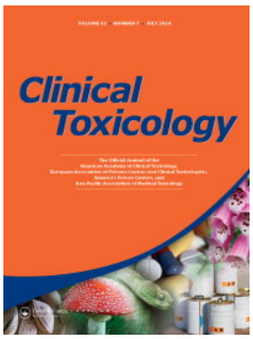

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POISON CENTRE RESEARCH

Assessment of high-dose acetylcysteine in acute high-risk paracetamol (acetaminophen) ingestion

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ABSTRACT

Background: Prompt acetylcysteine treatment with standard doses (300 mg/kg over 21 h in divided doses) is almost universally effective in preventing hepatotoxicity after paracetamol (acetaminophen) overdose. However, hepatotoxicity is reported despite early treatment when paracetamol concentrations exceed 300 mg/L (1,985 μmol/L) at 4 h. Prior studies evaluating high-dose acetylcysteine to treat high-risk ingestions have shown mixed results. We compared outcomes in patients with high-risk ingestions receiving standard or high-dose acetylcysteine.

Methods: Records from a single poison center were reviewed from 1 January 2017 to 31 December 2022. We included cases of acute paracetamol ingestion treated with intravenous acetylcysteine with an initial paracetamol concentration above the "300 mg/L" (1,985 μmol/L) line on the Rumack-Matthew nomogram. We compared standard and high-dose acetylcysteine groups by odds ratios and multivariable logistic regression. We defined hepatotoxicity as aminotransferase activity >1,000 U/L.

Results: We included 190 cases. Fifty-six percent received standard-dose acetylcysteine while 44% received high-dose acetylcysteine. Treatment within 8 h yielded no difference in hepatotoxicity between groups (odds ratio 1.67, 95% CI 0.067–42.3). Among patients treated after 8 h, hepatoxicity was more common in the high-dose group (odds ratio 3.39, 95% CI 1.25–9.2) though odds of liver failure were similar (odds ratio 2.78, 95% CI 0.89–8.69). Eighty-eight percent of patients with hepatotoxicity had elevated aminotransferase activity at presentation. No patient died or received a liver transplant.

Discussion: Rates of hepatotoxicity were low in patients treated within 8 h regardless of acetylcysteine dose. Unexpectedly, high-dose acetylcysteine treatment was associated with an increased odds of hepatoxicity in those treated after 8 h, but most had abnormal aminotransferase activities at presentation and there was no difference in rates of liver failure. Limitations include the use of retrospective, voluntarily reported poison center data.

Conclusions: Prompt treatment with acetylcysteine, regardless of dose, prevented hepatotoxicity in high-risk paracetamol ingestion.

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Paracetamol; acetaminophen; acetylcysteine; toxicity; overdose; hepatotoxicity

Introduction

Paracetamol (acetaminophen) is one of the commonest drug overdoses reported to United States (US) poison centers each year [1]. In addition, paracetamol overdose is consistently one of the top causes of death reported by America's Poison Centers [2–5]. The standard treatment for patients with paracetamol overdose is acetylcysteine, which has historically been highly effective at preventing hepatotoxicity and liver failure if administered within 8 h of paracetamol ingestion [6,7].

Some patients with paracetamol overdose are at a higher risk of hepatotoxicity and liver failure in spite of treatment with acetylcysteine, namely those patients with greater serum paracetamol concentrations at presentation and those receiving acetylcysteine more than 8 h after paracetamol ingestion [1,8,9]. The emergence of this literature has prompted the designation of "massive" or "high-risk" ingestions. Patients falling into this category are those with a paracetamol ingestion >30 g and/or a serum paracetamol concentration plotting above the 300 mg/L (1,985 μmol/L) line on the Rumack-Matthew nomogram [1,10].

The recognition of this higher-risk subset of paracetamol-overdosed patients has prompted new thinking regarding appropriate management strategies for these patients. It has been hypothesized that larger ingestions of paracetamol result in increased production of the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI) in excess of the detoxifying ability of glutathione and standard acetylcysteine doses. To resolve this deficit, one treatment strategy for patients with "massive" paracetamol ingestions is the use of

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increased doses of acetylcysteine [11]. Hendrickson [9] proposed a graduated schema for acetylcysteine dosing which anticipates the amount of acetylcysteine needed to detoxify various subsets of high-risk paracetamol ingestion.

