception and convulsions
- Gynaecomastia

Interactions
- Potassium
- Calcium

- Magnesium
- Amiodarone and Diltiazem

? How does digoxin interact with the above?

Indications

- Atrial fibrillation
  - Slow ventricular rate
- Cardiac failure in patients who remain symptomatic despite optimal use of anti-failure drugs
- Which are the drugs used in heart failure?
  - Diuretics
  - ACEI/ARBs
  - Spironolactone
  - Beta adrenoceptor blocker

Other Drugs that increase myocardial contractility

- ß1 - adrenoceptor agonists - dobutamine
  - Positive inotropic action, used in cardiogenic or septic shock
- Glucagon - ↑ cAMP
  - Used in overdose of ß-blockers
- Phosphodiesterase inhibitors
  - Amrinone and milrinone

Antihypertensives

14 June 2017 20:43

Epidemiology

- HT is the leading CV disease and the commonest cause of chronic heart disease in Kenya. Worldwide, it is the most important cause r atherosclerotic coronary artery disease and chronic heart disease, responsible for 35%- 45% annual CV morbidity and mortality.
- Affects 20% whites, 30% blacks in the US above 18 years
- Affects all ages and both sexes but prevalence increases with age, 64% at 65 - 75 years
- Prevalence increases with age, sex, race, education and other variables
- Risk of end organ damage higher with blacks and is relatively less with premenopausal women than men
- Other positive risk factors are smoking, obesity, alcoholism, hyperlipidaemia, diabetes, stress, diet and family history of HT

Classification and Aetiology

- Essential (primary) HT
  - 90% of all cases
  - No identifiable cause
- Secondary HT
  - 5-10% of all cases
- Renal disease accounts to majority of secondary HT
- Other causes
  - Cushing's disease
  - Acromegaly
  - Thyrotoxicosis
  - Coarctation of the aorta
  - Conn's disease
  - Phaeochromocytoma
  - HyperPTH
  - Oral corticosteroids/oestrogenic pills
  - Others

Arterial HT

- Systolic HT with wide pulse pressure
  - Decreased compliance of aorta - atherosclerosis
  - Increased stroke volume
  - Aortic regurgitation, thyrotoxicosis, hyperkinetic heart syndrome, fever, AV fistula, PDA
- Systolic and Diastolic HT
  - Renal-chronic pyelonephritis, glomerulonephritis, polycystic renal disease, renal artery stenosis, renin producing tumours
  - Endocrine
  - Neurogenic-psychogenic, diencephalic syndrome, familial dysautonomia, polynephritis, increased ICP, spinal cord section
  - Miscellaneous
    - Coactation of aorta, PAN, hypercalcaemia, iatrogenic
  - Unknown aetiology
    - Essential HT, toxaemia of pregnancy, acute intermittent porphyria

Genetic Factors

- Genetic hereditability about 30%
- Supported by epidemiologic data. In majority of cases genes unknown, but 3 monogenetic syndromes genes identified so far
    - Glucocorticoid remediable syndrome
        - Aldosterone high, involves 11ß-hydroxylase gene involved
    - Syndrome of apparent mineralocorticoid excess
        - A low renin state, defect in 11ß-OH steroid DH
    - Elevated aldosterone activity, with suppressed renin activity and hypokalaemia. Plasma aldosterone is however, normal.
    - Amiloride sensitive Na+ channels involved

Complications of HT

- Eye
    - Retinopathy
    - Retinal haemorrhage
    - Blindness
- CNS
    - Stroke, mainly haemorrhagic
    - Hypertensive encephalopathy which presents with severe headache, mental confusion and apprehension
    - Blurred vision
    - NV
    - Focal neurologic deficit
    - Untreated, may progress over 12 - 48 hours to seizures, stupor, coma and death
- Heart
    - HT heart disease (CCF)
    - Coronary artery disease
- Renal
    - Renal failure

HT emergencies

- ICU care
- Parenteral anti-HT used for rapid reduction of BP
- Orals should be started at the same time or as soon as practical
- In the first few hours, reduce BP by 25%, maintaining diastole at 100-110mmHg. Then slowly reduce to normal over several weeks
- Sodium nitroprusside most commonly used
- Others
    - Fenoldopam
    - Nitroglycerin
    - Labetolol
    - Calcium antagonists
    - Diazoxanide
    - Hydrallazine
- Diuretics, frusemide - always given with vasodilators
- Esmolol used in intra-operative situations

Diagnosis

- High BP of 2 or more readings at different visits
- 90% of adult cases of hypertension, have mild disease

Treatment

- Stepped care approach

    - Malignant/accelerated HT - treat immediately
    - Severe/moderate - treat gradually
    - Mild - diet/lifestyle/diuretics
    - Education
- BP = CO x PVR
- CO = HR x SV
- For mild to moderate HT, at least two abnormal reading at different times
- If lifestyle changes doesn't work, give drugs
- First drugs can be diuretics, ß-blockers or ACE inhibitors

Drugs

- Diuretics
- ß-blockers
    - Selective/Non-selective
    - α/ß inhibitors
- Sympatholytics
    - Centrally acting
    - Peripherally acting
- ACE inhibitors
- Angiotensin Receptor Blocking Agents
    - Lorsatan, etc
- Calcium channel blockers
    - Dihydropyridines
    - Diltiazem
- α-receptor blockers
    - Selective
        - Prazosin
    - Non-selective
        - Phenoxybenzamine
- Vasodilators
    - Direct
        - Hydrallazine
        - Minoxidil
        - Diazoxide
        - Fenoldopam
        - Sodium nitroprusside
- Ganglion blockers
    - Trimethaphan

Centrally Acting Sympathoplegic Drugs

14 June 2017 20:45

Classification

- Diuretics
- Sympathoplegic (sympatholytic) agents
- ACE Inhibitors
- Angiotensin II receptor antagonists
- Direct renin inhibitor
- Vasodilators
    - Includes Ca^{2+} channel blockers

Diuretics

- Thiazide diuretics (usually)
- Loop diuretics
- Potassium sparing drugs

Sympatholytics

- ß receptor antagonists
- α receptor antagonists
- Mixed α-ß receptor antagonists
- Centrally acting adrenergic agents
- _
- Direct renin inhibitor
    - _

General Mechanism of Action

- Diuretics
    - Deplete the body of sodium and water and ↓ blood volume
- Sympathoplegic agents
    - ↓ PVR
    - Inhibit cardiac function and ↑ venous pooling in capacitance vessels (the latter two effects ↓ CO)
- Direct vasodilators
    - Relax vascular smooth muscle (↓ PVR)
- Agent that block production or action of angiotensin
    - ↓ PVR

Note:

- All agents that ↓ BP by altering sympathetic function can elicit compensatory effects e.g.
    - Retention of sodium
    - Expansion of blood volume
- Therefore, sympathoplegic antihypertensive drugs are used concomitantly with a diuretic

Centrally Acting Sympathoplegic Drugs

- Clonidine
- Methyldopa
- Guanabenz
- Guanfacine

MoA

- They reduce the sympathetic outflow from the vasomotor centres in the brain stem
- They have α-agonist effects in the CNS
- Though to act as an agonist at presynaptic α_2 adrenergic receptors in the brain stem
    - This attenuates NE release and thereby reduces the output of vasoconstrictor adrenergic signals to the peripheral SNS

Methyldopa

- It's a prodrug
- It is an analogue of dopa
- Methyldopa is converted by decarboxylase (in adrenergic neurons of the brain) to α-methyldopamine and then to α-methylnorepinephrine
- α-methylNE replaces NE in adrenergic nerve vesicles (a false transmitter)
- Both metabolites stimulate central α receptors

PK

- PO, IV
- Rapid absorption
- Peak concentrations in plasma occur after 2 - 3 hours
- Peak effect is delayed for 6 - 8 hours (regardless of route of administration)
- Discrepancy between peak concentration and effects related to the time required for
    - Transport into the CNS
    - Conversion to the active metabolite
    - Storage and release of -methylNE
- Half-life - ~2 hours
- DoA of a single dose: about 24 hours
    - Once or twice daily dosing
- Excreted in the urine as
    - A sulphate conjugate (50 - 70%)
    - Parent drug (25%)
    - Other metabolites
    - Half-life: 4 - 6 hour in renal failure

AE

- Sedation
    - Most common, transient
    - If once daily dose, administer at night
- Impaired concentration
- Nightmares
- Mental depression
- Extrapyramidal signs (Parkinson's Signs)
- Vertigo
- Hyperprolactinemia
    - Lactation and gynaecomastia in men and women
- Diminished libido
- Postural (orthostatic) hypotension
- Severe bradycardia and sinus arrest
- Mouth dryness
- Positive Coombs test
    - Occurs in 20%
    - After 1 year of Rx
    - Due to autoantibodies against Rh antigen on RBC

    - 1-5% get haemolytic anaemia
    - Stop drug in those patients - resolves in weeks
    - Severe haemolysis - use glucocorticoids
- Due to those adverse effects, other antihypertensive agents are preferred
    - Still used for hypertension in pregnancy because it has a record for safety

Clonidine, Guanabenz and Guanfacine

- Stimulate the a_{2A} subtype of a_2 adrenergic receptor in the brainstem
    - Reduce sympathetic outflow in the CNS
- BP lowered by
    - ↓ CO
    - ↓ PVR
    - ↓ renal vascular resistance and maintenance of renal blood flow
- May cause postural hypotension

Clonidine

- A 2-imidazoline derivative
- Additional MoA
    - Binds to the imidazole receptor
        - May also mediate antihypertensive effects
- Other imidazolines used as antihypertensives
    - Rilmenidine
    - Moxonidine
    - Thought to act mainly through the imidazoline receptor
- a_2 agonists reduce intraocular pressure by decreasing the production of aqueous humour
- Clonidine lowers systemic BP even when applied topically to the eye
- Derivatives of Clonidine
    - Apraclonidine
        - Does not cross BBB
    - Brimonidine
        - Crosses BBB
    - Both decrease intraocular pressure with little or no effect on systemic BP
- Stimulates parasympathetic outflow
    - Slows HR
        - Also due to diminished sympathetic drive
    - Activates presynaptic a_2 receptors
        - Suppress the release of NE from post ganglionic sympathetic nerves
- IV clonidine
    - Causes an acute rise in BP
    - Thought to be due to activation of postsynaptic a_2 receptors in vascular smooth muscle
    - It is a partial agonist with relatively low efficacy at these sites
    - This is followed by a more prolonged hypotensive response
        - Due to decreased sympathetic outflow from the CNS
- Oral
    - Well absorbed
    - Oral bioavailability is nearly 100%
    - Peak concentration in plasma and the maximal hypotensive effects are observed 1 - 3 hours after ab oral dose
    - Half-life: 6 - 24 hours
    - About 50% excreted unchanged in urine
- Transdermal patch
    - The drug is released at an approximately constant rate for a week
    - 3 - 4 days are required to reach steady state concentration in plasma

- When the patch is removed, plasma concentrations remain stable for ~8 hours and then decline gradually over a period of several days

Clinical Uses

- Off label uses
  - Treatment of Tourette Syndrome
  - Ease withdrawal of narcotics, benzodiazepines, alcohol and nicotine.
  - Opiate withdrawal symptoms by reducing the sympathetic nervous system response such as tachycardia and hypertension
  - Psychiatric disorders including stress, hyper-arousal from PTSD, sleep disorders, anxiety disorders
  - Mild sedative and can be used as premedication before surgery
  - Restless leg syndrome
  - Topically used for diabetic nephropathy
  - Migraine headaches and hot flashes associated with menopause
  - Diarrhoea associated with IBD, foetal incontinence, diabetes, withdrawal-associated (including opiate), intestinal failure, neuroendocrine tumours and cholera.

Adverse Effects

- Dry mouth and sedation are common
  - Occur in at least 50%
  - May require drug discontinuation
  - May diminish in intensity after several weeks
  - Less frequent with transdermal patch because high peak concentrations are avoided
- Postural hypotension
- Less common CNS effects
  - Sleep disturbances with vivid dreams
  - Restlessness
  - Depression
- Marked bradycardia
- Erectile dysfunction
  - Both related to dose
- Contact dermatitis
  - 15 - 20%
  - Transdermal patch
- Withdrawal of Clonidine after protracted use can result in life-threatening hypertensive crisis in some patients
  - Missing 1 or 2 doses
  - Occur in 18 - 36 hours after the drug is stopped
  - There is ↑ sympathetic nervous activity
    - Headache, apprehension, tremour, abdominal pain, sweating and tachycardia
- Stop gradually while substituting other antihypertensive agents
- Also occurs with transdermal patch
- Avoid in patients who do not adhere/compliant to treatment

Guanfacine

- Oral, well absorbed after oral administration
- Volume of distribution (4-6 L/kg)
- About 50% appears unchanged in the urine
- Half-life: 12- 24 hours

Adverse Effects

- Like Clonidine
- Also withdrawal syndrome after the abrupt discontinuation

Use

- Hypertension
- ADHD in children aged 6 - 17 years

Guanabenz

- Half-life: 4 - 6 hours
- Extensively metabolised by the liver
- Consider dose adjustment in hepatic cirrhosis

AE

- Like Clonidine

Clonidine, Gunabenz, Guanfacine (Cont.)

Drug interactions

- Diuretics potentiate the hypotensive effects
- Tricyclic Antidepressants may inhibit the antihypertensive effects of clonidine
    - Mechanism of this interaction is not known

Adrenoceptor Antagonists

14 June 2017 20:48

Selected actions of Adrenoceptors

	Tissue	Actions
□1	• Vascular SM • Heart • Prostate	Contract ↑ force of contraction Contraction
$a2$	• Vascular SM	Contract
ß1	• Heart • Juxtaglomerular cells	↑ rate and force of contraction ↑ renin release
ß2	• Vascular SM (skeletal Muscles	

Propranolol and Prazosin

- Propranolol is a ß blocker, prazosin is a blocker

ß-adrenergic Receptor

- Non-selective ß-adrenergic antagonists (1st generation agents)
    - Propanolol
    - Timolol
    - Pentabutolol*
    - Levobunolol
    - Nadolol
    - Pindolol*
    - Sotolol
    - Metiprolol

*Drugs with intrinsic sympathomimetic activity

- Selective ß1 adrenergic antagonists (2nd generation)
    - Metoprolol
    - Esmolol
    - Bisoprolol
    - Atenolol
    - Acebutolol*

ß-adrenergic antagonists

- Non-selective ß-adrenergic antagonists with additional actions (3rd Gen)
    - Labetalol
    - #Cavedilol***
    - Bevantolol***
    - @Carteolol
    - Bucindolol

        Note
        - □ They also block $a1$ receptors
        - □ *** - block Ca2+ entry into smooth muscle
        - □ # - antioxidant
        - □ @ - vasodilation through release of NO
- Selective ß1 - adrenergic antagonists with additional actions (3rd Gen)

        - Betaxolol***
        - Nebivolol
        - Celiprolol*
        - Bopindolol
            - Vasodilation through release of NO

MoA

- Drugs without ISA
    - Note: BP = CO x PVR
    - Initial ↓ CO and a reflex-induced rise in PVR
        - No change in BP
        - ↑ PVR (ß2 blockade and ↑ SNS activity on α receptors)
    - PVR returns to pre-treatment levels in a few hours to days
    - Finally, there is reduced CO and normal PVR
    - ↑ TG and ↓ HDL cholesterol. Normal Total cholesterol
    - Note:
        - Lipid changes also occur with other α and ß- adrenoceptor antagonists - ?? Clinical significance
- Drugs with ISA (intrinsic sympathomimetic activity)
    - Stimulate vascular ß2-adrenergic receptors
        - ↓ PVR (vasodilation)
    - Produce < effect on resting HR and CO
- All ß blockers are equally effective for treatment for HT despite differences in
    - Lipid solubility
    - Selectivity for ß1 receptors
    - Presence of ISA
- Inhibit the stimulation of renin production by catecholamines
    - ↓ angiotensin II and aldosterone levels
- Other effects
    - Reduce RBF and GFR for a short time
    - Not associated with reduction in renal function

Propranolol

PK

- Highly lipophilic
- Oral, IV
- 30% bioavailability (FPE in liver)
    - Bioavailability ↑ by administration with food and long term use
- Volume of distribution: 4 L/kg
- Readily enters the CNS
- ~90% bound to plasma proteins
- Half-life: 3 - Hours
- Extensively metabolised in the liver
    - One metabolite has ß-blocking activity
- Excreted in urine
    - Dose not adjusted in moderate renal insufficiency
- Doses can be adjusted using reduction in:
    - HR (both at rest and during exercise)
    - BP
- Monitoring plasma is of little clinical use

AEs

- Due to beta blockade in various tissues
- Allergic reactions are rare
  - Rash, fever
- CNS
  - Sedation
  - Sleep disturbances
  - Depression
  - Psychosis
- RS
  - Worsen asthma and other forms of COAD
- CVS
  - Depress myocardial contractility
  - Severe bradycardia
  - Hypotension
- DM
  - Hypoglycaemia not detected.

Caution in patients with:

- Bradycardia
- Cardiac conduction disease
- Asthma
- Peripheral vascular insufficiency
- Diabetes Mellitus (hypoglycaemia causes SNS hyperactivity → tachycardia, palpitation, sweating, tremours)

Contraindications

- As initial drugs in hypertensive patients with CCF
  - CCF made worse by ↓ CO and ↑ PVR
  - Control the CCF first (use a drug that reduces PVR)

ß blockers

- Withdrawal syndrome
  - Occurs when propranolol is discontinued after prolonged regular use
  - Due to sympathetic hyperactivity
  - Due to up regulation or super-sensitivity of ß receptors
  - Don’t discontinue abruptly
    - Taper off drug gradually (10 - 14 days)
  - Symptoms
    - Nervousness
    - Tachycardia
    - Increased intensity of angina
    - Rebound hypertension to levels higher than those that existed before treatment
    - MI
- Treatment of HT
- Not associated with retention of salt and water so can be used alone without diuretics
- NSAIDS + Propranolol
  - Blunt the antihypertensive effect of propranolol
  - Due to inhibition of prostacyclin synthesis and retention of Na+

"Paradoxical" hypertensive responses

- Beta blockers + epinephrine
- Due to unopposed stimulation of α-adrenergic receptors when vascular ß2-receptors are blocked
- Also noted in patients with

    - Hypoglycaemia
    - Phaeochromocytoma
    - During withdrawal of clonidine
    - Cocaine abuse

Metoprolol

- Blocks ß1>ß2
- Therefore, more cardio-selective
- Thought to be better than propranolol for patients with
    - Asthma
    - DM
    - Peripheral vascular disease
- Useful in severe HT patients on vasodilators
    - Prevents reflex tachycardia
- Drugs whose doses should be adjusted in renal failure
    - Nadolol and Cartelol
    - Atenolol
    - Due to little metabolism and excretion through urine

Esmolol

- Selective ß1-blocker
- Short half-life: 9 - 10 minutes
    - Due to hydrolysis by RBC esterases
- Continuous IV infusions (titrated)
- Used for intraoperative and postoperative HT

Uses of ß receptor blocking drugs

- Hypertension
- Ischaemic heart disease
- Cardiac arrhythmias
- Heart failure
- Obstructive cardiomyopathy
- Dissecting aortic aneurysm
- Glaucoma
- Hyperthyroidism
- Migraine
- Tremours
- Anxiety
- Treatment of alcohol withdrawal
- Reduction of portal vein pressure (liver cirrhosis)

a_1- adrenergic receptor antagonist

- Prazosin
- Terazosin
- Doxazosin

a_1-adrenergic receptor antagonists

- Pharmacologic effects
- ↓ BP by dilating arterioles and veins
- There is SNS mediated reflex increase in HR and renin activity
- Cause _

Prazosin

- Oral
- Bioavailability: 50 - 70%
- 95% PPB
  - Mainly α1-acid glycoprotein
- Half-life: 3 - 4 hours
- Metabolism in the liver
- Renal excretion

α_1 blockers - Adverse Effects

- Postural hypotension (mech. Is not known)
  - First-dose phenomenon
  - Precipitous drop of standing BP in some patients sone after the first dose is absorbed (30 - 90 minutes)
- May also occur when
  - Dosage is increased rapidly
  - A second antiHT is administered
- Occurs in up to 50% of patients
- Postural hypotension
  - Therefore, the first dose should be small and be administered at bedtime
  - Introduce additional antiHT drugs cautiously
  - Note in long term treatment
    - Tolerance develops quickly
    - Check this by measuring both standing and recumbent BP
- Non-specific, mild and infrequent effects
  - Dizziness
  - Palpitations
  - Headache
  - Lassitude (Asthenia)
  - Positive antinuclear factor test (prazosin)

α_1 blockers Use

- Because of the risk of CCF monotherapy is not recommended
- Use with diuretics, ß blockers and other anti-HT drugs
- Not used for phaeochromocytoma because epinephrine can still cause vasoconstriction through α2 recetor stimulation
- Used in patients with BPH and HT

Non-selective α blockers

- Phentolamine
- Phenoxybenzamine
  - Used for treatment of phaemchromocytoma
  - Phentolamine + propranolol used in the treatment clonidine withdrawal syndrome

Uses of α blockers

- Phaechromocytoma
- HT emergencies
- Chronic HT
- Peripheral vascular disease
- Urinary obstruction
- Erectile dysfunction

Mixed adrenergic receptor antagonists

- Treatment of HT in phaechromocytoma and HT emergencies

Adrenergic Neuron Blocking Drugs

- Examples
  - Guanethidine
  - Guanadrel
  - Reserpine
  - Bethanidine
  - Debisoquine
- These drugs lower BP by preventing normal_

Guanadrel

MoA

- It specifically inhibits the function of_
- It reaches its site of action by active transport into the neuron. It uses norepinephrine transporter (NET)
- Guanadrel is then concentrated within the neurosecretory/storage vesicles where it replaces NE
- Acts as a substitute neurotransmitter
- Released by stimuli that release NE but it is an inactive neurotransmitter
- This is thought to be the principal mechanism, of its neuron-blocking action

PK

- IV
  - Initial release of NE
- Oral
  - NE is released slowly and degraded by MAO
- Contraindicated on phaeochromocytoma due to its potential for NE release
- Rapidly absorbed
- Maximum effect on BP is not seen until 4- 5 hours
- Half-life: 5 - 10 hours for the drug in plasma
- Half-life for the pharmacological effect is ≥ 10 hours
- Renal excretion
  - Impaired in renal insufficiency

Pharmacological Effects

- All therapeutic and adverse effects are due to sympathetic blockade
- Anti-HT effect is through a reduction in PVR (sympathetically mediated vasoconstriction is inhibited)
- BP reduction is modest in the supine position (sympathetic activity is usually low)
- BP falls to a greater extent during
  - Assumption of an upright posture
  - Exercise
  - Depletion of plasma volume
- In these situations, reflex sympathetic activity is a mechanism for maintaining BP
- Renal blood floe and GFR are moderately increased
  - No clinical consequence
- Renin secretion is not reduced
- Plasma volume often becomes expanded

Adverse Effects

- Symptomatic hypotension during
  - Standing
  - Exercise
  - Alcohol ingestion
  - Hot weather
- Due to lack of sympathetic compensation during these stresses
- General feeling of lassitude and weakness (↓ BP)
- Rare
  - Precipitates CCF
- Sexual dysfunction
  - Delayed or retrograde
  - Ejaculation
- Diarrhoea

Drug Interactions

- Drugs that inhibit uptake of NE inhibit the effect of G e.g.
  - Tricyclic antidepressants
  - Cocaine
  - Chlopromazine
  - Ephedrine
  - [phenylpropanolamine
  - Amphetamine

Uses

- Not used as monotherapy
- Used as an additional agent inpatients poorly controlled on two or more other agents

Guanethidine

MoA

- Similar to Guanedrel

- Drugs that block the catecholamine uptake process or displace amines from the nerve terminal block its effects
  - See previous lust
  - + phenothiazines and phenoxybenzamines
- G increases the sensitivity to the HT effects of exogenously administered sympathomimetic agents
- The hypotensive effect
  - Initially associated with reduced CO
- PVR reduced
- Compensatory sodium and water retention occurs

PK

- Long half-life: 5 days
- Gradual onset and termination of sympathoplegia - 1 - 2 weeks
- Dose adjustments after 2 weeks

Toxicity

- Postural hypotension
- Hypotension following exercise

- Delayed or retrograde ejaculation into the bladder
- Diarrhoea

Interactions

- Sympathomimetics in OTC cold preparations
  - HT
- G + tricyclic antidepressants
  - G anti-HT effect is attenuated
  - Severe HT may follow
- G can cause HT in patients with phaeochromocytoma

Reserpine

- An alkaloid derived root of a climbing shrub in India (Rauwolfia serpentina)

MoA

- Binds tightly to the storage vesicles in central and peripheral adrenergic neurons
- It inhibits the vesicular membrane associated transporter (VMAT)
- The storage vesicles are rendered dysfunctional. The nerve endings lose there ability to concentrate and store NE and dopamine
- Catecholamines leak to the cytoplasm where they are destroyed by MAO
- Little or no active NT is discharged from the nerve ending when it is depolarised
- A similar effect occurs at storage sites for 5-HT
- Recovery of sympathetic function requires synthesis of new storage vesicles
  - Days to weeks after drug discontinuation
- Its anti-HT effects are thought to be related to both its CNS and peripheral actions

Pharmacological Effects

- ↓ CO
- ↓ PVR
- Orthostatic hypotension may occur but does not cause symptoms
- HR and renin secretion falls

PK

- Little is known due to lack of an assay
- Reserpine that is bound to storage vesicles cannot be removed by dialysis
- It is 100% metabolised
- None of the parent drug is excreted unchanged

Adverse Effects

- Most are due to its effect on the CNS
  - They may occur at any time
- Most common
  - Sedation
  - Inability to concentrate
  - Inability to perform complex task
- Psychotic depression that can lead to suicide
  - Gradual onset
  - Stop reserpine
  - May persist for months after the drug is discontinued
- Night mares
- Parkinsonism symptoms due to dopamine depletion in the brain (corpus striatum)

- Nasal stiffness
- Exacerbation of PUD
    - Increases gastric acid secretion
    - May be wise to avoid in patients with PUD
    - Mild diarrhoea and GIT cramps

Use

- Rarely used as anti-HT
    - CNS adverse effects
    - Better tolerated
- Usually used with a diuretic
- Several weeks are necessary to achieve a maximum effect

Debrisoquine

- Similar to Guanethidine
- Genetic polymorphisms exist
    - CYP2D6 dependent oxidations are impaired
    - Autosomal recessive trait
    - Poor metabolisers are prone to excessive hypotension
- Abrupt cessation of treatment may lead to rebound HT

Calcium Channel Blockers

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Classification

- Dihydropridines
  - Nifedipine
  - Amlodipine
  - Isradipine
  - Nimodipine
  - Felodipine
  - Nicardipine
  - Nitrndipine
- Phenylalkylamines
  - Verapamil
- Benzothiazepines
  - Diltiazem
- Diphenylpiperazines
  - Flunnarizine
  - Trimetazidine
  - Ranolazine
- Diarylaminopropylamines
  - Bepridil
- The drugs important in HT treatment currently are verapamil, diltiazem and dihydropyridines
- The drugs are also important in treatment of
  - Angina (diltiazem and dihydrpyridines)
  - Cardiac arrhythmias
    - Verapamil
    - Diltiazem
  - Subarachnoid haemorrhage
    - Nimodipine
  - Raynauld's phenomenon
    - Nifedipine
    - Felodipine

Mechanism of Action

- Several calcium channels types are now known
  - L-type - muscles, neurons (Verapamil)
  - T-type - heart and neurons (Flunarizine)
  - N-type - neurons
  - P/Q type - cerebellar purkinje neurons
  - R-type - neurons
- L-type are the CC dominant in cardiac and smooth muscles. They are known to contain several receptor types. Dihydropyridines bind to one site, Verapamil and Diltiazem bind to closely related but different receptor in another region
- The receptors are stereo-selective
- They act on the inner side of the membranes and bind more effectively on depolarised ones
- Frequency of opening in response to depolarisation is reduced. The markedly reduced transmembrane calcium current causes smooth muscle long lasting relaxation, reduced contractility throughout the heart, decreased sinus node pacemaker rate and reduced AV node conduction velocity

- SM response to receptor operated CC are also reduced but not markedly
- Elevated levels of calcium and sympathomimetics can partially reduce the block
- Other types of CC are less sensitive to blockade by these drugs, so that neurons and most secretory glands are much less affected
- Verapamil is most effective on the heart, minimally on SM, dihydropyridines on the SM, minimally on the heart, Diltiazem moderate on both

Pharmacodynamics

- Smooth muscle
  - Vascular SM are the most sensitive.
  - Other SM - bronchiolar, GIT and uterine minimally sensitive
  - Arterioles are more sensitive than the veins
  - All CCB reduce BP. Women more sensitive to hypotensive effect of Diltiazem. Reduced peripheral vascular resistance beneficial in effort angina and in variant angina
  - Dihydropyridines differ in their potency in various vascular beds e.g. Nimodipine is more on the cerebral vasculature
- Cardiac Muscle
  - Cardiac muscle is highly dependant on normal calcium influx for normal function.
  - SA node, rate, AV node conduction velocity and cardiac mechanical function are all reduced
  - Cardiac sodium channel block is modest with Verapamil and even less with Diltiazem and negligible with dihydropyridines. Diltiazem and Verapamil block tachycardia in the calcium dependent cells
- Skeletal muscles
  - Not affected
- Cerebral vasospasm and infarct following subarachnoid haemorrhage
  - Nimodipine effective for reducing vasospasm
- Other Effects
  - Verapamil shown to reduce insulin secretion, but doses required greater than those for angina
  - Verapamil inhibits p-glycoprotein pump in cancer cells and in plasmodium
  - Has been shown to reverse resistance in vitro

Pharmacokinetics

- CCB are all orally active and characterised by high first-pass effect, high plasma protein binding and extensive metabolism.
- Verapamil and Diltiazem are also used IV. Nifedipine is available as oral, sublingual and IV preparations
- Nifedipine
  - Oral bioavailability of 45-70%
  - Half-life of 4 hours
- Amlodipine
  - Bioavailability 65 - 90%
  - Half-life of 30 - 50 hours
- Other dihydropyridines
  - Bioavailability of 10 - 25%
  - Half-lives of 2 - 12 hours
- Verapamil
  - Bioavailability of 20 - 35%
  - Half-life of 6 hours
- Diltiazem
  - Oral bioavailability of 40 - 65%
  - Half-life of 3 - 4 hours

- Excretion is mainly renal

Clinical Uses

- Angina
  - DHP
  - Diltiazem
  - Verapamil
- Arrhythmias, Supraventricular tachycardias
  - Verapamil
  - Diltiazem
- HT
  - Long acting CCB
- Raynauld's phenomenon
- Hypertrophic cardiomyopathy
- Migraine
- Dihydropyridines can be used in patients with cardiac diseases - AV Blocks
- Only amlodipine can be safely used in CCF
- In patients with low BP, only Verapamil or Diltiazem may be used
- Immediate release short acting CCB contraindicated in unstable angina
- In non-Q-wave MI diltiazem decreases frequency of post-infarction angina

Adverse Effects

- Mainly extension of therapeutic effects.
  - Cardiac depression including cardiac arrest, bradycardia, AV block and heart failure.
  - Rare in clinical use
- Short acting Nifedipine
  - Myocardial Infarction in hypertensives
- Minor adverse effects including flushing, dizziness, headaches, nausea, peripheral oedema and constipation

Interactions

- Beta blockers increase myocardial depressant effect, may worsen heart failure
- Verapamil may increase Digoxin blood levels

Inhibitors of Angiotensin

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- Include:
  - RAAS
  - High renin HT
  - ACE inhibitors
  - ARB's

Important value

- Slow diabetic complications
- Chronic renal disease. Glomerulosclerosis +/- HT
- Left ventricular hypertrophy (LVH)
- Ischaemic heart disease (IHD)/post Acute Myocardial Infarction (AMI)

Renal Artery Stenosis
In RAS, the afferent pressure is reduced by the narrowed vessel, hence autoregulation is almost exclusively dependent on changes in post-glomerular arteriolar tone.

Because ACEIs interfere with the production of angiotensin II, autoregulation is impaired, glomerular perfusion falls, renal ischaemic nephropathy develops and renal failure ensues.

Captopril

- Inhibits ACE
- Kininase II inhibition
  - Increase NO and prostacyclin
- Enalapril
  - Pro-drug de-esterified to Enalaprilat
- Lisinopril is a lysine derivative of Enalaprilat
- Other long acting prodrugs include:
  - Benazepril
  - Fosinopril
  - Moexipril
  - Perindopril
  - Quinapril
  - Ramipril
  - Trandolapril

Effects

- Decrease PVR
- No reflex sympathetic activation - safe in IHD
- Decrease proteinuria as a result of lower glomerular efferent arteriolar pressure
- CCF, AMI

Pharmacokinetics

- PO
- BA 70% - Captopril
- Metabolism - conjugation to disulphide
- <50% excreted in urine unchanged
- Distributed in most body tissue except the brain
- Half-life: 3 hours c.f. Enalaprilat 11 hours
- All except Fosinopril and Moexipril, are excreted renally

Toxicity

- First dose hypotension
- Acute renal failure - RAS bilateral/solitary kidney
- Hyperkalaemia, cough and angioedema
- Avoid in pregnancy - foetal hypotension, anuria, RF and malformations
- Neutropenia and proteinuria
- Allergic rash and drug fever

Interactions

- Spironolactone
  - Rise of K+, particularly unsafe in patients with renal failure
- NSAIDS
  - K+ rise
- Diuretics
  - ACEI blunts the normal response of aldosterone to Na+ loss.
  - Very small doses of diuretics may substantially improve the anti-HT effects

Angiotensin Receptor Blockers (ARBs)

- AT-1 receptor blockade
- Include
  - Lorsartan
  - Valsartan
  - Candesartan
  - Irbesartan
  - Eprosartan
  - Telmisartan
- Why isn't Saralasin a ARB?
- No-peptide antagonist for angiotensin 11 receptors

- MoA
  - On receptors c.f. enzymes (ACEI)
- No effects on substance P and bradykinin
- Reduction in cough and andioedema

Effects

- Relax smooth muscle
- Vasodilation
- Increase renal salt and water excretion
- Reduce plasma volume
- Decrease cellular hypertrophy

Receptors of Angiotensin II

- AT1 and AT2
- Type 1 receptor
  - Vascular and heart, brain, kidney and adrenal glomerulosa cells
  - Feedback inhibition to renin release imply increase in renin and angiotensin II during AT1 antagonism
- Type 2
  - Adrenal medulla, kidney and brain
  - They have a role in vascular development, antigrowth and anti-proliferative responses

? Question

- Review the mechanisms of action of ACEI and ARBs, note their pharmacodynamic difference in signal transduction, then compare their relative safety and difference in the side effect profiles
- Review the indications of Ca2+ blocking drugs and angiotensin blocking agents

Vasodilators

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Oral vasodilators

- Oral for outpatients
- Examples:
  - Hydralazine
  - Minoxidil

IV Vasodilators

- Nitroprusside - hypertensive emergencies
- Diazoxanide
- Fenoldapam
- Calcium channel blockers
  - Also oral
  - HT, AMI, arrhythmias
- Nitrates - angina

MoA

- Relax vascular smooth muscle or arterioles
- Reduce systemic vascular resistance
- Sodium nitroprusside and nitrates also relax veins
- Release NO - nitroprusside and nitrates, hydralazine, nitrates, histamine, Ach
- Reduction of Ca2+ channels - verapamil
- Hyperpolarisation of smooth muscle through K+ channel opening
- Activation of dopamine release

Effects

- Decrease SVR
- ↓ arteriole resistance
- ↓ MAP
- Compensatory responses mediated by baroreceptors, RAAS, catecholamines since the sympathetic reflexes are intact thus
- No postural BP ↓ or ED

Combination therapy

- That oppose the compensatory CVS reflexes

Hydralazine

- Hydrazine derivative
- Dilates arterioles but not veins
- Used with nitrates in heart failure

PK

- Well absorbed PO
- Rapid metabolised by the liver during FPE
- BA: 25% bur variable
- Acetylation, bimodal metabolism
- Half-life: 1.5 - 3 hours

- Avid binding to tissue thus DoA: >3hours
- SLE like syndrome in higher doses
- Given 3X daily
- ? List drugs that can cause an SLE like syndrome

Toxicity

- Headache
- Nausea
- Anorexia
- Palpitations
- Sweating
- Flushing
- Reflex tachycardia and sympathetic stimulation may precipitate angina and ischaemia
- SLE like syndrome with no renal involvement and reverses on drug discontinuation

Minoxidil

- PO
- K^+ channel opener
- Dilates arterioles and not veins
- Replace hydralazine in renal failure and severe HT

PK

- Reflex sympathetic stimulation
- Sodium and fluid retention
- Must be used with ß-adrenoceptor drugs and loop diuretics

Toxicity

- Tachycardia
- Palpitations
- Angina
- Oedema
- Headache
- Sweating
- Hypertrichosis
- Topical stimulation of hair growth

Sodium Nitroprusside

- IV
- HT emergencies
- Severe heart failure
- Dilates both arteriole and venous vessels

MoA

- Activation of cGMP directly by enzyme stimulation or via NO
- ↑ cGMP relaxes vascular smooth muscles
- ↓ BP in absence of CCF
- In CHF and low CO, CO ↑ due to afterload ↓

PK

- Complex of iron, CN and nitroso moiety
- Rapidly metabolised by uptake in RBCs with liberation of cyanide
- Enzyme rhodanase metabolise cyanide in presence of sulphur to less toxic thiocyanate

- Thicyanate is eliminated in the kidney
- Rapidly lowers BP
- Effect disappears 1 - 10 minutes following discontinuation
- IV infusion
- Sensitive to light
- Infusion pump

Toxicity

- Accumulation of cyanide
- Metabolic acidosis
- Arrhythmias
- Excessive hypotension
- Defect in cyanide metabolism may see toxicity in small doses, corrected by sodium thiosulphate as sulphur donor
- Hydroxycobolamin + cyanide - non-toxic cyanocobolamin
- Thiocynate toxicity
    - Weaknes
    - Disorientation
    - Psychosis
    - Muscle spasms
    - Convulsions
- Delayed hypothyroidism
- Methaemoglobinaemia

Diaxozide

- Effective and long acting
- Parenteral
- Arteriolar dilator
- Treatment of HT emergencies
- Rapid fall SVR and MAP
- MoA
    - Opens K^+ channels

PK

- Similar chemically to thiazide diuretics
- No diuretic activity
- Bound extensively to albumin and vascular tissue
- Partly metabolised
- Rest lost unchanged
- Half-life: 24 hours
- Dose: Slow titration

Toxicity

- HT ↓
- Reflex sympathetic response - angina, cerebrovascular accidents (CVA), AMI
- Inhibit insulin release
- Used in insulinoma to treat hypoglycaemia
- Unlike thiazides causes salt and water retention

Fenoldopam

- Peripheral arteriole dilator
- Post-op HT and HT emergencies

- Agonist of dopamine D_1 receptors
- Peripheral artery dilatation and natriuresis
- R-isomer active racemic form

PK

- Rapidly metabolised
- Conjugation
- Half-life: 10 minutes
- Continuous IV infusion
- Upward dose titration

Toxicity

- Reflex tachycardia
- Headache
- Flushing
- Increased intraocular pressure
    - Avoid in glaucoma

Anti-Anginal Drugs

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Heart

- Large metabolic need
- Relative poor perfusion
- Coronary blood flow/myocardial oxygen consumption

Angina

- Oxygen supply to the myocardium is insufficient for its needs
- Pain chest, arm, neck ↑ exertion and excitement
- May be due to K+, H+ and adenosine which stimulate nociceptors

Stable angina

- Predictable pain
- Fixed narrowing of the coronary vessel
- Almost always due to atheroma
- Treatment
    - Organic nitrates, ß-adrenoceptor antagonists an/or calcium antagonists
        - Statins and anti-platelets

Unstable angina

- Pain occurs with less and less exertion and culminates in pain at rest
- Pathology
    - Platelet-fibrin thrombus associated with ruptures atheromatous plaque, but without complete occlusion of th vessel
- Risk of infarction is substantial
- Aspirin halves the risk of MI
    - Heparin and glycoprotein receptor antagonists adds to this benefits

Variant Angina

- Uncommon
- Occurs at rest
- Caused by coronary artery spasms
- Usually associated with atheromatous disease
- Treatment with vasodilators e.g. organic nitrates and calcium antagonists

Antianginal drugs

- Drugs used to
    - Improve perfusion of the myocardium
    - And/or reduce metabolic demands
- Organic nitrates and calcium antagonists do both
- ß-adrenoceptor antagonists slow HR and ↓ metabolic demand

Organic Nitrates

- Amyl nitrate initial agent
- Glyceryl trinitrate
- Isosorbide mono-nitrate - longer duration of action

Actions of Organic Nitrates

- Relax vascular, oesophageal and biliary smooth muscle
- Venorelaxation and ↓ CVP i.e. reduced pre-load and ↓ SV
- Venous pooling and postural hypotension can occur
- Marked effect on larger muscular vessels than small resistance arteries
- Direct effect on coronary artery tone
- Improved myocardial oxygen consumption

MoA

- NO donor
- NO activates soluble guanylyl cyclase thus ↑ cGMP which activates protein kinase G and leads to a cascade of effect in smooth muscles, resulting to dephosphorylation of myosin light chains and sequestration od intracellular Ca^{2+} and subsequent relaxation

Tolerance

- Diminished relaxation of smooth muscle following repeated administration
- Partly due to depletion of -SH groups
- Occurs with longer acting isosorbide mononitrate and not glyceryl trinitrate
- Also occurs why glyceryl trinitrate is administered as a prolonged infusion or frequent administration of slow-release transdermal patch

Adverse Effects

- Postural hypotension
- Headaches
- Methaemoglobinaemia

PK

- Glyceryl trinitrate is rapidly inactivated by hepatic enzymes
- First pass metabolism high if taken orally
- PO, sublingual tab. Or spray
- DoA: 30 min
- Absorbed through the skin - transdermal patch
- Volatile and short shelf life once the bottle is opened
- Isosorbide mononitrtite much longer acting - 4 hours half-life
- PO
- BD a.m. and at lunch for prophylaxis
- Slow release once daily in the morning

Indications

- Stable angina
  - Prevention regular isosorbide mononitrite or sublingual glyceryl trinitrite for treatment
- Unstable angina
  - IV glyceryl trinitrite
- Acute heart failure
  - IV glyceryl trinitirite
- Chronic heart failure
  - Isosorbide mononitrite with hydrallazine when ACEI are contraindicated
- Other smooth muscle relaxation being investigated

Potassium Channel Activators

- Include
  - Nicorandil

- K+ channel activation and NO donor
- Arterial and venodilator
- ADRs
    - Headache
    - Flushing
    - Dizziness
- For patients refractory to other antianginal drugs while awaiting angioplasty

ß-adrenoceptor antagonists

- Prophylaxis of angina
- ↓ myocardial oxygen consumption
- May increase coronary spasm, thus avoided in variant angina

Ca^{2+} channel blocking drugs

- Arteriolar dilation
- Used as anti-arrhythmics, antihypertensives and antianginals
- ? Which calcium channel blocking drug would you use for arrhythmias, HT and angina?

Respiratory Pharmacology

Monday, 19 December 2016 12:21 PM

Introduction

- The respiratory system is made up of
  - The lungs
    - For gaseous exchange between the blood and inspired air
    - It is made up of the bronchial tree and alveoli
  - The respiratory passages
    - For ventilation
    - Is made up of
      - Nasal cavities
      - Nasal pharynx
      - Mouth
      - Oral pharynx
      - Larynx
      - Trachea
- The covering
  - The lungs are covered by the pleural cavity bounded by the internal and external pleural membranes and the ribcage
  - The respiratory muscles are the intercostals, the diaphragm and the neck muscles
  - The lung circulation system - pulmonary artery, capillaries and pulmonary vein
- The nares have hair and a mucous epithelium for filtering dust/particles and moistening and warming the air. The turbinates and sinuses enhance this activity. The 5th nerve supplies these areas
- The nasopharynx and oropharynx further warm and moisturise the air. In deep respiration and when the nose is blocked, the mouth is used for respiration
- The pharynx is supplied by the pharyngeal plexus and pterygopalatine ganglion
- The nasal cavity and the oral cavity is supplied by sympathetic fibres from the superior cervical ganglion, 7th nerve to glands and sensory 5th nerve
- The larynx is a valve to the lungs and also serves as the voce box. It is supplied by the 9th, 10th and 11th cranial nerve fibres
- The sympathetic fibres from the superior cervical ganglion supply the larynx
- The trachea is supplied by the recurrent laryngeal nerve and sympathetic fibres from each sympathetic trunk, but mainly from the middle cervical ganglion
- The trachea has in its walls, semi-circular cartilages, incomplete posteriorly where it is joined by smooth muscles, trachealis
- The mucosa has a psuedostratified columnar ciliated epithelium. It has many goblet cells and the cilia beat in a continuous motion setting up an upward mucous stream
- The trachea divides into the 2 main bronchi, left and right, which subdivide into lobar bronchi, segmental bronchi, sub-segmental bronchi and bronchioles until terminal bronchioles which are about 1mm in diameter.
- When the cartilages disappear the smooth muscles completely surround the airway
- Each terminal bronchiole divides into 1 or more respiratory bronchioles, on whose walls, alveoli start to appear
- The respiratory bronchioles divide into alveolar ducts which lead to atria and pulmonary alveoli
- The alveoli are lined by flattened and incomplete epithelium immediately in contact with thin walled capillaries
- An alveolar duct with its cluster of atria and alveoli, constitutes a primary lobule
- Aggregation of primary lobules form secondary lobules or broncho-pulmonary segments
- The left lung has 2 lobes and the left has 3

- The lungs are surrounded by the pleural cavity and the chest wall

Nerve Supply

- Parasympathetic fibres from the Vagus nerve and sympathetic fibres from the 2nd, 3rd and 4th para-vertebral ganglia
- They become mixed at the root of the lung and form anterior and posterior pulmonary plexuses, from which nerves are distributed to each lung in the company of the bronchi and the blood vessels
- Efferent fibres go to the smooth muscles of the blood vessels and the bronchial tree
- Pulmonary arteries receive dual innervation and stimulation causes vasodilation
- The pulmonary muscles have dual innervation;
    - Sympathetic through β_2 receptor causing bronchodilation
    - Parasympathetic causing vasoconstriction through M_2 receptors
- Glandular secretions are increased by parasympathetic stimulation of M_3 receptors
- Secretion reduced by sympathetic stimulation of α_1 and β_2 receptors
- Afferent fibres arise from bronchial tree epithelium and walls of alveoli; sensory fibres are stimulated by substances in the lumen and stretching of the alveolar walls
- Impulses are carried to the medulla which controls respiration

Control of Respiration

- Respiratory centres are in the pons and medulla. One is stimulatory, one inhibitory and one neutral
- They work in coordination and respond to lung sensory stimulation (and from other areas e.g. GIT, ear), stretch reflexes, oxygen levels, pH and to impulses from higher centres
- May be stimulated or inhibited by drugs

Common Lung Diseases

- Obstructive
    - Asthma
    - COPD (chronic bronchitis and emphysema)
    - Bronchiectasis
    - Cystic fibrosis
    - Bronchiolitis
- Restrictive - lung
    - Sarcoidosis
    - Idiopathic pulmonary fibrosis
    - Pneumoconiosis
    - Drug or radiation induced interstitial lung disease
- Restrictive - systemic
- Neuromuscular
    - Diaphragmatic weakness
    - Paralysis
    - MG
    - GBS
    - Muscular dystrophies
- Cervical spine injury
- Chest wall
    - Kyphoscoliosis
    - Obesity
    - Ankylosing spondylitis

The Drugs

- Anti-asthmatics
- Antitussives
- Mucolytics
- Respiratory stimulants - analeptics
- Others

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Drugs in Asthma

- There is chronic inflammation of the mucosa from trachea to terminal bronchioles
- Acute inflammatory episodes correspond to asthma attacks
- Chronic inflammation results in:
  - Airway oedema
  - Smooth muscle hypertrophy
  - Epithelial shedding
  - Bronchial hyper-reactivity to stimuli
  - May cause ↑ parasympathetic tone → bronchial narrowing
- Airway narrowing → airflow obstruction
- Usually reversible
- Asthma causes recurring episodes of
  - Wheezing
  - Breathlessness
  - Chest tightness
  - Coughing (night or early morning)
- The main drugs for asthma
  - Bronchodilators
    - Cause rapid relief of symptoms (relax airway smooth muscle)
  - Controllers
    - Inhibit the underlying inflammatory process
  - Quick relief drugs (bronchodilators)
    - Adrenergic receptor agonists
    - Methylxanthines
    - Anticholinergics
  - Long-term controller drugs
    - Corticosteroids
    - Long acting β_2 agonists
    - Mast cell stabilising agents
    - Leukotriene pathways inhibitors
    - Omalizumab

Methylxanthines (M)

- Examples
  - Theophylline (T)
  - Aminophylline
    - Theophylline + ethylenediamine
  - Oxtriphylline
  - Dyphylline
  - Enprofylline
  - Dosophylline
- Other examples and sources
  - Tea - contains T, caffeine and theobromine
  - Coffee - caffeine
  - Cocoa - theobromine + caffeine
- The solubility of the M is low
- Solubility is enhanced by formation of

    - Complexes e.g. aminophylline
    - Salts e.g. oxtriphylline
- These salts or complexes dissociate in aqueous solution to yield the parent M

MoA

- M inhibit phosphodiesterase (PDE) subtypes non-selectively
    - They prevent breakdown of cAMP and cGMP
    - cAMP causes
        - Bronchodilation
        - Stimulates cardiac function
        - ↓ immune and inflammatory activity and WBCs
            - By apoptosis
            - Inhibits synthesis and secretion of inflammatory mediator cells e.g. mast cells and basophils
- T is a competitive antagonist at adenosine receptors
    - Enprophylline - devoid of adenosine antagonist activity
    - Doxyphylline - < antagonist activity
        - Adenosine can
            - Cause bronchoconstriction by releasing histamines and leukotrienes
        - Adenosine receptor antagonism may be responsible for arrhythmias and seizures
- T activates histone deacetylases in the nucleus
    - Deacetylation of histones may ↓ the transcription of pro-inflammatory genes and potentiate the effect of corticosteroids
- T also inhibits synthesis and secretion of inflammatory mediators from numerous cell types
    - E.g. mast cells and basophils
- Reduce infiltration of eosinophils and T lymphocytes
- Promotes apoptosis
    - Eosinophils
    - Neutrophils
    - _
- Tolerance to bronchodilation does not develop

Organ System Effects

- RS
- CNS
    - Mild cortical arousal
        - ↑ alertness
        - Deferral of sleep (esp. caffeine)
    - Nervousness
    - Insomnia
    - High doses
        - Tremours
        - Medullary stimulation and convulsions
- CVS
    - Positive chronotropic and inotropic effects
        - ↑ catecholamine release at nerve endings (due to inhibition of pre-synaptic adenosine receptors)
        - ↑cAMP may ↑ calcium influx
    - ↑ CO
    - ↑ PVR - BP slightly raised
    - Large doses can also relax vascular smooth muscle
        - Except in cerebral blood vessels (contraction)
    - M decrease blood viscosity

        - MoA unknown
        - Pentoxifylline
            - Indicated for intermittent claudication
- GIT
    - Stimulate secretion of gastric acid and enzymes
- Kidney
    - Weak diuretic
    - Not therapeutically useful
- Skeletal muscle
    - Improve contractility and reverse fatigue of the diaphragm in patients with COPD

Pharmacokinetics

- PO, IV, IM (intense pain), rectal
- Well absorbed after PO admin.
- Absorption from rectal suppositories is slow and unreliable
- Theophylline
    - Liquids or uncoated tablets formulations are absorbed rapidly and completely
    - Peak plasma concentrations within 2 hours
    - Food slows down rate but does not limit the extent of absorption of these formulations
    - Sustained release preparations of T
        - Some formulations are completely absorbed
        - Marked interpatient variability with regard to the rate and extent of absorption
        - Food may ↑ or ↓ bioavailability
        - ∴, calibrate a given preparation in a given patient
        - Avoid substitution of sustained release preparations
    - Plasma protein bonding of T - 60%
        - It is ↓ to 40% in new-borns and hepatic cirrhosis
    - First-order elimination kinetics at therapeutic doses
    - Zero-order kinetics at higher doses
        - Due to saturation of metabolic enzymes
        - This prolongs the decline of theophylline concentrations
- M are widely distributed including
    - Placenta
    - Breast milk
- M are metabolised in the liver
- <15% administered T is recovered in the urine unchanged
- Half-life:
    - 3.5 hours in young children
    - 8 - 9 hours in adults
    - 20 - 36 hours in pre-terms
- Metabolism can also be influenced by other diseases or drugs
- The following ↑ half-life (reduce clearance)
    - Hepatic cirrhosis
    - Congestive heart failure
    - Acute pulmonary oedema, pneumonia
    - Viral infections
    - Vaccination
    - High carbohydrate diet
    - Old age
    - Drugs that inhibit enzymes
        - Cimetidine
        - Erythromycin
        - Ciprofloxacin
        - Allopurinol

        - Fluvoxamine
        - Zileuton
        - Zafrilukast
    - Reduce doses by half and monitor levels for factors that reduce clearance
- The following ↓ half-life
    - Phenytoin, barbiturates
    - Cigarette and marijuana smoking
    - Ethanol
    - Rifampin
    - Oral contraceptives
    - High protein, low carbohydrate diet
    - Barbecued meat
    - Childhood (1 - 16 years)
- Theophylline is converted into caffeine in pre-terms
- In adults, minimal caffeine is detected
- Excreted in urine

Adverse Effects

- Rapid IV aminophylline can cause sudden death due to arrhythmias
    - Inject slowly over 20 to 30 minutes
- CNS
    - Most common
        - Headache
        - Restlessness
    - Agitation
    - Nervousness
    - Tremour
    - Convulsions, death
        - Seizures can occur without prior signs
    - May cause in children
        - Behavioural disturbances
        - Learning difficulties
- CVS
    - Palpitation
    - Tachycardia
    - Arrhythmias
    - Precordial pain
- Dizziness
- NV, abdominal discomfort
- Increased acid secretion
- Diuresis
- Most effects due to PDE inhibition
- Adenosine receptor antagonism effects
    - Arrhythmias
    - Seizures
    - Diuresis
- Drugs with less adenosine receptor antagonist activity
    - < arrhythmias
    - < seizures
- Treatment of convulsions
        - Diazepam
        - Phenytoin
        - Phenobarbital
    - May be refractory to anticonvulsant therapy
        - General anaesthesia

- Ventricular arrhythmias
    - Phenytoin
    - Lignocaine
- Poisoning with sustained-release preparations of theophylline
    - Prevent continued absorption
    - Used activated charcoal
    - Sorbitol (a cathartic)
- When plasma concentrations exceed 100mg/ml
    - Haemo-perfusion is required
- Theophylline
    - Has a narrow therapeutic window
        - Requires monitoring of drug levels

Other indications for M

- Apnoea of preterm infants
- Intermittent claudication
    - Pentoxifylline
- COAD

Corticosteroids

- Examples
    - Inhaled
        - Beclomethasone
        - Budesonide
        - Flunisolide
        - Fluticasone
        - Mometasone
        - Triamcinolone
        - Ciclesonide
    - Systemic
        - Prednisone (oral)
        - Hydrocortisone (IV)
        - Methylprednisolone (IV)
        - Triamcinolone (IM)
- The major effect of corticosteroid is to switch off the transcription of multiple activated genes that encode inflammatory proteins such as cytokines
- This is through various mechanisms e.g.
    - Promote histone deacetylase-2 activity
        - Reverses histone acetylation which is associated with increased gene transcription
    - Activate anti-inflammatory genes such as
        - Mitogen-activated protein (MAO) kinase phosphatase-1
    - They increase the expression of β_2-receptors

MoA

- Inhibit production of inflammatory cytokines
- Inhibit eicosanoid synthesis
- Inhibit accumulation of basophils, eosinophils and other leukocytes in lung tissues
- Decrease vascular permeability
- Contract engorged vessels in the bronchial mucosa
- They are not bronchodilators

- The most effective anti-inflammatory medications
- Not curative
- Routes
    - Inhaled
    - IV, IM or oral - severe illness
- Effects are not immediate
    - 6 hours after initial administration
    - Maximal improvement of lung function after several weeks of treatment

General PK
- Inhaled, PO, parenteral
- Rapidly absorbed from GIT
- Rapidly distributed to all body tissues
- Cross the placenta, secreted in breast milk
- Extensively bound to plasma proteins
    - Corticosteroid globulin (mainly)
    - Albumin
- Metabolised in the liver and kidney
- Excreted in urine

Fluticasone
- Limited absorption from the GIT
- Almost complete first-pass metabolism
- Oral F is <1%
- Therefore, negligible systemic effects

Ciclesonide
- Inhaled as a prodrug
- Activated by esterases in bronchial epithelial cells
- Absorbed drug is tightly bound to serum proteins
    - Minimal access to glucocorticoid receptors
- < risk of causing skin thinning, cataracts, osteoporosis or slow growth

IM Triamcinolone
- A depot preparation
- Occasionally used in non-compliant patients
- Proximal myopathy is a major problem

Adverse Effects
- Systemic Treatment
    - Long term oral therapy is tapered to avoid adrenal insufficiency
    - Treatment for 5 - 10 days is associated with a little toxicity
        - Mood disturbances
        - ↑ appetite
        - Loss of glucose control in DM
        - Candidiasis
    - Truncal obesity
    - Bruising
    - Osteoporosis
    - Diabetes
    - HT
    - Gastric ulceration
    - Proximal myopathy
    - Depression
    - Cataract

- Inhaled
    - Reduces systemic side effects
        - 10 - 20% of the inhaled dose reaches the lungs
        - 80 - 90% is swallowed
            - Reduced by a large volume spacer
        - Systemic absorption is via the lungs and GIT
    - Higher doses of inhaled steroids are associated with systemic adverse effects
        - Adrenal suppression
        - ??Bone resorption (osteoporosis)
        - Skin thinning
        - Purpura
    - Hoarseness
    - Oral candidiasis
        - Patients gurgle water and spit after each inhaled treatment
        - Using spacer devices to ↓ drug deposition in the oral cavity
    - ?? Transient slowed rate of growth in children

Inhaled

- Used for
    - Long-term prevention of symptoms
    - Minimise acute attacks

Leukotriene Pathway Inhibitors

- 5-lipoxygenase inhibitors
    - Zileuton
- Cys-LT_1 receptor antagonists
    - Zafirlukast
    - Montelukast
    - Pranlukast

MoA

- Ref. above
- Result in
    - Bronchodilation (one third of salbutamol effect)
    - ↓ microvascular leakage
    - ↓ mucous secretion
    - ↓ WBC influx into the airways

Zafirlukast

- PO, rapid absorbed
- > 90% F
- > 99% PPB
- Metabolised in the liver by CYP2C9
- Metabolites < 10% activity of parent drug
- Half-life: ~10 hours

- Leukotriene pathway inhibitors
    - Used to prevent aspirin induced asthma
    - Inhibit exercise-induced asthma
    - Their bronchodilator effect is additive with β_2-agonists
    - They are used as add-on therapy for mild to moderate asthma, that is not controlled by β_2-agonists and inhaled steroids
    - Not all patrients respond to leukotriene modifiers
    - Try the drugs for 1 month

- If there is no improvement, stop treatment

AE

- Zileuton
  - ↑ liver enzymes
  - Reduces clearance of both theophylline and warfarin (↑ levels in blood)
- LT_1 receptor antagonists
  - Reduces clearance of warfarin

Sympathomimetic Agents

- Non-selective adrenergic agonists
  - Epinephrine (adrenaline)
  - Ephedrine
  - isoproterenol
- β_2-adrenergic receptor agonists
  - Classification
    - Short acting agents
      - Used for symptomatic relief
      - Are the most effective drugs bronchodilators
      - Include
        - Salbutamol (albuterol)
        - Metaproterenol
        - Terbutaline
        - Bambuterol (a prodrug of terbutaline)
        - Pirbuterol
    - Long acting agents
      - Used for prophylaxis
      - Include
        - Salmeterol
        - Formoterol
        - Fenoterol
        - Reproterol
        - Bitolterol

β_2-adrenergic receptor agonists

MoA

- $ß_2$-receptor stimulation → activation of adenylyl cyclase → ↑cAMP → relaxation of airway smooth muscle
- Note:
  - There is down-regulation of $ß_2$ receptor but this does not reduce the bronchodilator response as there is a large receptor reserve in airway smooth muscle cells
  - No tolerance occurs
- They increase the conductance of K^+ channels in airway muscle → membrane hyperpolarisation and relaxation
  - This is independent of adenylyl cyclase activity
- There are $ß_2$-receptors on mast cells, basophils, eosinophils, neutrophils and lymphocytes
- Stimulation → ↑ cAMP → signalling cascade that leads to inhibition of inflammatory mediator and cytokine release
  - Chronic treatment often leads to receptor desensitisation and diminution of effect
- May also inhibit microvascular leakage and airway oedema
- ↑ mucous secretion which ↑ ciliary activity
- No effect on chronic inflammation
- ↓ neurotransmission in airway cholinergic nerves by acting at presynaptic β_2 receptors to inhibit acetylcholine release

    - This may contribute to bronchodilator effects by reducing reflex cholinergic bronchoconstriction

Inhalational Route

- Produces the greatest effect on airway smooth muscle with the least systemic toxicity
- Optimal size of partices is 2 - 5µm
    - 8 - 90% of the total dose is deposited into the muoth 😂 or pharynx
    - Smaller particles are suspended in air and may be exhaled

Short acting Agents

- Administered through inhalation
    - Onset of action: 1 - 5minutes
    - Maximal bronchodilation is 15 - 30 minutes
    - DoA: 3 - 4hours
- Oral preparations
    - Terbutaline, Salbutamol and metoproterenol
- Terbutaline - SC
- Longer DoA: terbutaline: 4 - 8 hours

Long Acting
Salmeterol and Formoterol
PK

- Inhaled
- Slow onset of action: ~30min
- DoA: >12 hours
- More lipophilic than Salbutamol
    - ∴, they persist in the membrane and dissociate from the receptor slowly
- Should not be used to reverse acute symptoms of asthma
- They don't control underlying inflammation
- Bitolterol
    - Inhaled
    - Has a rapid onset of action
    - Its active metabolite is colterol
    - Used for treatment and not prophylaxis of bronchospasm

Non-selective

- Epinephrine
    - Inhalation, SC
    - Maximum bronchodilation 15 minutes after inhalation
    - DoA: 60 - 90minutes
- Ephedrine
    - PO
    - Longer DoA than epinephrine with more CNS effects
- Isoproterenol
    - Inhalational
    - Maximum bronchodilation, 😂 5 minutes after inhalation
    - DoA: 60 - 90 minutes

AE

- Skeletal muscle tremours
    - Commonest
    - β_2-receptor stimulation in skeletal muscle
    - Tolerance develops
- Hypoxeia

    - Due to ventilation-perfusion mismatch
    - Hypoxia causes vasoconstriction
    - Drugs vasodilate and shunt blood to poorly ventilated areas of the lung
    - Give oxygen
- Tachycardia
    - Through atrial β_2-receptor and myocardial β_1-receptor
    - Reflex effect from vasodilation (β_2-receptor)
- Hypokalaemia
    - β_2-receptors promote K^+ entry into skeletal muscle
    - May cause arryhthmias
- Restlessness
- Anxiety
- Nervousness
- Weakness
- Apprehension
- Metabolic effects (high doses)
    - ↑ glucose and FFA in plasma
    - ↑ insulin, pyruvate and lactate

Anti-Cholinergic Agents

MoA

- Block the effects of vagus nerve activity
    - Contraction of airway smooth muscle
    - ↑ secretion of mucus

- Examples
    - Ipratropium bromide
    - tropium
    - Oxitropium
    - Atropine (IV, inhalational)

Ipratopium Bromide

- A quaternary ammonium conpound
- Inhalational
- Poor absorption systemically and into the CNS
- Onset of action is slow
- Maximum effect: 30 - 60 minutes
- DoA: 6 - 8 hours

Tiotropium

- Inhalational
- Longer acting
    - DoA: 24 hours

- Bronchodilation is slow and less intense than that produced by adrenergic agonists
- There is variation in response between patients
    - ∴, therapeutic trials recommended
- Combination with β_2-adrenergic agonists produces greater and prolonged bronchodilation😂
- An option for patients intolerant to β-agonists and methylxanthines
    - Patient with coexistent heart disease

AE

- Side effects are not usually a problem as there is little or no systemic absorption

- The most common side effect is xerostomia
- In elderly patients, urinary retention and glaucoma occur
- Bitter taste
    - Inhaled ipratropium
    - May affect adherance
- Glaucoma
    - Direct effect on the eye
    - Nebulise with mouth piece (not face mask)
- Paradoxical bronchoconstriction by ipratropium
    - ? Hypotonic nebuliser solution
    - ? Antibacterial additives
        - Benzalkonium chloride
        - EDTA

Mast Cell-Stabilising Agents

- Also called Cromones
    - Cromolyn sodium (sodium chromoglycate)
    - Nedocromil sodium

Routes of Admin.

- Aerosol (both poorly absorbed throughout the GIT)
- Short DoA
    - Administered 4 times a day
- Swallowed drug is excreted in urine and faeces

MoA

- Alter the function of delayed chloride channels in the cell membranes
- This inhibits cell activation
- On airway nerves → inhibition of cough
- On mast cells → inhibits early response to antigen challenge
- On eosinophils → inhibits inflammatory response
- No effect on basophils which also release mediators
- Nedocromil also inhibits appearance of the late response given after mast cell degranulation has occurred
- They prevent antigen and exercise induced asthma
- Not bronchodilators
- Effective for prophylaxis
- A therapeutic trial for 4 - 6 weeks
- Young patients are more likely to respond
- Cromolyn is given 15 - 20 minutes before exposure to trigger
- Not as potent as inhaled corticosteroid
- Use of nedocromil and inhaled corticosteroids improves asthma control

AE

- Throat irritation
- Cough
- Xerostomia
- Rare
    - Chest tightness
    - Wheezing
- Prevented by inhaling a β_2 agonist before taking these drugs
- Other rare AE
    - Dermatitis

    - Myositis
    - Gastrosnteritis
    - Pulonary 😂 infiltration with eosinophiia 😂
    - Anaphylaxis

Omalizumab

- An anti-IgE monoclonal Ab

MoA

- It inhibits the binding of IgE to mast cells
- May inhibt 😂 IgE synthesis
  Does not activate IgE already bound to mast cells therefore, no mast cell degranulation

PK

- IV, SC
- SC given every 2 - 4 weeks
- F: 62% (SC)
- Half-life: ~26 days
- Metabolised in the liver
- Excreted in bile
- No significant adverse effects
- Expensive
    - Used in patients with severe dsease
- Give 3 - 4 months trial therapy to decide if effective
- Reduced frequency and severity of asthma

Other Agents

Magnesium Sulphate

- Used as an additional bronchodilator in acute severe asthma
- IV or nebulised
- Side Effect
    - Flushing
    - Nausea
- It reduces cytosolic Ca^{2+} concentration in airway smooth muscle

ANP

- E.g. Urodilatin
- Activates guanylyl cyclase (through NO) and increases cGMP, leading to bronchodilation

- Many other agents being studied for the use in asthma e.g.
    - Ultra long acting β_2-agonists
        - Inhaled indacaterol
    - Inhaled long acting antimuscarinic agents
        - Aclidinium
- Antihistamines are not recommnded in the routine management of asthma
    - Sedatives (strictly avoid)
    - Mucolytic drugs (may worsen cough)

Inhaler Techniques

- Maximal expiration
- Slow steady inhalation
- Hold breath

- Slow exhale
- With spacer, 5 - 9 breaths

The face mask
- <3 years
- Need to wash face

Bottle Spacers
- As good as valved varieties
- Easy to make
- Affordable
- 300-500ml bottles
- Can add a face mask

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Antitussive Agents

- Include
  - Cough suppressants
  - Expectorants

The Cough Reflex

- A protective reflex that helps in expelling irritant matter from the respiratory tract
- Irritation of respiratory tracts at various sites produces a tussal impulse and bronchospams which stimulates stretch receptors.
- Vagus afferent fibres and sympathetic afferents, cough centre in medulla, cough muscles.

Aetiology

- Asthma
- Allergy
- Infection
- Inflamed, enlarged tonsils
- Acute lung infections, pleural disease
- Chronic pulmonary disease
- Secondary to acute cardiac failure
- Foreign bodies (FBS) in bronchial tree, secretions
- Central stimulation
- Bronchiectasis
  - Disease where there is permanent enlargements of parts of the airways in the lungs
  - Symptoms include a chronic cough productive of mucus
- Lung abscess
- Outside respiratory tract
  - External auditory canal
  - Ear drum
  - Pericardium
  - Stomach
- Psychogenic cough

Management

- Treat cause
- Mild cough
  - No treatment unless it's persistent and irritating
- Drugs - antitussives

Anti-Tussive Agents

Classification

Classification

a. Pharyngeal demulcents, local sialogogues - syrups, linctuses
b. Drugs that increase respiratory secretions - expectorants
c. Cough suppressors - codeine, morphine.

