Al-Mustaqbal University College
Department of Pharmacy
5th stage
Clinical Toxicology
Lecture: 2

Anticholinergic & Acetaminophen Toxicity

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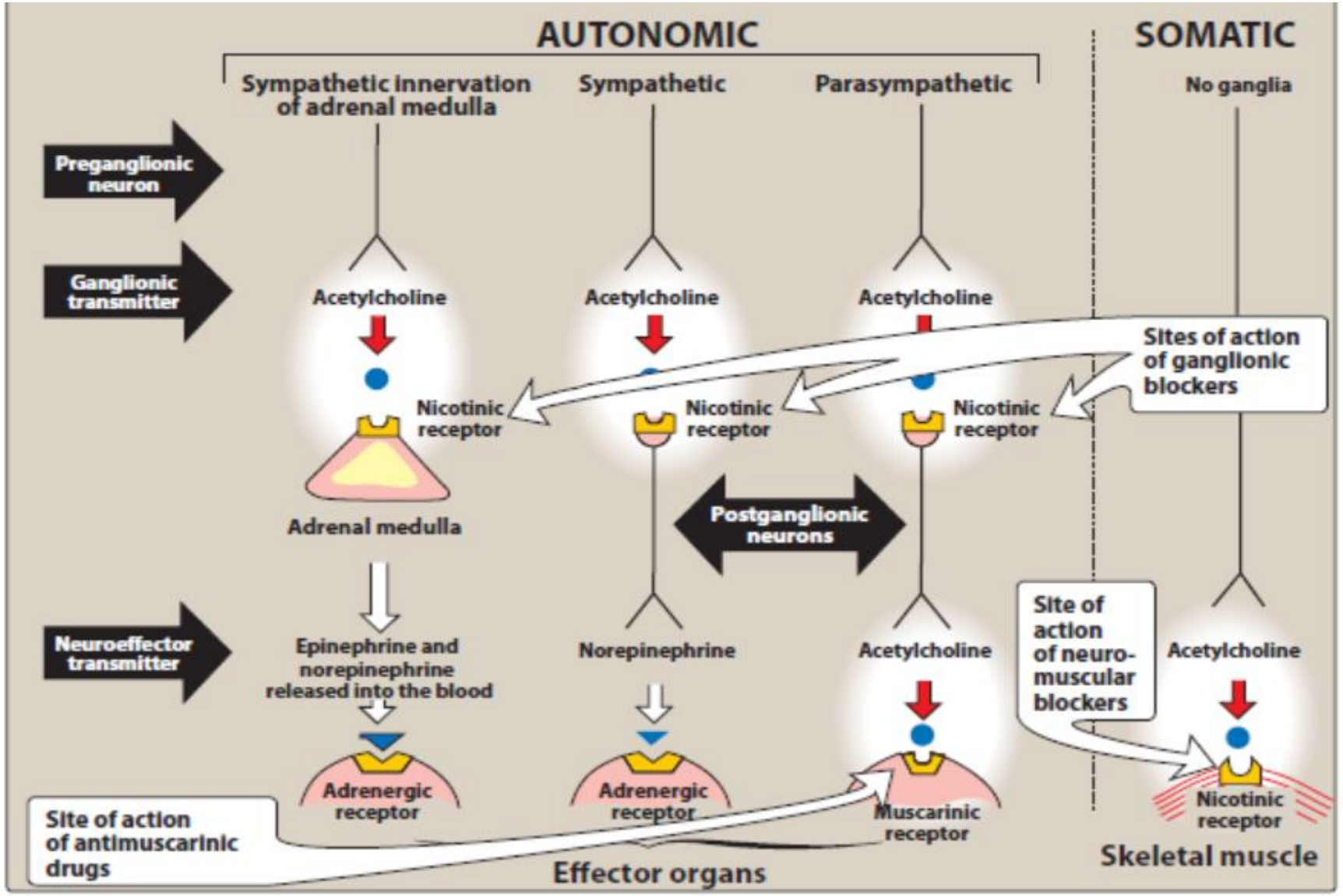
Anticholinergic Drug Toxicity

Cholinergic antagonist is an agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists.

