Acute Poisoning

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Learning Objectives

At the end of this session, learners should be able to do the following:

- List general and common clinical features of Poisoning.
- Understand the pathogenesis, clinical features and management of specific poisoning listed below:
  - Organophosphate
  - Paracetamol
  - Salicylate
  - Warfarin
  - Digoxin
- Know common antidotes for specific poisoning

Introduction

- In developed countries, poisoning causes approximately 10% of acute hospital medical presentations.
- Statistics are not readily available for the developing countries including Zambia.
- Most cases of poisoning are usually by self-administration of prescribed and over-the-counter medicines, or illicit drug.
- Common cases of poisoning seen in emergency departments include the following:
  - Organophosphate
  - Paracetamol
  - Salicylate
  - Warfarin
  - Digoxin

Common clinical features of Poisoning

Clinical features	Likely Poisoning
Constricted pupils (miosis)	Opioids, organophosphorus insecticides, nerve agents
Dilated pupils (mydriasis)	Tricyclic antidepressants, amphetamines, cocaine, antimuscarinic drugs
Divergent strabismus	Tricyclic antidepressants
Nystagmus	Carbamazepine, phenytoin
Loss of vision	Methanol, quinine
Papilloedema	Carbon monoxide, methanol
Convulsions	Tricyclic antidepressants, theophylline, opioids, mefenamic acid, isoniazid, amphetamines
Dystonic reactions	Metoclopramide, phenothiazines
Delirium and hallucinations	Amphetamines, antimuscarinic drugs, cannabis, recovery from tricyclic antidepressant poisoning
Hypertonia and hyper- reflexia	Tricyclic antidepressants, antimuscarinic drugs
Tinnitus and deafness	Salicylates, quinine
Hyperventilation	Salicylates, phenoxyacetate herbicides, theophylline
Hyperthermia	Ecstasy (MDMA), salicylates
Blisters	Usually occur in comatose patients

Organophosphate poisoning(OPP)

Introduction

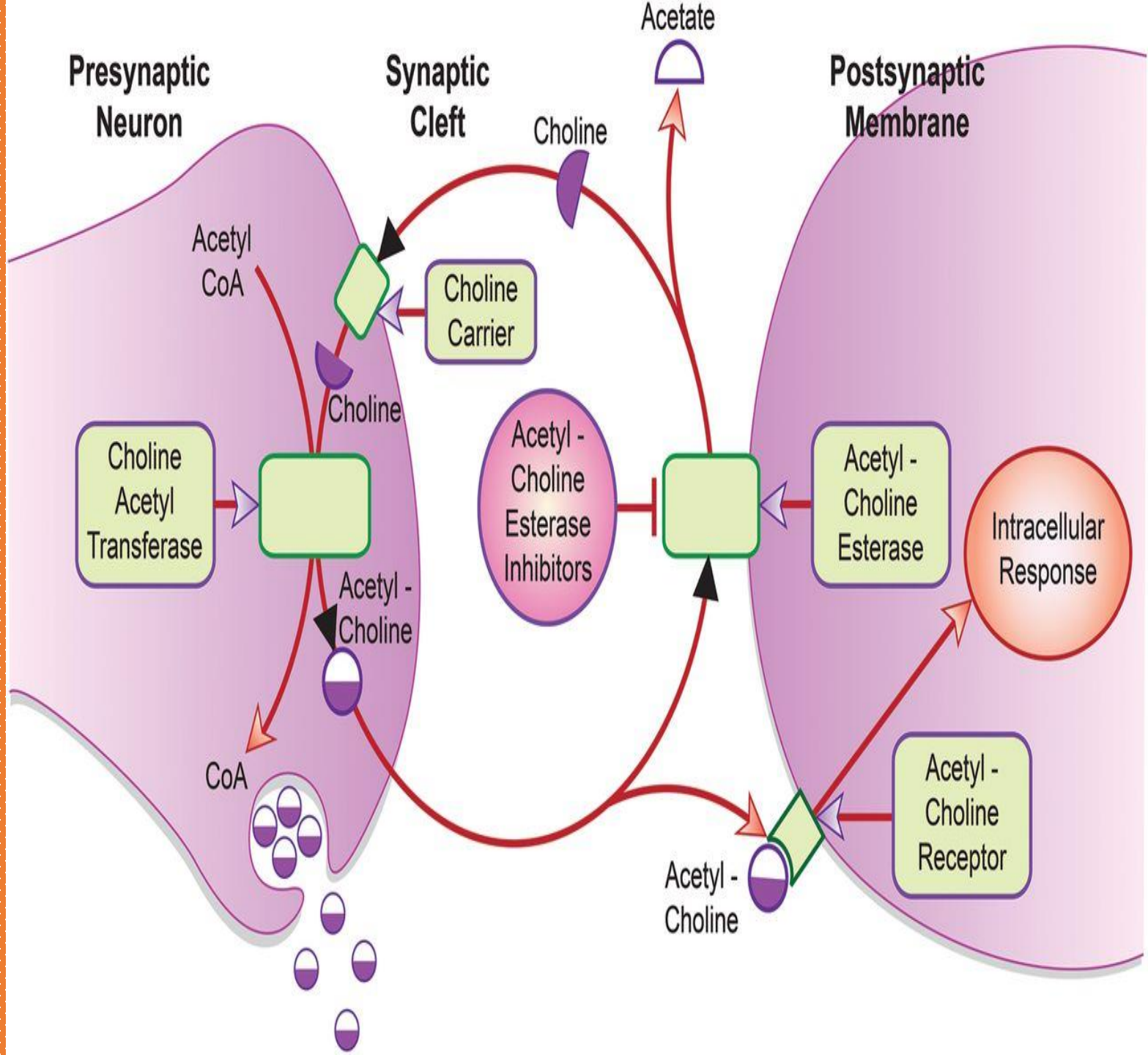
- Organophosphates (OP) are used as insecticides in agricultural and domestic settings throughout the world.
- As nerve agents, they have also been used in warfare terrorist attacks.

