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Clinical impact of fomepizole as an adjunct therapy in high-risk acetaminophen overdose

Hayley T. Gartner [a,*], Reeves E. Simmons [a], Molly Stott [a], Victor Perez [b], Justin Crespo [a], Brittany Allison [a], Alex Howard [b], Amber Patt [c], Herbert Z. Wan [a], Colleen Cowdery [b], Dawn R. Sollee [a,b], Sonya S. Rashid [a,b], Tim P. Moran [d], Brent Morgan [c,d], Sophia Sheikh [a,b]

[a] Florida/USVI Poison Information Center Jacksonville, University of Florida Health Jacksonville, Jacksonville, FL, USA
[b] Department of Emergency Medicine, University of Florida College of Medicine Jacksonville, Jacksonville, FL, USA
[c] Georgia Poison Center, Atlanta, GA, USA
[d] Department of Emergency Medicine, Emory University, Atlanta, GA, USA

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ABSTRACT

Introduction: The objectives of this study were to characterize and compare clinical outcomes in patients with high-risk acetaminophen overdose who received fomepizole as an adjunct to *N*-acetylcysteine treatment to those who received *N*-acetylcysteine only.
Material and methods: This was a retrospective cohort study of patients reported to four United States poison control centers between January 2018 and December 2022. Patients with high-risk acetaminophen ingestion—defined as a serum concentration ≥ 300 μg/mL at 4 h or more post-ingestion, or a multiplication product (acetaminophen concentration in mcg/mL multiplied by either aspartate aminotransferase in units per liter or alanine aminotransferase in units per liter) ≥10,000—upon admission who received *N*-acetylcysteine were included. Exclusion criteria included documented history of pre-existing liver disease, insufficient case details, or co-ingestion of either a toxic alcohol or another hepatotoxic substance. Clinical characteristics and outcomes were compared using logistic regressions between patients who received fomepizole as an adjunct to *N*-acetylcysteine treatment to those who received *N*-acetylcysteine only. A subgroup analysis assessed the impact of fomepizole timing (≤24 h versus >24 h) after *N*-acetylcysteine initiation.
Results: Among the 391 patients included, there were no significant differences in National Poison Data System outcome severity, intensive care unit stay, or *N*-acetylcysteine duration between patients who received fomepizole and those who did not. In the subgroup analysis of fomepizole recipients, outcomes were also similar regardless of whether fomepizole was administered within or after 24 h of *N*-acetylcysteine initiation.
Discussion: Fomepizole as an adjunct to *N*-acetylcysteine in patients with high-risk acetaminophen overdose did not improve clinical outcomes. Although no adverse effects to fomepizole were reported, routine use in this setting remains unsupported by this study.

1. Introduction

Acetaminophen ranks among the most commonly used over-the-counter medications worldwide [1]. Although acetaminophen is an effective and well-tolerated antipyretic and analgesic, exceeding therapeutic doses leads to hepatotoxicity, renal failure, and death [2]. It is also the leading cause of acute liver failure in the United States, accounting for approximately 46% of all cases [3]. In 2023, poison control centers received over 110,000 acetaminophen-related calls, and acetaminophen alone was associated with the most fatalities among all other substances [4]. Acetaminophen produces toxicity primarily through the hepatic formation of a reactive metabolite, *N*-acetyl-p-benzoquinone imine (NAPQI) via cytochrome P450 2E1 (CYP2E1), which depletes glutathione and covalently binds to cellular proteins, leading to oxidative stress, mitochondrial dysfunction, and hepatocellular necrosis [3,5,6]. In 2004, the United States Food and Drug Administration approved the 21-h intravenous *N*-acetylcysteine (NAC) protocol, which is effective at preventing severe hepatic injury when initiated within eight hours of acetaminophen overdose [7]. NAC works by replenishing

* Corresponding author.
E-mail address: hayley.gartner@jax.ufl.edu (H.T. Gartner).

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intracellular glutathione, enhancing the detoxification of NAPQI, and reducing oxidative stress, thereby preventing or limiting acetaminophen-induced liver injury [8].

