CLINICAL TOXICOLOGY LAB.

5TH STAGE / 1ST SEMESTER

(2021 – 2022)

CLINICAL TOXICITY OF ACETAMINOPHEN

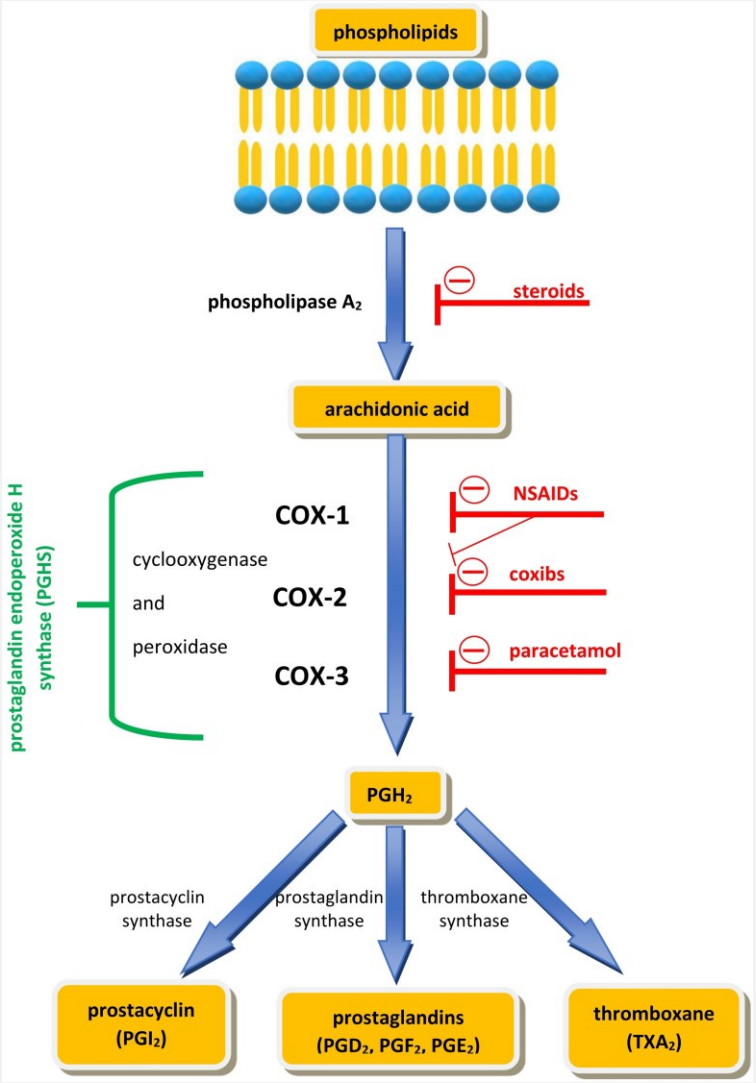
Assis. Lecturer

Zeena A. Hussein

Nibras J. Tahseen

BACKGROUND & MECHANISM:

- Acetaminophen is also known as (paracetamol) or n-acetyl Para aminophenol (APAP)
- It is a potent antipyretic and analgesic, but with very weak anti-inflammatory activity? (because it is a weak inhibitor of peripheral cyclooxygenase enzymes [COX1 & COX2])
- The mechanism of its analgesic and antipyretic activity is not completely understood, but it appears to inhibit COX3 centrally (in the brain) and reducing PGE2