Mechanism of action

- Mechanism of action is through the inhibition of the enzyme acetylcholinesterase, leading to the accumulation of acetylcholine at cholinergic synapses.
- Excess acetylcholine causes constant acetylcholine receptor triggering, resulting in malfunction of the autonomic, somatic and central nervous systems

Normal neuromuscular junction physiology

- Acetylcholine (ACh) is synthesized from choline and acetyl-CoA through the action catalysed by choline acetyl-transferase in Cholinergic neurons.
- An action potential in presynaptic neuron triggers influx of Ca^{2+}
- Ca^{2+} stimulate exocytosis of presynaptic vesicles containing ACh, which is t released into the synaptic cleft.
- ACh binds to ACh receptors (muscarinic and nicotinic receptors) on the post-synaptic membrane resulting in nerve transmission.
- Acetylcholinesterase (AchE), located on the post-synaptic membrane, terminates the signal transmission by hydrolyzing Ach.

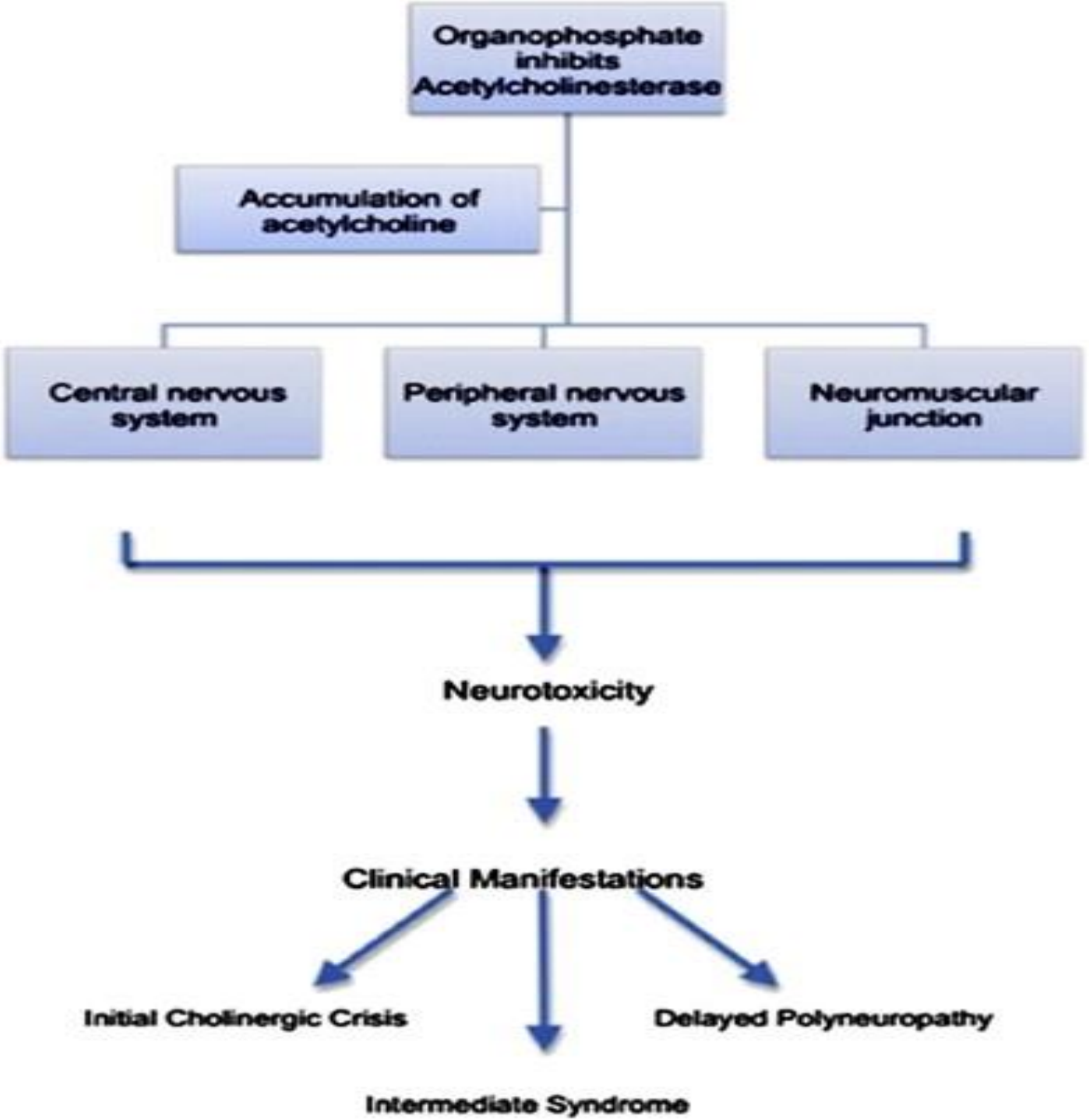


Pathophysiology of OPP

- Organophosphates acts as AchE inhibitor .
- ACh accumulates throughout the nervous system, resulting in overstimulation of cholinergic junctions (muscarinic effects), and at autonomic ganglia (nicotinic effects).

Signs and symptoms of organophosphate poisoning can be divided into three broad categories:

- **Muscarinic effects**
- **Nicotinic effects**
- **Central nervous system effects**



Clinical manifestations of acute organophosphate poisoning

Muscarinic

- Diarrhoea
- Urinary incontinence
- Miosis
- Bradycardia
- Bronchospasms
- Bronchorrhoea
- Bronchoconstriction
- Rhinorrhea