Despite the robust data on the effectiveness of NAC, reports describe instances of treatment failure, resulting in hepatic injury, even when clinicians administered NAC within 8 h of acetaminophen ingestion [9,10]. Risk factors for NAC failure include a single acute ingestion of more than 30 g, serum acetaminophen concentration of 300 micrograms per milliliter (mcg/mL) or more at 4 h post-ingestion, or cases in which acetaminophen concentration in mcg/ml multiplied by either aspartate aminotransferase (AST) in units per liter or alanine aminotransferase (ALT) in units per liter is greater than or equal to 10,000 [5,6,9,11-13]. While NAC remains the standard of care for acetaminophen overdose, the use of fomepizole has been proposed as an adjunct in cases of high-risk ingestions. Fomepizole as an adjunct to NAC therapy likely provides additional hepatoprotection via two distinct pathways. First, as a potent inhibitor of the cytochrome P450 2E1 (CYP2E1) enzyme, fomepizole reduces the metabolism of acetaminophen to its hepatotoxic metabolite, NAPQI [3]. Second, fomepizole prevents activation of c-Jun- N-terminal kinase (JNK) to its phosphorylated form (P-JNK). Once formed, P-JNK translocates across the mitochondrial membrane and inhibits the electron transport chain, leading to production of reactive oxygen species, DNA fragmentation, and ultimately cell death [8,14].

The recently published acetaminophen poisoning consensus guidelines did not recommend the routine use of fomepizole for high-risk acetaminophen overdose, citing insufficient evidence in the existing literature [10]. The current evidence supporting fomepizole as an adjunct to NAC includes animal studies, mechanistic data, and small case series or case reports in humans, all of which lack control groups and do not provide comparative efficacy data [8,15-18]. Its use in acetaminophen poisoning has risen sharply, increasing from 0.31% of cases in 2016 to 5% in 2024 [19]. Given the limited clinical evidence, our objective was to evaluate whether adjunctive fomepizole use was associated with differences in clinical outcomes among patients with high-risk acetaminophen overdose. To address this, we compared outcomes between patients who received fomepizole and those who did not.

2. Materials and methods

2.1. Study design and case selection

This was a retrospective observational cohort study of acetaminophen exposures reported to four poison control centers in the United States. Exposures reported to each center are documented as an individual chart within the ToxSentry® electronic medical record system. ToxSentry® utilizes both standardized coded data elements derived from the National Poison Data System (NPDS), as well as supplemental free-text fields for documentation of additional clinical details beyond the discrete NPDS coding elements [20]. NPDS standardized coding exists for certain clinical effects, treatments, and medical outcomes (See Supplemental Table S1 for further details). The Institutional Review Boards at the University of Florida and Emory University approved this study as exempt.

A query of the ToxSentry® database identified cases involving acetaminophen exposures reported between January 1, 2018, and December 31, 2022. Any high-risk acetaminophen exposure in a patient between the ages of 0–100 was eligible for study inclusion. A high-risk acetaminophen exposure was defined as either a serum acetaminophen concentration ≥ 300 μg/mL or more at *4 h or later* post-ingestion *OR* a multiplication product ≥10,000 at the time of initial laboratory evaluation (calculated as the initial serum acetaminophen concentration multiplied by the higher of the initial AST or ALT values). All patients included in the analysis received treatment with NAC. Cases were excluded if there was documentation that the patient: (1) may have co-ingested a substance, other than acetaminophen, where treatment with fomepizole may be indicated (e.g. methanol or ethylene glycol ingestion); (2) has a known history of alcohol use disorder, underlying liver disease, or cirrhosis; or (3) co-ingested a hepatotoxic medication other than acetaminophen (see Supplemental Table S2). Patients with chronic alcohol use were excluded because ethanol exposure can alter acetaminophen metabolism via CYP2E1 induction and glutathione depletion, introducing variability that could confound assessment of fomepizole's effect. Cases were also excluded if there were insufficient case details (e.g. NPDS coding of case “not followed” or “unable to follow”) or if the poison center and/or clinical teams determined that the patient's clinical symptoms/course were not related to acetaminophen toxicity (e.g. NPDS code “exposure probably not responsible for effect”).

2.2. Data abstraction methodology and variables collected

Trained reviewers extracted demographic, exposure history, clinical, and clinical outcome data from charts using a standardized data collection tool. Data abstraction was performed by eleven trained independent, non-blinded reviewers, all of whom are either a physician or pharmacist (HG, MS, RS, JC, BA, AH, VP, SS, AP, SR, CC). Three reviewers performed secondary review of all cases to ensure consistency and accuracy (HG, RS, SS). All data collectors extracted data directly from ToxSentry® using the same standardized approach, therefore, interrate reliability was not assessed.

Demographic and ingestion history variables collected included age, gender, relevant medical history, date and time of ingestion, initial and peak acetaminophen levels, and multiplication product at the time of first laboratory evaluation.

Collected clinical data included reported clinical effects, laboratory test values, treatments, disposition and admission, and clinical outcomes. Extracted clinical effects from NPDS-coded data included, nausea, vomiting, abdominal pain, acidosis, jaundice, elevated bilirubin, AST/ALT >100 but <1000 IU/L, AST/ALT ≥1000 IU/L, prolonged prothrombin time (PT)/international normalized ratio (INR), increased creatinine, renal failure, oliguria or anuria, and additional non-coded clinical effects (such as encephalopathy) documented in the free-text sections of the electronic record. Laboratory values were collected for initial and peak AST, ALT, PT/INR, and acetaminophen concentrations.