Previous work has shown conflicting results when treating high-risk paracetamol-overdosed patients with increased doses of acetylcysteine. A prospective observational study by Chiew et al. showed the benefit of increased doses of acetylcysteine administered to 43 patients presenting with massive overdose [9]. In contrast, two retrospective analyses of statewide poison center data (117 and 24 patients) found no statistically significant benefit when high-dose acetylcysteine was administered to high-risk paracetamol overdose patients [12,13]. With conflicting data, it remains unclear whether patients presenting with high-risk paracetamol ingestion may benefit from increased doses of acetylcysteine [14]. The purpose of our study is to evaluate patient outcomes after the administration of high-dose acetylcysteine following high-risk paracetamol overdose.

Methods

We conducted a retrospective review of patient records from a single poison center from 1 January 2017 to 31 December 2022. The poison center established guidelines for recommending high-dose acetylcysteine for patients with a paracetamol concentration above the 300 mg/L line on the Rumack-Matthew nomogram without requiring toxicologist consultation beginning in January 2020. Before the institution of the guideline, the poison center occasionally recommended high-dose acetylcysteine in consultation with the on-call toxicologist but there was no standard practice. This allowed a review of approximately 3 years of data before and after the change in practice. We adapted acetylcysteine dosing outlined by Hendrickson [10] and recommended a standard 150 mg/kg intravenous (IV) loading dose followed by a 20 h infusion of either 12.5, 18.75, or 25 mg/kg/h for paracetamol concentrations above the 300 mg/L (1,985 μmol/L), 450 mg/L (2,977 μmol/L), or 600 mg/L (3,969 μmol/L) nomogram lines, respectively. The poison center utilizes the standard US Food and Drug Administration (FDA) approved 3-bag acetylcysteine protocol of a 150 mg/kg loading dose over 1 h, a second infusion of 50 mg/kg over 4 h, followed by 100 mg/kg over 16 h. The increased dose regimens were administered by increasing the dose in both the second and/or third infusions. Whether this was consolidated to a single 20 h infusion or left as separate 4 and 16 h infusions with an increased dose was left to the discretion of treating providers.

The poison center utilizes toxiCALL® (Aurora, CO, USA) for electronic health record keeping. Poison center staff routinely collect information on each case including documentation of prespecified and hard coded data on the agents ingested, therapies administered, clinical effects, and medical outcomes with multiple follow-up calls to providers. We searched the database for all patients with acute paracetamol exposures (using all America's Poison Centers generic codes for single ingredient and combination paracetamol products) that also received intravenous (IV) acetylcysteine. Oral acetylcysteine is very infrequently utilized in our region and these cases were not included. An acute ingestion was defined as occurring within a 60 min time period to select a group with a well-defined high-risk ingestion, rather than utilizing more broad definitions (e.g., ingestion within a 24 h period) that could overestimate the risk stratification of a paracetamol concentration. We screened and included all cases with a paracetamol concentration obtained at least 4 h after ingestion plotting above the 300 mg/L line.

Cases were excluded for unknown time of ingestion, more than 2 h interruption in acetylcysteine treatment, inconsistent acetylcysteine dosing (e.g., received multiple different acetylcysteine infusion rates after the loading dose), miscoded chronicity (e.g., actually acute-on-chronic or chronic based on case narrative review), incomplete data, or elevation of activities of either aspartate aminotransferase or alanine aminotransferase confounded by an alternative cause (e.g., rhabdomyolysis, ischemic liver injury, other non-paracetamol drug-induced liver injury). We did not exclude cases solely due to ingestion of substances other than paracetamol.

Chart reviewers were pharmacists with certification for Specialists in Poison Information or faculty medical toxicologists. All reviewers received specific training on chart abstraction from the lead author using a standardized data collection instrument with the review of 10 cases by the lead author for accuracy before completing the chart review. Data abstracted from charts included patient demographics, paracetamol formulation, ingested dose (only obtained if exact dose known), co-ingestion of alcohol/opioids/anticholinergic agents, reason for exposure, laboratory values (including serial paracetamol concentrations, aspartate aminotransferase activity, alanine aminotransferase activity, and whether the international normalized ratio [INR] was >2), acetylcysteine dose received after loading dose as either standard (FDA protocol: 150 mg/kg over 1 h, 50 mg/kg over 4 h, 100 mg/kg over 16 h) or any high-dose regimen (e.g., 12.5, 18.75, or 25 mg/kg/h for 20 h after a 150 mg/kg loading dose), total duration of acetylcysteine therapy, gastrointestinal decontamination, administration of fomepizole, need for hemodialysis, adverse effects of acetylcysteine therapy, and medical outcome. Paracetamol ratio was defined as the first paracetamol concentration divided by the corresponding concentration on the 150 mg/L line (e.g., a concentration of 450 mg/L [2,977 μmol/L)] at 4 h yields a paracetamol ratio of 3). Hepatotoxicity was defined as a peak aspartate aminotransferase or alanine aminotransferase activity $>1{,}000$ U/L. Liver failure was defined as hepatotoxicity with an INR > 2.0.

