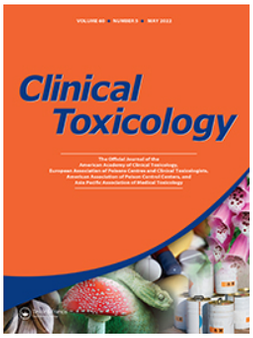

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Fomepizole as an adjunctive therapy for acetaminophen poisoning: cases reported to the toxicology investigators consortium (ToxIC) database 2015–2020

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ABSTRACT

Introduction: Fomepizole inhibits formation of toxic acetaminophen (APAP) metabolites and may prevent or reverse mitochondrial toxicity. Given these mechanisms, it may be beneficial in patients with severe APAP toxicity. Current patterns of use for this indication are not well-studied.

Methods: This is a secondary analysis of patients enrolled in the Toxicology Investigators Consortium (ToxIC) database from January 2015 to July 2020. We queried cases in which APAP was listed as an ingested agent and fomepizole was also administered. We excluded cases in which APAP was not the primary agent, N-acetylcysteine (NAC) was not administered, or fomepizole was explicitly administered for another indication. Additionally, we sent a survey to each ToxIC site that administered fomepizole for APAP toxicity to better understand when, why, and how they were using it for this indication.

Results: Twenty-five cases of fomepizole administration following an APAP ingestion met our inclusion criteria. There were one to four cases per year between 2015 and 2019 and eight cases in 2020. Seventeen of 25 (68%) cases were for a known acute ingestion. Eighteen of 25 (72%) patients developed hepatotoxicity (AST or ALT $>$ 1000 IU/L) and 10 of 25 (40%) developed coagulopathy (PT $>$ 15s). This was an ill patient population, with 18 of 25 (72%) developing metabolic acidosis (pH $<$7.20), 12 of 25 (48%) were intubated, 9 of 25 (36%) receiving vasopressors, and 6 of 25 (24%) receiving continuous renal replacement therapy. Overall, mortality was 24%.

Conclusion: The use of fomepizole is increasing in frequency in a small subset of critically ill and acutely APAP-poisoned patients.

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Introduction

Acetaminophen (APAP) is a widely used analgesic and antipyretic. It is popular as both monotherapy and in combination products, with use prevalence in American adults exceeding 50% over a 6-month span [1]. Because of its popularity, it remains the leading cause of acute liver failure in the United States and United Kingdom [2]. It is also the most common cause of single-substance fatalities reported to US Poison Centers [3].

Although the liver conjugates the majority of APAP to non-toxic products, hepatic CYP 2E1 also converts a small portion to the toxic electrophile *N*-acetyl-*p*-benzoquinone imine (NAPQI) [4]. Endogenous glutathione is sufficient to detoxify NAPQI in therapeutic APAP exposures. Following an overdose, glutathione depletion yields a cascade of oxidative stress, mitochondrial dysfunction, and hepatocellular necrosis [5]. Since the 1970s, antidotal strategies have centered on the use of N-acetylcysteine (NAC) to scavenge NAPQI and mitigate the oxidative stress and resultant hepatotoxicity [4]. Although NAC is an effective antidote in the majority of cases, it may be insufficient as monotherapy in the event of a very large overdose or delayed presentation [6].

Fomepizole (4-methylpyrazole, Antizol®), a CYP2E1 and alcohol dehydrogenase inhibitor, is gaining interest as an antidotal adjunct in severe acetaminophen poisoning [7–9]. Animal models suggest that in addition to protecting against NAPQI formation [10], fomepizole downregulates apoptotic pathways and mitigates against ongoing hepatic injury [11]. Fomepizole reduced oxidative metabolite formation in human volunteers receiving supra-therapeutic doses of APAP [12]. Despite a number of recent case reports [13,14] and case series [15,16], there is a dearth of high-quality data on fomepizole use in acetaminophen poisoning. There is currently no overarching consensus on how and when to deploy fomepizole for this indication [8,9].

In this study, we report data on the use of fomepizole in acetaminophen poisoning captured by the Toxicology Investigators Consortium (ToxIC) database between 2015 and 2020. We aim to examine existing practice patterns and attitudes toward the use of fomepizole for this indication.

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Methods

We performed a secondary analysis of patients enrolled in the ToxIC database from January 2015 to July 2020. The ToxIC registry represents a prospective data collection network of bedside medical toxicology consulting services with 50 participating sites. Standardized forms record qualitative and quantitative clinical data and patient demographic information [17]. The ToxIC Registry has been reviewed and approved by the Western Institutional Review Board (IRB), and all patient data are de-identified and HIPAA compliant.

