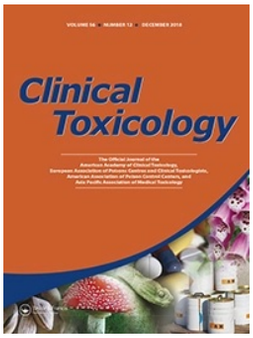

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POISON CENTRE RESEARCH

Single bag high dose intravenous N-acetylcysteine associated with decreased hepatotoxicity compared to triple bag intravenous N-acetylcysteine in high-risk acetaminophen ingestions

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ABSTRACT

Introduction: There is controversy that the triple bag intravenous (IV) N-acetylcysteine (NAC) regimen may be underdosing the sickest patients in its current, common usage. We hypothesize that a higher dose IV NAC regimen improves some outcomes.

Methods: We conducted a poison center based retrospective observational study from January 1, 2016 to December 31, 2017 comparing a single bag higher dose IV NAC regimen (150 mg/kg over 1 h, 15 mg/kg/hour) to the triple bag IV NAC regimen (150 mg/kg over 1 h, 12.5 mg/kg/hour for 4 h, 6.25 mg/kg/hour). In a high-risk population of patients with acetaminophen ingestion (defined as multiplication product $\geq$ 10,000 mg/L IU/L, not acute ingestions receiving NAC within 8 h, and not hepatotoxic on first contact), we evaluated the rate of hepatotoxicity, peak transaminase, and rate of laboratory coagulopathy.

Results: 89 patients met the inclusion criteria. 12 of the 23 patients (52%) who received triple bag NAC became hepatotoxic and 10 (43%) became coagulopathic, while only 19 of 66 patients (29%) who received single bag NAC became hepatotoxic and 15 (23%) became coagulopathic; $p = .043$ and .057, resp. Mean peak transaminase was 4481 IU/L vs 2143 IU/L in those receiving triple bag NAC vs single bag NAC, difference of means 2338 IU/L; $p = .026$.

Conclusion: In this exploratory study of a high-risk population of patients with acetaminophen ingestions, the single bag IV NAC regimen was associated with lower peak transaminase and fewer patients becoming hepatotoxic as compared to the triple bag IV NAC regimen.

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Introduction

Acetaminophen, also known as paracetamol or N-acetyl-para-aminophenol (APAP), is the leading cause of acute liver failure in the United States of America (USA) and United Kingdom [1]. N-acetylcysteine (NAC) is the mainstay of treating APAP toxicity. In the USA, the only Food and Drug Administration (FDA) regimen approved for any acuity and chronicity of APAP ingestion is oral NAC, dosed as an initial loading regimen of 140 mg/kg and subsequently dosed as 70 mg/kg every 4 h afterwards. This provides 490 mg/kg in the first 21 h, and then 420 mg/kg on day 2 and beyond. Of note, while oral NAC has low bioavailability [2], an animal study suggests a large first-pass effect that leads to this low bioavailability [3]. As the liver is the primary organ of toxicity in APAP ingestions, oral NAC is highly bioavailable for treating this site.

With the approval of a commercial intravenous (IV) formation of NAC, the use of oral NAC for the treatment of APAP toxicity has declined significantly. The current FDA approved IV regimen (Acetadote®) is a triple bag IV NAC regimen dosed as 300 mg/kg over 21 h on day 1 in the form of 150 mg/kg over 1 h, 12.5 mg/kg/hour for 4 h, and 6.25 mg/kg/hour for 16 h. For patients who need further NAC treatment, most off-label protocols continue the third bag at 6.25 mg/kg/hour until medical clearance, thereby providing just 150 mg/kg on day 2 and beyond. Notably, unlike the PO NAC regimen's wide indication, the FDA approved indication for Acetadote® IV NAC is only for treating single, acute ingestions presenting within 8–10 h of ingestion and for 21 h in total.