The most clinically useful of these agents are selective blockers of muscarinic receptors.

The effects of parasympathetic innervation are, thus, interrupted, and the actions of sympathetic stimulation are left unopposed.

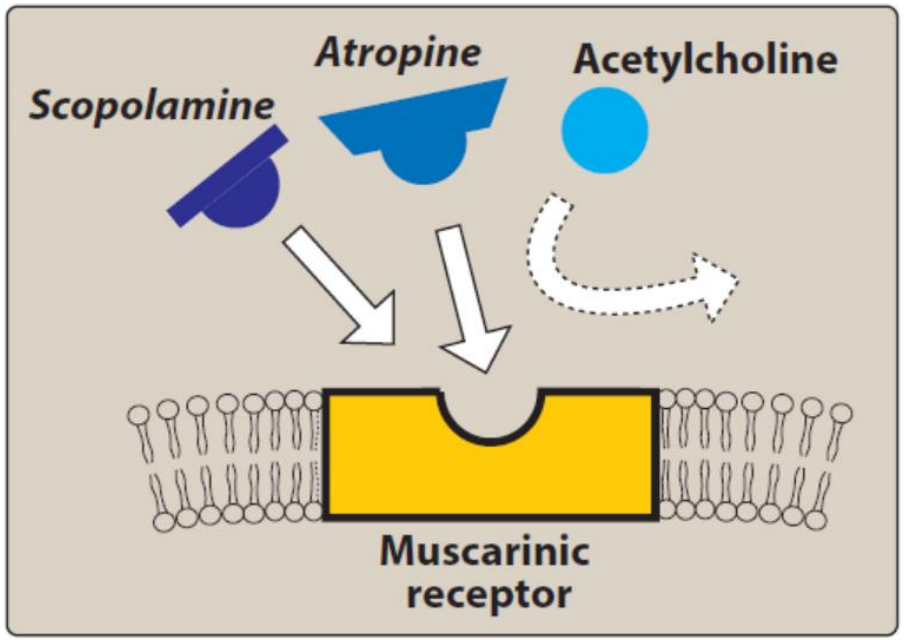


Sites of actions of cholinergic antagonists.

Anticholinergic Drug Toxicity

Anticholinergic syndrome is produced by the inhibition of cholinergic neurotransmission at muscarinic receptor sites.

It commonly follows the ingestion of a wide variety of prescription and over-the-counter medications.