Demographic and case information were summarized with descriptive statistics using Microsoft Excel. Groups were compared by chi-squared analysis for categorical variables and Mann–Whitney *U* test for nonparametric continuous variables. Odds ratios with 95% CI were calculated for outcomes of hepatotoxicity and liver failure between standard and high-dose acetylcysteine groups. Groups were assigned based on the actual treatment received. We did not assess whether the dose recommendation was made appropriately or whether providers followed the recommendation. Univariable logistic regression analysis was performed for all

included cases for age, gender, paracetamol ratio, whether aminotransferase activity was elevated at presentation, acetylcysteine treatment within 8 h, and treatment with high-dose acetylcysteine. Similar to Lewis and colleagues [12], multivariable logistic regression was performed using variables of clinical interest including paracetamol ratio, whether aminotransferase activity was elevated at presentation, acetylcysteine treatment <8 h after ingestion, and whether the patient was treated with high-dose acetylcysteine. JASP software (JASP Team, version 0.17.3) was used for chi-squared analysis, odds ratios, and logistic regression analysis.

The study was approved by the University of Utah Institutional Review Board and did not receive any funding.

Results

A total of 345 cases met inclusion criteria with 155 cases excluded, leaving 190 cases for analysis. Reasons for exclusion were: >24 h to acetylcysteine treatment (25), incomplete data (six), miscoded (one), acetylcysteine interruption (21), inconsistent acetylcysteine dosing (31), and unknown time of ingestion (71). Though not part of our initial exclusion criteria, two patients in the high-dose acetylcysteine group already had hepatotoxicity at presentation (18 and 19 h after ingestion, respectively) and were excluded from all hepatotoxicity analyses. We included these patients in the liver failure analyses as neither had an INR > 2 at presentation.

The median age was 18 years (interquartile range 15–27) and 138 (72.6%) were female. Groups were largely similar at baseline, with more patients in the high-dose acetylcysteine group receiving activated charcoal and having acetylcysteine initiated within 8 h of ingestion (Table 1). All but three cases were suspected suicide attempts. Two patients received fomepizole, both in the high-dose acetylcysteine group (see Supplementary Information). No patient received hemodialysis or kidney replacement therapy. Most patients (81%) in the increased dose acetylcysteine group received a 12.5 mg/kg/h infusion for 20 h following the loading dose. Due to the lower number of patients receiving 18.75 or 25 mg/kg/h infusions, we combined all increased dose acetylcysteine patients into a single group for analysis. Other than a single patient with a paracetamol concentration of 1,096 mg/L (7,250 μmol/L), the highest paracetamol concentration in the rest of the entire cohort was 625 mg/L (4,135 μmol/L). A comparison of patients treated before and after the high-dose acetylcysteine guideline implementation is shown in Table 2.

Among patients treated with acetylcysteine within 8 h of ingestion, one developed hepatotoxicity which progressed to liver failure in the high-dose acetylcysteine group (see Supplementary Information).

Table 1. Comparison of baseline characteristics of standard-dose and high-dose acetylcysteine patients.