Treatment characteristics for NAC, fomepizole, dialysis, and liver transplantation were also collected. Information collected for NAC therapy included timing and duration of administration (start and end dates), need for additional dosing beyond the standard regimen (i.e. 21-h intravenous and 72-h oral protocols) and reported adverse effects. Information collected for fomepizole treatment included whether it was administered, number and timing of repeat doses, adverse effects, and administration start and end dates. Dialysis administration and transplantation data, including involvement of the transplant team and whether the patient underwent liver transplantation were recorded. Disposition and admission data included intensive care unit (ICU) admission, ICU length of stay (days), in-hospital mortality, NPDS medical outcome severity, and NPDS duration of effect (see Supplemental Table S1 for further details). Of note, ICU length of stay was calculated based on manual chart review by the independent reviewers.

2.3. Data analyses

A descriptive analysis was conducted to characterize the overall study population. Categorical variables were described using frequencies and percentages. Continuous/scale variables were described using medians and interquartile ranges.

Ordinal outcomes were evaluated using ordinal logistic regressions, binary outcomes were evaluated using binary logistic regressions, and NAC duration (available as integer number of days) was evaluated using a Poisson regression. All models were conducted using a doubly robust regression approach to address potential confounding [21]. This

approach is explained in detail below. All analyses were conducted using R (v4.5; R Core Team).

For the regressions, patients were stratified into two groups – patients who received fomepizole therapy in addition to standard treatment with NAC (fomepizole group) and patients who did not (NAC only group). The groups were compared on the primary outcome of NPDS medical outcome severity and secondary outcomes of NAC treatment duration and ICU stay (yes/no). First, covariates were used to generate balancing weights, similar to inverse-weighted propensity score weights. Entropy balancing weights were found to produce the best covariate balance [22]. Outcomes were then evaluated in regression using both the weights and covariates. Covariates that may have an independent relationship with the primary study outcome were selected a priori based on clinical reasoning (age, sex, peak AST, peak ALT, metabolic acidosis, increased serum creatinine/renal failure) and published evidence (acetaminophen multiplication product of >10,000 mg/L × IU/L strongly associated with a high risk of subsequent hepatotoxicity) [5,6,23]. Comparisons of the groups before and after weighting are presented in supplemental materials (Supplemental Fig. S1).

To determine whether the timing of fomepizole administration may lead to differences in study outcomes, a subgroup analysis was performed in the fomepizole group comparing those who received fomepizole therapy within 24 h or less of NAC initiation to those who received fomepizole more than 24 h later. NPDS medical outcome severity was the primary outcome. NPDS medical outcome severity is a standardized outcome collected for all exposure calls that captures both acute and prolonged clinical effects. Although the NPDS medical outcome severity does not capture all elements of acetaminophen toxicity, it represents the most comprehensive and uniformly available measure of downstream clinical impact in this retrospective dataset. Secondary outcomes included NAC treatment duration, ICU stay (yes/no), final poison center disposition, and in-hospital mortality. Duration of *N*-acetylcysteine (NAC) therapy and ICU stay were included as pragmatic surrogates for clinician-perceived severity and ongoing risk, as decisions regarding continued antidotal therapy and ICU-level care are guided by objective markers of clinical improvement; as such, meaningful mitigation of acetaminophen toxicity by adjunctive fomepizole in large overdoses would be expected to translate into earlier clinical stabilization or shorter NAC courses. Covariates used in the first regression analyses were also used in the subanalysis. Comparisons before and after weighting are presented in supplemental materials (Supplemental Fig. S2).

To assess whether the risk of severe clinical outcomes increases disproportionately above a threshold serum acetaminophen concentration, a logistic regression analysis incorporating natural cubic splines, a form of piecewise regression, was performed using peak acetaminophen level as the primary independent variable. Based on prior toxicologic literature and clinical convention, a threshold of 300 μg/mL was selected to define the breakpoint for "high-risk" ingestion [9,10]. The model estimated separate slopes for acetaminophen concentrations below and above the 300 μg/mL threshold. The model fit was compared to a standard linear-only model with statistical significance set at $p < 0.05$.