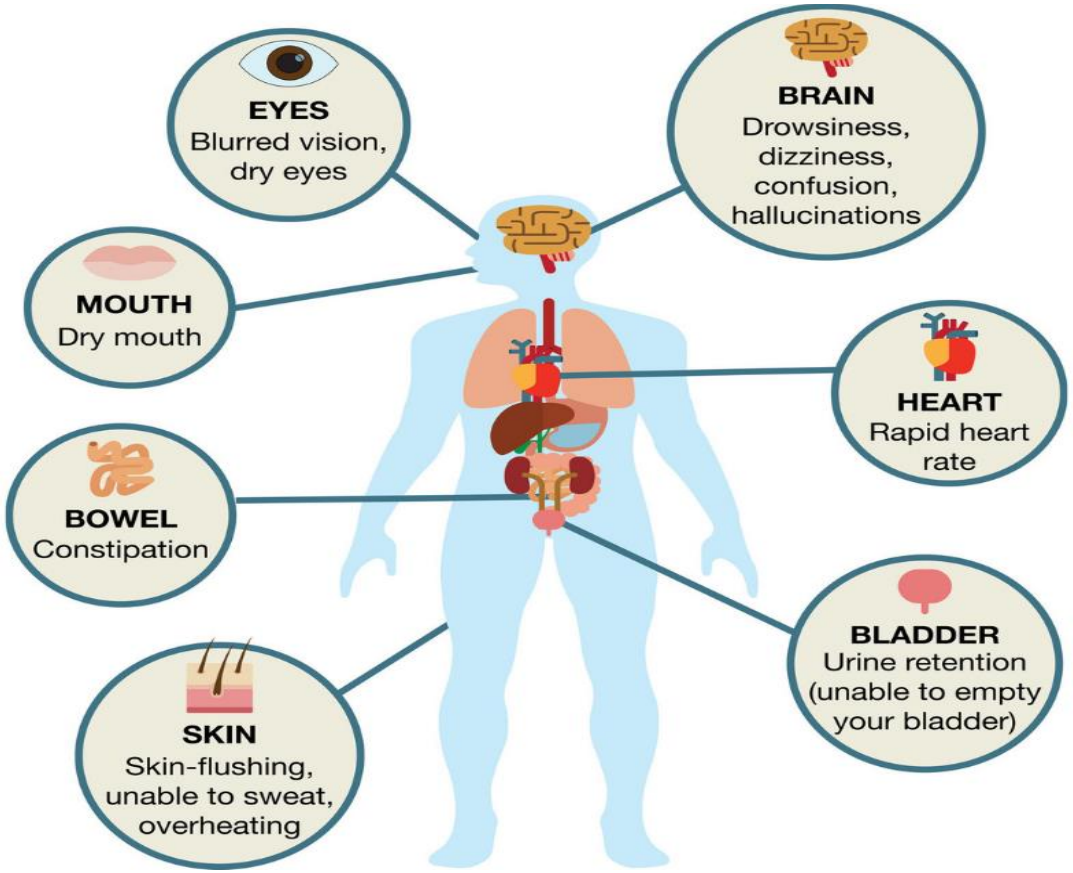
Anticholinergic Drug Toxicity

Signs and symptoms:

Clinical manifestations are caused by:

- **CNS effects**
- **Peripheral nervous system effects**
- **Or both**

Anticholinergic Drug Toxicity



Anticholinergic Drug Toxicity

Clinical manifestations may include:

- **Flushing**
- **Dry skin and mucous membranes**
- **Mydriasis with loss of accommodation**
- **Altered mental status**
- **Fever**

Anticholinergic Drug Toxicity

Additional manifestations include the following:

- **Sinus tachycardia**
- **Decreased bowel sounds**
- **Urinary retention**
- **Hypertension**

Anticholinergic Drug Toxicity

Agents with anticholinergic properties are as follows:

1. Anticholinergics

- ✓ **Atropine**
- ✓ **scopolamine**

2. Antihistamines

- ✓ **Chlorpheniramine**
- ✓ **Cyproheptadine**
- ✓ **Diphenhydramine**
- ✓ **Promethazine**

Anticholinergic Drug Toxicity

Agents with anticholinergic properties are as follows:

3. Antipsychotics

- ✓ **Chlorpromazine**
- ✓ **Clozapine**
- ✓ **Thioridazine**

4. Antispasmodics

- ✓ **Clidinium**
- ✓ **Hyoscyamine**
- ✓ **Propantheline**

Anticholinergic Drug Toxicity

Treatment:

- ✓ **Initial assessment and stabilization are required**
- ✓ **Ensure an adequate airway and check that breathing is present and maintained.**
- ✓ **Assess circulation and initiate cardiac and pulse monitoring.**
- ✓ **GI decontamination with activated charcoal is recommended.**
- ✓ **Ipecac syrup is contraindicated.**
- ✓ **Ventricular arrhythmias can be treated with lidocaine.**
- ✓ **Manage seizures with benzodiazepines.**

Anticholinergic Drug Toxicity

The antidote for anticholinergic toxicity is physostigmine salicylate.

Physostigmine is the only reversible acetylcholinesterase inhibitor capable of directly antagonizing the CNS manifestations of anticholinergic toxicity.

It is an uncharged tertiary amine that efficiently crosses the blood brain barrier.

Anticholinergic Drug Toxicity

By inhibiting acetylcholinesterase, the enzyme responsible for the hydrolysis of acetylcholine, an increased concentration of acetylcholine augments stimulation at muscarinic and nicotinic receptors.

Physostigmine can reverse the central effects of coma, seizures, severe dyskinesias, hallucinations, agitation, and respiratory depression.

The most common indication for physostigmine is to control agitated delirium.

Physostigmine is contraindicated in patients with cardiac conduction disturbances (prolonged PR and QRS intervals) on ECG analysis.