	Standard-dose acetylcysteine ($n = 84$)	High-dose acetylcysteine ($n = 106$)	*P*-value
Gender			
Female, *n* (%)	63 (75)	75 (71)	0.515
Male, *n* (%)	21 (25)	31 (29)	
Age (median, IQR)	18 (15–27)	18 (15–27)	0.817
Reason for exposure			
Misuse, *n* (%)	–	1 (1)	0.663
Suspected suicide, *n* (%)	83 (99)	104 (98)	
Unintentional, *n* (%)	1 (1)	1 (1)	
Co-ingestion			
Opioids, *n* (%)	4/84 (5)	3/106 (3)	0.483
Anticholinergics, *n* (%)	16/84 (19)	15/106 (14)	0.364
Alcohol, *n* (%)	2/84 (2)	6/106 (6)	0.264
Acetylcysteine started <8 h	31/84 (37)	57/106 (54)	**0.021**
Time to acetylcysteine			
<8 h, *n* (%)	31 (37)	57 (54)	**0.029**
>8–≤12 h, *n* (%)	16 (19)	24 (23)	
>12–≤16 h, *n* (%)	20 (24)	16 (15)	
>16–≤20 h, *n* (%)	13 (16)	5 (5)	
>20–<24 h, *n* (%)	4 (5)	4 (4)	
Aspartate aminotransferase or alanine aminotransferase activity >50 IU/L at presentation, *n* (%)	17/84 (20)	20/106 (19)	0.813
Aspartate aminotransferase activity at presentation (median, IQR)	26 (21–48)	25 (20–35)	0.34
Alanine aminotransferase activity at presentation (median, IQR)	25 (19–41)	23 (15–36)	0.40
Received activated charcoal, *n* (%)	4/84 (5)	14/106 (13)	**0.048**
Acetylcysteine dose			
Standard, *n* (%)	84 (100%)		
12.5 mg/kg/h, *n* (%)		81 (76)	
18.75 mg/kg/h, *n* (%)		13 (12)	
25 mg/kg/h, *n* (%)		12 (11)	
Paracetamol ratio			
≥2 and <3, *n* (%)	58/84 (69)	69/106 (65)	0.751
≥3 and <4, *n* (%)	11/84 (13)	18/106 (17)	
≥ 4, *n* (%)	15/84 (18)	19/106 (18)	

IQR: interquartile range.
Bold values indicate $P < 0.05$ by chi-squared testing.

Table 2. Proportion of patients treated with high-dose acetylcysteine stratified by paracetamol ratio pre and post implementation of a high-dose acetylcysteine guideline with baseline characteristics and outcomes.

	Pre-guideline ($n = 92$)	Post-guideline ($n = 98$)
Patients receiving high-dose acetylcysteine by paracetamol ratio		
>2–3, *n* (%)	17/62 (27)	52/65 (80)
>3–4, *n* (%)	6/13 (46)	13/16 (81)
>4, *n* (%)	3/17 (18)	15/17 (88)
Total, *n* (%)	26/92 (28)	80/98 (82)
Acetylcysteine started <8 h, *n* (%)	45/92 (49)	43/98 (44)
Aspartate or alanine aminotransferase activity elevated at presentation, *n* (%)	16/92 (17)	21/98 (21)
Outcomes		
Aspartate or alanine aminotransferase activity >1,000 IU/L, *n* (%)	8/92 (9)	16/96 (17)
International normalized ratio >2, *n* (%)	6/92 (7)	11/98 (11)

Two patients in the post-guideline group were excluded from the hepatotoxicity analysis as they presented with hepatotoxicity.

Among patients treated with acetylcysteine more than 8 h after ingestion, the high-dose acetylcysteine group had greater odds of developing hepatotoxicity. Rates of liver failure and duration of acetylcysteine treatment were similar between groups (Table 3). To investigate whether the increased odds of hepatotoxicity in those treated after 8 h was related to a higher paracetamol ratio or the presence of elevated aminotransferase activity at presentation, we further analyzed these subgroups. There was no association with paracetamol ratio. An increased odds of hepatotoxicity among those with an abnormal aminotransferase activity at presentation persisted in those treated with high-dose acetylcysteine.

Of all patients with elevated aminotransferase activity at presentation, excluding the two previously mentioned patients with hepatotoxicity at presentation, 21 of 35 (69%) went on to develop hepatotoxicity. These 21 patients accounted for 88% of those that would ultimately develop hepatotoxicity. All three patients who developed hepatotoxicity but had normal aminotransferase activity at presentation had acetylcysteine treatment initiated at least 10 h from ingestion. Of these three, one received standard dose acetylcysteine and two received high-dose acetylcysteine.

No patient developed an anaphylactoid reaction to acetylcysteine. There were no deaths or liver transplants in the entire study population. Figure 1 shows initial paracetamol concentrations (but not time to acetylcysteine treatment) and outcomes for each case.

Univariable and multivariable logistic regression analysis of variables potentially associated with hepatotoxicity are shown in Table 4. Patients treated with acetylcysteine within 8 h of ingestion had decreased odds of developing hepatotoxicity (odds ratio 0.039 95% CI 0.003–0.38). The presence of abnormal aminotransferase activity at presentation was the most predictive of hepatotoxicity (odds ratio 117.9 95% CI 21.29–684.66). High-dose acetylcysteine was associated with increased odds of hepatotoxicity (odds ratio 8.64 95% CI 1.56–47.95).