3. Results

Fig. 1 illustrates the case selection process from the initial ToxSentry® query, including reasons for exclusion as outlined in the methods. After applying all exclusion criteria, 391 patients remained for inclusion in the final analysis. Table 1 characterizes demographics, exposure history, clinical interventions, and outcomes for the study population. Overall, demographic and clinical characteristics were similar between the groups; however, the fomepizole group had a higher proportion of women and patients with acidosis compared to the NAC only group but lower median AST and ALT multiplication products. Table 2 characterizes fomepizole dosing. No adverse effects to fomepizole were reported and sixteen patients had a documented adverse effect to *N*-acetylcysteine.

Tables 3 and 5 show the results of the regression models comparing study outcomes between the two groups and based on timing of fomepizole administration. After adjusting for relevant covariates as described in the methods, NPDS medical outcome severity, ICU stay, or duration of NAC treatment did not significantly differ between the two groups (Table 3). Six patients in the NAC only group underwent liver transplantation, while no patients in the fomepizole group received a liver transplant. Table 4 characterizes demographics, exposure history, clinical interventions, and outcomes for the fomepizole group based on timing of administration. The subgroup analysis also revealed no significant differences in outcomes based on fomepizole timing after accounting for covariates (Table 5).

In the piecewise logistic regression model using 300 μg/mL as the threshold for high-risk acetaminophen toxicity, the probability of major effect or death rose significantly above this point. The slope of the outcome curve increased sharply beyond 300 μg/mL, indicating an accelerated risk of severe outcomes in patients with massive ingestions. This piecewise model provided a significantly better fit than a linear-only model ($p < 0.01$), supporting the presence of a clinically relevant inflection point (Supplemental Fig. S3).

4. Discussion

The use of fomepizole as an adjunct to NAC in high-risk acetaminophen overdose has gained interest in recent years, despite limited

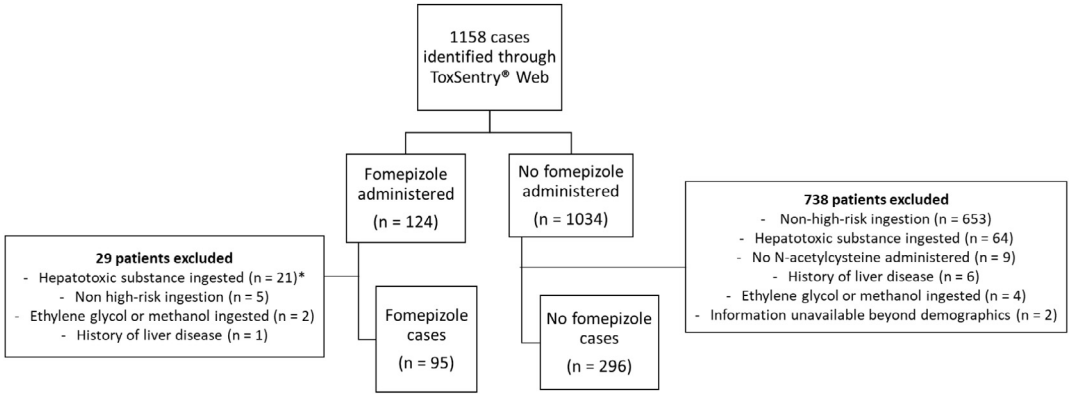

Fig. 1. Patient screening and inclusion.
*Hepatotoxic coingestants included alcohol and 3,4-methylenedioxymethamphetamine. See supplemental Table S2.

Table 1
Demographic and clinical data stratified by fomepizole administration in high-risk acetaminophen overdose.

