



# Application and mechanism of antidote in pharmaceutical chemistry



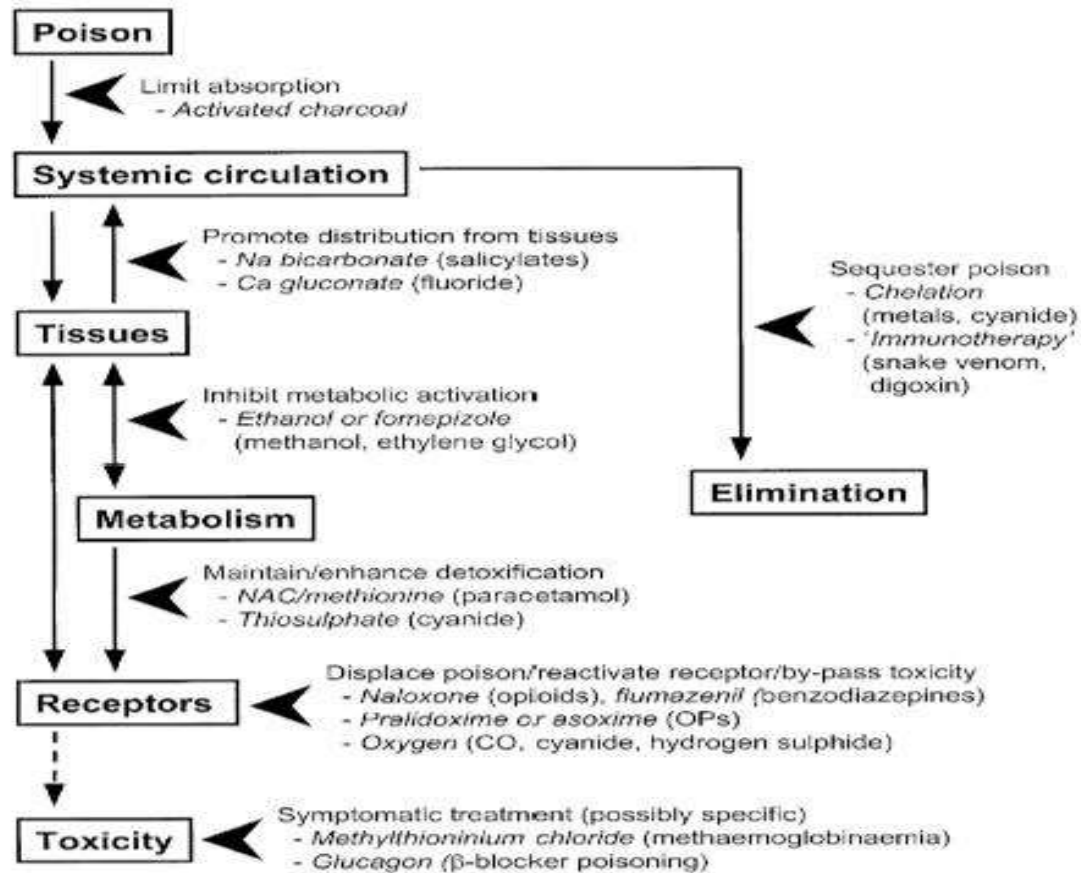
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## Introduction

- Antidotes are drugs, chelating or chemical substances that counteract the effects of drugs or poison.
- Antidotes for some particular toxins are manufactured by injecting the toxin into an animal in small dose and extracting the resulting antidotes from animal blood.
- Some toxins have no known antidotes for example poison aconitine, is fatal when it enters the human body.
- Patient survival including supportive therapy and correct antidotes
- Administration of antidotes can be life saving also reduce morbidity and health cost by shortening duration of treatment

## Mechanism of action of some antidotes



**Figure 1.1:** Simplified summary of the sites/mechanism of action of some antidotes (adapted from Saviuc and Danel, 1993)

Classification of antidotes:

1-physical antidotes

1. Adsorbing : is adhesion of atoms,ions or molecules from gas,liquid or dissolved solid to surface for example activated charcoal.
2. Coating
3. Dissolving

What is activated charcoal?