A. Pharyngeal demulcents

- Come in the following formulations
  - Lozenges
  - Troches
  - Cough drops
  - Linctuses
- Lemon drops, candy sugar, glycerol, menthol and glycerhiza
- These agents act by stimulating the flow of saliva (best, natural demulcent) producing a protective and soothing effect
- The syrup part of most cough syrups serves the same function
- Mainly useful in
  - Coughs due to irritation of pharyngeal mucosa, above the epiglottis

Expectorants
- Direct stimulants
  - Volatile oils like eucalyptus, anise, lemon, alcohol, cedar, wood oil, crescotes, gusiscols, glyceryl guaiacolate
- Reflex expectorants
  - Act by increaing gastric reflexes which help increase respiratoey secretion
  - They iritate the gastric mucosa and in large doses, may cause NV
  - Include:
    - Saline expectorant:
      - Ammonium salts
        - NH_4Cl
        - NH_4HCO_3
      - Potassium salts
        - PI
    - Ipecacuanha
    - Alcohol vasicine, vasicinone, squill, anaphenesin
- Mixed action

Central Cough Suppressants
- Opioids
  - Codeine
  - Hydrocodone
  - Morphine
- Non-opioids
  - Noscapine, levo

B. Expectorants

3 groups

a. Direct stimulant
- Volatile oils like eucalyptus, anise, lemon, alcohol, cedar wood oil, crescotes, guaicols, glyceryl guaiacolate.
- Admin PO or inhale; stimulate respiratory fluid production.

b. Reflex expectorants
- Act by increasing gastric reflexes which help to increase the respiratory secretions.
- They irritate the gastric mucosa; cause N in large doses.
- Include saline expectorants like ammonium salts and potassium salts.
  - Ammonium salts can be given as syrups to mask the taste.
  - Best results with maximum tolerated doses; up to 300mg salt in a tincture mixture.
  - ADRs include: smell and taste; NV; metabolic acidosis.

- Potassium salts, especially potassium iodide are used.
- Acts both directly and by reflex
- Also liquefies the thick, viscous fluid that has blocked the airway.
- Typically used in chronic bronchitis, asthma and emphysema.
- Dose: 300mg tds in tincture
- ADRs(iodidism):
  i. Conjunctival swelling
  ii. Oedema of _ 😟😔😟😟😟😟😟
  iii. Lacrimation
  iv. Increase respiratory tract secretions
  v. Oedema and ulcers of the pharynx
  vi. Headaches
  vii. Skin rashes
  viii. May also cause goitre of hypothyroidism.

- Pecacuanha:
  - Tincture solution
  - Increase respiratory tract secretions
  - Lowers sputum viscosity
  - Mixture also contains emetine.
- Alkaloid vasicine, its derivative vasicinone, squill and anaphenesin:
  - Clinically used to treat cough due to respiratory tract irritations below the epiglottis.
  - Cough due to asthma
  - Cough in young children
  - Conditions with thick and viscous secretions.

c. Mixed action

C. Central Cough Suppressants.

1. Opioids:

a. Codeine
- Actions like morphine but weaker action
- Tolerance is not common and drug dependency is rare.
- Preparations include linctus of codeine, 12 mg codeine phosphate.
- Oral dose 5mls
- ADR: some constipation

b. Morphine
- Morphine and its derivatives suppress cough but in large doses.
- Relief probably comes from analgesic and euphoric actions allowing patients to tolerate the cough.
- C/I in emphysema

c. Hydrocodone
d. Hydromorphone
e. Morphine

f. Dextromethapan
- D-isomer of codeine, analogue of levophenol
- Elevates cough threshold
- Action equipotent to codeine, fewer side effects

- No analgesic or addictive properties and shares the central binding sites with caraminophen.
- Dose: 10-30mg tds (can go up to 6 times a day if the cough is intensive)

g. Levoproxyphene: similar to dextromethapan

h. Pholcodeine
   - morphine derivative with no opioid action
   - Long half-life therefore, OD or BD; longer than codeine.

1. Non - opioids
   a. Noscapine
      - A benzyl quinoline
      - Alkaloid obtained from opium
      - Has smooth muscle relaxant action
      - In large doses it acts as a bronchodilator
      - Antitussive properties similar to codeine but it causes no constipation, narcosis or addiction.
      - ADR: N important
      - 3-4 mg tds/qid
      - Highly effective - safest antitussive agent
      - Caution: very large doses can release histamine

   b. Antihistamines - diphenylhydramine, chlorcyclizine, dimethoxanate
      - Used in allergic coughs

   c. Local anaesthetics - benzonatate
      - Long chain polyglycerol derivative related to procaine.
      - Thought to act on the stretch or cough receptors in the lungs as well as centrally.
      - Usual dose: 8 mg tds

A. Misc

- Piperidone
- Ethyl dibunate
- Pimetine
- Carbetapentate
- Caraminophen
- Clophedicol.

Mucolytics

- Acetyl Cysteine
  - L-cysteine derivative.
  - Rapidly metabolised in the body
  - 10-20% solution
  - Direct administration via tracheostomy tube/bronchoscope/percutaneous intra-thoracic catheter.
  - Can also be aerosolized
  - ADR
    - ◇ Can cause bronchospasms
    - ◇ NV
    - ◇ Fever
    - ◇ Rhinorrhoea
    - ◇ Haemoptysis
    - ◇ May also react with metals and rubber.

    - Usual dose: 200ml in water tds
- Bromhexine

Decongestants

Bronchodilators:

- Ephedrine and pseudoephedrine
- Commonly mixed with cough syrups
- Useful in coughs with bronchospasms

Common cough syrups composition

- Central cough suppressant
- Antihistamine
- Expectorant
- Syrup based flavour
- Bronchodilator - sometimes
- Mucolytic - sometimes

- All cough suppressants are dangerous in excessive secretions because they accumulate and cause problems. Give with a mucolytic.
- All C/I in respiratory failure.

CNS Pharmacology

Tuesday, 17 January 2017 11:21 AM

Intro to CNS Pharmacology

Ion Channels and Neurotransmitter Receptors

- Nerve cells contain two type of receptors classified on the basis of the mechanisms of their gating:
  - Voltage-gated: these respond to changes in membrane potential.
  - Ligand-gated: Neurotransmitters exert their effect via these receptors and they can be divided into two classes
    a. **Ionotropic**
      - ◇ consists of subunits and opens when the ligand binds.
      - ◇ Are insensitive/weakly receptive to membrane potential changes.
      - ◇ Activation results in brief opening of the channel and is responsible for the fast synaptic transmission of neurotransmitters.

    b. **Metabotropic**
      - ◇ G-protein coupled receptors. Binding to this receptor results in 2nd messengers that modulate the voltage-gated channels i.e. membrane-delimited.
      - ◇ Generally affects the calcium and potassium channels.
      - ◇ They inhibit calcium function when activated and this accounts for presynaptic inhibition.
      - ◇ When they're postsynaptic they activate potassium channels resulting in slow postsynaptic inhibition.
      - ◇ They can also modulate voltage-gated channels by diffusible 2nd messengers e.g. activation of adenylyl cyclase.
      - ◇ When these receptors are activated their effects can last tens of seconds to minutes, in contrast with ionotropic receptors (milliseconds).
      - ◇ They predominate in the diffuse neuronal systems in the CNS.

The Synapse and Synaptic Potential

- The communication between neurons occurs between chemical synapses.
- The events of synaptic transmission occur as follows:
  - An action potential in the presynaptic fibre propagates into the synaptic terminal and activates voltage-sensitive calcium channels in the membrane of the terminal.
    - ◇ The calcium channels responsible for the release of transmitter are generally resistant to certain calcium channel-blocking agents but are sensitive to blockade by certain marine toxins and metal ions.
  - Calcium flows into the terminal, and the increase in intraterminal calcium concentration promotes the fusion of synaptic vesicles with the presynaptic membrane.
  - The transmitter contained in the vesicles is released into the synaptic cleft and diffuses to the receptors on the postsynaptic membrane.
  - Binding of the transmitter to its receptor causes a brief change in membrane conductance (permeability to ions) of the postsynaptic cell.
  - The time delay from the arrival of the presynaptic action potential to the onset of the postsynaptic response is approximately 0.5 m/s. Most of this delay is consumed by the release process, particularly the time required for calcium channels to open.
- When an **excitatory pathway** is stimulated, a small depolarization or excitatory postsynaptic potential (EPSP) is recorded.

- This potential is due to the excitatory transmitter acting on an ionotropic receptor, causing an increase in cation permeability.
- When a sufficient number of excitatory fibres are activated, the excitatory postsynaptic potential depolarizes the postsynaptic cell to threshold, and an all-or-none action potential is generated.
- When an **inhibitory pathway** is stimulated, the postsynaptic membrane is hyperpolarized owing to the selective opening of chloride channels, producing an inhibitory postsynaptic potential (IPSP).
    - However, because the equilibrium potential for chloride is only slightly more negative than the resting potential (~ –65 mV), the hyperpolarization is small and contributes only modestly to the inhibitory action.
- The opening of the chloride channel during the inhibitory postsynaptic potential makes the neuron "leaky" so that changes in membrane potential are more difficult to achieve.
- This is enough for an excitatory postsynaptic potential evoked under resting conditions to fail to evoke an action potential during the inhibitory action potential.
- A **presynaptic inhibition** occurs when activated, axoaxonic synapses reduce the amount of transmitter released from the terminals of sensory fibres.

SITES OF DRUG ACTION

- Virtually all the drugs that act in the CNS produce their effects by modifying some step in chemical synaptic transmission and can be divided into:
    - Presynaptic
        - ◇ Synthesis
        - ◇ Storage e.g. reserpine
        - ◇ Metabolism
        - ◇ Release e.g. amphetamines and catecholamines, capsaicin and Substance P
    - Postsynaptic
        - ◇ Uptake e.g. cocaine and catecholamines
        - ◇ Degradation e.g. anticholinesterases
        - ◇ Receptor agonism or antagonism
        - ◇ Receptor induced increase or decrease of ionic conductance
        - ◇ Retrograde signalling

Cellular Organisation of the Brain

- This is divided into two
    - Hierarchical systems
        - ◇ include all the pathways directly involved in sensory perception and motor control.
        - ◇ The pathways are generally clearly delineated, being composed of large myelinated fibres that can often conduct action potentials at a rate of more than 50 m/s.
        - ◇ The information is typically phasic and occurs in bursts of action potentials.
        - ◇ In sensory systems, the information is processed sequentially by successive integrations at each relay nucleus on its way to the cortex.
        - ◇ A lesion at any link incapacitates the system.
        - ◇ Within each nucleus and in the cortex, there are two types of cells: **relay or projection neurons** and **local circuit neurons**.
        - ◇ The excitatory substance is usually **glutamate and aspartate**.
        - ◇ The inhibitory substance is usually **GABA or glycine**.
        - ◇ The fact that this system uses so few transmitters means manipulation results in profound CNS effects.
    - Neuronal or diffuse systems
        - ◇ Contains the monoamines.
        - ◇ Also includes some peptide-containing pathways and some pathways from the reticular formation.
        - ◇ Noradrenergic cell bodies are found primarily in a compact cell group called the **locus**

caeruleus located in the cauda pontine central grey matter.

- ◇ These axons are fine and unmyelinated and conduct at about 0.5m/s and also branch repeatedly.
- ◇ They have a tangential organization in the neocortex and can monosynaptically influence a large area of the cortex.
- ◇ Most neurotransmitters utilized by diffuse neuronal systems, including norepinephrine, act—perhaps exclusively—on metabotropic receptors and therefore initiate long-lasting synaptic effects.
- ◇ Due to this, this system covers large areas of the CNS and are affected uniformly, which explains their relation to such activities as sleeping, waking, attention, appetite and emotional states.

Central Neurotransmitters

- **Amino Acids**
  - **Glutamate**
    - ◇ Acidic amino acid
    - ◇ Mediates excitatory transmission
    - ◇ Released into the synaptic cleft by Ca^{2+}-dependent exocytosis
    - ◇ The released glutamate acts on postsynaptic glutamate receptors and is cleared by glutamate transporters present on surrounding glia
      - ◆ In glia glutamate is converted to glutamine by glutamine synthetase
      - ◆ It is then released
      - ◆ The nerve terminal takes it back up
      - ◆ The glutamine is converted back to glutamate by glutaminase
    - ◇ The high concentration of glutamate in synaptic transporters is achieved by the ***vesicular glutamate transporter (VGLUT)***.
    - ◇ This excitation is mediated by activating:
      - ◆ Ionotropic receptors (based on the action of selected agonists), all composed of subunits :
        - □ α-amino-3-hydroxy-5-methylisoxazole-4-proprionicacid (AMPA)
          - ▪ Majority are permeable to K^+ and Na^+ but not Ca^{2+}.
          - ▪ Activation causes channel opening at resting membrane potential
        - □ Kainic acid (KA)
          - ▪ Not as uniformly represented as the others
          - ▪ High concentrations in the hippocampus
          - ▪ Permeable to K+ and Na^+ and in some subunit conformations Ca^{2+}.
          - ▪ Activation causes channel opening at resting membrane potential
        - □ *N*-methyl-D-aspartate (NMDA)
          - ▪ Essentially ubiquitous in the CNS (like AMPA)
          - ▪ Highly permeable to Ca^{2+} as well as K^+ and Na^+
          - ▪ In addition to glutamate binding the receptor also requires the binding of glycine at a separate site
          - ▪ Activation doesn't allow channel opening at resting membrane potential due to voltage-dependent block by extracellular Mg^{2+}
          - ▪ When the neuron is strongly depolarized, as occurs with intense activation of the synapse or activation of neighbouring synapses, Mg^{2+} is expelled and the channel opens
          - ▪ The rise in intracellular Ca^{2+} that accompanies channel opening results in a long-lasting enhancement in synaptic strength that is referred to as ***long-term potentiation (LTP)***
  - **GABA and Glycine**
    - ◇ Inhibitory neurotransmitters typically released from local interneurons

        - ◇ Neurons that release glycine are typically restricted to the spinal cord while GABA neurons occur throughout the CNS including the spinal cord
        - ◇ GABA receptors are divided into
            - ◆ $GABA_A$, which is the fast component of inhibitory neurotransmitters are ionotropic, like glycine receptors
            - ◆ $GABA_B$, which is the slow component of inhibitory neurotransmitters are metabotropic
            - ◆ The difference lies in the coupling of receptors to the ion channels
            - ◆ $GABA_B$ are restricted to the perisynaptic region and require spill over of GABA from the synaptic cleft.
- **Acetylcholine**
    - ○ Has muscarinic and nicotinic receptors
    - ○ A number of pathways contain acetylcholine, including neurons in the neostriatum, the medial septal nucleus, and the reticular formation
    - ○ Cholinergic pathways appear to have importance in cognitive functions, especially memory
- **Monoamine**s
    - ○ **Dopamine**
        - ◇ Generally exerts a slow inhibitory effect on the CNS
        - ◇ The major pathways containing dopamine include
            - ◆ the projection linking the substantia nigra to the neostriatum where antiparkinsonism drugs are thought to work
            - ◆ The projection linking the ventral tegmental region to limbic structures especially the limbic cortex where antipsychotic drugs are thought to work
            - ◆ Receptors include D_1-D_5.
            - ◆ There are four main dopaminergic pathways in the brain:
                - □ The *nigrostriatal pathway*, accounting for about 75% of the dopamine in the brain, consists of cell bodies largely in the substantia nigra whose axons terminate in the corpus striatum.
                    - ▪ These fibres run in the medial forebrain bundle along with other monoamine-containing fibres.
                - □ The *mesolimbic pathway*, whose cell bodies occur in the midbrain ventral tegmental area (VTA), adjacent to the substantia nigra, and whose fibres project via the medial forebrain bundle to parts of the limbic system, especially the nucleus accumbens and the amygdaloid nucleus.
                - □ The *mesocortical pathway*, whose cell bodies also lie in the VTA and which project via the medial forebrain bundle to the frontal cortex.
                - □ The *tuberohypophyseal (or tuberoinfundibular) system* is a group of short neurons running from the ventral hypothalamus to the median eminence and pituitary gland, the secretions of which they regulate.

    - ○ **Norepinephrine**
        - ◇ Most of these neurons are located in the local caeruleus and lateral tegmental area of the reticular formation
    - ○ **5-HT**
        - ◇ Most pathways originate in the raphe or midline regions of the pons and upper brainstem
        - ◇ Has a strong inhibitory action
- **Peptides**
    - ○ Includes:
        - ◇ Opioid peptides
        - ◇ Substance P
        - ◇ Somatostatin
        - ◇ Cholecystokinin
        - ◇ Neurotensin

        - ◇ Vasoactive Intestinal Polypeptide
        - ◇ Neuropeptide Y
        - ◇ Thyrotropin-releasing hormone
- **Nitric Oxide**
- **Endocannabinoids**
    - These ligands are not stored, as are classic neurotransmitters, but instead are rapidly synthesized by neurons in response to depolarization and consequent calcium influx.
    - In further contradistinction to classic neurotransmitters, endogenous cannabinoids can function as retrograde synaptic messengers
    - This can be transient or long-lasting depending on the pattern of activity
    - Endocannabinoids can have effects on memory, cognition and pain perception by this mechanism.

Blood-Brain Barrier

- A key factor in CNS pharmacology is the blood–brain barrier penetration of which requires molecules to traverse the vascular endothelial cells rather than going between them.
- Inflammation can disrupt the integrity of the blood–brain barrier, allowing previously impermeable drugs such as penicillin to cross.
- In general, only small non-polar molecules can diffuse passively across cell membrane so drugs can cross the barrier via:
    - Actively diffusing across the barrier
    - Transporters, which either facilitate entry into the brain or diminish it by pumping the compound from the endothelial cell interior back into the bloodstream. Such drugs include
        - ◇ Levodopa
        - ◇ Valproate
        - ◇ Various sedative histamine antagonists
- Active extrusion of drugs from the brain occurs via P-glycoprotein, an ATP-driven drug efflux transporter, and related transporter proteins.
    - Many antibacterial and anticancer drugs are excluded from the brain while some CNS-acting drugs – including certain opioid, antidepressant, antipsychotic and antiepileptic drugs – are actively extruded from the brain.
- Variation in the activity of efflux transporters between individuals is an important consideration.
- *The chemoreceptor trigger zone (CTZ) located in the area postrema in the floor of the fourth ventricle sits outside the blood-brain barrier and is an area of weakness.*

Introduction to Anti-Seizure drugs

Tuesday, 17 January 2017 11:21 AM

Introduction to Anti-Seizure drugs

Definition

- **Seizure**
  - A paroxysmal involuntary disturbance of brain function, caused by an abnormal, excessive activity of cerebral function
  - May manifest as
    - Impairment or loss of consciousness
    - Abnormal sensory disturbances
    - Autonomic dysfunction
- **Convulsion**
  - A seizure that is accompanied by motor manifestation
- **Epilepsy**
  - Recurrent (≥2) seizures unrelated to fever or an acute cerebral insult

Pathophysiology

- Genetic epilepsies
  - Mutation causes increase in excitability or brain abnormalities
    - Most genes involved here code for neuronal ion channels that are closely involved in controlling action potential generation.
    - Other genes encode proteins that interact with neuronal ion channels.
- Acquired epilepsy
  - Physical insult to the brain leads to changes that cause seizures to develop
  - Trauma, brain tumours, stroke, CNS infections, febrile seizures can all lead to development of epilepsy
- *Epileptogenesis* can arise if excitatory transmission is facilitated or inhibitory transmission is reduced (exemplified by $GABA_A$ receptor antagonists causing convulsions).
- Neurons from which the epileptic discharge originates display an unusual type of electrical behaviour termed the **paroxysmal depolarising shift (PDS)**, during which the membrane potential suddenly decreases by about 30 mV and remains depolarised for up to a few seconds before returning to normal.

Classification of Seizures

- Is based on the clinical features of seizures and associated EEG findings
- Seizures are classified into 2 broad categories
  - Partial (focal) seizures
    - Simple partial seizures
      - Focal
      - Consciousness is preserved
      - Discharge begin and may remain locally
      - Symptoms depend on brain region involvement
        - Involuntary muscle contraction
        - Abnormal sensory experience
        - Autonomic discharge
        - Mood and behaviour (psychomotor epilepsy) e.g. TLE
      - Local cerebral lesion
        - ↑ with age
    - Complex partial seizures
      - Local onset (usually in the temporal lobe) then spreads
      - Impaired consciousness
    - Partial seizures with secondary generalisation
      - Partial seizure initially followed by generalised tonic-clonic seizures
      - Loss of consciousness????

- Generalised seizures
  - Involves the whole brain
  - Includes the _
  - Generalised tonic-clonic seizures (formerly *grand mal* seizures)
    - Most common
    - Prodrome
      - Period where the patient feels unwell
    - Aura
      - Patient is able to tell they are about to have a seizure
    - Ictus
      - Strong contraction of whole musculature, involuntary cry, respiration stops, loss of sphincter control, tonic with suffused blue face ~1min (differentiates it from syncope which is a pale, ashen face. The clonic phase 2-4 min (longer than this - status epilepticus)
    - Post-ictal - sleep
    - Recovery - residual confusion
    - Aura → cry → unconsciousness → tonic phase → clonic phase
      - Tonic phase
        - Sustained powerful muscle contraction (involving all body musculature) which arrests ventilation
      - Clonic phase
        - Interchanging contraction and relaxation of musculature
  - Absence (formerly *petit mal*) seizures
    - Usually in children
    - Pathophysiology involves oscillatory feedback between the cortex and the thalamus and especially the T-type Ca^{2+} channels of thalamic neurons.
    - Less dramatic
    - More frequent times in the day
    - Momentary loss of consciousness
    - No convulsions
    - Vacant stare
  - Atonic (static/drop) seizures
    - Sudden loss of postural tone
  - Myoclonic seizures
    - Isolated momentary muscle contractions/jerks
    - No loss of postural control
    - Brief bursts of multiple spikes on the EEG
  - Infantile spasms
    - An epileptic syndrome
    - Characterised by brief recurrent myoclonic jerks (muscle spasm) of the body and limbs
    - Progressive mental deterioration
  - Tonic seizures

Principles of Drug treatment of Epilepsy

- The choice of anti-seizure drug depends on the classification of the seizure determined by the history and EEG findings

Chemical classification of AS drugs

- 2 broad classes
  - Structurally related AS drugs
  - Structurally dissimilar AS drugs

Structurally related AS drugs

- Have a heterocyclic ring structure in common
- Include most of the older AS drugs
- Classes
  - Barbiturates
    - Phenobarbital
    - Mephobarbital

        - Primidone
    - Hydantoins
        - Phenytoin
        - Mephenytoin
        - Ethotoin
    - Oxazolidinediones
        - Trimethadione
    - Succinimides
        - Ethosuximide
        - Phensuximide
        - Methsuximide
    - Acetylurea

Structurally dissimilar AS drugs

- Iminostilbenes
    - Carbamazepine
    - Oxcarbezepine
    - Eslicarbazepine
- Fatty carboxylic acids
    - Valproic acid
    - Sodium valproate
- Benzodiazepines
    - Diazepam
    - Lorazepam
    - Clonazepam
    - Nitrazepam
- Carbamate
    - Felbamate
- GABA analogs
    - Gabapentin
    - Pregabalin
    - Vigabatrin
- Phenyltriazine
    - Lamotrigine
- Nipecotic acid derivatives
    - Tiagabine
    - Retigabine
- Piracetam analog
    - Levetiracetam
- Sulfonamide derivative
    - Zonisamide
- Carbonic anhydrase inhibitor diuretic
    - Acetazolamide
- Substituted monosaccharide
    - Topiramate
- Amino-acid related compound
    - Lacosamide
- Triazole derivative
    - Rufinamide

MoA of AS drugs

- The general effect of AS drugs is to suppress repetitive action potentials in epileptic foci in the brain
- Different mechanisms are involved in achieving this effect
- Include
    - Modification of voltage-gated ion channel conductance
    - Enhancement of GABA mediated inhibitory synaptic transmission
    - Neuronal membrane hyperpolarisation
    - Reduction of excitatory glutamate mediated neurotransmission

Modification of voltage gated ion channel conductance

- Blockade of voltage gated sodium channels
  - At therapeutic concentrations, the following block voltage-gated sodium channels in neuronal membranes
    - Phenytoin
    - Carbamazepine
    - Lamotrigine
    - Zonisamide
  - Results in prolongation of the inactivated state of the sodium channel and the refractory period of the channel
  - Note:
    - Phenobarbitone, Valproic Acid and Topiramate may have similar effects in high concentrations
- Calcium channel blockade
  - The following inhibit calcium ion entry through low threshold (T-type) calcium channels
    - Ethosuximide
    - Valproic acid
    - Gabapentine
    - Pregabalin
    - Trimethadione

1. The do so especially in the thalamic neurons that act as pacemakers to generate rhythmic cortical discharge

Enhancement of GABA mediated inhibitory synaptic transmission

- Benzodiazepines
  - Interact with specific receptors on the $GABA_A$ receptor-chloride ion channel macromolecular complex to facilitate inhibitory effects of GABA
- Barbiturates
  - Also enhance the inhibitory actions of GABA but interact with a different receptor site on the chloride ion channels
- Vigabatrine
  - At therapeutic plasma levels, it irreversibly inactivates the enzyme GABA amino transaminase (GABA-T) which is important in terminating the action of GABA
    - Enhances the effects of GABA at synaptic sites
- Valproic acid
  - At high concentration inhibits GABA-T
- Tiagabine
  - Inhibits a GABA transporter (GAT-1) in neurons and glia, prolonging the action of the neurotransmitter
- Other drugs that facilitate the inhibitory actions of GABA include Felbamate and Topiramate

Neuronal membrane hyperpolarisation possibly by enhancing the potassium channel permeability

- Valproic acid
- Retigabine

Reduction of excitatory glutamate-mediated neurotransmission

- Felbamate blocks glutamate NMDA receptors
- Phenobarbitone and Topiramate block some glutamate receptors

Pharmacokinetics of AS drugs

- Generally well absorbed orally
- Good bioavailability (80 - 100%)
- Most are not highly bound to plasma proteins except
  - Phenytoin
  - Valproic Acids
  - Tiagabine
  - Benzodiazepines
- Phenytoin and Valproic Acid may displace other highly plasma protein bound drugs, including other anti-seizure drugs
- Most anti-seizure drugs are metabolised by hepatic enzymes
  - Except Gabapentin and Vigabatrin

- Some are converted to active metabolites which are also cleared by the liver e.g.
  - Primidone
  - Trimethadione
  - Benzodiazepines
- AS drugs are predominantly distributed into total body water
- Plasma clearance is relatively low
  - Many are a medium to long-acting drugs
- Some have half-life > 12 hours e.g.
  - Lamotrigine
  - Felbamate
  - Lacosamide
  - Topiramate
  - Zonisamide
  - Ethosuximide
  - Valproate
- Toxicity may occur in the presence of drugs that inhibit anti-seizure drug metabolism or displace them from plasma protein binding sites
- CYP450 enzyme inducers e.g. rifampin may lead to lowered plasma levels of AS drugs
- Phenobarbitone, Phenytoin and Carbamazepine are inducers of hepatic microsomal enzyme activity
- Compliance is better with less frequent administration
  - Hence extended release formulation which allow for OD or BD administration may offer an advantage

Choice of AS drugs

- **Tonic-Clonic Seizures**
  - DOC
    - Valproic Acid
    - Carbamazepine
    - Phenytoin
  - AD
    - Phenobarbital (or Primidone) in adults
    - Phenobarbital in infants
  - Other drugs that can be used
    - Lamotrigine
    - Topiramate
- **Partial seizures**
  - DOC
    - Carbamazepine (or oxcarbazepine)
    - Lamotrigine
    - Phenytoin
  - AD
    - Felbamate
    - Phenobarbitone
    - Topiramate
    - Valproic Acid
  - Others
    - Gabapentine
    - Pregabalin
- **Absence seizures**
  - DOC
    - Ethosuximide (block T-type Ca^{2+} channels)
    - Valproic Acid
  - AD
    - Clonazepam
  - Others
    - Lamotrigine
    - Levetiracetam
    - Zonisamide
- **Myoclonic seizures**
  - DOC
    - Valproic Acid

    - AD
        - Lamotrigine
    - Others
        - Clonazepam
        - Levetiracetam
        - Topiramate
        - Zonisamide
        - Felbamate
- **Infantine spasms**
    - DOC
        - Vigabatrin is effective and is considered DOC by many paediatric neurologists
    - Other drugs widely used are the benzodiazepines
        - Clonazepam
        - Nitrazepam
    - IM corticotrophin (ACTH) or oral prednisone have also been used to modulate inflammation
- **Status epilepticus**
    - Status epilepticus refers to continuous seizures or repetitive, discrete seizures with impaired consciousness in the inter-seizure period
    - Treatment
        - IV Diazepam or Lorazepam is usually effective in terminating attacks and providing short term control
        - For prolonged therapy, IV Phenytoin is usually used because it is highly effective and less sedating than benzodiazepines or barbiturates
            - However, phenytoin may be cardiotoxic and Fosphenytoin (water soluble) may be safer
            - Phenobarbital has also been used in status epilepticus especially in children, or for seizures not responding to Fosphenytoin treatment
        - In very severe status epilepticus that does not respond to these measures GA (Propofol or Midozolam or Pentobarbital) may be used

Other clinical uses of AS drugs

- Bipolar affective disorders (treatment of mania)
    - Valproic Acid
    - Carbamazepine
    - Lamotrigine
- Neuropathic pain e.g.
    - Post-herpertic neuralgia
        - Gabapentin
        - Pregabalin
    - Trigeminal neuralgia
        - Carbamazepine is the DOC
        - Oxcarbezepine may provide similar analgesia with fewer AE
- Migraine
    - Gabapentine
    - Phenytoin
    - Topiramate

Hydantoins

- Include
    - Phenytoin
    - Mephenytoin
    - Ethotoin
    - Phenacemide

Phenytoin

- Pharmacological effects in the CNS
- AS activity
- Does not cause general depression of the CNS
- Non-sedating
    - But may occur with large doses

- MoA
  - Major
    - Blocks sustained high frequency repetitive firing of action potentials
    - It preferentially binds to the inactivated state of the sodium channels (it also prolongs this inactivated state)
  - Alters Na^+, K^+ and Ca^{2+} conductance (alters membrane potentials)
  - Alters the concentrations of neurotransmitters
    - NE, Ach, GABA
    - Synaptic release of
      - Glutamate ↓
      - GABA enhanced
  - Paradoxical excitation of some cerebral neurons
  - ↓ Ca^{2+} permeability into cells
    - May inhibit calcium-induced secretory processes (e.g. release of hormones and neurotransmitters)
- PK
  - PO
    - Absorption is nearly complete
  - IM
    - Some precipitation occurs
    - Absorption unpredictable
    - Not recommended

- *Fosphenytoin*
  - Prodrug
  - IV, IM
  - More water soluble than phenytoin
  - It is converted to Phenytoin by phosphatases in the liver and RBCs
  - Half-life = 8-15 minutes
  - Accumulates in brain, liver, muscle and fat
  - 90% bound mainly to albumin
  - CSF concentration proportionate with plasma concentration of free drug
  - Metabolised in the liver by CYP450 (hydroxylation) and conjugation with glucuronic acid
  - Excreted through bile and urine (5% unchanged)
  - Elimination
    - First order kinetics (low plasma concentration)
      - Half-life = 24 hours
      - 5 - 7 days to reach steady state levels
    - Zero order kinetics (high therapeutic plasma concentration)
      - Half-life = 20 - 30 hours
      - 4-6 weeks to reach steady state levels
  - ∴, plasma levels ↑ disproportionately as dosage is ↑ even for levels in the therapeutic range
  - Various preparations of phenytoin differ significantly in
    - Bioavailability
    - Rate of absorption
  - Oral formulation
    - Rapid release and extended release forms
    - Vary in particle size and pharmaceutical additives
  - Patients should be treated with the drug product of a single manufacturer

AE

- IM
  - Tissue damage
- Rapid IV administration (Fosphenytoin)
  - Arrhythmias
  - Hypotension
- Phlebitis
- CNS
  - Cerebellar and vestibular effect
    - Acute overdoses
    - Chronic medication

        - Cerebellar atrophy(high doses)
        - Behavioural changes
        - Diplopia and ataxia most common dose related (↓ dose)
            - Ataxia = loss of control of voluntary movements, especially gait
        - Nystagmus (high doses)
            - Constant, involuntary movement if the eyeball
- GIT
- Gingival hyperplasia (20%)
    - Common in children and young adolescents
    - Though to be due to altered collagen metabolism
    - Toothless portion of gum are not affected
    - Can be minimised by good oral hygiene
- Coarsened facial features
- Hirsutism (concern to female patients)
- ↑ liver enzymes
- Endocrine
    - Inhibit the release of ADH
    - Inhibit insulin release → hyperglycaemia and glycosuria
- Osteomalacia
    - Altered Vitamin D metabolism
    - Inhibition of intestinal absorption of calcium
    - Associated with hypocalcemia and ↑ alkaline phosphatase levels
- Allergy
    - Skin rashes - mild to severe
    - Hepatic necrosis (Rare)
    - Neutropenia
    - Red cell aplasia, agranulocytosis and thrombocytopnia (rare)
    - Stop treatment
- Megaloblastic anaemia - altered folate metabolism
- Lymphadenopathy
- Hypoprothrombinemia
    - Phenytoin ↑ metabolism of Vitamin K
    - Haemorrhage may occur in new-borns of mothers on treatment
    - Administer Vitamin K for treatment and prophylaxis
- Fetal hydantoin syndrome
    - Abnormal facial features
    - Low birth weight
    - Distal nail hypoplasia
- Neural tube defects - folate deficiency
- Mild peripheral neuropathy
- Fever

Plasma drug levels useful in monitoring drug concentration

DI

- Drug interactions related to protein binding or to metabolism
- A decrease in protein binding
    - Hypoglobinemia
    - Renal disease
- Cimetidine, Ethanol and Isoniazid
    - ↓ phenytoin metabolism
- Phenytoin displaced from binding sites by salicylates
- Carbamazepine and Phenytoin
    - Phenytoin can induce the metabolism of Cimetidine
    - Cimetidine can also induce the metabolism of Phenytoin
- Sodium Valproate
    - ↓ Phenytoin metabolism

    - ↓ Phenytoin plasma protein binding (competes for binding sites)
- Phenytoin and Phenobarbital
    - ↑ metabolism pf phenytoin
    - ↓ metabolism of Phenytoin
    - ↓ oral absorption of Phenytoin
    - Sometimes ↑ phenobarbital levels
- Phenytoin and oral contraceptives (Ocs)
    - P induces various CYP450 isoforms
    - Ocs metabolised by CYP3A4 which is also induced
    - Unplanned pregnancy
    - Potential teratogenic effects
- Phenytoin and Warfarin
    - P inhibits the metabolism of warfarin
    - Risk of bleeding
- Effects on TFTs
    - Phenytoin has an affinity for thyroid-binding globulin
    - Confuses some tests of thyroid function
    - Measure TSH

Therapeutic uses
- Epilepsy
    - All types of partial and generalised seizures except absence seizures
- Trigeminal neuralgia
    - Carbamazepine is preferred
- Cardiac arrhythmias

Mephenytoin
- Sedative
- Its metabolite, Nirvanol, contributes most of the AS activity
- Indication and AE
    - Like Phenytoin

Ethotoin
- Low efficacy
    - Used as adjunct therapy
- May be used if hypersensitive to Phenytoin

Phenacemide
- Analog of Phenytoin
- Unknown MoA
- AE
    - Behavioural
    - Idiosyncratic reactions
        - Hepatitis
        - Nephritis
        - Aplastic anaemia

Hydantoin Contraindications
- Known hypersensitivity to the drugs
- Patients with arrhythmias
- Pregnancy (Ethotoin and Phenytoin are Pregnancy Category D)
- Lactation
- Ethotoin in patients with hepatic abnormalities

Hydantoin - Cautions
- Liver or kidney disease
- Neurologic disorders
- Phenytoin

    - Hypotension
    - Severe myocardial insufficiency

Lamotrigine
MoA
- Blocks sodium channels and inhibits the generation of repetitive action potentials
- May also inhibit Ca2+ channels
    - Possible mechanism in absence attacks
- Decreases the synaptic release of glutamate

PK
- PO
- Almost completely absorbed
- Protein binding - 55%
- Metabolised by the liver
- Half-life = 24 - 35 hours
- Excreted in urine

AE
- Most common
    - Dizziness
    - Headache
    - Ataxia
    - Blurred or double vision (diplopia)
    - NV
    - Rash
- Somnolence
- Rare
    - SJS
        - More common in paediatric than adult patients
    - DIC

Therapeutic Use
- Partial seizures
- Generalised seizures including absence and myoclonic seizures
- **Lennox-Gastaut syndrome (LGS)**
    - a type of epilepsy with multiple different types of seizures, particularly tonic (stiffening) and atonic (drop) seizures. Intellectual development is usually, but not always, impaired.
    - The EEG shows a classic pattern of background slowing and spike-wave bursts at frequencies less than 2.5 per second. The cause of the disorder is unknown in 1 out of 4 children.
    - LGS is often treatment resistant and characterised by
        - Multiple seizure types
        - Mental retardation
        - Refractoriness to other anticonvulsants
- Bipolar disorder

DI
- ↓ Lamotrigine (L) levels if used with
    - Phenytoin
    - Phenobarbital
    - Carbamazepine
    - Primidone
- L and Sodium Valproate
    - ↓ Sodium Valproate
    - ↓ L metabolism
- L and Carbamazepine (C)
    - ↑ C metabolism to form ↑ C epoxide which is toxic

Antiepileptic Drugs

Monday, 20 March 2017 11:18 AM

Introduction

- Epilepsy
  - Seizures
  - Episodic neuronal discharge
  - Cause
    - Idiopathic
    - Secondary
      - Infection
      - Trauma
      - Tumour
      - Metabolic
      - Vascular events
      - Neurodegenerative diseases
      - Drugs
  - Pathology
    - Point of origin - focus
    - May spread
    - Symptoms related to area of involvement
      - Motor cortex - convulsions
      - Hypothalamus - peripheral autonomic discharge
      - Reticular formation and brainstem - loss of consciousness
  - Diagnosis
    - Site and type
    - Electroencephalography
    - Structural abnormalities
      - MRI
      - PET - positron emission tomography

Jacksonian Epilepsy

- Named after Hughlings Jackson, a 19th-century neurologist who spoke about it in his book, *Annals of the West Riding Lunatic Asylum*.
- An epileptic focus in the motor cortex results in attacks, consisting of repetitive jerking of a particular muscle group, beginning on one side of the body, often in the thumb, big toe or angle of the mouth, which spreads and may involve much of the body within about 2 min before dying out.
- The patient loses voluntary control of the affected parts of the body but does not necessarily lose consciousness.

Manifestation of psychomotor epilepsy

- In psychomotor epilepsy the attack may consist of stereotyped purposive movements such as rubbing or patting movements, or much more complex behaviour such as dressing, walking or hair combing.
- The seizure usually lasts for a few minutes, after which the patient recovers with no recollection of the event.
- The behaviour during the seizure can be bizarre and accompanied by a strong emotional response.

Distinguish between syncope from a generalised seizure

- Syncope fits often involve the face turning pale and ashen while the face turns blue in generalised seizures due to respiration stopping for about a minute in the *tonic phase*.

Describe the typical EEG tracing in absence seizures

- The EEG pattern shows a characteristic rhythmic discharge during the period of the seizure. The rhythmicity appears to be due to oscillatory feedback between the cortex and the thalamus.
- The special properties of the thalamic neurons are dependent on the T-type calcium channels that they express.
- The pattern differs from that of partial seizures, where a high-frequency asynchronous discharge spreads out from a local focus.
- Naturally, the treatment will involve a drug that blocks T-type Ca^{2+} channel activity.

What is status epilepticus?

- A state of continuous, uninterrupted seizures requiring emergency medical intervention.

Antiepileptic Drugs

Iminostilbines

Carbamazepine

- Wide use
- Chemically related to tricyclic antidepressants (c.f. Imipramine)

MoA

- Na^+ channel blockade
- Pre-synaptically decrease synaptic transmission
- Potentiation of voltage-gated K channels

Indications

- Generalised seizures
- Partial seizures
  - E.g. psychomotor epilepsy
- Neuropathic pain
- Trigeminal neuralgia
- Bipolar disorder - controls mania

Pharmacokinetics

- PO
  - Slow but well absorbed
- Half-life:
  - 30-36 hours as single dose
- Strong inducer of hepatic enzymes
- Plasma half-life shortens to 8-15 hour when given repeatedly - it induces CYP3A4 which is also the enzyme that metabolizes it.
- Active metabolites (carbamazepine epoxide)
- Slow release preparations to ↓ ADRs
  - Avoids high concentration peaks
- Peak concentration 6-8 hours
- Tolerability ↑ by giving drug after meals
- PPB 70%
- Volume of distribution - 1L/Kg

Adverse Effects

- Drowsiness, dizziness and ataxia
  - Therapeutic doses may not be sedative
- Water retention - hyponatraemia
- Severe bone marrow depression - neutropenia
- Hypersensitivity reactions

Cytochrome P450 inducer

- ↑ metabolism of Phenytoin, oral contraceptives and warfarin
  - Review possible interaction of carbamazepine with the above
  - ? Would you initiate carbamazepine using loading dose or small doses gradually escalated
    - Small doses gradually escalated are advised; when adequate control is realised, it should be gradually decreased to the effective minimum dosage

Drug Interactions

- Increase metabolism of primidone, phenytoin, Ethosuximide, Valproate, Clonazepam
- Phenobarbitone and Phenytoin ↑ carbamazepine disposition
- No interaction causing displacement_

Others

- Retrospective case control studies have shown people of Chinese ancestry have an increased risk of developing SJS/TEN due to the presence of an inherited variant of the HLA-B gene, HLA-B*1502 - in fact, if this allele is present in a person of any ethnicity the risk is increased.

Oxcarbazepine

- Prodrug metabolised to compounds closely resembling Carbamazepine
- _

PK

- Half-life
  - 1-2 hours
- Eslicarbazepine metabolite last 8-12 hour c.f Carbamazepine
- Excreted as glucuronide

Why Oxcarbazepine?

- Less efficacious
- Less ADRs, fewer hypersensitivity
- More hyponatraemia
- Less enzyme induction not always seen

Succinimides

- Include
  - Ethosuximide
  - Phensuximide
  - methsuximide

Ethosuximide

- Active against pentylene-tetrazole induced convulsions in animals and absence seizures

MoA

- Inhibition of T-type calcium channels
- Reducing current on the low threshold T-type Ca^{2+} channels
- Act at the thalamus

PK

- Well absorbed PO
- Peak
  - 3-7 hours0pp
- Not PPB
- Metabolised by hydroxylation
- Excretion is slow

AE

- Nausea, anorexia
- Lethargy, dizziness
- May precipitate tonic-clonic seizures
- Hypersensitivity reactions

Drug Interaction and Toxicity

- Clearance ↓ by Valproate
- Gastric distress, NV
- Lethargy, fatigue, headache and dizziness
- Hiccough and euphoria
- _

Barbiturates

Phenobarbital (Gardenol, Luminal)

Chemistry

- Is a derivative of barbituric acid
- To the nucleus, barbituric acid is added a phenyl group at position 5
- An acidic compound of pKa of 7.3 - 7.9 and affected by small pH changes
- Its 3D conformation is similar to Phenytoin
- Both are effective against GTS

MoA

- Not clear
- Enhances inhibitory responses in the GABA channels and suppresses excitatory responses in the other channels
- Action on GABA channels
  - In high doses, it suppresses high frequency repetitive firing in neurons through sodium conductance
- Also blocks calcium currents in the L and N type calcium channels
- Blocks excitatory responses induced by glutamate through the AMPA glutamate receptors

PK

- Given PO and parenterally
- PO
  - Well and rapidly absorbed
  - Lipid soluble
  - Weakly acidic
- Following absorption, well distributed to CNS with rapid onset of action followed by a phase of redistribution from the brain to highly perfused tissues e.g. skeletal muscles and finally to the poorly perfused tissues e.g. adipose tissue
- Volume of distribution
  - 0.5L/Kg
- PPB - 50%
- Crosses the placental barrier
- Metabolism
  - In the liver
  - Involves oxidation at the C5 position, producing acids and ketones which are then conjugated to glucuronic acid (urine excretion)
  - Also glycosylated at the L1 and N3 positions
- 20 - 30% excreted in the urine unchanged
- Half-life is variable
  - 80 - 120 hours
  - May be 4 - 5 days in neonates
  - 40 hours in children

Therapeutic Uses

- Therapeutic levels are 20 - 40µg/ml obtained with the 30 - 180ml/d in 1-2 divided doses in adults, 3-8ml/kg/day in children and 3-4mg/day in neonates
- Give IV.IM 50 - 200 mg stat and then repeated PRN, maximum of 600mg in status epilepticus

Indications

- Generalised tonic-clonic seizures
- Used in absence seizures
- In myoclonus
- Partial seizures
- Childhood epilepsy syndromes like Lennox-Gestaut syndrome
- Status epilepticus
- Lung maturation in premature infants

Caution
- Renal and hepatic disease
- In geriatrics
  - Instead of sedation may cause excitation with confusion and restlessness
- In patients with pain
  - May worsen the pain
- In debilitated patients
  - Malnourished children
  - May be subject to severe respiratory failure

Contraindications
- Acute intermittent porphyria patients
- Patients prone to drug abuse
- Avoid in children with hyperkinetic syndromes

Drug Interaction
- Do not take with alcohol
  - Worsen side effects
- May induce liver enzymes and induce the following drug breakdowns
  - Steroids
  - TCAs
  - Doxycycline
  - Vitamin D
  - Oral contraceptives
  - Sulpthime
    - A common sweetener in food and drinks

Adverse Effects
- Can cause depression and mental retardation in children
- Tolerance and dependence
- High doses will cause nystagmus and ataxia
- Drowsiness, lethargy and depression
- Allergic skin rashes
- Paradoxical excitement, restlessness and confusion in the elderly
- Hyperkinesia
- Folate responsive megaloblastic anaemia
- Hepatitis - rare
- Photosensitive dermatitis

Deoxybarbiturate

Primidone (Mysolin)

Chemistry
- The oxygen in the 2 position is replaced by carbon
- Broken down to phenytoin and phenylethylmalonic acid (PEMA)
  - PEMA also active

MoA
- Thought to be due to the two metabolite and mother molecule
- The Primidone effect is weaker than the phenytoin effect
- Half-life of PEMA is 8-12 hours and for Phenobarbital is 80-120hours and Primidone is 6-8 hours

Indications

- Essential tremors in the elderly
- Partial seizures with secondary generalisation
- Lennox Gastaut syndrome
- Absence seizures

Sodium Valproate

- Is also used as the free acid, valproic acid
- Valproic acid is fully ionised a body pH
    - Therefore, the active form of the drug may be assumed to be valproate ion regardless of whether valproic acid or its salt is administered

Chemistry

- Valproic acid is a simple branched chain carboxylic acid
- The amides and esters of valproic acid are also active anti-seizure agents

MoA

- The time course of Valproate's anticonvulsant activity, appears to be poorly coordinated with blood or tissue levels of the parent drug
- Like phenytoin and Carbamazepine, Valproate blocks sustained high frequency repetitive firing of neurons in culture at therapeutically relevant concentration
- Its action against partial seizures may be a consequence of this effect on sodium currents
- Blockade of NMDA receptor mediated excitation may also be important
- There are increased levels of GABA in the brain after administration of Valproate
    - The mechanism of this increase is unclear
- Valproate facilitates glutamic acid decarboxylase (GAD), the enzyme responsible for GABA synthesis
- It may also have an inhibitory effect on the GABA transporter, GAT-1
- At very high concentrations, Valproate inhibits GABA transaminase in the brain to block degradation of GABA
- It is a potent inhibitor of histone deacetylase
    - Through this mechanism, it changes the transcription of many genes

Pharmacokinetics

- It is well absorbed after oral administration with a bioavailability of >80%
- Peak blood levels
    - 1-4 hours
- Food may delay absorption and decreased toxicity ay result if the drug is given after meals
- It is 90% PPB, although the bound fraction is fairly reduced at blood levels >150µg/ml
- Valproate is both highly ionised and highly protein bound
    - Therefore, its distribution is essentially confined to extracellular water with a volume of distribution of ~ 0.2L/Kg
- Its clearance is low and dose dependent
- 95% of Valproate undergoes hepatic metabolism, mainly by glucuronidation and ß-oxidation
- Metabolism by CYP2C9 and CYP2C19 accounts for a minor portion of its elimination
- Some of its metabolites are nearly as potent anti-seizure agents as the parent drug
- Half-life
    - 9-18 hours
- ~20% of the drug is excreted as a direct conjugate or Valproate
- <5% is excreted unchanged

Formulations available for clinical use

- The sodium salt of Valproate is marketed as a tablet and is quite hygroscopic (tendency to absorb and hold water molecules).
    - It is also available for paediatric use
- The magnesium salt is also available and is considerably less hygroscopic
- An enteric coated tablet of divalproex sodium is also marketed
    - This improved product is 1:1 coordination compound of Valproic acid and Sodium Valproate
    - It is bioavailable as the Valproate capsule but is absorbed much slowly and is preferred by many patients

    - Peak concentrations following administration of the enteric coated tablets, occur in 3-4 hours
- Various extended release preparations are available
    - However, not all are bioequivalent and may require dosage adjustment

Therapeutic Levels and Dosage
- The initial daily dose is usually 15mg/kg. this is increased at weekly intervals by 5-10mg/kg/day
- Dosages of 25-30mg/kg/day in divided doses may be adequate in some patients, but others may require ≥ 60mg/kg/day
- Therapeutic levels of Valproate range from 50-100µg/ml

Clinical Use of Valproate
- It is very effective against absence seizures
    - Ethosuximide is the DOC when absence seizures occur alone
    - However, Valproate is preferred when the patient has concomitant generalised tonic-clonic seizures
    - Ethosuximide is preferred for uncomplicated absence seizures because of Valproate's idiosyncratic hepatotoxicity
- Valproate is unique in its ability to control certain types of myoclonic seizures
    - In some case, the effect is very dramatic
- Valproate is effective on GTCS, esp. those that are primarily generalised
- A few patients with atonic attacks may also respond
- Some evidence suggests that it is effective in partial seizures

Other uses of Valproate
- Management of bipolar mood disorder
- Migraine prophylaxis

Drug Interactions
- The clearance of Valproate is dose dependent due to changes in both the intrinsic clearance and protein binding
- At higher doses, there is an increased free fraction of valproate, resulting in lower total drug levels than expected
    - It might be clinically useful, therefore, to measure both total and free drug levels
- Valproate displaces Phenytoin from plasma proteins
- It also inhibits the metabolism of the following drugs, leading to their higher steady-state concentrations
    - Phenobarbital
    - Phenytoin
    - Lamotrigine
    - Carbamazepine
    - Lorazepam
- The inhibition of Phenobarbital metabolism may cause its levels to rise steeply causing stupor or coma

Adverse Effects
- The most common dose related AE are transient GIT symptoms such as NV, abdominal pain and heartburn, which occur in approx. 16% of patients
    - The drug should be started at a low dose and increased gradually to avoid these symptoms
- The CNS AE include sedation, ataxia and tremor
    - Sedation is uncommon with valproate alone, but may be significant when Valproate is added to Phenobarbital
    - A fine tremor is frequently seen at higher levels
- Valproate causes idiosyncratic hepatotoxicity, which may be severe
    - Its risk is greatest for patients <2 years old, and for patients taking multiple medications
    - Initial AST values may be normal in susceptible patients
        - These levels eventually become normal
    - Most fatalities occur within 4 months after treatment initiation
    - It is recommended to treat a patient with oral or IV L-carnitine as soon as severe hepatotoxicity is suspected
    - Careful monitoring of LFTs is recommended when starting the drug
        - The hepatotoxicity is reversible in some patients if the drug is withdrawn
- The other observed idiosyncratic response with Valproate is thrombocytopenia_
- Increased incidence of spina bifida, CVS, orofacial and digital abnormalities in offspring of women who took Valproate during pregnancy

- Other reversible AE seen in a small number of patients
  - Weight gain
  - Increased appetite
  - Alopecia
- Note:
  - Valproate is an effective and popular AS drug and only a small number of patients have had severe toxic effect from its use

Oxazolidinediones

- Include
  - Trimethadione
  - Paramethadione
  - Dimethadione
- The use of the above is currently very limited since the introduction of succinimides

Chemistry

- They contain an oxazolide heterocyclic ring
- They are similar in structure to the older AS drugs
- The structure includes only short chain alkyl substituents on the heterocyclic ring, with no attached phenyl group

MoA

- Trimethadione raises the threshold for seizure discharges following repetitive thalamic stimulation
- Trimethadione and its active metabolite, Dimethadione, have the same effect on thalamic calcium currents, as Ethosuximide (reducing the T-type calcium current)
  - Suppression of absence seizures is likely to depend on inhibiting the pacemaker action of the thalamic neurons

PK

- Trimethadione is rapidly absorbed w/ peak levels reached within an hour of admin.
- It is not PPB
- It is completely metabolised in the liver by demethylation to dimethadione, which may exert the major anti-seizure activity
- Dimethadione has a very long half-life of 240 hours (10 days)
- The therapeutic plasma level range for Trimethadione has never been established
  - Trimethadione blood levels >20µg/ml and dimethadione levels >700µg/ml have been suggested
- A dosage of 30mg/kg/day of Trimethadione is necessary to achieve these levels in adults

AE

- The most common and bothersome dose related adverse effect is sedation
- Trimethadione has been associated with many other toxic adverse effects, some of which are severe
- These drugs should not be used during pregnancy

Benzodiazepines, Gabapentin, Vigabatrin and Other Anti-Seizure Medications

Tuesday, 21 March 2017 2:13 PM

- BDZs are characterised based on elimination half-life
  - Short-acting (half-life: 1-12 hours
    - Midazolam
    - Triazolam
    - Brotizolam
  - Intermediate acting (half-life: 12-40 hours)
    - Alprazolam
    - Lorazepam
    - Temazepam
    - Estazolam
    - Flunitrazepam
    - Nitrazepam
    - Lormetazepam
  - Long-acting (half-life: 40-250 hours)
    - Diazepam
    - Flurazepam
    - Chlordiazepam
- BDZ are usually used as sedative hypnotics
- 6 compounds also have anti-seizure properties
  - Diazepam
  - Lorazepam
  - Clonazepam
  - Clorazepate dipotassium
  - Clobazam
  - Nitrazepam

PK

- Clorazepate is a prodrug that is converted to desmethyldiazepam (Nordiazepam)
- Cross placental barrier in pregnancy and may depress foetal vital sign
- Metabolised via CYP3A4 to active metabolites (e.g. Desmethyldiazepam, half-life: 40 hours, active metabolite of Diazepam and Clorazepete)
- Excreted in urine

MoA

- BDZs bind to BZ receptors on the GABA-BZ receptor complex, potentiating the effects of GABA
- This results in hyperpolarisation at target neurons, making them less responsive to excitatory stimuli

_

Clonazepam

_

Clorazepate Dipotassium

- Adjunct in treatment of complex partial seizures in adults
- Side effects
  - _

Clobazam
- Causes less sedation than other BDZs
- Half-life
  - 18 hours
- Active metabolite
  - Norclobazam
- Approved for he treatment of Lennox-Gastaut Syndrome

Nitrazepam
- Less potent than Clonazepam
- Useful in myoclonic seizures and infantile spasms

Clinical Applications
- Anxiolytic
  - GAD, PTSD, OCD
  - Panic disorder
  - Specific phobias
- Anticonvulsant
- Muscle relaxant
- Sleep aid
- Pre-operative anaesthesia

Limitations of BDZs
- Are potent anticonvulsant agents but are limited by:
  - Marked sedative effect
    - Children may have paradoxical hyper excitability instead
  - Tolerance
    - Seizures may respond initially but recur after several months of therapy

Toxicity
- CNS
  - Drowsiness
  - Impaired judgement
  - Reduced motor skills
  - Anterograde amnesia
  - Confusion in the elderly
- Hypersensitivity reactions e.g. rash
- Teratogenicity

Drug Interactions
- Additive effects with other CNS depressants, alcohol, opioids, phenothiazines and TCAs

Gabapentin and Pregabalin

Gabapentin
- Consists of a GABA molecule covalently bound to a lipophilic cyclohexane ring
- Its high lipid solubility facilitates transfer across the BBB
- Pregabalin is a related compound, consisting of a GABA molecule covalently bound to isobutane

MoA
- Do not directly act in GABA receptors
- However, may modify synaptic release of GABA

- Gabapentin is transported into the brain by the L-amino acid transporter → binds to the $a_2\delta$ subunit of voltage gated calcium channels → ↓Calcium entry → ↓ presynaptic _

PK
- Both are well absorbed after oral dosing
- Not metabolised in humans
  - Less drug-drug interactions
- Not PPB
- Excreted unchanged in urine
- Half-life:
  - 6 hours
- No known interactions with other anticonvulsants

Therapeutic Uses - Gabapentin
- Adjunct against partial seizures and GTCS
- Others
  - Migraine
  - Chronic pain
  - Bipolar disorder
  - Post herpertic neuralgia

Therapeutic Uses - Pregabalin
- Effective for partial seizures, w/ and w/o secondary generalisation (adjunct
- Painful diabetic peripheral neuropathy
- Post-herpertic neuralgia
- Fibromylagia
- Generalised anxiety disorder

Toxicity
- May cause somnolence, dizziness, ataxia and fatigue (resolve within 2 weeks)

Vigabatrin
- Structural analog of GABA
- Irreversibly inhibits the major degradative enzyme for GABA (GABA-transaminase)
- This leads to increased concentrations of GABA in the brain, enhancing GABA-mediated inhibition of impulses

Therapeutic Uses
- Adjunctive therapy of refractory partial complex seizures in adults
- Infantile spasms

Toxicity
- May cause progressive and permanent bilateral vision loss
- Thus must be reserved for patients who have failed several alternative therapies
- Other toxicities
  - Dizziness
  - Drowsiness
  - Weight gain
  - Agitation
  - Confusion
  - Psychosis

Topiramate

- Is a substituted monosaccharide

MoA

- Blocks voltage-gated sodium channels
- Potentiates inhibitory effect of GABA, acting at a different site from BDZ or barbiturates

PK

- 80% bioavailability
- Absorption not affected by presence of food
- 15% PPB
- No active metabolites
- Primarily excreted unchanged in the urine
- Half-life:
    - 20-30 hours

Uses and Toxicity

- Useful as monotherapy in partial and GTCS and migraines
- Toxicity
    - Somnolence
    - Fatigue
    - Dizziness
    - Cognitive slowing
    - Paraesthesia
    - Nervousness
    - Urolithiasis
    - Confusion
- Acute myopia and glaucoma may require prompt drug withdrawal

Other AS agents

- Zonisamide
- Rufinamide
- Lacosamide
- Acetazolamide

Sedative and Hypnotic Drugs

Thursday, 23 March 2017 8:35 AM

1. Benzodiazepines e.g. Diazepam, Clorazepam & Clordiazepam
2. Beta adrenoceptor antagonists e.g. Propranolol
3. Anti-Seizure Drugs
    - Examples
        - Gabapentin
        - Pregabalin
        - Tiagabine
        - Valproate
        - Levetiracetam
    - They are effective in the treatment of generalised anxiety disorder
4. Buspirone
    - Partial agonist at 5-HT_{1A} receptors
5. Some atypical antipsychotic agents such as Olanzepine, Risperidone, Quetiapine and Zipresidone
    - May be effective in generalised anxiety disorder and PTSD
    - However, their incidence of SEs may be greater than with other anxiolytic drugs
6. Antidepressants
    - Effective in the treatment of
        - Generalised anxiety disorders
        - Phobias
        - Social anxiety disorder
        - PTSD
    - They include the following:
        - SSRIs e.g. Fluoxetine, Paroxetine and Sertraline
        - SNRIs e.g. Venlafaxine and Duloxetine
        - Older antidepressants
            - TCAs
            - MAOIs
    - SSRIs are preferred because they have less side effects
    - Antidepressants have the additional advantage of reducing any depression that may be associated w/ anxiety

Chemical Classification of Hypnotics

- Melatonin receptor agonists
    - Include
        - Melatonin
        - Ramelteon
        - Tasimelteon
    - Are agonists at MT1 and MT2 receptors
- Selective BZ receptor agonists
    - Include:
        - Zaleplon
        - Zolpidem
        - Zopiclone
    - They are short acting hypnotics
    - They are chemically distinct
    - Their MoA is similar to that of BDZs
    - They lack appreciable anxiolytic activity
- Benzodiazepines
    - Short acting BDZs e.g. Estazolam, Oxazepam, Lorazepam, Temazepam, Triazolam

are used for treatment of insomnia because they have little hangover effect
    - Diazepam, which is a longer-acting BDZ, can be used to treat insomnia associated with daytime anxiety
- Chlormethiazole
    - It acts as a positive allosteric modulator of $GABA_A$ receptors at a site distinct from BDZs
- Antihistamines
    - Diphenhydramine and Promethazine can be used to induce sleep
        - They are included in various OTC preparation
    - Doxepin is an SNRI antidepressant w/ histamine H1 and H2 receptor agonist properties
        - It can be used to treat insomnia
- Orexin Receptor Antagonist
    - Includes Suvorexant
        - It is in development as a hypnotic
        - Is an antagonist of OX1 and OX2 receptors
    - Orexins are peptide transmitters in the CNS that are important in setting diurnal rhythm
    - Orexin levels are normally high in daylight and high at night
    - Hence, Suvorexant reduces wakefulness
- Miscellaneous drugs
    - Meprobamate (Carbamate)
    - Alcohols
        - Ethanol
        - Chloral hydrate
        - Trichloroethanol
        - Paraldehyde
    - Methaqualone
        - These are no longer recommended, but they are occasionally used

Melatonin Receptor Agonists

MoA

- Melatonin receptors are thought to be involved in maintaining the underlying circadian rhythms underlying the sleep-wake cycle
- Ramelteon and Tasimelteon are agonists at MT1 ns MT2 melatonin receptors located in suprachiasmatic nucleus of the brain
- In patients w/ chronic insomnia, Ramelteon has the following effects
    - It reduces the latency to persistent sleep w/…
    - No effects on sleep architecture
    - No rebound insomnia or significant withdrawal symptoms

PK of Ramelteon

- Rapidly absorbed after oral administration
- Undergoes extensive first-pass metabolism, to form an active metabolite w/ longer half-life (2-5h) than the parent drug
- The CYP1A4 isoform is mainly responsible for its metabolism
    - The CYp2C9 isoform is also involved

Drug Interactions and Caution

- Ramelteon should not be used in combination w/ inhibitors of CYP1A2 (e.g. Ciprofloxacn, Fluvoxamine, Zileuton) or CYP2C9 (e.g. Fluconazole) which increase its plasma concentration
- It should be used w/ caution in patients w/ liver dysfunction
- The CYP inducer, Rifampin, markedly reduced the plasma levels of both Ramelteon and

its active metabolite

Clinical Use

- MRAs are effective in treatment of insomnia in the elderly and autistic children
- Ramelteon is a hypnotic drug used specifically for patients who have difficulty in falling asleep
- Tasimelteon is similar

AE of Ramelteon

- Dizziness
- Somnolence
- Fatigue
- Endocrine changes
  - Reduced testosterone
  - increased prolactin
- Note:
  - Ramelteon is not a controlled substance

Buspirone

- 5HT1A partial agonist

–

Clinical Use

- Has selective anxiolytic effects
  - It relieves anxiety w/o causing marked sedative hypnotic or euphoric effects
- Unlike BDZs, it has no anticonvulsant or muscle relaxant properties
- It is used in generalised anxiety states,
  - however, it is less effective in panic disorders because of its low onset of action (1 week)
  - Unsuitable for management of acute anxiety states
- Buspirone-treated patient show no rebound anxiety or withdrawal sign on abrupt discontinuation
- It is not effective in blocking the acute withdrawal syndrome resulting from abrupt cessation of BDZs or other sedative hypnotics
- It causes less psychomotor impairment than BDZs
- It does not affect driving skills
- It does not potentiate effects of conventional sedative hypnotic drugs, ethanol or TCAs
- Elderly patients do not appear to be more sensitive to its actions
- It has minimal abuse liability

AE

- Non-specific chest pain
- Tachycardia
- Palpitations
- Nervousness
- Tinnitus
- GIT disturbances
- Paresthesias
- Dose-dependent pupillary constriction may occur
- Blood pressure may be significantly elevated in patients receiving MAOIs
- Buspirone is an FDA category B drug in terms of its use in pregnancy
  - FDA category B
    - Animal studies have not demonstrated a foetal risk but there are no controlled

studies in pregnant women

PK of other Sedative Hypnotics

Absorption and Distribution

- When used to treat anxiety or sleep disorders, sedative hypnotics are usually administered orally
- The rates of oral absorption of sedative hypnotics differ depending on the number of factor including lipophilicity
    - E.g.
        - The absorption of Triazolam is extremely rapid
        - That of Diazepam and the active metabolite of chlorazepate is more rapid than other more commonly used BDZs
        - Clorazepate is a prodrug, which is converted to its active form, desmethyldiazepam (nordiazepam) by acid hydrolysis in the stomach
- Most of the barbiturates and other older sedative hypnotics, as well as the newer sedative hypnotics (Eszopiclone, Zaleplon, Zolpidem), are absorbed rapidly into the blood following oral administration
- Lipid solubility plays a major role in determining the rate at which S-Hs enter the CNS
    - High lipid solubility is responsible for the rapid onset of CNS effects of Triazolam, Thiopental and the newer hypnotics
    - In contrast, Phenobarbital and Meprobamate have low lipid solubility and penetrate the brain slowly
- All S-H cross the placental barrier during pregnancy
- If given during the pre-delivery period, they may depress the neonatal vital functions
- S-H are also detectable in breastmilk and may cause depressant effects in the breastfeeding infant

Biotransformation

- Metabolic transformation to more water-soluble metabolites is necessary for clearance of S-S from the body
- The microsomal drug metabolising enzyme systems of the liver are most important for metabolism
- Few S-H are excreted from the body in unchanged form
- Therefore, elimination half-life depends on the rate of metabolic transformation
- Bio-transformation of certain drugs

BDZs

- All are cleared by hepatic metabolism
- Most undergo microsomal oxidation (phase 1) catalysed by CYP isozymes esp. CYP3A4
- The metabolites are subsequently conjugated to form glucoronides that are excreted in the urine
    - Many phase I metabolites of BDZs are pharmacologically active, some w/ longer half-lives than the parent drug
- Examples
    - Desmethyldiazepam (Nordiazepam) which has an elimination half-life of 40-60 hours, is an active metabolite of Chlordiazepoxide, Prazepam, Diazepam and Chlorazepate
    - Active metabolites of Chlordiazepoxide include Desmethylchlordiazepoxide and Demoxepam
    - Flurazepam (hypnotic) is oxidised by hepatic enzymes to 3 active metabolites i.e. Desalkyl-flurazepam, Hydroxyethyl-flurazepam and Flurazepam aldehyde
        - These metabolites have half-lives ranging from 30-100 hours
    - Prazolam and Triazolam undergo alpha-hydroxylation
        - The resulting metabolites have short half-lives and are rapidly conjugated to form inactive glucuronides
    - Cumulative and residual effects such as excessive drowsiness appear to be less of a

problem w/ drugs such as Estazolam, Oxazepam and Lorazepam, which have short half-lives and metabolised directly into inactive glucoronides
    - The metabolism of several commonly used BDZs, including Diazepam, Midazolam and Triazolam is affected by inhibitors and inducers of hepatic CYP isozymes

Barbiturates

- w/ the exception of Phenobarbital, part of which is excreted unchanged in urine, the barbiturates are extensively metabolised in the liver
- The major metabolic pathways involve oxidation by hepatic enzymes to form alcohols, acids and ketones, which appear in the urine as glucoronide conjugates
- Most of the metabolites of the barbiturates are pharmacologically inactive
- The elimination half-lives of Secobarbital and Pentobarbital range from 18-48 hours in different individuals
- The elimination half-life of Phenobarbital is 4-5 days
- Multiple dosing w/ these drugs can leads to cumulative effects
- Chloral hydrate
    - It is oxidised to Trichloroethanol , an inactive metabolite

Newer Hypnotics

- Zolpidem
    - After PO of the standard formulation, Zolpidem reaches **peak plasma levels in 1-3 hours**
    - Sublingual and oral spray formulation are also available
    - Rapidly metabolised o inactive metabolised via oxidation and hydroxylation by hepatic CYP3A4 isozyme
    - The elimination half-life of is 1.5-3.5 hours
        - Greater in women
        - Increased significantly in elderly patients
    - A biphasic extended release formulation extends plasma levels by ~2 hours
- Zaleplon
    - Metabolised to inactive metabolites mainly by hepatic aldehyde oxidase and partly by the CYP3A4 isozyme
    - Its half-life: ~1 hour
    - Dosage should be reduced in patients w/ hepatic impairment and in the elderly
    - Drug interactions
        - Cimetidine, which inhibits both aldehyde dehydrogenase and CYP3A4, markedly increases the peak plasma level of Zaleplon
- Eszopiclone
    - It is metabolised by hepatic CYPs esp. CYP3A4 to from the inactive N-oxide derivative and weakly acting desmethyleszopliclone
    - Its elimination half-life of approx. 6 hours and is prolonged in the elderly and in the presence of inhibitors of CYP3A4 (e.g. Ketoconazole)
    - Inducers of CYP3A4 increase its hepatic metabolism

Excretion

- Most S-H are excreted mainly via the kidney
- In most cases, however, changes in renal function do not have a marked effect on the elimination of the parent drugs
- 20-30% of the dose Phenobarbital is excreted unchanged in urine
- Its elimination rate can be increased significantly by alkalinisation of the urine, partly because it is a weak acid w/ a pKa of 7.4 and therefore, it undergoes increased ionisation at alkaline pH
- Only trace amount of the BDZs and <10% of Meprobamate appear in the urine unchanged