- Nausea
- Vomiting
- Hypersalivation
- Lacrimation
- Emesis
- Hypotension
- Cardiac arrhythmias
- Diaphoresis
- Fecal incontinence

Nicotinic

- Muscle fasciculations
- Tremors
- Muscle weakness
- Hypertension
- Tachycardia
- Sweating
- Mydriasis
- Muscle cramps
- Diaphragmatic and respiratory failure

CNS and Neuropsychiatric Effects

- Anxiety
- Emotional lability
- Restlessness
- Confusion
- Ataxia
- Tremors
- Seizures
- Coma
- Impaired memory
- Confusion
- Irritability
- Lethargy
- Psychosis

Treatment

General Treatment

- Airway control
- Adequate oxygenation
- Intubation may be an indication in patients severe respiratory distress due to:
  - Laryngospasm
  - Bronchospasm
  - Bronchorrhea
  - Seizures.

- Gastric lavage should be done for decontamination in patients presenting early.

Specific treatment

This involves administration of specific drags including the following

- Atropine
- Pralidoxime
- Magnesium sulphate
- Diazepam

Atropine

- Anticholinergic & parasympatholytic
- Competitive muscarinic antagonist of OP
- Blocks OP binding to muscarinic receptor thus preventing or reducing the mucarinic response to acetylcholine.
- Full atropinization is achieved when there is:
  - Mydriasis
  - Pulmonary secretions are dry
  - Adequate oxygenation.
  - Tachycardia

Pralidoxime

- Pralidoxime is an AchE is re-activator
- AchE has a serine site and anionic site.
- OP binds to the serine site of AchE, phosphorylating and inactivating it.
- Pralidoxime reactive AchE by binding the anionic site.
- Reactivated AchE then breaks down Ach thus reducing it concentration if the synaptic cleft.