- It is simply burnt wood mainly use in drug over dose and chemical poisoning by binding drugs within GIT.
- The absorption result from weak intramolecular force.
- Example on most common drug poison treating with charcoal is aspirin.

2\_Chemical antidotes: are agents which change the chemical nature of poison.

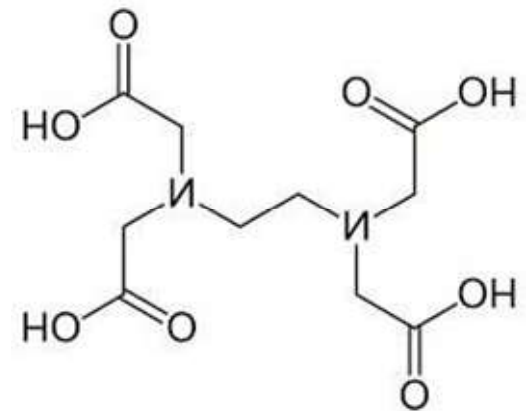
- Mainly acts by two mechanism:

1. Complex formation :for example

- Dimercaprol have sulfhydryl group that bind metal such as As and pb



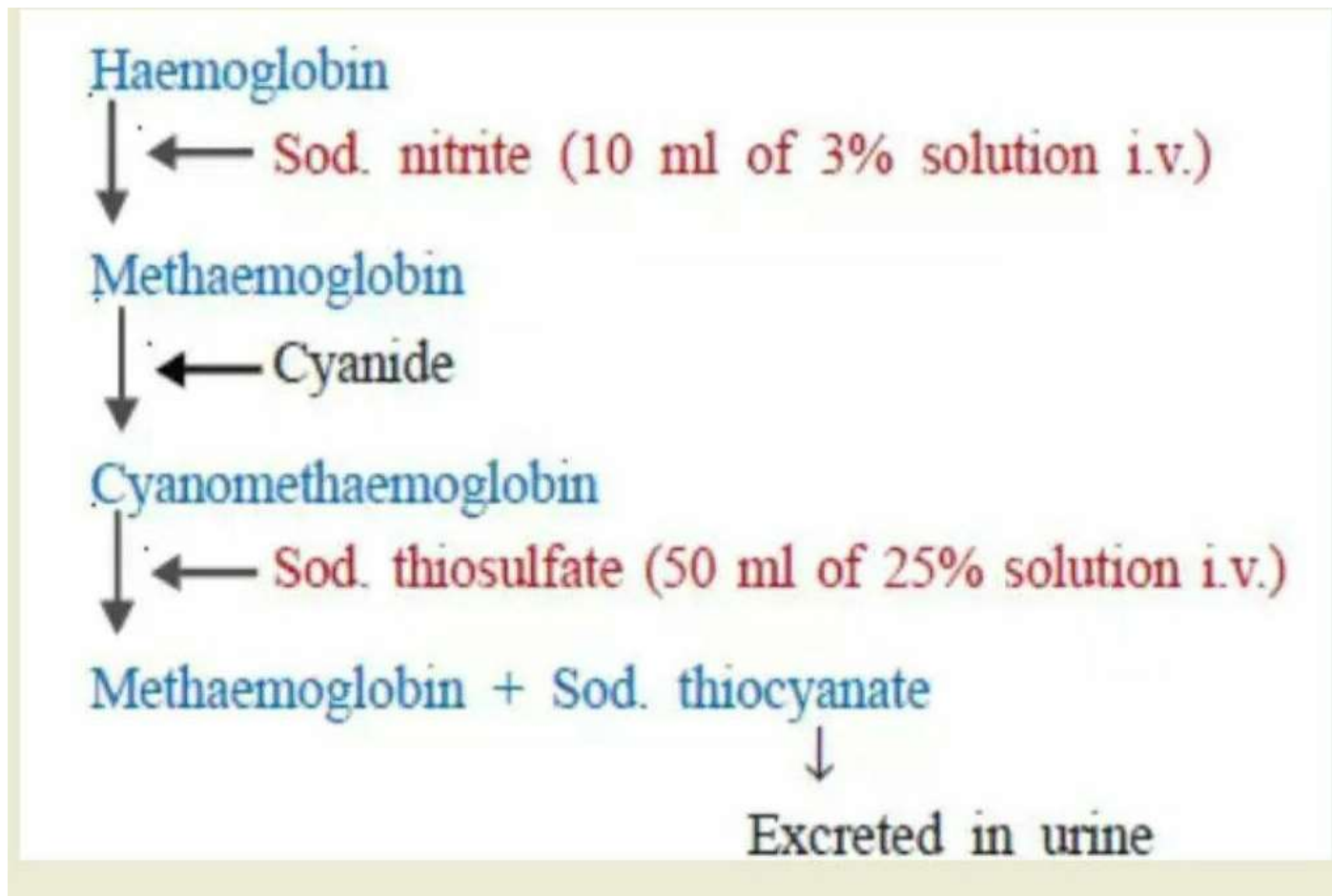
- EDTA for lead and zinc poisoning.



