

ANTIDOTAL THERAPY

Introduction

- **The mainstay of therapy for poisoning is good support of the airway, breathing, circulation (ABC), & vital metabolic processes of the poisoned patient until the poison is eliminated from the body;**
- **Specific antidotes are rarely required.**

Intro 2

- **Commonly used specific antidotes include:**
 - i.* ***N*-acetyl-*L*-cysteine for acetaminophen poisoning**
 - ii. Opioid antagonists for opioid overdose**
 - iii. Chelating agents for poisoning from certain metal ions.**

Intro 3

- **Selective antidotes are available for only a few classes of toxins.**

GENERAL MoA of ANTIDOTES

- **Antidotal therapy involves antagonism or chemical inactivation of an absorbed poison.**
- **The general MoA of antidotes are:**
 - A. Alteration of the PD of a poison**
 - B. Alteration of the PK of a poison**
 - C. Nonspecific functional antidotes**

General MoA 2

A. Antidotal therapy based on altered PD of a poison

1. Competitive antagonism

- The PD of a poison can be altered by competition at a receptor, e.g the antagonism provided by naloxone therapy in heroin overdose

General MoA 3

2. A physiological antidote uses a different cellular mechanism to overcome the effects of a poison

➤ **Example: the use of glucagon to stimulate an alternative to the blocked β adrenoceptor & $\uparrow$ se cellular cAMP in propranolol & other β adrenergic antagonists overdose.**

General MoA 4

3. Chemical antagonism

- **Anti-venoms and chelating agents bind and directly inactivate poisons**

General MoA 5

B. Antidotal therapy based on altered PK

- **The biotransformation of a drug can also be altered by an antidote;**
 - **E.g fomepizole inhibits alcohol dehydrogenase to stop the formation of toxic acid metabolites from ethylene glycol & methanol**

General MoA 6

C. Nonspecific functional antidotes.

- Many drugs used in the supportive care of a poisoned patient may be considered nonspecific functional antidotes.
 - These include anticonvulsants, vasoconstricting agents, etc

Intro 4

- The major antidotes and their characteristics are listed in Table 1 (compiled from **Tabl 58–4 Katz 14th Ed, 2018 & Table 4–9 Goodman & Gilman 13th Ed, 2018**)

Poison(s)	Antidote	Comments
Acetaminophen	Acetylcysteine Methionine	Best results if given within 8–10 hrs of overdose. Monitor LFTs & acetaminophen blood levels. Acetylcysteine is given IV; Methionine, orally.

Poison(s)	Antidote	Comments
β adrenergic antagonists	Glucagon hydrochloride	5–10 mg IV bolus may reverse hypotension and bradycardia.

Poison(s)	Antidote	Comments
Delirium caused by Anticholinergic agents;	Physostigmine salicylate NB: do not use for TCA overdose	Adult dose is 0.5–1 mg IV slowly. The effects are transient (30–60 mins) The lowest effective dose may be repeated when symptoms return. May cause ↓HR, ↑sed bronchial secretions, seizures.

Antimuscarinic Anticholinergic agents cont

- **Should have atropine ready to reverse excess effects of Physostigmine**

Poison(s)	Antidote	Comments
Anticholinesterases: Organophosphates & carbamates	Atropine	A initial dose of 1–2 mg (for children, 0.05 mg/kg) given IV & repeated until symptoms of atropinism appear. Dose may be doubled every 10–15 mins if there is no response. Therapeutic end point: decreased wheezing & pulmonary secretions

Symptoms of atropinism:

- a. Tachycardia**
- b. Dilated pupils**
- c. Ileus**

Poison(s)	Antidote	Comments
Benzodiazepines	Flumazenil	Adult dose is 0.2 mg IV, repeated as necessary to a maximum of 3 mg. Do not give to patients with seizures, benzodiazepine dependence, or TCA overdose.

