Paracetamol Toxicity

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Acetaminophen (Paracetamol)

In any poisoning case be sure to…

- If the person is conscious:
  - Help them into a comfortable position
  - Ask them what they have taken
  - Reassure them while you talk to them
  - Monitor and record the vital signs
  - Look for evidence that might help you to identify the poison; drug container and take it with you to hospital.
- If the person is unconscious:
  - Open the airway and check breathing, pulse.
  - CPR if needed.

Topics to be covered....

- Introduction
- Clinical pharmacology
- Toxic dose
- Pathophysiology
- Clinical presentation and life-threatening complication
- Diagnosis
- Treatment

Introduction

- Common antipyretic and analgesic OTC drug:
  - Found as single preparations or
  - combined with other drugs like opiods, codeine, analgesics, sedatives, decongestants & antihistamines.
- One of the most common pharmaceutical agent for suicide. (should be considered even in unknown or multiple drugs).
- Antidote therapy is readily available and very effective when administered soon after an acute overdose.

Epidemiology:

- 1966:first overdose toxicity cases.
- Annually, more than 150 deaths in UK and USA, over 100.000 calls to USA poison centers (AAPCC).
- As for Jordan our statistics shows that 13.43% of all enquiries are about paracetamol exposure.

Clinical pharmacology

- Gastric emptying is the rate limiting step.

- After oral therapeutic dose time to peak is 45 minutes.
- Liquid preparations time to peak 30 minutes.
- Supp. in children time to peak 107-288 minutes.

- With ingestion of excessive doses absorption may be delayed but is complete within 4 hrs. (peak serum level).

- Agents that slaw gastric emptying will delay establishing peak serum level e.g. diphenhydramine.

- Elimination half-life 2.5-4hrs, may be prolonged with liver damage.

Dose:

- **Therapeutic:**
  - **Adult:** 650-1000mg every 4-6hrs. up to max. 4g/day.
  - **Children:** 15mg/kg every 4hrs. up to max. 5doses/day.

- **Toxic:**
  - **Acute :** more than 150-200mg/kg in children or 7.5g in adults is potentially hepatotoxic.
  - **Chronic :** 4-6g/day by alcoholic patients, and as little 60-150mg/kg/day for 2-8days for children.