2\_Metabolic conversion:detoxification compounds to less toxic product for example cyanide antidote

- Exposure to cyanide may be encountered in work place accident or as sideeffect of sodium nitroprusside infusion.
- Cyanide inhibit cellular respiratory by binding reversible to cytochrom oxidase so clinical feature are due to tissue hypoxia .

Cyanide antidote:



Cyanide antidote:

## characteristics of cyanide toxicity and recommended antidotes

### ■ Severe toxicity

**Symptoms:** severe metabolic acidosis, coma, hypotension

**Antidotes:** oxygen, hydroxocobalamin (if available). Otherwise, dicobalt edetate may be used, but only if the diagnosis is certain, or sodium nitrite with sodium thiosulphate

### ■ Moderate toxicity

**Symptoms:** short-lived drowsiness, vomiting, mild metabolic acidosis

**Antidotes:** oxygen, sodium thiosulphate

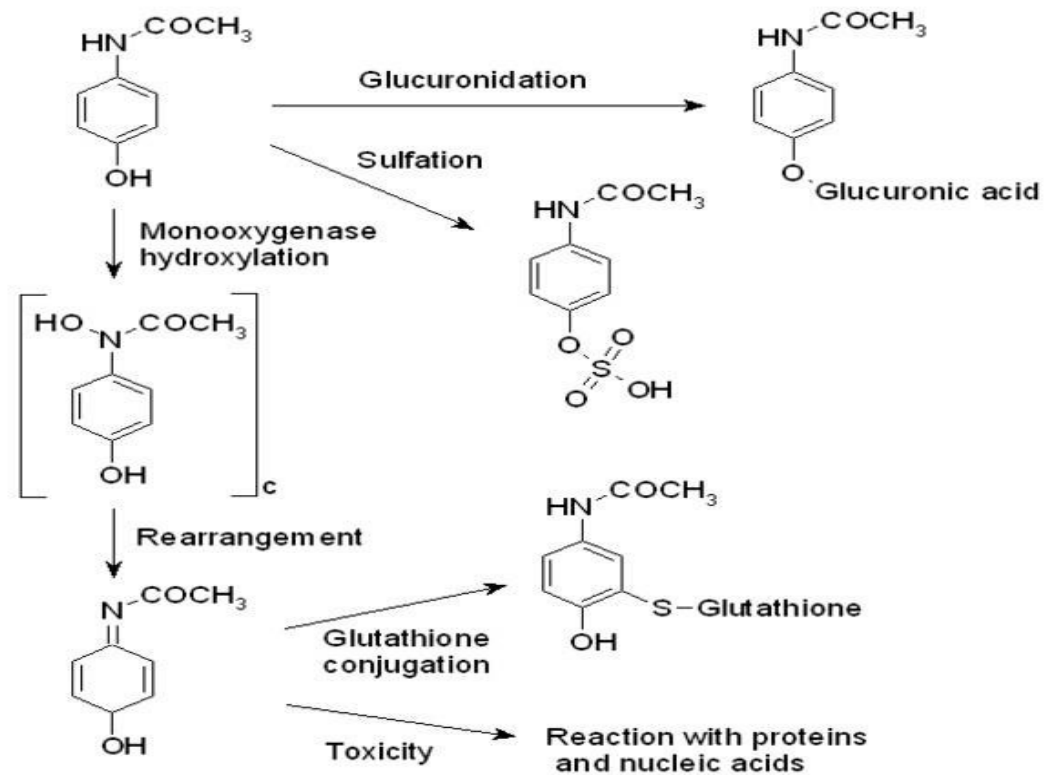