Acetaminophen Toxicity

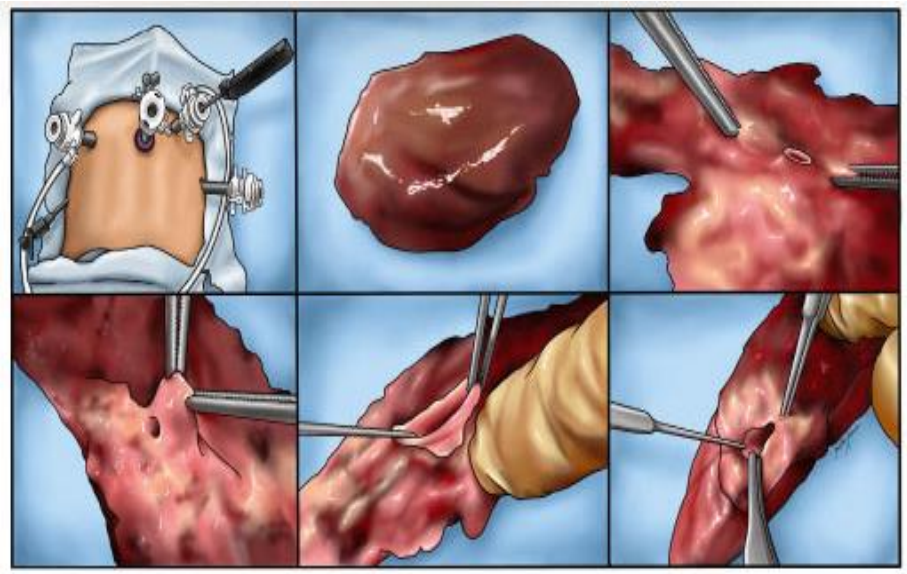
Acetaminophen also known as **paracetamol** and by its chemical name, N-acetyl-p-aminophenol (**APAP**).

Acetaminophen has an excellent safety profile when administered in proper therapeutic doses, but hepatotoxicity can occur with misuse and overdose.

Acetaminophen Toxicity

Acetaminophen toxicity is the most common cause of hepatic failure requiring liver transplantation in Great Britain.

In the United States, acetaminophen toxicity is the second most common cause of liver failure requiring transplantation.



Acetaminophen Toxicity

Signs and symptoms:

Most patients who have taken an overdose of acetaminophen will initially be asymptomatic, as clinical evidence of end-organ toxicity often does not manifest until 24-48 hours after an acute ingestion.

To identify whether a patient is at risk, the clinician should determine the time(s) of ingestion, the quantity, and the formulation of acetaminophen ingested.

Acetaminophen Toxicity

Signs and symptoms:

Minimum toxic doses of acetaminophen for a single ingestion, posing significant risk of severe hepatotoxicity, are as follows:

- **Adults: 7.5 -10 g**
- **Children: 150 mg/kg in healthy children aged 1-6 years**

Acetaminophen Toxicity

The clinical course of acetaminophen toxicity generally is divided into four phases.

Physical findings vary, depending primarily on the level of hepatotoxicity.

Phase 1:

- ✓ **0.5-24 hours after ingestion**
- ✓ **Patients may be asymptomatic or report anorexia, nausea or vomiting, and malaise**
- ✓ **Physical examination may reveal pallor, diaphoresis, malaise, and fatigue.**

Acetaminophen Toxicity

Phase 2:

- ✓ **18-72 hour after ingestion**
- ✓ **Patients generally develop right upper quadrant abdominal pain, anorexia, nausea, and vomiting**
- ✓ **Right upper quadrant tenderness may be present**
- ✓ **Tachycardia and hypotension indicate ongoing volume losses**
- ✓ **Some patients may report decreased urinary output (oliguria)**

Acetaminophen Toxicity

Phase 3: (Hepatic Phase)

- ✓**72-96 hour** after ingestion
- ✓Patients may have **continued** nausea and vomiting, abdominal pain, and a tender hepatic edge
- ✓Hepatic **necrosis** and **dysfunction** are associated with jaundice, coagulopathy, hypoglycemia, and hepatic encephalopathy
- ✓**Acute renal failure** develops in some critically ill patients
- ✓**Death** from multi-organ failure may occur

Acetaminophen Toxicity

Diagnosis:

The serum acetaminophen concentration is the basis for diagnosis and treatment.