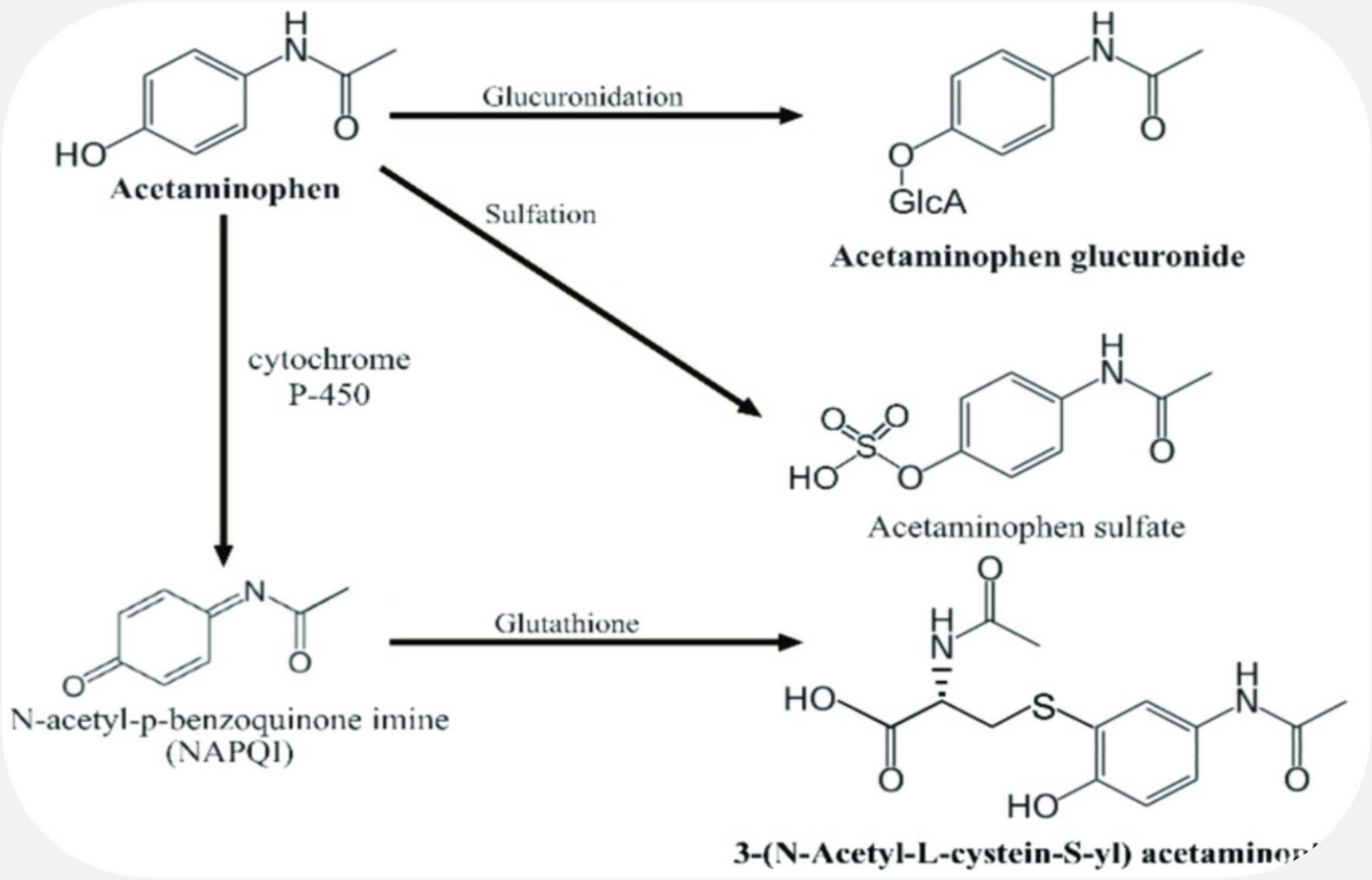
EPIDEMIOLOGY:

- It is contained in over 100 OTC preparations.
- liver failure from APAP overdose is the second most common cause of liver transplantation
- More than 100.000 analgesic overdoses per year, over 200 deaths, 60% due to Acetaminophen.
- Acetaminophen has replaced aspirin as the analgesic-antipyretic of choice, especially for children secondary to safety (why?). Aspirin is associated with Reyes syndrome specially in children and teenagers with viral infection or flu (this syndrome is a rare but serious condition that causes swelling in the liver and brain)

METABOLISM & EXCRETION:

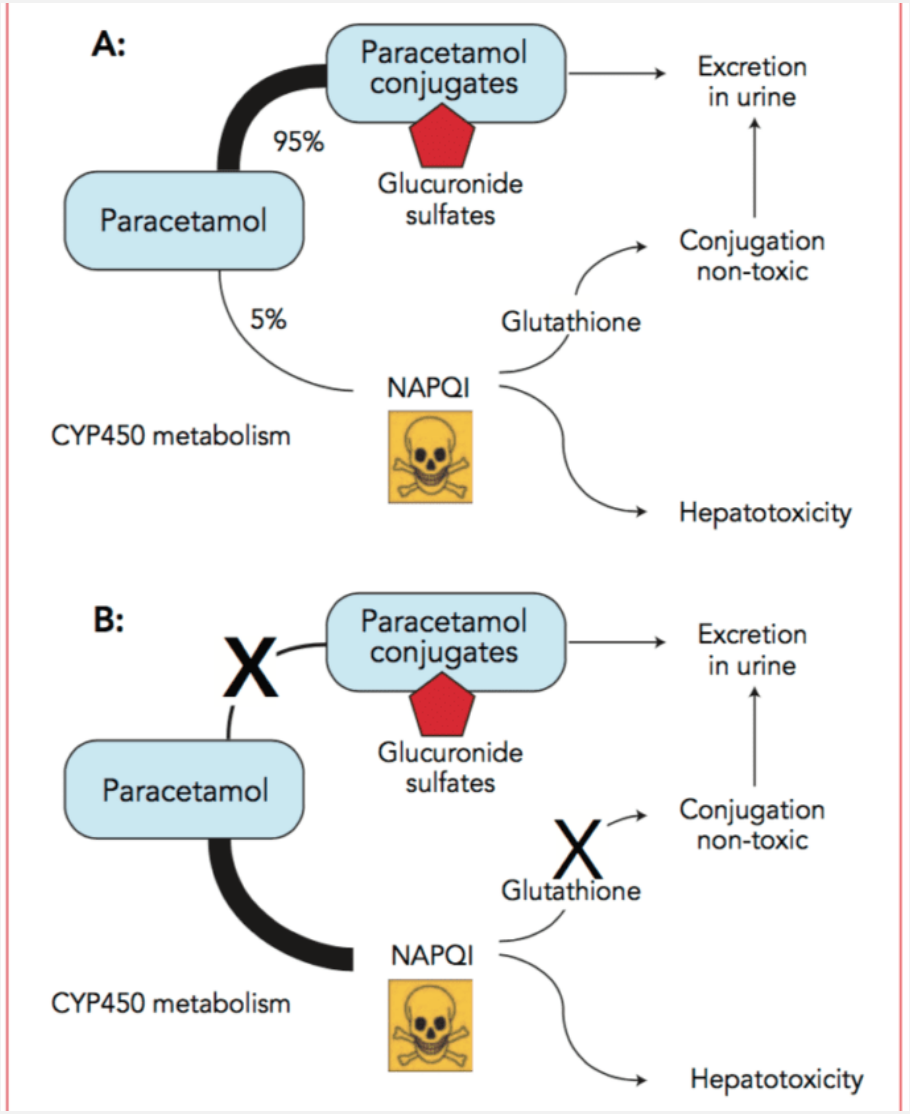
- 90% of acetaminophen is hepatically metabolized to harmless glucuronide (60%) and sulfate (30%) metabolites excreted in urine .
- 5-15% is oxidized by cytoP450 oxidase to potentially hepatotoxic **N-acetyl-p-benzoquinoneimine NAPQI**
- **NAPQI** is normally immediately detoxified by hepatic glutathione conjugation to non toxic **mercapturic and cysteine conjugates** which is readily excreted.

NORMAL PARACETAMOL METABOLISM:



MECHANISM OF TOXICITY:

- When excessive amounts of NAPQI are formed, or when glutathione levels are low or depleted. NAPQI production exceed hepatic ability to detoxify NAPQI by glutathione conjugation.
- NAPQI covalently bound to hepatocytes macromolecules forming acetaminophen-protein
- The binding of acetaminophen to hepatocyte macromolecules is believed to lead to centrilobular hepatic necrosis
- Even in the absence of hepatotoxicity, renal failure can occur because of renal papillary necrosis.