This poison center's (PC) IV NAC protocol is a single bag protocol that provides 450 mg/kg of NAC over the first 21 h on day 1 in the form of 150 mg/kg over 1 h and 15 mg/kg/hour until medical clearance. On day 2 and beyond, this PC IV NAC protocol provides 360 mg/kg/day, which more closely approximates oral NAC. Several other poison centers and institutions also use this alternate protocol [4–6]. Table 1 compares these three regimens.

Retrospective studies have suggested that the multiplication product of the acetaminophen concentration multiplied by the higher transaminase (aspartate transaminase (AST) or

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Supplemental data for this article can be accessed here.

Table 1. Comparison of NAC doses provided in three currently used regimens, with the first 21 h of Day 1 used for an appropriate comparison as Acetadote® is a 21 h regimen.

	Oral NAC	PC IV NAC	Triple Bag IV NAC
Day 1 (21 h)	490 mg/kg	450 mg/kg	300 mg/kg
Day 2+	420 mg/kg/day	360 mg/kg/day	150 mg/kg/day

alanine transaminase (ALT)) has a strong correlation with the chance a patient will develop hepatotoxicity, as defined by peak transaminase $\geq$ 1000 IU/L. Specifically, a multiplication product $\geq$ 10,000 mg/L IU/L is strongly predictive of hepatotoxicity, with a positive likelihood ratio of 250 [7]. Studies also suggest that if NAC is given within 8 h of a single ingestion, the patient is likely to have very low risk of hepatotoxicity [7,8]. As such, patients who have an elevated multiplication product and who do not receive NAC within 8 h of a single acute ingestion likely represent a high-risk cohort at significant danger for hepatotoxicity.

We hypothesize that using this PC single bag IV NAC protocol, which provides more NAC, will lead to less hepatotoxicity than the FDA approved triple bag IV therapy in this high-risk cohort of APAP ingestions.

Methods

This is an Institutional Review Board-approved retrospective observational cohort study following STROBE guidelines [9]. The PC's ToxiCall® database is a secure database of patient details for cases managed. We queried ToxiCall from January 1, 2016 to December 31, 2017 for all cases with an "acetaminophen" generic product code coded as an ingestion that were referred to a hospital. The acetaminophen generic product codes used in the query are listed in Supplement 1. Each entry's full text case notes were read by a single, unblinded abstractor (author KS) who had been trained in using the database after using it on a daily basis for over a year in the course of a medical toxicology fellowship. We used this two year inclusion time frame because the PC's acetaminophen guidelines underwent a major revision in 2015, so 2016 was the first full year with standardization of PC recommendations and documentation. Furthermore, 2017 was the last full year the author was not involved in any management of the study population.

The patient's age, gender, initial APAP concentration, and transaminases were collected into a structured data collection form. Patients were not included if no APAP concentration and transaminase were documented. The transaminases (i.e., AST and ALT) that were available within one hour of the APAP concentration were recorded; if unavailable, then the first later set of transaminases available after the APAP concentration was used. For acute ingestions, the four-hour APAP concentration was used for the calculation, if time of ingestion was available. If the four-hour APAP concentration was unavailable, the first APAP concentration after four hours from ingestion was used, along with the transaminases within one hour or later to this concentration. If the multiplication product was equal to or greater than 10,000 mg/L IU/L, they met the initial inclusion criteria and a detailed PC chart review was performed; if the patient was at a health care system facility with electronic medical record (EMR) access available to the PC, this electronic record was examined as well. Location of the institution was recorded.

