Practical Clinical Toxicology

Toxicity of Acetaminophen

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Pharmacology:

- Acetaminophen [N-acetyl-para-aminophenol (APAP)], also known as paracetamol, is one of the most common used drugs worldwide.

  Since its clinical introduction in 1955, it has become the most widely utilized analgesic/anti-pyretic in many countries around the world

- Analgesic activity is reported at a serum acetaminophen concentration of 10 µg/ mL & antipyretic activity at 4 to 18 µg/mL.

- Therapeutic peak concentrations of APAP (10–20 µg/mL) are detected as quickly as 90 min after its oral ingestion due to its fast absorption in the duodenum.
- Serum half-life for a healthy individual taking a therapeutic dose ranges from 1.5 to 3 h. However, a prolonged half-life of more than 4 h can occur in individuals that either consume an overdose of APAP or that exhibit a clinical history of hepatic injury or chronic liver disease

Acetaminophen metabolic pathway:

- APAP is metabolized in the hepatocyte through three different pathways (Figure 1).
  - 2% is excreted through the urine unchanged,
  - 85–90% is converted into glucuronidated & sulfated non-toxic metabolites, &
  - 10% is oxidized by cytochrome CYP2E1 generating the highly reactive & toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI).

- NAPQI is then conjugated with gluthatione (GSH) resulting in non-toxic metabolites.

  During APAP overdose or susceptible in patients, as the ones with chronic liver disease, glucuronidation & sulfation pathways become saturated & more APAP is metabolized through CYP2E1 which increases NAPQI generation depleting GSH liver stores.

  Free unconjugated NAPQI reacts with proteins generating NAPQI-protein adducts in hepatocytes leading to mitochondrial dysfunction & cell death.