Even in the absence of symptoms, because of the delay in onset of clinical manifestations of toxicity.

There are recommended serum studies should be done as soon as possible.

Acetaminophen Toxicity

Recommended tests are :

- ✓ **Liver function tests** (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), bilirubin [total and fractionated], alkaline phosphatase)
- ✓ **Prothrombin time** (PT)
- ✓ **Glucose**
- ✓ **Renal function studies** (electrolytes, BUN, creatinine)

Acetaminophen Toxicity

Recommended tests are :

- ✓ **ECG**
- ✓ **Lipase and amylase (in patients with abdominal pain)**
- ✓ **Serum human chorionic gonadotropin (hCG) (in females of childbearing age)**
- ✓ **Arterial blood gas and ammonia (in clinically compromised patients)**

Acetaminophen Toxicity

Laboratory findings in the phases of acetaminophen hepatotoxicity are as follows:

- ✓**Phase 1:** Approximately **12 hours** after an acute ingestion, liver function studies show a **subclinical** rise in serum **transaminases** levels (ALT, AST)
- ✓**Phase 2:** Elevated ALT and AST levels, **PT**, and **bilirubin** values; renal function abnormalities may also be present and indicate **nephrotoxicity**
- ✓**Phase 3:** Severe hepatotoxicity is evident on serum studies; hepatic **centrilobular necrosis** is diagnosed on liver biopsy.

Acetaminophen Toxicity

Pathophysiology:

Oral acetaminophen is rapidly absorbed from the stomach and small intestine.

Peak plasma levels occur within 4 hours after ingestion of an overdose of an immediate-release preparation.

It is primarily metabolized by conjugation in the liver to nontoxic, water-soluble compounds that are eliminated in the urine.

In acute overdose metabolism by conjugation becomes saturated, and excess APAP is oxidatively metabolized by the CYP enzymes to the hepatotoxic reactive metabolite, N -acetyl-p -benzoquinoneimine (NAPQI).

Acetaminophen Toxicity

Pathophysiology:

NAPQI has an extremely short half-life and is rapidly conjugated with glutathione, a sulfhydryl donor, and is then renally excreted.

Under conditions of excessive NAPQI formation or a reduction in glutathione stores by approximately 70%, NAPQI covalently binds to the cysteinyl sulfhydryl groups of hepatocellular proteins, forming NAPQI-protein adducts.

The subsequent inflammatory response propagates hepatocellular injury, necrosis, hepatic failure, and death.

Acetaminophen Toxicity

Pathophysiology:

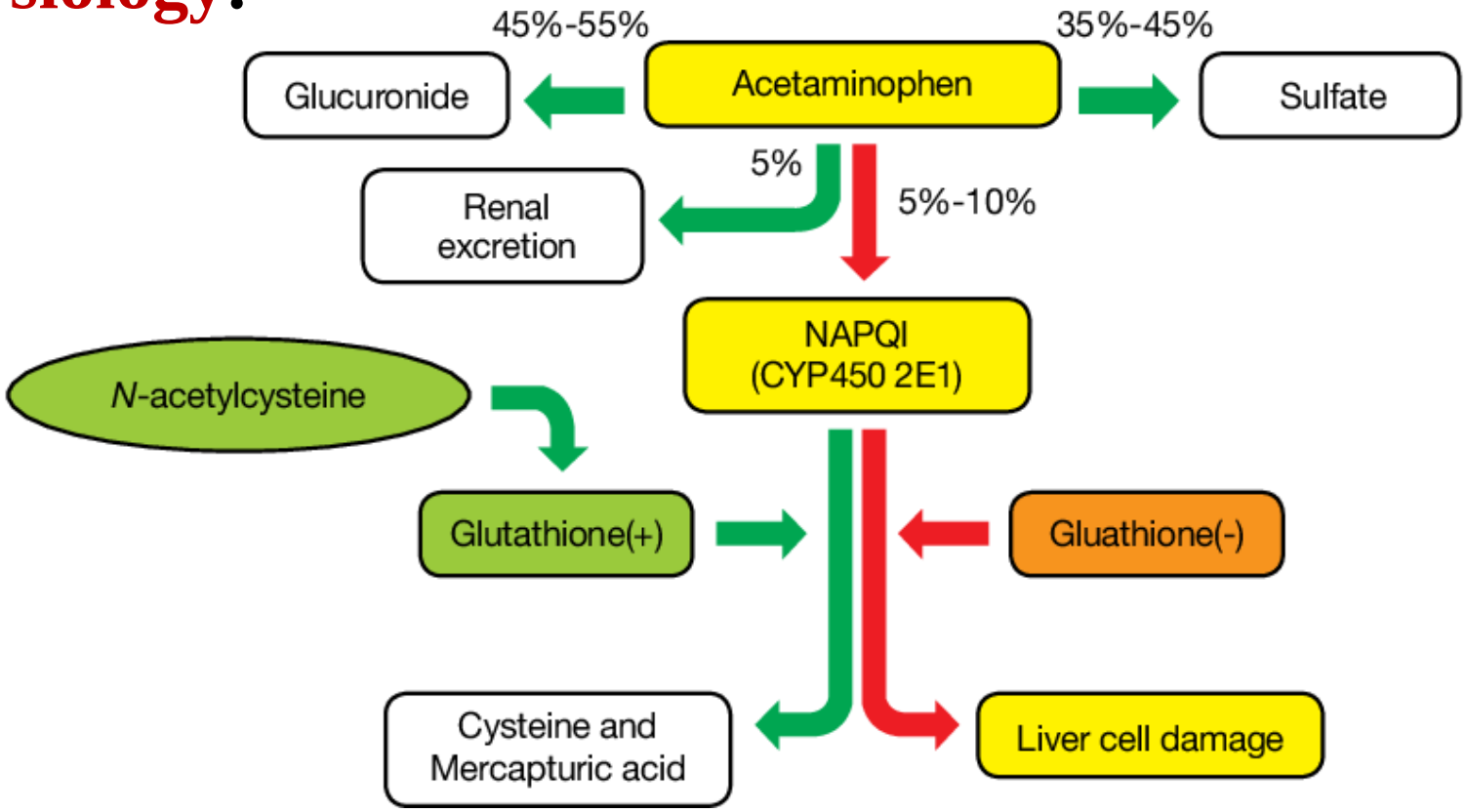
The antidote for acetaminophen poisoning, N-acetylcysteine (NAC), is theorized to work through a number of protective mechanisms.

Since NAC is a precursor of glutathione, it increases the concentration of glutathione available for the conjugation of NAPQI.

NAC also enhances sulfate conjugation of unmetabolized APAP, also it act as an anti-inflammatory and antioxidant, and has positive inotropic effect.

Acetaminophen Toxicity

Pathophysiology:



Acetaminophen Toxicity

Management and treatment

Initial appropriate supportive care is essential in acetaminophen poisoning.

Immediate assessment of the patient's airway, breathing, and fluid status (ie, ABCs) is critical before treatment for suspected acetaminophen overdose is initiated.

In addition, assessing for other potential life-threatening co-ingestions (eg, salicylate) is very important.

Acetaminophen Toxicity

Management and treatment

Gastrointestinal decontamination agents can be used in the emergency department setting in the immediate post-ingestion time frame.

Administer activated charcoal if the patient is alert and presents, ideally, within 1 hour post ingestion.

This time frame can be extended if the patient ingested an acetaminophen-based sustained-release medication.

Acetaminophen Toxicity

Management and treatment

Admit patients with elevated acetaminophen plasma levels for treatment with N-acetylcysteine (NAC).

NAC is nearly 100% hepatoprotective when it is given within 8 hours after an acute acetaminophen ingestion.

NAC can be beneficial in patients who present more than 24 hours after ingestion.

NAC is approved for both oral and IV administration.

THANK YOU
FOR YOUR ATTENTION