### ■ Mild toxicity

**Symptoms:** asymptomatic or mild dizziness, nausea, no metabolic acidosis

**Antidotes:** none, unless clinical deterioration



3\_pharmacological antidotes: Some examples on drugs using as  
antidotes  
paracetamol poisoning.

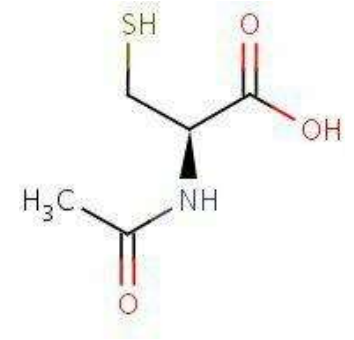


The antidote choice is intravenous N-acetylcysteine .

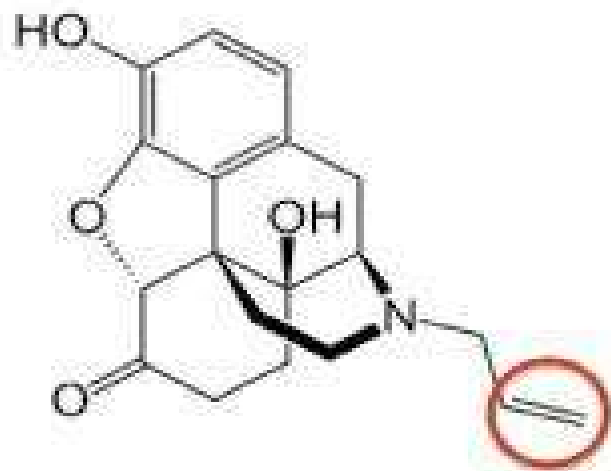
- NAC act as glutathione conjugate.
- NAC associated with anaphylactic reaction ,which are dose depending
- Given first infusion over 60 minutes rather than 15 minutes.

### Opioid poisoning

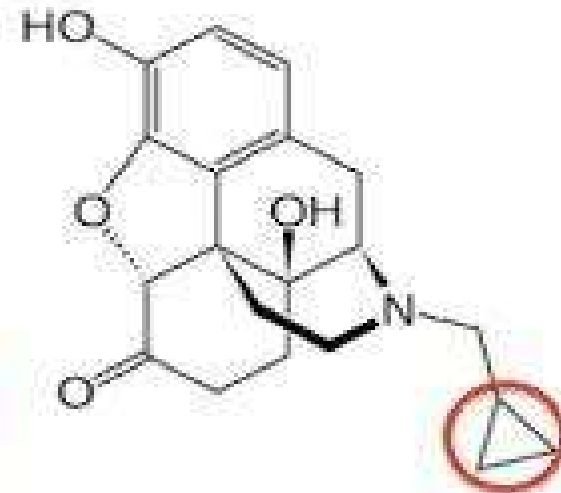
- Nalaxone is synthetic N\_allyl derivative of oxymorphone and is opioid antagonist
- It can be administration IV
- Nalmefen is long acting parenteral antagonist whose use in the acute care
- Naltrexone is oral antagonist ,not using in acute opioid toxicity.