Diazepam

- Given to patients with OPP and seizures

Magnesium phosphate

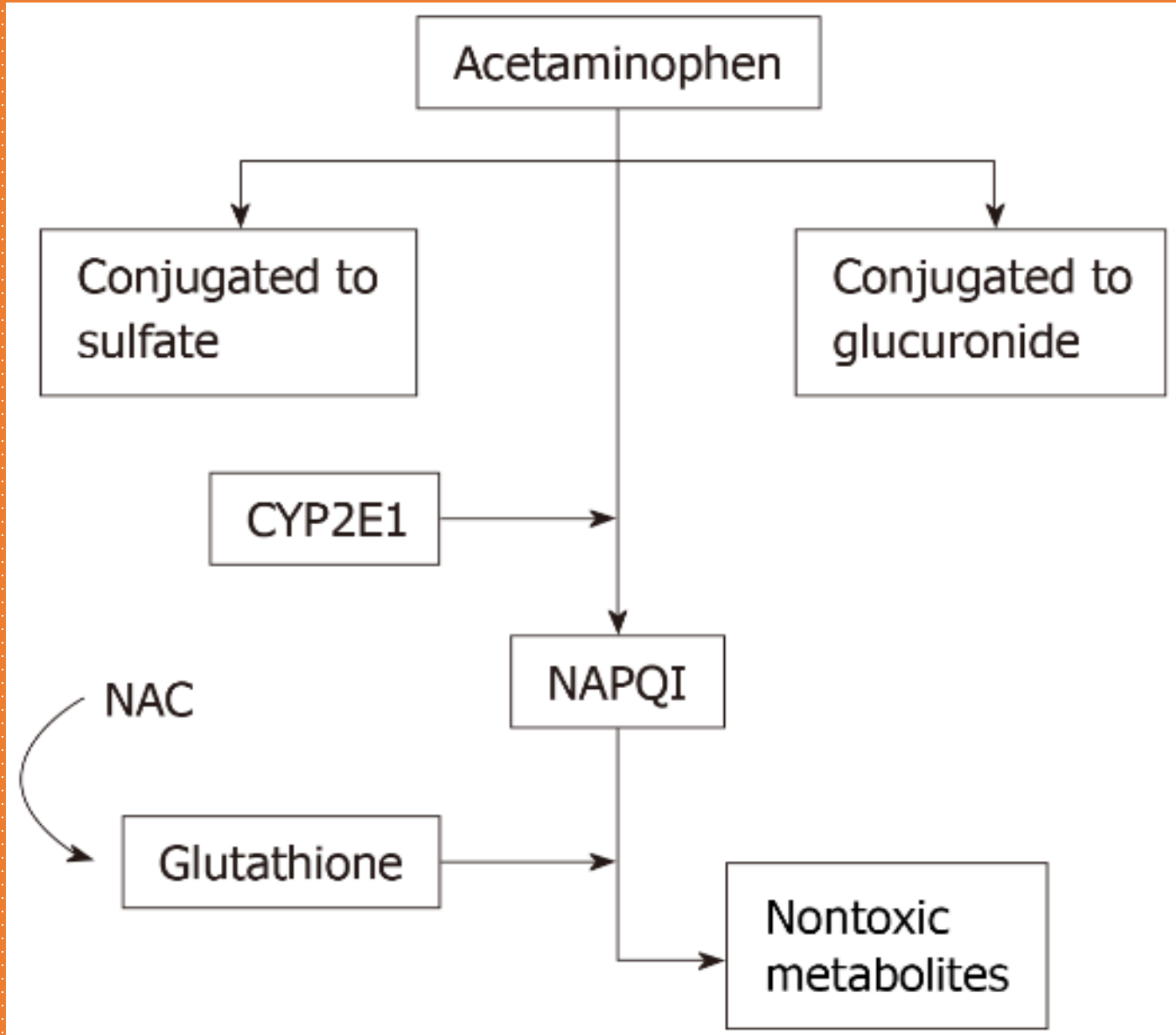
- Used in OPP patients with Torsades de pointes

Paracetamol Poisoning

- Paracetamol poisoning is one the common overdoses reported to poison centers globally.
- In U.K Paracetamol accounts about 50% of self-poisoning cases causing around 200 deaths every year.
- It is the second most common cause of liver failure requiring transplantation in the United States.
- Records of paracetamol poisoning in Zambia are not readily available.
- Both unintentional and intentional acetaminophen overdose remains a serious public health concern.
- The number of liver failure cases in Zambia, due to Paracetamol toxicity are most likely less when compared with that of the western countries.

Pathophysiology of Paracetamol Toxicity

- Paracetamol is metabolized in the liver via three pathways:
  - **Glucuronidation**
  - **Sulfation**
  - **Via the hepatic cytochrome P450 enzyme system**
- Toxic effects of Paracetamol are due to alkylating metabolite N-acetyl-P-benzo-quinone imine (NAPQI)
- Endogenous glutathione in the liver converts NAPQI to a nontoxic metabolite, mercapturic acid, which is excreted in the urine.



- Recommended Paracetamol dose is 15 mg/kg for adults.
- Paracetamol a higher dose of 150 mg/kg is associated with toxicity
- When an overdose occurs normal metabolic pathways become saturated and more acetaminophen is shunted through the P450 system high amounts of NAPQI.
- When glutathione is depleted by 70% excessive amounts of NAPQI bind to hepatocytes, causing cellular toxicity, which is manifest as hepatic necrosis.

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Clinical features of acetaminophen toxicity can be divided into 4 stages:

Stage 1-First 24hrs

- Patient may be relatively asymptomatic during first few hours.
- Over 24 hours gastrointestinal symptoms like nausea, abdominal pain and vomiting manifest and predominate

Second stage (12 to 48 hours post ingestion)

- Gastrointestinal discomfort may resolve, but subclinical hepatotoxicity progresses.
- Abdominal pain may reappear and the patient may complain of right upper quadrant pain.
- An acute transaminitis characterized by increase the aspartate (AST) and alanine transaminase (ALT) become apparent.
- International normalized ratio (INR) also increases.