	All patients (n = 391)	NAC only (n = 296)	Fomepizole (n = 95)
Age in years, median (IQR)	36 (20–58)	37 (20–58)	30 (17–60)
Gender, n (%)			
Male	127 (33)	104 (35)	23 (24)
Female	264 (68)	192 (65)	72 (76)
N*-acetylcysteine administration, n (%)*			
Intravenous	390 (100)	296 (100)	94 (99)
Oral	3 (1)	0 (<1)	3 (3)
Initial APAP level in mcg/ml, median (IQR)	97 (40–211)	93 (37–186)	145 (57–318)
Peak APAP level in mcg/ml, median (IQR)	99 (41–220)	93 (38–188)	145 (57–329)
High-risk ingestion criteria, n (%)***			
APAP level ≥ 300 μg/ml	70 (18)	39 (13)	31 (33)
Multiplication product of ≥10,000	347 (89)	260 (87)	87 (92)
Clinical effects, n (%)			
Nausea, vomiting, abdominal pain	250 (64)	190 (64)	60 (63)
Encephalopathy	92 (24)	65 (22)	27 (28)
Acidosis	106 (27)	66 (22)	40 (42)
Jaundice	19 (5)	13 (4)	6 (6)
Increased bilirubin	86 (22)	65 (22)	21 (22)
AST/ALT >100 but <1000	91 (23)	76 (26)	15 (16)
AST/ALT >1000	267 (68)	203 (69)	64 (67)
Prolonged PT/INR	292 (75)	221 (75)	71 (75)
Increased creatinine, renal failure, or oliguria/anuria	91 (23)	69 (23)	22 (23)
Location of admission, n (%)			
Intensive care unit	258 (66)	193 (65)	65 (68)
Non-intensive care unit	120 (31)	96 (32)	24 (25)
Unknown	13 (3)	7 (2)	6 (6)
Length of stay in intensive care unit in days, median (IQR) n = 258	4 (3–6)	4 (3–6)	4 (3–5)
Days of *N*-acetylcysteine, median (IQR)	4 (3–5)	4 (3–5)	4 (3–6)
Dialysis initiated, n (%)	28 (7)	20 (7)	8 (8)
Laboratory parameters, median (IQR)			
Initial PT (seconds)	18 (14–26)	18.1 (14–27)	17.7 (15–21)
Initial INR	1.5 (1.2–2.3)	1.6 (1.2–2.3)	1.5 (1.3–2.4)
Initial AST (U/L)	424 (112–2074)	529 (136–2182)	282 (71–1994)
Initial ALT (U/L)	386 (138–1518)	442 (150–1543)	271 (59–1392)
Peak PT (seconds)	23 (16–33)	23 (16–36)	21 (16–30)
Peak INR	2 (1.4–3.1)	2 (1.4–3.2)	2.2 (1.5–3)
Peak AST (U/L)	3271 (485–6844)	3197 (489–6616)	3566 (479–7500)
Peak ALT (U/L)	3045 (510–6315)	3186 (498–6187)	3300 (535–7011)
Multiplication product AST*	33,616 (13572–105,952)	34,996 (13743–105,415)	28,514 (13360–106,925)
Multiplication product ALT*	29,700 (14000–87,894)	31,356 (14448–84,603)	21,544 (12980–95,410)
Liver transplant team involved, n (%)	39 (10)	22 (7)	17 (18)
Patient received liver transplant, n (%)	6 (2)	6 (2)	0 (<1)
Clinical outcome severity, n (%)			
Minor effect	72 (18)	54 (18)	18 (19)
Moderate effect	171 (44)	132 (45)	39 (41)
Major effect	120 (31)	88 (30)	32 (34)
Death	28 (7)	22 (7)	6 (6)
Duration of clinical effect, n (%)			
>2 h to ≤8 h	2 (<1)	2 (<1)	0 (<1)
>8 h to ≤24 h	31 (8)	22 (7)	9 (9)
>24 h to ≤3 days	121 (31)	101 (34)	20 (21)
>3 days to ≤1 week	142 (36)	104 (35)	38 (40)
>1 week to ≤1 month	49 (13)	33 (11)	16 (17)
Anticipated permanent	31 (8)	25 (8)	6 (6)
Unknown	15 (4)	9 (3)	6 (6)

Abbreviations— NAC: *N*-acetylcysteine, IQR: interquartile range, mcg/ml: microgram per milliliter, U/L: units per liter, INR: international normalized ratio, PT: prothrombin time, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

* Initial [APAP] multiplied by initial AST or ALT.

** Patients may have received both intravenous and/or oral *N*-acetylcysteine.

*** Patients may have met both high-risk definitions. See methods section for specific details regarding definitions.

Table 2
Fomepizole dosing and number of doses administered.

	Fomepizole (n = 95)
Initial dose in milligrams, n (%)	
15 mg/kg	91 (96)
11 mg/kg	1 (1)
Unknown	3 (3)
Total number of doses, n (%)	
1	78 (82)
2	5 (5)
3	4 (4)
Unknown	8 (8)

Abbreviations—mg/kg: milligram per kilogram.

clinical data supporting its effectiveness. While mechanistic and animal studies suggest potential benefits through CYP2E1 inhibition and mitigation of oxidative injury, the clinical impact of adjunctive fomepizole

Table 3
Comparison of clinical outcomes in patients with high-risk acetaminophen overdose who received fomepizole as an adjunct to *N*-acetylcysteine treatment (N = 95) to those who received *N*-acetylcysteine only (N = 296).

Outcome	Effect	95% CI	*p* Value
Outcome severity, Odds Ratio	1.01	0.66–1.55	0.95
ICU stay, Odds Ratio	0.74	0.46–1.17	0.20
N-acetylcysteine duration, Rate Ratio	0.95	0.81–1.12	0.58

Abbreviations—ICU: intensive care unit. CI: confidence interval.

Table 4
Demographic and clinical data stratified by timing of fomepizole administration in high-risk acetaminophen overdose.