Each case was classified as acute, defined as a single, acute ingestion of APAP, or non-acute, which included known multiple ingestions as well as unknown acuity of ingestions. Stated time of ingestion for acute ingestions was recorded, if available, as well as stated time of NAC initiation; if time of ingestion was not known but it was still stated by the institution as a single acute ingestion, the case was still classified as acute. If both time of ingestion and time of NAC initiation were reported, then time to NAC initiation from ingestion for acute ingestions was calculated. The NAC regimen received by the patient was classified as oral NAC, PC IV NAC, or triple bag IV NAC. If the patient received 12.5 mg/kg/hour and then 6.25 mg/kg/hour, the patient was classified as triple bag IV NAC regimen. If the patient received 15 mg/kg/hour, the patient was classified as PC IV NAC regimen. Peak transaminase was recorded, and if the peak transaminase was $\geq$1000 IU/L, the patient was classified as hepatotoxic. Peak INR was also recorded, with laboratory coagulopathy defined as peak INR $\geq$ 2, consistent with a prior multiplication product study [7].

Exclusions were no NAC given, oral NAC given primarily in the first 24 h (defined by at least 2 doses), multiple loading doses given, initial transaminase $\geq$ 1000 IU/L, patients transferred to institutions outside of the area covered by the PC, delay to NAC infusion (defined as at least one hour delay in starting NAC infusion after completion of the NAC bolus), use of multiple different IV regimens, unknown IV regimen, or NAC infusion gap of at least one hour (either reported by the institution or discovered during EMR review). These exclusions were to limit confounders and result in a sample with a known total cumulative NAC dosage specified using a known regimen. As the multiplication product includes the outcome of interest, i.e., peak transaminase $\geq$ 1000 IU/L, we also excluded patients who on initial labs already were hepatotoxic. Patients receiving IV NAC within 8 h of an acute ingestion were excluded but the incidence of hepatotoxicity was calculated. All excluded cases were reviewed by both authors and agreement was reached on 100% of these cases.

No power calculation was performed as no expected difference in the literature has been reported for different IV NAC regimens in this cohort. As such, a feasible sample that the lead author could survey in a timeframe that limited confounders was chosen as the starting point, along with the expected 2–5% of patients presenting with a >1500 mg/L IU/L multiplication product noted from prior literature [7,10,11].

Chi-squared test was used for rate of hepatotoxicity and laboratory coagulopathy. Student's *t*-test was used to compare difference of means; two-tailed *p*-values were calculated, with significance defined as $p < .05$. A Kolmogorov Smirnov (K-S) test was performed to assess for normal distribution of continuous variables, with significance defined as $p < .05$. If a nonparametric distribution was found, median and interquartile range (IQR) were reported instead of mean and standard deviation (SD), with a Mann-Whitney U test