    Febrile children:>75mg/kg/day

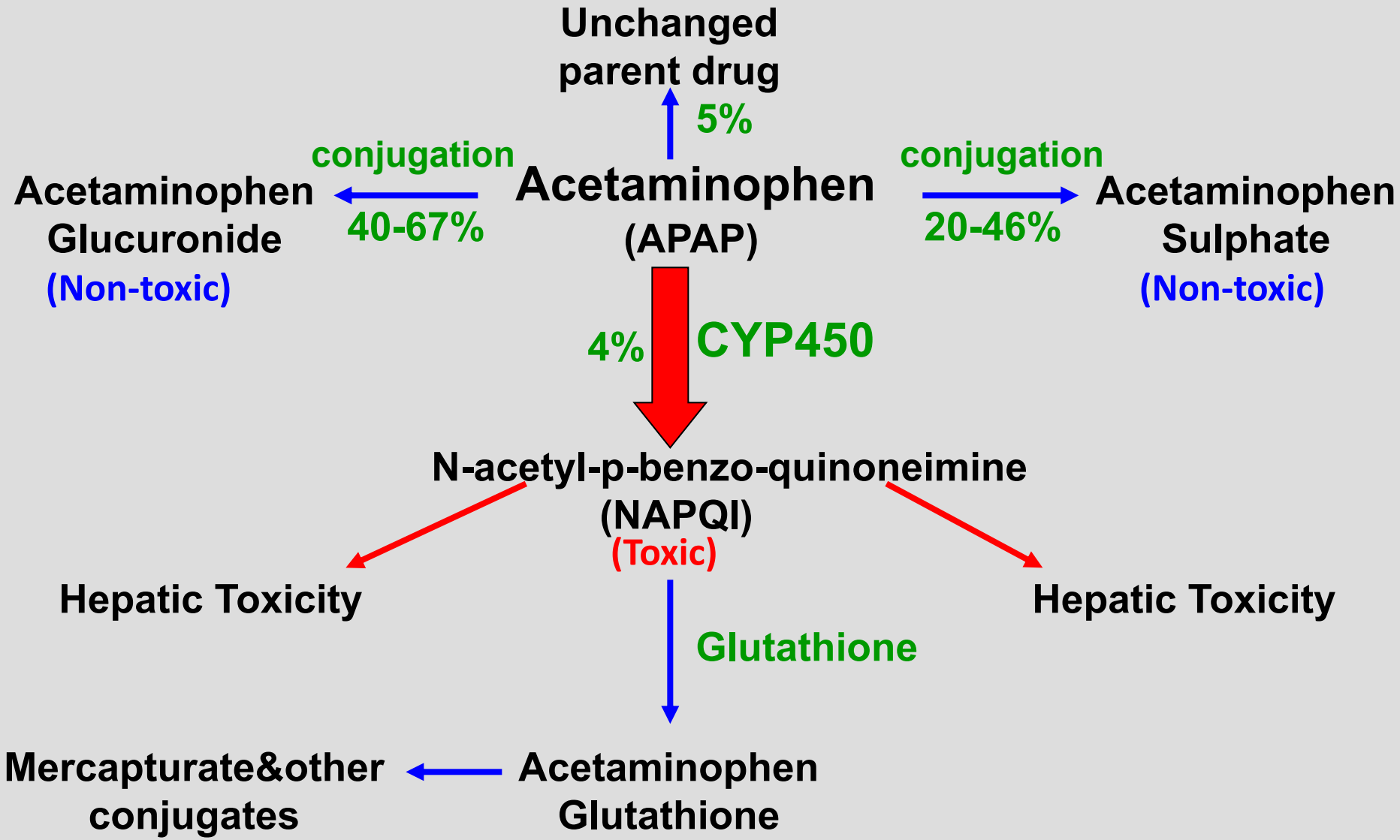
Pathophysiology

- Metabolism of acetaminophen is the basis of its toxicity.
- An example of hepatic toxification rather than detoxification.
- NAPQI is short lived, half life of nanoseconds, if not neutralized binds to hepatic cell membrane.
- Hepatic glutathione is the primary antioxidant.

Modulators of toxicity(high risk pt.):

- Inducers of CYP450: ethanol, rifampin, isoniazid, carbamazepine.
- Depletion of glutathione: malnutrition, chronic alcoholics.
- Age.

APAP metabolism and overdose



Clinical presentation

- Vary depending on the dose, time of presentation, and whether acute or chronic ingestion.
- Symptoms are divided into 4 phases:

1. **Phase I (0.5-24 hrs):**
    - Anorexia, nausea, or vomiting and occasionally lethargy.(Importance of obtaining level).
2. **Phase II (24-72 hrs): onset of liver injury**
    - Blood chemistries abnormal with abnormal INR, PT and bilirubin.
    - Elevation of liver enzymes AST and ALT(AST elevation may occur as early as 8-12 hrs).

3. **Phase III (72-96 hrs): (Maximal hepatotoxicity)**

- Hepatic necrosis such as hepatic encephalopathy.
- AST, ALT could reach 100,000 IU/L .
- Coagulation defects, jaundice, renal failure & myocardial pathology may be present.
- Nausea, vomiting may reappear.
- Death occur most frequently as a complication of cerebral edema or sepsis.

4. **Phase IV (4 days-2 weeks):**

- Patients who survive phase III do not have permanent liver damage.
- LFT's may take several weeks to normalize.
- May develop acute pancreatitis.