Discussion

Our study was unable to demonstrate a benefit from high-dose acetylcysteine in high-risk paracetamol overdose patients and, surprisingly, showed increased odds of hepatotoxicity in patients treated with high-dose acetylcysteine more than 8 h post-ingestion. Rates of liver failure were similar between patients receiving standard-dose and high-dose acetylcysteine. Hepatotoxicity occurred most frequently in patients with elevated aminotransferase activity at presentation and in those treated more than 8 h post ingestion. Our findings support the importance of prompt treatment with acetylcysteine and increased odds of hepatotoxicity associated with delayed treatment [6,7].

Chiew and colleagues [9] described 79 patients with a paracetamol ratio >2 who received high-dose acetylcysteine within 8 h of ingestion and had a 73% decreased risk of hepatotoxicity, suggesting benefit from high-dose acetylcysteine. Other studies have since reported contradictory findings. Lewis and colleagues [12] reported that of patients with a paracetamol ratio >2, there was no difference in rates of hepatotoxicity between patients treated with high-dose IV acetylcysteine, standard-dose IV acetylcysteine or oral acetylcysteine. Abnormal aminotransferase activity at presentation conferred higher odds of developing hepatotoxicity [12]. An abstract by McElroy and colleagues [13] reported that 24 patients with a paracetamol ratio >2 who received high-dose acetylcysteine showed no difference in the incidence of hepatotoxicity when compared with patients receiving standard acetylcysteine dosing. Finally, a study by Downs and colleagues [15] evaluated patients with a high-risk paracetamol ingestion treated only with standard dose acetylcysteine. They found that a delay in presentation and treatment was associated with hepatotoxicity.

Interestingly, our study found increased odds of hepatotoxicity in late-presenting patients treated with high-dose acetylcysteine. We stratified these outcomes by paracetamol ratio and the presence of elevated aminotransferase activity at admission to evaluate whether the high-dose acetylcysteine group contained a higher-risk subgroup. There was an increased odds of hepatotoxicity in the high-dose acetylcysteine group for those with abnormal aminotransferase activity at presentation. This increased risk of hepatotoxicity with high-dose acetylcysteine is of questionable clinical significance as there was no increase in liver failure or duration of acetylcysteine treatment. It is possible that this finding reflects an increased risk of hepatotoxicity in patients who have elevated aminotransferase activity at presentation [12]. Even so, the use of high-dose acetylcysteine was still associated with hepatotoxicity after multivariable regression analysis.

With the addition of our findings, several studies now show no benefit of high-dose acetylcysteine for paracetamol ingestions with a paracetamol ratio >2, suggesting that

Table 3. Comparison of outcomes between standard-dose and high-dose acetylcysteine groups.

	Standard-dose acetylcysteine, *n* (%)	High-dose acetylcysteine, *n* (%)	Odds ratio (95% confidence interval)
Hepatotoxicity			
Acetylcysteine started <8 h	0/31	1/57 (1.8%)	1.67 (0.07–42.3)
Acetylcysteine started >8 h	7/53 (13.2%)	16/47 (34%)	3.39 (1.25–9.2)
Paracetamol ratio			
>2–3	3/30 (10)	5/21 (24)	2.81 (0.59–13.37)
>3–4	0/9	5/12 (42)	13.93 (0.66–293.97)
>4	4/14 (29)	6/14 (42.9)	1.88 (0.39–9.01)
Aspartate or alanine aminotransferase activity elevated at presentation			
Yes	6/12 (50)	14/15 (93.3)	14.0 (1.37–142.9)
No	1/41 (2.4)	2/32 (6.3)	2.67 (0.23–30.8)
Liver failure			
Acetylcysteine <8 h	0/31	1/57 (1.8)	1.67 (0.067–42.3)
Acetylcysteine >8 h	5/53 (9.4%)	11/49 (22.5)	2.78 (0.89–8.69)
Paracetamol ratio			
>2–3	1/30 (3%)	1/21 (5)	1.45 (0.09–24.57)
>3–4	0/9	3/12 (25)	7.0 (0.32–154.865)
>4	4/14 (29)	7/16 (44)	1.94 (0.42–8.92)
Aspartate or alanine aminotransferase activity elevated at presentation			
Yes	5/12 (42)	10/17 (58.8)	2.00 (0.45–8.96)
No	0/41	1/32 (3)	3.95 (0.156–100.31)
Mean duration of acetylcysteine therapy (h)	30.4	29.1	$P = 0.297$