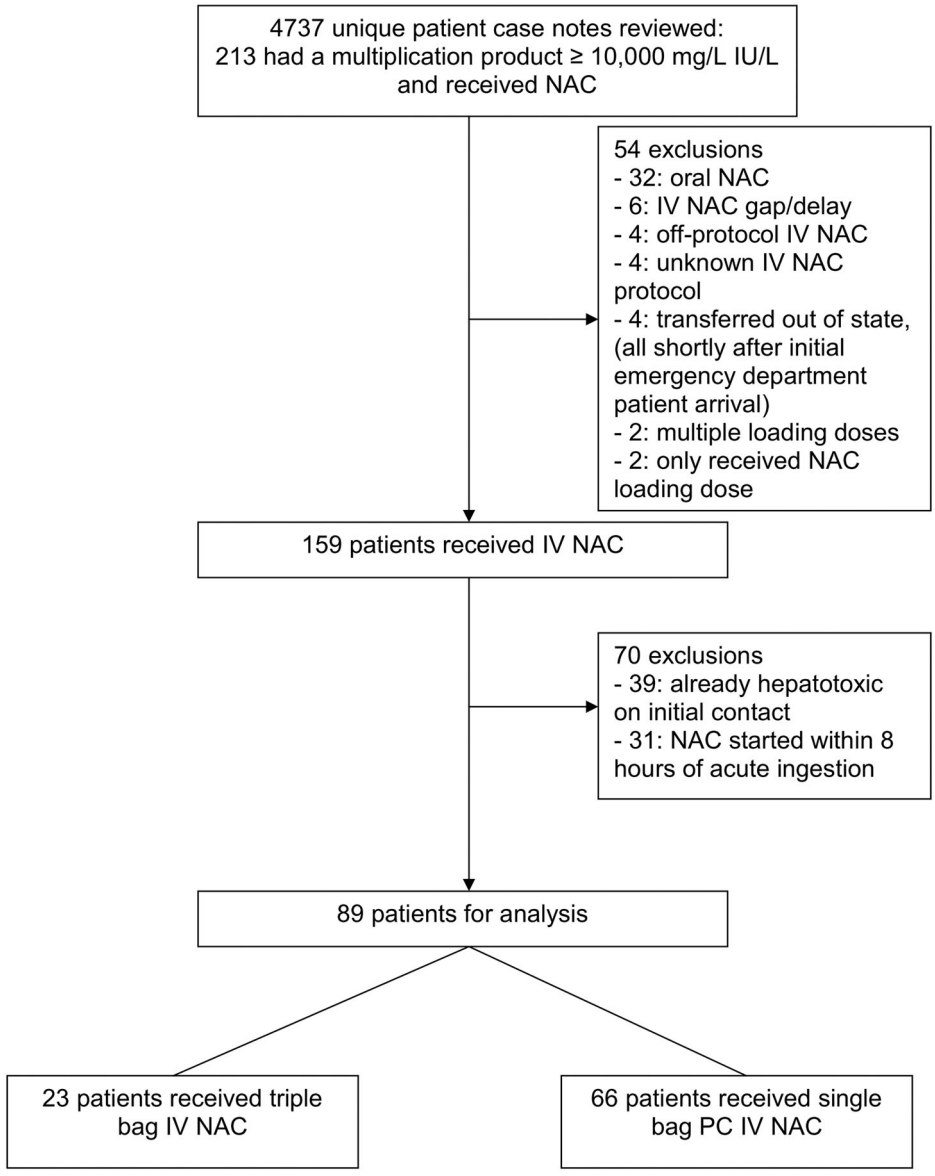

Figure 1. Flow chart of patient inclusion.

calculated and significance defined as $p < .05$. Statistics were calculated *via* Microsoft Excel® (Redmond, WA).

Results

Our initial query retrieved 4737 unique patients, of whom 213 patients met initial inclusion criteria. 54 patients were excluded for receiving NAC with an alternative regimen or transport out of state, leaving 159 patients. An additional 70 patients were excluded due to early NAC administration or hepatotoxicity on presentation, leaving 89 patients for analysis. Of these, 23 patients received triple bag IV NAC while 66 patients received PC IV NAC (Figure 1). The 89 patients were from 53 separate institutions, with no institution having more than 7 patients.

31 patients had a multiplication product $\geq$ 10,000 mg/L IU/L and received IV NAC within 8 h of an acute ingestion; 1 (3%) became hepatotoxic after having received the PC IV NAC protocol. These 31 patients were not included in the final analysis.

Mean age, gender, EMR access, mean initial multiplication product, mean initial [APAP], mean initial transaminase, mean initial INR, percent acute ingestions, percent acute ingestions with known time of ingestion, and median time of ingestion to NAC administration in these acute ingestions are given in Table 2; none of these differences were statistically significant, though we could not calculate a test of significance for acute ingestions with known time of ingestion due to the small sample size in that group. Otherwise, the K-S test had $p > .05$ (i.e., normally distributed) for all continuous variables in Tables 2 and 3.

Twelve of the 23 patients (52%) who received triple bag IV NAC became hepatotoxic, while only 19 of 66 patients (29%) who received the PC IV NAC became hepatotoxic ($p = .043$). Mean peak transaminase in the 23 patients receiving triple bag IV NAC was 4481 IU/L while it was 2143 IU/L in the 66 patients receiving the PC IV NAC (difference of means

Table 2. Baseline characteristics.

