1-800-222-1222
New Jersey Poison Center

RUTGERS HEALTH
New Jersey Medical School

New Jersey Poison Information and Education System Clinical Guideline:
Fomepizole for acetaminophen toxicity

There is increasing interest in the use of fomepizole (4-MP) in acetaminophen (APAP) poisoning in the context of reports of treatment failure in patients with massive ingestions or delayed presentations. In the development of this guideline, we reviewed the existing literature regarding the use of fomepizole in acetaminophen poisoning. A framework for consultants to assist in selecting the appropriate patient and clinical scenario for the use of this antidote is provided.

Background: Available preclinical animal data, largely using mouse models of acetaminophen poisoning and in vitro studies of human hepatocytes, suggest two mechanisms for the beneficial action of fomepizole. First, fomepizole effectively prevents APAP-induced liver injury by inhibiting CYP2E1 when provided early.[1,3] Second, when provided after the generation of NAPQI, fomepizole promotes hepatocyte survival via inhibition of c-Jun N-terminal kinase (JNK) and reduced oxidant stress.[1-3] Human data are limited to a number of case reports and case series, and a single human volunteer study in which participants were provided sub-toxic supratherapeutic doses (80 mg/kg) of acetaminophen and were treated with fomepizole. The treatment group had substantially reduced concentrations of oxidative metabolites of acetaminophen compared to controls.[4,5] To date, no randomized controlled clinical trial data are available, however one such trial is in active recruitment (ClinicalTrials.gov Identifier: NCT05517668).

While evidence is limited, the preclinical efficacy data and the good safety profile of fomepizole make it an attractive option in patients who are at risk of developing significant hepatotoxicity despite provision of NAC. The cost of fomepizole is currently ~$1000 per 1.5 mL (1g/mL concentration).

CONSIDERATIONS FOR USE OF FOMEPIZOLE:

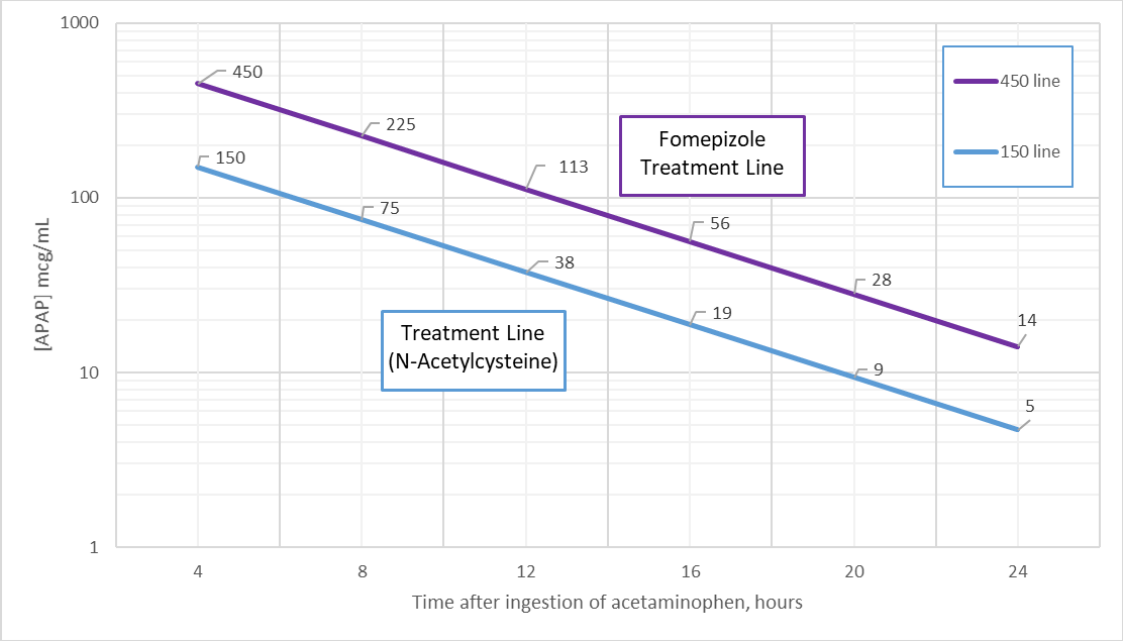
1. **Single acute ingestion of acetaminophen, presenting within 8 hours of ingestion**

- Patients whose acetaminophen concentration plots above the 450 mcg/mL line on the Rumack-Matthew nomogram.
-Patients who are being considered for HD (e.g., patients who present with an [APAP] > 900 mcg/mL and altered mental status, metabolic acidosis and an elevated lactate).[6]

2. **Elevated transaminases or established hepatotoxicity secondary to delayed presentation or a repeated supratherapeutic ingestion**

-Patient has any of the following:

- An APAP multiplication product (AST or ALT, whichever is higher, multiplied by [APAP] in mcg/mL) > 10,000.
- Hepatotoxicity (defined by an [AST] > 1000 IU/L) plus **one** of the following:
    - pH < 7.3
    - INR > 6.5
    - Creatinine > 3.4 mg/dL
    - Lactate > 3.5 mmol/L after fluid resuscitation
    - Phosphate > 3.75 mg/dL
    - Grade III or IV encephalopathy



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We recommend fomepizole be dosed as follows:

- Loading dose of 15 mg/kg
- Followed by one additional dose of 10 mg/kg after 12 hours.
- The decision to continue fomepizole beyond this point should be made on a case by case basis in consultation with a medical toxicologist or poison control center at 1-800-222-1222.

References:

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5. Link SL, Rampon G, Osmon S, Scalzo AJ, Rumack BH. Fomepizole as an adjunct in acetylcysteine treated acetaminophen overdose patients: a case series. *Clin Toxicol (Phila)*. Apr 2022;60(4):472-477. doi:10.1080/15563650.2021.1996591
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