## Opiod antidote



Ethylene



Cyclopropane

## Toxic alcohol

- Ethylene glycol and methanol are metabolized by alcohol dehydrogenase enzyme, ethylene glycol is metabolized to glycolic acid which cause metabolic acidosis, finally to oxalic acid lead to hypocalcemia.
- Methanol is metabolized to form formic acid which cause metabolic and lactic acidosis.
- Antidotal treatment involve blocking the action ADH by giving ethanol or fomepizole.



#181196490

## Sulphonylureas poisoning:

- Over dose of sulphonylureas cause hypoglycemia.
- Treatment:
  1. Administration of intravenous dextrose(10\_20)% but have some problem.
  2. Diazoxide is directly inhibit pancreatic insulin release but it is limited efficacy and cause hypotension.
  3. Octereotide is long acting somatostatin analoge.

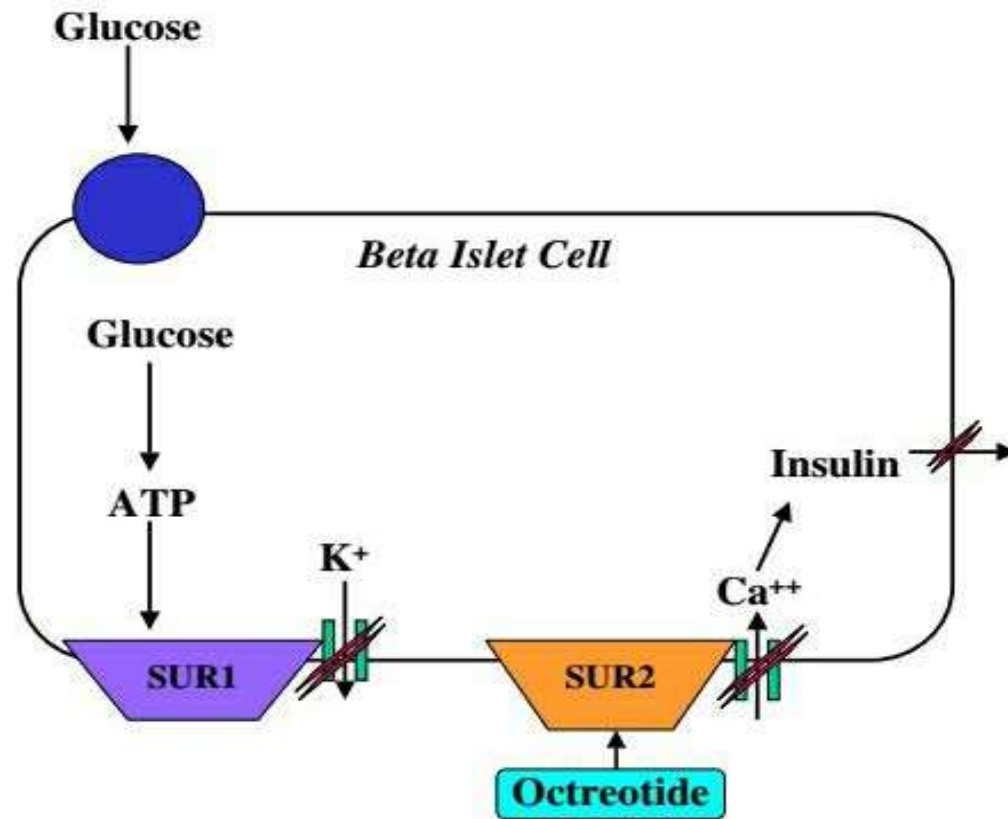


Fig. 3. Basic mechanism of action of octreotide on the pancreatic beta cell. Octreotide binds to a second sulfonylurea receptor (SUR2) on the pancreatic beta cells, inhibits calcium influx, and thereby reduces the secretion of insulin after depolarization. Ca, calcium; K, potassium.