Stage 3 (48 to 96 hours)

- Liver injury accelerates and manifests as:
  - **Bleeding**
  - **Encephalopathy**
  - **Jaundice**
  - **Acidosis**
  - **Renal failure**

Stage 4(>96 hours)

- If the patient survives insults of stage 3, they progress to the final stage of recovery.
- AST,ALT and INR begin to normalize to normal physiological values.
- Bleeding and encephalopathy gradually subsides

Treatment

General measures

- GI decontamination is recommended in those presenting <4h after OD.
- Activated charcoal 1g/kg (max 50g) is the treatment of choice
- Activated charcoal helps to reduce serum levels more than gastric lavage and limiting liver injury.

Specific treatment

N*- *acetylcysteine

- ***N*- *acetylcysteine*** is the antidote and is given by IVI with 5% dextrose.

Methionine

- Methionine is given orally as alternative to ***N*- *acetylcysteine*.**
- Absorption is unreliable if patient vomiting.

Salicylate Poisoning

- Salicylate poisoning continues to be an important overdose that frequently presents to emergency departments globally.
- Statistical data on salicylate poisoning in Zambia are not readily available.
- Salicylate refers to any of a group of chemicals that are derived from salicylic acid.
- Best known Salicylate is acetylsalicylic acid commonly referred to as aspirin.
- Can present as acute or chronic poisoning.
- Familiarity with the clinical presentation during the various stages of acute and chronic aspirin poisoning is important to institute appropriate treatment.

Pathophysiologic of Salicylate poisoning

- The principal pathophysiologic mechanism in salicylate poisoning is interference with aerobic metabolism by uncoupling the mitochondrial oxidative phosphorylation.
- It is characterized by interruption of a series of enzyme-mediated mitochondrial functions.
- There is increased anaerobic metabolism with cellular conversion of pyruvate to lactate and resultant lactic acidosis.
- Impaired oxidative phosphorylation by salicylate results in abnormal glucose homeostasis manifesting as:
  - **Glycogen depletion**
  - **Impaired gluconeogenesis**
  - **Catabolism of proteins and free fatty acids,**
  - **Central nervous system (CNS) hypoglycemia**

- Salicylate toxicity has direct stimulatory effects on the respiratory centers of the cerebral medulla initially will create a pure respiratory alkalosis due hyperventilation.
- Metabolic acidosis later develops in the advanced stages of salicylate poisoning.

Clinical features

Classic salicylism

- The triad of salicylate poisoning consists of:
  - **Hyperventilation**
  - **Tinnitus**
  - **Gastrointestinal (GI) irritation**
- Vital signs may reflect the following:
  - **Emotional agitation**
  - **CNS stimulation**
  - **Tachycardia**
  - **Increased work of breathing (increased minute ventilation)**
  - **Overall autonomic up-regulation**

- Late features of salicylate poisoning include:
  - Metabolic acidosis
  - Pulmonary and cerebral edema
  - Myocardial depression and hypotension
  - CNS depression
  - Seizures secondary to hypoxia, hypoglycemia, and direct CNS toxicity
  - Cardiopulmonary arrest

Treatment

- Due to volume depletion as a result of fluid losses caused by increased respiration, fever, and metabolic activity, volume resuscitation with alkalinized intravenous fluids is reasonable and advisable.
- Restoration of intravascular volume and alkalinization of the serum and urine is the important first-line treatment for acetasalicylic acid toxicity
- Decontamination with activated charcoal has been shown to decrease serum levels of salicylate , but this has not translated into an improved morbidity or mortality rate.
- Urgent haemodialysis should be instituted is advanced and overt salicylate poisoning.

Indication for haemodialysis in Salicylate poisoning include the following:

- Severe acidosis or hypotension refractory to optimal supportive care (regardless of absolute serum aspirin concentration.
- Evidence of end-organ injury (ie, seizures, rhabdomyolysis, pulmonary edema)
- Renal failure
- High serum aspirin concentration (>100 mg/dL) despite relatively stable metabolic picture

