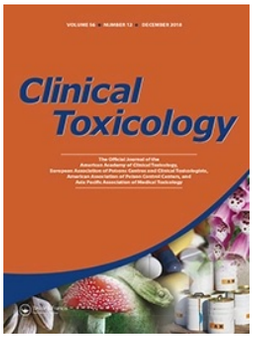

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LETTER TO THE EDITOR

Fomepizole as an adjunctive treatment in severe acetaminophen ingestions: a case series

Dear Editor,

In this retrospective IRB-approved case series, we describe two acetaminophen (APAP) toxic patients reported to a regional poison center who manifested arterial acidemia after fluid resuscitation, a marker for poor prognosis (likely death without liver transplantation). However, both survived to hospital discharge without extracorporeal elimination after dual N-acetylcysteine (NAC)-fomepizole therapy. Case details were verified *via* hospital electronic medical record review.

A 44-year-old female with ethanol and polysubstance use disorder was brought to the hospital with altered mental status. After 40 cc/kg intravenous (IV) crystalloid, her initial laboratory values included total bilirubin 1.3 mg/dL, creatinine 1.21 mg/dL, lactate 14.3 mmol/L, arterial pH 7.276. 13 h after arrival, AST 1516 IU/L and ALT 1190 IU/L triggered ordering of an APAP concentration that was 108.1 mg/L. Ethanol and salicylate were undetectable. Six weeks prior, her transaminases were normal. Oral NAC 140 mg/kg loading dose and 70 mg/kg every 4 h were started 19 h after arrival. Fomepizole 15 mg/kg IV was given per poison center recommendation. On day three, IV NAC 150 mg/kg loading dose and 15 mg/kg/h infusion were started due to shock. Hepatitis A, B and C testing was negative. Peak laboratory values (INR 6.7, ALT $>$ 5000 IU/L, AST 8372 IU/L) occurred on day three.

A 56-year-old female with breast cancer, bipolar disorder and chronic pain syndrome was found with depressed mental status and APAP pills around her. Time of ingestion was unknown. She had no history of ethanol abuse, no new medications in the last month, and normal transaminases 1 week prior. Initial laboratory values included APAP concentration 298 mg/L, AST 245 IU/L, ALT 366 IU/L, undetectable ethanol and salicylate. After 40 cc/kg IV crystalloid, total bilirubin 1.3 mg/dL, creatinine 1.32 mg/dL, lactate 9.3 mmol/L, and arterial pH 6.9 resulted. IV NAC 150 mg/kg loading dose followed by 15 mg/kg/h infusion was started. Repeat APAP concentration 19 h after the initial value was $>$300 mg/L, and fomepizole IV 15 mg/kg was given per poison center recommendation. Hepatitis C antibody testing was positive. Peak laboratory values (INR 5.8, ALT 4553 IU/L, AST 2579 IU/L) occurred on day four. Both patients survived to hospital discharge.

Preclinical and anecdotal human data support fomepizole use in APAP toxicity. Fomepizole 15 mg/kg in humans results in serum levels of over 100 micromoles/L, sufficient to inhibit the majority of NAPQI creation from CYP 2E1 [1], for at least 24 h [2]. As such, we recommended one dose of 15 mg/kg IV fomepizole. Animal studies of APAP toxicity show decreased transaminases and mitochondrial oxidative damage with fomepizole use [3]. Fomepizole pretreatment in human supratherapeutic acetaminophen ingestions decreased toxic oxidative urinary acetaminophen metabolites [4]. Finally, post-marketing surveillance has demonstrated fomepizole's safety [5].

Our report is anecdotal and, therefore, uncontrolled. As such, causation of survival cannot be attributed to fomepizole. However, based on the pathophysiology of NAPQI, preclinical studies, early human data, and safety profile, in addition to these two cases, fomepizole warrants further study as an adjunct to NAC in the treatment of severe APAP toxicity.

Disclosure statement

The authors report no declarations of interest.

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