## Antichlenergetic posining:

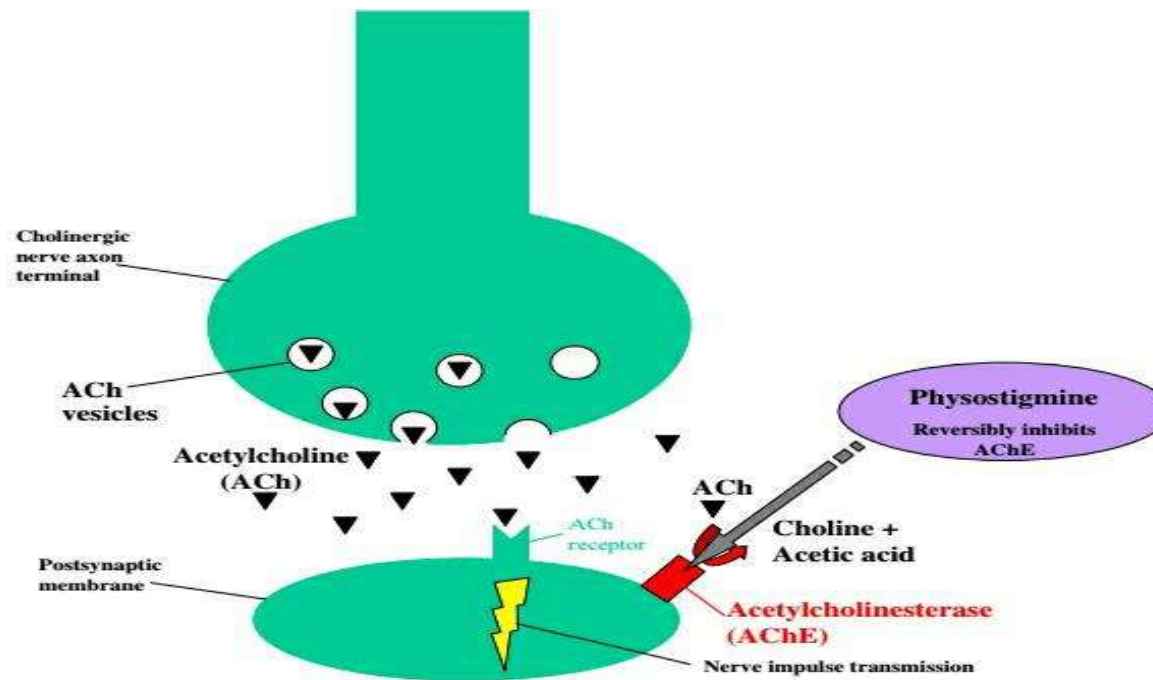


Fig. 4. Physostigmine. Impulse transmission at cholinergic synapse. ACh is released from stored vesicles in the presynaptic nerve terminal into the synaptic cleft. ACh diffuses across the cleft and binds with postsynaptic cholinergic receptors (either muscarinic or nicotinic), transmitting the impulse. AChE bound to the postsynaptic membrane hydrolyzes ACh and stops further neuronal stimulation. When AChE is inhibited by physostigmine, ACh builds up in the synapse, and continued stimulation of the postsynaptic membrane occurs.

Antidote for beta blocker and calcium channel blocker:

- Glucagon: is 29 amino acid polypeptide produced by the pancreas.
- It is used as antidote for beta blocker and calcium channel blocker over dose