PD of S-H

1. MoA
    - The BDZs, barbiturates, Zolpidem, Zaleplon and Eszopiclone, bind to molecular components of the $GABA_A$ receptor present in neuronal membranes, in the CNS
    - The $GABA_A$ receptors is a transmembrane glycoprotein which functions as a chloride ion channel
    - The GABAA receptor is activated by GABA, the major inhibitory neurotransmitter in the CNS
    - It is assembled from 5 subunits
    - GABA appears to interact at two sites between α and ß subunits to trigger chloride ion channel opening w/ resulting membrane hyperpolarisation
    - MoA of BDZs
        - Receptors for BDZs (the BZ site of the GABAA receptor) are present in many regions of the brain
        - Binding BDZs and the newer hypnotic drugs such as Zolpidem, occurs at a single site between α and γ subunits
            - This facilitates the process of chloride ion channel opening
        - The BDZs antagonist Flumazenil also binds at this site and can reverse the hypnotic effects of Zolpidem
        - In contrast to BDZs, Zolpidem, Zaleplon and Eszoplicone bind more selectively because they interact only w/ $GABA_A$ receptor isoforms that contain α_1 subunits
    - MoA of Barbiturates
        - They also facilitate the actions of GABA at multiple sites in the CNS
            - They bind to multiple isoforms of the $GABA_A$ receptors but at different sites from those which the BDZs interact
            - However, in contrast to the BDZ, they appear to increase the duration of GABA-mediated chloride channel opening
        - At high concentrations, the barbiturates may also directly activate chloride channels, by binding to sites which are distinct from the BDZ binding sites
        - Barbiturates also depress the actions of excitatory neurotransmitters e.g. Glutamic acid
        - The multiple sites of action of barbiturates may be the basis for
            - Ability to induce full surgical anaesthesia
            - More pronounced CNS depressant effects. This result in their low margin of safety, compared to BDZs and the newer hypnotics
2. Organ Level Effects of S-H
    - S-H cause graded dose dependent depression of CNS function (i.e. their CNS effects depend on their dose)
    - However, individual drugs differ in the relationship between the dose and the grade of CNS effect
    - The CNS effects of the S-h range from sedation and relief of anxiety (Anxiolysis) through hypnosis (facilitation of sleep) to anaesthesia and coma
    - Depressant effect are additive when 2 or more S-H are given together
      The linear slop is typical of many of the older S-H including the barbiturates and alcohols
    - With such drugs, an increase in dose above that required for hypnosis may lead to a stage of GA
    - At still higher doses of depression of the respiratory and vasomotor centres in the medulla, may occur, leading to coma and death
    - The BDZs have flatter dose -response curves and therefore, have a greater margin of safety in clinical use
    - They would require proportionally greater dosage increments to achieve CNS depression more profound than hypnosis

    a. Sedation
        - BDZs, barbiturates and most older S-H drugs exert calming effects w/ concomitant reduction of anxiety at their lowest effective doses
            - In most cases, however, the anxiolysis is accompanied by some depressant effects on psychomotor and cognitive functions

- Disinhibition of previously suppressed behaviour may also occur
- This disinhibition is not a characteristic of the TCAs and antihistamines
- Behavioural disinhibitory effects of S-H include euphoria, impaired judgement and loss of self-control
    - These can occur at dosages used for management of anxiety
- The BDZs also exert dose-dependent anterograde amnesic effects (inability to remember event occurring during the drug's duration of action)
- Busipirone is a selective anxiolytic w/ minimal depressant effects on the CNS
    - It does not cause sedation or cognitive impairments

b. Hypnosis
    - All S-H induce sleep if high enough doses are given
    - Zolpidem exerts hypnotic activity w/ minimal muscle relaxing or anticonvulsant effects and w/ less amnestic effects than BDZs
    - The general effects of BDZs and older sedative hypnotics on patterns of normal sleep, are as follows
        - The latency of sleep onset is decreased (time to fall asleep is reduced)
        - The duration of stage 2 non-REM sleep is increased
        - The duration of REM sleep is decreased
        - The duration of stage 4 non-REM slow-wav sleep is decreased
        - Note:
            - REM sleep is the stage in which the most recallable dreams occur
    - The newer hypnotics all decrease the latency to persistent sleep
    - Zolpidem decreases REM sleep but has minimal effect on slow-wave sleep
    - Zaleplon decreases the latency of sleep onset w/ little effect on the REM and non-REM sleep
    - Eszopiclone increase total sleep time mainly via increasing stage 2 no-REM sleep, and at low doses, has little effect on sleep patterns
    - At the highest recommended dose, Eszopiclone decreases REM sleep
        - More rapid onset of sleep and prolongation of stage 2 are presumed to be clinically useful effects
    - Rebound increase in REM sleep "REM rebound" can be detected following abruptly cessation of drug treatment w/ older sedative hypnotics, especially when drugs w/ short durations of action (e.g. Triazolam) are used at high doses
    - There is little evidence of REM rebound w/ Zolpidem and the other newer hypnotics when discontinued after use if recommended doses
    - However, rebound insomnia occurs w/ both Zolpidem and Zaleplon if used at higher doses
    - The use of sedative hypnotics for more than 1-2 weeks, leads to some tolerance to their effects on sleep patterns

c. Anaesthesia
    - At high doses, certain S-H may lead to stage III of GA (loss of consciousness, amnesia and suppression of reflexes)
    - Among the barbiturates, Thiopental and Methohexital are very lipid soluble, and penetrate brain tissue rapidly, following IV administration
        - This characteristic favours their use for induction of GA
    - Certain BDZs including, Diazepam, Lorazepam and Midazolam, are used IV in GA often in combination w/ other drugs
        - However, they are not fully successful in producing surgical anaesthesia (stage III) by themselves

d. Anti-convulsant Effects
    - Suppression of seizure activities, occur w/ high doses of most of the barbiturate and some of the BDZs
      Several BDZs including, Clonazepam, Nitrazepam, Lorazepam and Diazepam, are sufficiently selective, to be clinically useful in the management of seizures
    - Among the Barbiturates, Phenobarbaital and Metharbital (converted to Phenobarbital in the body) are effective in the treatment of GTCS
    - Zolpidem, Zaleplon and Eszopiclone lack anti-convulsant activity

e. Muscle Relaxation
    - Relaxation of skeletal muscle occurs w/ high doses of most S-H
        - Diazepam is effective at sedative levels for specific spasticity states including cerebral palsy
        - Meprobamate also has some selectivity as a muscle relaxant
f. Medullary depression
    - High doses can cause depression of medullary neurons, leading to respiratory arrest, hypertension and CVS collapse
    - These effects are the cause of death in suicidal overdose
    - Respiratory and CVS effects are more marked when sedative hypnotics are given IV

Major Tranquilisers

Friday, 24 March 2017 11:18 AM

Introduction
- Antipsychotic drugs
    - Neuroleptics - increase EPS
    - Anti-schizophrenic
    - Major tranquilisers

Indications
- Schizophrenia
- Mania
    - Bipolar disorder
- Psychotic depression
- Senile psychoses
- Organic psychoses
- Drug-induced psychoses
- Acute behavioural disturbances

Additional Effects
- Improve mood
- Reduce anxiety
- Improve sleep

Target of Drug Action
- Dopamine receptors - antagonists
- 5HT - receptors

Schizophrenia
- Common 1%
- Young people
- Chronic and disabling
- Hereditary
- "Split mind"
- Psychosis
    - Delusions
    - Hallucinations
    - Disorganised behaviour

Other causes of Psychosis
- Substance abuse - recreational drugs
- Steroid induced psychosis
- Manic-depressive psychosis
- Manic-depressive psychosis - bipolar illness
- Alzheimer's disease

Positive Symptoms
- Delusions - paranoid
- Hallucinations
    - Auditory or exhortatory
- Thought disorders
- Abnormal disorganised behaviour

    - Stereotypy
    - Aggression
    - Disorientation
- Catatonia

Negative symptoms
- Withdrawal from social contacts
- Flat affect
- Anhedonia (no pleasure)
- Reluctance to perform every day tasks

Cognitive Function Change
- Deficit in attention
- Deficit in memory

Other manifestations
- Anxiety
- Guilt
- Depression
- Self-punishment/suicide

- Dramatic in young
    - Positive symptoms
    - Relapsing/remitting
- Insidious in older people
    - Negative symptoms
    - Poorer prognosis
    - Chronic
- Selective inattention

Aetiology
- Genetic predisposition
    - 10% first degree relative
    - _
- _

Pathology
- Anatomical
    - Mesolimbic pathway - positive symptoms
        - Increased dopaminergic activity
    - Mesocortical pathway - negative symptoms
        - Decreased dopaminergic activity
- Biochemical
    - Dopamine
    - Glutamate

Dopamine Theory
- Amphetamine release dopamine
    - Acute schizophreniform episode
- L-DOPA
    - Used in Parkinson's Disease
    - ADR
        - Hallucinations
- Dopamine release

        - Sterotypy
            - Repetitive behaviour
- Bromocriptine
    - Dopamine 2 receptor agonist increases symptoms of schizophrenia
- Reserpine
    - D antagonist controls positive symptoms

Glutamate Theory
- NMDA receptor antagonists
    - (NMDA receptor hypofunction)
        - Phencyclidine, Ketamine and Dizoclipine can produce positive and negative cognitive defects
- Reduced glutamate reuptake transporter in schizophrenia

Neurodegeneration
- Related to schizophrenia and dementia

Implications on Management
- Dopamine receptor antagonists
- Inhibition of NMDA receptor
    - Phencyclidine which act via NMDA receptors cause schizophrenia-like syndrome
- Transporters of glutamate and dopamine
- Multifactorial and environmental factor modification

Classification of Antipsychotic drugs
- First generation (typical, conventional)
    - Chlorpromazine
    - Haloperidol
    - Fluphenazine
    - Flupenthixiol
    - Clopenthixol
- Second generation (atypical)
    - Clozapine
    - Risperidone
    - Sertindole
    - Quentapine
    - Amisulpride
    - Ariprazole
    - Zotepine
    - Ziprasidone

Second Generation
- Receptor profile may other than dopamine
- Reduce extrapyramidal ADRs
- Efficacious in treatment of resistant group of patients e.g. Clozapine
- Efficacious against negative symptoms

Phenothiazines
- Chlorpromazine prototype
- Block histamine, catecholamines, acetylcholine, 5HT and dopamine
- Largactil
    - Multiple mediator blockade
- Dopamine blockade main deterrent for antipsychotic action

Treatment
Resistant

- 30% of patients
- Polyporphisms dopamine and 5HT receptors
- Use Clozapine
- Control positive symptoms
- Most effective against negative symptoms
  - Emotional falttenind
  - Social isolation
- Limitation
  - ADRs
  - Arrthmogenesis

Actiyity 1_

_
Pharmacological Properties

- Antagonism of D2 receptors in mesolimbic pathways, relieves positive symptoms of schizophrenia
- Block the other D2 receptors in other brain pathways
  - Nigrostriatal - motor effects
  - Tuberofundibular - increased prolactin
  - Reward component of mesolimbic - reduced pleasures
  - Pre-fontal cortex - worsen negative signs
    - Mitigated effect on 5HT
- Delayed effect despite expedition of receptor binding
- May lead to tardive dyskinesia
- Sedative effect immediately

Action on 5HT receptors

- LSD, 5HT receptor agonist hallucinogenic
- Target 5HT2A and 5HT1A for schizophrenia treatment
- 5HT2A antagonists
  - Risperidone and Olanzapine
- _

Adverse Effects

- Extrapyramidal
  - Acute dystonia
  - Tardive dyskinesia
- Nigrostriatal pathway blockade
- Greatest w/ first generation drugs

Acute Dystonia

- Involuntary movements
  - Restlessness
  - Muscle spasms
  - Protruding tongue
  - Fixed upward gaze
- Plus symptoms of Parkinson's Disease
- Occur in the first few weeks
- Decline w/ time
- Reversible on stopping drug
- α to nigrostriatal blockade

- Mitigated by concomitant blockade of 5HT2A receptors

Tardive Dyskinesia
- Takes months or years to develop
- Disabling and irreversible
- Worsen when drug stopped
- Severe disabling involuntary movement of the tongue, face, trunk and limbs
- Commonest in patients > 50 years

Activity 3
- List drugs with the least propensity to cause EPS effects

Endocrine effects
- Increase prolactin concentration
    - Dopamine act on tuberohypophyseal pathway
- Decrease GH

Other Effects
- Blockade of Ach, Histamine, NE, 5HT receptors
- Decreased libido - D2, M, Alpha1
- Drowsiness and sedation
- Muscarinic receptor blockade
    - Blurring of vision, increasing intraocular pressure, dry mouth , constipation, urine retention
- Alpha receptors
    - Orthostatic hypotension
- Wt gain- H1, 5HT and M antagonism
- QT prolongation

Idiosyncratic rxns
- Cholestatic jaundice - CPZ
- Leucopoenia and agranulocytosis- Olanzapine least likely
- Urticaria
- Antipsychotic Malignant syndrome

PK
- Chlorpromazine
    - Erratic absorption PO
    - Unpredictable clinical dose effect response
    - Plasma t1/2 15-30hrs
    - Clearance hepatic oxidative and conjugation
    - PO, IM, Slow release

Study questions
- List 4 drugs that increase the activity of dopamine
- What would the effect of these drugs be on a patient suffering from schizophrenia with ref to drugs of qn 1.
- Antipsychotic are classified as typical and atypical
    - Classify the antipsychotic on basis of the chemical classification (Katzung)

Antidepressants (Thymoleptics)

Monday, 27 March 2017 11:17 AM

Depression

- Most common of the affective disorders (disorders of mood rather than disturbances of thought or cognition)
- May range from a very mild condition bordering on normality, to severe (psychotic) depression, accompanied by hallucinations and delusions
- Major cause of disability and premature death worldwide

Symptoms

- Emotional components (symptoms)
  - Misery, apathy and pessimism
  - Low self-esteem
    - Feelings of guilt, inadequacy and ugliness
  - Indecisiveness, loss of motivation
- Biological components (symptoms)
  - Retardation of thought and action
  - Loss of libido
  - Sleep disturbance and loss of appetite

Depression

- Unipolar
  - Mood swings are always in the same directions
- Bipolar affective disorder
  - Depression alternates w/ mania
    - Mania
      - Excessive exuberance, enthusiasm and self-confidence, accompanied by impulsive actions, often being combined w/ irritability , impatience, aggression and sometimes w/ grandiose delusions of Napoleonic kind

Unipolar Depression

- Commonly (about 75% of cases) non-familial
- Clearly associated w/ stressful life events, accompanied by symptoms of anxiety and agitation; this type sometimes termed as reactive depression
- Other patients (about 25%, sometimes termed as endogenous depression) show familial pattern unrelated to external stresses, and w/ somewhat different symptomatology

Bipolar Depression

- Usually appears in early adult life
- Less common and results in oscillating depression and mania over a period of a few weeks
- Strong hereditary tendency, but no gene or genes have been identified

Mono Amine Theory of Depression

- Depression results in functionally deficient monoaminergic (NA and/or 5-HT) transmission in the CNS
  - Antidepressant drugs (TCAs and MAOIs) facilitate monoaminergic transmission,

while such drugs as Reserpine cause depression

Rationale for drug use in major depression

- Relieve psychological and physical symptoms
- Enhance functional capacity
- Reduce the likelihood of self-harm or suicide

Drugs used for treatment of depression fall mainly into 3 categories:

- Tricyclic/Polycyclic antidepressants
- Selective serotonin reuptake inhibitors (SSRIs)
- MAOIs

Note:

- All antidepressant drugs potentiate either directly or indirectly the actions of noradrenaline, dopamine and/or serotonin in the brain

Antidepressant Classification

- TCAs
  - Amitrypline
  - Clomipramine
  - Decipramine
  - Imipramine
  - Trimipramine
  - Dothiepin
  - Nortriptyline
  - Doxepin
  - Protriptyline
  - Mianserin
- Heterocyclics
  - Second Gen
    - Amoxapin
    - Maprotiline
    - Trazodone*
    - Bupropion*
  - Third Gen
    - Mirtazapine*
    - Venlafaxine
    - Nefazodone*
    - Duloxetine
- SSRIs
  - Fluoxetine
  - Paroxetine
  - Fluvoxamine
  - Sertraline
  - Citalopram
  - Escitalopram
- MAOIs
  - Phenelzine
  - Tranylcypromine
  - Isocarboxazide

    - Moclobemide (selective for MAO-A)
    - Selegeline - selective for MAO-B and used in Parkinson's Disease

Tricyclic/Polycyclic Antidepressants

- Similar therapeutic efficacy
- Choice of drug depends on tolerance of side effects and duration of action
- Patients who do not respond to one TCA, may benefit from a different drug in the group

MoA

- Block noradrenaline, dopamine and serotonin reuptake into synaptic nerve terminals
    - Increased concentrations od monoamines in the synaptic cleft, resulting in antidepressant effect
- Also block serotonergic, alpha-adrenergic, histamine and muscarinic receptors (not known which of these, if any, accounts for therapeutic effects)
- Antidepressant effects realised after 2-3 weeks following initiation of treatment
- The drugs elevate mood, improve mental alertness, increase physical activity and reduce morbid preoccupation in 50-70% of individuals w/ major depression
- Do not produce CNS stimulation or mood elevation in normal individual and so drug abuse is seldom a problem
- Can be used for prolonged treatment of depression w/o tolerance
- Tolerance to cholinergic properties, however, develops within a short time

Therapeutic Uses

- Treatment of severe endogenous depression
- Some episodic phobias
- Nocturnal enuresis
    - Unconscious or involuntary passage of urine
        - Imipramine is useful in controlling bedwetting in children (>6 years) by causing contraction of the internal sphincter of the bladder
- Adjunct in pain management
- ADHD (third line treatment)
- Migraine prophylaxis

Pharmacokinetics

- Fairly well absorbed PO
- Lipophilic, therefore widely distributed and readily penetrates into the CNS
- Long half-lives e.g. 12 hours for Imipramine and 30 hours for its active metabolites
- Variable firstpass metabolism in the liver
    - Low and inconsistent
        - Use patient response to adjust dosage
- Most are given once daily. Extended release preparations for short half-life drugs e.g. Bupropion and Venlafaxine for once daily administration
- Initial treatment period is 4-8 weeks
- Metabolised by hepatic microsomal enzymes and conjugated by glucuronic acid
- Some metabolites are pharmacologically active e.g. Imipramine is methylated to Desipramine
- Metabolites excreted through the kidneys

Adverse Effects

- Antimuscarinic effects
    - Blockade of muscarinic receptors leads to:
        - Blurred vision

        - Xerostomia (dry mouth)
        - Urinary retention
        - Constipation
        - Aggravation of glaucoma
- Cardiovascular
    - Increased catecholamine activity results in cardiac overstimulation
        - Can be fatal in overdose situation
    - Slowing of AV conduction amongst depressed elderly patients is of particular concern
    - Orthostatic hypotension and reflex tachycardia as a result of blockade of alpha-adrenergic receptors
- CNS
    - Sedation especially during the first several weeks of treatment

Interactions

- W/ direct acting adrenergic (sympathomimetic) drugs by preventing their removal from the synaptic cleft
    - Potentiation of effect
- W/ MAOIs, leads to enhancement of effect
    - HT
    - Hyperpyrexia
    - Convulsions
    - Coma
- W/ ethanol and other CNS depressants
    - Toxic sedation
- W/ indirect acting sympathomimetic drugs by preventing the drugs from reaching their intracellular sites of action

Precautions

- May aggravate epilepsy and glaucoma
- May unmask manic behaviour in manic-depressed individuals

Note:

- Maprotiline
    - Potent (selective) reuptake inhibitor of NA and has fewer sedative and muscarinic actions
- Reboxetine
    - Inhibits NA reuptake; weakly inhibits serotonin reuptake
- Nefazodone
    - Potent inhibitor of CYP3A4 isozyme
- Mirtazapine
    - Potent antihistaminic drug w/ greater sedative effects than the other second and third generation antidepressant drugs. Use may be associated w/ weight gain
- Venlafaxine
    - Potent inhibitor of serotonin reuptake and a weaker inhibitor of NA transport
- Desvenlafaxine
    - Major active metabolite of Venlafaxine
- Duloxetine
    - Inhibits both serotonin and noradrenaline reuptake
- Abomelatin
    - Melatonin receptor (MT_1 and MT_2) agonist and $5HT_{2C}$ receptor antagonist

SSRIs

Indications

- Major depression
- Anxiety disorders e.g. panic disorder, OCD
- Bulimia nervosa
- Premenstrual dysphoric disorder

- Structurally distinct from the tricyclic molecules
- Specifically inhibit serotonin reuptake into synaptic nerve terminals
- Compared w/ TCAs, these drugs may cause fewer anticholinergic effects and cardiotoxicity
- Efficacy comparable to that of TCA

Fluoxetine

- Has a long half-life i.e. 50 hours for the parent compound and 240 hours for its active metabolite, norfluoxetine (desmethylfuoxetine) is
- Inhibits various drug metabolising enzymes)
    - Interacts w/ many drugs
- Useful in the treatment of patients w/ depression that is accompanied w/ marked agitation, anxiety, insomnia (OCDs)
- Also useful for those unable to tolerate the anti-cholinergic side effects of TCAs

- Sertraline and Paroxetine PK parameters similar to those of TCAs
- Citalopram and Fluvoxamine resemble fluoxetine

Adverse Effects

- Nausea
- Decreased libido and even decreased sexual function
- Interaction w/ MAOIs result in marked increases in serotonin in the synapses leading to serotonin syndrome which may be fatal
    - Serotonin syndrome includes
        - Hyperthermia
        - Myoclonus
        - Rapid changes in mental status and vital signs

MAOIs

- May irreversibly or reversibly inactivate the MAO
    - The neurotransmitters escape degradation and accumulate within the presynaptic neuron and also leak into the synaptic space
        - This causes activation of noradrenaline and serotonin receptors and may be responsible for their antidepressant effect
- Antidepressant action delated for 2-4 weeks following initiation of treatment but MAO is fully inhibited after several days of treatment
- Have mild amphetamine-like CNS stimulation

Therapeutic Uses

- Major depression (second line)
    - Indicated for those unresponsive or allergic to those who experience strong anxiety
- Treatment of hypersomnia
- Some anxiety disorders including phobic disorders and panic disorder (second line)

PK

- Well absorbed PO
- Enzyme regeneration, when irreversibly inactivated, occurs several weeks after

termination of the drug
- Note:
  - When switching antidepressant agent, allow a minimum delay of 2 weeks after termination of MAOI therapy
- Metabolised and excreted in urine

Adverse Effects
- Severe and unpredictable
- Hypertensive crisis if given w/ foods containing tyramine
  - Management w/ phentolamine or Prazosin
- Drowsiness, orthostatic hypotension, blurred vision, dryness of mouth, dysuria and constipation

Lithium Salts (Li_2CO_3)
- Lithium is a small monovalent cation
- In the body Li+ substitutes for Na+ and K+ and this can exert profound effect on a number of metabolic processes
- Probability acts by altering the cellular concentration of the second messenger Inositol Triphosphate (IP3). Also inhibits dopamine release and enhances serotonin release

PK
- Completely absorbed from the GIT within 6-8 hours
- Peak plasma levels within 30 minutes to 2 hours
- Distributes in TBW
  - Initial Vd is 0.5L/kg BWt rising to 0.7-0.9 L/kg
- No PPB
- Sequestration in bone
- Not metabolised
- >95% of dose excreted by the kidney; small amounts in sweat and saliva
- Renal clearance of lithium correlates w/ renal creatinine clearance (i.e. Li clearance~20% of creatinine clearance)
- Half-life
  - 20 hours

Uses
- Prevention of manic of depressive episodes in bipolar disorder
- Treatment of acute mania
- Schizoaffective disorder and chronic schizophrenia
- Note:
  - Can take up to 10 days to take effect
- Therapeutic range of Lithium for prophylaxis is between 0.4 and 1.2 mmol/L through adequate control can be obtained w/ plasma levels of 0.4-0.6 mmol/L
- Lithium salts are very toxic
  - Their safety factor and therapeutic index are extremely low and comparable to digitalis
- Toxic symptoms begin to occur when serum concentrations exceeds 1.5 mmol/L and so regular serum estimation is required

Unwanted Effects
- GIT
  - Persistent VD w/ fluid and electrolyte imbalance
- Note:
  - Diuretic therapy can precipitate toxic levels of lithium

- Polyuria, polydipsia, oedema and weight gain
- Fine tremours
- At higher concentrations
    - Drowsiness, blurred vision, course tremours, ataxia and dysarthria (loss of articulation) which may progress to delirium and convulsions, coma and death
- Long term effects
    - Non-toxic goitre, hypothyroidism and nephrogenic diabetes insipidus

Caution

- Should not be prescribed to pregnant women particularly in the first trimester
    - Risk of damage to the new-born
- Should not be given to nursing mothers
    - Secreted in milk in high concentrations
- Contraindicated in those w/ bradycardia-tachycardia ("sick sinus") syndrome because Lithium further depresses the sinus node

Parkinson's Disease

Friday, 31 March 2017 8:42 AM

- Is movement disease where the dopamine releasing neurons/dopaminergic neurons in the substantia nigra of the brain, undergo degeneration
- It is a progressive, adult-onset disease
    - Affect >1% of individuals over 60 years

Aetiology

- Usually, there is no known cause
- There might be a genetic cause in a few cases
    - Mutations in the PINK1, PARKIN or ALPHA SYNUCLEIN genes
- Rarely, might be caused by MPTP
    - A toxic impurity found in the recreational drug, MPPP (synthetic opioid)
- Thought to be a autoimmune disease, provoked by some virus or bacteria that has some antigens that are shared by the neurons in the dopaminergic region of the brain
- Risk factors
    - Pesticide exposure
    - Gene variants
        - Like LRRK2

- Pathology
    - Destruction of dopaminergic neurons in the basal ganglia, specifically in the substantia nigra. This area is darker than the rest of the areas of the brain and is found on either side of the midbrain. The basal ganglia is a collection of brain regions that controls movement through its connection to the motor cortex.
    - In Parkinson's Disease the substantia nigra gradually disappears
        - Under a microscope:
            - Lewy bodies are present before the neurons in the substantia nigra die
                - Eosinophilic, round inclusions made of alpha-synuclein protein
                - Also found in Lewy Body Dementia and Multiple System Atrophy
    - The substantia nigra can be divided into two regions
        - Pars Reticulata
            - Receives signals from the striatum (made up of the caudate and putamen) and relays information to the thalamus via neurons rich in GABA
        - Pars Compacta
            - Affected area in Parkinson's Disease
            - Sends impulses to the striatum via neurons rich in dopamine, forming the nigrostriatal pathway (helps stimulate the cerebral cortex and initiate movement)
            - When these neurons die, the individual might be in a hypokinetic state
        - The substantia nigra helps calibrate and fine tune how movements occur
- Characterised by
    - Bradykinesia (slow movement) or hypokinesia (little movement) or akinesia (no movement)
        - From difficulty initiating movement
            - Example
                - The legs freezing up when trying to walk
                - Walking with a shuffling gait
        - Unlike Essential tremour
            - Hallmark feature is action tremour
    - Rigidity

        - Stiffness that can appear as "cogwheel rigidity"
            - Occurs when there are stalls in a person's hands or legs when it is passively moved by someone else
        - Contributes to the stiff posture and almost expressionless face of an individual suffering from Parkinson's Disease
    - Tremors
        - Involuntary shakiness most noticeable in the hands
            - "pill rolling" tremour because it looks like someone is rolling a pill between their thumb and index finger
        - It is a resting tremour
            - Present at rest
            - Diminishes with increased movement
        - Unlike in cerebellar diseases
            - Result in action/intention tremour - tremour worsens with movement
    - Postural instability - occurs late in the disease
        - Problems with balance
        - Can lead to falls
        - Unlike Essential tremour
            - Hallmark feature is action tremour
- Parkinson's Disease DOES NOT cause weakness
    - Unlike other motor cortex or corticospinal pathway diseases
- Non-motor functions can also be affected
    - Depression
    - Dementia
    - Sleep disturbances
    - Difficulty smelling
- The above are thought to come about due to:
    - Dysfunction in dopaminergic signalling in other parts of the brain, beyond the substantia nigra
        - E.g. in prefrontal cortex leading to pre-cognitive symptoms
    - Dysfunction in other NT e.g. Acetylcholine

- Parkinson's Disease can be caused by a number of encephalitic diseases

Treatment - help with the symptoms but non stop the neurodegeneration

- Strategy: increase the amount of dopamine signalling in the brain
- Levodopa
    - Dopamine itself cannot cross the BBB but its precursor, Levodopa.
    - Once on the brain, it is converted to dopamine by DOPA decarboxylase, within the remaining nigrostriatal neurons
- Carbidopa
    - Peripheral DOPA decarboxylase also exists, which can metabolise the Levodopa into dopamine before it gets through the BBB and also, via other enzymes, be metabolised into catecholamines e.g. epinephrine, which can cause unwanted side effects such as arrhythmias.
    - This is why Levodopa is co-administered with Carbidopa, a DOPA decarboxylase inhibitor, that isn't able to cross the BBB
- Amantidine
    - Antiviral medication that increases endogenous dopamine production (MoA unknown)
- Dopamine agonists - stimulate dopamine receptors
    - E.g.
        - Bromocriptine - Ergot derivative
        - Pramipexole - non-ergot derivative
        - Ropinirole - non-ergot derivative
- COMT inhibitors

    - COMT is an enzyme that degrades dopamine
    - Include
        - Entecapone
        - Tolcapone
- Selegeline
    - Inhibits MAO-B that metabolises dopamine
- Anticholinergics
    - Since there is usually a signalling balance between dopamine and acetylcholine reaching the striatum, a loss of dopamine increases the relative amount of acetylcholine signalling there
    - Anticholinergics can be given to restore the balance
        - E.g.,
            - Benztropine - helps improve the tremours
- Deep brain stimulation
    - Involves an implantable device that directly send signals to the basal ganglia, which counteracts the aberrant signalling in PD

Alcohol

Thursday, 30 March 2017 8:34 AM

- Alcohol:
  - Hydrocarbons containing a hydroxyl group from fermentation of sugars in presence of yeast (Zymase) and water
    - $C6H12O6 \rightarrow 2(CH3CH2CH) + 2CO2$

Types of Alcohol
- Methanol (methyl alcohol, wood alcohol)
- Ethanol (ethyl alcohol, grain alcohol)
- Isopropranol (isopropyl alcohol, rubbing alcohol)
- Ethylene glycol

Alcoholic Beverages
- Malted liquors
  - Fermentation of germinating cereals, mostly barley
  - Beers, stout (3-6%)
- Wines
  - Fermentation of natural sugars (46%)
    - Grapes
    - Apples
    - Other fruits
- Spirits
  - Rum (distilled molasses)
  - Whiskey (distilled grains)
  - Brandy (distilled grapes)
  - Gin (any sugar source)
  - 40-55%

Ethanol
- Small water soluble molecule absorbed rapidly by simple diffusion
- 20% absorbed from the stomach, 80% in the small intestines: (reduced gastric emptying and absorption0
- FPE in stomach and liver
- Maximal blood concentration within 30-90 minutes
- Can also be absorbed via lungs and skin

Factors Affecting Rate of Absorption
- Alcohol concentration of ingested beverage
  - Optimal absorption occurs for beverages with alcohol concentration between 10% alcohol v/v
  - Beverages <10% don't present a large concentration gradient

MEOS
- Uses NADPH as a cofactor
- Consists of CYP2E1, 1A2, 3A4
- Useful when ethanol concentration is greater than 100mg/dL (ADH pathway saturated due to depletion of NAD+)
- Induction of MEOS w/ chronic alcohol consumption also increases the metabolism of other drugs

Elimination

- Elimination of alcohol from the blood
  - Follows zero-order kinetics: independent of blood concentration and linear w/ time
  - Average rate of elimination is 15mg/100mL/hour
  - Is fixed and unaffected by coffee/fresh air/ eating/sleep/showering etc.

Acute Effects of Alcohol on the Body

- Vasodilation
  - Creates a feeling of warmth when alcoholic beverages are consumed
- Disinhibition
  - Responsible for the "stimulant" effect of alcohol
  - Euphoria, increased talkativeness, increased sociability (behavioural excitability)
  - Due to inhibition of inhibitory CNS pathways
- CNS depressant
  - Non-selective depression of brain and spinal cord
  - Sedated → sleepy → stuperous → unconscious
  - Effects are additive w/ other CNS depressants
- Kidney
  - Diuresis - due to increased water ingestion and inhibition of ADH
- Uterus
  - Relaxation of uterine muscles
- Endocrine:
  - Low dose - adrenaline release and hyperglycaemia
  - High dose - hypoglycaemia
- GIT
  - Pylorospasm, gastritis, vomiting, reflux

Alcohol & Death

- Primary mechanism for death due to acute alcohol intoxication is respiratory depression
- Average BAC at which respiratory paralysis occurs is 350mg/100ml
- Death can occur at much lower BAC where aspiration of vomit occurs

Alcohol in Breath

- Alcohol is volatile
  - At physiological temperatures, alcohol will diffuse from the blood to the alveolar air of the lung and into the breath
  - Henry's Law*

Henry's Law

- At a given temperature, the ration of the concentration of a volatile compound in solution and the concentration of the volatile compound in the air above the solution is fixed
- Basis for breath alcohol testing
- Concentration in exhaled air is 0.05% of BAC. This is fixed

Tolerance

- May be:
  - Functional
    - Decreased sensitivity to the CNS depressant effects of ethanol
  - Metabolic
    - Enzyme induction resulting in an enhanced metabolic rate (>40mg/100mL/hr)

Methanol (Methyl Alcohol)

- Used in
    - Industrial production of synthetic organic compounds
    - Commercial solvents
    - Windshield-washing products

Pharmacokinetics
- Can be absorbed through the skin, respiratory and GI tracts
- Then distributed in body water
- Primarily eliminated via oxidation to formaldehyde, formic acid and carbon dioxide

Features of Methanol Poisoning
- Blurred vision
- Formaldehyde odour in breath or urine
- Bradycardia
- Prolonged coma
- Seizures
- Resistant acidosis
- Cause of death = sudden cessation of respiration

Treatment
- Initial - respiratory support
- Suppression of metabolism - ethanol, Fomepizole
- Haemodialysis
- Sodium bicarbonate

Role of Fomepizole
- Inhibits alcohol dehydrogenase
- Also approved for treatment of ethylene glycol poisoning
- Expensive
- AE
    - Headache
    - Nausea
    - Dizziness

Role of Folic Acid
- Folate may be useful to enhance oxidation of_

Ethylene Glycol
- Used in heat exchanger, in antifreeze formulation and as industrial solvents
- Sweet taste
- Ethylene glycol itself is relatively harmless and eliminated by the kidney
- However, it is metabolised to toxic aldehydes and oxalate

Treatment
- Fomepizole
    - ↓ concentrations of toxic metabolites in blood and urine and prevents renal injury
    - Started immediately IV and continued until serum concentrations of ethylene glycol is < 20mg/dL
- Ethanol infusion
- haemodialysis

Drugs of Abuse

Monday, 27 March 2017 2:34 PM

Classification

- Positive drugs
  - Drugs that have therapeutic effect but they have a euphoric effect that makes them liable to abuse
  - Include
    - Narcotics
      - Morphine
      - Codeine
      - Pethidine
      - Antihistamine
      - Ephedrine
    - Amphetamines
- Negative drugs
  - Addictive and habit forming
  - Socially acceptible and not prohibited but is regulated
  - Include
    - Tobacco
    - Alcohol
    - Miraa
    - Coffee and tea
- Hard drugs
  - Habit forming and harmful
  - Prohibited by law
  - Include
    - Cannabis
    - Heroine
    - Lsd
    - Cocaine
  - They may
    - Alter perception
    - Stmulate or depress the CNS

Drug

- Anything that alters the normal physiological function of a cell but is not intended to kill (if intended to kill = poison)

Addiction

- Implies habit forming

Tolerance

- Initial physiological effect wanes and larger doses are required to elicit similar response

Dependence

- Implies a physiological rection when the drug is stopped or there is a drop in levels in the blood

Addiction to Alcohol, Nicotine and BDZs

Tuesday, 28 March 2017 11:16 AM

Addiction to Alcohol
Pharmacology

- Complex
- Alters the function of several ionotropic receptors and ion channels
    - GABAA receptors
    - Kir3 channels
    - Glycine_
    - _

How alcohol attacks the brain

- First, alcohol attacks the forebrain and assaults the motor coordination and decision makins
- Then alcohol knocks out the midbrain and you lose control over your emotions and increases the chance of blackout
- Finally, the alcohol batters the brainstem as It affects heart rate, body temp. _

Features on Alcohol Dependence

- 6-12 hours after cessation of heavy drinking
    - Features of withdrawal noted
        - Tremour (mainly of the hands)
        - NV
        - Excessive sweating
        - Anxiety
        - Agitation
- 12-24 hours after cessation
    - Visual, tactile and auditory hallucinations
- 24-48 hours after cessation
    - Generalised seizures
- 48-72 hours after cessation
    - Delirium tremens - hallucinations, disorientation and autonomic instability _

Management of Alcohol Withdrawal

- Objectives
    - Prevention of seizures
    - Delirium
    - Arrhythmias
- Ensure potassium, magnesium and phosphate balance
- Thiamine to prevent Wernicke-Korsakoff Syndrome

Detoxification

- Involves substitution of a long-acting sedative hypnotic e.g. BDZs
- Long acting agents e.g. Chlordiazepoxide and Diazepam
- Lorazepam and Oxazepam preferred in patients w/ liver dysfunction
    - Rapidly converted to water soluble metabolites that will not accumulate

Adjuncts to Management of Alcoholism

- Psychosocial support/counselling/rehabilitation
- Medical adjuncts
    - Naltreone

    - Acamprosate
    - Disulfirum

Naltrexone
- Long acting opioid antagonist at μ receptors
- Shown to:
    - Reduce the rate of relapse back to alcohol dependence
    - Reduce craving of alcohol

Acamprosate
- Stabilises the chemical balance in the brain disrupted by alcoholism, possible by blocking NMDA receptors, while GABA type A receptors are activated
- Reduces the symptoms of protacted withdrawal, such as insomnia, anxiety restlessness and dysphoria
- _

Disulfiram
- Inhibits aldehyde dehydrogenase
- Flushing, throbbing headache, NV, seating, hypotension and confusion occur within a few minutes after an individual taking disulfirum drinks alcohol
- Poor compliance

Addiction to Nicotine
Introduction
- One of the most addictive drugs
- Relapse after attempted cessation very common
- Nicotine exposure is via smoking, chewing or snuffing tobacco

Mechanisms
- Stimulates adrenal glands → adrenaline → stimulates CNS →↑ BP, respiration and HR
- Leads to release of glucose → suppressed insulin excretion → chronically elevated blood glucose
- Increases levels of dopamine
- Long term brain changes

Pharmacology
- Nicotine is a selective agonist of the nicotinic acetylcholine receptors (nAChR)
- Rewarding effect of nicotine requires involvement of the VTA, in which nAChRs are expressed on the dopamine neurons
- When nicotine excites projection neurons, dopamine is released in the nucleus accumbens, thus fulfilling the dopamine requirement of addictive drugs

Nicotine Withdrawal
- Irritability
- Sleep problems
- Attention difficulties
- Increased appetite
- Powerful craving for tobacco

Treatment
- Nicotine substitution
    - Gum
    - Transdermal patch
    - Nasal spray

- All these do not achieve peak nicotine level - but suppress the withdrawal symptoms
- Also eliminate exposure to toxic smoke constituents
- Drugs include
    - Varenicline
        - Partial agonist of nicotinic receptors (α-4 ß-2) thought to be involved in the rewarding effects of nicotine
        - Blocks the ability of nicotine to activate dopamine release
        - Reduces tobacco craving and supports abstinence from smoking
        - AE
            - Suicidal ideation
            - Impaired ability to drive
    - Bupropion
        - Originally marketed as an antidepressant
        - Has mild stimulant effects through blockade of the reuptake od catecholamines, esp. Norepinephrine and dopamine
        - Supresses tobacco craving and promotes cessation without concomitant weight gain
        - Should be combined w/ behavioural therapy

Addiction to BDZs
Introduction
- BDZ abuse most often occurs concomitant w/ other drugs e.g. to attenuate anxiety during withdrawal from opioids
- Mild euphoric effect

Withdrawal from BDZs
- Occurs within days of stopping the medication. Symptoms include:
    - Irritability
    - Insomnia
    - Phonophobia and photophobia
    - Depression
    - Muscle crumps
    - Seizures
- These symptoms taper off within 1-2 weeks

Pharmacology
- The rewarding effects of BDZs are mediated by α1 containing GABAa receptors expressed on the VTA neurons
- Leads to disinhibition of dopamine neurons

Treatment of BDZ addiction
- Gradual reduction of dose
- Long acting BDZ can be used for substitution
- Withdrawal symptoms treatment by Phenobarbitone
- Specific antagonist
    - Flumazenil

Addiction to Opioids, Cocaine and Amphetamine

Tuesday, 28 March 2017 12:11 PM

- All addictive drugs increase dopamine concentrations in target structures of the mesolimbic projections

Opioids

- Opioids act at three G protein-coupled receptors
  - μ, κ and d opioid receptors
- These receptors are coupled to inhibitory G proteins
  - They all inhibit adenylyl cyclase
- Actions in the ventral tegmental area (VTA)
  - This is the region where the mesolimbic dopamine system begins
  - μ opioid receptors inhibit GABA neurons
  - κ opioid receptors inhibit dopamine neurons
  - This may explain why μ agonists cause euphoria while κ agonists induce dysphoria
- Commonly abused μ opioids
  - Morphine
  - Heroine
  - Codeine
  - Oxycodone
  - Meperidine (among health professionals)
- Heroine
  - Is also called diacetylmorphine
  - It is metabolised to morphine
  - IV, smoked or snorted
- These drugs induce strong tolerance and dependence
- The withdrawal syndrome
  - May be very severe - except for codeine
  - Intense dysphoria
  - NVD
  - Muscle aches
  - Lacrimation
  - Rhinorrhea
  - Mydriasis
  - Piloerection
  - Sweating
  - Yawning
  - Fever
- The withdrawal syndrome
  - Lasts 5-7 days
- When opioids are used as analgesics, addiction rarely developns
- When taken recreational purpose, opioids are highly addictive

Treatment of Withdrawal Syndrome

- Methadone
- Eventually taper the dose by 10-20% daily
- If opioid not available, relief of symptoms
  - Diarrhoea w/ Loperamide
  - "sniffles" w/ decongestants
  - Pain w/ NSAIDS e.g. Ibuprofen

        - Clonidine to decrease SNS overactivity
            - Monitor BP
        - BDZs to decrease agitations and promote sleep
- IV heroine
    - Can produce an allergic reaction
    - Probably due to adulterants
- Features are:
    - ↓ alertness
    - Frothy pulmonary oedema
    - ↑ eosinophils in the blood
- IV overdose
    - Shallow and slow respirations
    - Miosis (mydriasis if brain anoxia develops)
    - Bradycardia
    - Hypothermia
    - Stupor or coma
- If not treated rapidly:
    - Respiratory depression
    - Cardiorespiratory arrest
    - Death

Management of Opioid Overdose

- Support vital signs
    - ABC
- Intubation if
    - Coma (prevents aspiration)
    - Pulmonary oedema (positive pressure breathing)
- Prevent further absorption if oral route
    - Activated charcoal
    - Gastric lavage
- Naloxone IV or IM (opioid antagonist)
    - It reverses the effects of morphine within 1-2 minutes
    - Titrate
        - To reduce respiratory depression and prevent withdrawal syndrome
    - Short acting
        - Monitor for 24 hours if heroine overdose
        - 72 hours if methadone overdose

Opioid Addiction treatment

- Use long acting opioid
    - Methdone
    - Levomethadyl acetate
    - Buprenorphine
- This is referred to as substitution therapy
    - Substitute long acting for a shorter acting agent
    - ↓ euphoria and craving
    - Drugs and education and counselling
- Methadone
    - Oral route
    - Once daily
        - ∴ supervised intake is possible
    - Abrupt termination invariably precipitates a withdrawal syndrome
        - The patient on substitution therapy remains dependent
    - Methadone treatment if for 6-12 months then taper by 5% weekly

- Note:
  - Substitution of heroine w/ heroine is done in some countries
  - This is done in controlled settings
  - Access to counselling
- Buprenorphine
  - Oral
  - A partial agonist
  - +/- naltrexone
    - Prevents abused if dissolved for IV abuse
- Drug free programs
  - No long term Methadone
  - Support groups
  - Counselling
    - How to cope w/ stress
    - How to address
      - Craving
      - Easy access to drugs
      - Lack of motivation
- Opioids for cancer patients
  - Can be used for severe pain
  - Fear of addiction is less important
- For chronic opioid medication
  - Use oral route
  - Slow-onset of action

Options For Cancer Patients

- Methadone
- Controlled-release oral morphine
- Controlled release oxycodone
- Long-term treatment w/ opioids should be used only after other alternatives have been exhausted
- Suspect abuse in patients on chronic pain treatment if the patient
- Returns for a new prescription earlier than scheduled
- Visits emergency rooms of different hospitals complaining of acute pan and asking for an opioid injection

Cocaine

- It is highly addictive
- Found in the leaves of Erythroxylon coca
- Clinical use
  - As a local anaesthetic (inhibits voltage-gated sodium channels in the peripheral nervous system)
- Early descriptions of cocaine by the South American Indians

Routes of administration for abuse

- IV
- Nasal snorting
  - 3-5 minutes to alter mood
- Inhaled
  - "crack cocaine" is smoked
  - It is produced by heating cocaine HCl in an alkaline solution, to transform it into the free base
  - It is rapidly absorbed in the lungs → brain
  - Rapid onset of action, 8-10 seconds
- Peak effects in 10-20 minutes

- DoA
  - ~1 hour
- Metabolised by esterases
- Excreted in urine
- Tolerance develops
- May need cocaine 2-3 times per hour
- Alcohol
  - Moderated high and dysphoria

Effects
- CNS effects
- It blocks transporters for the uptake of
  - Dopamine
  - Noradrenaline
  - Serotonin
- It increases dopamine concentrations in the nucleus accumbens
- It activates the SNS
  - Acute increase in arterial pressure
  - Tachycardia, ventricular arrhythmias
  - Loss of appetite
  - Hyperactivity
  - Insomnia
- Increases the risk for
  - Intracranial haemorrhage
  - Ischaemic stroke
  - MI
  - Seizures
- Cocaine overdose may cause
  - Hyperthermia
  - Coma
  - Death
- A few exposures to cocaine cause strong cravings for the substance
- Can lead to dependence and addiction
- Causes a withdrawal syndrome
- No specific antagonist is available
- Management of intoxication is supportive

Cocaine Overdose
- A medical emergency
- ICU admission may be needed
- Hyperadrenergic state
- IV diazepam for seizures
- IV propranolol for ventricular arrhythmias
- Consider intoxication w/ other drugs
  - E.g. heroine

Effects of Chronic Use
- Paranoid ideation
- Visual and auditory hallucinations
- Severe depression ("crashing") following cocaine intoxication
- Loss of libido
- Impotence and gynaecomastia in males
  - Persist for long periods following cessation of drug use
- Galactorrhoea, amenorrhoea and infertility in females

- Abstinence causes
    - Depression
    - Guilt
    - Insomnia
    - Anorexia
- Psychotherapy
- Family therapy
- Peer support groups

Amphetamines

- They are club drugs
- E.g. Amphetamines, Methamphetamine
- Synthetic, indirect acting sympathomimetic drugs
- Result in release of endogenic amines such as dopamine and noradrenaline
- Cf. amphetamines MOA under ANS drugs
- Increases dopamine, serotonin and NE
- Increase NE
    - Increase arousal
    - Reduce sleep
- Increased Dopamine
    - Euphoria
    - Abnormal movements
    - Precipitate psychotic episodes
- Increased serotonin
    - Hallucination
    - Anorexia
    - Hyperthermia
- Amphetamines are neurotoxic
- Affect mainly serotonin and dopamine neurons
- Routes
    - PO, Smoked, IV
- Effects observed within hours of oral admin
    - Increase alertness, reduce fatigue
    - Agitation
    - Euphoria
    - Confusion
    - Bruxism
    - Skin flushing
    - Tachycardia and arrhythmias
    - Hypertensive crisis - stroke
- Chronic use
    - Tolerance may develop
- Withdrawal
    - Dysphoria
    - Drowsiness
    - Insomnia
    - Irritability
- Methamphetamine overdose Rx
    - Symptomatic
    - NH4CL may acidify urine and enhance clearance
    - Hypertension
        - Sodium nitroprusside
        - Alpha adrenergic antagonist
    - Sedatives reduce agitations

- Chronic methamphetamine dependence is like cocaine

Addiction to Cannabinoids, Psychedelic Agents and Inhalants

Tuesday, 28 March 2017 2:10 PM

Cannabinoids (Marijuana)

- From the cannabis plant
- The smoke from the burning cannabis contains many chemicals (includes 61 different cannabinoids)
- 9-tetracannabinoil (9-THC)
    - Produces most of the characteristic pharmacological effects of smoked marijuana
- Cannabinoid receptors
    - CB_1 (mainly CNS)
    - CB_2 (peripheral)
- Anandamide is an endogenous ligand for CB receptors
- Intoxication w/ marijuana produces changes in
    - Mood ("high" and "mellowing out")
        - This is the reason for abuse
        - Mellow out (slang) = to sbecome detached from worry, strife, stress etc.
    - Perception
    - Motivation
- Effects vary w/ dose
    - Last ~2 hours
    - During the high
        - Impaired cognitive function, perception, reaction time, learning and memory
    - Coordination may be impaired for several hours more
        - Affects operation of a motor vehicle and performance in the workplace or at school
- Other effects
    - Giddiness (dizzy)
    - Increased hunger
    - Unpleasant reactions
        - Panic, hallucinations, acute psychosis may occur w/
            - Higher doses
            - Oral ingestion rather than smoked marijuana
                - Smoking permits the titration of dose according to the effects
    - Lack of motivation
        - Drop out of social activities
        - Little interest in school, work etc.
    - Tolerance
        - Develops rapidly to most of the effects of marijuana
    - Withdrawal syndrome is not common
        - Occurs if daily oral doses are suddenly stopped

Marijuana Withdrawal Syndrome

- Restlessness
- Irritability
- Mild agitation
- Insomnia
- Nausea and cramps

- Marijuana abuse and addiction
    - No specific treatments
    - If depression, try antidepressants

Psychedelic Agents

- Drugs whose primary effect
    - Disturbances of perception, thought or mood at low doses
    - Minimal effects on memory and orientation
        - Hallucinogenic drugs
- Perception distortions
    - Hallucinations
    - Illusions
    - Paranoia

Classification

- Indoleamine hallucinogens
    - Lysergic acid diethylamide (LSD)
    - N,N-dimethyltryptamine (DMT)
    - Psilocybin
- Phenethylamines
    - Mescaline
    - Dimethoxymethylamphetamine (DOM)
    - Methylenedioxyamphetamine (MDA)
    - Methylenedioxymethamphetamine (MDMA ,"ecstasy")

- Have high affinity for 5-HT2 receptors (main receptors)
- Differ in their affinity for other 50HT receptors
- The effects of hallucinogenic drugs are variable
    - Even in the same individual

LSD

- PO, absorbed rapidly
- Effects
    - Begin 40-60 minutes
    - Peak at 2-4 hours
    - Gradually reduce over 6-8 hours
- Effects
    - Perceptual distortions (sometimes hallucinations)
    - Mood changes
        - Elation, paranoia or depression
    - Visual effects are prominent
        - Colours seem more intense
        - Shapes may appear altered
- Effects
    - Pupillary dilation
    - Increased BP and HR
    - Flushing
    - Salivation
    - Lacrimation
    - Hyperreflexia
- Can cause a "bad trip"
    - Usually severe anxiety
    - May also have depression and suicidal thoughts
- Repeated use of psychedelic drugs is unusual
    - Tolerance is not common
    - Tolerance does develop to the behavioural effects of LSD after three to four daily

doses
    - No withdrawal syndrome

Management
- May be indicated for "bad trips"
- Severe agitation
    - "talking down" by reassurance is the management of first choice
    - Try Diazepam
    - Antipsychotic medication
        - May intensify the experience
        - Not indicated

MDMA (Ecstasy) and MDA
- Have both stimulant and psychedelic effects
- Acute effects
    - Feelings of energy
    - Altered sense of time

Negative effects
- Tachycardia
- Dry mouth
- Jaw clenching, muscle aches
- Visual hallucinations
- Agitation
- Hyperthermia
- Panic attacks

Phencyclidine (PCP)
- Was used as an anaesthetic
- Had a high frequency of post-operative delirium w/ hallucination
- Now drug of abuse
- PO, smoked

Effects
- Emotional withdrawal
- Catatonic posturing
- Hostile or assaultive behaviour
- Anaesthetic effects - stupor or coma
- Muscular rigidity, rhabdomyolysis and hyperthermia
- Hypertension
- Dilated pupils

- PCP blocks of N-methyl-D-aspartate (NMDA)- type glutamate receptors
    - Ketamine is also abused and also acts on NMDA
- LSD and other psychedelics do not bind to NMDA receptors

PCP Overdose
- Must be treated by life support
- There is no antagonists
- No proven way to enhance excretion
- PCP coma may last 7-10 days
- Agitated or psychotic state

- Diazepam
- If prolonged use, anti psychotic medication
- PCP has anticholinergic activity
    - Avoid antipsychotic agents w/ significant anticholinergic effects e.g. Chlorpromazine

Inhalants

- Abused inhalants
- Many types of chemicals
- Are volatile at room temperature
- Produce abrupt changes in mental state when inhaled
- Examples
    - Toluene
    - Kerosene
    - Gasoline
    - Carbon tetrachloride
    - Amyl nitrate
    - NO
    - Aerosol sprays containing fluorocarbon propellants

Toluene

- Used by children
- Placed in a plastic bag and the vapours inhaled
- After several minutes of inhalation, dizziness and intoxication occur

Effects of Inhalants

- Effects of prolonged exposure or daily use of inhalants
    - Cardiac arrhythmias
    - Bone marrow depression]cerebral degeneration
    - Damage to liver, kidney, peripheral nerves

Anaesthetic gases

- Nitrous oxide and halothane
    - Abused by medical personnel
- NO is abused by food-service
    - It is a propellant for whipping cream canisters
        - Euphoria, analgesia
        - Overdose causes coma
        - Chronic use causes neuropathy

Management of overdose

- Supportive

GIT Pharmacology

25 April 2017 05:35

INTRODUCTION

- The blood vessels and the glands (exocrine, endocrine and paracrine) of the gastrointestinal tract are under both neuronal and hormonal control.

Neuronal Control

- There are two intramural plexuses:
  - Auerbach's/Myenteric
    - ◊ Located between the outer, longitudinal and middle, circular muscle layers
  - Meissner's/Submucous
    - ◊ Located on the luminal side of the circular muscle layer.
- They are mostly cholinergic and excitatory although a few are inhibitory.
- The plexuses are interconnected and their ganglion cells receive pre-ganglionic parasympathetic innervation from the Vagus.
- Incoming sympathetic fibres are mostly post-ganglionic.
- The two, along with other nerves in the GIT constitute the enteric nervous system.
- The neurons secrete adrenaline, noradrenaline, 5-HT, NO and other pharmacologically active peptides.

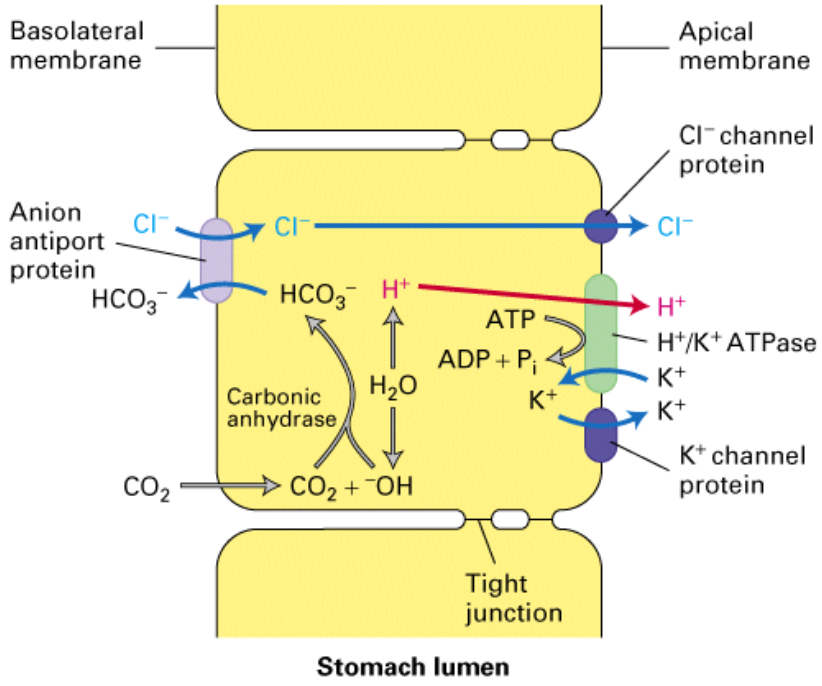
Hormonal Control

- Both endocrine and paracrine
- Endocrine hormones are secreted by the mucosa, examples include gastrin and cholecystokinin.
- Paracrine secretions are from the many special cells along the GIT; some also function as neurotransmitters.
- Some important pharmacological targets in the GIT include:
  - Gastric secretion
  - N,V
  - Gut motility and defecation
  - Formation and excretion of bile

Gastric Secretion

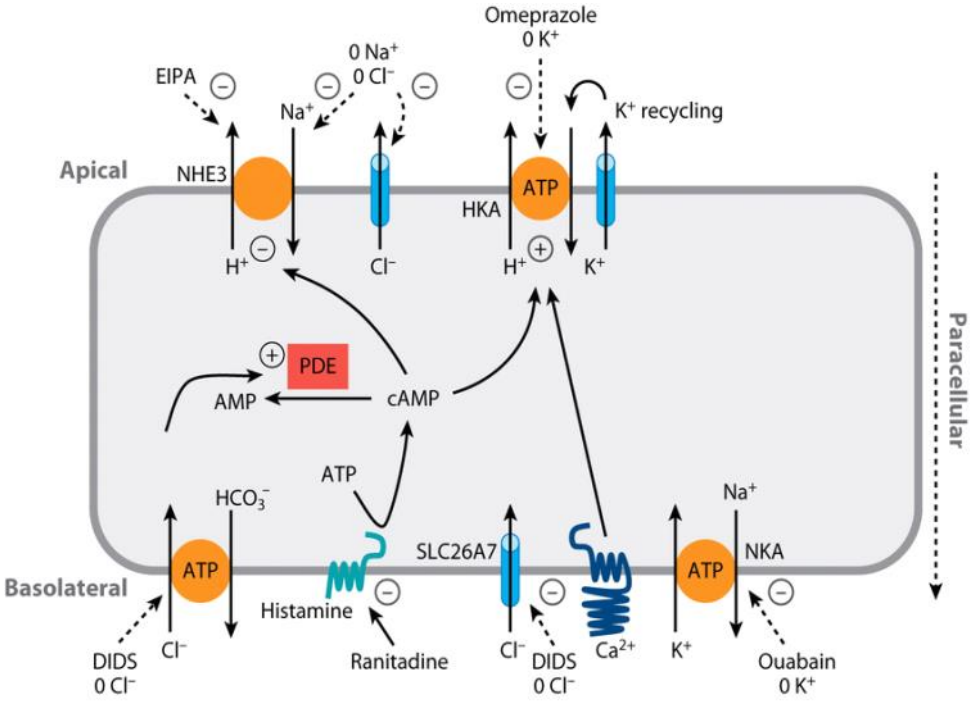
- The stomach secretes approx. 2.5L of acid daily
- Most of these are proenzymes such as
  - Prorenin and pepsinogen by the chief/peptic cells
  - HCL and intrinsic factor by the parietal/oxyntic cells
- These acids aid in proteolysis, ion absorption and killing pathogens.
- Mucous-secreting cells also abound
- Bicarbonate ions are secreted and are trapped in the mucous, creating a gel-like protective barrier. This aids in keeping the mucosal surface at a pH of 6-7 compared to the pH of 1-2 of the lumen.
- Local prostaglandins also have a constitutive role in maintaining this delicate homeostasis by stimulating mucous and bicarbonate secretion.
- Alcohol and bile can disrupt this layer (also NSAIDs)
- Disruptions in the protective and secretory mechanisms underlie the pathogenesis of *peptic ulcer disease*.

Regulation of acid secretion by parietal cells



A schematic illustration of the secretion of hydrochloric acid by the gastric parietal cell.

- The secretion of the parietal cells is an isotonic solution of HCl (150 mmol/l) with a pH less than 1, the concentration of hydrogen ions being more than a million times higher than that of the plasma.
- The principal mediators that directly or indirectly affect parietal cell output are:
  - Histamine - stimulatory local hormone
    - ◇ Released from the enterochromaffin-like cells (ECL cells)
    - ◇ Act in a paracrine manner on parietal H_1 receptors, increasing cAMP. (the concentration released is below the threshold required to activate vascular H_2 receptors)
  - Gastrin - stimulatory peptide hormone
    - ◇ From G cells in the gastric antrum and secreted into portal blood (endocrine)
    - ◇ Stimulates ECL cells via the gastrin/cholecystokinin receptors (CCK_2) receptors that increases intracellular Ca^{2+}
    - ◇ Also stimulates histamine synthesis by ECL cells and indirectly increases pepsinogen secretion
    - ◇ Stimulates blood flow
    - ◇ Increases gastric motility
    - ◇ Amino acids and small peptides stimulate the gastrin secreting cells as well as milk and calcium salts
  - Acetylcholine - stimulatory neurotransmitter
    - ◇ Stimulates M_3 receptors on parietal cells, increasing intracellular Ca^{2+} and proton release
    - ◇ Inhibits somatostatin release from D cells which potentiates its effects on parietal cell acid secretion
  - PGI_2 PGE_2 - inhibit acid secretion
    - ◇ Increase bicarbonate secretion via $EP_{1/2}$ receptors
    - ◇ Increase release of protective mucin via EP_4 receptor
    - ◇ Reduces gastric output via $EP_{2/3}$ receptors on parietal cells and preventing the vasoconstriction (and thus damage to the mucosa) that follows injury/insult.
  - Somatostatin - inhibitory peptide hormone
    - ◇ From D cells all over the stomach
    - ◇ Acts on SST_2 receptor and exerts paracrine inhibitory effects
    - ◇ Inhibits gastrin release from G cells, histamine release from ECL cells as well as directly on parietal cell output



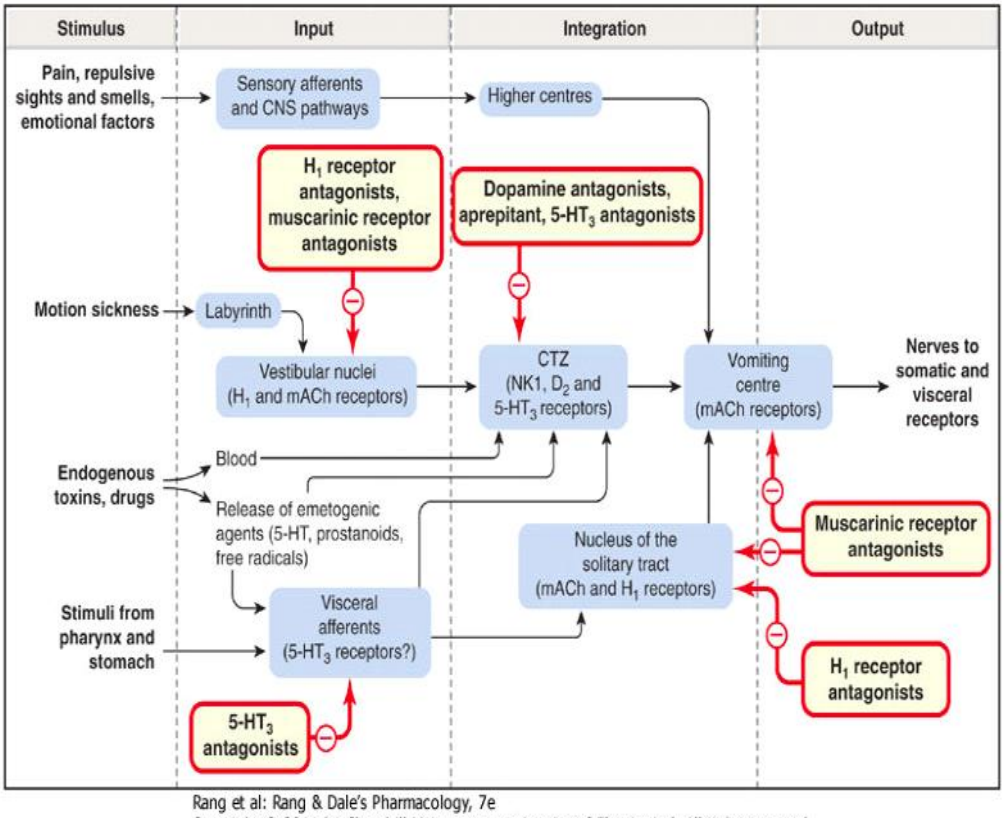
Geibel JP, Hebert SC. 2009.
Annu. Rev. Physiol. 71:205–17

Schematic diagram showing the regulation of the acid-secreting gastric parietal cell, illustrating the site of action of drugs influencing acid secretion.

- Direct vagal stimulation can also provoke acid secretion ('stress ulcers') via acetylcholine as described above

Vomiting

- This is coordinated centrally by the vomiting/emetic centre in the medulla which is a neural pathway that integrates signals from other locations
- One of these in the *area postrema* is the chemoreceptor trigger zone, CTZ, which receives input from the labyrinth in the inner ear through the vestibular nuclei (motion sickness) and vagal afferents rising from the GIT.
- CTZ is therefore, a site of action of many antiemetic drugs.
- The emetic centre also receives signals directly from the vagal afferents
- There is also input form higher cortical areas which explains why sights, smells and emotional states can induce nausea and vomiting.



Rang et al: Rang & Dale's Pharmacology, 7e
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Schematic diagram of the factors involved in the control of vomiting, with the probable sites of action of antiemetic drugs.

THE MOTILITY OF THE GASTROINTESTINAL TRACT

- Drugs that alter the motility of the gastrointestinal tract include:
  - purgatives, which accelerate the passage of food through the intestine
  - agents that increase the motility of the gastrointestinal smooth muscle without causing purgation
  - antidiarrheal drugs, which decrease motility
  - antispasmodic drugs, which decrease smooth muscle tone.