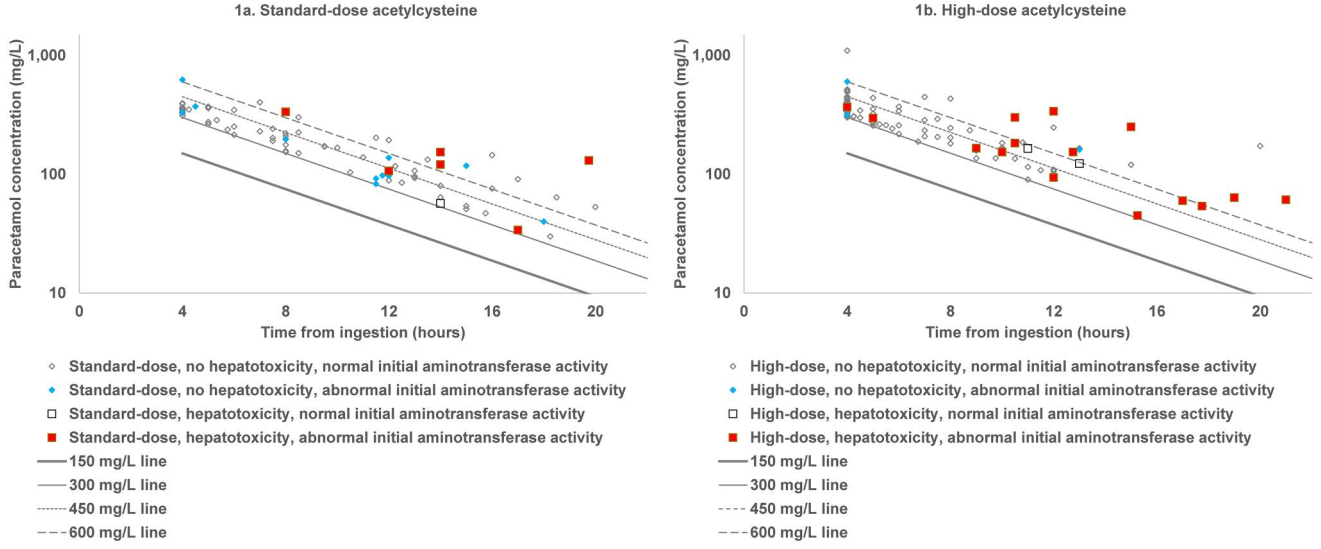

Figure 1. Initial paracetamol concentrations plotted with hepatotoxicity outcomes in patients treated with (a) standard-dose acetylcysteine and (b) high-dose acetylcysteine. Patients with abnormal aminotransferase activity at presentation are highlighted. Seven patients developed hepatotoxicity in the standard dose group and 17 in the high-dose group.

Table 4. Unadjusted and adjusted odds ratios by logistic regression for development of hepatotoxicity (aminotransferase activity >1,000 U/L).

	Odds ratio	*P*-values
Unadjusted odds ratio		
Paracetamol ratio	1.40	0.002
Aspartate or alanine aminotransferase activity elevated at presentation	75.0	<0.001
Acetylcysteine started <8 h	0.038	0.002
High-dose acetylcysteine	2.15	0.11
Age	1.0	0.73
Gender	1.41	0.466
Adjusted odds ratio		95% Confidence interval
Paracetamol ratio	1.1	0.86–1.38
Aspartate or alanine aminotransferase activity elevated at presentation	117.9	20.29–684.66
Acetylcysteine started <8 h	0.039	0.003–0.38
High-dose acetylcysteine	8.64	1.56–47.95

increased acetylcysteine does not provide benefit beyond prompt standard-dose acetylcysteine. Given the relatively small number of patients with a paracetamol ratio >3 across all these studies, it is not possible to assess whether that subgroup of high-risk ingestions may benefit from high-dose acetylcysteine.