	Fomepizole (n = 95)	Early Admin (*n* = 57)	Late Admin (*n* = 30)	Unknown (*n* = 8)
Age in years, median (IQR)	30 (17–60)	30 (19–63)	30 (15–50)	32 (18–58)
Gender, n (%)				
Male	23 (24)	16 (28)	6 (20)	1 (13)
Female	72 (76)	41 (72)	24 (80)	7 (88)
N*-acetylcysteine administration, n (%)*				
Intravenous	94 (99)	56 (98)	30 (100)	8 (100)
Oral	3 (3)	2 (4)	1 (3)	0 (<1)
Initial APAP level in mcg/ml, median (IQR)	145 (57–318)	130 (57–302)	195 (63–361)	111 (35–474)
Peak APAP level in mcg/ml, median (IQR)	145 (57–329)	130 (57–302)	195 (63–430)	111 (35–474)
Clinical effects, n (%)				
Nausea, vomiting, abdominal pain	60 (63)	36 (63)	21 (70)	3 (38)
Encephalopathy	27 (28)	14 (25)	11 (37)	2 (25)
Acidosis	40 (42)	25 (44)	12 (40)	3 (38)
Jaundice	6 (6)	3 (5)	2 (7)	1 (13)
Increased bilirubin	21 (22)	12 (21)	6 (20)	3 (38)
AST/ALT >100 but <1000	15 (16)	9 (16)	5 (17)	1 (13)
AST/ALT >1000	64 (67)	38 (67)	23 (77)	3 (38)
Prolonged PT/INR	71 (75)	42 (74)	25 (83)	4 (50)
Increased creatinine, renal failure, oliguria/anuria	22 (23)	15 (26)	6 (20)	1 (13)
Location of admission, n (%)				
Intensive care unit	65 (68)	37 (65)	21 (70)	7 (88)
Non-intensive care unit	24 (25)	16 (28)	7 (23)	1 (13)
Unknown	6 (6)	4 (7)	2 (7)	0 (<1)
Length of stay in intensive care units in days, median (IQR)	4 (3–5)	4 (3–5)	5 (4–6)	4 (0.8–7)
Days of *N*-acetylcysteine, median (IQR)	4 (3–6)	4 (3–7)	5 (3–6)	4 (3–5)
Dialysis initiated, n (%)	8 (8)	5 (9)	2 (7)	1 (13)
Laboratory parameters, median (IQR)				
Initial PT (seconds)	17.7 (15–21)	17.1 (15.5–21.1)	17 (12.7–25.3)	20 (18–25.8)
Initial INR	1.5 (1.3–2.4)	1.8 (1.3–2.4)	1.4 (1.2–1.7)	1.7 (1.2–2.5)
Initial AST (U/L)	282 (71–1994)	297 (72–2063)	186 (57–748)	357 (75–2200)
Initial ALT (U/L)	271 (59–1392)	338 (70–1779)	201 (48–816)	273 (83–1455)
Peak PT (seconds)	21 (16–30)	20.50 (15.7-–28.8)	22.6 (17.3–35.4)	28.7 (19.4–30)
Peak INR	2.2 (1.5–3)	1.9 (1.4–3)	2.5 (1.8–3.2)	2.1 (1.3–2.9)
Peak AST (U/L)	3566 (479–7500)	3000 (463–6868)	4696 (924–9473)	3544 (171–7501)
Peak ALT (U/L)	3300 (535–7011)	2524 (615–5361)	6189 (472–9095)	3733 (76–6682)
Multiplication product AST*	28,514 (13360–106,925)	27,576 (14,046–119,800)	24,713 (12,500–108,848)	31,065 (19,687–82,897)
Multiplication product ALT*	21,544 (12980–95,410)	30,430 (13,977–99,804)	20,131 (12,798–96,150)	17,722 (13,000–100,243)
Liver transplant team involved, n (%)	17 (18)	8 (14)	8 (27)	1 (13)
Patient received liver transplant, n (%)	0 (<1)	0 (<1)	0 (<1)	0 (<1)
Clinical outcome severity, n (%)				
Minor effect	18 (19)	12 (21)	5 (17)	1 (13)
Moderate effect	39 (41)	25 (44)	9 (30)	5 (63)
Major effect	32 (34)	16 (28)	14 (47)	2 (25)
Death	6 (6)	4 (7)	2 (7)	0 (<1)
Duration of clinical effect, n (%)				
>2 h to ≤8 h	0 (<1)	0 (<1)	0 (<1)	0 (<1)
>8 h to ≤24 h	9 (9)	6 (11)	2 (7)	1 (13)
>24 h to ≤3 days	20 (21)	12 (21)	6 (20)	2 (25)
>3 days to ≤1 week	38 (40)	23 (40)	12 (40)	3 (38)
>1 week to ≤1 month	16 (17)	8 (14)	7 (23)	1 (13)
Anticipated permanent	6 (6)	4 (7)	2 (7)	0 (<1)
Unknown	6 (6)	4 (7)	1 (3)	1 (13)

Abbreviations— NAC: *N*-acetylcysteine, IQR: interquartile range, mcg/ml: microgram per milliliter, U/L: units per liter, INR: international normalized ratio, PT: prothrombin time, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

* Initial [APAP] multiplied by initial AST or ALT.