ACUTE PARACETAMOL POISONING:

- **Phase 1**/ (up to 24) hours, asymptomatic or known specific symptoms, anorexia, malaise, nausea, vomiting, pallor, patient may appear normal
- **Phase 2**/ (24-72) hours, onset of hepatic injury, RUQ pain, high (AST), (ALT), and bilirubin, increased prothrombin time (PT). Renal function begins to deteriorate
- **Phase 3**/ (72-96) hours, hepatic necrosis, coagulopathy, jaundice, encephalopathy, nausea, vomiting, coma, all LFTs high, renal failure (25%) with anuria. Hepatic failure may end by death
- **Phase 4**/ (4 days-2weeks), Recovery, from complete hepatic regeneration in survivors if there is not irreversible damage occurred in stage three.

CHRONIC PARACETAMOL POISONING:

- Analgesic nephropathy is injury to the kidney caused by analgesic medications such as aspirin, phenacetin, and paracetamol
- Because APAP is phenacetin metabolite, renal papillary necrosis and nephrotic syndrome are possible producing what is known as chronic analgesic nephropathy
- Use of opioid-acetaminophen combinations appears to be particularly harmful, because habituation to the opioid may occur with a gradual increase in opioid- acetaminophen combination dosing over days or weeks

TOXIC DOSE:

- Acute overdose is usually considered to be a single ingestion
  - Dose for adult = 7.5 gm
  - Dose for children (1 – 6 years) = 150mg/kg – 200mg/kg
- A dose of 15 g for adults, or 4 g for children, is normally sufficient to cause significant liver injury and death.
- The incidence of hepatotoxicity in children is lower than in adults **(Why?)**
  - Age-dependent rate of glutathione turn over that can younger tolerate higher doses. Another meaning increases in the rate of glutathione synthesis and in the ability to stimulate glutathione production in response to acute depletion in children might explain their decreased susceptibility to acetaminophen hepatotoxicity.
  - Early spontaneous emesis in children
  - Differences between children & adults for APAP metabolism

RISK FACTORS:

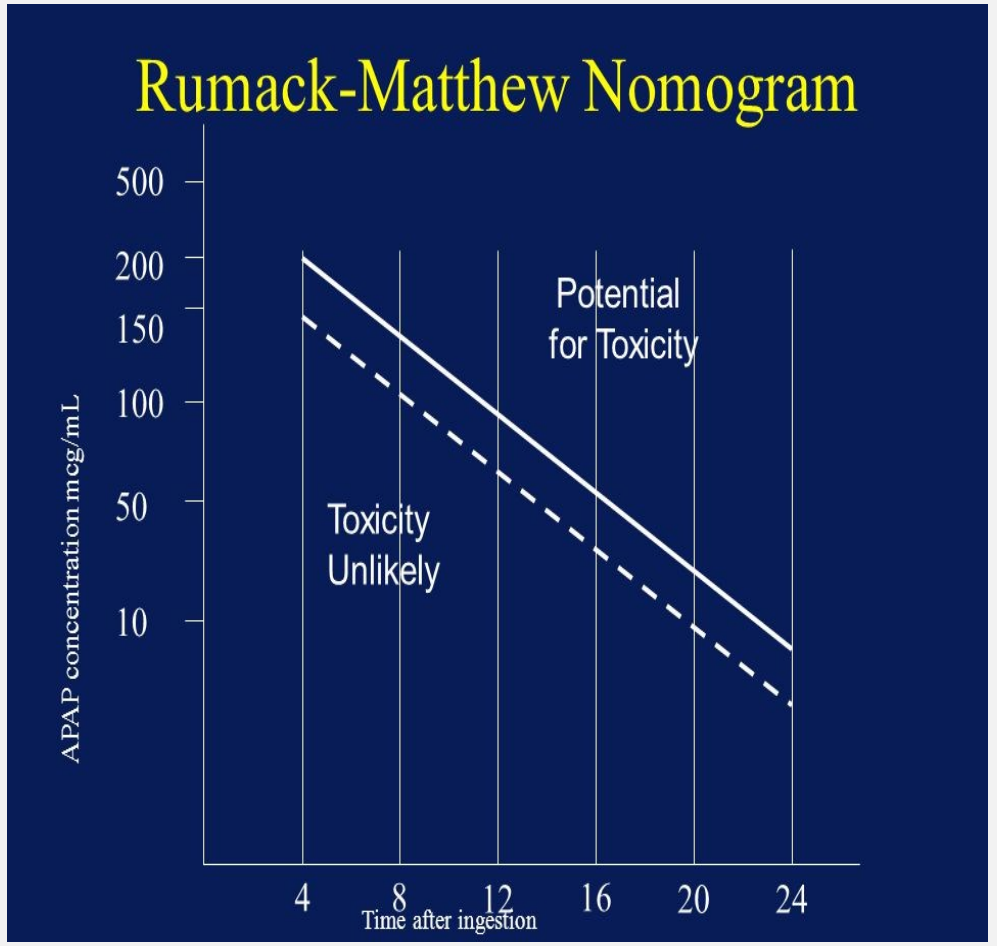
- Increased NAPQI production as a result of cytoP450 enzyme induction (from INH, rifampin, most anticonvulsant, ethanol).
- Reduced glutathione stores (alcoholism, HIV/AIDS, malnutrition, starvation) are at increased risk of hepatotoxicity from APAP.
- Presence of other diseases like cirrhosis, cholestatic jaundice & viral hepatitis