Drugs in the Management of PUD

Monday, 3 April 2017 11:11 AM

H_2 receptor antagonists

- Bind selectively and competitively to the histamine H2 receptor on the basolateral membrane of the parietal cell
- As well ad inhibiting gastric acid release by histamine, they inhibit acetylcholine and gastrin mediated acid secretion
- Avoid taking with antacids
- The inhibitory effect can be overcome, particularly when gastrin levels are high, as occurs postprandially
- In addition, tolerance may develop, probably as a result of down-regulation of receptors

Indications

- PUD
- Gastro-oesophageal reflux disease (GORD/GERD)
- Dyspepsia
- Stress ulcer prophylaxis (Ranitidine)
- Peptic ulcer healing w/ H2-receptor antagonists correlates best w/ suppression of nocturnal acid secretion
    - Preferably, give these drugs as a single evening dose
- The usual ulcer healing course is 8 weeks

H_2 Blockers

- Cimetidine
- Ranitidine
- Famotidine
- Nizatidine

Pharmacokinetics

- Rapidly absorbed from the intestine
- Cimetidine, Ranitidine and Famotidine undergo first-pass metabolism
    - Bioavailability - 50%
        - For Nizatidine, 100%
- Half-lives:
    - 1.1-4 hours but duration of action depends on dose administered
- Elimination by metabolism, glomerular filtration and renal tubular secretion
- Reduce dose in those w/:
    - Moderate to severe renal insufficiency
    - Severe hepatic insufficiency
- In elderly, decline of up to 50% in drug clearance and significant reduction in volume of distribution

Adverse Effects

- AE occur in less than 3% of patients and include diarrhoea, headache, fatigue, myalgias and constipation
- CNS effects
    - W/ IV administration esp. in ICU patients
    - Confusion
    - Agitation
    - Hallucinations may occur
- Cross the placenta and also secreted in breastmilk
    - May affect nursing infant
- Rapid IV infusion may block cardiac H2 receptors and cause bradycardia
    - Give as slow infusion

Cimetidine

- First H_2-receptor antagonist to be used in clinical practice
- AE and interactions are few in short-term use
- Anti-androgenic effects e.g. gynaecomastia, galactorrhoea, impotence and decreased libido in males
- In the elderly, particularly, it may cause CNS disturbances including lethargy, confusion and hallucinations
- Inhibits cytochromes P450, in particular, CYP1A2 and 3A4

- Potential increased effect from other drugs w/ a low therapeutic index that is inactivated by these isozymes e.g. Warfarin, Phenytoin

Ranitidine, Famotidine, Nizatidine

- The MoA, uses and therapeutic efficacy are essentially those of cimetidine
- Do not inhibit hepatic microsomal enzymes and do not block androgen receptors
- Famotidine is more potent than Cimetidine and Ranitidine

Proton Pump Inhibitors

- Irreversible inactivation of the H^+/K^+-ATPase enzyme system (proton pump) in parietal cells, which is the final common pathway for acid production
- Include
  - Omeprazole
  - Esomeprazole
  - Lansoprazole
  - Pantoprazole
  - Rabeprazole
- All are similar in efficacy and MoA

PPI Indications

- PUD
- GORD
- Dyspepsia
- Zollinger-Ellison Syndrome
- Scleroderma oesophagus
- H.pylori eradication, as part of an effective regimen
- Prevention and/or treatment of upper GI adverse effects of NSAIDS
- In selected patients for stress ulcer prophylaxis, acute upper GI bleeding, prevention of acid aspiration
- All PPIs have similar efficacy and adverse effects
- May differ in their potential to cause drug interactions
- Omeprazole, Pantoprazole and Esomeprazole available as injection and oral preparations

Precaution

- Exclude gastric carcinoma before starting treatment of gastric ulcers
  - May mask symptoms and delay diagnosis
  - Risk of accumulation when higher doses used in hepatic impairment
    - Monitor for adverse effects

Omeprazole

- A prodrug, in common w/ all PPIs
- It enters the parietal cell from the blood by non-ionic diffusion, and becomes ionised in the acid milleu around the secretory canaliculus, where it is trapped and concentrated
- Irreversible inactivates the enzyme causing inhibition of acid secretion
- The H+/K+-ATPase regenerates when the PPI discontinued
- Degraded at low pH and must be given in enteric-coated granules
- Systemic availability increases w/ dose and also in time, owing to decreased inactivation of the prodrug as gastric acidity is reduced

Adverse Effects

- Include ND, headache, constipation and rash, but are uncommon
- Inhibits the 2C family of the cytochrome P450 system reduced metabolism of Warfarin, Diazepam, Carbamazepine and Phenytoin, and enhances the effect of these drugs (but inhibition is less than Cimetidine0
- Note:
  - Long-term use of powerful anti-secretory drugs may increase the risk of gastric neoplasia

Mucosal Protective Agents

- Sucralfate
- Colloidal Bismuth Compounds
  - Bismuth chelates

        - Colloidal bismuth subcitrate
        - Tripotassium dicitrato bismuthate
        - Bismuth subsalicylate
        - Bismuth dinitrate
    - Liquorice Derivatives
        - Carbenoxolone
        - Deglycerrhizinised liquorice
    - Prostaglandins
        - Misoprostol

Sucralfate

- A salt of sucrose complexed to sulfated aluminium hydroxide
- Treatment of GU and DU ulcers and may act by protecting the mucosa from acid-pepsin attack
- At pH below 4, there is extensive polymerisation and cross linking of the sucralfate
    - Condensed polymer is a very sticky, viscid, yellow-white gel
- Gel adheres strongly to the epithelial cells and to the base of the ulcer craters
- Affinity for the crater base is much higher than that for the epithelial surface and it is difficult to wash the gel from the crater
- Side effects:
    - Dry mouth
    - Vomiting
    - Constipation
- Drug Interactions
    - Can absorb and reduce the bioavailability of other drugs e.g. Fluoroquinolone antibiotics, Tetracycline, Theophylline, Amitryptyline and Digoxin
    - Efficacy reduced by antacids given concurrently because sucralfate requires an acidic environment for activation

MoA

- The binding to the ulcer craters probably represents the main therapeutic action
- Proposed that sucralfate stimulated the formation of PGs by the gastric mucosa and therefore, exerting a "cytoprotective" effect
- May also bind epithelial growth factor and fibroblast growth factor, enhancing mucosal repair

Bismuth Compounds

- Bismuth chelates promote healing of gastric or duodenal ulcers
- May act by coating the ulcer or stimulating PGs, mucus and bicarbonate secretions
- Have direct action against H. pylori and may be used in multi-drug regimens for eradication of H. pylori infection

Treatment of H. Pylori Infection

- H.pylori is indicated in the production of peptic ulcers, particularly duodenal ulcers and is a risk factor for gastric cancer
- Combination of 3 drug is employed to eradicate H. pylori usually
    - Omeprazole + Amoxicillin + Metronidazole
    - Omeprazole + Clarithromycin + Amoxicillin
    - Tetracycline + Metronidazole + Bismuth Chelates

- Over 90% of Bismuth appears in the stool
- Less than 10% is absorbed, stored in the tissues and slowly excreted through the renal route
- Note:
    - Bismuth agents should only be used for short periods
    - Avoid in patients w/ renal insufficiency

Adverse Effects

- Excellent safety profile
- NV
- Blackening of stool which may be confused w/ GIT bleeding
- Darkening of tongue by liquid preparations
- Prolonged use rarely leads to Bismuth toxicity resulting in encephalopathy (ataxia, toxicity, headache, confusion and seizures)
- High dosage of bismuth subsalicylate may lead to salicylate toxicity

Prostaglandin Analogues

- PG e.g. PGE2 are cytoprotective and also participate in feedback regulation of acid secretion by inhibition of both adenylyl cyclase activity and release of gastrin
- Interference w/ protective functions of PGs by inhibition of their synthesis is thought to account for much of the ulcerogenic

effect of ASA-like drugs

Misoprostol
- Synthetic analogue of PGE1 (Alprostadil) promotes gastric and duodenal ulcer healing
- Protects the GI mucosa by increasing secretion of mucus in the stomach and stimulating bicarbonate secretion in the duodenum
- Inhibits basal and stimulated acid secretion by direct action on gastric parietal cells
- Can protect against NSAID-associated gastric ulcers but not dyspepsia
- As effective as H2 receptor antagonists in promoting duodenal ulcer healing

PK
- Rapidly absorbed following oral administration
- Metabolised to metabolically active free acid
- Half-life less than 30 minutes, therefore given 3X/4X daily
- Excreted in urine but dose reduction is not necessary in those w/ renal insufficiency

Side effects
- ND
- Abdominal pain
- Dyspepsia
- Flatulence
- The effects are self-limiting i.e. do not interfere w/ therapy
- Contraindicated in pregnancy because it increases uterine tone

Carbenozolone
- Liquorice extract used as anti-ulcer since 1962
- An oleandane derivative obtained from glycyrrhiza
- Has steroidal structure and possesses significant mineralocorticoid activity
- Effective in healing both GU and DU

MoA
- Alters composition of mucus and enhances mucosal barrier to diffusion of acid
  - Increases protection, secretion and viscousity of intestinal mucus
- Other suggested therapeutic effects:
  - Augmentation of glycoprotein synthesis
  - Inhibition of enzymes than inactivate PGs
  - Suppression of activation of pepsinogen
- Appears to be as effective as _

Adverse Effects
- Results frequently from its mineralocorticoid (aldosterone like) actions
  - Hypokalaemia
  - Fluid retention
  - Hypertension
- Impaired glucose tolerance has also been observed
- The side effects are major deterrents to its clinical usefulness
- Concurrent administration of Spirolactone controls liquid retention but abolishes ulcer-healing effect
- Thiazides prevent sodium retention without abolishing the ulcer healing effects.

Deglycyrrhizinised Liquorice
- Similar actions as carbenoxolone on the gastroduodenal mucosa but lacks mineralocorticoid effect

Anti-Muscarinics
- Include
  - Pirenzepine
  - Telenzepine
- Vagal stimulation produces an increased secretion of histamine and gastic acid
  - This can be blocked by nicotinic or M1 muscarinic antagonists
- Muscarinic antagonists can reduce basal secretion of gastric acid by 40-50%
- Selective antagonists at M1 receptor are less likely o produce the adverse effects that are charactweristic of cholinergic blockade (e.g. dry mouth, tachycardia)

Pirezepine

- Treatment of gastric and duodenal ulcers
- Selective M1 anti-muscarinic drug
- Inhibits gastric acid and pepsin secretion
- As effective as Cimetidine in healing gastric and duodenal ulcers
- Used w. H2 antagonists in resistent cases
- More potent than Telenzepine

Side Effect

- Occasionally dry mouth and visual disturbances
- Agranulocytosis and thrombocytopenia have been reported

Metoclopramide

- A prokinetic agent
- Has been used in the treatment of PU with the intention of augmenting normal peristalsis and abolishing the enterogastric reflux of bile which is thought to be a factor in the pathogenesis of many GU and DU
- Has some value in gastric ulcer but its efficacy has been poor in DU
- Reduces gastro-oesophageal reflux and is used in the Mx of reflux oesophagitis

Drugs Affecting GIT Water Flux and Motility

Monday, 3 April 2017 2:17 PM

- Laxatives
- Cathartics
- Purgatives
- Aperients
- Evacuants

Definitions
- Laxation
  - The evacuation of formed faecal material from the rectum
- Catharsis
  - The evacuation of unformed, usually watery faecal material
  - Low dose cathartics may cause laxative effects

Introduction
- Stool volume and consistency is determined by fluid content
- The amount of fluid in stool depends on
  - Oral intake
  - GIT secretions
  - GIT absorptions
  - GIT motility
- Approx. 100ml of water in faeces per day
  - If less = constipation
  - If more = diarrhoea
- Constipation can be corrected w/o drugs usually
  - Fibre-rich diet
  - Adequate fluid intake
  - Appropriate bowel habits and training
  - Avoid constipating drugs or adjust doses
- Drugs are used if above measures fail

Classification
- Luminally active drugs
  - Hydrophilic colloids
    - Bulk forming agents
      - Bran
      - Psyllium
      - Methylcellulose
      - Calcium polycarbophil
      - Malt soup extract
  - Osmotic agents
    - Saline laxatives
      - Sodium phosphates
      - Magnesium sulphate
      - Magnesium hydroxide
      - Magnesium citrate
    - Non-digestible sugars and alcohols
      - Lactulose
      - Sorbitol

            - Mannitol
        - Polyethylene glycol solutions
    - Stool-wetting agents
        - Surfactants
            - Poloxamers
            - Docusates
    - Emollients
        - Mineral oil
- Non-specific stimulants or irritants
    - Diphenylmethane derivatives
        - Bisacodyl
        - Phenolphthalein (not used - carcinogenic)
        - Sodium picosulphate
    - Anthraquinones
        - Aloe
        - Cascara
        - Senna
    - Castor oil
- Prokinetic agents
    - Dopamine receptor antagonists
        - Metoclopramide
        - Domperidone
    - Motilides
        - Erythromycin
    - 5-HT4 receptor agonists
        - Prucalopride
        - Cisapride

- Soften faeces in 1-3 days
    - Bulk forming agents
    - Surfactants
- Soft or semi-fluid stools in 6-8 hours
    - Anthraquinone derivatives
- Watery evacuation in 1-3 hours
    - Osmotic laxatives
    - Castor oil
- Fibre - that part of food that resists enzymatic digestion
- Colonic bacteria ferment fibre to varying degrees
- Fermentation
    - Produces short chain fatty acids that are trophic for colonic epithelium
        - May have a prokinetic effect
    - Increase bacterial mass
        - May contribute to stool volume
- Unfermented fibre can attract water and increased stool bulk
- Insoluble, poorly fermentable fibres are most effective in increasing stool bulk and transit

Types of Fibres

- Nonpolysaccharides
    - Poor water solubility
        - Lignin (zero% fermented)
        - Cellulose (15%)
    - Non-cellulose polysaccharides
        - Good water solubility
            - Hemicellulose (56-87%)
            - Mucilage and gums (85-95%)

- Pectins (90-95%)

Bulk Forming Agent

- Bran
  - From cereal grains
  - Wheat bran (high lignin content) is most effective at increasing stool weight
- Psyllium husk
  - From the seed of the plantago herb
  - Contains a hydrophilic mucilloid that is fermented
    - Increase in colonic bacterial mass
- Fibre is contraindicated in
  - GIT obstruction
  - Megacolon or megarectum
  - Phenylketonuria
    - If sugar-free bulk laxatives w/ aspartame
- _
- _

Stimulant (Irritant) Laxatives

_

Bisacodyle

- Swallow tablets whole (don't chew or crush)
  - This prevents gastric irritation
- Approx. 5% is absorbed
- Activates by esterases in the bowel
- Laxative effects of an oral doe produced after 6 hours
- Rectal suppositories work within 30-60 minutes
- Mainly excreted in stool
- AE
  - Catharsis (overdose)
  - Fluid and electrolyte deficits (overdose)
  - Damage the mucosa from inflammation
  - Gastric irritation
  - Cramps
- Avoid administration w/ milk and antacid medication within 1 hour of administration
  - Prevent s activation of the drug in the stomach
- Should not be used for > 10 consecutive days
  - May cause colon atony

Anthraquinone Laxatives

- These are plant derivatives
- They are converted to monoanthrones b bacteria in the colon
- Monoarthrones irritate the mucosa

MoA

- Produce propulsive colonic contractions
- Induce water and electrolyte secretion

PK

- Poorly absorbed
- Absorbed portions are excreted in bile, saliva, milk and urine
- Laxative effect in 6-12hours after ingestion
  - Activated in the colon

AE

- Of long term use
    - Melanosis coli (pigmentation of the colon)
        - If used for > 4-9 months
        - Reversible (stop laxative use)
    - Cathartic colon
        - Due to laxative abuse (for years)
            - Usually in women
            - Symptoms
                - Bloating
                - A feeling of fullness
                - Abdominal pain
                - Incomplete faecal evacuation

Castor Oil

- From the bean of the castor plant
- GIT lipases release the active agent, ricinoleic acid)
- Stimulate secretion of fluid and electrolytes
- Increases intestinal transit

AE

- Unpleasant taste

Prokinetic Agent

- Prokinetic interaction w/ specific receptors involved in the regulation of motility e.g.
    - Prucalopride
- Act as a 5-HT4 agonist

Other Agents for Constipation

- Misoprostol
    - Stimulates colonic contractions
- Colchicine
    - Unknown MoA
- Neurotrophin - 3 (NT-3)
    - Unknown MoA
- Lubiprostone
    - ?? Binds to EP4 receptors
    - Promotes secretion of fluids
    - Activates motility
    - Use
        - Irritable bowel syndrome w/ constipation (IBS-C) in adult women
- Linaclotide
    - An agonist of guanylate cylase C that stimulates secretion and motility through Chloride 2 channels
    - _

Opioid-Induced Constipation

- Peripherally active μ opioid receptor antagonists
    - E.g. Methylnaltrexone and Alvimopan
        - Both are μ receptor antagonist
        - Initiate bowel movement
        - They lack anti-analgesic effects

Post-operative Ileus

- Dexpanthenol
    - A precursor of co-enzyme A, which enhances acetylcholine synthesis
        - Acetylcholine is the major excitatory neurotransmitter in the gut

Enemas
- Normal saline solution
- Sodium phosphate solution

Suppositories
- Glycerin
    - A hygroscopic agent and lubricant
- NaHCO3 and Potassium Bitartrate
    - They produce CO2 which causes rectal distention and initiate bowel movement

Appetite Stimulants and Suppressants

Tuesday, 4 April 2017 11:42 AM

Background
- Intermittent food supply provide continuous energy requirement
- Storage of fuel for energy as TGs of fat controlled by the thrifty gene
- Obesity on the increase in affluent society that take high calorie-rich food
- CNS - hypothalamus interacts w/ the adipose tissue through a homeostatic mechanism that involves hormones from the_

Obesity
- Excess body fat
- Body weight exceeds 20% of the ideal
- Ideal measured using BMI
- BMI is the body mass in kg divided by the square of the height in metres

Control of Energy Balance
- Depends upon food intake, energy storage and energy expenditure
- Leptin acts on region of the brain that controls appetite
- Leptin reduces food intake and body weight

Leptin
- Leptin mRNA is expressed in fat cells
- Its synthesis is increased by glucocorticoids, insulin and oestrogen
- Reduced by ß-adrenoceptor agonists
- Pulsatile concentration that is inversely proportional to hydrocortisone levels
- Enter saturable transport on reaching the brain
- Entry to the brain proportional to the plasma level
- Acts on the hypothalamus-leptin receptors
- Sensor of body fat

Insulin
- Stimulate leptin expression in fat cells
- Adipose tissue is an endocrine organ that secretes a host of autocrine, paracrine and endocrine mediators

Energy Balance
- The arcuate nucleus in the hypothalamus contains receptors for leptin/insulin
- Reduced leptin levels activates the peptide neuropeptide and agouti related peptide to increase appetite, food intake and reduce energy expenditure
- Increased leptin stimulates the protein POMC receptor that releases α-MSH to de crease food intake and increase energy expenditure

Expenditure of Energy
- Metabolism
  - Cardiorespiratory
  - Enzymes
- Physical activity
  - Increases the metabolism
- Thermogenesis
  - Sympathetic NS
  - White and brown fat cells - NE increase lipolysis

Food Intake

- Cholecystokinin in the GIT in response to mechanical and physical stimuli act locally on cholecystokinin A receptors and transmits a signal through the Vagus to decrease food intake
- Cholecystokinin is also a NT that acts in B receptors in the brain to express satiety
- Insulin stimulates leptin release from fat to decrease food intake
- Type 2 diabetic increase weight due to effect of insulin on blood sugar

Obesity

- Epidemic - global 10%
- 36% USA adults
- 15-20% Europe
- Increase type II DM
- Increase HT, TGs, Gallstones, HD
- Cancer of the colon, breast, prostate, gallbladder, ovary, uterus
- Osteoarthritis, increased uric acid, hypogonadism

Pathophysiology

- Resistance to leptin - defect in synthesis of leptin, transport in circulation and CNS
    - Defective hypothalamus receptors
    - Post signalling
    - Dysfunction of other mediators
    - Increase TNFa
    - Reduced insulin sensitivity in muscle and fat
    - Reduced ß3-adrenoceptors in rown fat
    - Alteration of transcription factors that regulate gene expression of enzymes associated w/ glucose and lipid metabolism

Therapy

- Genetic
    - No recourse
    - Food intake -
    - Physical exercise_
    - Pharmacologucal therapies

Pharmacological Therapies

- Orlistat
    - Decrease fat absortpion by preventing the breakdown of dietary fat
- _
    - _

Orlistat

- Pancreatic lipase inhibitor
- Prevents breakdown of fat to fatty acid and glycerol
- Increase in faecal fat loss up to 32%
- Modest c.f. Placebo
- Poorly absorbed
- What the potential AE of Orlistat?
    - Abdominal cramps, flatus, faecal incontinence, borbogymi (a rumbling or gurgling noise made by the movement of fluid and gas in the intestines), oily spotting
    - Decrease absorption of oral contraceptive agents
    - Need to supplement fat-soluble vitamins

Sibutramine

- Antidepressant, anti-obesity
- Reduce food intake and enhance satiety
- Reduce LDL, TGs and increase HDL
- Increases energy expediture
- MoA
    - Inhibitor of 5H/NE reuptake at the hypothalamus
- Orally well absorbed extensive FPE to active metabolites
- Adverse Effects
    - Dry mouth
    - Constipation
    - Insomnia
    - Increas in HR and BP (hypertension)

Potential New Agents

- Mazindol - adrenergic agonist
- Posatirelin - TRH analogue
- Sertraline - SSRI
- Bupropion - dopamine reuptake inhibitor
- Enterostatin
- pegylated leptin

Emetics, Antiemetics and Pro-Kinetic Agents

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Vomiting

- Can occur as a result of stimulation of the vomiting centre by taste, smell or odour or by stimulationof the CRTZ (Chemoreceptor trigger zone) by
  - Toxins or drugs
  - Radiation
  - Vestibular disorders
  - Systemic disorders or infections
  - Pregnancies
  - CNS infections or increased ICP
  - Hepatobiliary disorders
  - GIT Obstructions
  - Dysmobility
- Drugs only given if the cause is known, chosen accordingly to aetiologyof vomiting
- Vomiting centre has a high concentration of M_1, 5HT, H_1. Also rich in D_2, NK (neurokinin), $5HT_3$ opioid
- Located in the 4th ventricle, area postrema, outside BBB, accessible to enterogenic stimuli in blood or CSF

Vestibular System

- Impaired in motion sickness via CN VIII
- Rich in muscarinic receptors, H1
- Vagal and spinal afferent nerves from GIT are rich in 5HT3 receptors
- Irritation og GIT mucosa and release of mucosal 5HT and activation of the receptors. This leads to stimulation of vagal afferent input to the vomiting centre and CRTZ
- CNS plays a role in vomiting, psychiatric disorders, stress and anticipatory vomiting prior to cancer chemotherapy

Emetics

- Usually given in management of poisoning

Ipecac (Syrap; Ipecacuanha)

- OTC drug
- Administration
  - Taken w/ a glass of water/fluid and w/ milk or a carbonated beverage
- Onset
  - Should occur in 20-30 minutes
  - If not dose repeated
  - Gastric lavage may be needed if no vomiting occurs
- Caution
  - Avoid if substance is caustic or petroleum

Apomorphine

- Used to induce vomiting
- Not recommended due to AE

Antiemetic

- Antihistamines
  - Promethazine
- Anticholinergics

- Dopamine antagonists
    - Phenathezines
    - Butyrophenones
    - Metaclopramide
- Domperidone
- BDZs
- 5HT antagonists
- Glucocorticoides
- Cannabinoids
- Aprepitant

Antihistamines and Anticholinergics
- Weak antiemetic properties as single agents
- Indications
    - Prevention and treatment of motion sickness
- Diphenhydramine and Dimenhydrinate
    - Significant anticholinergic properties but are sedating
    - Used w/ other antiemetics for treatment of emesis due to chemotherapy
- Meclizine
    - Minimal anticholinergic properties
    - Less sedating
    - For prevention of motion sickness
    - Given as transdermal patch

Phenothiazines and Butyrophenones
- Antipsychotics and block dopamine receptors
- Commonly used as antiemetics
    - Promethazine
    - Prochlorperazine
    - Thiethylperazine
- Antiemetic MoA
    - Inhibition of dopamine and muscarinic receptors while sedating efects is due to H1 blockade
- Droperidol
    - A butyrophenone
    - Exerts antiemetic effect by blocking dopamine receptors
    - Given IM or IV
    - May prolong QT interval

BDZs
- Diazepam and Lorazepam
    - Used as anziolytics prior toirritation of chemotherapy to reduce anticipatory vomiting or vomiting due to anxiety

Serotonin Antagonists
- Include
    - Ondansetron
    - Dolasetron
    - Tropisetrin
    - Granisetron
- PD
    - Potent antiemetic properties
    - Effect mediated through 5HT3 receptor blockade on intestinal vagal afferents and probably also in CTRZ and vomiting centres

    - Effect restricted to emesis attributable to vagal stimulation, other emetic stimuli e.g. motion sickness are poorly controlled
    - No effect on GIT motility but may slow colonic transit
- PK
    - PO or IV
    - Half-life: 4-9 hours
    - Extensive hepatic excretion
    - Dose adjustment unnecessary in geriatrics and renal impairment
- AE
    - Headache, dizziness, confusion
    - Small but significaant prolongationof GT interval - more pronounced w/ Dolasetron
- DI
    - Hepatic clearance may be reduced by other drugs, altering their half=lives
- CU
    - Prevention and treatment of chemotherapy-induced NV
    - Most effective if given IV, 30 minutes prior to chemotherapy and repeated 24 hours
    - Prevention and treatment of post-operative NV
    - In patients undergoing radiation therapy

Glucocorticoids
- Include
    - Dexamethasone
    - Methylprednisone
- Have antiemetic properties but most are not well documented
- Appear to enhance efficacy of 5HT3 receptor antagonists for prevention of acute and delayed NV in patients receiving moderately to highly emetogenic chemotherapy regimens

Neurokinin Receptor Antagonists
- Includes
    - Aprepitant
- Selective NK1 receptor antagonist, crosses BBB and occupies these receptors in the brain
- No affinity for serotonin, dopamine or corticosteroid receptors
- PK
    - PO
    - BA: 65%
    - T0.5: 12h
    - Biotransformed by CYP3A4
        - Inhibits metabolism of some drugs e.g. warfarin
        - Its metabolism is inhibited by drugs e.g. Ketoconazole
- CU
    - In combination w/ 5HT3 receptor antagonists and corticosteroids for prevention of acute and delated NV from highly emetogenic chemotherapy regimens

Cannabinoids
- Include
    - Dronabinol
        - A major psychoactive chemical in marijuana
        - Used as an effective stimulant and antiemetic
        - Not commonly used
        - Synergistic antiemetic effect if given w/ Phenothoazines to prevent chemotherapy induced NV
        - AE
            - Euphoria, dysphoria, hallucination, sedation
            - Increased appetite
            - Tachycardia, orthostatic HT

Metoclopramide

- Prokinetic
  - Stimulate GIT motor function and enhance gastric emptying
- MoA
  - Block D2 receptors in the GIT, enhancing cholinergic smooth muscle stimulation responsible for prokinetic effect
    - Increase oesophageal persitaltic amplitude and increases _ and enhance gastric emptying
  - Has no effect on small intestines or colon motility
  - Block D2 receptors in CTRZ of medulla, area postrema > antiN and antiemetic action
- AE
  - CNS, restlessness, drowsiness, insomnia, anxiety, agitation
  - Extrapyramidal
    - Dystonia
    - Akathisia
    - Parkinsonism
    - Tardive dyskinesia (may be irreversible
  - Both M and D elevate PRL levels
    - Galactorrhoea
    - Gynaecomastia
    - Impotence
    - Increased menstrual disorders
  - D is well tolerated and doesn't cross BBB

Drugs in Treatment of Irritable Bowel Disease

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IBD
- Diarrhoea
  - Loperamide
- Constipation
  - Fibre soften stool and reduce straining
- Osmotic laxatives to increase frequency of opening bowel in patients w/ constipation
- Chronic pain
  - TCAs
    - Amityptyline
    - Desipramine

TCAs
- Alter processing of visceral afferent
- Anticholinergic effect on GIT motility and secretion. Reduce stool frequency and liquidity
- Alter receptors for enteric neurotransmitters that affect visceral afferent sensation such as serotonin

D/Dx of Irritable Bowel Disease out
- Irritable bowel syndrome and inflammatory bowel disease
- S/S
  - Diarrhoea
  - Constipation
  - Abdominal pain

Aetiogenesis
- Not known
- Psychological factors implicated
- Ulcerative colitis and Crohn's disease are forms of IBD - colon and ileum

What
Ulcerative Colitis and Crohn's
- Autoimmune inflammatory disorders
- Progressive and can be severe

Treatment of Ulcerative Colitis and Crohn's disease
- Anti-inflammatory drugs
- Immunosuppressants
- Surgery resection

Glucocorticoids
- Potent anti-inflammatory
- Prednisone and Udesonide choice drugs
- Route:
  - PO, locally
  - Suppositories or enema
- Used in acute attacks

Aminosalicylates
- Used for long term maintenance therapy
- Include
  - Sulfasalazine
  - Olasalazine
  - Balasalazine

Sulfasalazine
- Consists of sulfonamide sulfapyridine linked to 5-aminosalicylic acid (5-ASA)
- 5-ASA is the active moiety released in the colon
- MoA
  - Reduce inflammation by
    - Removing free radicals
    - Inhibition of prostaglandins
    - Decrease neutrophil chemotaxis
    - Generates superoxides
- Aes
  - Diarrhoea
  - Salicylate hypersensitivity
  - Interstitial nephritis

- What are the other indications of corticosteroids?
- How do steroids work in the above mentioned conditions (MoA)?
- Review and list the adverse effects of corticosteroids addressing the diverse ADRs in various systems?
- How would you manage these ADRs

    - Sulfapyridine associated w/ side effects of sulfonamides

Immunosuppressants

- Include
    - Methotraxate
    - Ciclosporin
    - Azathioprine
        - 6-mercaptopurine

Biologics

- Monoclonal antibodies directed against TNFa
    - Infliximab
    - Adalimumab

Treatment of Portal Hypertension and Variceal Bleeding

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Portal HT

- Consequent to chronic liver disease
- Increased blood flow within the portal venous system
- Increased resistance to portal flow within the liver
- Splanchnic blood flow is increased to patients w/ cirrhosis due to low arteriolar resistance mediated by increased circulating vasodilators and decreased sensitivity to vasoconstrictors
- Intra-hepatic resistance to blood flow in cirrhosis is increased due to fixed fibrosis within the space of Disse and hepatic vein w/…
- …reversible vasoconstriction of hepatic sinusoids and venules

Consequences

- Ascites
- Hepatic encephalopathy
- Porto-systemic collaterals - gastric and oesophageal varices

Somatostatin and its analogues

- Reduces portal blood flow
- Reduces variceal pressure
- MoA poorly understood
- No direct action on smooth muscle
  May cause alteration of mesenteric blood flow by inhibition of glucagon and other gut neuropeptides

Vasopressin and Terlipressin

- Antidiuretic hormone
- Polypeptide secreted by the hypothalamus
- Stored in the posterior pituitary
- Arteriolar vasoconstrictor
- Physiologic role of maintaining osmolality

Vasopressin

- Causes splanchnic vasoconstriction
- Lowers portal pressures
- Angiographic infusion in acute bleed
- Indications
  - Small and large bowel bleed
  - Diverticulosis

Side Effects

- Common
- Vasospasms
- HT, AMI, Mesenteric infarction
- Co-administer w/ Nitroglycerin
- ND, abdominal cramps
- Antidiuretic effects
  - Fluid retention and hyponatraemia
  - Pulmonary oedema

Terlipressin

- Vasopressin w/ fewer side effects

Beta-adrenoceptor blocking agents

- Reduce portal venous blood flow
- Due to decreased CO ß1
- Splanchnic constriction ß2
- Allowing unopposed systemic effects of a activity
- Which agents would you use?
    - Propranolol
    - Nadolol
- Cirrhosis and variceal bleeding
- Reduces incidence of bleeding

Study activity 1

- Review classification of beta adrenoceptor blocking drugs
- Clear note the following distinct differences
    - Selective and non selective
    - Dual beta and alpha blocking agents
    - Those with intrinsic sympathomimetic activity
- What is the unique property of nebivolol

Activity 2

- Which beta adrenoceptor agent would you use in
    - Heart failure
    - Portal HT
    - Thyrotoxicosis
    - Essential tremors
    - Acute HT emergencies
- List 4 major contraindications of beta adrenoceptor prescription

Pancreatic Enzyme Supplements

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Introduction

- Exocrine pancreatic insufficiency is cause by
  - Cystic fibrosis
  - Chorionic pancreatitis
  - Pancreatic resection
- Enzyme secretion ≤10% leads to fat and protein malabsorption
- Pancreatic enzyme supplements (mixture of amylase, lipase, proteases) are mainstay treatment
- Two major types
  - Pancreatin
  - Pacrelipase

Pancreatin

- Alcohol derived extract of hog pancreas
- Low concentrations of lipase and proteolytic enzymes
- No longer in clinical use

Pancrelipase

- Enriched preparation than Pancreatin
  - 12X more lipolytic
  - 4X more proteolytic
- Available as enteric and non-enteric coated
- Rapidly and permanently inactivated by gastric acids
  - Non-enteric should be given w/ acid suppressants (PPI, H2 blockers)
- Given w/ each meal and snack
- Individualised dosing
- Goal is to reduce steatorrhoea to clinically insignificant level
- Suboptimal response
  - Poor mixing w/ food
  - Slow dissolution and release of enzymes
- Well tolerated
- Capsules should be swallowed (don't chew - will cause mucositis)
- High doses
  - Diarrhoea, abdominal pain
  - Hyperuricosuria, renal stones (high purine content)
  - Colonic strictures

Medium Chain Triglycerides

- Additional source of calories in poor response to diet and pancreatic lipase
- Degraded by gastric and pancreatic lipase
- Do not require bile for digestion]directly absorbed in intestine

Enzyme Deficiencies

- Congenital or acquired deficiencies lead to malabsorption
  - Lactose intolerance
  - Sucrase - isomaltase deficiency

Lactose Intolerance

- Reduce dietary intake of lactose (milk, dairy products)

- Enzyme replacement
    - Bacterial or yeast derived galactosidases

Sucrase - Isomaltase Deficiency

- Treatment w/ enzyme replacement
    - Sacrosidase taken w/ meals

Bile Acid Therapy for Gallstones

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Ursodiol (Ursodeoxycholic acid)

- Naturally occurring bile acid (≤5%)
- PO
- Conjugated in the liver w/ glycine or taurine
- Excreted in bile
- Undergoes extensive enterohepatic recirculation
- Half-life is 100 hours
- W/ long-term use_
- Unabsorbed conjugated or unconjugated Ursodiol passes into the colon
    - Excreted
    - Undergoes dehydroxylation by colonic bacteria to Lithocolic Acid (hepatotoxic)

Pharmacodynamics

- Expands bile acid pool
- Decreases cholesterol content of bile (reduced hepatic cholesterol secretion)
- Stabilise hepatocyte canalicular membranes
    - Reduce concentration of endogenous bile acids
    - Inhibits immune-mediated hepatocyte destruction

Clinical Use

- Dissolution of small cholesterol gallstones (refuse cholecystectomy)
- Prevention of gall stone in obese who undergo rapid weight loss therapy
- Early stage primary biliary cirrhosis
    - Reduce liver function abnormalities
    - Improve liver histology

Adverse Effects

- Practically free of adverse effects
- Bile salt induced diarrhoea is uncommon

Antidiarrhoea Agents

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- Acute diarrhoea
  - Is usually self-limiting
  - No evaluation or treatment needed
  - Dehydration may occur
  - Oral rehydration salts (ORS)/appropriate IV fluids used to correct dehydration and electrolyte imbalance
- Sodium and chloride absorption is linked to glucose uptake by the enterocyte in the small intestine
- This is followed by movement in the same direction
- Anti-diarrhoeal agents
  - Do not treat underlying cause
  - Used for symptomatic relief
  - Do no prevent dehydration
  - Have AE
  - May delay expulsion of pathogens
  - Not recommended for children
  - For persistent or significant symptoms
- Should not be used in patients w/
  - Bloody diarrhoea
  - High fever
  - Systemic toxicity
  - Diarrhoea that is worsening
- Treat the dehydration and correct electrolyte imbalance
- Address the primary cause of diarrhoea
  - Infective osmotic
  - Malabsorption
- Drugs

Classification

- Intraluminal Agents
  - Bulk forming and hydroscopic agents
    - Hydrophilic colloids
      - Calcium polycarbophil
      - Carboxymethylcelluose
    - Silicates
      - Kaolin
      - Attapulgate
  - Bile salt binding resins
    - Cholestyramine
    - Colestipol
    - colesevalam
  - Bismuth
- Antimotility and antisecretory agents
  - Opioids
  - Acetorphan (racecadotril)
  - $a2$ adrenergic receptor agonists
  - Ocreotide
  - Berberine
  - Calmodulin inhibitors

Opioids

- Include
  - Loperamide
  - Difenoxylate
  - Difenoxin
- They act on both the μ and δ receptors of the GIT to alter motility and secretion
- Activation of the μ receptror
  - ↑ anal sphincter tone
  - Disruption of normal peristaltic movements
  - ↓ secretions in the GIT
  - Enhanced NaCl and water absorption
- Activation of the δ receptor
  - ↓ secretory activity
  - Enhanced NaCl and water absorption

Diphenoxylate

- Well absorbed from the GIT
- Metabolised to difenoxin (Active)
- Excreted in faeces mainly
- Diphenoxylate and Difenoxin are usually combined w/ Atropine
- Dependence - little risk on short term use
- Combined w/ atropine in preparations to prevent abuse
- AE
  - ANV
  - Paralytic ileus, toxic megacolon
  - Constipation
  - Euphoria, CNS depression
  - Hypersensitivity
  - Dry mouth, blurred vision
- Precautions
  - Hepatic dysfunction
  - Children
  - Inflammatory bowel syndrome
  - Dysentery
  - Pseudomembranous colitis
  - CNS depression

Loperamide

- 40-50 times more potent than Morphine as anti-diarrhoeal agent
- 40% absorbed in the GIT
- Penetrates CNS poorly
- First-pass metabolism by the liver
- Half-life = 11hours
- AE and caution
  - C.F Diphenoxylate

Other Opioids

- Codeine
- Paregoric
  - =camphorated opioid tincture
  - Contains 2 mg of morphine per 5 ml
- Deodorised tincture od opium

    - Is X25 stronger
    - Contains 50mg of morphine per 5ml

Acetorphan
- An enkephalinase inhibitor
- Increases enkephalin concentration
- Antisecretory
- Does not prolong intestinal transit time

Bismuth Subsalicylate
- An antacid w/ antidiarrhoeal properties
- MoA
    - Not clear
    - ? Adsorption of bacterial toxins by bismuth salts
    - ? Local anti-inflammatory actions of salicylate
    - ? Anti-secretory effects
- PK
    - Poorly absorbed
    - Some bismuth retained in bones and tissues
    - Crosses the placenta
    - Absorbed portion excreted in urine mainly
    - Excreted for 12 weeks after stopping treatment
- AE
    - Bismuth Poisoning
        - Encephalopathy
        - NV
        - Dark faeces (Bismuth sulphide)
        - Discoloured mucous membranes
        - Blue band on gums
        - Renal and liver failure

Ocreotide
- Synthetic analog of somatostatin
- MoA
    - Inhibits hormone secretion in tumour associated diarrhoea
    - Inhibits intestinal fluids and bicarbonate secretion
    - ↓↓ smooth muscle contractility
- PK
    - SC/IV administration
    - Half-life:
        - 1.5 hours (somatostatin, half-life = 2 minutes)
    - Long acting Lanreotide is administered IM
    - _
- AE
    - Short-term therapy
        - NVD
        - Steatorrhoea
        - Flatulence
        - Abdomonal discomfort
    - Long term therapy
        - Gall stones
        - Hyper/hypoglycaemia
        - Hypothyroidism
- Therapeutic use

    - GIT tumours
        - Carcinoid, glucagonoma, gastrinoma, insulinoma, VIPoma
    - AIDS related diarrhoea
    - Diarrhoea induced by gold, _
    - _

Intraluminal Agents
Silicates

- Adsorbents of toxins and ater
- Pectin adsorbs bacteria

Calcium polycarbophil, Carbomethylcellulose

- ↑ viscosity of stool
- Adsorb water
- May bind bacterial toxins and bile salts

- Usually for constipation
- _

Other

- Steroids
    - Inflammatory bowel disease
- Clonidine
    - Diabetic (mellitus) diarrhoea
- Proton Pump Inhibitors
    - Zollinger-Ellison syndrome
- Bile salt binding resins
    - Bile salt induced diarrhoea
- Alosetron
    - A 5-HT3 receptor antagonists
    - Used in the treatment of irritable bowel syndrome

Berberine

- Is a plant alkaloid
- Used in traditional Indian and Chinese medicine
- Used in bacterial diarrhoea and cholera
- Has anti-microbial actions
- Inhibits smooth muscle contraction and delays intestinal transit by
    - Antagonising the effects of acetylcholine
    - Blocking the entry of Ca2+ into cells
- It inhibits intestinal secretion

Calmodulin Inhibitors

- Include
    - Zaldaride Maleate
- Reduces secretion w/o affecting intestinal motility
- For traveller's diarrhoea

Endocrine Pharmacology

Tuesday, 11 April 2017 11:40 AM

The Endocrine System

- A system of ductless glands that secrete hormones
- Hormones are messenger molecules that circulate in blood
- Act on distant target cells that have receptors for the specific hormones
- Hormones are secreted in small amounts and often in bursts (pulsatile secretion)

Endocrine Functions

- Maintain internal homeostasis
- Support cell growth
- Coordinate development
- Coordinate reproduction, fertility and sexual function

Basic Categories of Hormones

- Amino acid based
  - Modified amino acids (or amines)
  - Peptides (short chains of AA)
  - Proteins (long chains of AA)
- Steroids
  - Lipid molecules derived from cholesterol
- The hormones can also be grouped in two genera; classes based in their solubility in water
  - Water soluble hormones
    - Amine (e.g. epinephrine) and peptide/protein hormones
    - Are secreted by exocytosis, travel freely in the bloodstream and bind to cell surface receptors
  - Lipid soluble
    - E.g.
      - Thyroid hormone
      - Steroid hormones
    - Diffuse across the cell membrane at source
    - Travel in the bloodstream bound to transport proteins
    - Diffuse through the membrane of target cells

Location of Receptors

- On ell surface
  - Peptides and proteins
- In cytoplasm
  - Steroids
- In nucleus
  - Thyroid hormones

Mechanisms of Hormone Release

- Humoral
  - In response to changing levels of ions or nutrients in the blood
- Neural
  - Stimulation by nerves
- Hormonal
  - Stimulation received from other hormones

Hormone Regulation

- Negative feedback (most common)
  - Endocrine gland over-secretes hormone
  - Tissue becomes too active
  - Endocrine gland decreases secretion via negative feedback loop
- Positive feedback
  - Hormone response leads to production of more hormones
    - E.g. oxytocin and uterine contractions during labour

Hypothalamus

- Produces releasing hormones (RH) and inhibiting hormones (IH) that respectively stimulate and suppress anterior pituitary hormones
- Produces ADH and oxytocin
  - Stored in posterior pituitary
  - Nerve impulses stimulate secretion

Pituitary Gland

- Anterior Pituitary
  - GH
  - TSH
  - ACTH
  - Prolactin
  - FSH
  - LH
- Posterior pituitary
  - Stores ADH and oxytocin

Thyroid Gland

- Releases
  - Thyroxine (T4) and Triiodothyronine (T3)
    - Produced by the follicular cells
  - Calcitonin
    - Produced by the parafollicular cells/C-cells
    - Reduces blood calcium levels via inhibition of osteoclasts in bone and inhibition of renal resorption of calcium and phosphate

Parathyroid Hormones

- Four glands in posterior capsule of thyroid
- Chief cells secrete parathyroid hormone (PTH)
  - Polypeptide containing 84 Aas
  - _

Adrenal Glands

- Suprarenal glands divided into:
  - Adrenal medulla
    - Secretes epinephrine and norepinephrine
  - Adrena cortex
    - Glucocorticoids e.g. cortisol
    - Mineralocoticoids e.g. aldosterone
  - Sex hormones

Pancreas

- Endocrine and exocrine
- Endocrine pancreas (islets of Langerhans)
  - Insulin (ß cells)

    - Glucagon (α cells)
    - Somatostatin (δ cells)

Sex Glands
- Ovaries and testes produce hormones to
    - Develop sexual characteristics
    - Maintain reproductive organs
- Ovaries - Oestrogen and Progesterone
- Testes - Testosterone

Thymus
- Mass of lymphoid tissue in the upper chest, superior to the heart
- Important in development of immunity
- Produces thymosin
    - Assists in maturity of T lymphocytes

Pineal Gland
- Con-shaped structure, posterior to midbrain
- Produces melatonin
    - Influences sleep-wake cycles
    - Appears to delay onset of puberty

Other Hormone Producing Organs
- Stomach
- Small intestines
- Kidneys
- Brain
- Atria of the heart
- Placenta

Classification of Hormones
- Mechanisms of Action of Hormones
    - Group I: bind to intracellular receptors
        - E.g.
            - Androgens
            - Oestrogens
            - Glucocorticoids
            - Progestins
    - Group II: Bind to cell surface receptors
        - cAMP as second messenger
            - ACTH, ADH, hCG, CRH, FSH, LH, PTH
        - cGMP as second messenger
            - ANP (atrial natriuretic peptide)
    - Group III: use calcium/phosphatidylinositol as a second messenger
        - GnRH, TRH
    - Group IV: Second messenger is a kinase/phosphatase cascade
        - Insulin, GH, Prolactin, insulin like growth factors (IGF-1, IGF-2)

Hypothalamic Hormones

Thursday, 13 April 2017 8:16 AM

Hormone	Effect on Anterior Pituitary
CRH • Analog: ○ _	Releases ACTH , corticotropin
TRH	_
GHRH (Somatorelin • Analog ○ Sermorelin	Releases GH (Somatotrophin) • Analog: ○ Somatrophin
GH release inhibiting hormone (Somatostatin) • Analogs ○ Ocreotide ○ Lanreotide	Inhibit release of GH
GnRH	Releases FSH and LH
Prolactin Releasing factor	Releases Prolactin
Prolactin release inhibiting factor (dopamine)	Inhibit prolactin release
MSH releasing factor	Releases MSH
MSH release inhibiting factor	Inhibits release of MSH

GHRH

- Control release of GH
- Released from the hypothalamus in a pulsatile manner w. 5-9 major pulses detected per day
- GHRH release in enhanced by an a2-adrenergic agonist (e.g. Clonidine), opioids and vigorous exercise
- Therapeutic use
  - Pulsatile SC delivery of GHRH, mimicking the normal endogenous patterns (e.g. approx. every 3 hours) has been used to stimulate GH release in patients w/ GH deficiency that is not of pituitary origin
  - IV, SC, intranasal
- Diagnostic use
  - To test pituitary function in patients w/ GH deficiency
  - If the primary defect is hypothalamic, as is most common, GHRH will elicit an increase in GH release
  - If the effect is at the level of the pituitary, there will be no increase of GH following GHRH administration

Somatostatin

- 14 amino acid peptide
- Produce in the hypothalamus, CNS, pancreas
- T0.5: 1-3 minutes
- Inhibits the release of
  - GH and TSH from the pituitary
  - Insulin and glucagon from the pancreas
  - Gastrin
- Analogs
  - Octreotide

    - Lanreotide
- Octreotide
    - Long acting analogue of somatostatin
    - More selective (45X more potent than somatostatin in inhibiting GH but only twice as potent in inhibiting insulin) → ↓ hyperglycaemia risk
    - $T_{0.5}$: 80 minutes
    - Given SC
    - Suppressant effect up to 8 hours
    - Uses
        - Hormone secreting tumours
            - Carcinoid (serotonin), gastrinomas, glucagonoma, insulinoma
        - Acromegaly
        - Diarrhoea
            - Secretory, HIV-associated, diabetic, chemotherapy or radiotherapy induced
        - It also constricts splanchnic blood vessels and is used to treat bleeding oesophageal varices
        - Used in treatment of portal hypotension
        - Gastrointestinal fistulas by decreasing GI secretions and inhibiting gastric motility.
    - AE
        - Pain at injection site
        - GI disturbances
        - Gallstones
        - Acute hepatitis or pancreatitis (rare)
        - CVS - sinus bradycardia, conduction abnormalities
        - Vitamin B12 deficiency

GnRH
- Decapeptide
- Pulsatile secretion stimulates gonadotrophs in anterior pituitary to release LH and FSH
- Binds to G-protein coupled receptors on gonadotroph cell membrane
- Sustained non-pulsatile administration of GnRH or GnRH analogs inhibits the release of FSH and LH by the pituitary → hypogonadotropic hypogonadism

Gonadorelin
- Acetate salt of synthetic GnRH
- IV,SC
- $T_{0.5}$ of IV Gonadorelin: 4 minutes

GnRH Analogs
- Produced by substitution of amino acids at position 6 e.g.
    - Goserelin
    - Buserelin
    - Histrelin
    - Leuprolide
    - Nafarelin
    - Triptorelin
- SC injection or implant and intranasal spray for Nafarelin
- PK
    - Pulsatile IV gonadorelin every 1-4 hours stimulates LH and FSH production
    - Sustained administration causes a biphasic response
        - Flare
            - Increased LH and FSH in first 7-10 days
        - Inhibition
            - Reduced gonadotropins and gonadal steroids due to downregulation od

receptors and changes in signalling pathways

- CU of GnRH agonists
  - Suppression of Gonadotropin Production
    - Controlled ovarian stimulation
      - Technique that provides multiple mature oocytes for IVF
      - Daily SC Leuprolide or nasal Nafarelin used
      - Suppresses endogenous LH surge that could trigger premature ovulation
    - Endometriosis
      - Extrauterine oestrogen-sensitive endometrium
      - Cyclical abdominal pain
      - GnRH agonists decrease oestrogen concentration and prevents cyclical changes
      - Treatment limited to 6 months (risk of decreased bone mineral density)
    - Uterine Fibroids
      - Benign, oestrogen-sensitive smooth muscle tumours
      - Treatment w/ GnRH agonist for 3-6 months of stopping treatment _
      - _
    - Prostate cancer
      - Testosterone dependent tumour
      - GnRH agonist + androgen receptor antagonist (e.g. Flutamide) = surgical castration in reduction of testosterone
      - Leuprolidem Goserelin, Histrelin, Buserelin and Triptorelin approved
      - Long acting depot forms 1-12 months of active drug treatment
  - Remember…
    - Flare response in first 7-10 days can worsen bone pain and neurologic systems in patients w/ metastatic disease as well as bladder obstruction
    - Avoided by combination w/ androgen receptor antagonist
  - Other uses
    - Central precocious puberty (onset of secondary sexual characteristics before 7 years of age in girls and 9 years in boys)
    - Advanced breast and uterine cancer
- AE - Gonadorelin
  - Headache, Light-headedness, nausea and flushing
  - Swelling at injection sites, dermatitis
  - Hypersensitivity reactions - bronchospasms, anaphylaxis
  - Sudden pituitary apoplexy and blindness (patients w/ gonadotropin-secreting pituitary tumours)
  - Women
    - Menopausal symptoms
    - Ovarian cysts
  - Men
    - Hot flashes
    - Gynaecomastia
    - Oedema
    - Reduced libido
    - Reduced haematocrit
  - Both sexes
    - Reduced bone mineral density
    - Osteoporosis
  - Nafarelin spray
    - Sinusitis

GnRH receptor Antagonists

- Include
  - Ganirelix
  - Cetrorelix

    - Abarelix
    - Degarelix
- Indications
    - Controlled ovarian stimulation
    - Advanced prostate cancer

CRH

- Stimulates secretion of ACTH and ß-endorphin
- Rarely used to distinguish Cushing's Disease from ectopic ACTH production
-

Growth Hormone

Thursday, 13 April 2017 8:58 AM

Synthesis

- Production and release controlled by two hypothalamic hormones
  - GHRH - Sermorelin
  - GHRIH (Somatostatin)

GH

- Peptide
- Highly potent
- Used for diagnosis and replacement therapy
  - Growth hormone deficiency and testing cure for acromegaly
- Given SC
  - Therapeutic dose: 2.4µm/kg 12 hourly

Somatostatin

- Tetradecapeptide (14AA), cysteine at position 3 and 14 joined by a disulphide bridge
- Prosomatostatin 28AA
- Synthetic analogue - Ocereotide, 8AAs
  - More potent than somatostatin
- 50-100µg SC 12 hourly
- Function
  - Inhibit GH release in response to a wide variety of stimuli
  - Causes a decrease in circulating insulin levels
  - Interferes w/ TRH's ability to release TSH
  - Inhibits the release of glucagon
  - Inhibit insulin release
  - Inhibits gastrin release
- In experimental rats, Prosomatostatin is 10X more potent in inhibiting insulin release and 2X more potent in inhibiting glucagon, than somatostatin
- PK
  - Rapid cleared from circulation w/ T0.5 - 1-3 minutes
  - Metabolism and excretion by the kidneys
- Octreotide is a synthetic analogue of Somatostatin
  - SC admin 12hourly
  - Indications
    - Reduces symptoms
      - Acromegaly
      - Carcinoid syndrome
      - Glucagonomas
      - Gastrinomas
      - Carcinoid syndromes
      - Achlorrhydria syndrome
    - Treatment of diabetic diarrhoea
  - Adverse effects
    - Abdominal cramps
    - Steatorrhoea
    - Initial glucose intolerance
    - Steatorrhoea

GH (Somatotropin)

- 191AA, 2 sulfhydryl bridges
- Synthetic preparation
    - Somatotrem produced by RDT (recombinant DNA Tech) - 191AA
        - Has an extra methionine residue at the amino terminal end
- PK
    - T0.5 - 20-25 minutes - circulating hormone
    - Metabolism predominantly in the liver
    - When GH is dissolved in bacteriostatic water and given IM, peak levels occur in 2-4 hours and active blood levels remain up to 36 hours
- PD
    - Has both anabolic and metabolic effects
    - Effects
        - When given, the initial effect is insulin like, initially w/ increase AA and increased glucose intake in tissues and decreased lipolysis
        - It then gives insulin antagonistic effects
            - Decreased glucose uptake
            - Increased lipolysis
        - Major anabolic effects is linear growth, which is mediated by somatomedins (insulin-like growth factor, two types, ILGF 1 and 2), mainly produced by the liver.
            - The is increased production of somatomedins
            - Increased intake of sulphates into bones
        - If normal amounts of GH is produced, it is present in the system in utero until 25 years where growth stops. There is marked growth spurt in teenage years
        - When there is deficiency of GH, there is dwarfism.
        - The achondroplastic dwarfs, have normal GH levels but impaired growth
        - GH is responsible for the increase in bone size and muscle mass. Patients that have reduced GH have decreased muscle mass and increased fat
        - Patients that have excess GH while still growing, they become giants
        - Acromegaly
            - Prominence of facial bones with long protruding jaws and sparsely spaced jones
            - Bif maxillary bones and foreheads
            - Large hands and finger
            - Large feet
            - Incoordination
            - Diabetes due to hyperglycaemia
    - Clinical uses
        - Replacement therapy
        - Growth augmentation
            - Used in turner's syndrome together with oestrogen
        - Experimental uses
            - Production of growth in short children
            - Chronic renal failure
            - Muscle preservation in catabolic states e.g. corticosteroid therapy, burns and caloric restriction
    - Toxicity
        - Are known to caused Creutzfeld-Jakob's Disease
        - Approx. 30% develop
        - Increased incidence of leukaemia
        - Contraindicated in
            - Patients who have stopped growing
            - Those w/ expanding intracranial mass

PRL

- Hormone responsible for lactation

- Linear polypeptide, 198AA
- Release inhibited by dopamine (prod. In hypothalamus)
- Effects
    - Growth and dev. Of breast
    - Production of milk in presence other hormones
        - Corticosteroids
        - Insulin
        - Oestrogen
        - Progesterone
    - Stimulatory effect of immunity
        - Increased expression of receptors on T lymphocytes
    - Hyperprolactinaemia causes decrease in gonadal hormones
        - May lead to
            - Hypergonadism
                - Reduced libido
            - In women
                - May interfere w/ normal cycles
    - Deficiency
        - Failure of lactation
    - Dopamine inhibitors

Gonadotropins

Tuesday, 18 April 2017 12:13 PM

Introduction

- Control the activity of the gonads i.e. testes and ovaries
- 3 gonadotropic hormones
    - FSH
    - LH
    - Chorionic gonadotropin
- Complex glycoproteins made up of alpha and beta AA chains
- The alpha chains are virtually identical while the beta chains are immunologically and chemically unique
- By itself, neither chain has biological activity
- Required for
    - Ovulation
    - Spermatogenesis
    - Biosynthesis of the sex steroids
- Gonadotropic preparations used to promote fertility and are only effective when given parenterally
- FSH and LH are produced and secreted by the basophils (delta cells or gonadotroph) of the anterior pituitary
    - Secretion regulated through a feedback inhibition of sex steroid in plasma
- hCG is LH-like and is secreted by the chorion and placenta

PK

- Usually given IM and some SC
- Clearance by glomerular filtration followed by degradation in the proximal renal tubule or excretion as unchanged in urine
- Also cleared by the liver

MoA

- LH, FSH and hCG exert their effects through G-protein coupled receptors.
- They increase the formation of cAMP in appropriate target tissues by stimulating adenylate cyclase
- Elevation of cAMP increases the amount of the mitochondrial enzyme complex that ordinarily cleaves the side chain of cholesterol > pregnenolone
- Gametogenesis is also mediated by cAMP
- Concentrations of FSH and LH low in infancy and pre-puberty
- Secretion increase at puberty owing to an increase in amplitude of GnRH
- In men, the plasma level of the hormones are relatively constant but in women, rates of secretion are higher and vary according to the phase of the menstrual cycle

FSH

- Along with LH, regulate gonadal function
- Principle action is stimulation of gametogenesis and follicular development in women and spermatogenesis in men
- Acts on immature follicle cells of the ovary and induces development of the mature follicle and oocyte
- Acts on Sertoli cells in the testes and stimulates their production of androgen binding protein

- Urine of postmenopausal women contains a substance w/ FSH-like properties w/ 4% of the potency and different dose-response curve. Such urine also contains LH-like

substance

Follitropin α and ß
- Given SC
- Recombinant FSH
- Treatment of
    - Infertile women
        - w/ proven hypopituitarism
        - Those who have not responded to the fertility drug, Clomiphene
    - Superovulation treatment for assisted conception
- Urofollitropin (SC, IM)
    - Extract of the urine of post-menopausal women containing FSH i.e. LH component removed
- Note:
    - At menopause, gonadotropin secretion increases because of loss of negative feedback
- Pregnant mare serum gonadotropin
    - Both FSH and LH activity

LH/ICSH
- T0.5 - 30 minutes
- Primarily responsible for regulation of gonadal steroid hormone production
- In ovary, acts in concert w/ FSH to stimulate follicular development
- Acts on mature follicles to induce ovulation and stimulates corpus luteum in the luteal phase of the menstrual cycle to produce progesterone and androgens
- Acts on testicular Leydig cells to stimulate testosterone production

hCG
- Hormone of human pregnancy - prod. By the placenta and excreted in the urine from which it is extracted and purified for use
- Has almost an identical structure, and actions of pituitary LH is used as LH substitute (i.e. no LH preparation available for clinical use) to treat both men and women of LH deficiency
- Stimulate gonadal steroid synthesis
    - Interstitial and corpus luteal cells of the female to produce progesterone and Leydig cells of the male to produce testosterone
- Detected in urine by immunoassay days before the first mense is missed
    - Basis of most commonly used pregnancy tests

PK
- IM injection and is well absorbed
- Biologic T0.5 - 8 hours
    - T0.5 measured by immunoassays greater than that measured by bioassay, implying that the hormone is modified by the body, prior to urinary excretion

Side effects
- Headache
- Depression
- Oedema
- Precocious puberty
- Gynaecomastia
- Production of antibodies against hCG

Uses
- In infertile (hypogonadotropic) women to promote ovulation by duplicating the LH surge
- To induce spermatogenesis in men w/ secondary hypogonadism

- In male children to stimulate interstitial cells in the treatment of undescended testes
- Diagnostically
    - In pre-pubertal boys w/ undescended gonads, to distinguish a truly retained testes from a retracted one
    - To distinguish patients w/ constitutional delay in puberty from those w/ hypogonadotropic hypogonadism

- Choriogonadotropin α (rhCG) is a recombinant form of hCG w/ greater consistency in biologic activity and Is the only preparation that is packaged and doses on basis of weight
    - Note:
        - Other gonadotropins are packaged and dosed on units of activity
- hCG purified from urine is administered IM whereas the rhCG is given by SC injection

Human Menopausal gonadotropins (hMG)

- Also known as menotropins
- A mixture of partially catabolised human FSH and LH extracted from the urine of post menopausal women and biologically standardised for FSH and LH (content) activity
- Treatment of infertility to stimulate the ovarian follicle development in women and spermatogenesis on men
- Used in conjunction w/ LH to permit ovulation and implantation in women and in men for testosterone production and full masculinisation
- Daily IM or SC injection for 14 da ys during which time the levels of FSH and LH gradually rise above their baselines and follicular maturation occurs. Followed by injection of hCG in an attempt to stimulate the LH surge and produce ovulation
- Indications
    - Pituitary or hypothalamic hypogonadism w/ infertility
    - May benefit anovulatory women w/ primary or secondary amenorrhoea, polycystic ovary syndrome and anovulatory cycles

Introduction to Adrenocorticoid Steroids

Thursday, 20 April 2017 8:26 AM

- The adrenal cortex synthesises 3 classes of steroids, namely:
  - Corticosteroids (glucocorticoids and mineralocorticoids) which have 21 carbon atoms
  - Androgens which have 19 carbons
  - Oestrogens
- The actions of corticosteroids have been described as
  - Glucocorticoid
    - Reflecting their carbohydrate metabolism regulating activity
  - Mineralocorticoid
    - Reflecting their electrolyte balance regulating activity, mainly salt retention
- In humans, cortisol (hydrocortisone) is the main glucocorticoid and aldosterone is the most important mineralocorticoid
- Quantitatively, dehydroepiandrosterone sulfate (DHEAS) is the major adrenal androgen
  - However, DHEA, androstenediol and androstenedione, are weak adrenal androgens
  - In addition androstenediol is a potent oestrogen
  - Androstenedione can be converted to testosterone and oestradiol in extra-adrenal tissues
- Adrenal androgens constitute the major endogenous precursor of oestrogen in women after menopause and in younger patients w/ deficient or absent ovarian function

Glucocorticoids

Thursday, 20 April 2017 9:04 AM

Glucocorticoids
- Naturally occurring
- Synthetic

Naturally Occurring: Cortisol (hydrocortisone)
Synthesis and Secretion
- The physiologic secretion of cortisol is regulated by ACTH
- It is very sensitive to negative feedback by the circulating cortisol and exogenous (synthetic) glucocorticoids
- Cortisol is synthesised from cholesterol
- In the normal adult, in the absence of stress, 10-20mg of cortisol, is secreted daily
- The rate of secretion, varies during the day (it follows a circadian rhythm)
- It is regulated by pulses of ACTH that peak in the early morning hours, before 8am and after meals
- Trough levels occur at 7-8pm or at night
- ACTH secretion is also pulsatile in nature
    - It is regulated by CRF released from the hypothalamus and vasopressin released from the posterior pituitary gland
- The release of both ACTH and CRF is reflexively inhibited by the resulting rising concentrations of glucocorticoids in the blood

PK
- When given PO, cortisol is well absorbed by the GIT
- It diffuses poorly across normal skin
    - It is readily absorbed across inflamed skin and mucous membranes
- In plasma, it is bound in circulating proteins, as follows
    - Corticosteroid-binding globulin (CBG), an $\alpha 2$ globulin synthesised by the liver, normally binds approx. 90-95% of the circulating cortisol
    - The reminder is free (approx. 5-10%) or loosely bound to albumin (approx. 5%) and is available to exert its effect on the target cells
- When plasma cortisol levels exceed 20-30µg/dL, CBG is saturated and the concentration of free cortisol rises rapidly
- CBG is increased in
    - Pregnancy
    - Following oestrogen administration
    - In hyperthyroidism
- CBG is decreased by
    - Hypothyroidism
    - Genetic defects in synthesis
    - Protein deficiency states
- Synthetic corticosteroids e.g. Dexamethasone are largely bound to albumin rather than CBG
- The T0.5 of cortisol in the circulation is normally approx. 60-90minutes
- It may be increased in:
    - When hydrocortisone (the pharmaceutical preparation of cortisol) is administered in large amount or
    - By stress, in liver disease
- Approx. 20% of cortisol is converted to cortisone by 11-hydroxysteroid dehydrogenase in the kidney and other tissues w/ mineralocorticoid receptors, before reaching the liver
- Most cortisol is metabolised in the liver

- Approx. 1/3 of the cortisol is excreted in the urine_
- Many cortisol metabolites are conjugated w/ glucuronic acid or sulphate at the C3 and C21 hydroxyls, respectively in the liver
- They are then excreted in the urine
- Only 1% of cortisol is excreted unchanged in the urine as free cortisol

PD
MoA

- Most of the known effects of glucocorticoids are mediated by widely distributed glucocorticoid receptors
- These are member of the superfamily of nuclear receptors, which include steroid, sterol (vitamin D), thyroid and retinoic acid receptors
- In the absence of the hormonal ligand, glucocorticoid receptors are primarily cytoplasmic, complexed w/ stabilising proteins called heat shock proteins (Hsp)
- The most important of these are 2 molecules of Hsp90, although other proteins are involved
- Free hormone from the plasma and interstitial fluid enters the cells and binds to the receptor
    - This induces a conformational change, that allows the receptor to dissociate from Hsp
- The steroid hormone receptor complex, is then actively transported into the nucleus, where is interacts w/ nuclear proteins
- It binds to glucocorticoid receptor elements (GRE) on the gene, to regulate gene transcription
- The resulting mRNA is edited and exported to the cytoplasm for the production of proteins that bring about the final hormone response
- Two genes for the corticoid receptor, have been identified:
    - One that encodes the classic glucocorticoid receptor (GR)
    - The other encodes the mineralocorticoid receptor (MR)
- 10-20% of expressed genes in the cell, are regulated by glucocorticoids
- Some of the effects of glucocorticoids, can be attributed to their binding to aldosterone receptors (AR)
- AR bind aldosterone and cortisol w/ similar affinity
- Prompt effects such as initial feedback suppression of pituitary ACTH occur within minutes
    - Therefore, they are too rapid to be explained on the basis of gene transcription and protein synthesis
- Proposed mechanisms on how these effects are mediated include
    - Direct effects on cell membrane receptors for the hormone
    - Non-genomic effects of the classic hormone-bound glucocorticoid receptor
- The presumed membrane receptors might be entirely different from the known intracellular receptors

Organ and Tissue Effects of Cortisol

- Physiologic
- Metabolic
- Catabolic and anti-anabolic
- Anti-inflammatory
- Immunosuppressive
- Other

Physiologic Effects

- The response of vascular and bronchial smooth muscle to catecholamines is diminished in the absence of cortisol and restored by physiologic amounts of cortisol
- Similarly, the lipolytic responses of fat cells to catecholamines, ACTH and GH are reduced in the absence of glucocorticoids

Metabolic Effects

- Glucocorticoids have important dose-related effects on carbohydrate, protein and fat metabolism
    - They cause both a decrease in the uptake and utilisation of glucose
    - They stimulate gluconeogenesis esp. in the fasting state
- As a result
    - Blood glucose rises
    - There is decreased protein synthesis and increased protein breakdown, particularly in muscle. This can lead to tissue wasting
    - Insulin secretion is stimulated, which results in increased glycogen storage
- Both lipolysis and lipogenesis are stimulated
    - Large doses of glucocorticoids, given over a long period, result in the redistribution of body fat characteristic of Cushing's Syndrome, w/ a net increase of fat deposition in areas such as the face, shoulder and back

Catabolic and Anti-anabolic Effects

- Glucocorticoids have catabolic and anti-anabolic effects in lymphoid and connective tissue, muscle, peripheral fat and skin
- Catabolic and anti-anabolic effects on the bone are the cause of osteoporosis
- It reduces growth in children

Anti-Inflammatory Effects

- Glucocorticoids have a dramatic effect on the distribution and function of leukocytes
- They increase neutrophils and decrease lymphocytes, eosinophils, basophils and monocytes
- They also inhibit migration of leukocytes
- The biochemical mechanisms underlying these cellular effects include:
    - The induced synthesis of an inhibitor of phospholipase A2
    - Decreased mRNA for COX-2
    - Decreased IL-2 and IL-3
    - Decreased PAF, an inflammatory cytokine

Immunosuppressive Effects

- Glucocorticoids inhibit cell-mediated immunologic functions, esp. those dependent on lymphocytes
- They are actively lymphotoxic and are therefore important in the treatment of haematological cancers
- They do not interfere w. the development of normal acquired immunity
    - However, they delay rejection reactions in patients w/ organ transplants

Other Effects

- Glucocorticoids such as cortisol, are required for normal renal excretion of water loads
- They also have effects on the CNS
    - When given in large doses, may cause profound behavioural changes
- Large doses also stimulate gastric acid secretion and decrease resistance to ulcer formation

Synthetic Glucocorticoids

MoA

- Is identical w/ that of cortisol
- Their properties (compared w/ cortisol) include
    - Longer half-life and duration of action
    - Reduced salt retaining effect
    - Better penetration of lipid barriers for topical activity

- Special glucocorticoids have been developed for use in asthma and other conditions in which good surface activity on mucous membranes or skin is required and systemic effects are to be avoided
    - Example
        - Beclomethasone and Budesonide readily penetrate the airway mucosa, nut have very short half-life after they enter the blood
            - Hence systemic effects and toxicity are greatly reduced

Clinical Uses of Glucocorticoids

- Adrenal disorders
    - Are essential to preserve life in patients w/ chronic adrenal cortical insufficiency (Addison's Disease)
    - They are necessary in acute adrenal insufficiency, associated w/ life-threatening shock, infection, or trauma
    - Are also used in certain types of congenital Adrenal hyperplasia, in which synthesis of abnormal forms of corticosteroids, are stimulated by ACTH
    - In these condition, administration of a potent, synthetic glucocorticoid, suppresses ACTH secretion sufficiently to reduce the synthesis of the abnormal steroids
- Non-adrenal Disorders

Antagonists of Adrenocortical Agents

- Inhibitors of steroid synthesis
    - These act at several different steps
- Glucocorticoid _
    - Acts_

Inhibitors of Steroid Synthesis

- Drugs that inhibits adrenal steroid synthesis include:
    - Ketoconazole
    - Aminoglutethimide
    - Metyrapone
    - Trilostane
    - Abiraterone

Aminoglutethimide

MoA

- It blocks the conversion of cholesterol to pregnenolone
    - It therefore inhibits synthesis of all hormonally active steroids

Clinical Use

- It has been used in conjunction w/ Dexamethasone or Hydrocortisone to reduce _
    - In a dosage of 1g/d it is well tolerated
        - However, w/ high doses, lethargy and skin rash is a common effect
    - Its use in breast cancer patients has now been replaced by Tamoxifen or the aromatase inhibitors
- It can be used in conjunction with Metyrapone or Ketoconazole to reduce steroid secretion in patients w/ Cushing's Syndrome due to adrenocorticoid cancer who do not respond to Mitotane

Drug Interactions

- Aminoglutethimide apparently increases the clearance of some steroids
    - It enhances the metabolism of Dexamethasone, reducing its half-life from 4-5 hours to 2 hours

Ketoconazole

- It is an antifungal imidazole derivative
- It is a potent and non-selective inhibitor of adrenal and gonadal steroid synthesis
- It inhibits the CYP enzymes necessary for the synthesis of all steroid

Clinical Use
- Its inhibitory effects on steroid biosynthesis are seem only at high doses
- It has been used for the treatment of patients with
    - Cushing's Syndrome due to several causes
    - Several condition where reduced steroid levels ae desirable e.g.
        - Adrenal Carcinoma
        - Hirsutism
        - Breast and Prostate Cancer
- Dosages of 200-1200mg/day have produced a reduction in hormone levels and clinical improvement in some patients

Caution
- May be hepatotoxic
    - It should therefore be started at 200mg/d and slowly increased by 200mg/d every 2-3 days up to a total daily dose of 1000mg

Metyrapone
MoA
- It is a relatively selective inhibitor of steroid 11-hydroxylation
    - It interferes w/ cortisol and corticosterone synthesis but not that of cortisol precursors
- In the presence of a normal pituitary gland, there is a compensatory increase in pituitary ACTH release and adrenal 11-deoxycortisol secretion
- This response is a measure of the capacity of the anterior pituitary to produce ACTH

AE
- Its toxicity is much lower than that of Mitotane
- It may produce transient dizziness and GIT disturbances
- The major AE are salt and water retention and hirsutism resulting from diversion of the 11-deoxycortisol precursor to DOC (deoxycorticosterone) and androgen synthesis

Clinical Use
- It has not been widely used in the treatment of Cushing's Syndrome
    - In doses of 0.23g BD to 1g QID, it can reduce cortisol production to normal levels in some patients w/ endogenous Cushing's Syndrome
    - It may therefore be used in the management of severe manifestations of cortisol excess while the cause of this condition is being determined or in conjunction w/ radiation or surgical treatment
    - Note
        - Metyrapone is the only adrenal-inhibiting medication that can be administered to pregnant women w/ Cushing's Syndrome
- It is commonly used in tests of adrenal function (to determine if cortisol excess is as a result of a cortisol-secreting adrenal carcinoma_

Trilostane
- It is a 3-17 hydroxysteroid dehydrogenase inhibitor, which interferes w/ the synthesis f adrenal and gonadal hormones
- It is comparable to aminoglutethimide

AE
- Predominantly in the GIT
- Occur in approx. 50% of patients w/ both use of Trilostane and Aminoglutethimide
- There is no cross-resistance or cross-over of SE between these compounds

Abiraterone

- Is the newest of the steroid synthesis inhibitors
- Orally active steroid prodrug which has been studied in the treatment of refractory prostate cancer

MoA

- Blocks 17-hydroxylase and 17,20-lyase
- Predictably reduces synthesis f cortisol and gonadal steroids in the adrenal and gonadal steroids in the gonads
- A compensatory increase occurs in ACTH and aldosterone synthesis
    - However, this can be prevented by concomitant administration of Dexamethasone

Glucocorticoid Receptor Antagonists - Mifepristone

- It is a pharmacological antagonist at the steroid receptors
- It has strong antiprogestin_
- High doses of Mifepristone exert anti-glucocorticoid activity by blocking the glucocorticoid receptor to which mifepristone binds w/ high affinity, causing:
    - Some stabilisation of the Hsp-glucocorticoid receptor complex and inhibition of the dissociation of the Mifepristone-bound glucocorticoid receptor from the Hsp proteins
    - Alteration of the interaction of the glucocorticoid receptor w/ co-regulators, favouring the formation of a transcriptionally inactive complex in the cell nucleus
    - This results in inhibition of glucocorticoid receptor activation

PKi

- Its mean T0.5 - 20 hours
- This is longer than that of many natural and synthetic glucocorticoid antagonists (e.g. Dexamethasone has a half-life of 4-5 hours)
- Its long plasma high-life results from extensive and strong binding to plasma proteins
- <5% of Mifepristone is found in the free form
- It can find to albumin and 1-acid glycoprotein, but id has no affinity for CBG
- <1% of the daily dose is excreted in the urine

CU

- In humans, Mifepristone causes generalised glucocorticoid resistance
- Given orally to patients w/ Cushing's Syndrome due to Ectopic ACTH production or adrenal carcinoma, it had the following effects
    - Reverses the cushingoid phenotype
    - Eliminates carbohydrate intolerance
    - Normalises BP
    - Corrects thyroid and gonadal hormone suppression
    - Improved psychological sequelae of hypercortisolism
- At present, this use of Mifepristone can only be recommended in inoperable patients w/ ectopic ACTH secretion or adrenal carcinoma who have failed to respond to other therapeutic manipulations
- It is also used as a progesterone antagonist in women

Mitotane

- It is a drug related to the DDT class of insecticides
- It has a non-selective cytotoxic action on the adrenal cortex in dogs and to a lesser extent, humans
- It is administered PO in divided doses, up to 12g daily
- Approx. 1/3 of patients w/ adrenal carcinoma, show a reduction in tumour mass
- In 80% of patients, the toxic effects are sufficiently severe to require dose reduction
- Toxic effects include

- NVD
- Depression
- Somnolence
- Skin rashes

Aldosterone, ADH and Oxytocin

21 April 2017 05:13

Aldosterone

- Main endogenous mineralocorticoid
- Produced by the adrenal cortex, zona glomerulosa
- Increased sodium reabsorption by action on the distal tubule_

Conn's Syndrome

- Excessive secretion of aldosterone
- Characterised by marked sodium and water retention resulting to reduce ECF
- Hypokalaemia, alkalosis and hypertension

Addisons' Disease

- Decreased secretion
- Sodium loss increased than water loss
- Reduced osmotic pressure of ECF thus shift of fluid into the intracellular compartment and _

Activity

- Based in the principles learnt on the effect of aldosterone, what are the s/s of Addison's disease
- What are the potential causes of Addison's disease

Aldosterone

- Mineralocorticoid hormone
- Controls absorption Na Cl
- ADH (vasopressin) controls water reabsorption
- Aldosterone promotes sodium reabsorption and potassium excretion
- It has a rapid effect through stimulation of Na+-H+ exchanger by action on the membrane aldosterone receptors
- Delayed effect
    - Binding to receptors within the cells and directs the synthesis of a specific mediator protein that activates sodium channels in the apical membrane, which allow transcellular passage of sodium
    - These channels are blocked by Amiloride and Triamterene

Activity

- Review RAAS
- MoA of K+ sparing Diuretics

Control of Aldosterone Secretion

- Indirectly by JGAs, sensitive to composition of the fluid in distal tubule
- Decrease in NaCl of filtrate sensed by macula densa and stimulate renin release and activates RAAS
- Spironolactone is antagonistic to action of aldosterone to cause diuresis

Activity

- What is the difference between the MoAs of Amiloride and Triamterene and Spironolactone?