** Patients may have received both intravenous and/or oral *N*-acetylcysteine.

Table 5
Clinical outcomes in patients who received fomepizole within 24 h of *N*-acetylcysteine administration (n = 57) compared to those who received fomepizole more than 24 h after *N*-acetylcysteine administration (n = 30).

	Effect	95% CI	*p* Value
Outcome severity, Odds Ratio	0.84	0.39–1.82	0.66
Intensive care unit stay, Odds Ratio	1.38	0.55–3.46	0.49
N-acetylcysteine duration, Rate Ratio	0.84	0.39–1.82	0.66
Death, Odds Ratio	0.91	0.14–5.95	0.92
Discharge to home, Odds Ratio	0.76	0.24–2.42	0.65
Discharge to psychiatric facility, Odds Ratio	1.07	0.43–2.64	0.89

Abbreviations – CI: confidence interval.

remains unclear. This study aimed to address that gap by evaluating clinical outcomes in patients with high-risk acetaminophen overdose who received fomepizole in addition to standard NAC therapy. To our knowledge, this study represents the largest comparative analysis to date. Within our study cohort, we found no significant differences in NPDS outcome severity, ICU stay, or NAC duration between patients who received fomepizole and those who received NAC therapy only. Similarly, among patients who received fomepizole, no differences in outcomes were observed based on the predefined timing of fomepizole administration relative to *N*-acetylcysteine initiation (≤24 h vs >24 h). These findings suggest that routine fomepizole use in high-risk acetaminophen ingestion was not associated with improved clinical outcomes in this cohort. Given the observational design and limitations of the dataset, including the selected timing cutoff, a randomized

controlled trial is needed to determine whether adjunctive fomepizole provides meaningful clinical benefit [24].

Although fomepizole inhibits CYP2E1—the primary enzyme responsible for converting acetaminophen into its hepatotoxic metabolite NAPQI—its overall impact in high-risk ingestions remains uncertain. CYP2E1 inhibition reduces NAPQI formation by approximately 74% and decreases thiol metabolite recovery by 69% [25]. Although Manyike et al. concluded that contributions from other P450 enzymes are generally negligible, the relevance of alternative pathways in massive overdoses is not fully established [25]. In such settings, CYP2E1 saturation or inhibition may theoretically allow compensatory metabolism through secondary isoenzymes known as P450 spillover [3,26]. CYP2D6, for example, can contribute 4.5% to 22.4% of NAPQI formation in human liver microsomes [26]. Inhibition of CYP2A6 and CYP2E1 reduces NAPQI generation, whereas CYP3A4 and CYP1A2 inhibition appears to have minimal impact [3]. Pharmacogenomic and physiologic factors may further influence NAPQI production when CYP2E1 is inhibited, including CYP2D6 metabolizer status, induction of CYP1A2, CYP2A6, or CYP3A4 from smoking or medications such as rifampin, reduced glutathione availability in fasting or malnourished patients, and alcohol-related upregulation of multiple P450 isoenzymes [3,25-28]. These unmeasured variables may have contributed to the heterogeneity observed in our retrospective cohort. Importantly, any benefit of fomepizole in massive acetaminophen overdose may not rely solely on CYP2E1 inhibition; inhibition of JNK activation—a key mediator of mitochondrial dysfunction and hepatocellular injury—may represent a more relevant therapeutic mechanism in patients with extremely high multiplication product values. Ultimately, a randomized controlled trial is needed to more definitively determine whether fomepizole provides meaningful clinical benefit in high-risk acetaminophen overdose.

Fomepizole carries a significant cost burden, especially when used in addition to the standard of care, NAC, for the treatment of acetaminophen overdose. For a 70-kg patient, a single 15 mg per kilogram dose of fomepizole costs approximately $1000 to $1500 per vial, whereas the full 21-h intravenous NAC regimen typically costs between $150 and $200 [8,29]. Any additional therapy inherently increases cost, so the key consideration is not simply that NAC monotherapy is more economical, but whether the substantial cost of fomepizole is justified by demonstrable clinical benefit given the currently limited evidence [15,16].