Diagnosis:

Acetaminophen measurement (**Rumack-Matthew Nomogram**)

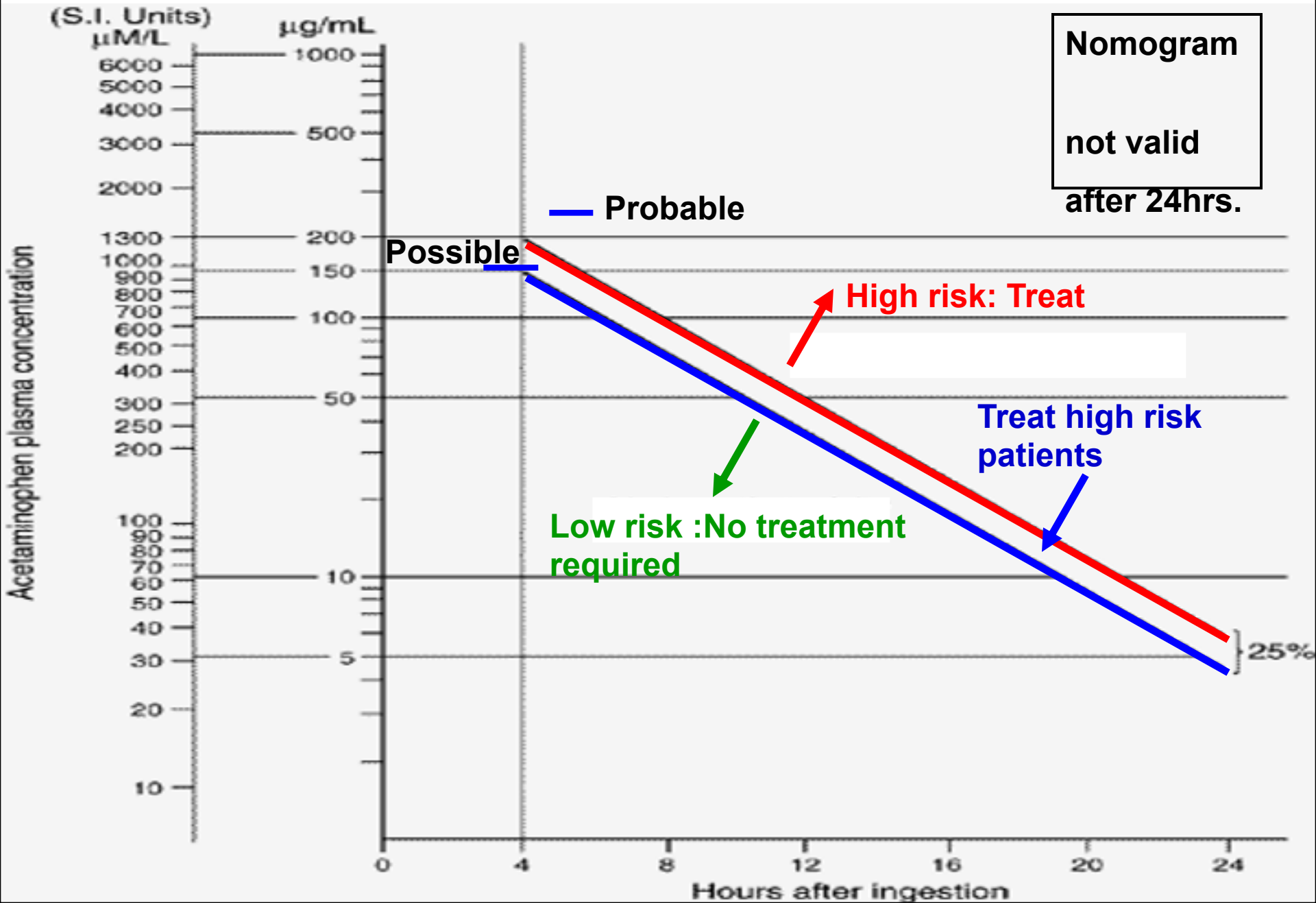
- **Timing:** obtain a plasma concentration level 4 or more hours post ingestion and plot it on the nomogram listed below. level interpreted between 4-24hr,greatest accuracy bet.4-12hr.
- **Liquid preparation:** levels taken 2hrs post ingestion, with NAC treatment if levels are at or above 225mg/L.
- **Other useful tests:** in toxic APAP levels obtain ALT,AST, BUN, PT on admission and daily until levels get to normal.