Warfarin Poisoning

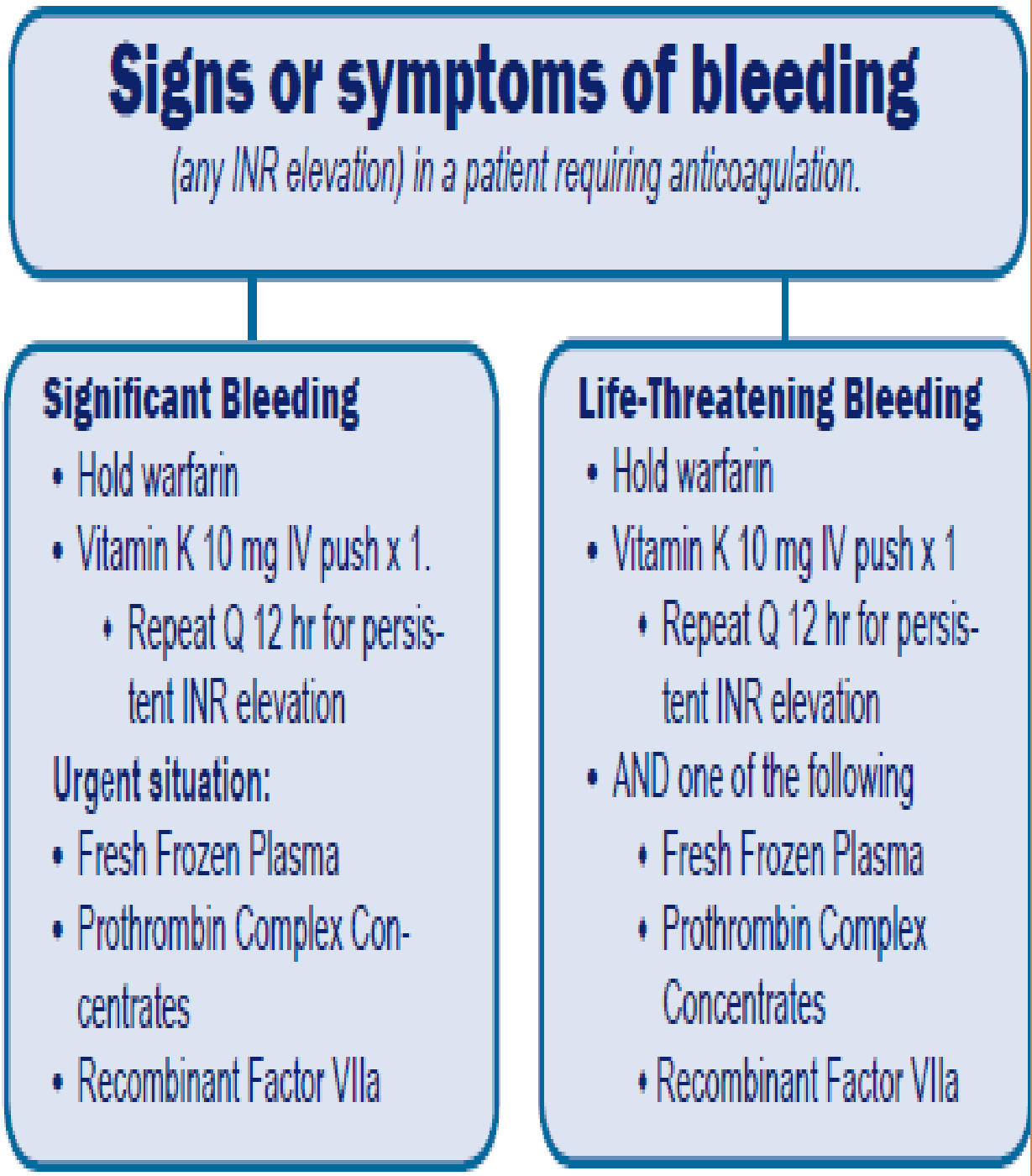
- Warfarin is an anticoagulant
- Warfarin inhibits Vitamin K and thus inhibits synthesis of all vitamin K dependent clotting factors, namely, factors II, VII, IX and X (plus protein C and S)
- The half-lives of the affected clotting factors are listed below:
  - Factor VII: 6 hours
  - Factor IX: 24 hours
  - Factor X: 36 hours
  - Factor II: 50 hours
- Peak anticoagulation occurs when active clotting factors are cleared from the blood and may take 2-3 days to be reflected by the INR.

Clinical features

- Usually asymptomatic
- Severe coagulopathy may present as :
  - Bruising
  - Petechial
  - Puerperal rashes
  - Gingival bleeding
  - Epistaxis
  - Gastrointestinal bleeding
  - Haematuria.