We queried cases in which APAP was listed as an ingested agent and fomepizole was also administered as an antidote. We excluded cases in which APAP was not the primary agent or NAC was not administered. We also identified and excluded cases in which fomepizole was explicitly administered for an indication other than APAP toxicity (e.g. toxic alcohol exposure, unknown metabolic acidosis).

We examined markers of critical illness in these patients: hepatotoxicity, metabolic acidosis, elevated anion gap, intubation, vasopressor use, renal replacement therapies, and death. We used laboratory markers defined *a priori* on the ToxIC data collection form: hepatotoxicity = AST or ALT > 1000 IU/L, metabolic acidosis = pH < 7.20, coagulopathy = PT >15 s, and elevated anion gap = AnGap >20 mmol/L. Additionally, we sent a 10-question survey (Table 1) to each ToxIC site that administered fomepizole for APAP toxicity to better understand when, why, and how they are using it for this indication. The survey was tested and revised multiple times prior to being sent. We sent the survey to the attending toxicologist listed in ToxIC for each entry. Each attending received a single request to complete the survey. Survey responses were anonymous and completed in SurveyMonkey. We analyzed all data using descriptive statistics.

Results

We identified 38 cases of fomepizole administration following an APAP ingestion. We excluded six cases in which a toxic alcohol was present or explicitly considered and an additional seven cases in which APAP was not the primary agent. Twenty-five cases were included in our final analysis (Figure 1). The highest frequency was reported in 2020 ($n = 8$) compared to any other year (range: 1–4 cases/year). Seventeen of 25 (68%) cases were for single APAP ingestions with a known time of ingestion, versus chronic or unknown timing. The median age of the included patients was 42 years old, and 60% of the included patients were female.

Patients in this cohort generally had severe toxicity (Figure 2). Eighteen of 25 (72%) patients developed hepatotoxicity, and 10 of 25 (40%) developed coagulopathy. Median reported lactate was 8.0 mmol/L ($n = 20$). Eighteen of 25 (72%) developed metabolic acidosis, 12 of 25 (48%) were

Table 1. Survey instrument for fomepizole use in APAP poisoning.

1. Your service has used fomepizole for acetaminophen intoxication. Are there specific agreed upon criteria you or your partners use to determine when to recommend it or is the recommendation based on the attending's gestalt/discretion?
A) Yes- agreed upon criteria; B) No- based on the attending's gestalt or discretion; C) I don't know
2. What type of acetaminophen ingestions do you use it or consider using it for?
A) acute; B) chronic; C) both
3. Do you order it based on the patient's presenting acetaminophen concentration?
A) Yes; B) No
4. In patients with a significant metabolic acidosis solely due to acetaminophen intoxication and not from another cause, would you treat them with fomepizole even if the acetaminophen concentration was low or negative?
A) Yes; B) No
5. What is the loading dose of fomepizole that you use in acetaminophen toxicity?
A) 15 mg/kg; B) Other (specify dose below)
6. Do you redose the fomepizole for acetaminophen toxicity?
A) Yes (if yes, when do you do this e.g. 12 h, 24 h, etc.); B) No
7. Would you consider using fomepizole with hemodialysis for acetaminophen toxicity?
A) Yes; B) No
8. Are you convinced that fomepizole is safe in acetaminophen poisoned patients with significant hepatotoxicity or metabolic acidosis?
A) Yes; B) No; C) Not Sure
9. If the answer to Question 8 is yes, is this based on (check all that apply):
A) Case reports; B) Animal studies; C) Experience with fomepizole with toxic alcohols; D) Not applicable
10. Do you think fomepizole has been shown to be effective in the treatment of acetaminophen poisoning?
A) Yes; B) No; C) If yes, is this based on animal studies, case reports, both or neither:

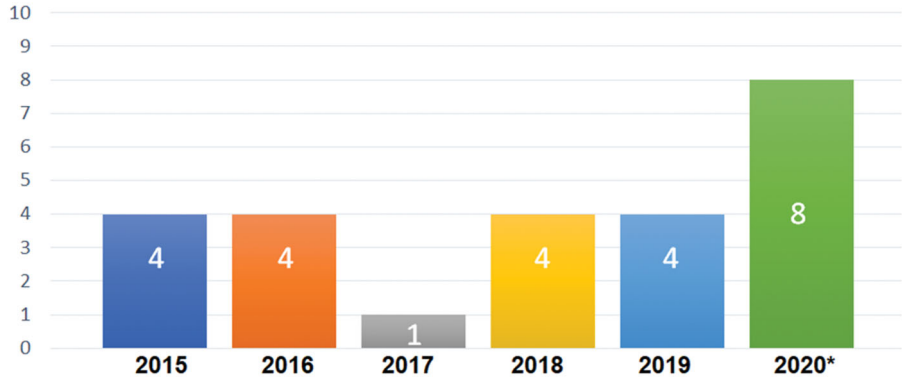

Figure 1. Included cases of fomepizole use for acetaminophen toxicity, January 2015 through July 2020 (* = first seven months of 2020).