MoA

- Binds to specific intracellular receptors
- Receptor found in the kidneys and transporting epithelia of colon and bladder
- Cells containing mineralocorticoid receptors also contain 11ß-hydroxysteroid dehydrogenase which converts glucocorticoids and not mineralocorticoids (MC) to metabolites that have low affinity for MC receptors
- Glucocorticoids have little MC effects
- Fludrocortisone PO increases sodium reabsorption in the DCT and increase K+ and H+ efflux
- Used w/ glucocorticoids in replacement therapy (in patients w/ adrenal hypofunction)
- Interaction of MC w/ receptors initiates DNA transcription of specific proteins resulting in increased sodium channels in apical membrane of the cell and increase of Na+/K+/ATPase molecules in the basolateral membrane
- Increased K+ excretion through the tubules
- Rapid effect through the Na+/H+ exchanger in apical membrane that causes Na+ efflux
- Spironolactone - competitive antagonist of Aldosterone
    - SE
        - Gynaecomastia and impotence due to its effects on other adrenal steroids
- Eplerone has similar action but less SE

Uses of Aldoseterone

- _

Activity

- What are clinical indication of Spironolactone?

ADH (Vasopressin)

- Sustained increase to water permeability
- Passive reabsorption
- Hormone secreted by posterior pituitary
- Binds on receptors on basolateral membrane
- V_2 receptors binding, increase in the number of aquaporins in the apical membrane

Inhibition of action of ADH

- Drugs
    - Lithium carbonate
    - Demeclocycline
    - Colchicine
    - Vinca alkaloids

Oxytocin

- Neurohypophyseal hormone
- Octapeptide
- Regulates myometrial activity
- Release stimulated by cervical dilation and suckling
- Synthetic for clinical use

Actions

- Uterine contraction
- Oestrogen induces oxytocin receptor synthesis and uterus at term is highly sensitive to this hormone
- IV slowly to induce labour
- Regular coordinated contractions from the fundus to cervix w/ complete relaxation in between
- Contraction dose dependent

- Larger doses incomplete relaxation
- Very high doses interfere w/ blood flow through the placenta causing foetal distress and death

Other Effects
- Contraction of myoepithelial cells in the mammary gland leading to milk expression from the alveoli to the ducts
- Vasodilator
- Weak antidiuretic - care in cardiac, renal disease and PET

Receptors
- Found in the
    - Uterus
    - Brain - limbic system. Important in parenting and mating behaviour

PK
- Given IV
- Inactivated by oxytocinase in the liver and kidney

Use
- Induce and augment labour
- Treat postpartum haemorrhage (c.f. Ergometrine, Carboprost)

Activity
- What are the uses of oxytocin in obstetric practice?

ADR
- Dose related hypotension (vasodilation)
- Reflex tachycardia
- Antidiuretic effect - water retention and hyponatraemia

Androgens and Analogues

Monday, 24 April 2017 12:04 PM

Androgens

- Testosterone is the main natural androgen
- Synthesised by the interstitial cells of the testes
- Smaller amounts from the ovaries and adrenal cortex
- Adrenal androgen production influenced by ACTH
- Cholesterol is the starting substance
- Dihydrotestosterone is an active metabolite of testosterone following reduction at 5α position
- Acts as an intracellular androgen receptor with greater affinity than testosterone
- Potency greater than testosterone because of a more stable complex with receptor

Weak Androgen Precursors

- Androstenedione - testosterone precursor
- Dihydroepiandrosterone - adrenal androgen
- 5$^{\alpha}$-androstane-3α,17ß-diol and_

Androgen Metabolism

- Etiocholanolone
- Androsterone
- Testosterone also aromatised to oestradiol in extra-glandular tissue accounting for oestrogens in male and PMP women
- This oestrogen may play a role in closure of epiphyses and feminisation in excess amounts
- Activity
    - Review the biosynthetic pathways of steroid synthesis.

Important intermediates

- DHEA
- Androstenedione
- Both are released from the gonads and adrenal cortex and converted to testosterone in the liver.

Actions of Androgens

- Depends on sex and age

- Prepubertal boys
    - Premature closure of epiphyses of long bones
    - Don't achieve full height expected
- Puberty
    - Rapid development of secondary sexual characteristics(facial, axillary, pubic hair)
    - Maturation of reproductive organs
    - Increase in muscular strength
- Adults
    - Anabolic
    - Retention of NaCl
    - Thickening and darkening of skin
    - Sebaceous glands are more active - acne
    - Body Wt and Muscle mass increase
    - Feeling of well being

    - Physical vigour
    - Increase/decrease libido
    - ? Influence sexual behaviours
    - Aggressive behaviour
    - Inhibits spermatogenesis and reduce male fertility
- In women
    - Masculinisation
    - Lower doses - normal female level restoration and improves sexual function following ovariectomy

MOA

- 5&-reductase enzyme converts testosterone to DHT
- Active metabolite
- Causes virilisation of genital tract in male embryo
- Regulates LH/ICSH production in the anterior pituitary cells
- Work through nuclear receptors

PK

- PO testosterone rapidly metabolise by the liver
- Avidly binds to sex steroid binding globulin
- T1/2 = 10-20minutes
- 90% - excreted as metabolites
- Converted in the liver to androstenedione which has weak androgenic activity
- Synthetic androgens preferred

Synthetic Androgens

- PO
    - Methenolone acetate
    - Testosterone undecanoate
    - Fluoxymesterone
    - 19-nortestosterone
- Transdermal
- SC implants
- Injectable biodegradable microcapsules
- Sublingual inclusion complexes

ADRs

- Reduced gonadotrophin release in continued use
- Leads to infertility, salt and water retention
- Adenocarcinoma of the liver
- Impaired growth in children
- Acne
- Masculinisation in girls

Clinical uses

- Hormonal replacement in males hypogonadism due to pituitary/testicular dx
- Female hyposexuality following ovariectomy
- Anti-androgens - flutamide, cyproterone used in Rx of prostatic Ca
- 5&-reductase inhibitors finasteride used in BPH

Androgen Level Peaks in Males

- Embryonic development - male phenotype differentiation
    - Starts from 8 weeks
- Neonatal period - drops to pre-pubertal levels at year 1
- Puberty - increased LH, FSH
- Throughout adulthood

- LH and FSH regulate testicular growth, spermatogenesis and steroidogenesis
- GH synergistic effect w/ LH on the testis
- Oestrogen decreases the effect of LH on secretion of testosterone
- FSH promotes spermatogenesis in the seminiferous tubule and LH regulates testosterone synthesis in the Leydig cells
- Both FSH and LH have growth promoting effects on the testes

Oestrogen in Men
- Synthesised in Leydig Cells and from androgens in the extra-glandular tissues

Ovarian and Adrenal Androgen
- Secrete testosterone
- Androstenedione and dehydroepiandrosterone
    - These can be converted
    - D to testosterone and oestrogen in peripheral tissues

Anabolic Steroids
- Androgens modified to alter he balance of anabolic effects
- Anabolic steroids
    - Nandralone

Effects of Anabolic Steroids
- Increase protein synthesis
- Muscle development
- Trial in debilitating disease poor results
- Aplastic anaemia
- Abuse by athletes

ADRs of high dose androgens
- Cholestatic jaundice
- Livet tumours
- Increased risk of coronary artery disease

Anti-Androgens
- Both oestrogens and progesterone have anti-androgen effect
- Oestrogen act by inhibiting gonadotrophin
- Progesterone compete at androgen receptors in target organs
- Useful in
    - Prostate CA and BPH
    - Acne
    - Male baldness
    - Virilising syndromes in females
    - Precocious puberty
    - Inhibition of sex drive in sexual offenders
- MoA
    - Inhibition of androgen synthesis
    - GnRH
    - _

Androgen Receptor Antagonists
- Cyproterone
- Flutamide

Cyproterone

- Derivative of progesterone
- Weak progestation activity
- Partial agonist at androgen receptors
- Competes w/ dihydrotestosterone for androgen receptors
- Depress the synthesis of gonadotrophin through the hypothalamus
- _
- Uses
    - Adjunct in treatment of prostatic CA during initiation of GnRH agonist treatment
    - Precocious puberty treatment
    - Treatment of masculinisation and acne in women
    - Hypersexuality in male sexual offenders as it reduces libido

Flutamide
- Non-steroidal anti-androgen
- Used in treatment of prostatic CA

Finasteride
- Inhibits enzyme 5α-reductase that converts testosterone to dihydrotestosterone
- Well absorbed PO
- T0.5: 7 hours
- Excreted in faeces and urine
- Used in treatment of BPH
- Tamsolusin and Terazosin, α_1-adrenoceptor antagonists are better agents

Male Contraception
- Ideal contraception
    - Simple
    - Acceptable
    - Reversible
    - Non-toxic
    - Efficacious

Challenges
- Difficult to inhibit spermatogenesis completely
- Many antiandrogens are toxic and have irreversible effects e.g. antineoplastic agents, cadmium nitrofuranes, α-chlorhydrin, dinitropyrrole

Gossypol
- Phenolic compound
- Source: Cotton plant
- Reduces sperm count and impairs sperm motility
- Restored counts following several months of discontinuation
- ADRs
    - Hypoklaemia and weakness
    - Diarrhoea
    - Oedema
    - Dyspnoea
    - Neuritis

Gonadol Steroids
- Suppresses FSH and decrease libido and potency
- May cause gynaecomastia
- Combination of androgens and progestins to reduce ADRs

Oestrogens

Tuesday, 25 April 2017 12:17 PM

Physiological Functions

- Oestrogen acts in concert w/ progesterone and induces synthesis of progesterone receptors in the uterus, vagina, anterior pituitary and hypothalamus
- Note
  - Progesterone deceases oestrogen receptor expression in the reproductive tract a, by reducing their synthesis
  - Prolactin increases the number of oestrogen receptors in the mammary glands but no effect on the oestrogen receptor response in the uterus
- Growth and development od reproductive organs (vagina, uterus, fallopian tubes)
- Development of secondary sexual characteristics (enlargement of breasts through promotion of ductal growth, stromal development and the deposition of fat in the thighs and hips) in these effects, pituitary hormones also play a part
- Bone growth
  - Contribute to moulding of bod contours, shaping the skeleton, and bring about the changes in the epiphysis of long bones that condition the pubertal spurt in growth and its culmination by fusion of the epiphyses
- Growth of axillary and pubic hair, regional pigmentation of the skin of the nipples and areolae and the genital region
- Sexual behaviour
- "Priming" action for progesterone receptors
- Feedback regulation of gonadotrophins, including stimulation of LH surge
- Anabolic effect but less well marked than that of androgens
- Act w/ progestogens in producing changes in the genital tract that occur in the menstrual cycle, and the maintenance of pregnancy
- Act w/ prolactin in stimulating lactation and maintaining it, but high doses inhibit lactation

Other Actions

- Mineralocorticoid (salt and water retention)
- Increase plasma concentration of HDLs
  - Relatively less risk of atheromatous in premenopausal women compared to men of the same age
- Increased coagulability of blood
  - Contraceptive pills containing a high oestrogen content increase the risk of thromboembolism (effect is dose related)

Metabolic Effects

- Decrease rate of bone resorption
  - Promote apoptosis of osteoclasts and antagonise osteoclastogenic and pro-osteoclastic effects of PTH and IL-6
- Alter metabolic effects in the liver, leading to increased production of transcortin, thyroxin-binding globulin, transferrin, renin substrate and fibrinogen
  - Increased levels of circulating thyroxine, oestrogen, testosterone, iron, copper etc.

Preparations

- Esters of benzoic, proprionic and cyclopentyl proprionic acids are administered IM for prolonged action
- Ethinyl oestradiol, mestranol and quinestrol are synthetic steroidal preparations
  - Well absorbed PO and are slowly inactivated in the liver and peripheral tissues
- Piperazine oestrone sulphate

    - Semi-synthetic and water soluble
- Conjugated oestrogens pregnant mare's urine extract
    - Effective PO, by injection and also used as a cream

Synthetic Oestrogens (Non-Steroidal)

- Diethylstilboestol
    - Simplest and most commonly used
- Chlorotrianisene
    - Converted to active oestrogen in the liver
- Dinestrol, Benzestrol
- Methllenestril, Methestrol, Hexestrol

PK or Oestrogens

- Lipophilic
    - Absorption generally good for appropriate preparations
- Aqueous and oil based preparations are administered IM to last several days or months
- Transdermal patches (of oestradiol or oestradiol + norethisterone acetate) deliver the hormones continuously through the skin
    - Changed once or twice daily
- Several preparations are used topically in the vagina
- Oestradiol not taken PO because it undergoes first pass hepatic metabolism
- Conjugated oestrogen are hydrolysed by enzymes present in the lower gut and absorbed
- Oestradiol is bound mainly to sex steroid-binding globulin (SSBG) and to a lesser extent, to serum albumin. In contrast, Ethinyl Oestradiol is bound extensively to serum albumin and not to SSBG
- Rapid hepatic biotransformation w/ short half-life (minutes) and metabolites excreted in urine

Uses of Oestrogen

- Replacement therapy
    - Corrections of disturbances associated w/ menopause; primary hypogonadism
- Treatment of prostatic hypertrophy and cancer and some forms of breast cancer
- Suppression of lactation
- In combination w/ progestogens as oral contraceptives
- Post coital contraception
    - Stilboestrol 25mg OD for 5-6 days.
    - Norethistone 5mg OD for 5 days beginning nor more than 48 hours after insemination

MoA of Oestrogens

- Bind to intracellular receptors ER and ERß
- The oestrogen receptor complex interacts w/ nuclear sites and subsequent genomic effects result in either gene transcription or gene repression

SE of Oestrogens

- GIT upset
- In large doses, oestrogens enhance reabsorption of sodium
    - Water retention
    - Oedema
    - HT
    - Possible cardiac failure
- Irregular menstrual bleeding ("spotting") may occur
- Breasts may become enlarged and tender
- In men, there is feminisation
- In the use of oestrogen-containing oral contraceptives there is increased thromboembolic

disorders
    - Increased level of clotting factors II, VII, IX and X and a decrease in factor III
- Prolonged exposure to unopposed oestrogens may lead to development od cancer of the vagina and uterus
- Breast CA may be exacerbated by oestrogens
- Cholestatic jaundice, changes in libido, depression, headache, leg cramps (rule out venous thrombosis) gall bladder disease
- Contact lenses may irritate
- Transdermal delivery system may cause contact sensitisation

Progestins

Thursday, 27 April 2017 8:15 AM

Progesterone

- Most important progestin
- Natural hormone of the corpus luteum
- Biosynthesised from steroid precursors in the adrenal cortex, ovary and testes and placenta
- An intermediary in the biosynthesis of adrenocortical hormones, androgens and oestrogens
- Most important sources are ovary (corpus luteum) and placenta
- Largely bound to plasma albumin
- T0.5: of injected progesterone is about 15 minutes
- Taken up in adipose tissue and slowly released
- Metabolised mainly in the liver, principally to pregnanediol, pregnanolone, allopregnanediol, 6-and 16-hydroxy derivatives
- Conjugated w/ glucuronic acid and the metabolites excreted mainly in urine and small proportion in faeces

Physiological Actions

- Acts on oestrogen-stimulated endometrium to transform it to a secretory endothelium
  - Change is necessary for acceptance to the fertilised ovum and subsequent implantation of the embryo during the early developmental stages
- Necessary for maintenance of pregnancy
- Continued influence during pregnancy cause an increase in weight of the uterus
- Suppression of production of gonadotropins
- Suppression of contractile response of myometrium to oxytocin
- Stimulates development of secretory alveoli of the mammary glands

Synthetic Progestins

- Progesterone and Analogues
  - Progesterone - IM
  - Hydroxyprogesterone caproate - IM
  - Medroxyprogesterone acetate - IM and PO
  - Megestrol acetate - PO
  - Dydrogesterone - PO
- Testosterone derivatives - PO
  - Dimethisterone
  - Norethisterone
  - Norgestrel
  - _
  - converted to testosterone and oestrogen

Use of Progestins

- Component of oral contraceptive pills in combination w/ oestrogen
- Prevention of habitual abortion if progesterone output if the patient's corpus luteum is deficient
- To control functional uterine bleeding and to produce regular cycles
- Postponement of menstruation
  - Norethisterone 5mg tds starting 3 days before anticipated onset of mense
- Management of endometriosis
- Used in conjunction w/ oestrogens in hormone replacement therapy in menopausal

women w/ an intact uterus
- Advocated for alleviation of premenstrual symptoms

Hormonal Contraception
Introduction
- Contraceptives allows you to enjoy sex w/o the risk of getting pregnant
- There are about 15 different methods of contraception and two types of contraceptives - hormonal and barrier contraception
- Barrier methods of contraception include:
  - Condoms (male or female)
  - Diaphragm
  - The cervical caps
  - Contraceptive sponges
  - Spermicides
  - Sterilisation (sterilisation implant, tubal ligation, vasectomy)
  - Intrauterine methods (copper IUD, hormonal IUD)
- This section will address hormonal contraceptives

Hormonal Methods of Contraception
- Include:
  - Combined oral contraceptives
  - Progestin-only pills
  - Contraceptive patch
  - Injectable contraceptives
- Hormonal contraceptives consist of one or more synthetic female sex hormones (oestrogen and progestin or progestin only)
- They are taken as regular doses in pill form(oral contraceptives) or administered through the skin by means of a patch impregnated w/ hormones
- They may also be given by three or two monthly injections or by subcutaneous implants of progestin
- Hormonal intrauterine devices or vaginal rings are also available

Oral Contraception
- Combination preparations
- Sequential preparations (triphasic or biphasic)
- Progestogen only

Oral Contraception - Combination Preparation
- Contain a mixture of oestrogen and a progestin in a fixed ratio of doses
- Oestrogen content range from 20-50µg. Generally a preparation w. the lowest oestrogen and progestin content which gives good cycle control w/ minimal side effects in the individual patient is chosen
- Two types of packages
  - 21 active tabs
  - 21 active tabs + 7 inactive tabs
- Inactive tabs are usually lactose or ferrous fumerate (Fe appended to the name)
- Oestrogen used is either ethinyl oestradiol or mestranol
- Progestins used include:
  - Norethisterone acetate
  - Ethnodiol diacetate
  - L-norgestrel
  - Desogestrel

Combination Preparation - Starting Routines
- Usually one active tab is taken daily for 21 days followed by 7 days interval or 7 day

inactive tabs during which withdrawal bleeding occurs (indistinguishable from a normal menstrual period)
- First course is usually started on 1st, 2nd or 3rd day of the cycle
- If starting on 4th day or later then additional precaution's are necessary for the 1st 7 days or 14 days if on an everyday tabs because course might accidentally start w/ an inactive tab

How do combination oral contraceptives prevent pregnancy?
- The oestrogen component inhibits follicular development by suppressing the release of FSH
- The progestogen modifies the secretory activity of the cervical mucus in such a way that the passage of the spermatozoa is impaired
- The properties of the endometrium are changed in such a way that it is unfavourable for the implantation to occur
- After a number of cycles there is decreased menstrual flow or even amenorrhoea
- On cessation of treatment
    - Pituitary secretory function recovers first
    - The ovarian responses to FSH and LH are restores
    - Lastly. The endometrial changes to endogenous oestradiol and progesterone recover
- CO preparations can be used for emergency contraception after unprotected intercourse
    - 2 tabs of a preparation containing Levonorgestrel 250µg + Ethinyloestradiol 50µg taken within 72 hour and 2 more tabs 12 hours later

Sequential Oral Contraceptives
- Consists of a low dose of oestrogen for 21 days with low but increasing doses of progestin for three successive periods of 7 days
- When the oral contraception is discontinued, the endometrium is shed
- Risk of contraceptive failure is high, if doses are missed or if the dose of oestrogen is too low
- 30-40µg oestrogen + 125µg - 1mg progestogen
- Biphasic combination preparations e.g.
    - Days 1 - 10 - Ethinyl oestradiol 35µg + norethindrone 0.5mg
    - Day 11-21 days Ethinyl oestradiol 35µg + norethindrone 1mg

Progestrogen Only Contraceptives
- Referred to as the "mini pill"
- Doses are slightly above the threshold for an infertility effect taken daily w/o interruption
- May be commenced soon after childbirth, before renewal of the menstrual period
- Examples
    - Megestrol acetate 0.8mg
    - Chlormadinone 0.5mg
    - Ethnodiol diacetate 0.5mg
    - Norethisterone 0.35mg
    - D-norgestrel 0.03mg
- Do not impair lactation
- Effect on the ovulation irregular
- Menstrual bleeding is very irregular and might not occur for several cycle but this resolves on long term treatment
- Suitable alternative when oestrogens are contraindicated by a higher failure rate than combination preparation
- Suitable for
    - Older women
    - Heavy smokers
    - HT

    - Valvular heart disease
    - DM
    - Migraines

Injectable Progestogen Only Contraceptives

- Medroxyprogesterone acetate aq. Suspension by deep IM three monthly
- Norethisterone enanthate oily by deep IM into G.max every 8 weeks
- Implantable progestin preparation (norplant system)
    - L-norgestrel (6 tubes of 36mg each)
    - Inserted sub-dermally on the lower surface of the upper arm and provides contraception for 5 years

Desirable Feature of Contraceptives

- Peace of mind
- Fewer ovarian cysts, ovarian and endometrial CA
- Fewer benign breast lesions
- Fewer heavy and irregular periods
- Less dysmenorrhoea, lower incidence of ectopic pregnancy

SE of Oral Contraceptives

- Gain in body weight, mild oedema, N, fullness of breasts, headache, dizziness, depressed feeling
- Changes in CHO metabolism, decrease in glucose tolerance
- Occasional alteration in LFT w/ elevation of SGOT, alkaline phosphatase an serum bilirubin
- Changes in clotting factors, increase in factors VII, VIII, IX, X
- Increase in concentration of thyroxine-binding globulin
- Inhibition of lactation
- In adolescents, delay in closure of epiphyses

Contraindication

- CVS disease
- Thromboembolic disease
- Impaired liver function
- CA of the breast or oestrogen dependent neoplasia
- Undiagnosed bleeding
- Pregnancy or suspected pregnancy
- Classical migraine

Anti-Thyroid Drugs

Tuesday, 2 May 2017 12:08 PM

Thyroid Hormone Synthesis

- Uptake of iodide
- Oxidation of iodide to iodine (peroxidase)
- Iodine organification (iodine + tyrosine = MIT, DIT)
- Coupling of iodotyrosine residues to for T3 and T4 (Peroxidase)
- Release of thyroid hormones
- Transport by TBG
- Metabolism of thyroid hormones (deiodinase)

Thioamides

- Includes:
  - Propylthiouracil (PTU, prototype)
  - Carbimazole
  - Methimazole
  - Carbimazole → Methimazole (10X more potent)
- Inhibit thyroid peroxidase catalysed reactions (inhibit synthesis of thyroid hormones)
- Inhibit peripheral deiodination of T4 to T3 (PTU >>>Methimazole)

PK

	PTU	Methimazole
Bioavailability	50-80%	100%
PPB	~75%	Nil
Plasma half-life	75 min	4-6 hours
Vd	~20L	~40L
Concentrated in thyroid	Yes	Yes
Metabolism - severe liver disease	Normal	Reduced
Metabolism - severe kidney disease	Normal	Normal
DoA	Short	Long
Dosing frequency	1-4X/day	1-2X a day
Transplacental passage	Low	Low
Levels in breastmilk	Low	Low
Excretion	Urine	Urine

Adverse Effects

- Rash (most common) - Mild, and subsides
- Agranulocytosis (most dangerous, <1%)
  - Sore throat
  - Fever
  - G-CSF - Rx
- Others
  - Hepatitis
  - Lupus like reaction
- Cross sensitivity - 50%

Therapeutic Use

- Treatment of hyperthyroidism
- Thyroid Storm
    - PTU preferred

Anion Inhibitors

- Include
    - Thiocyanate
    - Perchlorate (aplastic anaemia)
        - 10X more active than Thiocyanate
    - Fluborate
    - Pertechnetate
    - Lithium
- MoA
    - Block uptake of iodide by the thyroid gland by competitive inhibition of the iodide transport system (sodium-iodide symporter)
- Therapeutic use
    - Iodide induced hyperthyroidism (e.g. Amiodarone)

Iodide Preparations

- Includes:
    - Potassium iodide
        - As a single agent
        - Lugol's iodine
            - 5% iodine + 10% potassium iodide
            - Iodine is reduced to iodide in the intestines before absorption
- MoA
    - Inhibit thyroid hormone release
    - Inhibits its own transport into the thyroid
    - Inhibits organification of iodine (Wolff-Chaikoff Effect)
    - Decreases the size and vascularity of the hyperplasic gland. Gland is firmer (less friable - less bleeding during surgery)
    - In susceptible individuals iodides induce
        - Hyperthyroidism (Jodbasedow Effect)
        - Hypothyroidism
    - Striking and rapid action within 24 hours
    - Maximal effect after 10-15 days of continuous treatment
    - Beneficial effects are transient
- Indications
    - Hyperthyroidism
        - Pre-operatively
    - Thyrotoxic crisis
        - Together w/ Anti-thyroid drugs
    - In radiation emergencies iodides protective if administered before radiation exposure
        - 1986 - Chernobyl nuclear reactor accident
- Adverse Effects
    - Hypersensitivity (IV)
        - Angioedema
        - Serum sickness symptoms
    - Iodism
        - Brassy taste, inflammation of the mouth, throat, gums
        - Increased salivation, enlargement if salivary glands

        - Coryza, sneezing, cough, pulmonary oedema
        - Eye irritation
        - Occur due to chronic use
        - Others
            - Skin lesions
            - A, D, Gastric irritation
            - Fever
            - Depression
            - Severe headaches
                - Thought to be due to sinusitis
        - Stop treatment
        - Reversible
        - Increase iodide excretion (severe iodism)
            - Diuretics that promote Chloride excretion

Radioactive Iodine

- I^{131}
    - Emits ß-particles ($T_{0.5}$ - 5 days)
    - I^{131} has a $T_{0.5}$ - 8 days
    - By 2 months, its radioactivity has effectively disappeared
    - ß-particles destroys thyroid tissues
    - Little effect on surrounding tissues
    - Does not appear to lead to future cancer
    - Advantages
        - No need for surgery
        - Does not cause hypoPTH
        - No need for hospitalisation
    - Disadvantages
        - Delayed hypothyroidism
        - Thyroid storm (rare)
    - Indications
        - Hyperthyroidism
        - Reduce the size of a large goitre causing compressive symptoms
    - Contraindications
        - Pregnancy and lactation
- I^{123}
    - $T_{0.5}$ - 13 hours
    - Emits γ particles
    - Thyroid scanning for diagnosis

Iodinated Contrast Media

- Include
    - Ipodate
    - Iopanoic acid
    - Diatriazoate
- MoA
    - Inhibit thyroid hormone release
    - Inhibit T_4 deiodination to T3

Adjuvant Therapy

- ß-adrenergic receptor antagonists - used for the ANS symptoms
    - Propanolol
        - Weak inhibitory action of deiodination
    - Atenolol
    - Esmolol

- Calcium channel blockers
    - Diltiazem
- Dexamethasone
    - Said to inhibit deiodination of T4 to T3
- Cholestyramine
- Other sympathoplegic agents e.g. Guanethidine

Glucagon

Tuesday, 11 April 2017 11:14 AM

- Produced by the A-cells in the pancreas
- Metabolised in the liver, kidney, its sites of action and plasma
- $T_{0.5}$: 3-6 minutes
- MoA
    - Acts on a glycoprotein receptor on membranes of target tissues → activation of adenylyl cyclase → reduction of cAMP
    - Promotes glycogenolysis (liver only)
    - Stimulates gluconeogenesis (liver)
    - Stimulates lipolysis (adipose tissues)
    - Increases force of contraction (heart)
        - Via glucagon receptors
    - Relaxes GIT smooth muscle
- Pharmacologic amounts of glucagon cause release of
    - Insulin from normal beta cells
    - Catecholamines from phaeochromocytoma
    - Calcitonin from medullary carcinoma cells
- Use
    - Treatment of severe hypoglycaemia (if unconscious and IV glucose not available)
        - IV, IM, subcutaneously
        - Hyperglycaemic response is transient
        - Inadequate response when hepatic stores of glycogen are depleted
        - Give oral glucose or food to prevent recurrent hypoglycaemia
    - Radiological studies of the GIT
    - Cardiac inotropic agent
        - If ß-agonists are rendered ineffective by prior use of ß-antagonists
        - E.g. in ß-blocker poisoning
    - In endocrine diagnostic tests
        - In phaeochromocytoma
            - Measure released catecholamine
        - In DM
            - Measure released insulin levels
    - Treatment of GIT diseases that cause spasms
        - Acute diverticulitis
        - Disorders of the biliary tract
- Adverse Effects
    - Transient NV
        - These are mild
- Contraindication
    - In patients w/ phaechromocytoma

Insulin

Thursday, 4 May 2017 8:20 AM

- Pancreatic endocrine hormone
- Controls intermediary metabolism
- Reduces blood sugar

Diabetes Mellitus
- DM is as a result of absolute or relative insulin deficiency
- Usually coupled w/ insulin resistance
- Copious sugary urine
- Osmotic diuresis
- Association w/ metabolic syndrome

Metabolic Syndrome
- Obesity
- Hypertension
- Obesity
- Dyslipidaemia - atherosclerosis

End Organ Damage
- Nephropathy
- Retinopathy
- Cerebrovascular events
- Peripheral Neuropathy
- Peripheral vascular disorder/diabetic foot

Control of Blood Sugar
- PO Glucose > IV → insulin increase
  - Incretin GIT - GIP, GLP-1
- Glucose less effective in stimulating insulin release in DM
- Exogenous insulin - hypoglycaemia
  - Reduction of endogenous insulin
  - Increase counter-regulatory hormones (glucagon, adrenaline, glucocorticoids, GH)

Activity 1
- Review the metabolic effects of these counter-regulatory hormones w/ special emphasis on blood sugar metabolism

- Precursor - preproinsulin 110AA translocated in the wall of the ER following 24AA N terminal cleavage → proinsulin → cleavage of the C peptide
- Disulphide bond linked A and B chain that has 21 and 30AA respectively (insulin)
- C peptide and insulin are equimolar - for each 1 C-peptide, there is 1 molecule of insulin

Chemistry
- Now synthesised by genetic engineering
- Hexameric and monomeric forms are present
- Insulin analogues formed by AA changes

Synthesis, Secretion and Degraded
- Islet cell of Langerhans - 4 types of cells
  - A - glucagon

    - B - insulin 60-80% of the cells
    - D - somatostatin
    - F - pancreatic polypeptide
- Synthesis and secretion of insulin
    - Beta cells - principle insulin censor
    - Preproinsulin cleaved 24AA, transported to the golgi apparatus where proinsulin is stored in vesicles
    - Pro-insulin has longer half-life c.f. insulin
    - Converted to insulin y Ca2+ dependent endoperoxidases found in the islets and neuro-endocrine cells
    - Follows C-peptide cleavage
- Regulation of secretion
    - GI hormones
    - Neurotransmitters
    - Pancreatic hormones

Activity 2

- Review the hormones above and their impact on insulin secretion

Regulation

- Glucose, AA,FFAs and ketone bodies stimulate release of insulin
- Innervation of the ß-cells are both adrenergic and cholinergic
- a2 adrenergic receptor agonists inhibit insulin release, ß adrenergic receptor agonists and vagal stimulation enhance insulin release
- hypoxia

Distribution and Degradation of insulin

- Monomer in blood
- Vd = ECF
- Pancreas secretes 40µg (1 unit) per hour in the portal vein
- Rise after ingestion of meal
- T0.5 = 5-6 minutes
- Increase in Diabetic who develop anti-insulin antibodies

Proinsulin

- Proinsulin has a longer half-life - 17 minutes
- 10% of immunoreactivity of insulin
- Increases in insulinoma
- 2% activity of insulin

C-Peptide

- Equimolar w/ Insulin
- Molar concentration in plasma higher due to its longer half-life of 30 minutes

Degradation

- Rapid in the liver and kidney and muscle
- 50% reaches the liver via portal circulation and is destroyed
- Insulin exogenously given, bypasses portal disposition
- Filtered by renal glomerulus and reabsorbed by the tubules

Receptors

- Cell surface receptors
- Liver, muscle and fat
- Blood cells, brain, gonad cells
- Larger receptor concentration in the former cells

Actions of Insulin

- Liver
  - Decrease gluconeogenesis and glycogenolysis
  - Stimulates e glucose uptake
- Muscle
  - Stimulate glucose uptake and inhibits flow of gluconeogenic precursors (alanine, lactate and pyruvate)
- Adipose tissue
  - Reducing circulating FFA
  - Promote TG storage in adipocyte

Classification

- Rapid acting (ultrashort)
- Short acting
- Intermediate acting
- Long acting

Regular - soluble insulin

- Clear, soluble
- No added protein
- No buffer
- Small quantity of zinc
- Onset 30min, peak in 2-4 hours, duration of 5-8hours

Intermediate

- NPH (Neutral Protamine Hagedon) Isophane
- Lente
- Cloudy NPH contains protamine and phosphate buffer
  - Help the insulin monomers to complex
- Lente has no protamine but has acetate buffer
- Onset 1-2 hours, peak 6-12hours, duration 18-24 hours

Slow Acting

- Ultra Lente (Lente)
- Protamine Zinc Insulin (PZI)
- Cloudy, UL has no protamine but has an acetate buffer unlike the phosphate in PZI
- Slow onset, 4-6hours

Insulin Analogues

- Lispro, Glulisine, Aspart - Ultrashort
- Glargine, Determir - Long Acting

Lispro

- Monomeric insulin
- B28 proline to B29 and replaces lysine which reverts to B28
- Decrease self association
- Preserved in cresol to increase shelf life
- Onset 5-15 minutes, peak 1 hour, DoA 4-6 hours

Aspart

- B28 substituted w/ aspartic acid
- Reduced in self association
- Kinetics c.f. Lispro

Glusiline

- Lysine in B3 for asparagine
- Glutamine or Lysine in B29
- Kinetics similar to Lispro and Aspart

Glargine

- Soluble
- Peak-less
- Long acting analogue
- Reproducible basal insulin
- 2 arginine added in B chain carboxyl terminal
- Substitute glycine for asparagine in A21
- Soluble in acid and precipitates a neutral pH
- SC injection precipitates to a crystalline depot with slow dissolution
- Onset of action - 1 hour
- Peak - 4-6hours
- DoA - 11-24 hours
- Given OD or BD in sensitive control
- Not to be mixed in syringe w/ short or rapid acting

Activity

- What are the indications of insulin in clinical practice?
- What adverse effects are associated with insulin therapy?
- How is insulin given (delivery systems)?
- The adverse effects of insulin
- Basis of using insulin ad a mixture proportion of short acting and long acting

Calcitonin

Tuesday, 9 May 2017 12:13 PM

- Secreted by the parafollicular cells or clear cells (C cells), situated amongst the follicles in thyroid gland
- Polypeptide chain w/ 32 AA.
- Its molecular weight is about 3,400
- Synthesised from procalcitonin

PK
- Serum level: 1 to 2 ng/dL
- T0.5: 5-10 minutes
- Metabolism
    - Is degraded and excreted by the liver and kidney respectively

Actions
- Important role in controlling the blood calcium levels
- Decreases the blood calcium level by acting on
    - Bones
    - Kidneys
    - Intestine

Bone
- Stimulates osteoblastic activity and facilitates the deposition of calcium in bones
- Suppresses the activity of osteoclasts, inhibiting resorption of calcium from bones
- Also inhibits development of new osteoclasts in bone

Kidney
- Increases excretion of calcium through urine, by inhibiting Ca2+ absorption from the renal tubules

Intestines
- Prevents absorption of calcium from intestines into the blood

Effects on Phosphate
- With respect to calcium, calcitonin is a PTH antagonist
- It has similar actions to PTH with respect to phosphate
- Decreases the blood level of phosphate by:
    - Inhibiting resorption of phosphate from bone
    - Stimulating deposition of phosphate in bone
    - Increasing urinary excretion of phosphate by inhibiting its reabsorption from renal tubules

Regulation of Calcitonin
- Hypercalcaemia stimulates calcitonin secretion through a calcium receptor in parafollicular cells
- Gastrin is also known to stimulate the release of calcitonin

Bisphosphonates

Introduction
- Non-hormonal agents used in Ca^{2+} homeostasis
- Most effective "antiresorptive" drugs at present

- BPN are analogues of pyrophosphates - carbon atom replacing "P-O-P skeleton"
- BPNs had selective affinity for calcium phosphate found in calcified tissues

Classification

BPN	Relative Potency
First Generation Etidronate Tiludonate	 1 10
Second Generation - amino or nitrogenous side chain Pamidronate Aledronate Ibadronate	 100 100-500 500-1000
Third Generation Risedronate Zoledronate	 1000 5000

Bone Remodelling

- Bone has 2 main components
  - Bone matrix
  - Solid mineral phase (hydroxyapatite)
- Normally, non-mineralised osteoid covers the mineralised bone matrix, preventing its resorption by osteoclasts
- For resorption
  - Osteoids must get dissolved such that osteoclasts can attach to the mineralised matrix
- Once resorptive pits are formed, an acidic zone is created at ruffled borders of osteoclasts, followed by resorption of matrix by acid hydrolases

BPN MoA

- Non-nitrogenous BPNs
  - Metabolised in the cell
  - Metabolised product replaces triphosphate in ATP
  - Leads the osteoclast to undergo apoptosis due to lack of cellular action
- Amino BPNs e.g. Aledronate and Risedronate block farnesyl pyrophosphate synthase
- This is an enzymes in the mevalonate pathway, critical for osteoclast survival

Other Cellular Effects

- Inhibition of 1,25 (OH)2 production
- Inhibition of intestinal calcium absorption
- Metabolic changes in the bone
  - Inhibition of glycolysis
  - Inhibition of cell growth
  - Changes in acid and alkaline phosphatase

PK

- <10% of an oral dose is absorbed
- Food reduces absorption even further
- Must be given on an empty stomach
- Pamidronate is not available as an PO preparation as it causes gastric irritation
- 50% of absorbed drug accumulates in bone
  - Retained for months to years
- Remainder excreted unchanged in urine

CI

- Decreased renal function
- Oesophageal motility disorders
- PUD
- IV formulation of Pamidronate, Zoledronate and Ibadronate reduces risk of the GI adverse effects

AE

- Gastric and oesophageal irritation
  - Minimised by taking the drug with a full glass of water and remaining upright for 30 minutes
- Osteonecrosis of the jaw
  - High doses of IV Zoledronate

Therapeutic Uses

- Osteoporosis
  - Post-menopausal
  - Steroid induced
  - Idiopathic
- Paget's Disease
  - Arrest osteolytic lesions
  - Reduce bone pain
  - Improve secondary symptoms
- Hypercalcaemia of malignancy
- Osteolytic bone metastasis

Fluoride

Introduction

- Used for prophylaxis of dental caries
- Under investigation for treatment of osteoporosis
- Fluoride is accumulated by bones and teeth, where it may stabilise the hydroxyapatite crystal
- Fluoride in drinking water is most effective in preventing dental caries if consumed before eruption of permanent teeth
- Optimum concentration in drinking water supplies is 0.5-1 ppm
- Excess fluoride in drinking water leads to teeth mottling of the enamel in proportion to the concentration above 1 ppm

AE

- Experimental studies look into the use of fluoride to stimulate new bone formation inconclusive
- Several AE at these doses noted
  - NV
  - GI blood loss
  - Arthralgia
  - Arthritis

Oral Anti-diabetic Agents

Wednesday, 10 May 2017 9:25 AM

- Oral ADA
  - Oral glucose lowering agents
  - Oral hypoglycaemic agents ???

Classification

- Agents that bind to the sulfonylurea receptor and stimulate insulin secretion (insulin secretagogues)
  - Sulfonylureas
  - Meglitinides
  - D-phenylalanine derivatives
- Agents that lower glucose levels by their actions on liver, muscle and adipose tissue
  - Biguanides
  - Thiazolidinediones
- Agents that principally slow the intestinal absorption of glucose
  - α-glucosidase inhibitors
- Agents that mimic incretin effect or prolong incretin action
  - Glucagon-like peptide 1 (GLP-1) receptor agonists
  - Dipeptidyl peptidase-4 (DDP-4) inhibitors
- Agents that inhibit the reabsorption of glucose in the kidney
  - Sodium-glucose co-transporter inhibitors (SGLTs)
- Agents that act by other or ill-defined mechanisms
  - Pramlintide
  - Bromocriptine
  - Colesevelam

Insulin Secretagogues

- Include
  - Sulfonylureas
    - First generation
      - Acetohexamide
      - Tolazamide
      - Tolbutamide
      - Chlorpropamide
    - Second generation
      - Glyburide (Glibenclamide)
      - Glipizide
      - Gliclazide
      - Glimepiride
  - Non-sulfonylureas (Glinides)
    - Meglitinides
      - Repaglinide
      - Mitiglinide
    - D-phenylalanine derivative
      - Nateglinide

Sulfonylureas

- Second generation agents

    - Are 100X more potent than first generation
        - Greater affinity for the sulfonylurea receptor
    - Have fewer AE
    - Have fewer DI
- MoA
    - Stimulate insulin release from pancreatic ß-cells
    - Reduce hepatic clearance of insulin
    - Bind to the sulfonylurea receptors that are associated with K+ channels on B-cells → inhibition of efflux of K+
        - This causes membrane depolarisation
    - Depolarisation opens voltage gated Ca2+ channels and results in influx of Ca2+ → release of preformed insulin
- Chronic treatment → down regulation of sulfonylurea receptors (secondary failure
- If treatment is stopped, acute response of pancreas to sulfonylureas is restored

PK

- All well absorbed from the GIT
- Food and hyperglycaemia reduced absorption of sulfonylureas
- Hyperglycaemia inhibits gastric motility
- 90-99% PPB
- T0.5
    - First generation except Chlorpropramide is 4-7 hours (BD
        - Chlorpropramide is 24-48 hours (OD)
    - Second generation is 3-5 hours (OD as duration of action is 12-24 hours)
- All metabolised in the liver
    - Some metabolites weakly active
- Excreted in urine
    - Second generation agents are partly excreted in bile

AE

- Hypoglycaemia
    - Elderly patients on long acting agents
    - IV glucose infusion for 24-48 hours
- Hypoglycaemia is also associated with
    - Delayed meals
    - Increased physical activity
    - Alcohol intake
    - Renal failure
- Weight gain
    - Due to increased insulin levels and improved blood sugar control
- NV
- Cholestatic jaundice
- Agranulocytosis, aplastic and haemolytic anaemias
- Rashes
- Alcohol induced flush (esp. Chlorpropamide)
- Hyponatraemia (esp. Chlorpropamide) - potentiate ADH action

Therapeutic Use

- Type II DM

Contraindications

- Type I DM
- Pregnancy
- Lactation

- Significant liver and renal dysfunction
- Elderly patients (chlorpropamide)

DI
- Displace sulfonylureas from binding sites
    - Sulfonamides
    - Salicylates
- Potentiate hypoglycaemia
    - Ethanol

Repaglinide
MoA
- C.f. Sulfonylureas

PK
- T0.5 - 1h
- DoA - 5-8h
- Therefore multiple prandial use
- Metabolised by the liver and kidney
- Major SE
    - Hypoglycaemia
- _

Nateglinide
- MoA
    - =sulfonylureas
    - Rapid onset of action
    - Short duration of action <4 h
    - Use 1-20 minutes before a meal

Biguanides

- Metformin
    - MoA
        - It increases the activity of AMP-dependent protein kinase (AMPK)
            - ↑ glycogen storage
            - ↓ hepatic glucose production
            - ↑ insulin sensitivity
            - ↓ blood glucose
    - Rarely causes hypoglycaemia (euglycaemic agent)
        - O insulin release from the pancreas
    - Does not promote weight gain
    - PK
        - Does no PPB
        - Not metabolised
        - Excreted in urine
    - AE
        - AND, abdominal discomfort (20% of patients)
        - Metallic taste
        - Minimise by ↑ drug doses slowly and taking the drug with meals
        - Transient, dose dependent
        - ↓ Vitamin B12 absorption
            - Annual screening for deficiency
        - Lactic acidosis (high doses)
            - Impaired hepatic metabolism of lactic acid
    - C/I

        - Renal and hepatic disease
        - Past history of lactic acidosis
        - CCF
        - Chronic hypoxic lung disease
        - Alcoholism

Thiazolidinediones

- Include
    - Rosiglitazone
    - Pioglitazone
- Are euglycaemic agents
- Maximum effects after 6-12 weeks
    - Act through gene regulation
- MoA
    - They are agonists for nuclear peroxisome proliferator-activated receptor γ
    - This receptor activates insulin responsive genes that regulate CHO and lipid metabolism
    - ↑ insulin sensitivity in tissues (or ↓ insulin resistance in tissues)
    - ↑ glucose transport into muscle and lipid tissues by ↑ synthesis of glucose transpoters
    - ??? Lower glucose production by the liver
- AE
    - Anaemia
    - Weight gain
    - Oedema
        - reduce renal sodium excretion
        - Increase vascular permeability
    - Plasma volume expansion
        - Discontinue if CCF develops
    - Macular oedema (Rosiglitazone)
    - Hepatotoxicity
        - Rare
        - Monitor liver function
    - Interfere with metabolism of oral contraceptives
- Not usd in
    - Hepatic disease or abnormal LFTs
    - Severe CCF
    - Pragnancy

α-glucosidase Inhibitors

- Include
    - Acarbose
    - Miglitol
    - Voglibose
- MoA
    - Inhibit α-glucosidases (e.g. sucrase, maltase) in the intestines
    - These enzymes convert starches and disaccharides to monosaccharides
        - Slows the absorption of carbohydrates
- Do not stimulate insulin release
    - No hypoglycaemia ∴ euglycaemic
- Used at the start of a meal
- Poorly absorbed
- AE

    - Malabsorption
    - Flatulence
    - Diarrhoea
    - Abdominal bloating
    - Acabose associated with increased liver enzymes
        - Caution in liver disease
    - If hypoglycaemia occurs while on these drugs, use glucose and not sucrose
- C/I
    - Inflammatory bowel disease
    - Renal impairment

Drugs that mimic incretin effect or prolong incretin action

- Oral glucose provokes higher insulin response as compared with an equivalent dose of IV glucose
    - Oral glucose causes a release of gut hormones (incretins) e.g.
        - Glucagon-like peptide-1 (GLP-1)
        - Glucose dependent insulinotropic peptide (GIP)
    - Incretins amplify the glucose-induced insulin secretion
- GIP-1 has other biological effects; it:
    - Suppresses glucagon secretion
    - Delays gastric emptying
    - Reduces apoptosis of human islet cells in culture
- Type II diabetic patient on GLP-1 therapy are less hungry
    - ? Related to the deceleration of gastric emptying
    - ? There is CNS effect

DPP-4 Inhibitors

- Examples
    - Sitagliptin (competitive inhibitor)
    - Saxagliptin (covalent enzyme binding)
    - Vildagliptin
    - Linagliptin
    - Alogliptin
- MoA
    - Inhibit inactivation of GLP-1 and GIP
    - Increased GLP-1 and GIP
    - Associated with increased insulin and reduced glucagon levels
    - No effect on body weight
- PK
    - Do not bind to albumin
    - Minimal metabolism in the liver
    - Excreted mainly unchanged in urine
    - The dose of Saxagliptin should be lowered when co-administered with strong CTP3A4 inhibitor
- AE
    - Sitagliptin
        - Common AE
            - Nasopharyngitis
            - URTI
            - Headaches
        - Hypoglycaemia
            - If combined with insulin secretagogues or insulin
        - Post-marketing reports

        - Acute pancreatitis
        - Severe allergic hypersensitivity reactions
        - Sitagliptin should be immediately discontinued if these AE occur
    - Other DDP-4 inhibitors also cause
        - URTI
            - Saxagliptin causes UTI
        - Headache
        - Hypersensitivity reactions

GLP-1 Receptor Agonists

- Include:
    - Exenatide
    - Liraglutide
    - Albiglutide
    - Dulaglutide
    - All above are subcutaneous
    - Semaglutide
        - PO
        - Application for approval Dec 2016

Exenatide

- SC before meals
    - Exenatide LAR is a once-weekly preparation
- DoA - 10hours
- Excreted by glomerular filtration (adjust dose in severe renal failure)
- Causes weight loss of 2-3 kg
- Reduce dose of sulfonylureas to avoid hypoglycaemia
- AE
    - N (44%)V
        - Nausea is dose dependent and declines with time
    - High-titre antibodies against Exenatide develop in about 6% of patients
        - Attenuation of glycaemic response

SGLT2 Inhibitors

- Glucose is filtered by the glomeruli and reabsorbed in the proximal tubules by sodium-glucose transporters (SGLTs)
- SGLT accounts for 90% of glucose reabsorption
- Inhibition of SGLT2 causes glycosuria and lowers glucose levels
- Examples
    - Canagliflozin
    - Dapagliflozin
    - Empagliflozin
- Used alone or in combination with other oral agents or insulin
- Modest weight loss of 2-5kg
- Efficacy is reduced in chronic kidney disease
    - Not used in severe renal disease
- AE
    - Genital infections and UTIs
    - Osmotic diuresis
        - Hypotension
        - Polyuria
        - Thirst
    - Increased LDL cholesterol

    - Dapagliflozin
        - Breast CA
        - Bladder CA

Amylin

- Derived from the pancreatic B-cells
- MoA
    - Reduces glucagon secretion
    - Slows gastric emptying
    - Increases appetite centrally

Pramlintide

- A synthetic analogue of amylin
- Used together with insulin
- Insulin and Pramlintide not injected with the same syringe
- Use S/c immediately before eating
- Rapidly absorbed
- DoA
    - 150 minutes
- Metabolised and excreted by the kidney
- AE
    - ANV

Colesevelam and Bromocriptin

- Have very modest efficacy in lowering glucose levels and their use for this purpose is questionable
- MoA are unknown

Antibiotics in Malaria; Malaria Chemoprophylaxis

Tuesday, 9 May 2017 2:11 PM

- When patients are counselled on the prevention of malaria, it is important to emphasize measures to prevent mosquito bites e.g. use of
  - Insect repellents
  - Insecticides
  - Bed nets
- This is because
  - Parasites are increasingly becoming resistant to multiple drugs
  - No chemoprophylaxis regimen a 100% effective and unwanted _
- In addition
  - Some of the regimens might be complex, requiring multiple drugs to be taken at different times
  - Different agents may be required for different travel destinations

Definition of Terms

- True causal Prophylaxis
  - The prevention of infection by killing of the sporozoites on entry into the host
    - This is not feasible with present drugs
      - However, it may be feasible in the future w/ vaccines
- All effective chemoprophylactic agents
  - Kill erythrocytic parasites before they increase sufficiently in number to cause clinical malaria attacks
  - They kill the parasites when they emerge from the liver after the pre-erythrocytic stage (i.e. they block the link between the exo-erythrocytic stage and the erythrocytic stage

Recommended Malaria Chemoprophylactic Regimens

- The recommended drug combinations vary depending on the
  - Patient
  - Area visited
  - Overall risk of infection
  - Presence of resistant forms of the disease
- Current recommendations from CDC 2016 include
  - The use of chloroquine (CQ) for chemoprophylaxis is recommended in the few areas infested by only CQ-sensitive malaria parasites (mainly the Caribbean and Central America west of the Panama Canal)
  - Mefloquine or Proguanil/atovaquone (Malarone or Malanil) for most for other malarious areas
  - Doxycycline for areas w/ very high prevalence of Multidrug resistant (MDR) falciparum malaria (mainly border areas of Thailand)
  - Terminal prophylaxis with primaquine to eradicate dormant hepatic stages of P. vivax and P. ovale after travel after travel may be required for travellers with major exposure to these parasites
    - Screen for G6PD deficiency before using primaquine

Drugs For The Prevention of Malaria in Travellers

Drug	Use	Adult Dosage
Chloroquine	Areas w/o resistnat P. falciparum	500mg weekly
Malarone or Malanil	Areas w/ CQ-resistant P. falciparum	1 tablet (250mg Atovaquone/100mg proguanil) daily

Mefloquine	Areas w/ CQ-resistant P. falciparum	250mg weekly
Doxycycline	Areas with MDR P. falciparum C/I in children <8 years of age and pregnant women	100mg daily
Primaquine	Terminal prophylaxis of P. vivax and P. ovale infections Alternative for primary prevention	52.6mg (30mg base) daily for 2 week after travel For primary prevention 52.6 mg daily

Note:

- CDC recommendations should be checked regularly because these may change in response to:
  - Changing resistance patterns
  - Increasing experience with new drugs
- In some circumstance, it may be advisable for travellers to carry supplies of drugs with them in case they develop a febrile illness while in malaria endemic areas when medical care is unavailable

Recommended Regimens for Self-Treatment

- Include
  - Artemisinin-based combination therapies e.g. Artemether/Lumefantrine (AL;Coartem*)
  - Malarone
  - Mefloquine
  - Quinine
- Malaria chemoprophylaxis drugs are given to individuals who intend to travel to an area where malaria is endemic
- Administration should be:
  - Started 1-2 weeks before entering the malaria endemic areas (Doxycyclin and Malarone may be started 2 days before travel)
  - Continued throughout the stay and for at least a month afterwards (except 1 week for Malarone)
- Continuation of prophylaxis for a month after leaving the malaria endemic area is aimed at eliminating asexual parasites emerging from the liver, weeks after exposure
- For travellers, chemoprophylaxis is started before entering the endemic area to asses tolerability and fore slowly eliminated drugs to build-up therapeutic concentrations
- Doxycycline and Malarone are good for last minute traveller because they can be started 1-2 days before travel
- Atovaquone-Proguanil, Doxycycline should be taken daily at the same time each day while in the malarious area
- Mefloquine, CQ and Hydroxychloroquine, should be taken weekly while in the malarious area

Specific Drugs
Chloquine
MoA

- Blood schizonticide
- Concentrated in the parasite and inhibits heme polymerase

PK

- PO active
- T0.5: 50 hours

AE

- GIT disturbances, dizziness and urticaria
- Bolus IV injections can cause dysrrhythmias
- Resistance is common

Caution

- May worsen psoriasis

Hydroxychloroquine Sulfate
- An alternative to CQ for prophylaxis only in areas w/ CQ-sensitive malaria
- Dose is 310mg base (400mg salt) orally

Proguanil
MoA
- Folate antagonist
- Slow blood schizonticide
- Also has come action on the primary liver forms of P. vivax

PK
- Orally active
- T0.5: 16 hours

Mefloquine
MoA
- Blood schizonticide
- Active against P. falciparum and vivax
- Acts by inhibiting the parasite heme polymerase

PK
- PO active
- T0.5: 30 days
- Slow onset of action

AE
- GIT disturbances
- Neurotoxicity
- Psychiatry problems

C/I
- People allergic to mefloquine or related compounds (Quinine and Quinidine)
- People w/
    - active depression
    - a recent history of depression
    - generalised anxiety disorder
    - Psychosis
    - Schizophrenia
    - Other major psychiatric problems
    - Seizures

Caution
- Use w/ caution in persons w/ psychiatric disturbances or a previous history of depression
- Not recommended for persons w/ cardiac conduction abnormalities

Atovaquone/Proguanil
- Used for prevention and for the treatment of acute uncomplicated P. falciparum malaria

AE
- NVD
- Nephrotoxicity
- Resistance to Atovaquone develops rapidly if it is given alone

C/I an Caution
- In people w/ severe renal impairment
- Non recommended for prophylaxis in children less than 5kg, pregnant women and women breastfeeding infants weighing <5kg

Special Consideration
- Should be taken w/ food or a milky drink

Primaquine
C/I

- People w/ G6PD deficiency
- During pregnancy and lactation unless the infant being breastfed has a documented normal G6PD levels

Other Drugs used for Malaria Prophylaxis

- Dapsone
- CQ/proguanil combination

WHO Recommendations: Malaria Prevention in Special Risk Groups

- Intermittnet Preventive Treatment in Pregnancy
    - In malaria endemic areas in Africa, all pregnant women should receive intermittent preventive treatment, w/ Sulfadoxine-Pyrimethamins (Fansidar) in their first and second pregnancy as part of ANC care (greatest risk)
    - Dosing should start in the second trimester of pregnancy and doses should be given at least 1 month apart to ensure 3 doses are given
- Seasonal Malaria Chemoprevention (SMC)
    - In areas w/ highly seasonal malaria transmission in sub-Sahara Africa, provide seasonal malaria chemoprevention w/ monthly Amodiaquine and Fansidar for all children < 6 years during each transmission season

Haematinics

21 May 2017 09:03

- Haematinics: Compounds necessary for the synthesis of RBCs
  - Iron
  - Folate
  - Vitamin B12
  - Vitamin B6
  - Copper
  - Manganese
  - Cobalt
  - Vitamin B2
- Anaemia is lack of blood
  - Normal Hb
    - Female 12-16g/dL
    - Male - 14-18 g/dL
  - Mild anaemia - >8g/dL
  - Moderate anaemia - 4.0-8.0g/dL
  - Severe anaemia - <4.0g/dL
- Anaemia may be due to deficiency of haematinics.
- Other causes of anaemia:
  - Haemolytic anaemia
  - Enzymopathies (e.g. G6PD deficiency)
  - Infections (e.g. malaria)
  - Haemorrhagic anaemias (Disseminated Intravascular Coagulopathy).

Iron Deficiency Anaemia.