  Cr., urinanalysis, electrolytes and glucose if liver function abnormalities develop.

AST, ALT is the best measure for conformation or exclusion of liver injury

INR is more appropriate to confirm resolution of serious hepatotoxicity

Acetaminophen Nomogram



Unknown time of ingestion

- **For more than 24hours: Determine APAP and AST**
  - AST elevated regardless of APAP → treat with NAC.
  - AST is normal and APAP below level of detection then narrow window of risk → NAC is unnecessary.
- **Time is completely unknown:**
  - APAP is detectable(>10mcg/ml) it is assumed pt. is at risk → NAC should be initiated (short course).

Chronic acetaminophen exposure

- **Common scenarios: pt. increase intake as it is a "safe drug" !! Or who use combination products along with acetaminophen.**
- **Threshold:**
  - >7.5g acetaminophen in 24hour period (adults).
  - >150mg/kg acetaminophen in 24hr period (children).

Pediatric acetaminophen exposure

- Reasons:

1. Substitution of adult for pediatric preparations.
2. Increase amount and frequency to maximize the effect.
3. Failure to read the label and dose carefully.

- Children can tolerate a higher level of acetaminophen without becoming toxic …..increased glutathione supply and regenerative capacity.
- Febrile children are at greater risk of acetaminophen toxicity …..glutathione supply affected.

Ethanol and risk determination

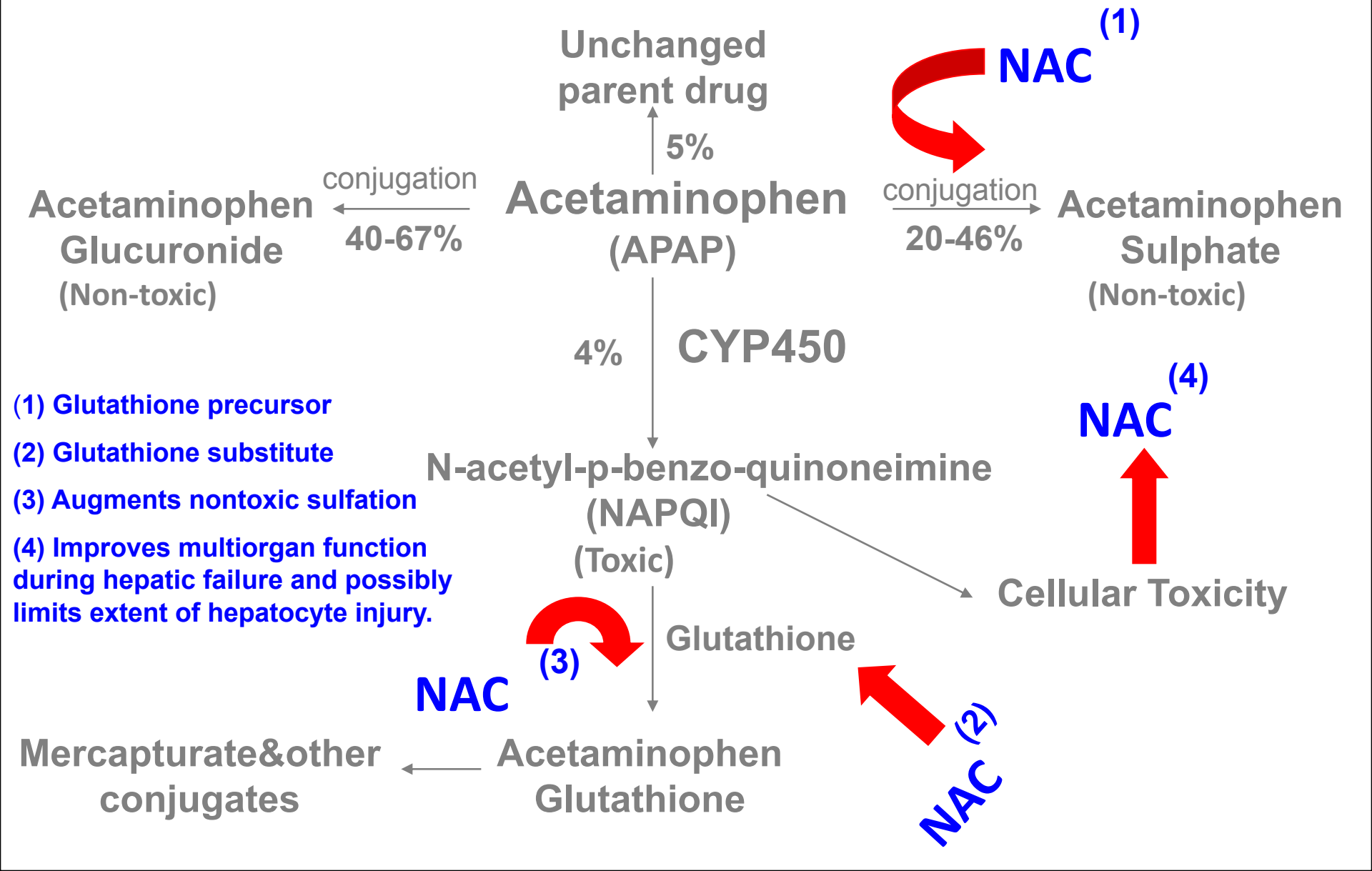
- The most imp. Unresolved issue in risk determination after acetaminophen.
- Ethanol is metabolized to some extent by P450 system… competitive inhibition to produce NAPQI in acute ethanol ingestion.
- Chronic ethanol ingestion: induced P450 APAP metabolism, GSH decreased supply or regeneration.
  - Acute acetaminophen ingestion is treated the same in patients who consume alcohol chronically.