Treatment

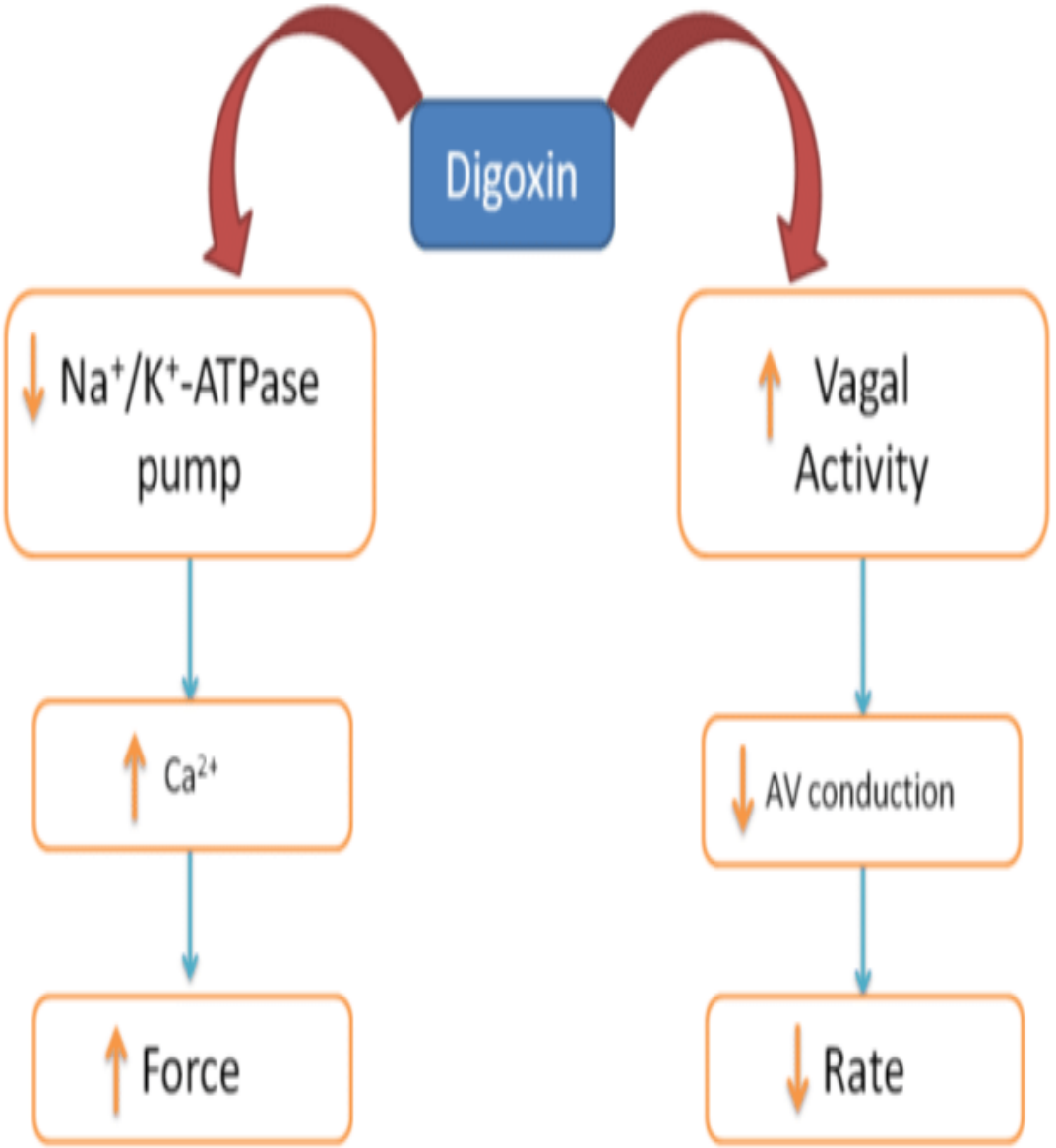
- Supratherapeutic INR values can be reversed in several ways:
  - **Omit warfarin doses**
  - **Administer vitamin K**
  - **Supplement deficient clotting factors**
- Vitamin K acts as a competitive inhibitor of warfarin and a substrate of vitamin K reductase, an enzyme responsible for activation of several coagulation factors.
- Fresh frozen plasma supplements all clotting factors
- Prothrombin complex concentrates supplement the factors inhibited by warfarin (II, VII, IX, and X).