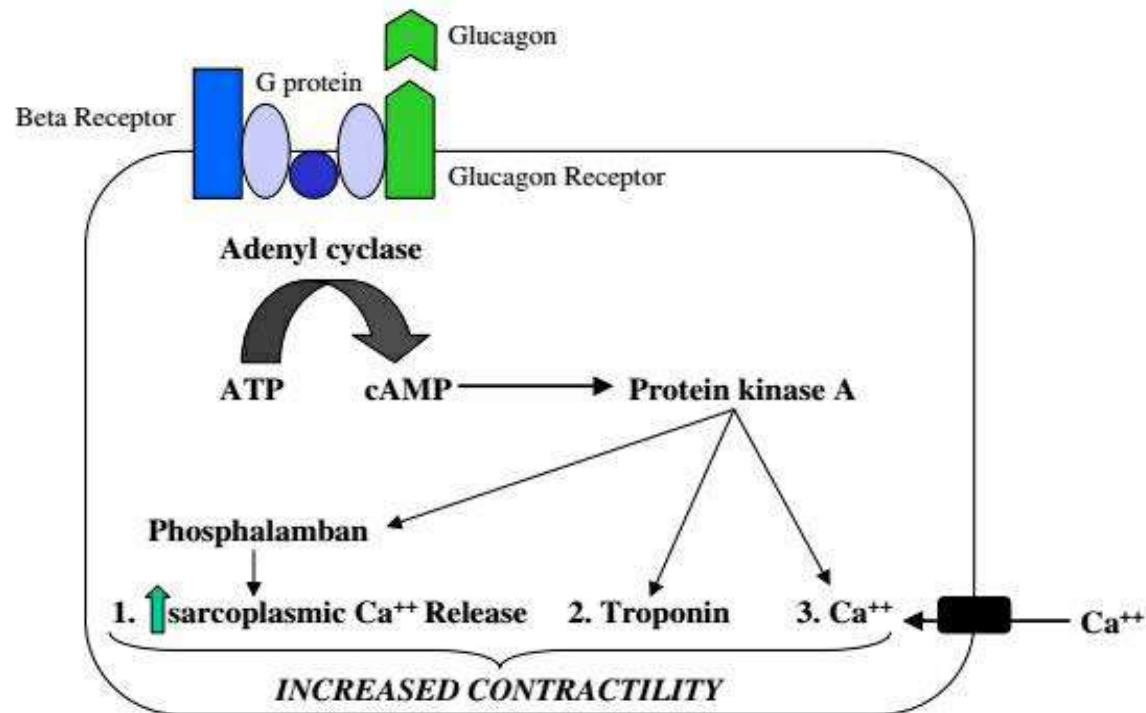


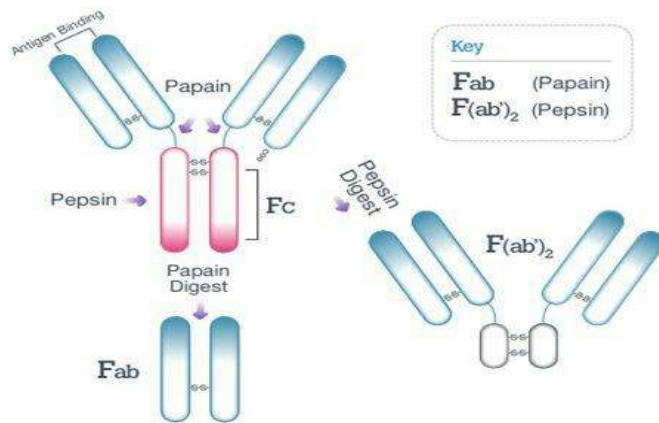
Fig. 1. Mechanism of action of glucagon in the myocyte. Ca, calcium.



