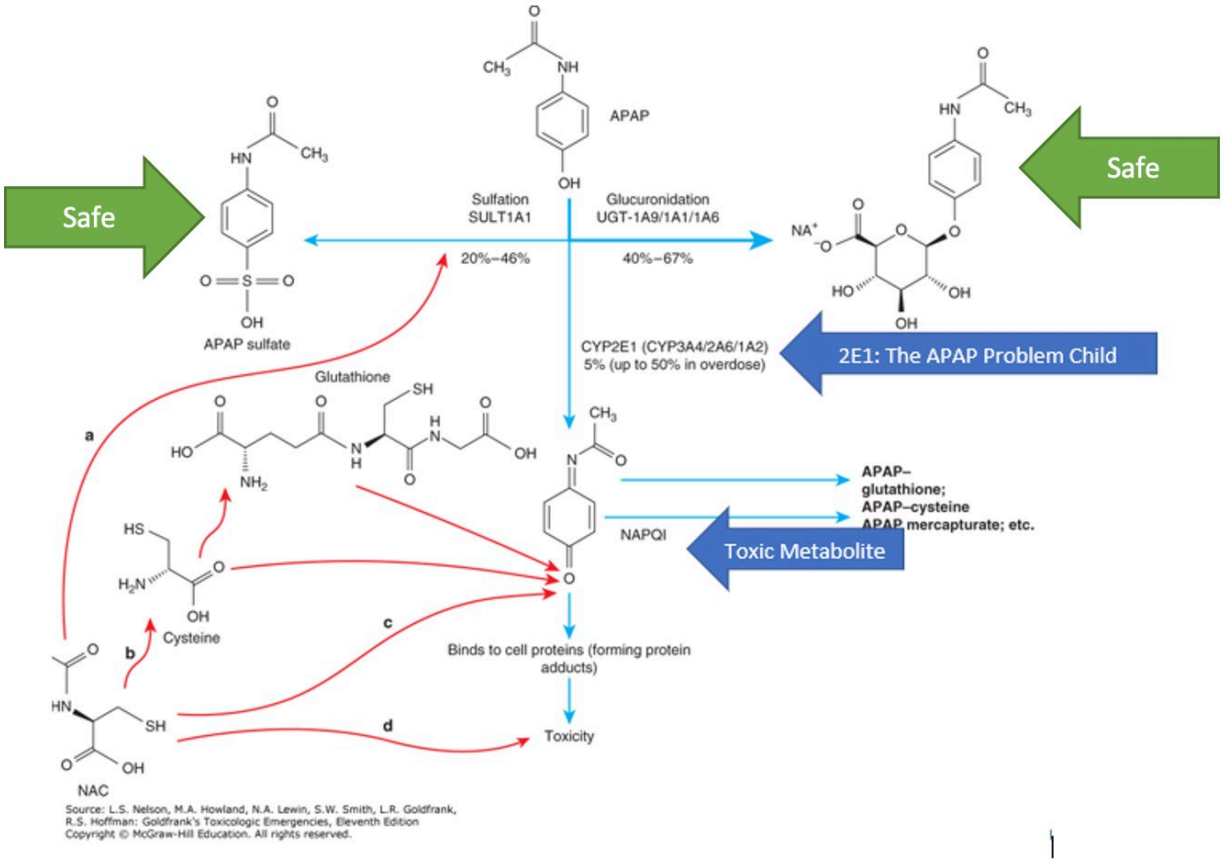
Clinical Pharmacology & Toxicology Pearl of the Week

Fomepizole for Acetaminophen Toxicity

Mechanisms

- There are two ways that fomepizole works to help prevent hepatotoxicity in APAP overdose.

- The primary mechanism involves inhibition of CYP450 2E1.
  - When a toxic amount of APAP is ingested, the pathways that convert it into nontoxic metabolites become overwhelmed.
  - Thus, more APAP gets converted into NAPQI.
  - Fomepizole inhibits the 2E1 pathway, thus preventing conversion of APAP into NAPQI.



- The second mechanism of action is the JNK ("junk") enzyme.
    - NAPQI-induced mitochondrial dysfunction leads to formation of reactive oxidant species. This oxidant stress leads to activation of c-jun N-terminal kinase, or JNK, enzyme.
    - This enzyme translocates to the mitochondria, amplifying oxidant stress, and ultimately resulting in the cessation of ATP production.
    - Additionally, the JNK enzyme can lead to the rupture of the outer mitochondrial membrane, causing release of intermembrane proteins, which can potentially lead to DNA fragmentation
    - Interestingly, it is thought that both metabolic acidosis, as well as elevated lactate levels, may be the result of alterations in mitochondrial respiratory function
    - Fomepizole works by preventing the APAP-induced activation of this enzyme.

Role in Acetaminophen poisoning management

- In cases where fomepizole and NAC were administered together, evidence has shown that the combination has contributed to a decrease in both hepatotoxicity and mortality. Most of the evidence has come from case reports and animal models.

- Currently, fomepizole is recommended for massive APAP ingestions (as in, ingestions over 500-600 mg/kg or in cases where 4-hour equivalent acetaminophen concentrations over 5000 umol/L).
    - These patients may have early (i.e. within 8 hours) presentation of coma, metabolic acidosis, and an elevated lactate (which can be related to an accumulation of 5-oxoproline and inhibition of the γ-glutamyl cycle from depleted glutathione).
    - The combination of fomepizole, IV NAC and hemodialysis is expected to keep APAP in the parent compound state, detoxify any metabolites, and remove APAP via dialysis
- Until there is more concrete evidence surrounding fomepizole use in APAP toxicity, its role should be reserved for massive APAP ingestions.
- IV NAC has been a safe and effective antidote for over 40 years, and is the only antidote required for most APAP exposures.

Dosing

- When used for APAP poisoning, fomepizole is dosed the same as for toxic alcohols:
    - 15mg/kg loading dose, then repeated at 10mg/kg every 12 hours for 48 hours.
    - If still being administered after 48 hours, it induces its own metabolism. Therefore, dosing must be increased to 15 mg/kg every 12 hours.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.