	Triple Bag IV NAC $N = 23$	PC IV NAC $N = 66$	
Mean age in years (SD)	41 (20)	41 (17)	$p = 1$
Females	13 (57%)	43 (65%)	$p = .46$
EMR access	2 (9%)	16 (24%)	$p = .11$
First recorded [APAP] in mg/L or post 4-hour [APAP] if acute (SD)	200 (185)	249 (304)	$p = .47$
Initial transaminase (larger of AST or ALT) in IU/L (SD)	355 (242)	261 (238)	$p = .11$
Patients with recorded initial INR	7 (30%)	24 (36%)	$p = .61$
Initial INR	1.84 (1.0)	1.41 (0.98)	$p = .32$
Initial multiplication product in mg/L IU/L (SD)	48272 (60859)	33663 (38768)	$p = .19$
Acute ingestion	12 (52%)	29 (44%)	$p = .5$
Acute ingestions with known time of ingestion	3 (13%)	8 (12%)	$p = .91$
Median time (min) from acute ingestion to NAC administration, when known (IQR)	607 (530–1390)	763 (661–991)	

Table 3. Hepatotoxicity and coagulopathy between the two IV NAC regimens.

	Triple Bag IV NAC $N = 23$	PC IV NAC $N = 66$	
Hepatotoxicity[a]	12 (52%)	19 (29%)	$p = .043$
Mean peak transaminase in IU/L (SD)	4481 (5256)	2143 (3853)	$p = .026$
Coagulopathy[b]	10 (43%)	15 (23%)	$p = .057$

[a]Hepatotoxicity was defined as peak transaminase $\geq$ 1000 IU/L.
[b]Coagulopathy was defined as peak INR $\geq$ 2.

2338 IU/L; 95% confidence interval 293–4385 IU/L; $p = .026$). Laboratory coagulopathy occurred in 10 of the 23 patients (43%) who received triple bag IV NAC vs 15 of 66 patients (23%) who received the PC IV NAC ($p = .057$, greater than the $p < .05$ significance level) (Table 3). Figure 2 displays these patients who became hepatotoxic with each regimen vs log of their initial multiplication product.

Discussion

APAP hepatotoxicity occurs primarily due to its metabolism to N-acetyl-p-benzoquinoneimine (NAPQI). Alteration of glutathione (GSH) was found to change the level of covalent binding of toxic metabolites. This provided a rationale for agents such as NAC to treat APAP toxicity. Stoichiometric calculations suggested a loading dose of 12 mg/kg/hour and a maintenance dose of 6 mg/kg/hour, using a 15.9 gram acetaminophen toxic dose. The oral NAC dosing protocol that was approved in the USA in 1985 had several multiples of safety factors, leading to a final dosing regimen of 140 mg/kg loading dose and 70 mg/kg every 4 h for 72 h.

An FDA approved version of IV NAC called Acetadote® was available in 2004. However, it was approved as a triple bag dosing regimen that gave less NAC than the oral regimen (Table 1) and was indicated only for acute ingestions presenting within 8–10 h. There was no IV regimen approved if there was clinical evidence suggesting that therapy be continued after the 21 h protocol was completed; simply continuing the infusion at 6.25 mg/kg/hr is barely above the rate believed needed to treat a mild to moderate hepatotoxic dose. In a retrospective study comparing oral NAC vs the triple bag IV regimen [12], the oral protocol was more effective than the IV protocol for ingestions receiving NAC after 18 h of an acute overdose, reflecting either a benefit to longer administration and/or additional dosing.