Poison(s)	Antidote	Comments
Ca²⁺ channel blockers; Fluoride	Calcium gluconate or chloride Others: - glucagon - high-dose insulin (0.5–1 unit/kg/h) plus glucose	Large doses may be required in severe calcium channel blocker overdose. Start with 15 mg/kg IV.

Poison(s)	Antidote	Comments
Carbon monoxide	Oxygen	Give 100% by high-flow nonrebreathing mask; use of hyperbaric chamber is controversial but often recommended for severe poisoning.

Poison(s)	Antidote	Comments
Cardiac glycosides	Digoxin antibodies	One vial binds 0.5 mg digoxin; indications include serious arrhythmias, hyperkalemia.

Poison(s)	Antidote	Comments
Membrane-depressant cardiotoxic drugs (TCAs, quinidine, etc)	Sodium Bicarbonate	1–2 mEq/kg IV bolus usually reverses cardiotoxic effects (wide QRS, hypotension). Give cautiously in heart failure (avoid sodium overload).

Poison(s)	Antidote
Coumarin, indanedione	Vitamin K ₁ (phytonadione)

Poison(s)	Antidote	Comments
Cyanide	Hydroxocobalamin	Adult dose is 5 g IV over 15 minutes. Converts cyanide to
	Sodium Thiosulfate	Cyanocobalamin (Vit B ₁₂)

Poison(s)	Antidote
Drug-induced dystonia	Benztropine, Diphenhydramine

Poison(s)	Antidote
Heavy metals ➤ Arsenic ➤ Copper ➤ Lead ➤ Mercury	Dimercaprol, Succimer, Penicillamine CaNa₂EDTA, Dimercaprol, Penicillamine, Succimer Penicillamine, Dimercaprol, Succimer

Poison(s)	Antidote	Comments
Iron salts	Deferoxamine	If poisoning is severe, give 15 mg/kg/h IV. 100 mg of deferoxamine binds 8.5 mg of iron.
Isoniazid seizures	Pyridoxine hydrochloride	

Poison(s)	Antidote
Malignant hyperthermia	Dantrolene

Poison(s)	Antidote	Comments
Methanol, ethylene glycol	Fomepizole; Ethanol	Fomepizole is More convenient than ethanol. Give 15 mg/kg; repeat every 12 hrs A loading dose Ethanol is calculated so as to give a blood level of ≥ 100 mg/dL (42 g/70 kg in adults).

Poison(s)	Antidote
Methemoglobinemia	Methylene blue
Methotrexate	Leucovorin calcium
Neuroleptic malignant syndrome	Bromocriptine

Poison(s)	Antidote	Comments
Rapid-onset mushroom poisoning with predominant muscarinic excess symptoms	Atropine	Useful for control of muscarinic symptoms. NB: is of no value in delayed-onset mushroom poisoning.

Poison(s)	Antidote	Comments
Narcotic drugs & other opioid Derivatives	Naloxone	A specific antagonist of opioids; give 0.4–2 mg initially by IV, IM, or SC inject. Larger doses may be needed to reverse the effects of overdose with propoxyphene, codeine, or fentanyl derivatives. Duration of actn (2–3 hrs) may be significantly shorter than that of the opioid being antagonized.

Poison(s)	Antidote	Comments
Organophosphate cholinesterase inhibitors	Pralidoxime (2-PAM)	Adult dose is 1 g IV, repeated every 3–4 hours as required or preferably as a constant infusion of 250–400 mg/h. Pediatric dose is ~250 mg. No proved benefit in carbamate poisoning.

Poison(s)	Antidote	Comments
Na ⁺ channel blocking drugs	Sodium Bicarbonate	
Sulfonylurea-induced hypoglycemia	Octreotide acetate	
Theophylline, caffeine, Metaproterenol	Esmolol	Short-acting β blocker. Infuse 25–50 mcg/kg/min IV.

Poison(s)	Antidote
Valproate hyperammonemia	Carnitine