- The most common cause of anaemia worldwide
  - 20% - adult women
  - 50% - pregnant women
  - 3% - adult males
  - 30% - pre-school children
- Normal iron distribution
  -

Protein	Total iron	Function
Haemoglobin	2500mgs	Oxygen transport in blood
Myoglobin	140mgs	Oxygen transport in muscle
Ferritin/Haemosiderin	1000mgs (♂) 400 mgs (♀)	Storage (liver, spleen, BM)
Transferrin	3mgs	Transport
Enzymes	~1gm	Oxygen utilisation

- Normal body content
  - Males - 50mg/kg
  - Females - 35mg/kg
- Average daily adult intake
  - 10-20mg/day
  - Only 5-10% absorbed

Pharmacokinetics

- Mineral iron converted to ferrous form and absorbed from duodenum and upper SI
- Iron from haemoglobin and other heme proteins absorbed as such
- Absorbed iron bound to transferrin and transported to bone marrow
- Normal plasma levels are 60-190µg/dL
- % transferrin saturation - 20-45%
- Metabolism is preservative
- Daily loss:
    - In men is 1mg/d
    - Menstruating women 2mg/day
        - Average loss on periods - 17mg
    - Net loss in pregnancy - 700mg = 2.5mg/day
- Requirements
    - In men, post-menopausal women - 0.5-1mg/day
    - Menstruating women 1.5mg/day
    - During pregnancy 2.5mg/day
    - In first year of life - 0.6mg/day
    - During childhood 1-1.5mg/day

Causes of IDA

- Include:
    - Insufficient intake
    - Impaired absorption
    - Increased requirement
    - Blood loss
- Many times, more than one factor is involved

Clinical Presentation

- Signs and symptoms depend on degree of anaemia
- Include:
    - Increased fatigability
    - Headache
    - Tachycardia
    - Exertional dyspnoea
    - Ankle oedema
    - Pallor
    - Pica
    - Premature greying of hair
    - Sore atrophic tongue
    - Sore mouth
    - Angular stomatitis
    - Thin fragile nails with spooning (koilonychia)
    - Dysphagia (Plummer-Vinson syndrome)
    - Menorrhagia
    - Amenorrhea
    - Retinal haemorrhages +/- exudates (Hb <5gm/dL)
    - Hepatomegaly
    - Dry skin w/ scanty hair

Laboratory Findings

- Hypochromic microcytic anaemia
- RBC counts may be normal, nearly normal or even higher than normal
- Reticulocytes usually normal
- WBC, platelets normal or slightly reduced

- Bone marrow - erythroid hyperplasia, no stainable iron
- Achlorhydria in up to 16% with gastric biopsy showing in may cases gastritis ot moderate atrophy
- TIBC - >400-450µg/dL
- Plasma ferritin levels at least 1/10th the normal (<10µg/L0

Treatment

- Seek for cause and treat
- Oral therapy - 200-300mg elemental iron daily, for 3-6 months
-

Preparation	Tab size (mg)	Elemental iron (mg)	Dose (per day)
$FeSO_4$ (hydrated)	325	65	3-4
$FeSO_4$ (desiccated)	200	65	3-4
FeGluc	320	37	3-4
Fe Fum	200	66	3-4
Fe Fum	325	106	2-3

Adverse Effects

- Include
  - ND
  - Epigastric discomfort
  - Abdominal cramps
- Are usually dose dependent
- Alleviate by lowering dose, taking with meals or changing form

Parenteral Iron

- Preserved for
  - Documented IDA
  - Those unable to tolerate orals
  - Those unable to absorb orals
  - Those with extensive blood loss
- Include
  - Iron dextran
    - Has 50mg/ml
    - Given IM by Z-track technique or IV
    - Grams of iron = Normal Hb - Patient Hb X 0.25
    - Usually 20-40mls of Iron dextran
    - Give as 10-20mls daily injections or infusion in 500mls saline in 1-2 hours
    - _

Adverse Effects

- Local pain
- Tissue staining
- Headache and light headedness
- Fever
- Arthralgia
- NV
- Back pains, flushing, urticaria
- Bronchospasm
- Rarely anaphylaxis and death

Vitamin B_{12} and Folate

Tuesday, 23 May 2017 12:18 PM

- Both essential for DNA synthesis
- Deficiencies lead to
  - Impaired DNA synthesis
  - Inhibition of normal mitosis
  - Abnormal maturation and of function if cells produce
- The changes most evident in rapidly proliferating tissues life GIT, BM
- Chief finding is severe megaloblastic anaemia with or without pancytopenia and neurologic abnormalities in Vitamin B_{12} deficiency

Vitamin B_{12} Chemistry

- Made up of a porphyrin-like ring with cobalt atom attached to a nucleotide. Various ligands attached to Co covalently
- Deoxyadenosylcobalamin and Methylcobalamin are the active forms in man
- Hydroxycobalamine and cyanocobalamine must be converted in the body to the active forms for utilisation

Sources

- Synthesised by bacteria.
- Found in liver, meat, eggs and dairy products
- Average diet has 5-39mcg/day. 1-5mcg absorbed
- Average storage pool in adults is 3000-5000µg.
- Only trace amounts lost in urine or stool.
- It takes 5 years for deficiency to develop

Pharmacokinetics

- In the stomach, dissolved, complexed with R-binder (intrinsic factor), produced by parietal cells.
- Absorbed mainly in the terminal ileum. Absorption is mainly in the terminal ileum
- Absorption is by highly specific receptor mediated transport system
- Once absorbed, initially bound to transcobalamine II
- Vitamin B_{12}-transcobalamine II complex is rapidly taken up by the liver, BM and other rapidly proliferating tissues
- Most Vitamin B_{12} in blood bound to TC I as TC II-Vitamin B_{12} complexes is rapidly cleared from blood. Half-life of 1 hour
- Normal blood levels 200-600pg/ml

Metabolic actions

- Two essential reactions require Vitamin B12:
  - Conversion of methanyl maloyl CoA to Succinyl CoA
    - Enzyme methyl malonyl CoA mutase, require adenosylcobalamine as co factor
    - In vitamin B12 deficiency, methylmaloyl CoA accumulates.
    - Aberrant fatty acids formed, incorporated into cell membranes.
    - Causes CNS manifestations
  - 5-Methyltetrahydrofolate + homocysteine converted to tetrahydrofolate + Methionine
    - Enzyme 5-methyltetrahydrofolate homocysteine methyltransferase requires Vitamin B12 as a cofactor
    - Cobalamin and methylcobalamine are interconverted in this reaction

    - In Vitamin B12 deficiency, the major dietary and storage 5-methyltetrahydrofolate called conjugated folate accumulates, as it cannot be converted to other forms of tetrahydrofolate my methyl transfer
    - N5-methyltrihydrofolate is a poor substitute for conjugated enzyme, remains unconjugated and slowly leaks out of the cell.
    - Folate deficiency develops. Called folate trap
    - DNA synthesis deficiency and megaloblastic maturation pattern occurs

Folic Acid (pteroyl glutamic acid)

- A compound made of:
    - Ptyridine heterocycle
    - PABA
    - Glutamic acid
- Various numbers of glutamate can be attached to the pteroyl moiety, giving mono-glutamates, tri-glutamates and poly-glutamates
- The fully oxidised ring can undergo reduction to 7,8-dihydrofolate, enzyme dihydrofolate reductase. And then fully reduced form 5,6,7,8 tetrahydrofolate (tetrahydrofolate)
- Tetrahydrofolate can be transformed to folate co-factors possessing one carbon moiety attached to
    - The N5 nitrogen - N5-tetrahydrofolate
    - The N10 nitrogen - N10-tetrahydrofolate
- Both positions - 5,10-methyltetrahydrofolate and 5,10-tetrahydrofolatefolate
- The folate cofactors are interconvertible by various enzymatic reactions and serve as donors of one carbon moiety at various levels of oxidation
- In most cases tetrahydrofolate is regenerated and is available for use

Sources

- Richest sources are yeast, liver, kidney and green vegetables
- Various forms available in a variety of animals and plants
- Average diet has 500-700µg/day. 50-200µg absorbed depending on metabolic requirements
- 5-20mg stored in the liver and other tissues
- They are excreted in urine and also catabolised
- Serum levels fall within a few days when not absorbed.
- Megaloblastic anaemia can develop in 1-6 months depending on nutritional status and rate of folate utilisation
- Unaltered folate is readily and completely absorbed in the proximal jejunum.
- Dietary folates are poly-glutamate forms of 5-methyltetrahydrofolate.
- Before absorption, all glutamate residues must be removed except one
- Enzyme α-L-glutamyl transferase in intestinal mucosa brush border
- The monoglutamates are transported into the blood stream by both active and passive processes and widely distributed in the body

Pharmacodynamics

- Folate necessary for one carbon moiety transfer reactions in DNA synthesis
- Methyl-tetrahydrofolate and 5,10-methyltetrahydrofolate donate their carbon units to carbons 2 and 8 of the purine heterocycle
- Synthesis of thymidilic acid (dTMP), an essential precursor of DNA. 5,10-CH2-H4-folate donates its one carbon to dUMP to form dTMP, enzyme thymidylate synthetase
- Tetrahydrofolate is oxidised to dihydrofolate produced
- The dihydrofolatefolate must be reduced to tetrahydrofolate; enzyme dihydrofolate reductase
- Tetrahydrofolate converted to methyldihydrofolate by enzyme serine

transhydroxymethylase, which can be used for further dTMP synthesis

Vitamin B_{12} Deficiency

- Megaloblastic anaemia
    - Manifests mainly in the GIT, RBC and CNS
    - May be accompanied by
        - Purpura due to thrombocytopenia
        - Weakness
        - Light headedness
        - Vertigo
        - Tinnitus
        - Slightly icteric skin or eyes
        - Palpitations
        - Angina
        - Symptoms of CCF
    - On exam
        - Pale
        - Jaundiced
        - Rapid pulse
        - Cardiomegaly
        - Liver and spleen mildly enlarged
        - Mild fever
        - Haemodynamic murmurs
    - In the GIT
        - Red beefy and smooth tongue
        - Sore mouth
        - Anorexia
        - Weight loss
        - D
    - In the CNS
        - Demyelination starts followed by axonal degeneration and neuronal death - irreversible
        - Affects mostly the spinal cord - posterior and lateral column - although the peripheral nerves and brain are also affected
        - Patient presents with
            - Numbness
            - Paraesthesia
            - Weakness
            - Ataxia
            - Faulty finger-nose test
            - Sphincter disturbances
            - Diminished or increased reflexes
            - Positive for Romberg's Sign
            - Babinski's Sign positive
            - Mental function impairments
                - Vary from mild irritability to forgetfulness and severe dementia and frank psychosis
- Neurological Manifestation

Folate Deficiency

- GIT effects more widespread and severe
- Related to:
    - Inadequate intake
    - Malabsorption

    - Increased demand
- Lab tests
    - Reduced plasma levels
    - MCV - minimum of 96_
    - Low reticulocyte count
    - Pancytopenia
    - PBF
        - Large, oval, fully haemoglobinised RBC w/ basophilic stippling and occasional nucleated RBC
        - Hyper-segmented nuclei in WBC
        - Bizarre shaped platelets
    - In BM
        - Typical hyper-cellular BM with reduced myeloid to erythroid ratio and abundant stainable iron
        - RBC precursors are large with immature nuclei and the nuclear chromatin condenses in a peculiar pattern
        - Abnormal mitosis is seen
        - _
    - LDH is increased
    - Shilling test positive

Treatment

- Vitamin B12 100µg/day for 2 weeks, then 100µg/week for 4 weeks then monthly 100µg for life
- Folate 1-5mg/day

Water Soluble Vitamins

Thursday, 25 May 2017 8:29 AM

- B-Complex
  - Thiamine
  - Riboflavin
  - Niacin
  - Pyridoxine
  - Folic Acid
  - Cyanocobalamine
  - Pantothenic Acid
  - Biotin

Niacin

- Also known as
  - Nicotinic acid
  - Pyridine-3-carboxylic acid
- Formed from tryptophan
  - 1mg from 60mg of Tryptophan???
- Metabolic product mainly ethylated products, main one n-methylnicotinamides and its derivatives

Pharmacodynamics

- Components of NAD, NADP
- Nicotinic acid → nicotinamide → nicotinamide mononucleotide → nicotinamide adenine dinucleotide → NADP
- Normal plasma levels - 3-6µg/ml
- Daily requirements
  - 20mg

Sources

- Dietary proteins
- Cereals
- Fruits and vegetables

Deficiency

- Dermatitis
- Glossitis
- Stomatitis
- Diarrhoea
- Dementia/mental depression
- Heartburns
- Abdominal pains
- Proctitis
- Vaginitis
- Dysphagia
- Amenorrhoea
- Pellagra - DDD - carcinoid syndrome, Hartnup's Disease
  - Diarrhoea
  - Dementia
  - Dermatitis
- Hartnup's disease

    - Autosomal disease that results in problem in absorbing vitamins
- The mental changes include:
    - Fatigue
    - Insomnia
    - Apathy that usually precedes an encephalopathy characterised by
        - Confusion
        - Disorientation
        - Hallucination
        - Memory loss
    - Frank organic psychosis
- Patient might have paraesthesia and pins and needles_

Diagnosis
- Suspicion
- Urine levels of tryptophan and nicotinic acid
- Plasma tryptophan levels
- Erythrocyte NAD/NADP
- Histopathology of skin
    - Hyperkeratosis
    - Hyperpigmentation
    - Desquamation

Treatment - supplementation
- Endemic pellagra
    - 10mg/day
- Hartnup's Disease
    - 40-200mg/day

Thiamine
- Synthesised by microorganisms and plants
- Oral absorption
    - 5mg/day
- Stores 20-30mg
    - 80% is as T.pyrophosphate
    - 10% as T.triphosphate
    - 10% as Free thiamine, thiamine monophosphate
- In muscles, liver, kidney and brain
- 3 intermediates involved in formation
    - Pyrophosphate kinase
    - Phosphoribosyl transferase
    - Pyrophosphatase
- Metabolites of thiamine are excreted in urine as
    - Thiamine
    - acetylated derivatives
    - pyrimidine carboxylic acid
    - thiazole acetate

Pharmacodynamics
- Thiamine diphosphate, co-enzyme in several reactions
- Cleavage of carbon-carbon bonds
- Oxidative decarboxylation of ketoacids
- Transketolase reaction in pentose phosphate pathway

- Thiamine and its related compounds are found on the axonal membranes of nerves.
- Electrical stimulation results in release of thiamine as di- and triphosphates

Requirements
- Plasma levels 10-64 ng/mL
- Daily intake - 1.5 mg/d

Sources
- Vegetables
- Cereals
- Meat
- Cooking above 70°C destroys it
- Absorption reduced by raw fish
- Can be lost in:
    - Diuretic therapy
    - Haemodialysis
    - Diarrhoea

Deficiency
- Beriberi
- Tachycardia
    - Resting
- Muscle weakness
    - Loss of deep tendon reflex
- Sensory neuropathy
- Malaise
- Headaches
- Nausea
- Wernicke-Korsakoff Syndrome

- [ ] Dry and Wet Beriberi
- [ ] CVS and CNS changes

Diagnosis
- Erythrocyte transketolase activity
- Trial therapy

Treatment
- 50mg IM for several days then 2-5mg/day
- Combine with other vitamins
- Alcoholics are deficient because thiamine is involved in the conversion of ethanol to acetyl-CoA so it is depleted
- Always supplement in convulsions

Pyridoxine
- Includes
    - Pyridoxal
    - Pyridoxine
    - Pyridoxamine
    - And their phosphate esters
- Active form pyridoxal-5-phosphate
    - A co-factor in many enzyme reaction involved in
        - AA metabolism

        - Transaminases
        - Synthetases
        - Hydroxylases
    - Needed for metabolism of
        - Tryptophan
        - Serine
        - Glycine
        - Glutamate
        - Sulfur Aas
    - For synthesis of heme precursor, δ-aminolevulinic acid
    - Coupled to muscle phosphorylase
    - Vital role in neuronal excitability

Requirements
- Serum levels
    - 30-80mg/ml
- Daily requirements
    - 2.5mg/ml

Deficiency
- EEG changes seen within 3 weeks, may have seizures
- Skin - seborrheic dermatitis
- GIT
    - Cheilosis
    - Glossitis
    - Nausea
    - Vomiting
- Weakness and dizziness
- Deficiency states are mainly seen
    - due to destruction of inprocesing e.g. infant formula
    - Pyridoxine antagonists
        - Hydrazines e.g. INH
        - Cycloserine
        - Penicillinamine

Diagnosis
- Pyridoxine or metabolites or oxalate excretion levels
- Tryptophan metabolites in urine after a loading dose (xanthuranic acid)
- Cystathione assay after tryptophan load
- Measurement of RBC glutamate/pyruvate transaminase levels

Treatment
- 30mg/day is enough in pregnancy, contraceptive users and INH patients
- 100mg/day for those on penicillamine
- Pyrazinamide and INH are antagonists of pyridoxine. Doses of 50mg OD are enough for prophylaxis

Riboflavin
- Essential for Redox reactions involving co-enzymes FMN and FAD
- Important in the structure of many enzymes
    - Succinyl DH
    - MAO
- Daily requirements
    - 2mg/day
- Excreted in free from in urine

- Deficiency
    - Due to inadequate intake and antagonists
    - Anaemia due to riboflavin deficiency. It has been described in combination with infection and protein deficiency
    - It is a pure red cell aplasia

Just go to the Comm Health notes

Haematopoietic Growth Factors

Friday, 26 May 2017 8:20 AM

- These are glycoprotein hormones that regulate proliferation and differentiation of haematopoietic progenitor cells in the BM.

Haematopoiesis

Erythropoietin (EPO)

- 34-39kDa glycoprotein produced by the kidneys
  - Tissue hypoxia→↑EPO gene transcription
- Normal serum levels EPO: <20 IU/L and this rises with a ↓ in Hb (except in chronic kidney disease, CKD)
- Patients with moderate anaemia serum EPO: ~100-500 IU/L
- Patients that are most likely to respond to exogenous EPO are those with low levels of serum EPO e.g. CKD patients.
  - Patients with high endogenous EPO levels are less likely to respond e.g. in primary BM failure and anaemia due to nutritional deficiencies especially folate, vitamin B_{12} and iron deficiencies.

Haematopoiesis

Erythropoiesis Stimulating Agents (ESAs)

- The drugs are
  - Epoetin alfa - recombinant human EPO (rHuEPO)
    - Given 3*weekly
  - Darbepoetin
    - More heavily glycosylated
    - 2-3 times longer $T^{0.5}$
    - Given once a week
    - Compliance is better
  - Methoxy polyethylene glycol epoetin beta
    - Isoform of EPO covalently attached to a lay polyethylene glycol polymer to ↑$T^{0.5}$
    - Given IV/SC
    - Given once every 2-4 weeks
- Pharmacokinetics
  - Serum $T_{0.5}$: 4-13 hours after IV administration in patients with chronic renal failure
  - Will not be removed by dialysis
  - Dose given in International Units (IU)
- MoA
  - EPO binds to EPO receptors on RBC progenitors
  - This is a JAK/STAT cytokine receptor
  - Leads to protein phosphorylation and activation of transcription factors that regulate cellular function
  - Also induces release of reticulocytes from the BM

Clinical Uses of ESAs

- Anaemia secondary to

    - Chronic kidney disease
        - ↑Hb in 2-6 weeks
        - Supplement iron (oral/parenteral)
        - Target Hb: 11g/dL
    - Cancer chemotherapy
    - Zidovudine
    - Patients with low Hb scheduled to undergo elective, non-cardiac, non-vascular surgery

Adverse Effects

- Hypertension
- Thrombotic events
    - Stroke
    - MI
    - Venous thrombosis
- Allergic reactions
- Pure red cell aplasia

Myeloid Growth Factors

- Include
    - G-CSF
    - GM-CSF

Preparations Available

- Recombinant human G-CSF (rHuG-CSF)
    - Also known as Filgrastim
    - Non-glycosylated peptide of 175 amino acids
    - MW: 18kDa
- Recombinant human GM-CSF (rHuGM-CSF)
    - AKA Sargramostin
    - Partially glycosylated peptide of 127 AA
    - MW: 15,500-19500 Da
    - Half-life for both: 2-7 hours after IV/SC administration
- Pegfilgrastim
    - Covalent conjunction product of Filgrastim and Polyethylene glycol
    - Longer half-life than recombinant G-CSF thus can be injected once per chemo cycle instead of daily
- Lenograstim
    - Glycosylated form of recombinant G-CSF

Pharmacodynamics

MoA

- Bind to receptors on myeloid progenitor cells
- Part of JAK/STAT receptor superfamily

MoA of :

- G-CSF
    - Stimulates proliferation of progenitors committed to the neutrophil lineage
    - Activates phagocytic activity of mature neutrophils
    - Prolongs neutrophil survival in the circulation
    - Mobilises haematopoietic stem cells, increasing their peripheral blood concentration (useful in haematopoietic stem cell transplantation)

- GM-CSF
  - Broader biologic action
    - Stimulates proliferation and differentiation of granulocytic, erythroid and megakaryocyte progenitors
    - Stimulates function of mature neutrophils
    - Acts with IL-2 to stimulate T-cell proliferation
    - Is a locally active factor at sites of inflammation
    - Increases mobilisation of the stem cells in BM to peripheral blood stream but is less efficacious thus G-CSF is preferred

Clinical Uses

- Cancer chemotherapy-induced neutropenia
  - G-CSF
    - Accelerates the rate of neutrophil recovery
    - Reduces the duration of neutropenia (also GM-CSF)
    - Raises nadir neutrophil count
  - Started 24-72 hours after completing chemo
  - Continued until neutrophil count > 10,000cells/µl of blood
- Neutropenia secondary to:
  - Myelodysplasia
  - Aplastic anaemia
  - Congenital and cyclic neutropenia
- Mobilisation of PBSCs (Peripheral blood stem cells)
  - Harvested for haematopoietic stem cell transplantation
- Note:
  - G-CSF can be combined with Plerixafor, a novel haematopoietic stem cell mobiliser

Toxicity

- G-CSF and Pegfilgastim can cause bone pain
- GM-CSF
  - Fever, malaise, arthralgia, myalgia
  - Capillary leak syndrome
    - Peripheral oedema and pleural or pericardial effusions
- Allergic reactions
- Splenic rupture (G-CSF used for PBSC mobilisation)

Megakaryocyte Growth Factors

Introduction

- Thrombopoietin (TPO) and IL-11 are key endogenous regulators of platelet production
- Agents approved for treatment of thrombocytopenia
  - Recombinant IL-11
  - Agonists of the thrombopoietin receptor Mpl:
    - Romiplostim
    - Eltrombopag

IL-11

- MW: 65-85kDa
- Produced by fibroblasts and stromal cells in the BM
- Recombinant form
  - Oprelvekin
- Produced by expression in E. coli

- Half-life: 7-8 hours when given SC

Romiplostim

- Peptide
- Does not induce antibodies to thrombopoietin
- Given SC once/week
- Eliminated by the RES
- Half-life: 3-4 hours (longer in patients with thrombocytopenia)

Eltrombopag

- Non-peptide TPO agonist
- Given PO
- Half-life: 26-35 hours
- Excreted in faeces

Pharmacodynamics

- IL-11
  - Acts through a cell surface cytokine receptor
  - Stimulates growth of lymphoid and myeloid cells
  - Stimulates growth of primitive megakaryocytic progenitors
  - Increases number of peripheral platelets and neutrophils
- Romiplostim and Eltrombopag
  - Induce signalling through the Mpl receptor pathway, causing a dose-dependent increase in platelet count
  - Peak platelet count response in ~2 weeks

Clinical Uses

- IL-11
  - Secondary prevention of cancer chemotherapy-induced thrombocytopenia
- TPO agonists
  - Chronic immune thrombocytopenia refractory to first-line therapy e.g. steroids, Igs
- Note:
  - Target platelet counts for both: >50,000 cells/μL

Toxicity

- IL-11
  - Fatigue, headache, dizziness
  - Dyspnoea, transient arrhythmias, hypokalaemia
- Eltrombopag
  - Hepatotoxic
- Romiplastim
  - Increases risk of progression to AML in patients with myelodysplasia
- Both
  - Portal vein thrombosis, marrow fibrosis, rebound thrombocytopenia when discontinued

Haemostasis

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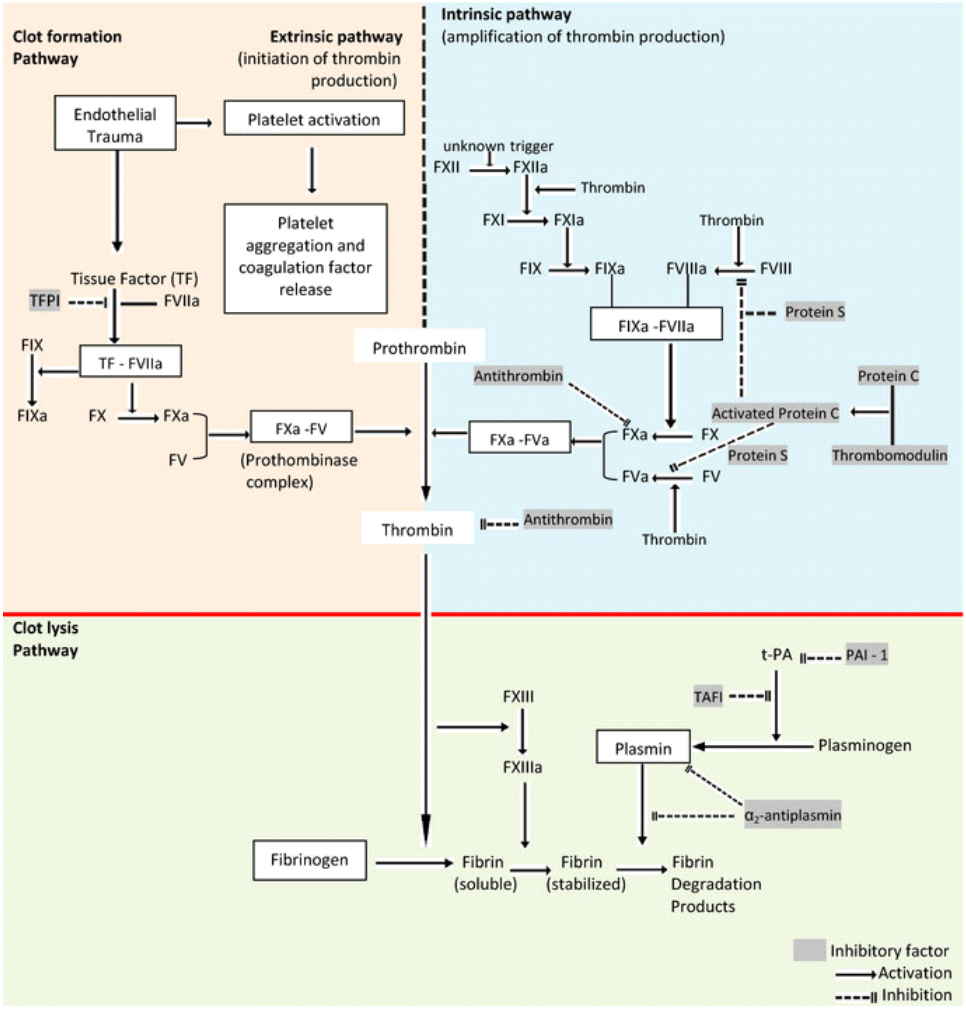
- Cessation of blood loss from a damaged blood vessel
- Broadly refers to the process of
  - Maintaining fluidity of blood
  - Repairing vascular injury
  - Limiting blood loss while avoiding
    - Vaso-occlusion
    - Inadequate perfusion
- Either extreme represents a breakdown of haemostasis

Mechanism of Blood Coagulation

- Vascular endothelium has anticoagulant characteristics hence circulating platelets and clotting factors don't adhere to it to a significant extent
- Vascular injury leads to rapid serious change of the endothelium resulting in a more procoagulant characteristic.
- Immediate haemostatic response to vascular damage is vasoconstriction
- Platelets adhere within seconds
  - To exposed collagen-platelet adhesion
  - To each other - platelet aggregation
- Platelets lose individual membranes and form a gelatinous mass to form a primary/platelet haemostatic plug, which stops bleeding
  - Reinforced with fibrin for long term effectiveness. The reinforcement occurs during the process of blood coagulation that activate simultaneously
- Vascular injury exposes reactive sub-endothelial matrix e.g. collagen and vWF
- This results in
  - Platelet adherence and activation
  - Secretion and synthesis of vasoconstrictors
  - Synthesis of platelet-recruiting and activation molecules as follows:
    - Thromboxane A_2 (TXA_2)
      - Is synthesised from arachidonic acid within platelets
      - It is a platelet activator and potent vasoconstrictor
    - Products secreted from platelet granules which include
      - Adenosine diphosphate (ADP)
        - Powerful inducer of platelet aggregation
      - Serotonin (5-HT)
        a) Stimulates platelet aggregation and vasoconstriction
- Activation of platelets results in a conformational change in the $\alpha_{IIb}/ß_{III}$ integrin (IIb/IIIa) receptor, enabling it to bind fibrinogen which cross links adjacent platelets
  - This results in platelet aggregation and formation of a platelet plug
- Thrombosis is a pathological process in which a platelet aggregate and/or a fibrin clot occludes a blood vessel
  - There are two kinds of thrombi formed from this process
    - White thrombus
      - found in arteries due to the high flow rate and shear stress environment
      - made up primarily of aggregated platelets in a fibrin mesh.
      - Has a capacity to cause occlusion leading to ischaemia or infarction (death) of tissue downstream.
      - Typically occludes cerebral vessels causing a CVA.

- Red thrombus
  - Venous thrombi which have more fibrin that trap large numbers of RBCs
  - Consists of a large white head and a jelly-like red tail similar to a blood clot.
  - Typical case is DVT
  - When it breaks away from its attachment and forms an embolus the (often deadly) consequence is a pulmonary embolism.

The Blood Coagulation Pathways (Cascade)



- Blood coagulation is the conversion of fluid to a solid gel or clot
- The main event is the transformation of soluble fibrinogen to insoluble fibrin, which is the last step in a complex enzyme cascade
- Several circulating proteins interact in a cascading series to bring about blood coagulation
- The clotting factors are present in blood as inactive precursors (zymogens) of proteolytic enzymes and co-factors
- At each step, a clotting factor zymogen is activated by proteolysis to become an active protease
- The active protease formed is designated by the suffix "a" (e.g. factor VII is converted into factor VIIa)
- Each protease factor, activates the next clotting factor in the sequence until finally, a solid fibrin clot (Ia) is formed
- Activation of a small amount of one factor catalyses the formation of larger amounts of the next factor, which catalyses the formation of still larger amounts of the next and so on
  - The cascade therefore provides a mechanism of amplification
- There are 2 main pathways of fibrin formation
  - The intrinsic pathways - the contact pathway

        - It is referred to as 'intrinsic' because all the components come from within the blood
    - The extrinsic pathway which is so called because some components come from outside
        - Especially important in controlling blood coagulation in the body
        - Also referred to as the in vivo pathway

The Extrinsic Pathway

- It is initiated by a complex of tissue factor (TF) and factor VII
- TF is a transmembrane protein which is ubiquitously expressed outside the vasculature
    - Is the cellular receptor and co-factor for factor VII
- The complex formed by TF and factor VII is inhibited and regulated by tissue factor pathway inhibitor (TFPI)
- TF is exposed on damaged endothelium or when blood extravasates into tissue
- Factor VII undergoes an active site transition on binding TF in presence of calcium
    - Calcium enhances factor VII's activity and results in its rapid activation to VIIa
- The TF-VIIa complex in turn activates factor IX and X
- Acidic phospholipids (PL) function as surface catalysts
    - These are provided during platelet activation which exposes acidic PLs which localise and activate various clotting factors
    - Platelets also contribute by secreting coagulation factors including factor Va and fibrinogen (factor I)
- Factor Xa in the presence of Calcium, PL and factor Va forms the prothrombinase complex on activated cells surfaces, which catalyses the conversion of prothrombin (Factor II) to thrombin (factor IIa)
- Thrombin in turn activates upstream factors, primarily factors V, VIII and XI, resulting in thrombin generation
- Therefore, after the initial activation of factor X by TF-VIIa, coagulation is sustained by feedback amplification of thrombin, throughout the intrinsic pathway, by further generation of factor Xa, by IXa-VIIa-Ca^{2+}-PL complex
- This is necessary because the TF-VIIa complex is rapidly inactivated in plasma by TFPI and by anti-thrombin III
- Thrombin (IIa) cleaves fibrinogen (I) producing fragments that polymerise to form fibrin, an essential component of a functional blood clot

The Intrinsic Pathway

- It commences when the Hageman Factor (factor XII) adheres to a negatively charged surface, e.g. glass
- Converges with the in vivo pathway at the point of factor X activation
- Note:
    - Patients with deficiency of factor VIII and IX (haemophilia A and B respectively) have a severe bleeding disorder, because amplification of thrombin does not occur
    - Coagulation mechanism in vivo does not occur in solution, but is localised to activated cell surfaces, expressing anionic PL, such as, phosphatidylserine
        - It is mediated by calcium bridging between the anionic phospholipids and γ-carboxyglutamic acid residues of the clotting factors
        - Ca^{2+} acts as the bridge between anionic phosphatidylserines (PS's) and γ-carboxyglutamic acid residues of the clotting factors
            - Carboxyglutamic acid is produced by post-translational carboxylation of glutamic acid residues. This creates an affinity for Ca^{2+} ions.
            - In the blood coagulation cascade, vitamin K is required to introduce the γ-carboxylation of clotting factors II, VII, IX, X and protein Z.
            - Phosphatidylserine is externalised from the inner membrane layer when platelets encounter sites of tissue injury; it is mediated by collagen and thrombin activation.

        - When it is externalised, it acts as a pro-coagulant surface which acts to orient coagulation proteases, specifically TF and Factor VII.
    - This is the basis for using calcium chelators such as EDTA or citrate to prevent blood from clotting in a test-tube

The Endogenous Anticoagulants

- Antithrombin (AT
    - A member of the serine protease inhibitor (Serpin) family
        - It inactivates the serine proteases IIa, IXa, Xa, XIa and XIIa
- Proteins C and S
    - They weaken the blood clotting cascade by proteolysis of the two co-factors Va and VIIIa
        - Defects in the natural anti-coagulants results in an increase risk of venous thrombosis

Classification of Drugs Which Affect Haemostasis

- Drugs used in bleeding disorder
    - Drugs that facilitate clotting
    - Include:
        - Vitamin K
        - Fibrinolytic inhibitors
        - Serine protease inhibitors
        - Plasma fractions
- Anti-clotting drugs
    - Anti-coagulant drugs
    - Thrombolytic drugs
    - Anti-platelet drugs

Anti-Coagulant Drugs

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General MoA of Anti-Coagulants

- They inhibit the formation of fibrin clots (factor Ia) - last step in the coagulation cascade
- Classification
    - By MoA
        - Indirect thrombin inhibitors (ITIs)
            - Heparins
        - Oral direct factor Xa inhibitors
        - Direct thrombin inhibitors (DTIs)
            - Parenteral
            - Oral
        - Warfarin and the coumarin anti-coagulants
    - By mode of administration
        - Parenteral anticoagulants
            - Heparin and related products
            - Parenteral DTIs
        - Oral anti-coagulants
            - Coumarin derivatives
            - Oral DTIs
            - Oral direct factor Xa inhibitors

Warfarin

Tuesday, 27 June 2017 7:26 AM

Chemistry

- Coumarin derivatives

Pharmacokinetics

- They are small, lipid-soluble molecules
- Are readily absorbed after oral administration
- Warfarin is highly bound to plasma proteins (>99%)
- Its elimination depends on metabolism by CYP450 system

MoA and Effects

- Coumarins inhibit Vitamin K epoxide reductase (VKOR) which normally converts Vitamin K epoxide (inactive) to reduced Vitamin K (active)
- They therefore interfere with the normal post-translational modification of clotting factors in the liver, a process that depends on reduced Vitamin K
    - Vitamin K is a co-factor for the enzymatic activation of clotting factors
        - Aids in the gamma-carboxylation of the factors IIa, VII, IX and X as well as protein C and S
        - The carboxylation is necessary for the proteins to function in the coagulation cascade
        - The gamma-carboxylation occurs in the glutamic acid residue of these factors
- The Vitamin K dependent factors include thrombin (factor IIa) and factors VII, IX and X
- The clotting factors have a half-life of 8-60 hours in the plasma
    - Therefore, an anticoagulant effect is observed only after sufficient time has passed for elimination of the normal preformed factors
    - Warfarin exhibits a delayed anti-coagulant effect
        - Onset of action of 8-12 hours
- Protein C and S are used in the anti-coagulant cascade
    - Therefore, without Vitamin K, are unable to exert anti-coagulation effect
- Factor VII is the first clotting factor to be reduced when Warfarin is administered
    - Has a half-life of about 6 hours - shortest half-life of all the coagulation factors

Reversal of Effects

- The action can be reversed by vitamin K,
    - Recovery required the synthesis of new, normal clotting factors and is therefore slow (6-24 hours)
- More rapid reversal can be achieved by transfusion with fresh plasma or fresh frozen plasma (FFP) which contains normal clotting factors
- Prothrombin concentrates
- Recombinant factor VII
- 4 factor concentrate containing factors IIa, VII, IX and X

Monitoring

- The effect is monitored by the prothrombin time test
    - It measures the function of the extrinsic coagulation pathway
    - Warfarin prolongs PT time because of inhibition of factor VII specifically
- International Normalising Ratio
    - Measure Warfarin activity
    - INR is normally 1 in normal circumstances, but Warfarin therapy sends it to higher

values
    - The recommended INR for prevention of thrombotic disease, is 2-3
    - There are instances where a higher INR 9of about 3.5) is preferred:
        - Patients with artificial heart valves
        - Medical conditions conferring increased thrombotic risk

Clinical Test

- Heparin is usually started concurrently with Warfarin and is continued for at least 4-5 days to allow Warfarin to achieve its full therapeutic effects
- Warfarin is used for chronic anticoagulation in all the clinical situations where heparin is indicated, except in pregnant women
- Indications include:
    - Unstable angina or acute MI
    - Atrial fibrillation
    - Following surgery requiring cardio-pulmonary bypass
    - After coronary angioplasty or coronary stent placement with GP IIb/IIIa inhibitors (anti-platelet drugs)
    - DVT
        - Patients usually take Warfarin for about 4-6 months following diagnosis of DVT, to ensure that the thrombus does not grow and to allow the body o naturally absorb the clot
    - Pulmonary embolism
    - Treatment of selected patients with DIC

Adverse Effects

- Bleeding is the most important AE
- Early in treatment, a period of hypercoagulability with subsequent dermal vascular necrosis can occur:
    - This is due to deficiency of protein C, an endogenous vitamin-K dependent anti-coagulant with a short half-life - similar to the half-life of Factor VII
    - Protein C levels drop up to 50% within the first day of Warfarin treatment
    - These leaves factor IIa, IX and X unchecked and exert a coagulable state
    - Give Heparin concurrently to avoid this.
- Warfarin can cause bone defects and haemorrhage in the developing foetus and is therefore contraindicated in pregnancy
    - Can cross the placenta and can not only cause a haemorrhagic disorder in the foetus, it can also inhibit important carboxylation reactions in the foetal bone, leading to abnormal bone formation

Drug Interactions

- Warfarin has a narrow therapeutic window, and therefore, its involvement in DI is of major concern
- Done by either altering:
    - CYP450 enzymes
        - CYP-inducing drugs e.g. Carbamazepine, Phenytoin
            - Increase Warfarin's clearance and reduce the anticoagulant effect of a given dose
        - CYP inhibitors e.g. Amiodarone, SSRIs, Cimetidine
            - Reduce Warfarin's clearance and increase the anti-coagulant effect of a given dose
    - Protein binding ability
    - GI absorption
- Note:
    - Genetic variability in either CYP2C9 isozyme or VKOR affect responses to Warfarin

Other Oral Anti-Coagulant Drugs

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Direct Thrombin Inhibitors

- Dabigatran Erexilate Mesylate is the first oral DTI in clinical use

Pharmacokinetics

- Following PO, it is converted to Dabigatran
- PO bioavailability
  - 3-7%
- Half-life - 12-17h
- Renal impairment results in prolonged drug clearance and may require dose adjustments
  - It should therefore be avoided in patients with severe renal impairments

Clinical Use

- Dabigatran is approved
  - For prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
  - For prevention of venous thromboembolism in patients who have undergone hip or knee replacement surgery

Drug Monitoring

- No monitoring is required
- Dabigatran prolongs the prothrombin time (PT) and thrombin time
  - These can be used to estimate drug effect if necessary

AE of Dabigatran

- Primary toxicity is bleeding
- It has been associated with
  - Increased GIT AE and bleeding compared to Warfarin
  - Increased bleeding in patients >75 years

Treatment of Dabigatran Toxicity

- There is no antidote for Dabigatran
- In a drug overdose, it is important to maintain renal function with dialysis if necessary
- Use of recombinant factor VIIa or prothrombin complex concentrates may be considered in cases if life-threatening bleeding associated with Dabigatran use
  - Their efficacy is unproven

Advantages of oral DTIs over Warfarin

- Predictable PK and F (bioavailability) allows for fixed dosing
- Predictable anti-coagulant response makes the routine coagulation monitoring unnecessary
- They do not significantly interact with CYP-interacting drugs
- Their rapid onset and offset of action, allow for immediate anti-coagulation
  - This voids the need for overlap with additional anticoagulant drugs

DI of Oral DTI

- Concomitant use of Ketoconazole, Amiodarone, Quinidine and Clopidogrel increases the

effect of Dabigatran
- It is a substrate for the P-glycoprotein efflux pump
    - However, P-glycoprotein inhibitors or inducers do not have a significant effect on its clearance

Direct Factor Xa Inhibitors

- Include
    - Rivaroxaban
    - Apixaban
    - Edoxaban

MoA

- They directly inhibit factor Xa, in the final common pathway of clotting

Pharmacokinetics

- Have a rapid onset of action and shorter half-lives than Warfarin
- The drugs are excreted in part by the kidneys and their half-lives may therefore be prolonged in elderly patients or those with renal impairment
    - Dosage may need to be reduced in these groups of patients

Clinical Use of Oral Factor Xa Inhibitors

- Given as fixed doses and do not require monitoring
    - Used for long term anticoagulation prophylaxis in atrial fibrillation
        - Irregular rhythm leads abnormal flow of blood in the heart increasing the risk of causing a clot that can embolism and cause a stroke
- No antidotes exist for direct factor Xa inhibitors
- Rivaroxaban is approved for prevention of thromboembolism following hip or knee surgery
    - The prophylactic dose is 10mg orally per day
    - Its safety and efficacy appear to be at least equivalent and possibly superior to LMW heparins
- Apixaban is approved for prevention of stroke in non-valvular atrial fibrillation
    - Its efficacy is comparable to that of LMW heparin in the treatment of venous thromboembolism
    - Dosage for atrial fibrillation is 5mg twice daily
- Edoxaban is in clinical development
    - Clinical trials have shown that it is comparable to Warfarin for treatment of DVT and pulmonary embolism and for prophylaxis of atrial fibrillation

Injectable Anti-Coagulants

Monday, 29 May 2017 2:16 PM

Haemostasis
Virchow's Triad
Coagulation
Formation of an arterial thrombus

Thrombus
- Arterial
  - Platelet and fibrin mesh
  - "White thrombus" - infarction
- Venous thrombus
  - Red thrombus - embolism
  - PTE
  - *CVA(?)

Thrombin
- Activated factor II
- Cleaves fibrinogen producing fragments that polymerise to form fibrin
- Activates factor XIII, a fibrinoligase that strengthen fibrin-fibrin link i.e. stable coagulum
- Platelet aggregant
- Stimulates cell proliferation and smooth muscle contraction

Injectable Anti-Coagulants
- Heparin LMWH and HMWH
- Newer anti-coagulants are given orally

Heparin

- First extracted from the liver
  - Anti-coagulant
- Family of sulfated glycosaminoglycans, a mucopolysaccharide
- Present with histamine in the granules of mast cells
- Commercial preparation from beef lung or hog intestine
- Potency varied
- Assay by international standards to units of activity

Low Molecular Weight Heparin

- Include:
  - Heparin fragmented
    - Enoxaparin
    - Dalteparin
  - Synthetic polysaccharide
    - Fondaparinux
- Fractionated
  - Effects are predictable
- Longer acting

- Not preferred in renal disease
    - They are exclusively disposed by the kidneys
- Shorter molecular chain than HMWH and can therefore only inhibit factor Xa
- Fondaparinux
    - Binds antithrombin III with even higher specificity than LMWH
        - Efficient inhibition of factor Xa with no action on thrombin

High Molecular Weight Heparin

- The largest molecule in all anti-coagulants
- Negatively charged sulfated glycosaminoglycans
- Because of its large size, it is able to inhibit multiple clotting factors
- Is referred to as an indirect anti-coagulant because it indirectly affects coagulation through anti-thrombin
    - Anti-thrombin III inhibits factors: - basically the entire intrinsic and common pathways
        - IIa - Thrombin
        - Xia
        - Xa
        - XIa
        - XIIa
- The heparin-antithrombin III complex binds with and irreversible inactivates thrombin and factor Xa
- Patients on HMWH require constant aPTT (measures the intrinsic pathway) monitoring to measure unfractionated Heparin levels

MoA

- Inhibition of coagulation by activating anti-thrombin III
- Anti-thrombin III inhibits thrombin (thus inhibiting activation of XII, VIII) and other serine proteases (e.g. Xa) by binding on their activated sites
- Heparin modifies the interaction of binding by binding on a unique pentasaccharide sequence, to antithrombin III changing its conformation and increasing its activity for serine proteases
- Heparin bind on enzyme and anti-thrombin III to inhibit thrombus formation
    - If given in an acute case of DVT, it can only prevent further development of the clot
- Bind n anti-thrombin III to inhibit Xa
- Anti-thrombin III deficiency rare
    - Heparin resistance

HMWH	**LMWH**
Unfractionated	Fractionated
High MW	Low MW
Safer in kidney disease - mostly eliminated by the liver	Not safe in kidney disease
Has to be monitored	Does not have to be monitored
Antithrombin complex inhibits all 3 factors	Antithrombin complex majorly inhibits factor Xa
Shorter bioavailability and half-life	Longer bioavailability and half-life -

Pharmacokinetics

- HMWH
    - Charge, HMW - not given PO
        - Given IV/SC

    - CI, IM
        - Haematoma
    - IV - rapid elimination, gradual disappearance
        - Saturable binding sites on the endothelium and macrophage
        - Slower non-saturable process - renal excretion
        - Half-life is dose dependent
    - Action immediate following IV
    - Onset is 60 minutes if given SC
    - Elimination half-life is 40-90 minutes
    - Bolus IV then continuous infusion
    - Monitor with APTT
    - APTT range - 1.5-2.5X control
- LMWH
    - Longer half-life
        - Independent of dose
        - Therefore fewer dosing frequency
    - Follows first-order kinetics
    - Predictable dose
    - OD, BD
    - Does not prolong APTT
    - Routine monitoring is not required
    - Elimination
        - Renal
        - Avoid in renal disease - extends serum half-life
    - Safety and efficacy comparable with unfractionated Heparin
    - Convenient

Clinical Use

- Acute DVT prophylaxis
- Prophylaxis and acute treatment of pulmonary embolism
    - A continuous infusion of heparin is given for about 5-10 days before the patient transitioned into a longer term anti-coagulant e.g. Warfarin
- Acute myocardial infarction
    - Results from the rupture of an artherosclerotic plaque, which leads to intraluminal thrombosis. This impairs distal blood flow and may lead to myocardial ischaemia, or infarction
    - Goal of anti-thrombotic treatment, is to prevent further clot extension and reformation
    - These patients are also immediately started on anti-platelet therapy
- Heparin is given IV in the above acute situations and an infusion continued until a definitive management, or transitioned into long-term treatment
- Heparin is safe during pregnancy as they do not cross the placenta
    - Fractionated Heparin e.g. Enoxaparin is usually preferred
        - Easier to administer
        - Predictable dose
        - Does not prolong APTT
        - Routine monitoring is not required

Adverse Drug Reactions

- Haemorrhage
    - Stop the drug
    - Give protamine sulfate
        - Protamine is a molecule the binds to Heparin, reversing its anti-coagulation activity

        - Protamine is a positively charged peptide that binds to the large negatively charged Heparin molecule
            - Therefore, less effective for LMWH and Fondaparinux
- Thrombosis
    - Paradoxical hypercoagulation state.
    - Associated with HIT (Heparin Induced Thrombocytopenia)
        - Occurs when the body makes anti-bodies against heparin complex with platelet factor 4
            - Transitory early, reduced platelets, more serious reduction - 14 days caused by IgM and IgG against complex of heparin and platelets
        - The antibodies activate platelets and can cause venous and arterial thrombosis
        - LMWH is less likely to induce HIT and Fondaparinux, even less
- Osteoporosis
    - Occurs with the HMWH
    - Decrease bone formation leading to reduced bone density and increased risk of fractures
        - 6 months, it may occur and the patient can end up with fractures
- Hypo-aldosteronism
    - 7 days treatment uncommon
    - Can lead to hyperkalaemia
    - Toxic effect on the adrenal cells that produce aldosterone
    - Considered a type IV renal tubular acidosis
- Hypersensitivity reaction - rare

Direct Thrombin Inhibitors

- Directly binding on active sites of thrombin
- Hirudin and Bivalirudin bind on both active and catalytic site of action
- Argatroban and Melagatran bind at the active site of thrombin
- Recombinant Hirudin
    - Lepirudin has little effect on platelets and bleeding time
- Used in the case Heparin causes HIT

Lepirudin

- Parenteral
- Monitor with aPTT
- Used in patients with Heparin induced thrombocytopenia
- Excreted in the kidney and care in patients with kidney disease
- No antidote
- Antigen-antibody complex in 40%
- Anaphylaxis

Bivalirudin

- Bivalent inhibitor of thrombin
- Related to the anti-coagulant that leeches use
- Given IV
- Rapid onset and offset of action
- Short half-life
- Renal clearance
- Used in
    - Percutaneous coronary angioplasty as It inhibits platelet activation

Argatroban

- Small molecule thrombin inhibitor
- Used in HIT (heparin induced thrombocytopenia)
- Short half-life and given as continuous IV infusion
- Monitor with aPTT
- Hepatic clearance
- Affects INR (international normalised ratio - therapeutic range for oral anti-coagulant therapy)

Review classification of anti-coagulants

- By MoA
  - Indirect thrombin inhibitors (ITIs)
    - Heparins
  - Oral direct factor Xa inhibitors
  - Direct thrombin inhibitors (DTIs)
    - Parenteral
    - Oral
  - Warfarin and the coumarin anti-coagulants
- By mode of administration
  - Parenteral anticoagulants
    - Heparin and related products
    - Parenteral DTIs
  - Oral anti-coagulants
    - Coumarin derivatives
    - Oral DTIs
    - Oral direct factor Xa inhibitors

Differences between LMWH and HMWH

Adverse reactions

Clinical indications of Heparin

Thrombolytic Drugs

Tuesday, 30 May 2017 11:24 AM

- Also known as fibrinolytic drugs
- Thrombosis
  - Pathological process in which a platelets aggregate and/or a fibrin clot, occludes a blood vessel and it can lead to inadequate perfusion of vital organs
- Fibrinolysis
  - Refers to the process of fibrin digestion by plasmin
- Fibrinolytic system similar to the coagulation system in that the precursor form of plasmin circulates in an inactive form as plasminogen
- In response to injury, endothelial cells synthesise and release tissue plasminogen activator referred to as t-PA, which converts plasminogen to plasmin
- Plasmin then remodels the thrombus and limits its extension by proteolytic digestion of fibrin
  - It is the active fibrinolytic enzyme
- Both plasminogen and plasmin , have specialised protein domains that bind to exposed lysins in the fibrin clot and impart clot specificity to the fibrinolytic process
- This clot specificity is only observed at physiologic levels of t-PA
- At the pharmacologic levels of t-PA used in thrombolytic therapy, clot specificity is lost and a systemic lytic state is created with associated increase in bleeding risk
- Fibrinolytic drugs rapidly lyse thrombi by catalysing the formation of the serine protease plasmin from plasminogen
- These drugs create a generalised lytic state when administered IV
- Therefore, both protective haemostatic thrombi and target thromboemboli are broken down
- As in the coagulation cascade, there are negative regulators of fibrinolysis
  - Endothelial cells synthesise and release plasminogen activator inhibitor (PAI) which inhibit t-PA
  - □2 anti-plasmin circulates in the blood at high concentrations
    - Under physiologic conditions, it rapidly inactivates any plasmin that is not clot bound
- However, this regulatory system is overwhelmed by therapeutic doses of plasminogen activators
- If the coagulation and fibrinolytic systems are pathologically activated, the haemostatic system may go out of control, leading to generalised intravascular clotting and bleeding
- This process is called DIC and may follow
  - Massive tissue injury
  - Advanced cancers
  - Obstetric emergencies such as abruptio placentae or retained products of conception
  - Bacterial sepsis
- The treatment of DIC is to control the underlying cause and transfusion
- D-dimer is one of the fibrin degradation products
  - Levels in blood can be used to detect on-going thrombosis in the body
    - This is because in thrombotic conditions e.g. PE, DVT or DIC, excessive thrombus formation is accompanied by excessive thrombus turnover, resulting in a high number of fibrin degradation products floating around

Regulation of the Fibrinolytic System

- Useful in therapeutics as follows
  - Increased fibrinolysis (fibrinolytic or thrombolytic therapy) is effective for treatment of thrombotic disease

    - Activators of thrombolysis:
        - T-PA
        - Urokinase
        - Streptokinase
- Conversely, decreased fibrinolysis (anti-plasmin drugs) protects clots from lysis and reduces the bleeding of haemostatic failure
    - Aminocaproic acid is a useful inhibitor of fibrinolysis
    - Note:
        - Heparin and oral anti-coagulants do not affect the fibrinolytic system

Pharmacology of Thromboplastic Drugs

Classification and Prototypes

- Those used commonly are
    - Streptokinase and its analog, Anistreplase
    - Forms of the endogenous t-PA
        - Alteplase
        - Tenecteplase
        - Reteplase
- All are give IV

Streptokinase

Source and Chemistry

- Protein synthesised by streptococci
- Obtained from bacterial cultures

MoA

- Is not itself, an enzyme
- Combines with the pro-activator, plasminogen
- This enzymatic complex, catalyses the conversion of inactive plasminogen to active plasmin
- Unlike, the forms of t-PA, it does not show specificity for fibrin-bound plasminogen

- Urokinase is a human enzyme synthesised by the kidney that directly converts plasminogen to active plasmin
- Plasmin itself cannot be used because naturally occurring inhibitors in plasma prevent its effects
- However, the absence of inhibitors for Urokinase and the Streptokinase-proactivator complex permits their use clinically
- Plasmin formed inside a thrombus by these activators is protected from plasma anti-plasmins, which allows it to lyse the thrombus from within
- The beneficial effect of Streptokinase is additive with Aspirin

Anistreplase

- Anisoylated plasminogen streptokinase activator complex (APSAC)
- It consists of a complex of purified human plasminogen and bacterial streptokinase that has been acylated to protect the enzyme's active site
- When administered, the acyl group spontaneously hydrolyses, freeing the activated streptokinase-proactivator complex
- This product allows for:
    - Rapid IV injection
    - Greater clot selectivity (i.e. more activity on plasminogen associated with clots than on the free plasminogen in the blood)

    - More thrombolytic activity

t-PAs

Alteplase

- Plasminogen can also be activated by t-PAs
- These activators preferentially activates plasminogen that is bound to fibrin
    - This, in theory confines fibrinolysis to the formed thrombus and avoids systemic activation
- It is a single chain recombinant human t-PA
- Manufactured by means of recombinant DNA technology

Duteplase

- Is a double-chain, recombinant human t-PA
- Both Alteplase and Duteplase, have short half-lives
    - Must be given as IV infusions

Reteplase

- It is a recombinant human t-PA from which several amino acid sequences have been deleted
- It is less expensive to produce than t-PA
- It lacks the major fibrin-binding domain
    - Therefore, less fibrin-specific than t-PA
- Reteplase has similar effects to t-PA. However, it has
    - A slightly faster onset of action
    - Longer DoA

Tenecteplase

- It is a mutant form of t-PA that has a longer half-life
- It an be given as an IV bolus
- It is slightly more fibrin specific than t-PA

Clinical Use

- Major application of thrombolytic agents is as an alternative to percutaneous coronary angioplasty in the emergency treatment of coronary artery thrombosis
    - Under ideal conditions (treatment within 6 hours), these agents can promptly re-canalise the occluded coronary vessel
    - Thrombolytic therapy in the management of acute myocardial infarction requires:
        - Careful patient selection
        - Use of a specific thrombolytic agent
        - The benefit of adjuvant therapy
- Ischaemic stroke
    - Very prompt use of t-PA (i.e. within 3 hours of the first symptoms is associated with a significantly better clinical outcome
    - Cerebral haemorrhage has to be ruled out before use
- Severe PE with haemodynamic instability
- Severe DVT such as the superior vena caval syndrome
- Ascending thrombophlebitis of the iliofemoral vein with severe lower extremity oedema
- Fibrinolytic drugs are also given intra-arterially, esp. for peripheral vascular disease
- Note:
    - These drugs affect both aPTT and PT time

ADR

- Bleeding is the most important hazard
  - It has about the same frequency with all the thrombolytic drugs
  - Cerebral haemorrhage is the most serious manifestation
  - If serious, bleeding can be treated with Tranexamic Acid, fresh plasma, Aminocaproic acid or coagulation factors
    - Aminocaproic Acid competitively inhibits plasminogen activation
    - Tranexamic Acid inhibits t-PA
- Immunologic reactions
  - Streptokinase is a bacterial protein
  - It can therefore invoke the production of antibodies, which appear 4 days or more after the initial dose
  - These antibodies may
    - Cause it to lose effectiveness
    - Induce severe allergic reactions on subsequent therapy
    - Patients who have had streptococcal infections may have preformed antibodies to Streptokinase
- Streptokinase also causes a burst of plasmin formation, generating kinins
  - It can cause hypotension
- The recombinant forms of t-PA are human proteins
  - They are therefore not antigenic
  - However, they are much more expensive than streptokinase and not much more effective
  - Recombinant t-PAs can be used in patients likely to have antibodies to streptokinase

CI

- Active internal bleeding
- Haemorrhagic cerebrovascular disease
- Bleeding diatheses
- Pregnancy
- Uncontrolled hypertension
- Invasive procedures in which haemostasis is important
- Recent trauma including vigorous cardiopulmonary resuscitation

Anti-Platelets

Tuesday, 30 May 2017 2:25 PM

Thrombogenesis

- Thromboxane A2
- 5HT
- Calcium
- Protein S
- Protein C
- Platelets
- Natural proteases

Cheki…angalia Katzung's

Platelets

- Are activated within seconds of injury
- Bind to the surface-exposed collagen
- Have special receptors for binding to injured surface and each other
- Bind to each other to form one large amorphous mass i.e. platelet plug
- Quickly arrests bleeding
- Reinforced by platelet plug
- Damaged endothelial lining exposes collagen and Von Willebrand Factor which provides a surface for platelet adherence
- Platelet attachment to the sub-endothelial lining is strengthened when it also binds to von Willebrand factor
- To do this, platelets have a special surface receptor designed to grab onto vWF, called glycoprotein 1b (GP 1B) - first step in platelet activation
- Once adhered, intracellular signals lead to platelet activation, which includes synthesis and secretion of more platelet activating and recruiting molecules to the local circulation
- Platelets then degranulate and release the following, which stimulate platelet aggregation:
    - ADP
        - Attaches to the P2-Y12 receptor on the platelets, causing aggregation
    - 5HT
        - Causes platelet aggregation and vasoconstriction
    - TXA2
        - Causes platelet aggregation and activation as well as vasoconstriction
        - Once the platelets detect TXA2, they change shape, release their granules and aggregate
        - Synthesis
            - It is synthesised within the platelet in the COX-1 pathway (COX-2 is expressed at sites of inflammation) from arachidonic acid

Regulatory factors for thrombogenesis

- Fall into 3 categories:
    - Those generated outside the platelet and interact membrane
        - Catecholamines
        - Thrombin
        - Prostacycline
        - Thromboxane
    - Generated within platelet that generate adhesion
        - ADP
        - PGD2

        - PGE2
        - 5HT
    - Compound produced within platelets that act on the surface and within the platelet
        - PG endoperoxidase
        - TXA2
        - cGMP
        - cAMP
        - Ca^{2+}

Targets for the Drugs

- PGs - TXA2 and Prostacycline
- ADP
- Member receptor
    - Glycoprotein 2B, 3A and 3B
- ADP is a powerful stimulant of platelet aggregation
- Thrombin releases ADP, stimulates synthesis of the PGs
- TXA2 induces thrombogenesis, vasoconstriction
- PGI2 directly opposes TXA2
- 5HT stimulates further aggregation and vasospasm
- Calcium binds prothrombin to platelet phospholipid surface
- Endogenous anti-coagulants C and S down regulate the amplification of the blood clotting mechanism by proteolysis of certain factors. Breakdown factor V and VIII
- Anti-thrombin III achieves serine protease IIa, IX, X, XI and XII
- Platelets play a central role to normal homeostasis and all thromboembolic disease
- Activated coagulation proteins that escape from injury site, is quickly broken down by plasma protease inhibitors
    - $a1$ antiprotease
    - $a2$ microglobulin

Disease of Platelet Function

- DIC
- PE
- DVT
- CAD
- Ischaemic Stroke
- PVD (peripheral Vascular Diseases) e.g. Raynauld's Phenomenon

Anti-Platelet Drugs

- ASA
- Clopidogrel, Ridogrel
- Abciximab
- Eptifibatife
- Tirofibam
- Dipyridamol
- Sulfinpyrazin
- Sulotroban, Vaviprost
- Dazoxiben, Pirmagel

ASA

- Irreversibly/covalently attaches an acetyl group to the serine residue near the active site of COX-1 and COX-2, halting the synthesis of TXA2
- Associated with 'pseudo-allergy'
    - It is not IgE mediated, but is due to excessive leukotriene synthesis in the setting of COX-inhibition

ADP Inhibitors

- Include
  - Clopidogrel
  - Ticagrelor
  - Prasugrel
- They inhibit the surface ADP receptors, P2-Y12.

Clinical Use of ASA and ADP inhibitors

- Reduce cardiac events in patients with peripheral artery disease
  - If ASA is not tolerated, give Clopidogrel instead
  - These agents are only use in the long-term management of cardiovascular events
    - They do not reduce the symptoms of PAD such as:
      - Atypical pain and claudication in the affected extremities
  - PAD puts you at risk for angina due to coronary artery artherosclerosis
- Reduce cardiac events with patients with coronary artery disease
  - Patients start with ASA as first-line agent but if allergic, start on Clopidogrel
- Use anti-platelet therapy in the setting of MI and other acute coronary syndromes
  - Give chewable ASA tablets to establish a high blood level quickly
- Dual anti-platelet therapy e.g. ASA and ADP receptor inhibitors, are used to prevent coronary stent thrombosis
- Treatment of acute ischaemic stroke

AE

- Ticlodipine is shown to induce neutropenia and granulocytopenia in >2% usually within the first 3 months of therapy

Glycoprotein Inhibitors

- Include
  - Abciximab
  - Eptifibatide
  - Tirofiban
- GP IIa/IIIa binds fibrinogen to promote platelet aggregation
- Circulating fibrinogen binds multiple GP IIb/IIIa, cross-linking adjacent platelets. This results in aggregation and formation of a platelet plug

Abciximab

- Comes in vials of 2ml and is given parenterally
- Is a monoclonal antibody preparation, which binds to glycoprotein 2B-3A receptors and other binding sites
- Indications
  - Prevention of ischaemic complications in patients undergoing percutaneous coronary intervention
  - Short term prevention of MI in patients with unstable angina (patients who do not respond to conventional drugs and yet are scheduled for percutaneous interventions)
- It is used only once since it is a protein
- CI
  - Active internal bleeding
  - Recent major surgery
  - Intracranial or intra-spinal surgery or trauma within the last two months
  - A stroke within the last two years
  - Intracranial neoplasm
  - An AV malformation or aneurysm
  - Severe HT

    - Any haemorrhagic diatheses
    - Thrombocytopenia
    - Vasculitis
    - Hypertensive or diabetic retinopathy
    - Severe hepatic or renal failure
    - Lactating mothers
- ADR
    - Bleeding
    - NV
    - Hypotension
    - Bradycardia
    - Chest pains with or without back pains
    - Headache
    - Fever
    - Puncture site pain
    - Thrombocytopenia
    - Cardiac tamponade
    - Acute respiratory distress syndrome (ARDS)
    - Allergic reactions
    - Discontinue use if there is uncontrollable bleeding or if there is urgent surgery

Eptifibatide

- A cyclic peptide derived from the venom of a rattle snake that contains a variation of the RGD motif.
- An analogue of the sequence at the extreme carboxyl terminal of the delta chain of fibrinogen
- Mediates binding fibrinogen to the glycoprotein IIb and IIIb receptors on the platelets
- Being an analogue of this delta chain, it will inhibit fibrinogen binding
- Use
    - Same as Abciximab
    - Used in conjunction with heparin and ASA in prevention of early MI
    - People with unstable angina
- Those with non ST segment elevation MI especially if its acute when event has occurred within the last 24 hours
- Protein and a short $T^{0.5}$ thus given parenterally IV
- Bolus 180µg/kg followed by a continuous infusion of 2µg/kg/min for 72 hours
- Acceptable for use in pregnancy
- CI
    - Hypersensitivity
    - Internal bleeding
    - Intracranial haemorrhage or neoplasm
    - CVA
    - Thrombocytopenia
    - AV malformation or aneurysm, aortic dissection, severe HT, acute pericarditis
    - Other parenteral GP IIb/IIIa

Tirofiban

- Peptidomimetic inhibitor of the RGD sequence motif
- Inhibit ligand binding to the IIb/IIIa receptor by their occupancy of the receptor but do not block the vitronectin receptor
- Short $T^{0.5}$
- CI
    - Similar to eptidibatide

- Anti-platelets increase bleeding time (used to asses platelet function)

Phosphodiesterase inhibtors

- Include
    - Dipyridamole
        - Its anti-platelet function can be used together with ASA to prevent stroke
    - Cilostazol
        - Causes arterial dilation
            - Treats symptoms of claudication due to peripheral artery disease
            - Watch out for coronary steal

- Inhibition of phosphodiesterase leads to an increase of cAMP, impairing platelet function

Dermatological Pharmacology

Monday, 5 June 2017 11:13 AM

Functions of Skin

- Protection
- Thermoregulation
- Immune responsiveness
- Biochemical synthesis
- Sensory detection
- Social and sexual communication

Structure

- Epidermis
  - Keratinocytes (keratin
  - Melanocytes
  - Langerhans cells
  - Merkel's cells (sensory)

Modalities of Therapy

- Systemic
  - PO
  - Parenteral
- Intralesional
  - Inflammatory
  - Warts
  - Neoplasms
- Topical
- UV light
  - Phototherapy

Percutaneous Absorption

- Limited by stratum corneum
- May be influenced by physiological factors
  - Hydration
    - Increased hydration enhance absorption
  - Occlusion
  - Age
    - Increased in infants and elderly (thin skin)
  - Disruption of skin
    - Eczema
    - Psoriasis
  - Dimethyl Sulfoxide, propyl glycol and urea increased penetration of drugs

Vehicles

- Powder
- Grease
- Liquid
- Shake lotion

- Creams
- Pastes
- Liposomes
- Microparticles

Topical Therapy

- 30gm to cover the entire body once
- Permeability depends on the thickness of the stratum corneum, drug penetration better on the face, intertriginous areas and perineum
- Altered stratum cornuem, like in eczema, increased absorption and thus the risk of toxicity following topical application
- Increased hydration (c.f. occlusion, lipophilic vehicle and soaking)_
- Vehicles
    - Soaks
    - Lotion
    - Solution
    - Cream
    - Ointment
- Age
    - Increased ratio of surface area
    - Increased permeability in children
    - Thin skin in neonates and elderly
- Application frequency

Glucocorticoids

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- Immunosuppresive and anti-inflammatory
- Given
  - Local
    - PO
    - Topical
    - Intra-lesional
  - Systemic
    - IM
    - IV
    - PO
- MoA
  - Inhibition of arachidonic acid cascade
  - Depression of cytokine production
  - Effect on inflammatory cells

Topical Glucocorticoids

- Hydrocortisone and halogenated corticosteroids
- Potency depends on
  - Vasoconstrictor assay
  - Psoriasis bioassay
  - Suppression of erythema and oedema
- Includes:
  - Betamethasone
  - Dexamethasone
  - Hydrocortisone
  - Other halogenated derivatives

Indications

- Inflammatory skin conditions
- Use hydrocortisone in the face and occluded area like the groin and axilla
- BID
- Tachyphylaxis can occur, switch to a different corticosteroid
- Triamcinolone intra-lesional due to long DoA

Toxicity and Monitoring

- Local
  - Skin atrophy
  - Striae
  - Telengectasia
  - Purpura
  - Acne
  - Perioral dermatitis
  - Overgrowth of fungus and bacteria
  - Hypopigmentation of skin
  - Rosacea
- Striae can be intertriginous and can be diffuse
- Halogenated preparation should be avoided in the face

- Long time application near eyes can cause cataracts and glaucoma
- Most potent through inflamed skin may in the presence of sufficient absorption cause systemic toxicity
- Intra-lesional steroids can cause cutaneous atrophy and hypopigmentation
- Limit the strength and quantity to minimise adverse effects

Systemic Glucocorticoids

- Life threatening dermatosis
- Pulse therapy of methylprednisolone for:
    - Pyoderma
    - Gangrenosum
    - Pemphigus vulgaris
    - Bollous pemphigoid
    - Organ threatening SLE
    - Dermatomyositis
- Monitor more vigorously for toxicity

List skin diseases that required steroids for therapy

Keratolytic and Destructive Agents

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Salicylates

- Includes:
  - Salicyclic acid
- MoA poorly understood
- Solubise cell surface protein that keep the stratum corneum intact
- Results in desquamation of keratotic debris
- 3-6% keratolytic, >6% tissue destructive
- Salicylism and death following topical administration. Rare but can occur
- High serum salicylate seen in children
- Treatment of choice - haemodialysis

Other ADR of Salicylates

- Urticaria
- Anaphylaxis
- Erythema multiforme
- Local irritation and ulceration with high concentration
- Care in extremities of diabetic ad patients with PVD

Propyl Glycol

- Keratolytic 40-70%
- Used with plastic occlusion or in gel with 6% SA
- Minimal absorption
- Absorbed SC oxidised to lactate and pyruvate
- 12-45% of absorbed excreted unchanged in urine
- Keratolytic and humectant
- Increase hydration of outermost skin layer due to it hygroscopic properties
- Used under polythene occlusion with 6% Salicylic acid for
  - Icthyosis palmar and plantar keratoderma
  - Psoriasis
  - Pityriasis rubra pilaris
  - Keratosis pilaris
  - Hypertrophic lichen planus
- High concentration - >5%
  - Irritant
  - Hypersensitivity (eczematous dermatitis)
  - Allergic contact dermatitis
  - Therefore recommend 4% as solution for patch testing

Urea

- Softening and moisturising stratum corneum
- Vehicle: Cream
- Cream and lotions feel less greasy with urea
- White crystalline powder with slight ammonia smell
- Absorbed percutaneously, distributed in the extracellular space and excreted in urine
- Systemic toxicity doesn't occur
- Hygroscopic

- Keratolytic
- Acts by altering keratin and pre-keratin increasing their solubilisation
- Breaks H^+ bonds that keeps stratum corneum intact
- Used as
    - 2-20% cream or lotions humectant
    - 20% keratolytic
    - 30-50% applied to nails prior to avulsion

Podophyllum resins and Podofilox

- Alcoholic extract of *podophylum peltatum*
- Treatment of condyloma acuminata and other verrucae
- Absorption occur due to its lipid solubility particularly in intertriginous areas
- Podophylotoxin and active derivatives are cytotoxic
- Application restricted to warts
- Wash of 2-3 hours post application
- Use up to 6 application and change modality if ineffective
- Toxicity
    - NV
    - Altered sensorium
    - Muscle weakness
    - Neuropathy with reduced DTR
    - Coma and death
    - Local irritation and conjunctivitis
    - Avoid in pregnancy due to cytotoxicity
- Indications
    - Condyloma acuminata

Fluorouracil

- Fluorinated pyrimidine metabolite
- Topical for multiple actinic keratosis
- Small quantity absorbed, metabolised and excreted
- Inhibit thymidylate synthetase activity thus interferes with DNA and RNA synthesis

Other agents

- NSAIDS - diclofenac
- Aminolevulinc acid

Anti-Pruritic Agents

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- Occurs in xerosis, malignancy
- Treatment includes preparations with :
  - Antihistamine
  - Emollient creams and ointment
  - Menthol, Camphor, Phenols, Pramoxine, Doxepin, Capsaicin, tat
- Systemic - antihistamines, doxepin and steroids
- Physical - methoxypsolarens and UV light, acupuncture, electrical stimulation

Topical Steroids and Antihistamines

- Atopic eczema
- Contact dermatitis
- Lichen simplex chronicus

Interventions

- Cholestatis associated pruritus - cholestyramine, Ursodeoxycholic acid, Ondansetron, Rifampicin, Nalmefene
- Uraemia induced pruritus - UVB radiation
- Prurigo - in addition to topical and intralesional steroids, Naltrexone or PPi's

General Measures in Pruritis Treatment

- Lukewarm baths
- Non-fragranced soap
- Mild soap
- Skin cooling
- Humidifiers
- Emollient creams

Topical Antimicrobials

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- Include:
  - Anti-bacterial
  - Antifungals
  - Antiviral agents
  - Ectoparasiticides

Topical Antiviral Agents

- Acyclovir, Valacyclovir, Pencicyclovir and Famicyclovir are synthetic guanine analogs with inhibitory activity against members of the herpesvirus family, including HSV1 and 2
- MoA covered in anti-viral agents
- Topical Acyclorir is available as a 5% ointment
- Topical Pencyclovir is available for the treatment of recurrent orolabial HSV infection in immunocompetent adults
- Adverse local reactions of Acyclovir and Pencyclorir may include pruritus and mild pain, with transient stinging or burning

Topical Anti-fungal agents

- For superficial fungal infections
  - Stratum corneum
  - Squamous mucosa
  - Cornea
- Such diseases include:
  - Dermatophytosis (ring worm)
  - Candidiasis
  - Tinea versicolor
  - Piedra
  - _
- Not useful for
  - Mycoses
    - Onychomycosis (nails)
    - Tinia capitis (hair)
  - Subcutaneous mycosis
    - Sporotrichosis
    - Chromoblastomycosis
- The efficacy of topical agents in the treatment of superficial mycoses depends on
  - The type of lesion
  - MoA of the drug
  - Characteristics of the formulations i.e.
    - Viscosity
    - Hydrophobicity
    - Acidity
- Regardless of the formulation, penetration of the topical drugs into hyperkeratotic lesions is often poor
- Removal of thick, infected keratin is sometimes a useful adjunct to therapy
  - This is the principle MoA of Whitefield's Ointment
- Similarly, 40% urea paste can be applied under occlusion to soften infected nails
- The older drugs which are used, include:
  - Gentian Violet

    - Carbol-fuchsin
    - Acrisorcin
    - Triacetin
    - Sulfur
    - Iodine
    - Aminacrine
- Among the topical agents, the preferred formulations for cutaneous application is usually a cream or solution
- Ointments are messy and they are too occlusive for macerated or fissured intertriginous lesions
- The use of powders, applied by shake containers or aerosol, is largely confined to the feet and moist lesions of the groin and other intertriginous areas
- Note:
    - Intertrigo
        - Chaffing (soreness or irritation of the skin caused by friction between two skin surfaces that are incontact) e.g. in the armpits, under the breasts and between the thighs
- Treatment of superficial fungal infections caused by dermatophytic fungi may be by either:
    - Topical antifungal agents
    - Orally administered agents
        - Griseofulvin
        - Terbinafine
        - Azoles
            - Ketoconazole
            - Fluconazole
            - _
- Superficial infections, caused by candida species, may be treated with topical applications of
    - Azoles e.g. Clotrimazole, Miconazole, Econazole, Ketoconazole, Oxiconazole
    - Ciclopirox olamine
    - Nystatin
    - Amphotericin B
- Chronic generalised mucocutaneous candidiasis responds to long-term therapy with oral ketoconazole

Specific Topical Anti-fungal Preparations

- Azole Derivatives
    - Clotrimazole
    - Miconazole
    - Econazole
    - Ketoconazole
    - Oxiconazole
    - Sulconazole
- Ciclopirox olamine
- Allylamines
    - Terbinafine
    - Naftifine
- Butenafine
- Tolnaftate
- Nystatin
- Amphotericin B

Ciclopirox Olamine

- It is a synthetic, broad spectrum anti-mycotic agent

MoA

- It appears to inhibit the uptake of precursors of macromolecular synthesis
    - Its site of action is probably the fungal cell membrane
    - It is fungicidal

Pharmacokinetics

- 1-2% of the dose is absorbed when applied as a solution under an occlusive dressing

Adverse Effects

- The incidence of adverse effects is low
- Pruritus and worsening of clinical disease have been reported
- The potential for delayed allergic contact hypersensitivity appears small