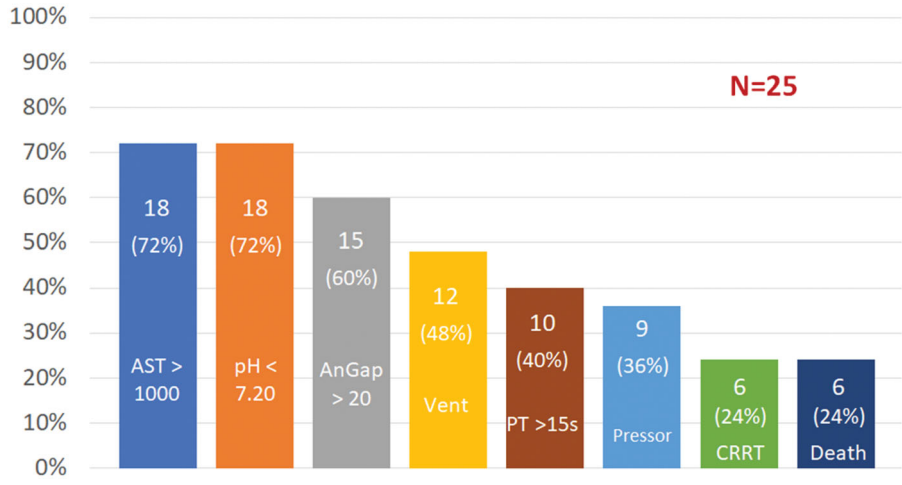

Figure 2. Characteristics of patients receiving fomepizole for acetaminophen toxicity. AST = Aspartate Aminotransferase, Vent = intubated, PT = prothrombin time, Pressor = receiving vasopressors, CRRT = continuous renal replacement therapy.

intubated, 9 of 25 (36%) received vasopressors, and 6 of 25 (24%) received continuous renal replacement therapy. Overall, mortality was 24%.

Among the 16 sites reporting fomepizole for acetaminophen ingestion, 12 reported using fomepizole for the distinct purpose of acetaminophen toxicity (Table 2). Two sites did not respond, and two sites responded that the attending physician did not direct the use of fomepizole for this purpose (e.g. the fellow ordered it but the attending would not have). Seven of 12 (58%) respondents considered using fomepizole for acute or chronic ingestion versus five of 12 (42%) who only considered fomepizole for an acute ingestion. No site considered use for chronic ingestion only. For 11 of 12 participants (92%), the decision to use fomepizole depended upon physician gestalt as opposed to protocolized indications. All 12 respondents used the 15 mg/kg dose of fomepizole. Five of 12 (42%) considered repeat dosing.

Ten of 12 respondents (83%), would consider giving fomepizole in conjunction with dialysis. Seven of 12 (58%) of respondents agreed that fomepizole is safe in patients with significant hepatotoxicity or metabolic acidosis. Three of 12 (33%) regarded fomepizole as having demonstrated effectiveness in severe APAP poisoning.

Discussion

Our data reveal this to be a critically ill subset of APAP poisoned patients. Strikingly, the majority (72%) of our patients would potentially satisfy the King's College Criteria for liver transplantation, currently the leading criteria for liver transplant after severe APAP poisoning, although some do advocate alternative criteria [18,19]. This specific assessment is limited by a lack of granular data regarding our patients' resuscitations and trajectories.

Fomepizole may have special utility in massive overdose, in which NAC alone may fail to prevent hepatotoxicity and critical illness. Several studies demonstrate specific risks of hepatotoxicity from massive overdose (>300 μg/mL or 1,985 μmol/L at 4 h post-ingestion by conservative definitions) despite timely administration of NAC [20,21]. Although some regimens propose terminal infusion rates up to 4-times standard dosing [22], higher doses of NAC may still fail to protect against hepatotoxicity [23]. Fomepizole is safe and well tolerated at standard doses for toxic alcohol poisoning [24]. The observed pattern of using a single 15 mg/kg loading dose is consistent with published data demonstrating that the standard dosing for fomepizole results in a serum concentration of at least 100 μmol/L [25], which blocks CYP2E1 in animal and human models [12,26].

Table 2. ToxIC site survey responses.