This study has many limitations including those inherent to a retrospective study design and those associated with poison center data [30]. Poison centers rely on voluntary reports from both the public and healthcare providers, making the data susceptible to recall bias and incompleteness. As reporting is not mandatory, some exposures within the poison centers' geographic coverage may not have been captured. Additionally, reporting bias may be present, as poison centers are more likely to be consulted for severe cases or when managing vulnerable populations, such as pediatric patients or those with significant symptoms where the primary team may feel less comfortable proceeding independently. Additional limitations of the study include missing data on potentially beneficial treatments including use of activated charcoal or high-dose NAC (increased infusion rate and/or concentration of third bag of 21-h protocol given with larger overdoses) which may have influenced clinical outcomes [31,32]. The control group was composed of patients only from a single state (three poison centers), whereas the fomepizole group included patients from two states (four poison centers). However, this difference is unlikely to have significantly influenced study findings, as all centers within the two states are within the same geographic region (Southeastern United States) and share similar acetaminophen overdose management and documentation practices. However, there may be other unmeasured factors not accounted for in this analysis.

Residual confounding by indication is also possible, as fomepizole may have been preferentially administered to patients perceived to be at higher risk based on clinical factors not fully captured in the NPDS dataset. Additionally, the exact timing of fomepizole administration was only recorded as occurring within or beyond 24 h of NAC initiation, limiting the ability to evaluate potential associations between timing and clinical outcomes or explore possible time-dependent patterns. The fact that the data set only included 95 patients who received fomepizole limited statistical power. While the sample size may have been sufficient to identify large differences in major clinical outcomes between the NAC and NAC plus fomepizole groups, the study was likely underpowered to detect smaller differences, such as modest reductions in NAC duration. Accordingly, findings related to these secondary outcomes and the fomepizole subgroup analyses should be interpreted as exploratory and hypothesis-generating rather than definitive.

Furthermore, assessment of acetaminophen overdose severity is inherently multifactorial, integrating laboratory trends, timing of ingestion, comorbidities, and clinical judgment, which are elements not fully captured within NPDS. NPDS medical outcome severities, assigned by trained toxicology specialists for all exposures, were selected as a standardized measure available across the entire cohort and suitable for comparing clinically meaningful outcomes in large populations. In the absence of differences in NPDS outcome severity, ICU stay, or NAC duration, any potential benefit of adjunctive fomepizole may be limited to specific subgroups or outcomes not captured by these measures. Lastly, while we found evidence of an increase in risk for concentrations above 300 μg/mL, we did not test for discontinuities at other concentrations. It is possible that a different threshold would result in even better fit. We also acknowledge that patients with very low acetaminophen concentrations may represent a distinct, higher-risk population due to delayed presentation after ingestion, when hepatotoxicity may already be evolving or established, and that restricting the analysis to patients presenting early after ingestion with evaluation of lower cutoffs may have provided a more clinically homogeneous comparison.

Despite a strong mechanistic rationale and promising results in preclinical models, the use of fomepizole in high-risk acetaminophen overdose was not associated with improved clinical outcomes in this first retrospective study evaluating its clinical use. Given fomepizole's high cost and limited evidence of benefit, its routine use is not supported by the findings of this study. Further study is needed to determine whether specific subpopulations, such as patients with delayed presentation, depleted glutathione reserves, or high-risk pharmacogenomic profiles, may benefit from adjunctive CYP2E1 inhibition or prevention of JNK activation.

5. Conclusion

Fomepizole as an adjunct to *N*-acetylcysteine in patients with high-risk acetaminophen overdose was not associated with improved clinical outcomes. Although no adverse effects to fomepizole were reported, routine use in this setting remains unsupported by this study.

Previous presentations

Preliminary results were presented at North American Congress of Clinical Toxicology, September 2023, Montreal, CAN.

CRediT authorship contribution statement

Hayley T. Gartner: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Reeves E. Simmons:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Molly Stott:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Victor Perez:** Writing – review & editing, Investigation. **Justin Crespo:** Writing – review & editing, Investigation. **Brittany**

Allison: Writing – review & editing, Investigation. **Alex Howard:** Writing – review & editing, Investigation. **Amber Patt:** Writing – review & editing, Investigation. **Herbert Z. Wan:** Writing – review & editing, Investigation. **Colleen Cowdery:** Writing – review & editing, Investigation. **Dawn R. Sollee:** Writing – review & editing, Resources, Investigation. **Sonya S. Rashid:** Writing – review & editing, Investigation. **Tim P. Moran:** Writing – review & editing, Software, Formal analysis. **Brent Morgan:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization. **Sophia Sheikh:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors report no disclosures or conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2026.03.014.

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