Clinical Use

- It has inhibitory activity against dermatophytes, candida species, and P obiculare
- It is available_
- Topical 8% Ciclopirox olamine is approved for the treatment of mild to moderate onychomychosis of fingernails and toe nails
- It is well tolerated with minimal side effects
    - The overall cure rates are less than 12%

Allylamines (Naftifine and Terbinafine)
MoA

- They selectively inhibit squalene epoxidase, a key enzyme for the synthesis of ergosterol
- This leads to accumulation of squalene which is toxic to fungi

Clinical Use

- Highly active against dermatophytes but less active against yeasts
- They are available as 1% creams and other forms for topical treatment of dermatophytosis
- They are applied on a BD dosing schedule
- Note
    - Terbinafine can also be given orally

AE

- Include local irritation, burning sensation and erythema
- Contact with mucous membranes should be avoided

Butenafine

- Butenafine hydrochloride is a benzylamine
- It is structurally related to the allylamines and has the same MoA
- Butenafine is available as a 1% cream to be applied OD for the treatment of superficial dermatophytosis

Tolnaftate
Chemistry

- A thiocarbamate synthetic anti-fungal compound

Clinical Use

- It is effective topically against dermatophyte infections caused by epidermophyton, Microsporum and Trichophyton
- It is also active against P orbiculare but not against Candidiasis
- Is available as a cream, solution, powder or powder aerosol for application BD to infected areas
- Recurrences following cessation of treatment are common
- Infections of the palms, soles and nails are usually unresponsive to Tolnaftate alone
- The powder or powder aerosol, may be used chronically following initial treatment in patients susceptible to Tinea infections

AE

- It is generally well tolerated and rarely causes irritation or allergic contact sensitisation

Nystatin and Amphotericin B

Chemistry

- Polyene antifungal agent

Clinical Use

- Both are useful in the topical therapy of C. albicans infections by ineffective in dermatophytes infections
- Nystatin
    - It is limited to topical treatment of cutaneous and mucosal candida infection because of:
        - Its narrow spectrum
        - Negligible absorption from the GIT following oral administration
    - The recommended dose for topical preparations of Nystatin for treatment of paronychial and intertriginous candidiasis is application BD or TDS
    - Oral candidiasis (thrush) is treated by holding 5 ml (infants, 2ml) of nystatin oral suspension for several minutes QID, before swallowing
    - Recurrent or persistently resistant perianal, vaginal, vulvar and diaper area candidiasis may respond to oral nystatin, 0.5-1 million units in adults (100,000 units in children) QID, in addition to local therapy
    - Vulvovaginal candidiasis may be treated by insertion of 1 vaginal tablet BD for 14 days, then nocte for an additional 14-21 days
- Amphotericin B
    - It has a broader antifungal spectrum than Nystatin
    - It is rarely used in the treatment of cutaneous candida infections
    - It is available for topical use in cream and lotion form
    - The recommended dose in the treatment of paronychial and intertriginous candidiasis is application X2-4 per day to the affected area

AE

- Nystatin
    - PO may be associated with mild ND and occasional V
    - Topical application is non-irritating and allergic contact hypersensitivity is very uncommon
- Amphotericin B
    - Topical amphotericin B is well tolerated and only occasionally locally irritating
    - Hypersensitivity is very rare
    - It may cause a temporary yellow staining of the skin, esp. when the cream vehicle is used

Azole Derivatives (Imidazoles nd Triazoles)

- Azole antifungals are used both topically and systemically

- Indications for their topical use include:
  - _
- Resistance to imidazoles and triazoles is rare among the fungi that cause ringworm
- Selection of one of an azole for topical use should be based on cost and availability, because testing in vitro for fungal susceptibility to azoles does no predict clinical Reponses

Modes of application

- Cutaneous application
  - Their use is effective for
    - Tinea corporis
    - Tinea pedis
    - Tinea cruris
    - Tinea versicolor
    - Cutaneous candidiasis
  - They should be applied BD for 3-6 weeks
  - The cutaneous formulations are not suitable for oral, vaginal or ocular use
- Vaginal application
  - Vaginal creams, suppositories and tablets for vaginal candidiasis are all used OD for 1-7 days, preferably at bed time to facilitate retention
  - Three vaginal formulation come in both high and low dose preparations
  - They include
    - Clotrimazole tablets
    - Miconazole suppositories
    - Terconazole cream
  - A shorter duration of therapy is recommended for the higher dose of each
  - These preparations are administered for 3-7 days
  - ~3-10% of the vaginal dose is absorbed
  - Although some imidazoles are teratogenic in rodents but no AE on the human foetus have_
  - The most common SE is vaginal burning and itching
  - A male sexual partner may experience mild penile irritation
  - Cross-allergenicity among these compounds is assumed to exist, based on their structural similarities
- Oral use
  - Use of the oral troche (medicated lozenge used to soothe the throat) of Clotrimazole is considered as topical therapy
  - The only indication for this 10-mg troche is oropharyngeal candidiasis
  - Anti-fungal activity is entirely due to the local concentration of the drug; these is no systemic effect

- The topical imidazoles, which include Clotrimazole, Econazole, Ketoconazole, Miconazole, Oxiconazole, Sulconazole and Sertaconazole, have a wide range of activity against
  - Dermatophytes which include epidermophyton, Microsporum and Tri_
  - _
- Miconazole is available for topical application as a cream or lotion and as vaginal cream or suppositories for use in vulvovaginal candidiasis
- Clotrimazole is available for topical application to the skin as a cream or lotion and as vaginal cream and tablets for use in vulvovaginal candidiasis
- Econazole is available as a cream for topical application
- Oxiconazole is available as a cream and lotion for topical use
- Ketoconazole is available as
  - A cream for topical treatment of dermatophytosis and candidiasis
  - As a shampoo for the treatment of seborrheic dermatitis
- Sulconazole is available as a cream or solution
- Sertaconazole is available as a cream or as a solution
- Topical antifungal/corticosteroid fixed combinations are also used to provide more rapid

symptomatic improvement than an anti-fungal agent alone e.g. Clotrimatole-Betamethasome dipropionate (Candid-B) cream

- OD or BD application to the affected area generally results in clearing of superficial dermtophyte infections in 2-3 weeks
    - The medicine should be continued until eradication of the organism is confirmed
- Paronychial and intertriginous candidiasis can be treated effectively by any of these drugs when applied 3-4 times daily
    - Paronychia
        - Infection in the tissues adjacent to a nail on a finger or toe
- Seborrheic dermatitis should be treated with BD application of Ketoconazole until clinical clearing is obtained
- Adverse local reactions to the imidazoles may include stinging, pruritus, erythema and local irritation
- Allergic contact dermatitis appears to be uncommon

Retinoids

Tuesday, 6 June 2017 2:10 PM

Definitions

- Natural and synthetic compounds that exhibit Vitamin A-like bioactivity or bind to nuclear receptors for retinoids
- Useful for management of acnes

Functions of Retinoids

- Role in vision
- Regulation of cell proliferations and differentiation
- Bone growth
- Immune defence
- Tumour suppression

First Generation

- Retinol (Vitamin A)
- Include:
  - Tretinoin (all transe-tretinoic acid, Vitamin A acid)
  - Isotretinoin (13-cis-retinoic acid)
  - Alitretinoin (9-cis-retinoic acid)

Second Generation

- AKA aromatic retinoids
- Include
  - Acitretin
  - Etretinate - Obsolete because it is teratogenic

Third Generation

- Were created after the discovery of specific retinoid receptors
- Designed to optimise receptor- selective binding
- Include
  - Tazarotene
  - Bexarotene
  - Adapalene

Pharmacodynamics

- Exert their effects on gene expression
- Activate 2 families of receptors
  - Retinoic acid receptors (RARs)
  - Retinoid X receptors (RXRs)
- RAR and RXR are members of the steroid receptor super family

MoA

- Upon retinoid binding, RARs and RXRs form heterodimers
- Subsequently bind specific DNA sequences called **retionoic acid- responsive elements** (RAREs)

- Activate transcription of genes whose products lead to pharmacologic effects

Therapeutic effects

- Retinoids that target RARs predominantly affect differentiation and proliferation
- Retinoids that target RXRs predominantly cause apoptosis

- Thus Tretinoin, Adapalene and Tazarotene which target RARs are used in acne, psoriasis and photoaging (disorders of differentiation and proliferation)
- Bexarotene and Alitretinoin which target RXRs are used in mycosis fangoides and KS to induce apoptosis of malignant cells

Tretinoin

- Acid form of Vitamin A
- Is an effective topical treatment of acne vulgaris
- <10% is absorbed into the circulation from the skin and excreted in bile and urine
- Optimal clinical response in 8-12 weeks

AE

- Erythema and dryness - resolve with continued therapy
- May increase tumogenic potential of UV radiation - Minimise sun exposure and a protective sunscreen
- Rare allergic contact dermatitis

Isotretinoin

- Synthetic retinoid
- Given orally for treatment of severe cystic acne non-responsive to standard therapies
- Is well absorbed
- Extensively bound to plasma albumin
- $T_{0.5}$ - 10-20 hours

MoA

- Inhibit sebaceous gland size and function
- Normalises keratinisation in sebaceous follicle
- Reduces P. acnes
- Clinical effects take 1-3 months

AE

- Common - Dryness and itching of the skin and mucous membranes
- Headache, corneal opacities, pseudotumour cerebri, IVS, anorexia, alopecia and myalgia and arthralgia
- Lipid abnormalities (increase TGs , HDL)

Use in Women of Child-Bearing Age

- Teratogenicity is a significant risk (CNS, craniofacial and CVS defects)
- Women and childbearing potential must use effective contraception for at least a month before starting Isotretinoin, throughout treatment and for 1 more menstrual cycles following discontinuation of treatment
- Negative serum pregnancy test must be obtained 2 weeks before starting therapy

Photo-Chemotherapy

Friday, 30 June 2017 7:00 AM

Introduction

- UV region of electromagnetic radiation is divided into:
  - UVA1 (340-400nm)
  - UVA2 (320-340nm)
  - UVB (290-320nm)
  - UVC (10-290nm)

- UVA radiation
  - 1000x less erythrogenic than UVB
  - Penetrates more deeply into the skin
  - Contributes to photoaging and photosensitivity reaction
- UVB
  - Is the most erythrogenic type of radiation
  - Major action spectrum for:
    - Sunburn
    - Tanning
    - Skin cancer
    - Photo agent
- UVC
  - Is almost completely absorbed by stratosphere and doesn't reach earth surface
  - Not used therapeutically

Definitions

- Photochemotherapy
  - Treatment method in which UVA light is used to induce a therapeutic response in the presence of photosensitizing drug (psolarens)
  - To be effective, the incident radiation must be absorbed by a target or chromophore in the skin - which In photochemotherapy is administered exogenously
  - Before initiation of photochemotherapy rule out use of other potential photosensistizing medications including:
    - Phenothiazines
    - Thiazides
    - Sulphonamides
    - NSAIDs
    - Sulphonylureas
    - Tetracyclines
    - Benzodiazepines
- Phototherapy
  - Utilises UVB which unlike UVA is effective without additional sensitisers

Psolarens

- Group of photoactive compounds that on absorption of UV light are both anti-proliferative and immunomodulatory
- Include
  - Methoxsalen (8-methoxypsolaren)
  - Trioxsalen
  - Bergapten (5- methoxypsolaren)
- PUVA = Psolarens + UVA

MoA

- PUVA administration leads to 2 distinct photoreactions:
  - Type 1
    - Involve the oxygen- independent photoaddition of psolarens to pyrimidine bases in DNA
  - Type 2
    - Oxygen dependent
    - Involve transfer of energy to molecular oxygen, creating ROS (reactive oxygen species)
- These phototoxic reactions:
  - Stimulate melanocytes
  - Induce antiproliferative, immunosuppressive and antiinflammatory effects - used in psoriasis
- PUVA also inhibits cytokine release and depletes both epidermal and dermal T-cells

Administration

- Methoxsalen is available in gelatin capsules for oral use
- Taken 1.5 - 2 hours before UVA exposure
- 1% methoxsalen lotion - topical application

Uses

- Psoriasis
- Vitiligo

Adverse Effects

- Acute
  - Phototoxic effects - erythema and blistering
  - Nausea, lethargy, headaches, pruritus and hyperpigmentation
  - Retinal damage
- Long term
  - Squamous cell carcinoma
  - Melanoma
  - Cataract formation

Protective Measures Post- PUVA Therapy

- After PUVA patients should:
  - Wear protective clothing
  - Use sunscreen that blocks UVA and UVB
  - Wear sunglasses that block UVA

Cytotoxics

Thursday, 8 June 2017 8:19 AM

Oncology
- Study of tumours including treatment approaches

Cancer
- Disease characterised by a shift in the control of cell proliferation and differentiation
- Cancers do not recognise a limit to their expansion

Necrosis
- Refers to cell death characterised by cell swelling and membrane disruption

Apoptosis
- Programmed cell death
- Note
  - CA chemotherapeutics can cause both necrosis and cell apoptosis

Protooncogenes
- Regulators of cell proliferation
- In an active state the y promote cell growth
- Their dis-regulation produces oncogenes

Oncogenes
- Are the genes encoded by tumour-forming viruses in animals

- These genes may be deleted or damaged resulting in neoplastic change e.g.
  - The p53 gene has been shown to be mutated in up to 50% of all human solid tumours

The Cell Cycle Kinetics
- Normal organs and CA cells share he property of having a population of cells in cycle and actively renewing and a population of cells not in cycle
- The cell cycle has phases that all cells must go through before and during cell division
- Differences occur in the duration of the cell cycle between cells of various types
- However, all cells display a similar pattern during the division process
- The cell cycle is characterised as follows
  - There is a pre-synthetic phase (G_1) during which synthesis of cellular components required for DNA synthesis occurs
  - The S phase during which there is synthesis of DNA
  - The G_2 phase during which there's synthesis of cellular components required for mitosis
  - The M phase (Mitosis phase) during which the G_2 cell, which contains a double component of DNA, divides into 2 daughter G_1 cells
  - Each of these 2 cells may immediately re-enter the cell cycle or pass into a non-proliferative stage, the G_0 phase
- Damaged cells that reach the G_1/S boundary undergo apoptosis if the p53 (tumour suppressor) gene is intact and exerts its normal checkpoint function
- However, if the p53 gene is mutated, and the checkpoint function fails, damaged cells are not diverted into the apoptotic pathway
  - These cells proceed through S phase and some emerge as a drug resistant population

Importance of the Neoplastic Cell Burden

- Most tumours follow a Gompertzian growth curve i.e. the growth fraction of a neoplasm starts at 100% with the first transformed cell and decreases exponentially over time
- By the time of diagnosis, the tumour burden is 1-5X10^9 tumour cells
- This corresponds to at least, 1cm diameter I size or 1g of tumour cells
- Without treatment intervention, the tumour kills a patient at a tumour burden of 10^{12} tumour cells, which corresponds to 1kg of tumour
- Each cycle of therapy usually kills less than 99% of the tumour cells
- It is therefore necessary to repeat treatment in multiple cycles to kill all the tumour cells

The Log-Kill Hypothesis

- For effective "cure" of CA
  - The killing of tumour cells should exceed regrowth
  - Drug resistance should not occur
- CA chemotherapeutic drugs act with first-order kinetics i.e. a given dose, kills a constant proportion of a cell population, other than a constant number of cells
- The log kill hypothesis proposes that the magnitude of tumour cell kill by anti-CA drugs is a logarithmic function e.g.
  - A 3-log kill dose of an effective drug, will reduce a CA cell population of 10^{12} cells to 10^9, and the same dose would reduce a starting population of 10^6 - 10^3 cells
  - In both cases, the dose reduces the number of cells by 3 orders of magnitude, or "3-logs"

Look at the diagram in Katzung and note the interpretation

Treatment of CA

- Divided into 4
  - Surgery
  - Radiotherapy
  - Chemotherapy
    - Including hormonal and molecular targeted therapy
  - Biologic therapy
    - Including immunotherapy and gene therapy
- Cancer chemotherapy is used in 3 main clinical settings
  - Primary chemotherapy
    - Administered as the primary treatment in patients who present with advanced cancer for which no alternative treatment exists
    - The purpose is usually to improve overall quality of life
    - Cancer chemotherapy can be curative in a small subset of cancers
      - Adults
        - AML
        - Hodgkin's and Non-Hodgkins lymphoma
        - Choriocarcinoma
        - Germ cell cancer
      - Children
        - ALL
        - Wilm's tumour
        - Embryonic rhabdomyosarcoma
        - Burkett's lymphoma
  - Neoadjuvant chemotherapy
    - refers to the use of chemotherapy in patients who present with localized cancer for which alternative local therapies, such as surgery, exist but which are less than completely effective.
    - Goal is to reduce the size of the tumour so that surgical resection can be made easier
    - Can be used for

            - Anal cancer
            - Bladder cancer
            - Oesophageal cancer
            - Breast cancer
            - Laryngeal cancer
            - Osteogenic sarcoma
            - Locally advanced Non-small cell lung cancer (NSCLC)
    - Adjuvant chemotherapy
        - Adjuvant to local modalities such as surgery
        - Given post-op to reduce the chances of recurrence and improve the overall outcome.
        - Can be used in
            - Breast cancer
            - Colon cancer
            - Wilm's tumour
            - NSCLC
            - Gastric cancer
            - Anaplastic astrocytoma
            - Osteogenic sarcoma
            - Primary malignant melanoma

Classification of Cancer Chemotherapeutic Agents

- DNA interacting drugs
    - Direct
    - Indirect
- Hormones and their antagonists
- Miscellaneous anti-CA drugs

DNA Interacting Agents

- Direct DNA Interacting Agents
    - Include
        - Alkylating agents
            - Cyclophosphamide
            - Platinum analogs
                - Cisplatin
            - Altretamine
            - Dacarbazine/Procarbazine
        - Antitumour antibiotics
            - Anthracyclins
                - Doxorubicin
                - Daunorubicin
            - Mitoxanthrone
            - Dactinomycin (Actinomycin D)
            - Mitomycin C
            - Bleomycin
        - Camptotherin
            - Irinotecan
            - Topotecan
        - Epipodophyllotoxins
            - Etoposide
            - Teniposide
- Indirect DNA Interacting Agents
    - Antimetabolites

            - Folate antagonists
                - Methotrexate
            - Purine antagonists
                - 6-mercptopurine
            - Pyrimidine antagonists
                - 5-fluorouracil
        - Anti-mitotic agents
            - Vinca alkaloids
                - Vincristine
                - Vinblastine
            - Taxanes
                - Docetaxel
                - Paclitaxel
- Hormones and their antagonists
    - Steroid homones
        - Glucocorticoids
    - Anti-steroid hormones
        - Aminoglutethimide
    - Progestins
        - Megestrol acetate
    - Oestrogens
        - Ehinyl estradiol
    - Anti-oestrogens
        - Tamoxifen
    - Androgens
        - Testosterone
    - Anti-androgens
        - Flutamide
    - Gonadotropin releasing hormone analogs
        - Leuprolide
- Miscellaneous
    - Proteins
        - Interferons
            - Interferon α
        - Interleukins
            - IL-2
        - Bone arrow growth factors
            - Erythropoietin
        - TNF
        - Monoclonal antibodies
            - Trastuzumab
            - Rituximab
    - Growth factor receptor inhibitors
        - Cetuximab
        - Bavacizumab
    - Asparaginase
    - Hydroxyurea
    - Retinoic acid derivatives
    - Arsenic trioxide
    - Imatinib

☐ Cell Cycle Effects of Major Classes of Anti-CA Drugs

- Cell cycle specific drugs
    - G1 + S Phase
        - Epidodophyllotoxin (Topo II Inhibitor)

        - Etoposide
        - Tenoposide
    - S Phase
        Antimetabolites
        - Cytarabine
        - Capecitabine
            - 5-Fluorouracil
        - 6-Mercaptopurine
        - 6-Thioguanine
        - Gemcitabine
        - Methotrexate
    - G2 Phase
        - Bleomycin
    - M Phase
        - Taxanes
            - Docetaxel
            - Paclitaxel
        - Vinca Aklaloids
            - Vincristine
            - Vinblastine
            - Vinrelbine
- Non-cell cycle specific drugs
    - Alkylating agents
        - Cyclophosphamide
        - Cisplatin
        - Melphalan
        - Busulfan
        - Carmustine
        - Procarbazine

Principles of CA Chemotherapy

- Combination chemotherapy regimes using drug with different toxicities and MoA are often use e.g.
    - Use of an alkylating agent (CCNS) + anti-metabolite (S-phase) + Mitotic spindle blocker (M-phase)
- Combination chemotherapy is aimed at overcoming the limited log-kill of individual anti-CA drugs
- If drugs have no overlapping toxicities, they can be used at almost full dosage
- In addition, sub-clones resistant to only one of the drugs can be potentially eradicated
- When dealing with CA chemotherapy toxicity, supportive care is important and includes the following where indicated
    - Platelet transfusion
    - Antibiotics
    - Haemopoietic growth factors
- Note:
    - Other delayed toxicities affecting the heart, lungs or kidneys may not be reversible and may lead to permanent organ damage or death

Alkylating Agents

Friday, 9 June 2017 8:23 AM

Class of Drugs

- Nitrogen mustards (Ethylamines)
  - Cyclophosphamide
  - Meclorethamine
  - Melphalan
  - Chlorambucil
  - Ifosfamide
- Alkyl sulfonates
  - Busulfan - CML
    - Has affinity for the granulocytes
- Ethylinimines
  - Methylmelamine
  - Triethylenemelamine
  - Thiotepa
    - Used in ovarian tumours
  - Altrelamine
- Nitrosoureas
  - Carmustine
  - Lomustine
  - Sermustine
- Triazenes
  - Dacarbazine
- Investigtional
  - Link various carrier molecules such as amino acids, nucleic acids, bases, hormones or sugar moieties to group capable of alkylation

MoA

- Transfer of an alkyl group to various cellular components
- Alkylation of DNA within the nucleus leads to cell death
- Drug reacts with SH, amino, OH, carboxy and phosphate groups of other cellular nucleophiles as well
- Nitrosoureas also additionally cause carbomylation of lysine residue through formation of isocyanates

Site of Action

- Guanine N7 is the major site
- N1 and N3 of adenine, N3 of cytosine, O6 of guanine
  - Phosphate and protein associated with DNA
- Cell more susceptible to alkylation in late G_1 and S phase
- Non-cell cycle specific and block G_2

MoR

- Acquired
  - Increased capacity to repair DNA
  - Decrease permeability of the cell to the drug
  - Increased glutathione that inactivate the alkylating agent through conjugation or

through increased glutathione s-transfuse activity

Pharmacologic Effects

- Direct vesicant effects at the site of injections
- Systemic toxicity i.e. in rapidly growing cells
    - Bone marrow
        - Myelosuppression
            - Do frequent blood count checks
    - GIT tract
    - Reproductive system
        - Infertility
        - Early menopause
        - Permanent azoospermia
        - Low sperm counts
- Toxicity is dose related
- NV within 30-60 minutes
    - Mechlorethamine
    - Cyclophosphamide
    - Carmustine
- Mediated centrally
    - Treatment with $5HT_3$ antagonist (Ondansetron, Granisetron)

Cyclophosphamide

- Cyclophosphamide is inactive
- Activated by CYP450 in the liver to an active form
- Metabolites
    - 4-hydroxycyclophosphamide which equilibrates with aldophosphamide
- Delivered to the normal and tumour cells
    - Attaches an alkyl group to the guanine base of DNA (N7)
    - This interferes with DNA replication by forming intrastrand DNA cross links
    - Cell cycle non-specific
- Non-enzymatic conversion of aldophosphamide to:
    - Phosphoramide mustard and Acrolein
        - Metabolised into Acrolein by the kidneys
- Liver protects through enzymatic formation of inactive metabolites
    - 4-ketocyclophosphamide and carboxyphosphamide
- PO administration
    - Cyclophosphamide
    - Melphalan
    - Chlorambucil
    - Busulfan
    - Temozolomide
- Cytotoxic effects c.f. IV
- Generally cross-resistance across the class but not necessarily Nitrosoureas
- Cyclophosphamide most widely used alkylating agent
    - Used for haematological disorders and solid tumours
        - Haematological
            - Leukaemias
            - Lymphomas
        - Tumours
            - Breast CA
            - Ovarian CA
    - Potent immunosuppressive agent

        - Treatment of
            - Nephrotic syndrome
            - Nephritis syndrome
            - Vasculitis
            - Autoimmune haemolytic syndrome
- AE
    - Myelosuppression
    - Haemorrhagic cystitis
        - Acrolein is excreted in the urine
        - Acrolein is toxic to uroepithelial cells and can cause cell death and necrosis if allowed to be in contact with these cells for a prolonged period of time
        - Watch for
            - Dysuria
            - Urinary frequency and urgency
            - Progressive haematuria
        - Prevented by:
            - Aggressive hydration
            - Co-administration of 2-mercaptoethanesulfanade (MESNA)
                - Sulfhydryl compound that binds and inactivates the toxic metabolite
    - Increases the risk for bladder CA (high grade transitional cell carcinoma) - dose dependent
    - Hyponatraemia
        - Due to SIADH
    - Infertility and early menopause

Busulfan

- MoA
    - Attaches an alkyl group to the guanine base of DNA (N7)
    - This interferes with DNA replication by forming intra-strand DNA cross links
    - Cell cycle non-specific
- PO
- Granulocytic series
- Used in myeloproliferative disorders
- Severely depletes the bone marrow
    - Useful as a conditioning agent prior to bone marrow transplantation
- Used in CML
- Leukopenia surrogate for drugs adequate absorption
- AE
    - Associated with lung toxicity
        - Acute lung injury
        - Interstitial fibrosis
        - Alveolar haemorrhage
    - Hyperpigmentation of skin ("busulfan tan")

Monitor - both Cyclophosphamide and Busulfan

- Blood counts
- Interrupt therapy if severe leukopenia and/or thrombocytopenia

Nitrosoureas

- Non-cross-resistant with other alkylating agent
- Non-enzymatic biotransformation to metabolites with alkylating and carbomylating activities

- Highly lipid soluble and cross the BBB
    - Thus useful in treatment of brain tumours
        - Glioblastoma multiform
- Form DNA crosslinks which prevent DNA replication which leads to apoptosis of the cell
- They can cause neurotoxicities
    - Convulsions
    - Dizziness
    - Ataxia

Lomustine

- PO
    - Peak plasma in 1-4 hours
- CNS
    - 30-40% of the plasma
- Initial plasma half-life is 6 hours, second half-life of 1-2 days
- Major elimination as urinary metabolites

Streptozocin

- Naturally occurring sugar containing nitrosoureas
- Treatment of islet cells-carcinoma of the pancreas
- Minimal bone-marrow toxicity

Which are the other BM sparing cytotoxic drugs?

- Vinblastine
- Bleomycin
- Asparaginase

Triazenes

Dacarbazine

- A synthetic compound
- Metabolic activation in the liver by oxidative N-demethylation to the monomethyl derivative.
- This metabolite spontaneously decomposes to diazomethane, which generates a methyl carbonium ion that is believed to be the key cytotoxic species.
- PK
    - Parenteral
- Indications
    - Malignant melanoma
    - Hodgkin's lymphoma
    - Soft tissue sarcomas
    - Neuroblastoma
- ADE
    - Dose-limited toxicity
        - Myelosuppression is the main one
        - NV - can be severe
        - A potent vesicant (causes blistering)
            - Care should be taken during administration to avoid extravasation.

Non-Classical Agents

Procarbazine

- Orally active methylhydrazine derivative
- Clinically indication for combination treatment in Hodgkin's and Non-Hodgkin's lymphoma and

brain tumours

- MoA
  - Not precisely known
  - Inhibits DNA, RNA and protein biosynthesis
  - Prolongs interphase
  - Produces chromosome breaks
- Metabolism
  - By microsomal enzymes and produces azoprocarbazine and H2O2
  - One metabolite is a weak MAOI
    - Do not administer with other MAOI's, TCAS, sympathomimetics, CNS depressants, antidiabetic agents, antihistamines, alcohol and tyramine containing foods (strong/aged cheeses; cured/smoked meat or fish; beers on tap; soy products
- Risks
  - Increased risk of secondary cancers in the form of acute leukaemia's
  - Carcinogenic potential is thought to be higher than other alkylating agents.

Bendamustine

- Apart from usual MoA of alkylating agents it also
  - Inhibits mitotic checkpoints and induces mitotic catastrophe
- Cross resistance with other alkylating agents is only partial
- Indications
  - Chronic lymphocytic leukaemia
  - Activity also observed in:
    - Hodgkin's and Non-Hodgkin's lymphoma
    - Multiple myeloma
    - Breast cancer
- ADE
  - Dose related toxicities
    - Myelosuppression
    - Mild NV
    - Rarely, hypersensitivity infusion reactions.

Platinum Co-ordination Complexes

Tuesday, 20 June 2017 8:23 AM

- Include
  - Cisplatin (divalent platinum complex)
  - Carboplatin (divalent)
  - Oxaliplatin
- No cross-resistance between Oxaliplatin and others due to different chemical structure

MoA

- ? Similar to alkylating agents
- It binds to guanine in DNA and forms intra-strand and inter-strand DNA cross-links. This inhibits both polymerases for DNA replication and RNA synthesis
  - Instead of crosslinking DNA with alkyl groups, they cross link it with platinum
    - At N7 adjacent guanines on the same strands or complimentary strands
    - They can also cross link with another protein
- Also binds to nuclear and cytoplasmic proteins

MoR

- Reduced active uptake
- Efflux transporters
- Increased repair of DNA
- Loss of function in the MMR proteins
  - They recognise platinum-DNA interaction and initiate apoptosis

Cisplatin

Pharmacokinetics

- IV
- Inactivated by aluminium - avoid such needles
- Half-life
  - 24 hours
- >90% covalently PPB
- High concentrations in the kidney, liver, intestine and testes
- Poor penetration into the CNS
- Excreted by the kidney mainly
- It sensitises cells to radiation therapy

Adverse Effects

- Nephrotoxic (dose-limiting)
  - By various mechanisms
    - Tubular epithelial cell toxicity
    - Vasoconstriction in the renal microvasculature
    - Pro-inflammatory effects
  - Can cause acute tubular necrosis (ATN)
    - Shows muddy brown epithelial cell casts
  - Prevent by pre-treatment hydration with 1-2L of normal saline (chloride diuresis)
    - Must be used by all patients using Cisplatin
  - Amifostine is a cytoprotective agent that reduces renal toxicity
    - Organic thiophosphate
    - Binds to and detoxifies the active metabolites of Cisplatin

        - Scavenges the free radicals produced by Cisplatin in the kidneys
- Ototoxicity
    - Tinnitus and high-frequency hearing loss
- Marked NV (may last to 5 days)
    - Use anti-emetics
- Peripheral neuropathy
    - Includes a subset of:
        - Paraesthesias
        - Numbness
        - Pain
- Myelosuppression
- Electrolyte disturbances
    - Hypomagnesaemia, hypocalcaemia (tubular damage)
    - Hypokalaemia and hypophosphataemia
- Rare
    - Anaphylactic-like reactions (within minutes)
        - Facial oedema
        - Bronchoconstriction
        - Tachycardia
        - Hypotension
        - Treatment
            - IV epinephrine
            - Corticosteroids
            - Antihistamines
- Late AE
    - AML
    - Pulmonary fibrosis

Carboplatin

Pharmacokinetics

- IV
- Minimal metabolism
- Remains in its parent form
- Mostly unbound to proteins
- Half-life is 2 hours
- Small fraction irreversibly bound to plasma proteins
    - Half-life is 5 days
- Excreted via kidneys
    - Adjust dose in renal failure

Adverse Effects

- Like Cisplatin but much less
- Dose-limiting toxicity is myelosuppression
- More likely to cause a hypersensitivity reaction

Oxaliplatin

MoA

- In addition to DNA suppression, it also suppresses expression of thymidylate synthase
- This is the target enzyme of 5-fluorouracil
- This may promote synergy of the two drugs

Adverse Effects

- Like Cisplatin
- Peripheral neuropathy can be triggered by exposure to cold liquids
    - Paraesthesias of extremities, mouth and throat
    - Due to rapid release of oxalate which depletes calcium and magnesium
    - Replace the electrolytes

- The platinum-co-ordination complexes are
    - Mutagenic
    - Teratogenic
    - Carcinogenic (secondary AML)

Indications

- Cancers of the
    - Ovary, cervix, endometrium, testes
    - Head and neck
    - Bladder
    - Oesophagus
    - Lung
    - Colon

Anti-Metabolites

Monday, 12 June 2017 11:43 AM

- They are cell cycle specific
  - S-phase
- Act as enzyme antagonists or as false substitutes for naturally occurring NA bases
- Include:
  - Dihydrofolate reductase inhibitors
  - Pyrimidine analogs
  - Purine analogs
- Note:
  - Some antibiotics have antimetabolite activity compared with antibacterial actions. Others act as alkylating agents

Analogues of Folic Acid

- Include:
  - Methotrexate
  - Pemetrexed
  - Raltitrexed
  - Aminopterin

Methotrexate

- Folic Acid analogue
- Acts as an antimetabolite to folic acid
- Enters the cell by active transport which normally mediates the entry of N5-methyl FH4
- At high concentrations, it enters the cell by diffusion

MoA and Site of Action

- Kills cells in the S-phase of the cell cycle and is more effective when cells are in logarithmic phase of growth
- Competes with dihydrofolate (FH2) for binding with the enzyme, NADPH-dependent dihydrofolate reductase
- Affinity of up to 10,000 that of folic acid
  - Inhibition practically impossible even by administration of_
- DHFR catalyses the reduction of folate and dihydrofolate to tetrahydrofolate
- Intracellular formation of poly glutamate derivatives is important for the activity of Methotrexate, and this is mediated by the enzyme, folypolyglutamate synthase (FPGS)
- Methotrexate polyglutamates are selectively retained within the cancer cells and exert their inhibitory effect on DHFR
- Inhibition of formation of tetrahydrofolate, produces acute intracellular deficiency of folate co-enzyme, with subsequent interruption or cessation of formation of DNA, RNA and key cellular proteins and hence, cell death
- Inhibits synthesis of thymidine, catabolised by thymidylate synthetase (methylates a phosphorylated uridine (dUMP) to dTMP). This is powered by the folate cycle
- Uridine is methylated to turn into thymidine and needs a carbon, which is donated by a methyl-tetrahydrofolate, where it loses folate to become dihydrofolate.
- The folate needs to be recycled and the DHF converted back to THF. This process is catalysed by DHF reductase (it adds two hydrogens). It is then methylated and the cycle continues
- Methotrexate binds to DHF and prevents its conversion to THF therefore irreversibly

halting formation of thymidine. There is also a build-up of DHF since it is not being converted to THF , which also inhibits de novo synthesis of purines hence interruption or cessation of formation of DNA, RNA. Key cellular proteins and therefore, death.

- MTX acts on rapidly dividing cells because they are the ones rapidly producing the nucleotides. MTX is S-phase specific.

PK

- The routes if administration include
  - PO
  - IM
  - IV
  - Intrathecal
- Small doses of Methotrexate, i.e. <25ml/m^2 are readily adsorbed orally and large doses are given IV
- Methotrexate is administered intrathecally for meningeal leukaemia and meningeal carcinomatosis to destroy the neoplastic in the sanctuary sites
- Triphasic drug disappearance
  - Phase I
    - Rapid distribution phase
  - Phase II
    - Half-life of 2 hours and reflects renal clearance
  - Phase III
    - Half-life of 8 hours and is prolonged by renal failure
- The drug slowly distributes into body spaces e.g. pleural and peritoneal cavities
- Methotrexate is 35% PPB
- It can be displaced from the binding sites by Sulfonamides, Salicylates, Tetracycline, Chloramphenicol, Phenytoin etc.
- Metabolism in the liver
- The metabolites and parent drug are excreted by the kidney
- Excretion is by GFR and active tubular secretion and is affected by actively secreted drugs like weak organic acids like Aspirin and by drugs that reduce renal blood flow, e.g. the NSAIDS and by nephrotoxic drugs e.g. Cisplatin due to competition for the organic acid carrier
- Smaller dose is excreted in stool, probably through the biliary tract
- Important to note that high urine output must be maintained when giving high doses of Methotrexate,

Folinic Acid and/or Thymidine

- Leucovorin and/or folic acid is administered when high doses of Methotrexate is given, to rescue the normal tissues from drug toxicity (leucovorin rescue)
- Leucovorin bypasses the blocked enzyme and replenishes the folate pool
  - Does not require DHF reductase
- Displaces MTX from inracellular binding sites and restores active folate stores for DNA and RNA synthesis
- Leucovorin is a fully reduced folate co-enzyme
- Taken up readily by normal cells, than tumour cells
- Keep doses of Leucovorin minimal, to avoid interference of anti-tumour action of anti-metabolites

Resistance to Methotrexate

- Increased production of DHFR necessitating the use of a higher dose of Methotrexate, with subsequent toxicity
- Modified, DHFR with decreased affinity for Methotrexate

- Less drug pumped into the cell i.e. change in carrier mechanism in pumping Methotrexate into the cell
- There may be decreased ability to synthesis Methotrexate polyglutamate
- Decreased thymydilate synthase activity

Therapeutic Applications

- ALL
- Choriocarcinoma
- Burkitt's lymphoma in children
- Head and neck carcinomas
- Also used in non-neoplastic diseases
    - Rheumatoid arthritis
    - Severe psoriasis
- Can be used in conjunction with Misoprostol as an abortifacient (termination of intrauterine pregnancy)
    - Inhibits trophoblast cellular division thus decreasing trophoblast survival, hindering implantation and encouraging expulsion
- DOC for an early un-ruptured ectopic pregnancy
    - Folate antagonists are effective against growth of rapidly proliferating cells in developing embryos
- Useful for immunosuppressive therapy - inhibits proliferation of immune cells
    - SLE
    - Vasculitis
    - Dermatomyositis
- Note
    - High dose Methotrexate used in the treatment of osteogenic sarcoma should be followed by Leucovorin to rescue the bone marrow

AE

- Most frequent
    - Stomatitis
    - Myelosuppression
    - Pancytopenia
    - Erythema
    - Rash
    - Urticaria
    - Alopecia
    - NVD
    - And some of these can be prevented by Leucovorin administration
- Renal damage is a complication of high dose
- Long term use, may lead to hepatic fibrosis
    - Direct damage to the hepatocytes
    - Routinely monitor LFTs
- Pulmonary fibrosis - restrictive lung disease
- Neurological toxicities, associated with intrathecal administration includes sub-acute meningeal irritation, stiff neck, headache and seizures, encephalopathy or paraplegia may occur but are rare
- Long lasting effects e.g. hearing disabilities, have been noted in children who receive the drugs intrathecally
- Megaloblastic anaemia
    - Due to folate deficiency
    - Nucleic acid metabolism is impaired, leading to reduced efficiency in cell division and nuclear-cytoplasmic dysynchrony

Pemetrexed

- Pyrolopyrimidine antifolate analagoues
- Acts in the S phase of the cell cycle
- As with Methotrexate , it is transported into the cell via reduced folate carrier
- Activated by same enzyme to yield (FPGS) polyglutamate forms
- Targets DHFR and enzymes involved in purine nucleotide synthesis
- Main site of action is via inhibition of thymidylate synthase
- Note:
    - Targets key folate-dependant enzymes necessary for the synthesis of purine and thymidine nucleotides necessary for cell replication

Therapeutic Indications:

- According to Rx protocol e.g. for malignant mesothelioma, non-squamous, non-small cell lung cancer
- AE: Myelosuppression, skin rash, mucositis, diarrhoea and fatigue

Raltitrexed

- Directly inhibits thymidylate synthase
- Thus interfering with thymidylic acid formation and thus DNA synthesis
- Indications - Colorectal cancer
- AE - cf Pemetrexed

Aminopterin

- Folate antagonist
- Same MoA as methotrexate
- Formerly used for Rx of leukaemia in children
- Serious toxicity limited usage
- Obsolete drug

Natural Products

Tuesday, 13 June 2017 11:30 AM

- Include
  - Antimitotic drugs
    - Vinca alkaloids
    - Taxanes
  - Epipodophyllotoxins
  - Camptothecines
  - Anti-biotics
  - Enzymes
  - Biological response modifiers

MoR

- Amplification of mdr-1 gene
  - P-glycoprotein drug efflux transporter increased
- Mutation or decreased topoisomerase II
- Mutations of the p53 tumour suppressor gene
  - P53 prevents normal cells from transforming into malignant ones

Vinca Alkaloids

Tuesday, 20 June 2017 8:21 AM

- Include:
  - Vincristine (-CHO)
  - Vinblastine (-CH3)
  - Vindesine
  - Vinorelbine (semi-synthetic)
- Mitotic spindle poisons
- The mitotic spindle
  - Consists of a system of microtubules and is part of a large intracellular skeleton (cytoskeleton)
  - Essential for internal movements occurring in the cytoplasm of all eukaryotic cells and for equal partitioning of DNA in the two new cells formed when a eukaryotic cell divides
- The vinca alkaloids are structured
- Derived from the periwinkle plant, *Vinca rosea*

Site of Action

- Cycle and phase specific
  - Inhibit mitosis of cells in metaphase through interaction with tubulin (microtubular protein)
  - M-phase specific
- The binding to tubulin disrupts the spindle apparatus and cause termination of assembly of the cytoskeleton protein
- Binding also causes depolymerisation of the microtubules which in turn prevents chromosomal segregation and cell proliferation
- Vincristine
  - Works by binding to tubulin building blocks and preventing their polymerisation, thus inhibiting microtubule production and the assembly of the mitotic spindle
- Vinblastine
  - Binds beta tubulin and inhibits polymerisation, thus inhibiting microtubule production and the assembly of the mitotic spindle

Pharmacokinetics

- Administered IV
  - Rapid cytotoxic effects and cell destruction
  - Release and degradation of purines, resulting in production of uric acid and hyperuricaemia
    - Amelorated by administration of XO inhibitor, allopurinol
- Metabolised in the liver and excreted in bile and faeces
  - Adjust dose in impaired LF or biliary obstruction
- Unchanged drugs and metabolites appear in urine
- PK differ because of side chain substitution:
  - Terminal half-life of Vincristine
    - 2-3 hours (-CHO or rather, aldehyde)
  - Terminal half-life of Vinblastine
    - 20 hours (-CH3 or rather, methyl group)
- Vinca alcaloids are generally administered in combination with other drugs

Therapeutic Indications

- Vincristine used in the treatment of

    - ALL in children
    - Wilm's tumour
    - Ewing's soft tissue sarcoma
    - Hodgkin's disease
    - Other rapidly proliferating neoplasms
    - Note
        - Vincristine (Oncovin) is the MOPP in treatment of Hodgkin's disease
- Vinblastine is daministered together with Bleomycine and Cisplatin for the treatment of metastatic testicular sarcomas. Also used in the treatment of systemic Hodgkin's Disease and other lymphomas
- Vindesin has similar range of clinical activity and side effects intermediate between Vincristine and Vinblastine
- Vinorelbine, a semi-synthetic vinca alkaloid is indicated for the trratment og advanced non-small call cancer
- Resistance
    - Efflux of the drugs from the resistant cells

Adverse Effects

- Common toxicities
    - Phlebitis and cellulitis if the drug extravasates during injection
    - NVD
    - Alopecia
- Predominant dose-limiting toxicity for
    - Vinbalstine - myelosuppression
    - Vinorelbin - granulocytopenia
    - Vincristine - peripheral and autonomic neuropathy (paraesthesias, loss of reflexes, foot drop and ataxia). Vincristine may also cause SIADH

Taxanes

Tuesday, 20 June 2017 8:22 AM

- Include
  - Paclitaxel
  - Docetaxel
- Taxanes are diterpenes produced by the plants of the genus, Taxus (yews)
- First derived from natural sources but some have been synthesised artificially

Paclitaxel

- Derived from the several species of the yews but primarily comes from the pacific yew_

MoA

- Mitotic spindle poison through enhancement of tubulin polymerisation
  - Note
    - The microtubules must be at a constant state of polymerisation and depolymerisation to function properly
- Binds to beta-subunit of tubulin, producing unnaturally stable microtubules that prevent depolarisation and cause cell death ("mitotic arrest")
- Primary effect occurs in early G_2 and early mitosis
- Cell kill depends on the drug concentration and duration of exposure

Resistance

- Drug efflux from the cells
- Alteration in tubulin

Adverse Effects

- Peripheral neuropathy (microtubules are essential for axonal transport in neurons)
  - Tubulin binding drugs directly perturb microtubule formation in Schwann cells and the axons of sciatic nerve
- Neutropenia
- Stocking-glove sensory neuropathy
- Mucositis
- Hypersensitivity reactions
  - Pre-treatment with Dexamethasone and anti-histamine

Pharmacokinetics

- Limited solubility and must be administered in a vehicle of 50% ethanol and 50% polyethoxylated castor oil
  - Probably responsible for hypersensitivity
- IV infusion
- Extensive P450-mediated hepatic metabolism by CYP3A4 and CYP2C8
- Less than 10% excreted unchanged in urine
- Primary metabolism is 6-OH Paclitaxel; saturable clearance
- Disappearance from plasma with the following half-lives (tri-phasic disappearance)
  - 0.2 hours
  - 2 hours
  - 20 hours
- Inducers of CYP3A4 e.g. Phenytoin, Phenobarbital and inhibitors e.g. antifungal imidazoles may alter drug clearance and toxicity

Uses

- In combination therapy regimens of ovarian cancer and in adjuvant therapy of breast cancer
- Also shown to be effective in lung, head and neck, oesophageal and bladder carcinomas

Docetaxel

- An analogue of Paclitaxel
- Management of advanced breast cancers
- Side effects
    - BM suppression especially in patients with pre-existing hepatic impairment

Epipodophyllotoxins

Tuesday, 20 June 2017 8:22 AM

- Include
  - Etoposide
  - Teniposide

MoA

- They form a complex with topoisomerase II and DNA and prevent resealing of breaks in DNA
  - Topoisomerase II induces transient breaks in both DNA strands simultaneously, relieving positive and negative supercoiling
  - Etoposide and Teniposide prevent religation of the double stranded break induced by topoisomerase II
- There is accumulation of DNA breaks which leads to cell death
- The cells most sensitive are those in the S and G_2 phases

MoR

- Amplification of mdr-1 gene
  - P-glycoprotein drug efflux transporter increased
- Mutation of decreased topoisomerase II
- Mutations of the p53 tumour suppressor gene
  - p53 prevents normal cells from transforming into malignant ones

Etoposide

PK

- A semi-synthetic derivative of the plant alkaloid, podophyllotoxin
- IV, PO
  - Variable absorption
- Bioavailability- 50%
  - The PO dose to be twice that of an IV dose
- CSF concentration
  - 1-10% of plasma levels
- 40% excreted intact in the urine
  - Reduce dose in renal disease
- Caution in advanced liver disease due to potential toxicity
  - Low albumin
    - Decreased drug binding
  - Elevated bilirubin
    - It displaces Etoposide from albumin

Teniposide

- IV
- <1% crosses BBB
- 80% is metabolised
- Dose not adjusted in renal disease
- Phenytoin induces its metabolism

Adverse Affect of The Epipodophyllotoxins

- BM suppression (major toxicity)
- NVD and stomatitis
- Alopecia
- Hypotension
- Hepatic toxicity (high-doses)
- Acute non-Lymphocytic Leukaemia (Etoposide 1-3 years later)

Indications of The Epipodophyllotoxins

- ALL and ANLL
- Small cell carcinomas of the lung
- Testicular tumours
- Large cell lymphomas
- Hodgkin's disease
- Kaposi sarcoma
- Glioblastoma (Teniposide)
- Neuroblastoma (Teniposide)

Camptothecin Analogues

Tuesday, 20 June 2017 8:23 AM

- They are natural products derived from the Camptotheca acuminata tree originally found in China
- Include
  - Irinotecan
  - Topotecan

MoA

- Inhibit the function of Topoisomerase I
  - Makes single stranded nicks to relieve supercoiling
- DNA breaks eventually lead to cell death
- S-phase specific drugs
  - Ongoing DNA synthesis is necessary for cytotoxicity

MoR

- Decreased intracellular drug accumulation
  - Efflux transporters
- Lack of carboxylesterase
  - Converts Irinotecan to active metabolites
- Mutations of decreased topoisomerase I
- Inhibition of topoisomerase I upregulates topoisomerase II
  - An alternative repair of DNA strand breaks

Irinotecan

- A prodrug
- IV infusion
- Converted to SN-38 by carboxylesterases in the liver
- Half-life of SN-38
  - 11.5 hours
- SN-38 is metabolised in the liver
- Glucoronidation converts SN-38 to its inactive metabolites, leading to reduced toxicity
- Metabolism is induced by anticonvulsants
- Excreted through bile mainly
- <40% through urine
- Bacterial glucuronidase may convert the glucuronide metabolite to SN-38 ad cause GI toxicity
- AE
  - Myelosuppression and diarrhoea
    - Most common AE
  - Two forms of diarrhoea
    - An early form (acute)
      - Occurs within 24 hours, ? Cholinergic event
      - Effectively treated with Atropine
    - A late form (delayed)
      - Occurs 2-10 days after treatment
      - Can be severe
        - Electrolyte imbalance
        - Dehydration

        - Rehydrate the patient and give Loperamide

Topotecan

- PO and IV infusion
- Excreted in urine
- Dose reduced in moderate renal dysfunction (creatinine clearance of 20-40ml/min)
- Not used in severe renal impairment (Creatinine clearance <20ml/min

AE of both Drugs

- Neutropenia +/- thrombocytopenia
- NVD and mucositis
- Elevated liver transaminases
- Topotecan
    - Fever
    - fatigue
    - Rash
- Irinotecan
    - Skin flushing
    - Alopecia
    - Dyspnoea and interstitial pneumonitis
    - Cholinergic syndrome
        - Irinotecan inhibits acetylcholinesterase
        - May occur within the first 24 hours after administration
        - Treatment and prevention with Atropine
        - Symptoms
            - Acute diarrhoeas
            - Diaphoresis
            - Hyper-salivation
            - Abdominal cramps
            - Visual accommodation disturbances
            - Lacrimation
            - Rhinorrhoea
            - Bradycardia

Indications

- Topotecan
    - Ovarian CA
    - Cervical CA
    - Small cell lung CA
- Irinotecan
    - Colorectal CA

Fluoropyrimidines (Purine and Pyrimidine Anti-Metabolites)

Thursday, 15 June 2017 8:15 AM

5-Fluorouracil

- Prodrug
- Pyrimidine analogue
- Activated via enzymatic reactions to active metabolites
  - Example: 5-fluoro-2'-deoxyuridine-5'monophosphate (fdUMP)
- FdUMP forms a covalent complex with thymidylate synthase
  - Inhibits DNA synthesis

Additional MoA

- 5-FU is converted to 5-fluorouridine-5'triphosphate (FUTP)
- FUTP is then incorporated into RNA
  - Interferes with RNA processing and mRNA translation
- 5-FU is also converted to 5-fluorodeoxyuridine-5'triphosphate (FdUTP)
  - Incorporated into cellular DNA
    - Inhibits DNA synthesis

PK

- Given IV
- Half-life is 10-15 minutes
- 80-85% is catabolised by dihydropyrimidine dehydrogenase (DPD)
- 5% of patients have partial or complete DPD deficiency
- Results in severe toxicity
  - Myelosuppression
  - NVD
  - neurotoxicity

Clinical Uses

- Solid tumours
  - Colorectal cancer
  - Breast CA
  - Stomach, pancreas, oesophagus, liver CA
  - Head and neck CA
  - Anus CA

The

Adverse Effects

- Myelosuppression
- Mucositis
- Diarrhoea
- Skin toxicity (hand and foot syndrome)
  - Erythema
  - Peeling of the skin
- Neurotoxicity
- Cutaneous complications
  - Photosensitivity
  - Hyperpigmentation reactions

- Leucovorin administration does not help

Cabecitabine
- OIs a fluoropyrimidine carbamate prodrug
- 70-80% bioavailability
- Undergoes extensive metabolism in the liver

Metabolism
Cabacitabine →→→ 5-FU

Clinical Use
- Metastatic breast CA
- Mestatic colorectal CA

Adverse Effects
- Diarrhoea
- Hand and foot syndrome
- Less myelosuppression, NV and mucositis than that seen in IV 5-FU

Deoxycitidine Analogues
Cytarabine (ara-C)
- Is an S-phase-specific anti-metabolite
- A pyrimidine analogue
- Converted by deoxycytidine kinase to the 5'mononucleotide (ara-CMP)
- Ara-CMP is further metabolised to the diphosphate and triphosphate metabolites

MoA
- Ara-CTP competitively inhibits DNA polymerase-α and DNA polymerase-β → results in blockade in DNA synthesis and repair respectively
- Ara-CTP is also incorporated into DNA → interferes with chain elongation

PK
- Given IV
- Cleared rapidly, with most being deaminated to inactive forms
- Because of its rapid degradation, it must be given by continuous infusion over a 5-7 day period

Clinical Uses
- Only useful against haematological disorders
  - AML
  - Non-Hodgkin's Lymphoma (NHL)

Adverse Effects
- Myelosuppression
- Mucositis
- NV
- Neurotoxicity

Gemcitabine

- Is fluorine-substituted deoxycitidine analogue
  - A pyrimidine analogue
- Phosphorylated initially by deoxycytidine kinase to the monophosphate form then to the diphosphate and triphosphate nucleotide forms

MoA

- Gemcitabine diphosphate inhibits ribonucleotide reductase
  - Reduces deoxyribonucleoside triphosphates required for DNA synthesis
- Gemcitabine triphosphate inhibits DNA polymerase-α and DNA polymerase-β
- Gemcitabine triphosphate is incorporated into DNA, inhibiting DNA elongation

Clinical Uses

- Useful in both haematological disorders and solid tumours
- Advanced pancreatic CA
- Non-small cell lung CA
- Bladder CA
- Ovarian CA
- Soft tissue sarcoma
- NHL

Adverse Effects

- Neutropenia - dose limiting
- NV - 70% of patients
- Flu-like syndrome
- Rarely - Haemolytic uraemic Syndrome

Purine Antagonists

- Include
  - 6-thiopurines
    - 6-mercaptopurine (6-MP)
    - 6-thioguanine (6-TP)
  - Fludarabine
  - Cladribine

6-Mercaptopurine

- ***Azathioprine is the prodrug of 6-MP
- Prodrug
  - Activated by HGPRT (hypoxanthine-guanine phosphoribosyl transferase)
- Inhibits de-novo purine synthesis nucleotide synthesis
  - The active metabolites from 6-MP blocks the enzymes involved in synthesis of IMP from PRPP → decreased nucleotide synthesis (AMP and GMP) → blocked DNA or RNA synthesis
- Acts at the S phase of the cell cycle
- Uses
  - Used in childhood acute leukaemia
    - ALL as part of a combination chemotherapy regimen
  - Inhibit proliferation of immune cells - useful in immunosuppressive therapy
    - DMARD - not as effective as MTX and is reserved for refractory illness
      - Rheumatoid arthritis
    - Autoimmune haemolytic anaemia
    - Treatment of graft rejection

    - Inflammatory bowel disease - use is limited due to concerns of toxicity
        - Crohn's Disease
        - Ulcerative colitis
- AE
    - Myelosuppression
        - Leukopenia
        - Thrombocytopenia
        - Immunosuppression can lead to increased risk of infections to the body or reactivated disease
    - Pancreatitis
    - Hepatitis
    - Inhibition of XO (e.g. with Allopurinol, increases the level of purine analogues (e.g. 6-MP) and leads to increased side effects

DI

- 6-MP is converted to inactive metabolite (6-thiouric acid) by XO
- Allopurinol (XO inhibitor) is used during the treatment of acute leukaemias to prevent hyperuricaemia secondary to tumour cell lysis
- Simultaneous therapy using Allopurinol and 6-MP results in 6-MP toxicity
- Dose of Mercaptopurine must be reduced by 50-75% is used together with Allopurinol

Fludarabine

- Triphosphate metabolite inhibits DNA polymerase-α and DNA polymerase-β
- Is a potent immunosuppressant → increased risk of opportunistic diseases
- Patients must receive PCP prophylaxis with Cotrimoxazole for up to 1 year after stopping Fludarabine therapy

Cladribine

- A purine analog
- Resistant to adenosine deaminase that normally degrades purine analogues and adenosine
    - Cladribine can reach very high intracellular levels
- MoA
    - After being phosphorylated into a triphosphate form, it is incorporated into DNA causing breaks
    - Inhibit DNA synthesis in repair by inhibiting DNA polymerase α and β
    - Arrests the cells in the S-phase specifically
- Uses
    - DOC for hairy cell leukaemia
        - Can cause complete remission in these patients
    - CLL
    - NHL
- AE
    - Myelosuppression
        - Can caused a prolonged decrease in T-lymphocyte levels and therefore, an increased risk for infection

Cytotoxic Anti-biotics

Tuesday, 27 June 2017 12:28 PM

- Include:
  - Anthracycline Anti-biotics
    - Doxirubicin (Adriamycin)
    - Daunorubicin
  - Dactinomycin
  - Bleomycon
  - Plicamycin (Mithramycin)
  - Mitomycin
- Interact with DNA leading to disruption of DNA function
- May cause DNA strand breaks or bind to DNA to block unwinding of helix
- Are cell cycle non-specific except for Bleomycin but they have greater effect in cycling cells

Anthracycline Anti-biotics

- Include:
  - Doxorubicin (Adriamycin)
  - Daunorubicin
- Produced by the fungus of Streptomyces spp.
- Have tetracycline ring structure with unusual sugar, daunosamine attached by glycosidic ring
- Major dose limiting toxicity, is myelosuppression
- Can cause
  - Mucositis and stomatitis
  - Alopecia

Site of Action

- Three major activities, all of which are maximal at the S-phase
  - Intercalation into the DNA
    - Drug inserts between adjacent base pairs and binds to the sugar-phosphate backbone od DNA, thus affecting DNA and RNA
  - Binding of the drug to cell membranes alters the function of transport process coupled to phosphatidyl inositol inactivation
  - Doxorubicin interacts with molecular oxygen producing superoxide ions which cause single strand breaks of DNA
    - Iron reductive process
    - Due to this, it is cardiotoxic, due to build-up of free radicals in the myocardium
      - Dose dependent
      - Symptoms of heart failure may occur months to stopping the drug
      - Dexrazoxane (iron chelator) prevents anthracycline-induced cardiotoxicity

PK

- Administer IV
- PPB 75-80% and tissues
- Alpha T half-life is 10-15 minutes, beta T half-life is 25-30 minutes
- Widely distributed but do not penetrate into the CNS
- Metabolised into cytotoxic products
- Biliary excretion - dose adjustments in hepatic impairment

- Renal excretion occurs but need not adjust dose in renal impairment
- Impart red colour to urine

Therapeutic Indication

- Doxorubicin for ALL, breast and lung CA, Hodgkin's disease
- Daunorubicin for treatment of AML
- Resistance due to
    - Decreased cellular uptake
    - Increased efflux via the transport glycoprotein
    - Possible decreased CYP450 reductase and DNA repair

Dactinomycin (Actinomycin D)

- First anti-biotic used in cancer chemotherapy

Site/Mode of Action

- Intercalates into he small groove of the double helix and binds to deoxyguanilic acid moieties , forming a stable, Dactinomycin-DNA complex
- The complex interferes primarily with DNA-dependent RNA polymerase although at high doses, Dactinomycin interferes with synthesis
- May also cause strand breaks, (like Doxorubicin)

Uses

- In combination with surgery and Vincristine for treatment of Wilm's tumour
- With Methotrexate in the treatment of gestational choriocarcinoma
- Rhabdomyosarcoma

PK

- Administered IV
- Poor penetrance into the CNS
- Metabolised in the liver
    - Parent drug and metabolites eliminated via bile and urine

Resistance

- May be due to DNA repair and/or due to efflux of the antibiotic from the cell

ADR

- Bone marrow suppression is the major dose-limiting toxicity
- NVD, stomatitis
- Alopecia
- Sensitisation to radiation
    - Inflammation at sites of prior radiation therapy may occur
- Note:
    - Extravasation causes serious problems

Bleomycin

- Mixture of different copper chelating glycopeptides
- Is a small peptide that contains a DNA binding region on one end and iron binding region one another end
- Cause breaks in DNA (and chromosomal aberrations) by an oxidative process
    - After binding to DNA, it chelates metal ions, producing a pseudoenzyme that reacts

with oxygen to produce free radicals i.e. superoxide and hydroxide that cleave DNA
- Cell cycle specific and causes cell to accumulate in the G2 phase
- Resistance probably due to DNA repair

Therapeutic Applications
- In combination with Vinblastine in the treatment of testicular tumours
  - ~90% or more response rate if Cisplatin added to the regimen
- Treatment of head and neck and lung CA
- Hodgkin's Lymphoma and NHL
- Effective but not curative in squamous cell carcinomas and lymphomas

PK
- Administered IV, SC and IM and intracavity
- Biphasic plasma elimination with alpha T half-life of 24 minutes and beta T half-life of 2-4 hours
- Drug is localised in epithelial organs such as skin, lung, peritoneum and lymphatic tissue
- Most of Bleomycin is excreted unchanged in urine
  - Adjust dose in renal impairment

ADR
- Dose-limiting toxicity is the development of an interstitial pulmonary fibrosis (pulmonary toxicity progresses from rales, cough and infiltrates to potentially fatal fibrosis)
- Anaphylactic reactions and high incidence of fever, chills and rigor
- Mucocutaneous reactions and alopecia are common
  - Mucositis
  - Stomatitis
- Skin toxicity
  - Hypertrophic skin changes (atrophic striae) and hyperpigmentation of the hands are prevalent
  - Rash
  - Exfoliation

Plicamycin (Mithramycin; Mithracin)
- Exerts its cytotoxicity through restriction of DNA function
- Has relative toxic specificity for osteoclasts, inhibiting bone resorption and lowers plasma calcium concentration in hypercalcaemic patients, especially those with bone tumours
- Used for treatment of hypercalcaemia
  - Acts within 24-48 hours
- Toxicity includes
  - Haemorrhage
  - Effects on bone marrow, liver and kidneys

Mitomycin
MoA
- Cell cycle non-specific
- Reduced to an active metabolite that cross links DNA, inhibiting its synthesis
- At high concentrations, RNA and protein synthesis may also be inhibited
- Employed in the treatment of a variety of solid tumours e.g. Anal and bladder CA
- Effectiveness limited by myelosuppression
- Potentiates the cardiotoxic effects of Doxorubicin (Adreamycin)

Hormonal Agents in Cancer

Thursday, 15 June 2017 9:27 AM

Glucocorticoids

MoA

- Bind to glucocorticoid receptor and suppress mitosis in lymphocytes
- Induce a program of gene expression leading to apoptosis e.g.
    - Prednisone
        - Acute and chronic leukaemia
        - Malignant lymphoma
        - Multiple myeloma
    - Dexamethasone
        - Reduces oedema in tumours in critical areas e.g.
            - Superior mediastinum
            - Brain
        - Dramatic but transient effects
        - Taper the dose
        - Abruptly stopped treatment causes recurrence of symptoms

Progestins

- Include
    - Medroxyprogesterone - IM, Depo - provera
    - Megestrel acetate - PO
    - Hydroxyprogesterone - IM
- Used in: breast CA
    - E.g. Tamoxifen and aromatase inhibitors preferred.
- Endometrial CA.
- Prostate CA.

Breast Cancer

- Aromatase Inhibitors
- Anti-oestrogens

Aromatase inhibitors

- Inhibits aromatase which converts androgens to oestrogens
- Includes
    - Aminoglutethimide (no longer used)
        - First generation
    - Androstenedione analogs (steroid agents)
        - Type 1 inhibitors
        - Irreversible binding reactive metabolites
        - Include
            - Formestane (IM) - second generation
            - Exemestane (PO) - third generation
    - Imidazoles (non-steroidal agents)
        - Type 2 inhibitors
        - Reversible binding
        - Include:
            - Anastrozole (PO) - third generation
            - Vorozole (PO)
            - Letrozole (PO) third generation
- Imidazole agents are preferred
    - PO

    - Rapid onset of action
    - More effective in lowering oestrogen levels
    - No need to adjust doses in renal dysfunction
    - Less toxic
    - No androgenic side effects (e.g. acne)

Aminoglutethimide (A)
MoA
- Inhibits conversion of cholesterol to pregnenolone
    - This is the first step in the synthesis of cortisol, aldosterone, dihydrotestosterone, estradiol
    - There may be subsequent adrenal insufficiency or increased ACTH that leads to excess cortisol production
    - Therefore, use together with Hydrocortisone
- It also inhibits the conversion of androstenedione to estrone (aromatase)
- Not used due to non-selective activity and adverse effects

Formestane
- IM, slow absorption
- Half-life - 5-10 days
- AE
    - Acne
    - Hair changes
    - Vaginal spotting
    - Hot flushes
    - Emotional lability
    - Nausea

Exemestane
- Given PO
- Similar toxicity to Formestane
- Adjust dose in renal dysfunction as metabolites are active and are excreted in urine

Anastrozole and Letrozole
- They have no inhibitory effect on glucocorticoid and mineralocorticoid synthesis
- Use
    - Metastatic breast cancer

Anti-Oestrogens
- Selective oestrogen receptor modulators (SERM)
    - Include
        - Tamoxifen
        - Tamoxifen agents
            - Toremefene
            - Droloxifene
            - Idoxifene
- Selective Oestrogen Receptor Down-regulators (SERD)
    - Includes
        - Fulvestrant
- Fixed Ring Compounds
    - Includes
        - Raloxifene
        - Lasofoxifene
        - Miproxifene
        - Levormeloxifene

Tamoxifen
MoA
- It is a competitive oestrogen receptor (ER) antagonist
- Also a partial agonist of the ER
- It reduces IGF-1 which promotes growth of breast cancer cells

PK
- PO
- Rapid and complete absorption
- Half-life is 7 days
- Metabolites are also active and have longer half-life - 14 days
- Excreted in faeces (mainly) and urine

Use
- Treatment and prevention of breast cancers

AE
- Most frequent
  - NV
  - Hot flushes
  - Hair loss
- Others
  - Menstrual irregularity
  - Vaginal discharge
  - Pruritus vaginalis
  - Dermatitis
- May cause endometrial cancer
  - Pelvic examinations annually
- Thromboembolic events
  - _

Fulvestrant
MoA
- Binds to the ER with an affinity > 100 times that Tamoxifen
- Inhibits binding of oestrogen
- Alters the receptor structure, thus promoting degradation
- Downregulation of ER
- Devoid of any oestrogen activity

PK
- IM monthly
- Peak levels ~7 days and maintained over 1 month
- Half-life is ~40 days
- Steady state concentration after 3 - 6 monthly injections
  - Use loading dose
- Metabolised by CYP3A4
- No known interactions so far

AE
- Common
  - Nausea
  - Asthenia
  - Hot flushes

        - Headache
        - Injection site reactions
            - Reduced by giving the injection slowly

Anti-Androgens (AA)
Classification
- Steroidal AA (synthetic progesterones)
    - Cyprosterone acetate
    - Megestrol acetate
- Non-steroidal AA
    - Flutamide
    - Nilutamide
    - Biclutamide

Steroidal AA
MoA
- Androgen receptor
    - Competitive antagonist
    - Weak partial agonists
- Progesterone agonist properties
    - Act like progesterone at the pituitary
        - Reduce LH secretion
        - Therefore reduce LH-stimulated testosterone

Non-Steroidal
MoA
- They inhibit the translocation of the androgen receptor from the cytoplasm to the nucleus

Flutamide
PK
- PO
- Rapid and complete absorption
- Both parent drug and metabolite are active

AE
- VD
- Reversible liver abnormalities
- Decreased libido
- Hot flushes
- Gynaecomastia
- Mastodynia (breast pain)

Nilutamide
- Diminished visual adaptation to darkness
- Allergic pneumonitis

Bicalutamide
- Most common AE
    - Gynaecomastia
    - Nipple tenderness

Use
- Anti-androgens are used in the treatment of prostate CA

Gonadotrophin-Releasing Hormone (GnRH) Analogues

- Examples
  - Leuprolide
  - Goserelin
  - Triptorelin
  - Buserelin
  - Gonadorelin
  - Deslorelin
  - Histrelin
  - Naferelin
- Routes
  - IM and SC
- They have biphasic effects on the pituitary
- Initially, they stimulate the secretion of FSH and LH
- Chronic administration results in reduced FSH and LH
- Testosterone and oestrogen concentrations are markedly reduced

AE

- Transient flare of cancer due to initial stimulation of the pituitary
  - Prevent this by giving Flutamide or Biclutamide
- Others due to reduced gonadotrophins
  - Hot flushes
  - Impotence
  - Gynaecomastia
  - Sweating
  - N fatigue
  - Reduced bone and mineral mass

Indications

- Prostate CA
- Breast CA
- Endometriosis
- Precocious puberty
- Uterine leiomyomas

GnRH antagonists

- Include
  - Degarelic
  - Cetrorelix
  - Ganirelix
- They do not cause the initial flare seen when GnRH analogs are used
- They suppress testoserone levels
- Degarelix
  - Prostate CA

Biological Response Modifiers

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- These include
  - Aromatase inhibitors:
    - Aminoglutithimide
    - Anastrazole
    - Exemestane
  - Tyrosine kinase inhibitors
    - Imatinib
    - Dasatinib
  - Growth factor receptor inhibitors
    - Cetuximab
    - Gefitinib
    - Erlotinib
    - Bevacizumab
  - Oestrogen receptor inhibitors
    - Tamoxifen

Tyrosine Kinase Inhibitors
Imatinib and Dasatinib

- Inhibit oncoprotein formation

PK

- Given PO
  - 400-600mg/d

Use

- CML
  - Blast crisis first line
- Second line in chronic phase
- Dasatinib used as above in CML and AIC (ALL???)

