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 acetaminophen (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.

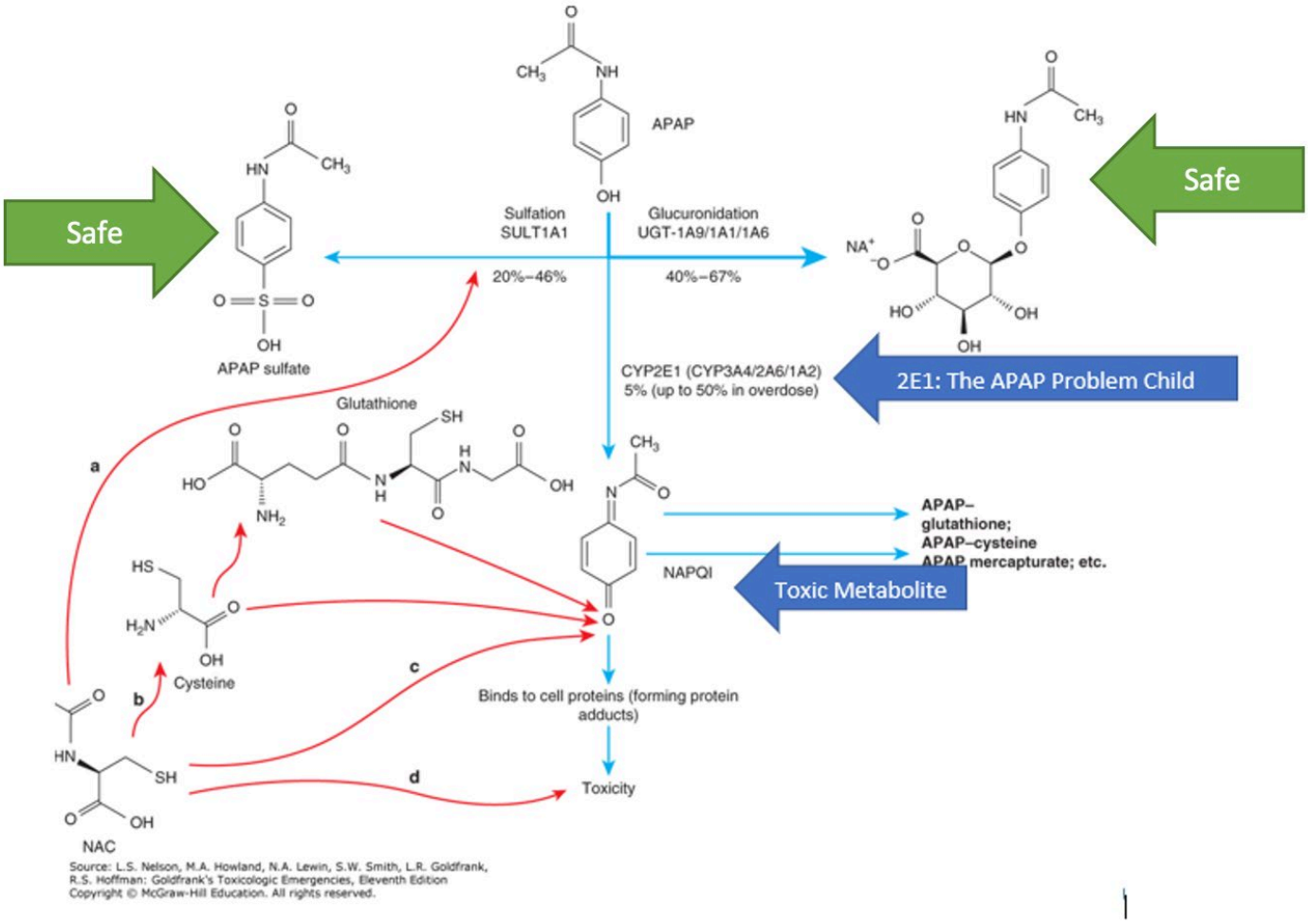
Role in Acetaminophen poisoning management

- ✓ 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 (ingestions over 500-600 mg/kg or in cases where 4-hour equivalent acetaminophen concentration is 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

Dosing

- ✓ The optimal dosing regimen for use during APAP poisoning remains unclear
- ✓ A minimum of a single dose of 15 mg/kg is recommended
- ✓ If additional doses are given, then it should be dosed similar to dosing for toxic alcohol poisoning:
    - After the loading dose, give 10mg/kg every 12 hours for 48 hours (every 4 hours during dialysis)
    - If still being administered after 48 hours, it induces its own metabolism. Therefore, dosing must be increased to 15 mg/kg every 12 hours



References

1. Dart et al. Management of Acetaminophen Poisoning in the US and Canada. A Consensus Statement. JAMA Network Open. 2023;6(8):e2327739.

2. Sivilotti et al. Five things to know about treating acetaminophen overdose. CMAJ 2022 April 19;194:E554. doi: 10.1503/cmaj.210703

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral, Specialist Link and through RAAPID. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

More CPT Pearls of the Week can be found HERE.

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