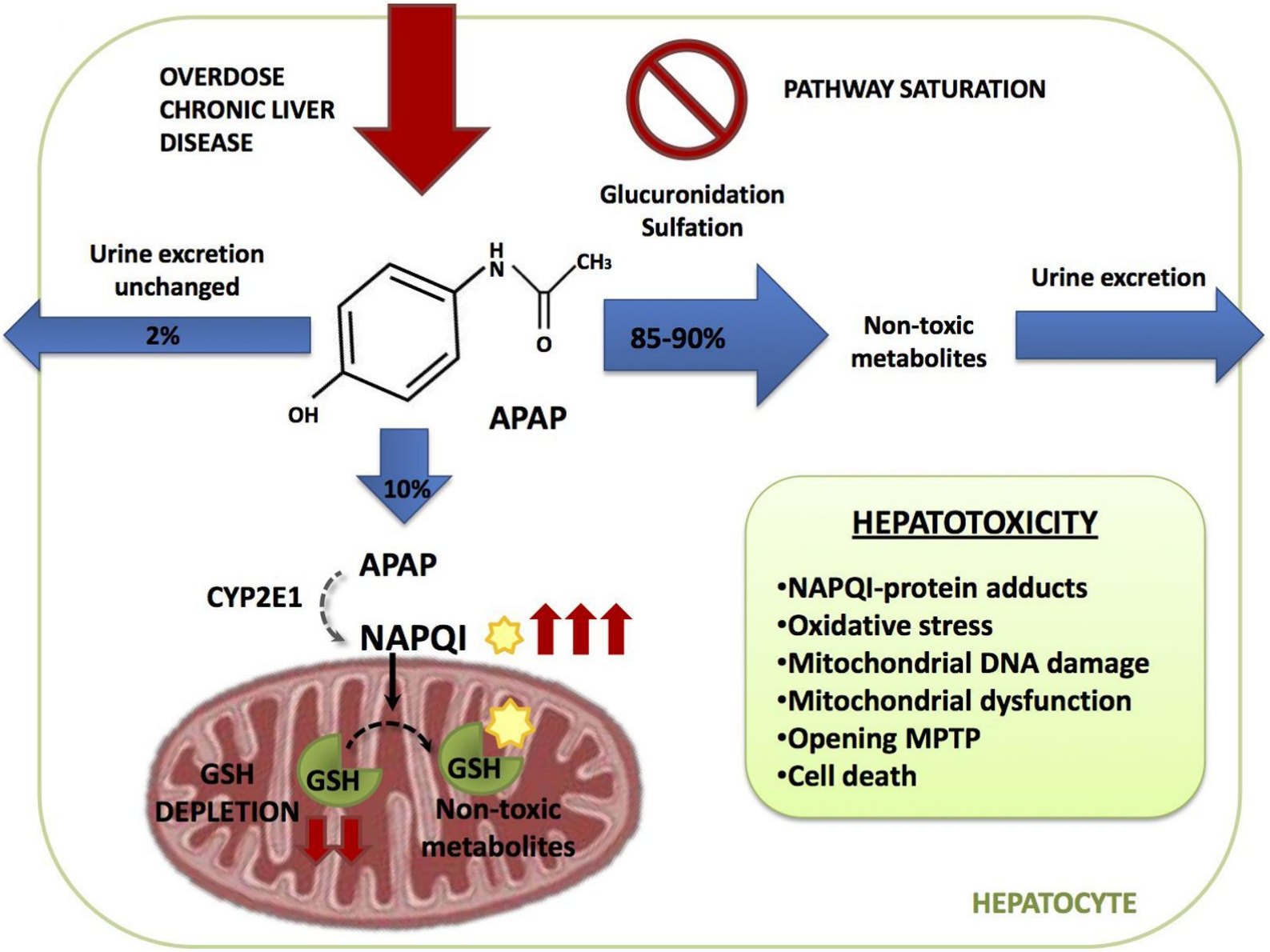

Figure 1. Acetaminophen (APAP) metabolic pathway.

Stages of acute acetaminophen poisoning:

Stage	Time Post-Ingestion	Characteristics
I	0 – 24 h	Anorexia, nausea, vomiting. Hepatic transaminases may start to rise.
II	24 – 72 h	May see improvement in clinical findings, some patients may report right upper quadrant abdominal pain. Elevated AST, ALT, bilirubin, INR.
III	72 – 96 h	Hepatic failure, acidosis, sometimes renal failure and pancreatitis. Peak AST, ALT, bilirubin, and INR levels.
IV	> 5 days	Progression to multiple organ failure (sometimes fatal) Resolution of hepatotoxicity in survivors

Factors that increase the risk of acetaminophen toxicity:

- Decreased hepatic capacity for glucoronidation
  - Gilbert's disease
  - zidovudine, trimethoprim/sulfamethoxazole

- Inducers of CYP2E1 (increase metabolism of acetaminophen into toxic NAPQI)
  - isoniazid, rifampicin, phenobarbital, phenytoin, carbamazepine

- Hepatic depletion of glutathione
  - chronic alcohol ingestion
  - chronic acetaminophen use
  - chronic liver disease
  - malnutrition

Risk determination after acute overdose:

With acute ingestions of APAP, the Rumack-Mathews nomogram (Figure 2) is a valuable tool to assess the risk of hepatotoxicity.

After an acute overdose, a 4-hour APAP level, or as soon thereafter as feasible, should be obtained & plotted on the Rumack-Matthew nomogram to assess risk.

