



DRUG INTERACTIONS

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SCOPE OF LECTURE

- **Define Drug Interactions (DIs)**
- **Discuss why DIs are important**
- **Classify DIs**
- **Discuss the clinical Significance of DIs**
- **Mechanisms of DIs**
- **Discuss in detail, with examples, specific types of DIs**

DEFINITION

- **When one drug (A) Alters the intensity of p'cological effects of another drug (B) Given concurrently.**

A = precipitant drug

B= the object drug

WHY ARE DIs IMPORTANT

- 1. The incidence of clinical drug-drug interactions (DIs) increases as the number of drugs used increases**
- 2. ~ 3% of hosp admissions are related to DIs**



3. The use of several drugs concurrently (polypharmacy) is often essential to obtain a desired therapeutic effect, or to Rx coexisting dxs e.g. in the Rx of:

i. Hypertension

ii. Heart failure

iii. Cancer

iv. Some infectious dxs e.g. TB, AIDS

- 4. Patients often receive several prescribed drugs, plus**
- i. Over -the-counter (OTC) medicines**
 - ii. ‘alternative’ remedies &**
 - iii. ‘lifestyle’ drugs taken for social reasons, e.g ethanol**
- These categories of substances may interact with each other or with prescribed drugs**

- **During polypharmacy the Dr needs to know whether a specific combinatn in a given ptnt has the potential to result in an interactn, & if so how to:-**
 - (i) Take advantage of the interactn if it leads to improvement in therapy (beneficial DIs) OR**
 - (ii) How to avoid the consequences of an adverse DI**

Mechanisms of DIs

I. Pharmaceutical

II. P'cokinetic (PK)

III. P'codynamic (PD)

IV. Combined DIs

I. PHARMACEUTICAL DIs

- **These occur by chemical rxn or physical interactn when drugs are mixed, e.g**
 - i. Thiopentone (IV Anaesthetic agent) & succinylcholine (Skeletal ms relaxant): Precipitation**
 - ii. Penicillin (antibiotic) & hydrocortisone (steroid): Inactivation of penicillin**

A. Absorption

1. Examples of DIs at GIT absorptn level

- i) Chelation**
- ii) Altered gastric pH**
- iii) Altered GIT motility**

Absorption 2

i) Chelation

- a. Al^{3+} , Ca^{2+} & Mg^{2+} ions contained in **antacids** form insoluble complexes with **tetracycline antibiotics(ABs), quinolone ABs, or thyroxine** leading to ↓**ced GIT absorptn** of the latter drugs

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Absorption 3

b. Colestyramine (Bile acid-binding resin used to Rx hyperlipidemia) binds (chelates) several drugs e.g. **Furosemide, thiazide diuretics, thyroxine, warfarin & digoxin** leading to their ↓ced absorptn

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Absorption 4

(ii) Altered gastric pH

- **Antacids ↑ se gastric pH & there4 ↓ ce the absorptn of itraconazole, Ketoconazole, digoxin, & atazanavir c require acid for absorptn**

Absorption 5

(iii) Altered GIT motility

- a. Atropine & Opioids** slow GIT absorptn of drugs by inhibiting gastric emptying
- b. Metoclopramide** (prokinetic drug) accelerates gastric emptying of drugs & hence accelerates their absorptn

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2. Example of a DI at subcutaneous absorptn level

- **Absorption from Sc sites can be slowed by vasoconstrictors given simultaneously**

DI at sc absorptn level 2

Example

- **Adrenaline** causes vasoconstriction & there4 slows the absorption of **lidocaine** (a local anaesthetic c is given by injection)
- It there4 prolongs lidocaine's local effect

B. Distribution

- **The mechanisms by which DIs alter drug distribution include:-**
 - 1. Competition for plasma protein binding**
 - 2. Displacement from tissue binding sites**
 - 3. If one drug alters the size of the physical compartment in which another drug distributes**
 - 4. Alteration in local tissue barriers e.g. P-glycoprotein inhibition in the blood-brain barrier (BBB)**

B. Distribution

Example of DIs at distribution level

1. Competitn for plasma protn binding

- a. Salicylates displace Methotrexate from binding sites on albumin**

Distribution 3

- 2. Several antiarrhythmic drugs (including **Quinidine, Verapamil & amiodarone** displace **digoxin** from tissue binding sites**
- **They can therefore cause severe arrhythmias thru digoxin toxicity**

Distribution 4

3. Changes in drug distribution can occur if one agent alters the size of the physical compartment in which another drug distributes.

Distribution 5

Example

a. Diuretics reduce total body water

- They can therefore ↑ plasma levels 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**

Metabolism 2

- 1. Enzyme induction (stimulation) of CYP isozymes in the liver & small intestine leads to enhancement of drug-metabolizing activity, following prolonged exposure to an inducing agent**

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Metabolism 3

- **Maximal effects usually occur after 7 – 10 days & require an equal or longer time to disappear after the enzyme inducer is stopped**

Examples of DIs due to enzyme induction

a. Rifampi(ci)n when given for $\geq 3/7$ induces the hepatic metabolism of :-

- i. Warfarin**, leading to $\uparrow$ sed bleeding
- ii. Tolbutamide** (oral antidiabetic agent) leading to hyperglycemia in diabetic ptnts on Rx
- iii. Theophylline**, leading to $\downarrow$ sed bronchodilator effect in asthmatics