AE

- Imatinib
  - Fluid retention with ankle and periorbital oedema and diarrhoea
  - Myalgia

Cetuximab

- A chimeric monoclonal antibody, inhibits EGRF
- Combined with Irinotecan and Oxaliplatin in advanced Colon CA
- Used with radiation in advanced neck and head tumour
- Dose
  - 400g/m^2 loading dose, then 250mg/m^2 IV weekly
- Major AE
  - Skin rashes
  - Interstitial lung disease
  - Infusion reaction

Gefitinib amd Erlotinib

- Inhibit tyrosine kinase domain related to EGFR
- Gefitinib 250 mg/d PO, Erlotinib 150mg/d PO

- For small cell cancer resistant to other treatment
- Erlotinib combined with gemcitabine in advanced pancreatic CA
- AE
    - Hypertension
    - Diarrhoea
    - Skin rash

Bevacizumab

- Vasculo-endothelial growth factor inhibitor (VEGF)
- A recombinant humanised monoclonal antibody
- May be combined with 5-FU, Irinotecan, Oxaliplatin for advanced colon CA
- Dose
    - 5mg/kg IV evert 2 weeks
- AE
    - Arterial thromboembolic disease
    - GIT perforation
    - Wound healing complications
    - Hypertension
    - Infusion reactions

Miscellaneous Agents

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Asparaginase

- Enzyme that hydrolyses circulating L-asparagine to aspartic acid and ammonia
- Tumour cells in ALL lack asparagine synthetase, that require an exogenous source of L-asparagine
- Depletion of L-asparagine results in effective inhibition of protein synthesis

Epidermal Growth Factor Receptor (EGFR) Inhibitors

- EGR is overexpressed in some solid tumours
- Involved in cellular growth and proliferation, metastasis and angiogenesis
- Inhibitors include:
  - Cetuximab
  - Panitumumab

Imatinib

- Inhibits the tyrosine kinase domain of the Bcr-Abl oncoprotein which leads to CML (chronic myelogenous leukaemia)
- AE
  - NVD
  - Oedema
  - Myalgia
  - CCF

Hydroxyurea

- UDP is the precursor for pyrimidine nucleosides
- Ribonucleotide reductase converts UDP into deoxy-UDP
- Once deoxy-UDP is dephosphorylated, it becomes dUMP
- Disrupts DNA replication by selectively inhibiting ribonucleoside diphosphate reductase
- S-phase specific
- Indications
  - CML
  - Sickle cell anaemia
    - Increases the level of HbF
    - Reduce the incidence of veno-occlusion
- AE
  - Myelosuppression
  - pancytopenia

Trastuzumab

- Monoclonal antibody useful in management of HER2 receptor positive breast CA
- HER2 gene expression is amplified in come breast CA
  - Accelerated tumour growth
- AE
  - Flu-like symptoms
  - CCF
  - Teratogenicity

Bortezomib

- A boronic acid, proteosome inhibitor

MoA

- Targets proteins in cancer cells and stops the cancer cells from growing
- Reversibly inhibits 26S proteasome impairing cell growth leading to apoptosis

Indications

- Treatment of multiple myeloma and mantle-cell lymphoma

ADR

- NVD
- Constipation
- Abdominal pain
- Anorexia
- Dizziness
- Peripheral neuropathy
- Headache
- Musculoskeletal pain
- Thrombocytopenia

Emergency Management of Poisoning

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Goals of Treatment

- Maintain the vital functions
- Reduce the concentration of poison
  - Prevent further absorption
  - Enhance elimination
- Combat the pharmacological and toxicological effects at the effector sites
- Supportive therapy is the priority
  - Treat the patient, not the poison
  - Admit the patient
  - Maintain respiration and circulation
    - ABCDE

ABCDE	Initial Treatment Approach for Acute Poisoning
Airway	Maintain patency
Breathing	Maintain adequate oxygenation and ventilation
Circulation	Maintain perfusion of vital organs
Disability	Assess for CNS dysfunction If neurological disability is noted, consider • Oxygen administration (check pulse oximetry) • Dextrose administration (check blood glucose concentration) • Naloxone administration (consider empiric trial) • Thiamine (for adult patients receiving dextrose)
Exposure	Assess "toxidrome"

- ABC: Consider if there is need for
  - Endotracheal intubation
  - Mechanical ventilation
  - BP support using drugs
- Toxidrome
  - Groups of signs and symptoms associated with specific syndromes
  - Common toxidromes
    -

Drug class	Mental status	HR	BP	RR	T	Pupil size	Other
Sympathomimetis	Agitation	↑	↑		↑	↑	• Tremour • diaphoresis
Anti-cholinergic	Delirium	↑	↑		↑	↑	• Ileus • Flushing
Cholineregic	Somnolence/coma		↑	↓			• SLUDGE[a] • Fasciculation
Opioid	Somnolence/coma	↓		↓		↓	
Sedative-hypnotic	Somnolence/coma		↓	↓			
Salicylates	Confusion	↑		↑	↑		• Diaphoresis • Vomiting
Calcium channel blocker		↓	↓				

      - SLUDGE
        - Salivation
        - Lacrimation

            - Urination
            - Defaecation
            - Gastric cramping
            - Emesis
- Poisoning may be by:
    - Inhalation
    - Dermal or mucosal absorption
    - Injection
    - Ingestion

Prevent Further Absorption

- Remove patient from site of inhalation exposure
- Wash eyes (irrigate with water for 15 minutes) and skin (soap and water)
    - Skin and mucosal exposure
    - Contaminated clothes (removal and double bag)
- Gastric emptying (now rarely recommended)
    - Emesis
    - Gastric lavage
- Chemical adsorption
- Chemical inactivation (rarely used)
- Purgation/cartharsis
- Enhance elimination
    - Urine elimination
    - Dialysis

Emesis

- After poisoning by oral ingestion
- Induce mechanically
    - Stroke the posterior pharynx
- Induce with emetic drugs
    - Ipecac
- Not recommended
    - Apomorphine
    - Copper sulfate
    - Salt water

Ipecac

- Contains cephaeline and emetine which act as emetics
- MoA
    - Local irritant effect on the GIT
    - Stimulates the CTZ in the medulla
- PK
    - PO
    - Takes 15-30 minutes to produce emesis
    - Emesis may fail to occur if the stomach is empty
        - Drink water after Ipecac
    - If emesis does not occur
        - Remove Ipecac by gastric lavage
    - Not administered routinely
        - Has variable effects
        - May reduce the efficacy of more effective treatment
            - Activate charcoal
            - Oral antidotes
            - Whole-bowel irrigation
- Indications
    - Conscious, alert patients
    - Within 60 minutes of poisoning
- May be effective for anti-emetic drug poisoning

- Toxic effects in the heart
  - Chronic abuse for weight loss
  - Cardiomyopathy
  - Ventricular fibrillation
- Electrolyte imbalance

Contraindications of Emesis

- Ingestion of corrosive poison
  - Strong alkali or acid
  - Risk of gastric perforation
- Coma, stupor or delirium
  - May cause aspiration of gastric contents
- Ingestion of a CNS stimulant
  - Further stimulation associated with vomiting may cause convulsions
- Ingestion of a petroleum distillate
  - E.g.
    - Kerosene
    - Petroleum-based liquid furniture polish
  - Aspiration causes chemical pneumonitis

Gastric Lavage

- Use a tube and a large syringe
  - Orogastric tube is preferred over NG tube
    - A larger tube can be used
  - Large tube allows free flow of food and poison
- Use an endotrachial tube with an inflatable cuff
  - To prevent aspiration if:
    - Comatose
    - Seizures
    - Loss of gag reflex
- Patient should lie on their left side (stomach position)
- The head should face the edge of the examining table
- Elevate the foot of the table
  - Reduces the chance of aspiration
- First take a sample for chemical analysis
- Use small volumes of fluid (10-15ml/kg for child, 250ml for adults) of normal saline per wash
  - Less risk of poison being pushed into the intestine
- Lavage is repeated until the effluent is clear
- Fluid should be at body temperature to prevent hypothermia
- Indications
  - Within 60 minutes of ingestion
- Contraindications
  - C.f. Emesis
- Complications
  - Trauma to throat and GIT
  - Aspiration
  - Vagus nerve stimulation

Chemical Adsorption

- Adsorption of poison
  - Is the binding of a poison to the surface of another substance
  - Poison may be less available for adsorption
- Activated charcoal (AC)
  - Is more effective at reducing drug absorption than emesis or gastric lavage
  - Used commonly
  - Avidly adsorbs poisons
  - Multiple doses of AC is used to promote elimination of adsorbed drug
  - Can interrupt the EHC of drugs

        - E.g. Theophylline and Phenobarbital
    - 10gof AC binds ~1 g of the drug
    - Adsorption diminishes over time
    - Not all chemicals are well absorbed by AC
        - Alcohol
        - Hydrocarbons
        - Metals (Fe, K)
        - Corrosives
        - Cyanide
    - Contraindications of AC
        - An unprotected airway
        - Presence of intestinal obstruction or reduced peristalsis
        - If the GIT is not intact
    - Complications
        - Vomiting and constipation
        - Pulmonary aspiration
    - AC is mixed in a glass of water
        - PO or via a gastric tube
        - Up to 1 hour after poison ingestion
    - AC should not be used simultaneously with Ipecac and Antidotes
        - It can adsorb them and reduce the drug's effect

Chemical Inactivation

- Rarely used
    - Valuable time may be lost
    - Emetics, AC and gastric lavage act rapidly
- Examples
    - Sodium bicarbonate converts ferrous iron to ferrous carbonate, which is poorly absorbed

Purgation

- Whole bowel irrigation
    - It promotes defaecation
    - Use polyethylene glycol-electrolyte solution
        - Via NG tube until rectal effluent is clear
- Indications
    - Enteric coated drugs
    - Packets of illicit drugs
    - Iron overdose
    - Ingested patch formulations
- Contraindications
    - Presence of bowel obstruction or perforations
- Complications
    - Abdominal distension
    - Pulmonary aspiration
- Osmotic cathartic (laxative) are not used
- Sorbitol
    - May be used to prevent constipation by AC

Urinary Excretion

- Forced diuresis (fluids and diuretics)
- May cause volume overload and electrolyte abnormalities
- Not recommended
- Urine alkalinisation
    - Urine alkalinisation increases urine elimination of acidic drugs
        - Chlorpromazine
        - Methotrexate

        - Phenobarbital
        - Salicylates
    - IV Sodium bicarbonate is used to alkalinise the urine
    - Urine alkalinisation is contraindicated
        - Compromised renal function or RF
        - CCF or pulmonary oedema
    - Hypokalaemia is the most common complication
        - Potassium supplements
    - Acetazolamide is not used to alkalinise urine as it promotes acidemia
- Urine acidification
    - Use ammonium chloride or ascorbic acid
    - Enhances the excretion of basic drugs e.g. amphetamine
    - Not recommended
        - May worsen renal complications from rhabdomyolysis (Amphetamine)

Extracorporeal Drug Removal

- Haemodialysis is more effective than peritoneal dialysis
    - PD is inefficient in removing most drugs
- Haemodialysis
    - Ideal drug properties
        - Low molecular weight
        - Low volume of distribution
        - High water solubility
        - Low protein binding
    - Effectiveness reduced by
        - Large volume of distribution
            - TCAs
        - Extensive PPB
- Haemoperfusion
    - Passage of blood through a column of charcoal or adsorbent resin
    - Has high adsorptive capacity
    - Some chemicals that are bound to plasma proteins can be removed
    - Main AE
        - Depletion of platelets

Chemical Inactivation of an Absorbed Poison

- If the poison acts as an agonist at a receptor
    - May use a receptor antagonist if available
    - Opioid receptor antagonists
- Functional antagonism
    - Anti-convulsant drugs to treat induced convulsions
- Opposing a poison's effects pharmacologically is not always promoted
    - CNS stimulants to reverse respiratory depression
        - Convulsions are a typical complication
        - Mechanical support of respiration is preferred

Organophosphorus Pesticides

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- Includes:
  - Azinphos-methyl
  - Diazinon
  - Dimethoate
  - Malathion
  - Parathion-methyl
  - Chlofenvinphos
  - Dichlorvos
  - Fenitrothion
  - Parathion
  - Trichlorfon
- Absorbed by skin, respiratory, GIT
- Rapid biotransformation

Acute Intoxication
Clinical

- Inhibit acetylcholinesterase
- Direct extension of pharmacologic actions
- Dominant initial signs are muscarinic excess
  - Miosis
  - Sweating
  - VD
  - Salivation
  - Bronchial constriction
- Followed by CNS involvement
  - Cognitive disturbance
  - Convulsions
  - Coma
- Followed by peripheral nicotinic effects
  - Depolarising neuromuscular blockade

Therapy

- Maintenance of vital signs
- Decontamination (prevent further absorption)
- High dose parenteral Atropine (control muscarinic excess)
- Cholinesterase regenerator compound (prevent ageing)
  - Pralidoxime
- Benzodiazepine (seizure control)

Cholinesterase Regenerator Compound

- Composed of substituted oximes
- Regenerate active enzyme from organophosphorus-cholinesterase complex
  - Pralidoxime (PAM)
  - Diacetylmonoxime (DAM)
  - Obidoxime
- High affinity for phosphorus atom

Pralidoxime
- Most effect in regenerating NMJ cholinesterase
- Ineffective in CNS effects
- Quaternary ammonium compound
- Given IV infusion
- Excess doses can induce neuromuscular weakness

Obidoxime
- Ineffective in central effects
- Quaternary ammonium compound

Diacetylmonoxime
- Crosses BBB
- Regenerate CNS cholinesterase

Chronic Toxicity
- Inhibition of neuropathy target esterases (NTE)
- Delayed neuropathy with axonal demyelination
    - Limb weakness
    - Unsteady gait
- 1-2 weeks after exposure
    - Lipophilic therefore in fat

Intermediate Syndrome
- 1-4 days after exposure
- Muscle weakness
- Cholinesterase inhibition

Amphetamine Poisoning
Introduction
- Stimulant drugs commonly abused:
    - Methamphetamine
    - methylenedioxymethmphetamine
    - Cocaine
    - Pseudoephedrine
    - Ephedrine
    - 3,4-methylenedioxypyrovalerone
    - Methcathinone

Clinical Effect
- Normal dose
    - Euphoria, wakefulness
    - Sense of power, well-being
- Higher dose
    - Restlessness, agitation
    - Hypertension, tachycardia
    - Prolonged muscular hyperactivity
    - Seizures (hyperthermia, rhabdomyolysis)
- Hyperthermia
    - Brain damage
    - Hypotension
    - Coagulopathy
    - Renal failure

Treatment

- General supportive measures
- No specific antidote
- Seizures - IV benzodiazepine
- Hyperthermia
    - Removing clothing
    - Spraying with tepid water
    - Fanning
    - Neuromuscular paralysis (abolish muscle activity)

Kerosene and Other Hydrocarbons

Exposure

- Accidental ingestion, inhalation
    - Improper storage
    - Mislabelled containers
- Intentional recreational abuse
- Oral ingestion
- Dermal exposure

Pathophysiology

- Hydrocarbons
    - Low viscosity (resistance to flow)
    - High volatility (ability to vaporise)
- More likely to be inhaled, aspirated into respiratory system

Pulmonary Effects

- Penetrate into tracheobronchial tree
- Displace alveolar oxygen - hypoxia
- Haemorrhage
- Oedema
- Surfactant inactivation
- Vascular thrombosis
- Complications
    - Atelectasis
    - Pneumonitis
    - Bronchospasm
    - ARDS
- High mortality rate in children

Other Effects

- GIT
    - Local irritation
        - Abdominal pain
        - NV
- Cardiac
    - Arrhythmias
    - Coronary vasospasm
    - Myocardial damage
- CNS
    - Narcotic like depression
    - Headache
    - Coma
- BM toxicity

- Hepatic, renal failure
- Local skin irritation
    - Contact dermatitis

Clinical Presentation
- Coughing
- Choking
- Vomiting
- Cyanosis
- Smell on child's skin, clothes or toys
- Fever
- Tachypnoea, wheeze
- Seizure
- Arrhythmia
- NVP
- Loss of consciousness
- Skin burns

Investigations
- FBC, LFT, ECG
- ABG or pulse oximetry (hypoxemia)
- CXR
    - Initially normal
    - Repeat after few hours
        - Perihilar opacities
        - Bibasilar infiltrates
        - Atelectasis

Management
- Admit
    - Breathing difficulties
        - Mechanical ventilation
        - Oxygenation
- Gastric lavage and emesis is contraindicated
    - Increased risk of chemical pneumonitis
- Activated charcoal not useful
    - Poorly adsorbs hydrocarbon
- No specific antidotes

Carbon Monoxide Poisoning

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Carbon Monoxide
- Colourless
- Tasteless
- Non-irritating
- Odourless
- Produced from incompletely burnt carbon e.g.
    - Inadequate venting of furnaces and automobiles

MoA
- Binds to the oxygen binding sites of haemoglobin
    - Its affinity is 220X that of oxygen
    - CO + Haemoglobin = Carboxyhaemoglobin
- Binds to cellular cytochromes in respiratory enzymes and myoglobin
- Carboxyhaemoglobin
    - Cannot transport oxygen
    - Interferes with the dissociation of oxygen from the remaining oxyhaemoglobin
    - Therefore, transfer of oxygen to tissues
- Carboxyhaemoglobin levels and effects
    - <15% - rarely produce symptoms
    - 40% - syncope
    - >60% - death

Effects
- Hypoxia produces the following sequential effects
- Psychomotor impairment
- Headache ant tightness in the temporal area
- Confusion, loss of visual acuity
- Tachycardia, tachypnoea, syncope and coma
- Deep coma, convulsion, shock, respiratory failure and death
- Prolonged hypoxia
    - Irreversible damage of the brain and myocardium
- Delayed neuropsychiatric symptoms may occur and recovery can be slow

Management
- Remove patient from the site of exposure
- Maintain respiration
    - CO is excreted through the lungs
- Give oxygen
    - It is the CO antagonist
    - Half-life of CO
        - 320 minutes in room air
    - Half-life of CO
        - 80 minutes with 100% oxygen
    - Half-life of CO
        - 20 minutes with hyperbaric oxygen
- Response to oxygen is evident when neurological function is restored
- Supportive care
    - Correct hypotension
    - Correct lactic acidosis

Cyanide Poisoning

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- Cyanide and hydrogen cyanide used in:
  - Photography
  - Metal cleaning
  - Ore refining
  - Rodenticides
  - Previously - executions
  - Suicide, homicide (abuse)
- Hydrogen cyanide is formed from burning
  - Plastics
  - Wool
- Cyanide is also released after ingestion of
  - Plants (e.g. cassava)
  - Seeds (e.g. apple, peach, apricot)
- It inhibits mitochondrial cytochrome oxidase thereby blocking electron transport and preventing oxygen utilisation and oxidative metabolism
- Lactic acidosis due to anaerobic metabolism
- Cyanide is rapidly absorbed from the stomach, lung, mucosal surfaces and unbroken skin
- Reacts with gastric acid to form hydrocyanic acid which is then absorbed
- 60% protein bound
- Concentrated in RBCs
- Mitochondrial rhodanase converts the cyanide ion to the less toxic thiocyanate which is excreted in urine
- Maifestations
  - Headache
  - NV
  - Syncope
  - Seizures
  - Coma
- Treatment
  - Supportive treatment
  - GIT decontamination follows specific treatment as the patient may die within minutes of exposure
  - Administer activated charcoal
    - Poor binding to cyanide but can reduce absorption
  - High dose of oxygen
    - Oxygen reverses the binding of cyanide to cytochrome oxidase sites and enhances the efficacy of sodium thiosulfate and nitrite
    - Also a substitute for metabolism
  - Administer sodium nitrate (IV) or amyl nitrite (inhalation)
    - The nitrite reacts with haemoglobin to produce methaemoglobin
    - Methaemoglobin has very high affinity for the CN-
    - This leads to regeneration of active cytochrome oxidase
    - There is production of cyanmethaemoglobin
    - Use of IV sodium thiosulfate produces the thiocyanate ion (SCN-) which is less toxic and is readily excreted in urine
    - If methaemoglobinaemia is excessive
      - Give IV methylene blue (it hastens recovery back to normal haemoglobin)
  - Other antidotes (all bind cyanide)
    - Hydroxycobalmin (Vitamin B12 precursor)
      - Forms cyanocobalamine

- Dimethylaminophenol
- Cobalt compounds

Acid and Alkali Poisoning

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- Common alkaline products
  - Sodium hypoclorite
  - Sodium hydroxide
  - Phosphates
  - Carbonates
  - Borates
  - Ammonia
- These are found in:
  - Bleach
  - Drain and surface cleaners
  - Detergents
  - Disk batteries
  - Denture cleaners
  - Clinitest tablets
- Common acid products
  - Hydrofluoric acid
  - Hydrochloric acid
  - Sulfuric acid
  - Phosphoric acid
  - Nitric acids
- Acid products are found in:
  - Toilet bowl cleaners
  - Antirust compounds
  - Battery fluid

Other Corrosives

- Include:
  - Hydrogen peroxide
  - Hydrazine
  - Phenol
- Cause burns in the GIT
- Cause necrosis and a high risk of perforation (alkalis > acids)
- Cause
  - Salivation
  - Dysphonia
  - Dysphagia
  - Vomiting
  - Epigastric pain
  - Erythema
  - Oedema
  - Ulceration
  - Necrosis
- Investigation
  - Endoscopy 12-24 hours after ingestion
  - Chest and abdominal x-ray (aspiration pneumonia, perforation)
  - Barium swallow
- Treatment
  - Burns on the skin are treated with copious amounts of water

- If ingested, dilute with water or milk
  - Neutralisation of acids with antacids or alkalis with acids (vinegar, orange or lemon juice) - controversial
    - The reaction may produce excessive heat
  - Bicarbonates used to treat acid poisoning produce CO_2 which may cause gastric distention or even perforation
- Avoid
  - Emesis and gastric lavage
    - Contraindicated as the risk for perforation increases
  - Activates charcoal (little adsorption)
  - Cathartics
    - GIT may be injured
- Glucocorticoids and oesophageal stents may prevent oesophageal strictures
- Broad spectrum anti-biotics
- Surgery for perforation

Opioid Poisoning

Thursday, 22 June 2017 1:20 PM

- May result from
  - Clinical overdose
  - Accidental over-dosage in addicts
  - Suicide attempts

Clinical Presentation

- Stupor or coma
- Low respiratory rate, apnoea and cyanosis
- Hypotension
- Pinpoint pupils
  - If severe hypoxia - dilated pupils
- Reduced urine formation
- Reduced body temperature
- Skin is cold and clammy
- The skeletal muscles are flaccid
  - The jaw is relaxed
  - The tongue may fall back and block the airway
- Convulsions may occur in children
- Death is nearly always from respiratory failure
- Pulmonary oedema may occur

Hints for Opioid Poisoning

- Triad
  - Coma
  - Pin-point pupils
  - Respiratory depression
- Needle marks suggestive of addiction
- Results of tests in urine and gastric contents
  - Too late to influence treatment
- Check if airway is patent
- Ventilate the patient

Market Categorisation of Drugs

20 June 2017 10:37

Market

- Any medium in which goods and services are exchanged for something of value
- A population/cohort that utilises a good/service leading to a mutually rewarding exchange
- Consists of buyers, sellers, consumers, products/service, logistics/infrastructures

Categorisation

- Means classification/grouping

Market Categorisation of Drugs

- Classification and subsequent segmentation of biologically active chemical compounds to better answer the needs of a target group/customer
- Include:
    - Therapeutic category
        - Anti-cancer drugs
        - Anti-biotics
        - Anti-virals
        - Vitamins
        - Cough and cold preparations
    - Chemical Structure
        - Steroids
        - Nucleotide analogues
        - Beta lactams
    - Target tissue
        - Dermatological preparations
        - CNS stimulants
        - Eye preparations
        - Bronchodilators
    - Drive for use
        - Serious illness - therapeutic e.g. Digoxin
        - Non-serious - lifestyle drugs e.g. Sildenafil
    - Value added/natural
        - Herbal preparations
        - Synthesised
    - By law
        - Part 1 poisons
            - Prescription only medications e.g. Digoxin
        - Part 1 poisons
            - Pharmacy only e.g. Chlorpheniramine
        - Part 2 poisons
            - OTC preparations e.g. Paracetamol
    - Innovation
        - Brand e.g. Panadol
        - Generic e.g. Paracetamol
    - Mode of delivery
        - Injectibles (IM/IV/SC)
        - Oral preparations
        - Pessaries e.g. Clotrimazole
        - Suppositories e.g. Diclofenac
    - Place of manufacture - perceived quality
        - Local e.g. Bronchomint
        - Imported e.g. Zinnat

- Age of the patient
  - Paediatric e.g. Zidovudine suspension
  - Adult e.g. Zidovudine tablets
- Preparation base/solvent
  - Oil
    - Ointments e.g. Betamethasone ointment
  - Water e.g. Betamethasone cream
  - Emulsions e.g. liquid paraffin emulsion
- Delivery systems
  - Metered dose inhalers e.g. Salbutamol
  - Powder e.g. Fluticasone propionate
  - Transdermal patch e.g. Nicorette

Drug Procurement

Friday, 23 June 2017 8:50 AM

- Authorised sellers
  - Manufacturer or his agent
    - Mark up of factory price of 10% to distributors
  - Distributors
    - Mark up of wholesale price 15% to wholesalers
  - Wholesalers
    - Mark up of trade price of 15% to retailers
  - Retailers
    - Mark up of retail price of 33.3% to the consumer
  - Consumer

Purchasing

- Spot purchases
- Quotation floatation to "certain suppliers"
- Open tender system
- Documents for purchases
  - LPO
  - Invoice
  - Delivery note
  - C.O.D (cash on delivery) or cheque

Respiratory Pharmacology

10 April 2017 00:56

- The main drugs for asthma
  - Bronchodilators
    - Cause rapid relief of symptoms (relax airway smooth muscle)
  - Controllers
    - Inhibit the underlying inflammatory process
  - Quick relief drugs (bronchodilators)
    - Adrenergic receptor agonists
    - Methylxanthines
      - Examples
        - Theophylline (T)
        - Aminophylline
          - Theophylline + ethylenediamine
        - Oxtriphylline
        - Dyphylline
        - Enpropylline
        - Dosophylline
    - Anticholinergics
  - Long-term controller drugs
    - Corticosteroids
      - Examples
        - Inhaled
          - Beclomethasone
          - Budesonide
          - Flunisolide
          - Fluticasone
          - Mometasone
          - Triamcinolone
          - Ciclesonide
        - Systemic
          - Prednisone (oral)
          - Hydrocortisone (IV)
          - Methylprednisolone (IV)
          - Triamcinolone (IM)
    - Long acting $ß_2$ agonists
      - Used for prophylaxis
      - Include
        - ◇ Salmeterol
        - ◇ Formoterol
        - ◇ Fenoterol
        - ◇ Reproterol
        - ◇ Bitolterol
    - Mast cell stabilising agents
    - Leukotriene pathways inhibitors
    - Omalizumab
- MoA of Methylxanthenes
  - They inhibit phosphodiesterase (PDE) subtypes non-selectively
    - They prevent breakdown of cAMP and cGMP
    - cAMP causes
      - Bronchodilation
      - Stimulates cardiac function

        - ↓ immune and inflammatory activity and WBCs
            - By apoptosis
            - Inhibits synthesis and secretion of inflammatory mediator cells e.g. mast cells and basophils
    - T is a competitive antagonist at adenosine receptors
        - Enprophylline - devoid of adenosine antagonist activity
        - Doxyphylline - < antagonist activity
            - Adenosine can
                - Cause bronchoconstriction by releasing histamines and leukotrienes
            - Adenosine receptor antagonism may be responsible for arrhythmias and seizures
    - T activates histone deacetylases in the nucleus
        - Deacetylation of histones may ↓ the transcription of pro-inflammatory genes and potentiate the effect of corticosteroids
    - T also inhibits synthesis and secretion of inflammatory mediators from numerous cell types
        - E.g. mast cells and basophiles
    - Reduce infiltration of eosinophils and T lymphocytes
    - Promotes apoptosis
        - Eosinophils
        - Neutrophils
- Sympathomimetic agents in Asthma
    - Non-selective adrenergic agonists
        - Epinephrine (adrenaline)
        - Ephedrine
        - isoproterenol
    - $ß_2$-adrenergic receptor agonists
        - Classification
            - Short acting agents
                - Used for symptomatic relief
                - Are the most effective drugs bronchodilators
                - Include
                    - Salbutamol (albuterol)
                    - Metaproterenol
                    - Terbutaline
                    - Bambuterol (a prodrug or terbutaline)
                    - Pirbuterol
            - Long acting agents
                - Used for prophylaxis
                - Include
                    - Salmeterol
                    - Formoterol
                    - Fenoterol
                    - Reproterol
                    - Bitolterol
- MoA of corticosteroids
    - Inhibit production of inflammatory cytokines
    - Inhibit eicosanoid synthesis
    - Inhibit accumulation of basophil, eosinophils and other leukocytes in lung tissues
    - Decrease vascular permeability
    - Contract engorged vessels in the bronchial mucosa
    - They are not bronchodilators
- MoA of mast cell stabilisers
    - Alter the function of delayed chloride channels in the cell membranes
    - This inhibits cell activation

    - On airway nerves → inhibition of cough
    - On mast cells → inhibits early response to antigen challenge
    - On eosinophils → inhibits inflammatory response
    - No effect on basophils which also release mediators
    - Nedocromil also inhibits appearance of the late response given after mast cell degranulation has occurred
    - They prevent antigen and exercise induced asthma
    - Not bronchodilator
- The following require trial therapy
    - Mast cell stabilising agents
    - Omalizumab
    - Zafirlukast
    - Anticholinergics
- MoA of Ipratopium Bromide
    - A quaternary ammonium conpound
    - Inhalational
    - Poor absorption systemically and into the CNS
    - Onset of action is slow
    - Maximum effect: 30 - 60 minutes
    - DoA: 6 - 8 hours
- MoA of Magnesium Sulfate
    - It reduces cytosolic Ca^{2+} concentration in airway smooth muscle

CNS Pharmacology: Anti-Convulsants

Tuesday, 30 May 2017 6:06 AM

- Seizures are classified into 2 broad categories
  - Partial (focal) seizures
    - Simple partial seizures
      - Focal
      - Consciousness is preserved
      - Discharge begin and may remain locally
      - Symptoms depend on brain region involvement
        - Involuntary muscle contraction
        - Abnormal sensory experience
        - Autonomic discharge
        - Mood and behaviour (psychomotor epilepsy) e.g. TLE
      - Local cerebral lesion
        - ↑ with age
    - Complex partial seizures
      - Local onset (usually in the temporal lobe) then spreads
      - Impaired consciousness
    - Partial seizures with secondary generalisation
      - Partial seizure initially followed by generalised tonic-clonic seizures
      - Loss of consciousness????
  - Generalised seizures
    - Involves the whole brain
    - Includes the _
    - Generalised tonic-clonic seizures (formerly *grand mal* seizures)
      - Most common
      - Prodrome
        - Period where the patient feels unwell
      - Aura
        - Patient is able to tell they are about to have a seizure
      - Ictus
        - Strong contraction of whole musculature, involuntary cry, respiration stops, loss of sphincter control, tonic with suffused blue face ~1min (differentiates it from syncope which is a pale, ashen face. The clonic phase 2-4 min (longer than this - status epilepticus)
      - Post-ictal - sleep
      - Recovery - residual confusion
      - Aura → cry → unconsciousness → tonic phase → clonic phase
        - Tonic phase
          - Sustained powerful muscle contraction (involving all body musculature) which arrests ventilation
        - Clonic phase
          - Interchanging contraction and relaxation of musculature
    - Absence (formerly *petit mal*) seizures
      - Usually in children
      - Pathophysiology involves oscillatory feedback between the cortex and the thalamus and especially the T-type Ca^{2+} channels of thalamic neurons.
      - Less dramatic
      - More frequent times in the day
      - Momentary loss of consciousness
      - No convulsions
      - Vacant stare

        - Atonic (static/drop) seizures
            - Sudden loss of postural tone
        - Myoclonic seizures
            - Isolated momentary muscle contractions/jerks
            - No loss of postural control
            - Brief bursts of multiple spikes on the EEG
        - Infantile spasms
            - An epileptic syndrome
            - Characterised by brief recurrent myoclonic jerks (muscle spasm) of the body and limbs
            - Progressive mental deterioration
        - Tonic seizures
- MoA of ASD
    - The general effect of AS drugs is to suppress repetitive action potentials in epileptic foci in the brain
    - Different mechanisms are involved in achieving this effect
    - Include
        - Modification of voltage-gated ion channel conductance
            - Blockade of voltage gated sodium channels
                - Results in prolongation of the inactivated state of the sodium channel and the refractory period of the channel
                - Include
                    - Phenytoin
                    - Carbamazepine
                    - Lamotrigine
                    - Zonisamide
            - Calcium channel blockade
                - The following inhibit calcium ion entry through low threshold (T-type) calcium channels
                    - Ethosuximide
                    - Valproic acid
                    - Gabapentine
                    - Pregabalin
                    - Trimethadione
                - The do so especially in the thalamic neurons that act as pacemakers to generate rhythmic cortical discharge
        - Enhancement of GABA mediated inhibitory synaptic transmission
            - Benzodiazepines
                - Interact with specific receptors on the $GABA_A$ receptor-chloride ion channel macromolecular complex to facilitate inhibitory effects of GABA
            - Barbiturates
                - Also enhance the inhibitory actions of GABA but interact with a different receptor site on the chloride ion channels
            - Vigabatrine
                - At therapeutic plasma levels, it irreversibly inactivates the enzyme GABA amino transaminase (GABA-T) which is important in terminating the action of GABA
                    - Enhances the effects of GABA at synaptic sites
            - Valproic acid
                - At high concentration inhibits GABA-T
            - Tiagabine
                - Inhibits a GABA transporter (GAT-1) in neurons and glia, prolonging the action of the neurotransmitter
            - Other drugs that facilitate the inhibitory actions of GABA include Felbamate and Topiramate

        - Neuronal membrane hyperpolarisation
            - Possibly through enhancing potassium permeability
                - Valproic acid
                - Retigabine
        - Reduction of excitatory glutamate mediated neurotransmission
            - Felbamate blocks glutamate NMDA receptors
            - Phenobarbitone and Topiramate block some glutamate receptors
- Adverse effects of Phenytoin
    - IM
        - Tissue damage
    - Rapid IV administration (Fosphenytoin)
        - Arrhythmias
        - Hypotension
    - Phlebitis
    - CNS
        - Cerebellar and vestibular effect
            - Acute overdoses
            - Chronic medication
                - Cerebellar atrophy (high doses)
                - Behavioural changes
                - Diplopia and ataxia most common dose related (↓ dose)
                    - Ataxia = loss of control of voluntary movements, especially gait
                - Nystagmus (high doses)
                    - Constant, involuntary movement if the eyeball
    - GIT
    - Gingival hyperplasia (20%)
        - Common in children and young adolescents
        - Though to be due to altered collagen metabolism
        - Toothless portion of gum are not affected
        - Can be minimised by good oral hygiene
    - Coarsened facial features
    - Hirsutism (concern to female patients)
    - ↑ liver enzymes
    - Endocrine
        - Inhibit the release of ADH
        - Inhibit insulin release → hyperglycaemia and glycosuria
    - Osteomalacia
        - Altered Vitamin D metabolism
        - Inhibition of intestinal absorption of calcium
        - Associated with hypocalcaemia and ↑ alkaline phosphatase levels
    - Allergy
        - Skin rashes - mild to severe
        - Hepatic necrosis (Rare)
        - Neutropenia
        - Red cell aplasia, agranulocytosis and thrombocytopenia (rare)
        - Stop treatment
    - Megaloblastic anaemia - altered folate metabolism
    - Lymphadenopathy
    - Hypoprothrombinemia
        - Phenytoin ↑ metabolism of Vitamin K
        - Haemorrhage may occur in new-borns of mothers on treatment
        - Administer Vitamin K for treatment and prophylaxis
    - Fetal hydantoin syndrome

        - Abnormal facial features
        - Low birth weight
        - Distal nail hypoplasia
    - Neural tube defects - folate deficiency
    - Mild peripheral neuropathy
    - Fever
- MoA of Phenobarbital
    - Not clear
    - Enhances inhibitory responses in the GABA channels and suppresses excitatory responses in the other channels
    - Action on GABA channels
        - In high doses, it suppresses high frequency repetitive firing in neurons through sodium conductance
    - Also blocks calcium currents in the L and N type calcium channels
    - Blocks excitatory responses induced by glutamate through the AMPA glutamate receptors
- MoA of Carbamazepine
    - Na^+ channel blockade
    - Pre-synaptically decrease synaptic transmission
    - Potentiation of voltage-gated K channels
- DoC for Seizures
    - **Tonic-Clonic Seizures**
        - DOC
            - Valproic Acid
            - Carbamazepine
            - Phenytoin
        - AD
            - Phenobarbital (or Primidone) in adults
            - Phenobarbital in infants
        - Other drugs that can be used
            - Lamotrigine
            - Topiramate
    - **Partial seizures**
        - DOC
            - Carbamazepine (or oxcarbazepine)
            - Lamotrigine
            - Phenytoin
        - AD
            - Felbamate
            - Phenobarbitone
            - Topiramate
            - Valproic Acid
        - Others
            - Gabapentine
            - Pregabalin
    - **Absence seizures**
        - DOC
            - Ethosuximide (block T-type Ca^{2+} channels)
            - Valproic Acid
        - AD
            - Clonazepam
        - Others
            - Lamotrigine
            - Levetiracetam
            - Zonisamide
    - **Myoclonic seizures**

        - DOC
            - Valproic Acid
        - AD
            - Lamotrigine
        - Others
            - Clonazepam
            - Levetiracetam
            - Topiramate
            - Zonisamide
            - Felbamate
    - **Infantine spasms**
        - DOC
            - Vigabatrin is effective and is considered DOC by many paediatric neurologists
        - Other drugs widely used are the benzodiazepines
            - Clonazepam
            - Nitrazepam
        - IM corticotrophin (ACTH) or oral prednisone have also been used to modulate inflammation
    - **Status epilepticus**
        - Status epilepticus refers to continuous seizures or repetitive, discrete seizures with impaired consciousness in the inter-seizure period
        - Treatment
            - IV Diazepam or Lorazepam is usually effective in terminating attacks and providing short term control
            - For prolonged therapy, IV Phenytoin is usually used because it is highly effective and less sedating than benzodiazepines or barbiturates
                - However, phenytoin may be cardiotoxic and Fosphenytoin (water soluble) may be safer
                - Phenobarbital has also been used in status epilepticus especially in children, or for seizures not responding to Fosphenytoin treatment
            - In very severe status epilepticus that does not respond to these measures GA (Propofol or Midozolam or Pentobarbital) may be used
- Other uses of ASD
    - Bipolar affective disorders (treatment of mania)
        - Valproic Acid
        - Carbamazepine
        - Lamotrigine
    - Neuropathic pain e.g.
        - Post-herpertic neuralgia
            - Gabapentin
            - Pregabalin
        - Trigeminal neuralgia
            - Carbamazepine is the DOC
            - Oxcarbezepine may provide similar analgesia with fewer AE
    - Migraine
        - Gabapentine
        - Phenytoin
        - Topiramate
- MoA of Sodium Valproate
    - Like phenytoin and Carbamazepine, Valproate blocks sustained high frequency repetitive firing of neurons in culture at therapeutically relevant concentration
    - Its action against partial seizures may be a consequence of this effect on sodium currents
    - Blockade of NMDA receptor mediated excitation may also be important
    - There are increased levels of GABA in the brain after administration of Valproate

        - The mechanism of this increase is unclear
    - Valproate facilitates glutamic acid decarboxylase (GAD), the enzyme responsible for GABA synthesis
    - It may also have an inhibitory effect on the GABA transporter, GAT-1
    - At very high concentrations, Valproate inhibits GABA transaminase in the brain to block degradation of GABA
    - It is a potent inhibitor of histone deacetylase
        - Through this mechanism, it changes the transcription of many genes
- ADR of Sodium Valproate
    - The most common dose related AE are transient GIT symptoms such as NV, abdominal pain and heartburn, which occur in approx. 16% of patients
        - The drug should be started at a low dose and increased gradually to avoid these symptoms
    - The CNS AE include sedation, ataxia and tremor
        - Sedation is uncommon with valproate alone, but may be significant when Valproate is added to Phenobarbital
        - A fine tremor is frequently seen at higher levels
    - Valproate causes idiosyncratic hepatotoxicity, which may be severe
        - Its risk is greatest for patients <2 years old, and for patients taking multiple medications
        - Initial AST values may be normal in susceptible patients
            - These levels eventually become normal
        - Most fatalities occur within 4 months after treatment initiation
        - It is recommended to treat a patient with oral or IV L-carnitine as soon as severe hepatotoxicity is suspected
        - Careful monitoring of LFTs is recommended when starting the drug
            - The hepatotoxicity is reversible in some patients if the drug is withdrawn
    - The other observed idiosyncratic response with Valproate is thrombocytopenia_
    - Increased incidence of spina bifida, CVS, orofacial and digital abnormalities in offspring of women who took Valproate during pregnancy
    - Other reversible AE seen in a small number of patients
        - Weight gain
        - Increased appetite
        - Alopecia
- Biotransformation of BDZs
    - Desmethyldiazepam (Nordiazepam)
        - Elimination half-life of 40-60 hours
        - Active metabolite of:
            - Chlordiazepoxide
            - Prazepam
            - Diazepam
            - Chlorazepate
    - Active metabolites of Chlordiazepoxide
        - Desmethylchlordiazepoxide
        - Demoxepam
    - Flurazepam (hypnotic)
        - Oxidised by hepatic enzymes to 3 active metabolites i.e.
            - Desalkyl-flurazepam
            - Hydroxyethyl-flurazepam
            - Flurazepam aldehyde
        - These metabolites have half-lives ranging from 30-100 hours
    - Prazolam and Triazolam undergo alpha-hydroxylation
        - The resulting metabolites have short half-lives and are rapidly conjugated to form inactive glucuronide

CNS Pharmacology: Sedative Hypnotics

Tuesday, 30 May 2017 12:34 PM

- Ramelteon
  - An agonist at the Mt1 and MT2 melatonin receptors in the brain
  - Converted into an active metabolite with a longer half-life
  - Fluconazole increases its plasma half-life
  - Used for treatment of insomnia in autistic and elderly children
  - Ramelteon should not be used in combination w/ inhibitors of CYP1A2 (e.g. Ciprofloxacn, Fluvoxamine, Zileuton) or CYP2C9 (e.g. Fluconazole) which increase its plasma concentration
  - It should be used w/ caution in patients w/ liver dysfunction
  - The CYP inducer, Rifampin, markedly reduced the plasma levels of both Ramelteon and its active metabolite

CNS Pharmacology: Anti-Depressants

Wednesday, 31 May 2017 5:37 AM

Lithium

- Narrow Therapeutic Index
- Half-life of 20 hours
- Not PPB
- Onset of action is 30min - 2 hours
- Causes nephrogenic DI

Adverse Effects of TCAs

- Antimuscarinic effects
    - Blockade of muscarinic receptors leads to:
        - Blurred vision
        - Xerostomia (dry mouth)
        - Urinary retention
        - Constipation
        - Aggravation of glaucoma
- Cardiovascular
    - Increased catecholamine activity results in cardiac overstimulation
        - Can be fatal in overdose situation
    - Slowing of AV conduction amongst depressed elderly patients is of particular concern
    - Orthostatic hypotension and reflex tachycardia as a result of blockade of alpha-adrenergic receptors
- CNS
    - Sedation especially during the first several weeks of treatment

Tardive Dyskinesia

- Takes months or years to develop
- Disabling and irreversible
- Worsen when drug stopped
- Severe disabling involuntary movement of the tongue, face, trunk and limbs
- Commonest in patients > 50 years

Therapeutic Uses of TCAs

- Treatment of severe endogenous depression
- Some episodic phobias
- Nocturnal enuresis
    - Unconscious or involuntary passage of urine
        - Imipramine is useful in controlling bedwetting in children (>6 years) by causing contraction of the internal sphincter of the bladder
- Adjunct in pain management
- ADHD (third line treatment)
- Migraine prophylaxis

CNS: Anti-Psychotics

Wednesday, 31 May 2017 5:42 AM

Classification of Antipsychotic drugs

- First generation (typical, conventional)
  - Chlorpromazine - low potency
  - Haloperidol - high potency
  - Fluphenazine
  - Flupenthixiol
  - Clopenthixol
- Second generation (atypical)
  - Clozapine
  - Risperidone
  - Sertindole
  - Quentapine
  - Amisulpride
  - Ariprazole
  - Zotepine
  - Ziprasidone

Haloperidol

- Is a phenylbutylpiperadine
- More potent that chlorpromazine
- Produces a higher incident of extrapyramidal effects than chlorpromazine
- Antagonises both D1 and D2 dopamine receptors

Phenothiazines

- Chlorpromazine prototype
- Block histamine, catecholamines, acetylcholine, 5HT and dopamine
- Largactil
  - Multiple mediator blockade
- Dopamine blockade main deterrent for antipsychotic action

CNS Pharmacology: Parkinson's Disease

Wednesday, 31 May 2017 6:20 AM

- Drugs used in Parkinsonism
  - Levodopa
    - Dopamine itself cannot cross the BBB but its precursor, Levodopa.
    - Once on the brain, it is converted to dopamine by DOPA decarboxylase, within the remaining nigrostriatal neurons
  - Carbidopa
    - Peripheral DOPA decarboxylase also exists, which can metabolise the Levodopa into dopamine before it gets through the BBB and also, via other enzymes, be metabolised into catecholamines e.g. epinephrine, which can cause unwanted side effects such as arrhythmias.
    - This is why Levodopa is co-administered with Carbidopa, a DOPA decarboxylase inhibitor, that isn't able to cross the BBB
  - Amantidine
    - Antiviral medication that increases endogenous dopamine production (MoA unknown)
  - Dopamine agonists - stimulate dopamine receptors
    - E.g.
      - Bromocriptine - Ergot derivative
      - Pramipexole - non-ergot derivative
      - Ropinirole - non-ergot derivative
  - COMT inhibitors
    - COMT is an enzyme that degrades dopamine
    - Include
      - Entecapone
      - Tolcapone
  - Selegeline
    - Inhibits MAO-B that metabolises dopamine
  - Anticholinergics
    - Since there is usually a signalling balance between dopamine and acetylcholine reaching the striatum, a loss of dopamine increases the relative amount of acetylcholine signalling there
    - Anticholinergics can be given to restore the balance
      - E.g.,
        - Benztropine - helps improve the tremours

- Pamidronate does not have an oral preparation (only given IV) due to GIT disturbances

Adverse Effects of oestrogen

- GIT upset
- In large doses, oestrogens enhance reabsorption of sodium
  - Water retention
  - Oedema
  - HT
  - Possible cardiac failure
- Irregular menstrual bleeding ("spotting") may occur
- Breasts may become enlarged and tender
- In men, there is feminisation
- In the use of oestrogen-containing oral contraceptives there is increased thromboembolic disorders
  - Increased level of clotting factors II, VII, IX and X and a decrease in factor III
- Prolonged exposure to unopposed oestrogens may lead to development od cancer of the vagina and uterus
- Breast CA may be exacerbated by oestrogens
- Cholestatic jaundice, changes in libido, depression, headache, leg cramps (rule out venous thrombosis) gall bladder disease
- Contact lenses may irritate
- Transdermal delivery system may cause contact sensitisation

Classification of Insulin

- Rapid acting (ultrashort)
  - Lispro
  - Aspart
  - Glusiline
- Short acting
  - Regular Insulin
- Intermediate acting
  - NPH
  - Lente
- *****Slow Acting*****???
  - PZI
  - Ultra Lente
- Long acting
  - Glargine
  - Detemir

Insulin Secretagogues

- Include
  - Sulfonylureas
    - First generation
      - Acetohexamide
      - Tolazamide

        - Tolbutamide
        - Chlorpropamide
    - Second generation
        - Glyburide (Glibenclamide)
        - Glipizide
        - Gliclazide
        - Glimepiride
- Non-sulfonylureas (Glinides)
    - Meglitinides
        - Repaglinide
        - Mitiglinide
    - D-phenylalanine derivative
        - Nateglinide

Actions of Insulin

- Liver
    - Decrease gluconeogenesis and glycogenolysis
    - Stimulates e glucose uptake
- Muscle
    - Stimulate glucose uptake and inhibits flow of gluconeogenic precursors (alanine, lactate and pyruvate)
- Adipose tissue
    - Reducing circulating FFA
    - Promote TG storage in adipocyte

MoA of Thioamines

- Inhibit thyroid peroxidase catalysed reactions (inhibit synthesis of thyroid hormones)
- Inhibit peripheral deiodination of T4 to T3 (PTU >>>Methimazole)

SE of Oral Contraceptives

- Gain in body weight, mild oedema, N, fullness of breasts, headache, dizziness, depressed feeling
- Changes in CHO metabolism, decrease in glucose tolerance
- Occasional alteration in LFT w/ elevation of SGOT, alkaline phosphatase an serum bilirubin
- Changes in clotting factors, increase in factors VII, VIII, IX, X
- Increase in concentration of thyroxine-binding globulin
- Inhibition of lactation
- In adolescents, delay in closure of epiphyses

MoA of Potassium iodide

- Inhibit thyroid hormone release
- Inhibits its own transport into the thyroid
- Inhibits organification of iodine (Wolff-Chaikoff Effect)
- Decreases the size and vascularity of the hyperplasic gland. Gland is firmer (less friable - less bleeding during surgery)
- In susceptible individuals iodides induce
    - Hyperthyroidism (Jodbasedow Effect)
    - Hypothyroidism

AE of Metformin

- AND, abdominal discomfort (20% of patients)
- Metallic taste
- Minimise by ↑ drug doses slowly and taking the drug with meals
- Transient, dose dependent
- ↓ Vitamin B12 absorption
  - Annual screening for deficiency
- Lactic acidosis (high doses)
  - Impaired hepatic metabolism of lactic acid

Use of Progestins

- Component of oral contraceptive pills in combination w/ oestrogen
- Prevention of habitual abortion if progesterone output if the patient's corpus luteum is deficient
- To control functional uterine bleeding and to produce regular cycles
- Postponement of menstruation
  - Norethisterone 5mg tds starting 3 days before anticipated onset of mense
- Management of endometriosis
- Used in conjunction w/ oestrogens in hormone replacement therapy in menopausal women w/ an intact uterus
- Advocated for alleviation of premenstrual symptoms

MoA of Metformin

- It increases the activity of AMP-dependent protein kinase (AMPK)
  - ↑ glycogen storage
  - ↓ hepatic glucose production
  - ↑ insulin sensitivity
  - ↓ blood glucose

GIT Pharmacology

Wednesday, 31 May 2017 5:39 AM

Renal Pharmacology

Wednesday, 31 May 2017 5:40 AM

Anti-Biotics

Friday, 2 June 2017 6:50 AM

1. List Examples of beta-lactam antibiotics
    - Penicillins
    - Cephalosporins
    - Carbapenems
        - Imipenem
    - Monobactams
        - Aztreonam
    - Beta-lactamase inhibitors
2. Penicillins
    a. Classify
        - Based on their spectra of activity
            - Narrow spectrum penicillins
                - Penicillin G
                - Penicillin V
            - Very Narrow Spectrum (Penicillinase resistant penicillin [anti-staphylococcal P])
                - The Isoxazolyl P
                    - Cloxacillin
                    - Flucloxacillin
                    - Oxacillin
                    - Dicloxacillin
                - Nafcillin
                - Methicillin (not used)
            - Broad spectrum P (extended spectrum P)
                - Aminopenicillin
                    - Amoxicillin
                    - Ampicillin
                        - Bacampicillin
                        - Pivampicillin
                        - Talampicillin
                        - Epicillin
                - Anti-pseudomonal P
                    - Carboxycillins
                        - Carbenicillin
                        - Ticarcillin
                    - Ureidopenicillin
                        - Piperacillin
                        - Mezlocillin
                        - Azlocillin

    b. MoA
        - ß-lactam antibiotics have a common mechanism of action
            - Inhibit synthesis of peptidoglycan cell wall
        - Mechanism
            - Inhibit the first step in bacterial cell wall synthesis
            - Cell walls - essential for normal bacterial growth
            - Cell wall is rigid and prevents cell lysis due to high osmotic pressure
            - Cell walls contains peptidoglycan which is composed of polysaccharides and polypeptides
            - A peptide is attached to the polysaccharides
            - This peptide terminates in D-alanyl-D-alanine
            - Penicillin binding proteins (PBP) catalyse a transpeptidase reaction that removes the terminal alanine to form a crosslink with a nearby peptide
            - This cross linking gives the cell wall its rigidity
            - ß-lactam antibiotics are structural analogs of D-ala-D-ala
            - P covalently bind to PBPs and inhibit the transpeptidation reaction
            - Therefore, cross linking of peptidoglycans does not occur
            - The bacteria is unable to synthesise a stable cell wall and is eventually lysed
            - P is only active if cells are growing and synthesising cell walls
    - MoR
        - Altered structure of PBP
            - Reduced affinity for ß-lactam antibiotics
        - Inability of P to penetrate site of action. Transpeptidase is bound to the cell membrane
            - Gram negatives have an outer membrane that contains pores. Antibiotics have to diffuse through the pores to reach the transpeptidase and act on them. Broad spectrum P penetrate more rapidly than Pen G
            - Absence or reduced production of porins
        - Bacteria produce ß-lactamases or penicillinases. These enzymes hydrolyse the ß-lactam ring
        - ß-lactamases have higher affinity for the antibiotic than the antibiotic for its target
            - ß-lactamases can be of different types
                - If the substrate is low, they are described as penicillinases or

cephalosporinases
- Others are more broad spectrum - they hydrolyse a variety of ß-lactam antibiotics
- Gram positive secrete this enzyme extracellularly
- Gram negatives secrete it into the periplasmic space between the inner and outer sell membrane
- Encoded in plasmids or chromosomes

3. Cephalosporins
   a. Spectra of activity for each generation
      - First
        - Active against gram positive and poor activity against gram negative
          - PEcK
            - P - Proteus
            - Ec - E. coli
            - K - Klebsiella
        - Exception of enterococci, MRSA and *S. epidermidis*
        - Oral cavity organisms are susceptible except B. fragilis
        - Good activity against *Moraxella catarrhalis*, *K. pneumoniae*, *E. coli* and *Proteus mirabilis* (produce extended spectrum ß-lactamases)
          - Cephalothin
          - Cefazolin
          - Cephalexin
          - Cefadroxil
      - Second
        - Increased activity against gram negative but still less than 3rd generation
          - HEN PEcKS
            - H - Haemophilus
            - Enterobacter
            - N- Neisseria
            - P - Proteus
            - Ec - E. Coli
            - K - Klebsiella
            - S - Serratia
        - Cefoxitin, Cefotetan and Cefometazole are active against *Bacteroides fragilis* (anaerobe)
        - Generally less active against gram positive (cf. 1st generation)
        - Active against **enterobacteriaceae** including beta lactamase producing ones (but not ESBLs-extended spectrum beta lactamases)
          - Cefamandole
          - Cefoxitin
          - Cefaclor
          - Loracarbef
          - Cefinicid
          - Cefotetan
          - Cefuroxime, Cefuroxime axetil
      - Third generation
        - More activity against gram negative, < on gram positive
        - Enterobacteriaceae; *Pseudomonas aeruginosa*, Serratia, *Neisseria gonorrhoeae*
        - *Staphylococci aureus, Streptococcus pneumoniae* efficacy similar to first generation
        - Activity against *B. fragilis* is inferior to *Cefoxotin* and
          - Cefotaxime
          - Cefpodoxime proxetil
          - Ceftizoxime
          - Ceftriaxone
          - Cefoperazone
          - Ceftazimide
      - Fourth generation
        - Comparable to third generation but more resistant to ß-lactamases
          - Cefepime
      - Fifth generation
        - Active against MRSA
          - Ceftobiprole
          - Ceftoriline
   b. Indications for Cefazolin - has minimal effectiveness to gram negative cocci, enterococci, MRSA and most gram negative rods
      - Infections caused by Staphylococci and common streptococci and many strains of E. coli and K. pneumoniae
      - Surgical prophylaxis in certain conditions
        - Surgical infection
        - Endocarditis
      - Mild to moderate cholecystitis
      - Uncomplicated UTI
      - Bacterial Keratitis
   c. Which ones are used in meningitis?
      - Ceftriaxone - 3rd

- Cefotaxime

d. Which are active against MRSA
   - Ceftarolin - 5th
   - Ceftobiprole - 5th

4. Monobactams
   a. Spectrum of activity
      - Differs from those of the other ß-lactam antibiotics and more closely resembles that of an aminoglycosides
      - Has activity only against gram negative bacteria; it has no activity against gram-positive bacteria and anaerobic organisms
      - Has excellent activity against:
        - *Enterobacterioceae*
        - *P.aeruginosa*
        - *H.influenzae*
        - *Gonococci*
5. Examples of beta-lactamase inhibitors
   - Clavulanic acid
     - Used with Amoxicillin
   - Tazobactam
     - Used together with Piperacillin
   - Sulbactam
     - Used with Ampicillin
6. Carbapanems
   a. Adverse Effects
      i. The common ones
         - Nausea, diarrhoea and vomiting
         - Skin rashes
         - Reactions at infusion sites
         - Seizures (1.5% of patients) - especially when high doses are given to patients with CNS lesions and those with renal insufficiency
         - Patients who are allergic to other ß-lactam antibiotics may have hypersensitivity reactions when given Imipenem
7. Glycopepetide
   a. Examples
      - Vancomycin
      - Teicoplanin
      - Telavancin
      - Dalbavancin
   b. Vancomycin
      i. Spectra of activity
         - Bactericidal for gram positive, ß-lactamase producers and those resistant to Nafcillin and Methicillin. Kills slowly and only dividing cells
         - Synergistic with Gentamycin and Streptomycin against *Enterococcus faecium* and *E. faecalis*
      ii. Routes of administration
         - PO
           - However, poor absorption
         - Given IV, parenterally
      iii. Indications
         - Vancomycin for Methicillin Resistant Staphylococci in Endocarditis and in Sepsis (bloodstream infections)
         - Combined with gentamycin, an alternative to treatment of enterococcal endocarditis in those with penicillin allergy
         - In combination with Cefotaxime, Ceftriaxone or Rifampicin in meningitis caused by highly penicillin resistant pneumococcus
         - Oral Vancomycin used to treat anti-biotic-associated Colitis caused by C. difficile
      iv. Adverse Effects
         - Seen in 10%. Most are minor
         - Irritation to the tissues, may cause phlebitis
         - Ototoxicity and nephrotoxity are rare. Mixing with other ototoxic or nephrotoxic drugs increases chances
         - Redman or red neck syndrome
           - Infusion related flushing caused by release of histamine
8. Adverse Effects of tetracyclines
   - Usually due to toxicities
     - GIT
       - NVDA
     - Bony structures and teeth - readily bind to calcium deposited in newly formed bone or teeth in children
       - Teeth
         - Fluorescence
         - Discolouration
         - Enamel dysplasia
       - Bone
         - Deformity

        - Growth inhibition
    - Hepatic function impairment and necrosis
    - Venous thrombosis in IV injection
    - Painful local irritation in IM injection - avoid
    - Tetracyclines + Diuretics = nitrogen retention - renal tubular necrosis
    - Photosensitivity - doxy and demeclocyline
    - Dizziness- minocycline and doxycycline
    - Expired drugs cause Fanconi's syndrome
    - Demeclocycline - nephrogenic DI
    - Super infection with candidiasis and C. Difficile

9. Macrolides
    a. Cross resistance with which drugs
        i. MLS drugs
        - Other Macrolides except Ketolides
        - clindamycin
        - streptogramin B
            - due to similar mechanism of resistance since they all work on 50S

    b. Drug Interactions
        - E inhibits CYP450 (14-atom lactone)
        - It therefore increases the concentration of drug such as
            - Theophylline
            - Oral anticoagulants
            - Cyclosporin
        - E + digoxin
            - Digoxin is metabolised by intestinal microflora
            - Digoxin bio-availability is increased
    c. Common adverse effects
        - GIT (most frequent and dose dependent)
            - ANVD, abdominal pain
            - E acts on motilin receptors to stimulate GIT motility
        - Acute cholestatic hepatitis
            - Especially the estolate
            - May be a hypersensitivity reaction
        - Arrhythmias
            - Macrolides prolong the QT interval
            - In patients on drugs that prolong the QT interval e.g. Cisapride
            - Other risk factors like hypokalaemia
        - Reversible hearing loss
        - Allergic reactions
            - Rash (mild to severe) - rare
            - Anaphylaxis, fever, eosinophilia
        - Overgrowth of non-susceptible micro organisms
            - Bacteria e.g. clostridium difficile
            - Fungi
    d. Example of a Ketolide
        - Telithromycin
        - Difference compared to Macrolides
            - Differ from Erythromycin by substitution of a 3-keto group for the neutral sugar l-cladinose
                - increase affinity for ribosome and so maybe used in macrolide resistance
            - 15 membered atom ring as opposed to the 14 membered atom ring.
        - Contraindications
            - Hepatic function impairment
            - Myasthenia gravis
10. Indication of Clindamycin
    - Skin and soft-tissue infections cased by streptococci and staphylococci
        - Active against community acquired strains of MRSA
    - Treatment of anaerobic infections caused by Bacteroides and others that participate in mixed infections
    - Used in combination with an aminoglycoside or cephalosporin in penetrating wounds of the gut
    - Infections originating from the female genital tract
        - Septic abortion
        - Pelvic abscesses
        - PID
    - Lung abscesses
    - Now recommended rather than Erythromycin for prophylaxis of Endocarditis in patients with valvular heart disease, who are undergoing certain dental procedures and are allergic to Penicillin
    - Clindamycin + Primaquine = effective alternative to Trimethroprim-Sulfamethoxazole for moderate to severe *Pneumocystic jirovecii* pneumonia in AIDS patients
    - Used in combination with Pyrimethamine for AIDS related Toxoplasmosis of the brain
11. Adverse effects of Chloramphenicol
    - GIT disturbance in adults, rare in children

    - Azithromycin
        - Good tissue concentration
        - Used for 3 days
        - Long half-life

        - NVD
    - Oral or vaginal candidiasis
        - Alteration of normal microbial flora
    - Dose-related reversible suppression of RBC production
    - Aplastic anaemia - rare
        - Idiosyncratic
        - Non-dose related
        - Does not matter the route of administration
        - Occurs more frequently with prolonged use
        - Irreversible and fatal
    - Grey Baby Syndrome
        - New-born infants lack an effective glucuronic acid conjugation mechanism for the degradation and detoxification of chloramphenicol, leading to drug accumulation
        - Includes
            - Vomiting
            - Flaccidity
            - Hypothermia
            - Grey colour
            - Shock
            - Vascular collapse
    - CYP inhibitor*

12. Oxazolidinones
    a. Examples
        - Linezolid
        - Tedizolid
    b. MoA
        - Inhibits protein synthesis
        - Binding to the P site (23S) of 50S ribosomal subunit
            - Prevents initiation of protein synthesis
            - no crossresistance with other 50S inhibitors
        - Active against other resistant strains
            - Penicillin resistant strains of *S. pneumoniae*
            - MRSA, VRSA
            - Vancomycin resistant enterococci
    c. Bacteriostatic and bactericidal activity
        - Has activity against *Mycobacteria tuberculosis*
        - Active against gram positive bacteria
            - Bacteriostatic:
                - Enterococci
                - Staphylococci
            - Bactericidal:
                - Streptococci
    d. Bioavailability
        - 100% after PO administration
    e. Principle toxicity
        - Haematologic
            - Reversible
            - Generally mild
            - Include
                - Thrombocytopenia - common when drug is administered for >2 weeks
                - Anaemia and neutropenia
                    - More common in patients with a predisposition to or underlying bone marrow suppression

13. Aminoglycosides
    a. Examples
        - Streptomycin
        - Neomycin
        - Kanamycin
        - Amikacin
        - Gentamycin
        - Tobramycin
        - Sisomycin
        - Netilmicin
    b. Routes of Administration
        - Poorly absorbed orally
        - Well absorbed IM or IV
        - topical G N
        - inhale T
        - IT for G*
    c. Explain concentration dependent killing, post antibiotic effect
        - Higher the concentration, higher the proportion of the bacteria killed
        - Note:
            - Post-antibiotic effect
                - Anti-bacterial activity persists beyond the time during which measurable drug

is present

d. Synergistic Effects
   - When it is administered with a cell-wall active antibiotic (β-lactam or Vancomycin) it exhibits synergistic killing against certain bacteria
   - Effect of drugs in combination is greater than the anticipated effect of each individual drug
e. Adverse Effects
   - Ototoxicity
     - Risk factors
       - Therapy for >5 days
       - Higher doses
       - Elderly
       - Renal insufficiency
     - Auditory damage
       - Tinnitus, high-frequency hearing loss
       - Neomycin, Kanamycin, Amikacin are most ototoxic
     - Vestibular damage
       - Vertigo, ataxia, loss of balance
       - Streptomycin and Gentamycin are most vestibulotoxic
   - Nephrotoxicity
     - Risk factors
       - As ototoxicity i.e.
         - Therapy for >5 days
         - Higher doses
         - Elderly
       - Concurrent use
         - Loop diuretics
         - Nephrotoxic, antimicrobial agents (Vancomycin, Amphotericin B
         - Avoid if possible
   - Others
     - Curare like effect with neuromuscular blockade
       - Respiratory paralysis
       - Reversible by Calcium gluconate, Neostigmine
     - Infrequent hypersensitivity
f. Advantages of once daily dose
   - Concentration-dependent killing
   - Post-antibiotic effect
   - Less labour
   - More compliance
   - Monitor drug levels less frequently
g. Those with activity against TB
   - Streptomycin
   - Amikacin, Kanamycin
h. Spectra of activity for Gentamycin
   - Alone
     - Many strains of staphylococci
     - Coliforms
     - Other gram negative bacteria
   - Synergistic with β-lactam antibiotics against:
     - *E.coli*
     - *Proteus*
     - *K.pneumoniae*
     - *Enterobacter*
     - *Stenotrophomas*
     - Other gram negative rods that may be resistant to multiple other antibiotics

14. Sulfonamides
    a. MoA
       - Are PABA (p-aminobenzoic acid) analogues
       - Inhibits dihydropteroate synthase
       - Mammalian cells depend on exogenous sources of folate (not affected)
    b. MoR
       - Lack enzymes for folate synthesis
       - Overproduction of PABA
       - Low affinity for sulphonamides
       - Impaired sulphonamide permeability
    c. Adverse Effects
       - Fever
       - Exfoliative dermatitis, photosensitivity, urticaria
       - Nausea, vomiting and diarrhoea
       - Stevens-Johnson's syndrome
       - Urinary tract - precipitate in acid pH (crystalluria) - urinary alkalinisation
       - Haemolytic anaemia, bone marrow suppression
    d. Cotrimoxazole
       i. Components

- Sulphamethoxazole
- Trimethoprim

ii. Why synergistics
- These drugs block sequential steps in the folate synthetic pathway blockade

iii. Indications
- Infections with
  - Pneumocystis jirovecii pneumonia
  - Toxoplasmosis
  - Nocardiosis

iv. Adverse effects
- Similar to sulphonamides except megaloblastic anaemia

15. Fluoroquinolones
    a. MoA
    - Block bacterial DNA synthesis by blocking bacterial topoisomerase II (DNA gyrase)…
      - Prevents the relaxation of positively supercoiled DNA required for normal
    - …and topoisomerase IV
      - Interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division

    b. Which do not have adequate systemic concentrations?
    - Norfloxacin
    - Nalidixic acid

    c. Which ones for TB?
    - Ciprofloxacin 750mg BD
    - Levofloxacin 500 - 750 OD, Orthofloxacin
    - Gatifloxacin, Moxifloxacin 400mg OD
      - Inhibits some strain of M. tuberculosis at concentrations of less than 2mcg/ml.
      - Moxifloxacin is the most active against M. tuberculosis
    - Levofloxacin more than ciprofloxacin against M. tuberculosis but ciprofloxacin more active on atypical mycobacteria. Used with at least 2 or more other active agents

    d. Which are the respiratory quinolones - enhance gram-positive bacteria
    - Levofloxacin
    - Gatifloxacin
    - Gemifloxacin
    - Moxifloxacin

    e. Adverse Effects
    - Common effects
      - NVD
      - Headache, dizziness, insomnia
      - Skin rash
      - Abnormal LFTs
    - Photosensitivity
      - Lomefloxacin
      - Pefloxacin
    - QT_C prolongation
      - Gatifloxacin
      - Levofloxacin
      - Genifloxacin
      - Moxifloxacin
    - Hyperglycaemia in diabetic patients and hypoglycaemia in patients receiving oral hypoglycaemic agents
      - Gatifloxacin
    - Arthropathy
      - Due to possible damage to growing cartilage
      - Reversible
    - Tendonitis - rare
      - In adults

Primary Resistance
- The first time a drug is administered and the patient does not respond to it

Secondary Resistance
- From mutations in the bacteria

Introduction

Friday, 23 June 2017 11:24 AM

- Pharmacokinetics
  - Definition
  - Routes of administration of drugs
    - Factors affecting PO absorption of drugs
      - Ionisation
        - Acidic drugs poorly absorbed in the stomach
      - Physical property of the drug
        - Solid/liquid
      - pKa of the drug
        - pH at which 50% of the drug is ionised
      - GIT transit time
      - Hormone levels
        - Thyrotoxic patients have high transit time
      - GIT or Hepatic blood flow
      - Absorptive surface
        - Certain diseases impair
          - IBD
        - Surgery
      - Food
      - Other drugs taken orally
  - Metabolism
    - Phases of metabolism
  - Rotes of drug excretion
- Pharmacodynamics
  - Definition
  - Definition of a drug
  - How drugs bring about the cellular changes
  - How drugs bind to receptors
    - Types of receptors
    - How the receptors work
      - Tyrosine kinase
      - Serine kinase
      - Cytokine kinase
  - Transduction reactions/mechanisms
  - Types of G proteins
  - Examples of second messengers