Class of ingestion	Acute	Chronic	Both
Type of ingestion considered for use?	5/12 (42%)	0/12 (0%)	7/12 (58%)
Specific indications for use	Yes	No	
Protocolized indication?	1/12 (8%)	11/12 (92%)	
Based off presenting APAP concentration?	8/12 (67%)	4/12 (33%)	
Consider even if APAP low or negative?	7/12 (58%)	5/12 (42%)	
Dosing strategies			
15mg/kg initial dose?	12/12 (100%)	0/12 (0%)	
Do you re-dose?	5/12 (42%)	7/12 (58%)	
If yes, do you uniformly re-dose q12h?	4/5 (80%)	1/5* (20%)	*Based off toxic alcohol dosing
Role in critical illness			
Consider with hemodialysis?	10/12 (83%)	2/12 (17%)	
Convinced of safety with significant acidosis or hepatotoxicity?	7/12 (58%)	5/12 (42%)	
Convinced of demonstrated effectiveness?	4/12 (33%)	8/12 (67%)	

In severe cases, hemodialysis (in addition to NAC) removes APAP and corrects metabolic acidosis. However, consensus guidelines do not strongly recommend dialysis to APAP poisoned patients receiving NAC unless APAP concentrations are above 900 μg/mL (5,954 μmol/L) [27]. Below this concentration, patients still risk developing hepatotoxicity despite prompt treatment with NAC. Few proposed treatment strategies address alternatives beyond NAC for APAP concentrations above 600 μg/mL (3,969 μmol/L) at 4 h post-ingestion who do not receive hemodialysis [22]. Fomepizole may serve a particular role in those with high APAP concentrations in whom hemodialysis is not warranted or available or cannot be initiated in a timely manner. Hemodialysis may also be poorly tolerated in severely poisoned patients with hemodynamic instability [28]. Those presenting with APAP level > 600 μg/mL (3,969 μmol/L) line, a (APAP X aminotransferase) cross-product >10,000 (IU/L) × (μg/mL) or 66,000 (IU/L) × (μmol/L) [29,30], or those who present with signs of fulminant liver failure already present [18] may be patients who would benefit from the addition of fomepizole to their treatment.

The decision to use fomepizole or hemodialysis in severely APAP poisoned patients is not mutually exclusive, i.e. patients can receive both. The concomitant use of hemodialysis and fomepizole has been previously reported [13], and the majority of survey respondents (83%) would consider using hemodialysis in patients receiving fomepizole for this indication. This is not surprising considering that toxicologists would administer fomepizole while waiting to initiate hemodialysis in patients with toxic exposures to methanol or ethylene glycol. While fomepizole is removed by hemodialysis, there is poor agreement on the need for re-dosing: 42% of survey respondents would consider re-dosing.

As fomepizole is an experimental therapy in APAP poisoning, concern over cost may be a potential barrier to treatment. Previous reviews [31] and economic analyses [32,33] place the inflation-adjusted cost of a 15 mg/kg dose of fomepizole between $643 and $1,392. A standard 20-hour infusion of NAC, estimated at $602–690 [34,35], is fairly similar in price to a single dose of fomepizole. When further compared against the cost of liver transplant, any protective benefit afforded by fomepizole comes at negligible expense. A 2009 review and meta-analysis estimated the costs of liver transplant (operation and initial hospital stay but excluding lifetime care) in the US as approaching $200,000 [36]. This figure ignores the additional lifetime costs and morbidity associated with liver transplantation. While fomepizole should not supplant NAC therapy as a mainstay of treatment, magnitudes of cost should be strongly considered in this critically ill patient population.

Although data were collected prospectively, they are limited by the secondary analysis and small sample size. While we did attempt to exclude cases in which fomepizole was administered for a reason other than severe APAP poisoning, ultimately we inferred the intent of use. It is unlikely that many instances of fomepizole use for toxic alcohols were captured: only four out of 16 sites (25%) did not confirm that they used fomepizole for acetaminophen toxicity. Two of the four sites did contact us directly stating that while the attending would not use it for this indication, the fellow on call may have ordered it prior to discussing the case with them. We cannot ascertain the intent of the two non-respondent sites. As we conservatively excluded 13 out of 38 (34%) patients in the queried population, we expect most cases in which fomepizole was not explicitly used for this indication would fall within this group. However, we could not confirm this on an individual basis. Aside from mortality, we could not derive patient centered outcomes such as hospital length of stay or long-term sequelae given limitations of the registry.

Conclusion

Despite increasing use of fomepizole for APAP poisoning, our data suggest that confidence in its safety and efficacy for this indication is still lacking. Fomepizole doses used follow those established for toxic alcohol poisoning, although the target inhibitory concentrations at the target enzymes may be different. Clinical human data with *a priori* defined indications will be necessary to support the routine use of this antidote. Until more robust data emerge, it appears reasonable to consider fomepizole within an escalating strategy of high-dose NAC and hemodialysis in select poisoned patients.

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