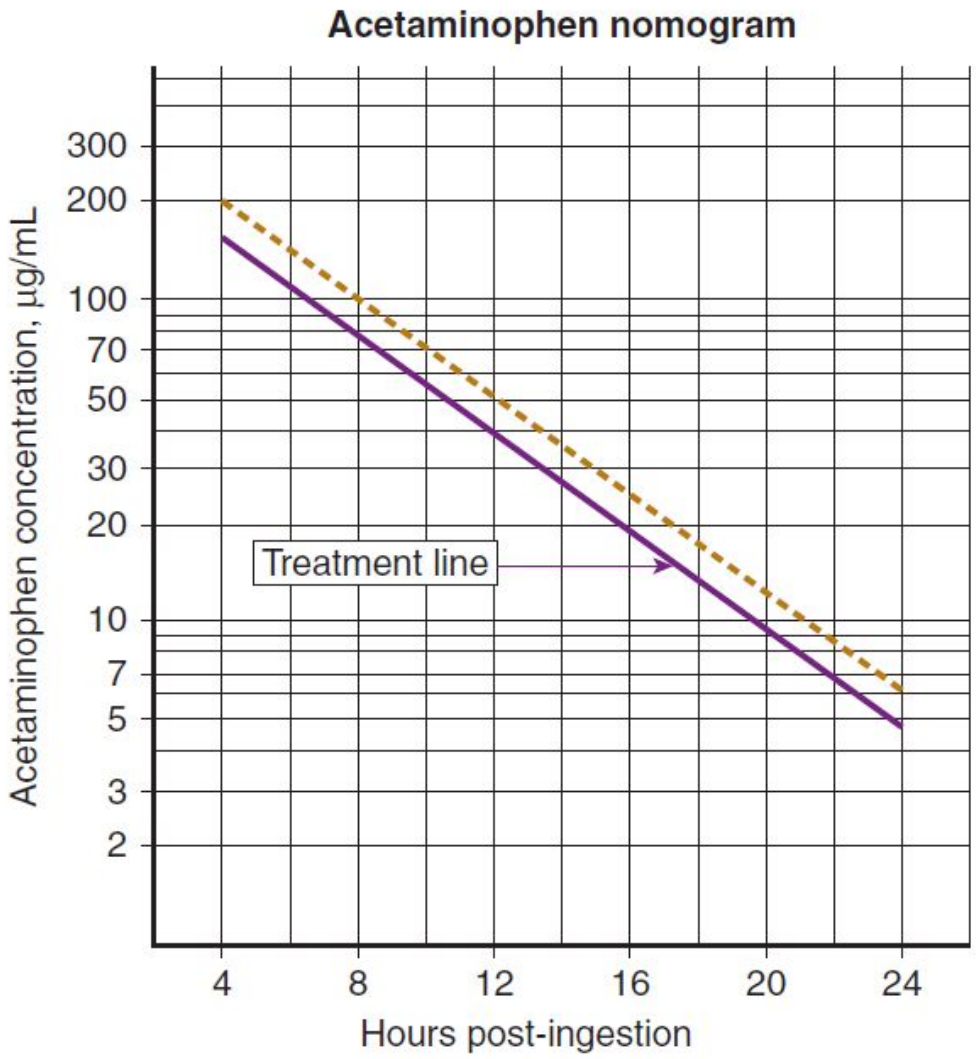

Figure 2. The Rumack-Matthew nomogram (reconstructed) for determining the risk of acetaminophen-induced hepatoxicity after a single acute ingestion. Serum concentrations above the treatment line on the nomogram indicate the need for N -acetylcysteine therapy.

Risk determination when the time of ingestion is unknown:

- If the time window during which the APAP ingestion has occurred cannot be established or is so broad that it encompasses a span of more than 24 hours, the following approach is suggested.

  Determine both [APAP] & aspartate aminotransferase (AST) concentrations.

  - If the AST concentration is elevated, regardless of [APAP], treat the patient with N -acetylcysteine (NAC).
  - If [APAP] is below the lower level of detection & the AST concentration is normal, there is little evidence that subsequent consequential hepatic injury is possible; NAC is unnecessary

Assessing actual toxicity: critical components of the diagnostic approach:

I. Initial testing:

- APAP concentration
- AST concentration
- Prothrombin time (PT)
- International normalized ratio (INR)

II. Ongoing monitoring & testing:

- If elevated AST concentration is noted, then PT & INR & creatinine concentration should be measured & repeated every 24 hours or more frequently if clinically indicated.
- If evidence of actual liver failure is noted, then careful monitoring of blood glucose, pH, PT & INR, creatinine, lactate, & phosphate concentrations are important in assessing extrahepatic organ toxicity & are vital in assessing hepatic function & the patient's potential need for transplant.

Management:

I. Gastrointestinal decontamination:

- Administration of activated charcoal (AC) shortly after APAP ingestion may decrease the number of patients who have an [APAP] above the treatment line.
- If delayed or repeated AC dosing is indicated because of suspected delayed absorption or coingestants, then a strategy using an IV NAC protocol should be considered.

II. Supportive care:

- Controlling nausea &vomiting & managing the hepatic injury, renal dysfunction, & other manifestations.
- Monitoring for & treatment of hypoglycemia as a result of liver failure are critical.
- If adequate viable hepatocytes are present, vitamin K may produce some improvement in coagulopathy.
- One of the most important advances is use of prolonged NAC for treatment of fulminant hepatic failure.

Antidotal therapy with N-acetylcysteine (NAC):

Mechanism of action:

- NAC prevents toxicity by serving as a glutathione precursor as a glutathione substitute, combining with NAPQI, & being converted to cysteine & mercaptate conjugates.
- NAC may also lead to increased substrate for nontoxic sulfation, allowing less metabolism by oxidation to NAPQI.

Administration of NAC:

- NAC is available both orally & intravenously.
- A 20-hour IV infusion of NAC has been widely used worldwide. This regimen includes a loading dose of 150 mg/kg IV over 15 minutes followed by 50 mg/kg over the next 4 hours (rate of 12.5 mg/kg/h) & then 100 mg/kg over the next 16 hours (rate of 6.25 mg/kg/h).
- The standard oral course of NAC is a 140 mg/kg loading dose followed by 70 mg/kg orally every 4 hours for a total of 18 doses over 72 hours.

Hepatic transplantation:

Liver transplantation may increase survival for a select group of severely ill patients who have acetaminophen induced fulminant hepatic failure.


Thank
you