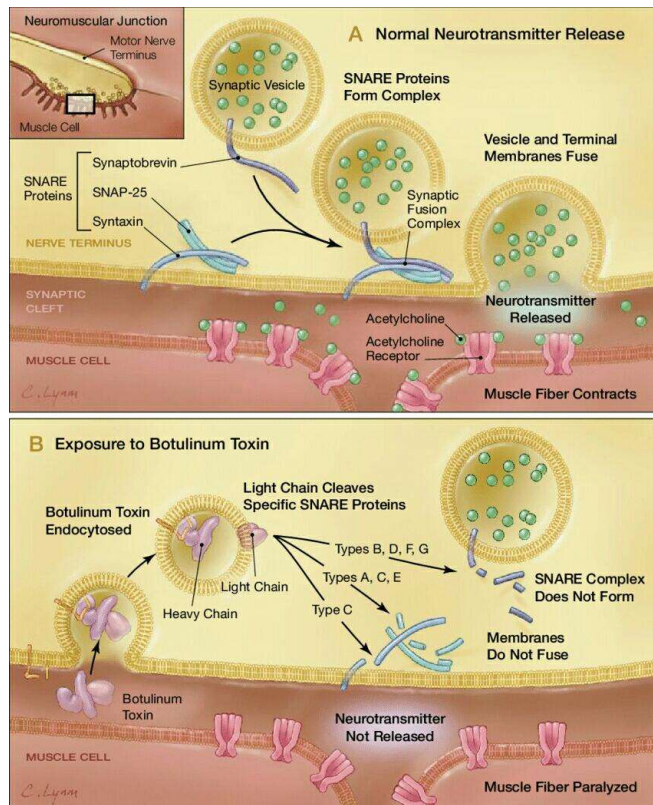
# Digoxin toxicity

## Antidote

- Digoxin immune fab (ovine)



# Botulinum Toxin



- Botulinum Antidote:
- Trivalent (A,B,E) botulinum antitoxin.
- Heptavalent (A,B,C,D,E,F,G) botulinum antitoxin.

## Conclusion:

- Although some antidotes are rarely used , but they have important , potentially life saving role in the treatment of toxic exposure.
- The use suitable antidote can prevent death and shorten hospitality as well as reduce the patient pain and suffering .
- The management of most cases of poisoning is supportive ,in minority cases antidote may be indicated, so in these situations the pharmacist plays key role in ensuring the timely provision and adequate supply of the drug.

## Summmary

<b>Antidote</b>	<b>Poisoning Indication</b>	<b>Minimum Stocking Recommendations</b>
<b>DMSA (Succimer, Chemet®)</b>	Heavy metals	2000 mg
<b>Folic acid</b>	Methanol	IV: 150 mg
<b>Flumazenil (Romazicon®)</b>	Benzodiazepines	10 mg
<b>Fomepizole (Antizol®)</b>	Ethylene glycol, methanol	12 grams
<b>Glucagon</b>	Beta blockers, calcium channel blockers	50 mg
<b>Hydroxocobalamin (Cyanokit®)</b>	Cyanide	10 grams
<b>Intravenous Fat Emulsion (Intralipid™)</b>	Lipophilic cardiotoxic drugs	200 mL (20%)
<b>Idarucizumab (Praxbind®)</b>	Dabigatran	5 grams
<b>L-Carnitine</b>	Valproic acid	12 grams
<b>Leucovorin</b>	Methotrexate	IV: 200 mg
<b>Methylene Blue</b>	Methemoglobinemia	1000 mg
<b>Naloxone</b>	Opioids	40 mg
<b>Octreotide (Sandostatin®)</b>	Sulfonylureas	1000 mcg
<b>Physostigmine</b>	Anticholinergics	20 mg
<b>Phytonadione (Vitamin K<sub>1</sub>)</b>	Warfarin, anticoagulant rodenticides	Oral: 100 mg IV: 100 mg
<b>Pralidoxime (2-PAM, Protopam®)</b>	Organophosphate insecticides, nerve gases	18 grams
<b>Protamine sulfate</b>	Heparin	500 mg
<b>Pyridoxine HCl (Vitamin B<sub>6</sub>)</b>	Isoniazid, ethylene glycol	IV: 8 grams
<b>Sodium Bicarbonate</b>	Sodium channel blockers (e.g. cyclic antidepressants), salicylates	84 grams
<b>Sodium thiosulfate</b>	Cyanide	50 grams
<b>Thiamine</b>	Ethylene glycol	IV: 100 mg

*Last updated Februarv 17. 2016*

Thank you for listening to me