Though it seems logical that higher doses of paracetamol would produce more NAPQI and thus require higher doses of acetylcysteine to prevent hepatotoxicity, no benefit to high-dose acetylcysteine has been demonstrated across multiple studies with the exception of the study by Chiew and colleagues [9]. There are several possible explanations for these observations. The most common regimen of high-dose acetylcysteine in our study was to increase the dose of the 16 h acetylcysteine infusion from 6.25 to 12.5 mg/kg/h. With this dosing, a patient receives no additional acetylcysteine beyond the standard protocol for at least 5 h after treatment initiation. It is possible that increased doses of acetylcysteine are needed earlier during toxicity. Other dosing regimens utilizing 18.75 or 25 mg/kg/h starting with the second infusion could provide more acetylcysteine earlier in the treatment course, but very few patients received these doses. Anecdotal experience from our poison center staff revealed poor adherence to recommendations for 18.75 or 25 mg/kg/h dosing. Glutathione stores may be depleted more rapidly in high-risk ingestions making acetylcysteine treatment necessary even sooner than the typical 6–8 h timeframe. However, our results showed excellent efficacy of acetylcysteine initiated within 8 h of ingestion. Other mechanisms of toxicity may be at play in high-risk ingestions [16]. Our cohort also fared very well compared to prior studies with a low rate of hepatotoxicity in the group treated within 8 h of ingestion. This could be due to the young age of our study group, the predominance of paracetamol ratios between 2 and 3, or other unidentified patient factors.

There are several limitations in this study. We relied on voluntarily reported retrospective data from a single poison center. Patients were not randomized to treatment or studied prospectively. The utilization of a pre/post practice guideline implementation design may help mitigate some confounders as there was an increase from 28% of patients receiving high-dose acetylcysteine to 82% following the practice change. Poison center staff or treating providers may have elected to utilize high-dose acetylcysteine in patients perceived to be at higher risk for hepatotoxicity, such as those with elevated aminotransferase activity at presentation or an elevated acetaminophen/aminotransferase multiplication product [17]. However, groups were similar with regard to paracetamol ratio and the presence of abnormal aminotransferase activity at presentation. It is possible providers did not initiate high-dose acetylcysteine until liver injury became apparent. However, if a patient received varying acetylcysteine infusion rates (e.g., started with a regular 16 h infusion of 6.25 mg/kg/h and then switched to 12.5 mg/kg/h) the case would have been excluded from analysis. The time of ingestion is based on provided history which may lead to misclassification of risk. The number of patients who received 18.75 or 25 mg/kg/h acetylcysteine infusions or had paracetamol ratios >3 was small so the power to detect a difference, if any, in these higher risk or higher dose scenarios was low. We did not perform a formal power analysis. Similarly, the small number of patients developing hepatotoxicity in the study lead to wide confidence intervals around predictor variables. Patients with a paracetamol ratio >3–4 are likely at much higher risk of hepatotoxicity compared to those just above a paracetamol ratio of 2. However, all patients regardless of paracetamol ratio fared well if treated within 8 h, and paracetamol ratio was not associated with development of hepatotoxicity in the multivariable model. Patients presenting after 8 h may have already developed hepatotoxicity, and elevated paracetamol concentrations could be more consistent with a hepatotoxicity related increase in paracetamol half-life rather than reflecting a true high-risk ingestion [18]. It is possible that by chance or selection bias, these high-risk patients were more likely to receive high-dose acetylcysteine, and that the outcome of increased hepatotoxicity in that group simply reflects reverse causation and a tendency to treat higher risk patients more aggressively, rather than the high-dose acetylcysteine causing hepatotoxicity.

Future studies should focus on including patients at the highest risk for hepatotoxicity despite prompt treatment within 8 h: those with a paracetamol ratio >3 [1]. Multicenter studies are likely required to achieve a sufficient sample size. Meta-analysis of published studies could also be undertaken. Other adjunctive treatments beyond acetylcysteine for these high-risk patients remain under investigation [16].

Conclusions

High-dose acetylcysteine therapy did not appear to decrease hepatotoxicity or liver failure in patients with high-risk paracetamol ingestions compared to standard therapy. Elevated aminotransferase activity at presentation was most associated with hepatotoxicity. Prompt treatment with acetylcysteine had the lowest odds of hepatotoxicity. Only one patient treated within 8 h of ingestion developed hepatotoxicity. Further research or meta-analysis of existing studies specifically evaluating patients with a paracetamol ratio >3 and utilizing higher doses of acetylcysteine are needed.

Disclosure statement

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Data availability statement

The data that support the findings of this study are available from the corresponding author, MM, upon reasonable request.

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