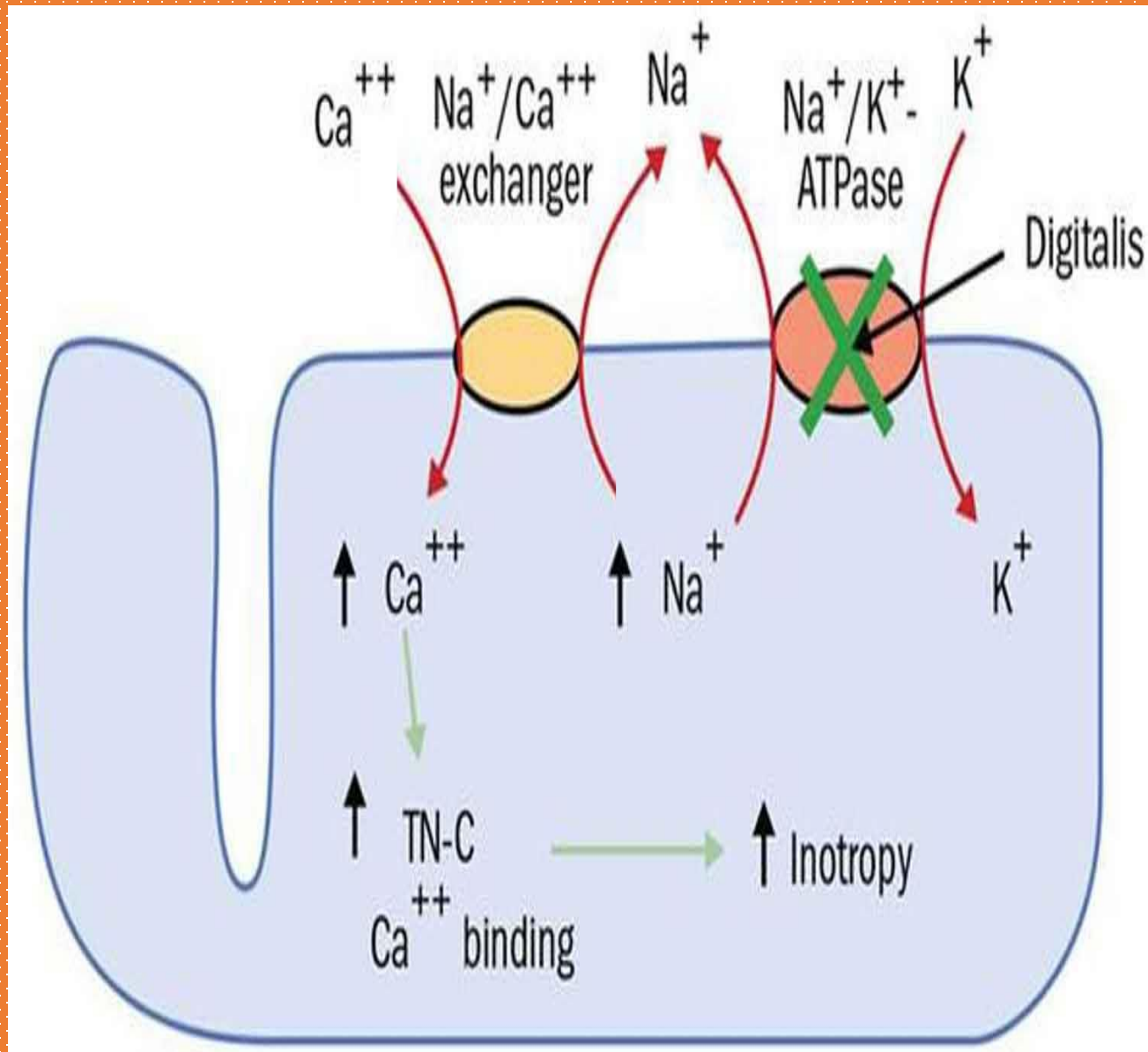
Digoxin Toxicity

- *Digoxin* belongs to a *class* of medications called cardiac glycosides.
- Digoxin **induces an increase in intracellular sodium that will drive an influx of calcium in the heart** and cause an increase in contractility.
- Digoxin exhibits its therapeutic and toxic effects by poisoning the sodium-potassium ATPase.
- Hypokalaemia potentiates digoxin toxicity.
- The subsequent increase in intracellular sodium leads to increased intracellular calcium by decreasing calcium expulsion through the sodium-calcium, cation exchanger.
- Patients who are elderly or have CKD, are more likely to develop toxicity.

Mechanism of action of Digoxin



Mechanism of Digoxin Toxicity



Clinical features

- Gastrointestinal upset is the most common symptom of digoxin toxicity presenting as nausea, vomiting, dizziness, anorexia .
- Patients also may report visual symptoms, which classically present as a yellow-green discoloration or halos.
- Cardiovascular symptoms include:
  - Palpitations
  - Dyspnea
  - Syncope
- ECG may manifest as :
  - Sinus bradycardia
  - Supraventricular arrhythmias
  - Heart block
  - ventricular premature beats
  - Ventricular tachycardia

Treatment

- Digoxin-specific antibody antigen-binding fragments (DSFab), brand name Digibind or Digifab, are an effective antidote that directly binds digoxin.

Antidotes of value in poisoning

Poison	**Antidote**
Benzodiazepines	Flumazenil
Opioids	Naloxone
Paracetamol	N- acetylcysteine
Heparin	Protamine sulphate
Warfarin	Phytomenadione (Vitamin K)
Organophosphorus	Atropine, HI-6, obidoxime,pralidoxime
Digoxin and digitoxin	Digoxin-specific antibody fragments
Dabigatran	Idarucizumab
Methanol	Ethanol
Copper	D-penicillamine
Iron Salts	Desferrioxamine

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QUESTIONS?????
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