This poison center has been recommending an alternative, higher dose, single bag IV NAC protocol since 2006 in which the total NAC given approximates oral NAC (Table 1). The recommended formulation of the IV NAC solution is 30 grams of NAC in 1 L D5W (3%) NAC solution; so, after the bolus is given from the bag, the rate of infusion at 15 mg/kg/hour should always be half the patient's weight in kilograms. In mL/kg, the bolus rate is five times the weight (i.e., 150 mg/kg divided by 30 mg/mL = 5 mL/kg over one hour), while the rate of infusion subsequently will be one half the patient's weight in kilograms (i.e., 15 mg/kg/hr divided by 30 mg/mL = 0.5 mL/kg/hr). A single standardized concentration and rate likely lead to decreased medication errors [4], which have been reported to be fatal [13,14], as opposed to creating three different bags at different concentrations and having to hang each one separately [15,16]. As NAC is dialyzable, absolute minimal dosing will require adjustment, but the 15 mg/kg/hour rate of NAC is less likely to require alteration during hemodialysis based on its mean extraction ratio of 51% [17]. Also, there are cases of death and liver transplant for patients treated with the triple bag regimen, both from halting at 21 h and even if the regimen is continued at the 6.25 mg/kg/hr [18,19].

While there has been considerable debate of the varying IV NAC protocols for years [6,20,21], no IV NAC protocol has ever been studied and demonstrated efficacy in both high-risk acute and non-acute ingestions. The only other study suggesting a difference in an alternative IV NAC regimen's efficacy is the ATOM-2 study, which noted that if the third bag in the triple bag IV NAC protocol was doubled to 12.5 mg/kg/hour for 16 h, the rate of hepatotoxicity in acute ingestions treated within 16 h fell from 28% to 9% [22]. Based on all this, we suspected that NAC is being underdosed in the sickest patients and focused our study on these patients by screening for high-risk patients and eliminating patients predicted to do well by early treatment within 8 h of acute ingestions.

Further concurrence of our findings with the published literature is demonstrated by a study that showed a 60% hepatotoxicity incidence for patients with a multiplication product $\geq$ 10,000 mg/L IU/L and treated with the triple bag IV NAC regimen, which is close to the 52% we found in our dataset [7]. The slight decrease may be explained because our methodology excluded initially hepatotoxic patients.

The minimal rate (3%) of hepatotoxicity in the patients with a multiplication product $\geq$ 10,000 mg/L IU/L but treated within 8 h of an acute ingestion reinforces the importance of time to NAC administration, suggests this cohort of patients

