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

Acetaminophen Toxicity

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Acetaminophen toxicity

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

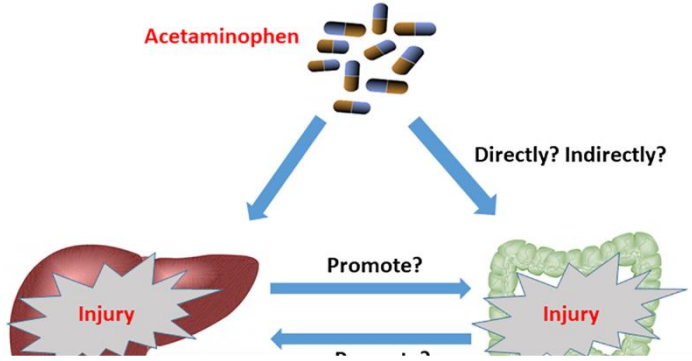
In the United States, acetaminophen toxicity is the second most common cause of liver failure requiring transplantation.

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

Toxic dose :

Minimum toxic doses of acetaminophen for a single ingestion, poising 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:(pre clinical toxic effects) if treated may develop transit liver injury but full recovery

- ✓ 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☹ (Hepatic injury)

- ✓ **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 failure)

- ✓ **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**
- ✓ **Sever ,untreated acetaminophen toxicity wiil result in death within 4-18 days after ingestion**

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 tests 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 :

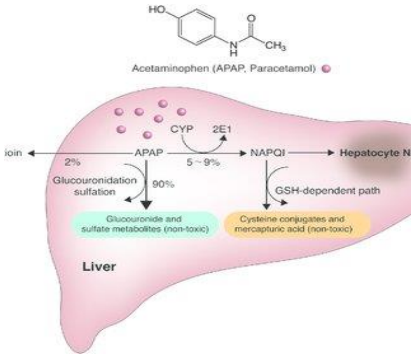
- ✓ **ECG**
- ✓ **Lipase and amylase (in patients with abdominal pain)**
- ✓ **Serum human chorionic gonadotropin (hCG) (in females of childbearing age)**
- ✓ **Arterial blood gas and ammonia (in clinically compromised patients)**

Phases of acetaminophen hepatotoxicity

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.

Pathophysiology:

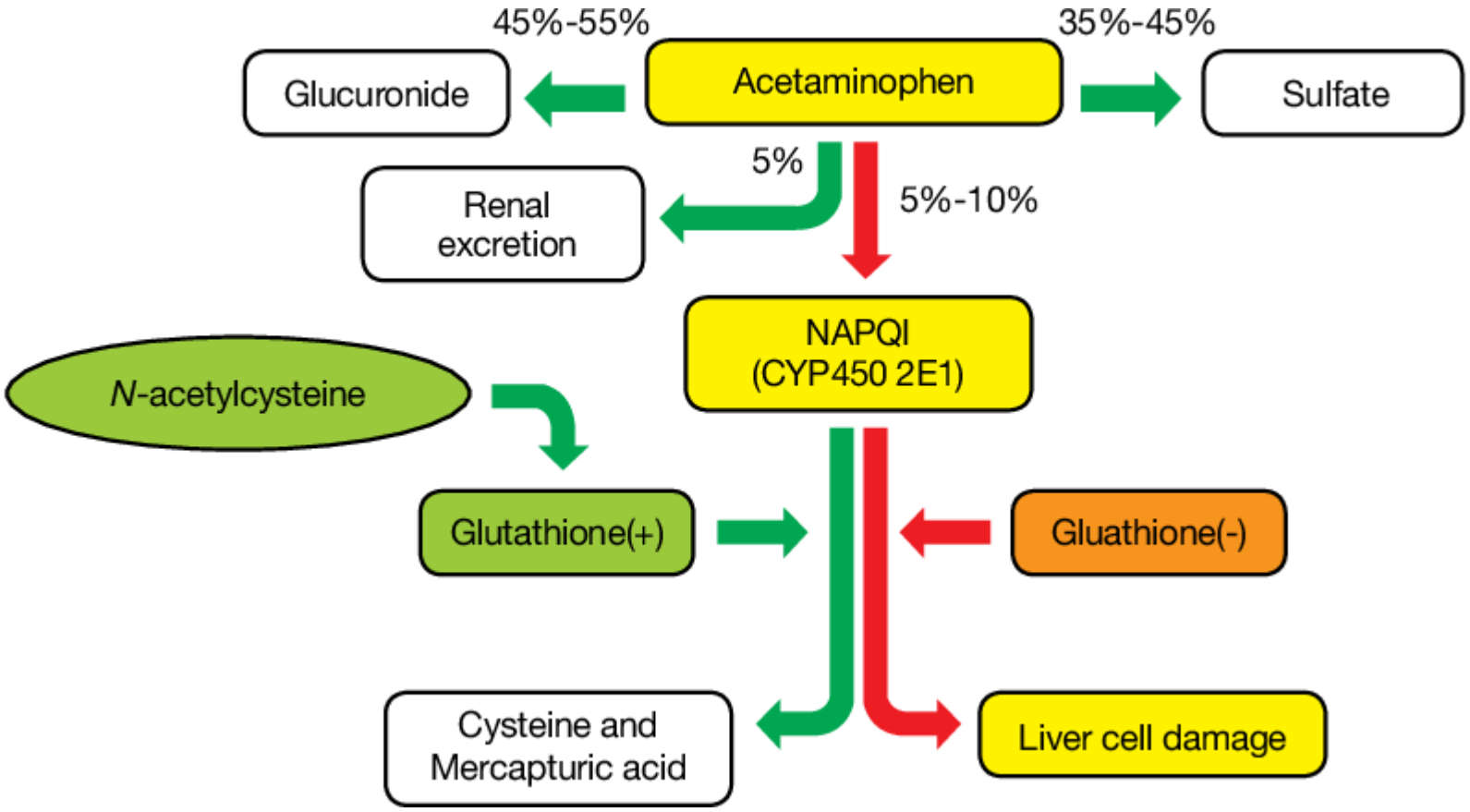


- Oral acetaminophen is rapidly **absorbed** from the **stomach and small intestine**.
- **Peak** plasma levels occur within **4 hours** after ingestion of an overdose of an immediate-release preparation.
- It is primarily metabolized by **conjugation** in the liver to **nontoxic, water-soluble** compounds 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)**.

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.**

N-acetylcysteine (NAC),



Management

- ✓ 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 t concentration of glutathione available for the conjugation NAPQI.
- ✓ NAC also enhances **sulfate conjugation** unmetabolized APAP, also it act as an **anti-inflammatory** and **antioxidant**, and has **positive inotropic effect**.

Management

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.

Management

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.

Management

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!