2. Enzyme inhibition

- **Inhibition of drug metabolizing enzymes generally takes place > quickly than enzyme induction**
- **It leads to an**
 - a. ↑se in the plasma conc of the parent drug & an ↑sed likelihood of its toxicity &**
 - b. ↓ctn in conc of the metabolite**

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Enzyme inhibition 2

- **These changes are most critical for drugs that are**
 - a. extensively metabolized &**
 - b. have a narrow therapeutic index**

Example of DIs due to enzyme inhibition

a. Cimetidine (H_2 histamine receptor antagonist used for Rx of PUD) inhibits hepatic metabolism of the following drugs leading to their toxicity:

i. **Diazepam** (benzodiazepine) →
↑ sed sedatn

ii. **Quinidine** → arrhythmias

iii. **Amiodarone** → ↑ sed hypotension

iv. **Theophylline** → Theophylline toxicity

Example of a DI due to enzyme inhibition 3

b. Erythromycin inhibits the metabolism of the following to
↑**se their toxicity**

- i. Ciclosporin**
- ii. Theophylline**
- iii. Carbamazepine**
- iv. Cisapride**
- v. Quinidine**
- vi. Sildenafil**
- vii. SSRIs**

3. reductn of drug clearance due to ↓ced hepatic blood flow

- **Propranolol** ↓ces hepatic blood flow & there4 reduces the clearance of **morphine & verapamil** c are metabolized in the liver

D. Excretion

- **The main mechanisms by which one drug can affect the rate of renal excretion of another are:-**
 - 1. Alteration of protein binding & hence filtration**
 - 2. Inhibition of tubular secretion**
 - 3. Alteration of urine flow & /or urine pH**

1. Inhibition of tubular secretion

- **Probenecid** inhibits active tubular secretion of the following leading to their ↓ renal excretion & hence prolonged action
 - a. **Penicillin (beneficial DI)**
 - b. **Zidovudine**
 - c. **Indomethacin**

2. Alteration of urine flow & pH

- **Drugs c alter urinary pH may change the ionizati~~n~~ state of drugs that are weak acids or weak bases leading to changes in their renal tubular reabsopt~~n~~**
- **This is clinically important when it is necessary to accelerate the excretn of drugs by the kidney e.g. in the case of overdose**

Alteration urine flow & pH 2

Examples

- a. When a ptnt takes an overdose of a weak acid drug e.g. **Aspirin** or **phenobarbitone**, its excretion may be accelerated by alkalinizing the urine e.g. by giving **NaHCO₃**

Alteration urine flow & pH 4

- b. Conversely, excretion of a weak base e.g. **Pyrimethamine** or **Pethidine** may be accelerated by acidifying the urine, e.g. by admin of **NH₄CL****

III. PD DIs

These may occur thru

1. Direct mechanism:

- **When drugs interact at a common receptor site**

OR

2. Indirect mechanism

- **When drugs have additive or inhibitory effects due to actns at different sites in an organ**

PD DIs 2

- **When drugs with similar p'cologic effects are admin concurrently, an additive or synergistic response is usually seen**
- **Conversely, drugs with opposing p'cologic effects may ↓ce the response to one or both drugs**

a. Interactions based on an additive effect

- **This describes the combined effect of two drugs that is equal to the sum of the effect of each drug given alone**
 - **Hence there is an arithmetic summing of the effects of the two drugs ($1+1=2$)**
- **The two drugs may or may not act on the same receptor to produce such an effect**

Examples of additive PD DIs

- i. The additive depressn of CNS fn caused by concurrent admin of **Diazepam** (a sedative-hypnotic) with **Pethidine** (an Opioid)
- ii. The concomitant use of several antihypertensive drugs with different mechanisms & sites of actn, to lower BP in hypertensive ptnts e.g.
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b. Interactions based on synergistic effects

- **Synergism is said to occur when the effects of ≥ 2 drugs used together are significantly greater than expected from their effects when used individually ($1+1 > 2$)**

Examples of Synergistic PD DIs

i. Trimethoprim & sulfamethoxazole in cotrimoxazole block two sequential steps in folic acid synthetic pathway

- **This results in killing of bacteria (bactericidal effect) as opposed to inhibition of bacterial growth (bacteriostatic effect) by use of either drug alone**

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c. Interactns based on antagonistic (opposing) actn or effect

- **In Antagonism, the effect of two drugs given together is less than the sum of the responses to the same doses given separately.**
 - **i.e, One drug interferes with the actn of another**

Examples

- i. **Propranolol** (β - adrenoceptor antagonist) diminishes the bronchodilator effect of **Salbutamol** (β_2 - adrenoceptor agonist) if given concurrently = harmful competitive antagonism
- ii. **Naloxone** reverses the respiratory depressn caused by opioids (e.g. **pethidine**) by competing for the same receptor site = beneficial competitive antagonism

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IV.COMBINED TOXICITY

- **The combined use of ≥ 2 drugs, each of c has toxic effects on the same organ can greatly $\uparrow$ se the likelihood of organ damage**

Example

- **Concurrent admin of **Gentamycin** (aminoglycoside AB) with **Vancomycin** (glycopeptide AB)**
both of c are nephrotoxic, ↑ses the likelihood of kidney damage, even tho the dose of either drug alone may be insufficient to produce nephrotoxicity