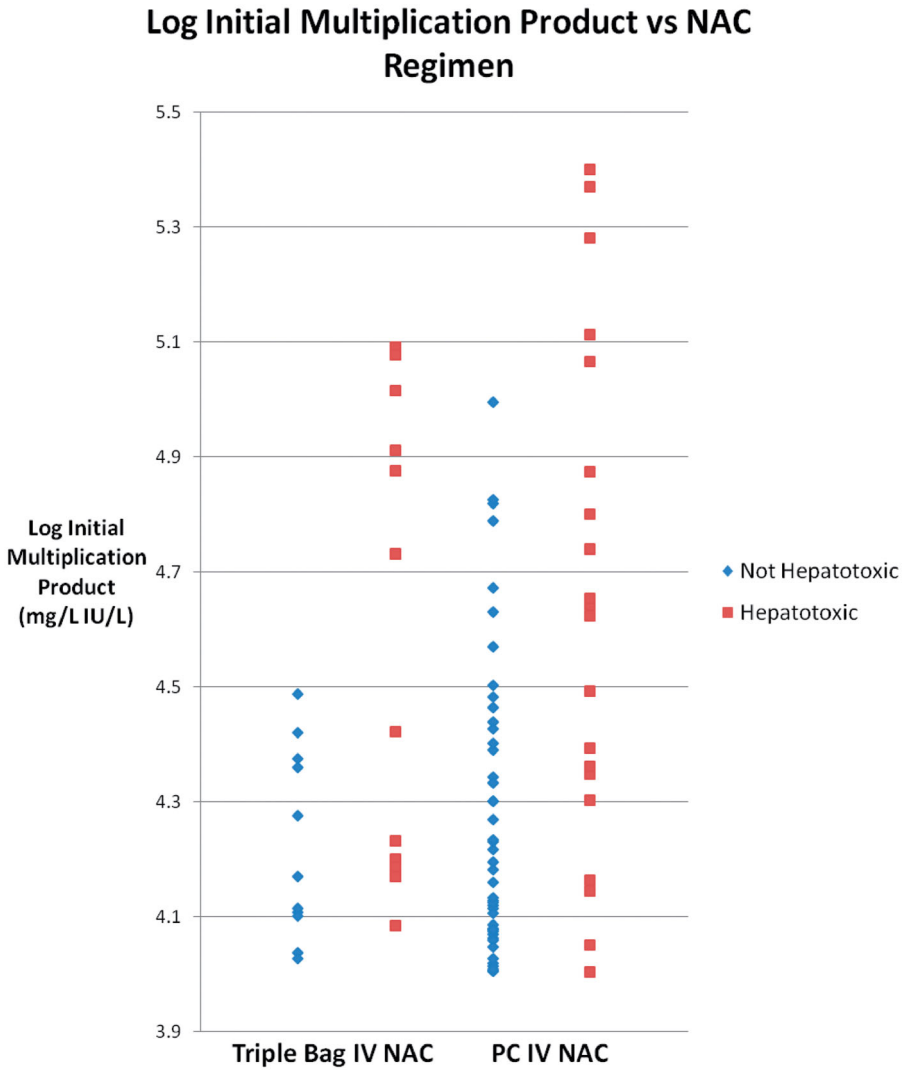

Figure 2. Log Intial Multiplication Product vs NAC Regimen.

is at lower risk of hepatotoxicity, and supports the exclusion of these patients in our analysis. It is similar to the data found in a validation study of the multiplication product, in which only one patient of 18 (6%) with a single acute ingestion and multiplication products >10,000 mg/L IU/L who presented within 8 h became hepatotoxic [7].

Strengths of this study include the broad search criteria used initially, uniform abstraction by a single reviewer, and reading all case notes to determine the timing of the clinical effects as well as to reduce the risk of poison center field coding errors [23,24].

Limitations include the retrospective nature of this study, lack of blinding to the hypothesis by the data abstractor, small sample size, and primarily laboratory marker-based outcomes. As this is a poison center study, it suffers additional limitations of not having access to all institutions' electronic medical records for verification of case details, such as timing of NAC administration, as well as potential referral bias of which cases are reported to a poison center. Another limitation of using retrospective poison center data is the lack of consistent documentation of other confounding variables, such as coingestants, gastric decontamination use, and patient comorbidities, thereby limiting the ability to balance these variables. This dataset is heterogeneous and multiple data points remain unrecorded, such as the interval from acetaminophen concentration to transaminase collection, time of ingestion, and time from ingestion to presentation. Furthermore, certain institutions tended to prefer the triple bag regimen, but other institutional practices in their standards of care could be affecting the patient outcomes; however, there was no predominant institution represented in our data. Thus, multiple potential confounders remain unable to be accounted for.

These data create a starting point of an expected difference in future prospective studies regarding NAC dosing and allow a power calculation to be performed. Our 23% absolute difference in hepatotoxicity rate is similar to the ATOM-2 study's 19% absolute difference. Prospective data collection

would help address several missing data points, and a larger sample size would decrease the risk of a type 2 statistical error.

Conclusion

Overall, in a high-risk population of APAP ingestions, the PC IV NAC regimen studied here (150 mg/kg loading dose, then 15 mg/kg/hr) was associated with fewer patients becoming hepatotoxic and lower peak hepatotoxicity as compared to patients receiving the triple bag IV NAC regimen. Prospectively collected, controlled data should be gathered to verify the validity of this finding and investigate any potential causative link between the IV NAC regimen and rate of hepatotoxicity.

Disclosure statement

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