DIAGNOSIS:

- Clinical signs and symptoms for hepatic injury
- Biochemical analysis:
  - ✓ Liver function test / ALT, AST, serum bilirubin (direct and indirect), and alkaline phosphatase
  - ✓ Prothrombin time and international normalized ration
  - ✓ Urinalysis and renal function test (electrolytes, BUN, and creatinine)
  - ✓ Arterial blood gases and ammonia
  - ✓ Serum acetaminophen concentration
- Blood levels of acetaminophen correlate with severity of hepatic injury (levels >300 μg/mL 4 h after ingestion are predictive of the development of severe damage; levels <150 μg/mL suggest that hepatic injury is highly unlikely)
- Whether or not a clear history of overdose can be elicited, clinical suspicion of acetaminophen hepatotoxicity should be raised by the presence of the extremely high aminotransferase levels in association with low bilirubin levels that are characteristic of this hyperacute injury

RUMACK – MATTHEW NOMOGRAM:

- Is a plot of serum acetaminophen conc. Versus time, which serves as a measurement of poisoning severity and a guide for management
- Criteria required to apply this nomogram:
  - ✓ Acute ingestion of acetaminophen
  - ✓ Single serum measurement of serum acetaminophen within 4hr – 24hr of ingestion
- Limitations of the nomogram:
  - Measurement of serum acetaminophen earlier than 4hr is not reliable
  - Can not be used if the patient presents more than 24hr after ingestion
  - Ingestion of multiple doses of acetaminophen
  - Ingestion of extended – release formulation of acetaminophen
  - co- ingestions of acetaminophen with agents that delay gastric emptying



TREATMENT PROTOCOL:

- Assess ABC if necessary
- Minimize absorption though:
  - Induce emesis (Syrup of Ipecac) or gastric lavage <<< less effective
  - Administer activated charcoal within few hours of ingestion <<< more effective
- Extracorporeal methods for elimination are not necessary **except** in case of severe poisoning or evidence of impaired renal function
- Administer antidote (N-Actyl Cysteine or methionine):
  - The key to effective treatment is to start therapy before the onset of liver injury
  - NAC should be administered within 8 hours of ingestion and acute dose to prevent liver injury
  - N-acetylcysteine is administered late following acetaminophen ingestion to patients with evidence of hepatic failure, it decreases mortality and improves hepatic and cerebral function

NAC VR. METHIONINE

NAC

- This agent provides sulfhydryl donor groups to replete glutathione, which is required to render harmless toxic metabolites
- Oral adverse effects / nausea & vomiting (most common), diarrhea
- IV adverse effects / anaphylactic reaction
- Starting dose = 140mg/kg
- Maintenance dose = 70mg/kg every 4hr for 12 – 17 doses

METHIONINE

- It acts by increasing glutathione synthesis.
- An alternative antidote; 2.5 g orally (adult dose) every 4 hours to a total of 4 doses up to a total of 10 grams orally
- less effective, especially after delayed presentation


Thank you
for your
attention