Treatment

Emergency & supportive measures:

- Decontamination: GL or a single dose of activated charcoal should be performed if the patient is seen within 1hr. of ingestion.
- Spontaneous vomiting may delay the administration of the antidote (must be treated aggressively).
- Provide general supportive care for hepatic or renal failure if it occurs.
- Emergency liver transplant may be necessary for fulminant hepatic failure.
- Encephalopathy, metabolic acidosis, hypoglycemia & progressive rise in the prothrombin time are indications of sever liver injury.
- Antidotal therapy (*N-Acetylcysteine)*

Mechanism of Action



- **Oral NAC:**
  - **Smells like Rotten Egg** so dilute 1:4 palatable liquid.
  - **Repeat dose** if pt. vomits within 1 hr adminstration consider antiemetics and nasogastric tube if vomiting persist.
- **Time:** best administered within the first 8hrs.
- **How to administer (2 NAC regimens):**

Regimen	Loading dose	Followed by	Total dose
72hr PO	140mg/kg	70mg/kg q4h for 17 doses	1330mg/kg
21hr IV	150mg/kg 1hr	50mg/kg over 4hr 100mg/kg over 16hr	300mg/kg

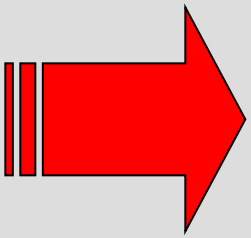
(nausea & vomitiog, 2-3%anaphy.rx)

(3-14% adverse rx. e.g. erythema, urticarial, hypotension)

Oral vs. IV NAC

- **Oral NAC:**
  - For early uncomplicated mild to moderate poisoning
  - History of previous reactions to NAC
  - Asthmatic patients

- **IV NAC:**
  - For serious poisoning or unconscious
  - Patient presenting late, pts. susceptible to hepototoxicity
  - Severe nausea and vomiting
  - Patients who have taken other drugs that could interfere with NAC absorption e.g. anticholinergics and narcotic analgesics.



"NAC is Too Late" does not exist. Improved mortality even in patients with hepatic failure when initiated 2-3 days after ingestion