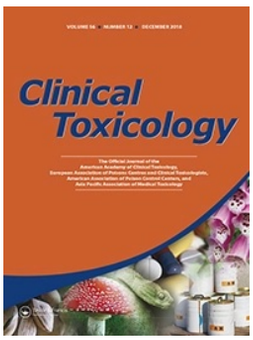

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POISON CENTRE RESEARCH

Clinical outcome of massive acetaminophen overdose treated with standard-dose N-acetylcysteine

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ABSTRACT

Background: Recent recognition of "massive" acetaminophen (APAP) overdoses has led to the question of whether standard dosing of N-acetylcysteine (NAC) is adequate to prevent hepatoxicity in these patients. The primary aim of this study was to evaluate the clinical outcome for patients with massive APAP overdose who received standard intravenous NAC dosing of 300 mg/kg over 21 h.

Methods: This was a single-center retrospective cohort study conducted by chart review of APAP overdoses reported to a regional poison center from 1 January 2010 to 31 December 2019. Massive APAP overdose was defined by single, acute overdose resulting in an APAP concentration exceeding 300 mcg/mL at 4 h post-ingestion. Standard univariate statistical analysis was conducted to describe the cohort, and a multivariate logistic model was utilized to calculate adjusted odds ratios for risk of hepatoxicity.

Results: 1425 cases of APAP overdose were reviewed. 104 cases met the inclusion criteria of massive APAP overdose. Overall, 79 cases (76%) had no acute liver injury or hepatotoxicity, and 25 (24%) developed hepatoxicity. Nine percent ($n = 4$) of cases receiving NAC within 8 h developed hepatotoxicity. Crude odds for hepatoxicity was 5.5-fold higher for cases who received NAC after 8 h.

Conclusions: Standard NAC dosing received within 8 h prevented hepatoxicity in 91% ($n = 40$) of cases in our series of massive APAP overdoses. Additional data is needed to determine the clinical outcomes of massive APAP overdose using current intravenous NAC dosing.

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Acetaminophen; massive; acetylcysteine; treatment

Introduction

Acetaminophen (APAP) overdose results in hepatic injury due to increased production of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). N-acetylcysteine (NAC) is highly effective at the prevention of hepatotoxicity if given within 8 h of acute overdose [1]. Traditionally, patients presenting after a single acute overdose are risk-stratified using the acetaminophen nomogram; those with APAP concentrations plotting at or above the 150 mcg/mL line on the nomogram are treated with NAC [2]. Rumack explained that toxicity was seen in historically untreated patients with a serum acetaminophen concentration greater than 200 mcg/mL at 4 h or 50 mcg/mL at 12 h.

Later, the FDA required a "safety" line be added 25% below the original line, which created the line we use in the United States today that starts at a 4-h APAP concentration of 150 mcg/mL and finishing at roughly 5 mcg/mL at 24 h. The standard NAC dosing was based on Rumack's original study that concluded the 70 kg male healthy volunteer would have to ingest 16 g of APAP to cause depletion of glutathione below 70% to cause hepatotoxicity [3]. The intravenous NAC dosing protocol approved by the FDA is a total NAC dose of 300 mg/kg over a 21-h infusion [2].

More recently, increasing attention has been given to patients presenting after a so-called "massive" APAP ingestion. Currently, there is no consensus on the definition of massive ingestion, however, a recent review defined a massive overdose as ingestion of APAP greater than 32 g or a serum APAP concentration plotted above a 300 mcg/mL nomogram line [4]. One study found that despite receiving NAC within 8 h, 12.5% of patients plotting between the 301–500 mcg/mL nomogram lines and 33% of patients plotting greater than the 500-line developed an acute liver injury, defined as peak serum ALT activity >150 U/L [5]. Another study found that 3% of patients with massive APAP concentrations treated with standard NAC dosing within 8 h developed hepatotoxicity [6]. One of these patients required a liver transplant despite NAC initiation within 2.5 h of ingestion. The authors suggested that higher-dose NAC regimens decreased the risk for hepatotoxicity. Hendrickson recently recommended that patients meeting "massive" APAP overdose criteria be treated with a larger dose of NAC during the continuous infusion phase of treatment; the phase of treatment is sometimes referred to as the "third bag" in the standard protocol [4]. Dosing errors are common with NAC administration [7], and changing current practice to a higher dose regimen could result in increased errors. Furthermore,

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decades of anecdotal clinical experience using standard NAC dosing without consideration of "massive" APAP concentrations seems to suggest that 300 mg/kg over the first 21 h NAC dosing has been adequate in most cases. Reports of cases with APAP concentrations exceeding 900 mcg/mL treated only with standard NAC dosing have also occurred [8]. Data describing the clinical outcomes of massive APAP overdose treated solely with standard NAC dosing is clearly needed. The primary aim of this study was to evaluate the clinical outcome for patients meeting massive APAP overdose criteria who were treated with a standard NAC dosing of 300 mg/kg in the first 21 h.

Methods

Study design

This was a retrospective cohort study conducted by chart review of electronic records reported to our regional poison center from 1 January 2010 to 31 December 2019. This study was deemed exempt by our institutional review board.

Setting and population

The Virginia Poison Center provides poison information and toxicology consultation in central and eastern Virginia with an annual call volume of approximately 27,000. The electronic database Toxicall™ (Computer Automation Systems, Aurora, CO) was searched to identify APAP overdoses cases during the study period using a combination of filters including all APAP generic codes, acute exposure, and intravenous N-acetylcysteine was given.

Study protocol

Initial electronic records search identified all APAP overdose cases as described above. Poison center charts for those cases were independently reviewed by study investigators to identify study cases, and data for the cases meeting study criteria were then abstracted onto a data collection tool with no patient identifying information. For the purposes of inclusion in the study, cases of massive APAP overdose were defined as a single, acute APAP overdose resulting in an APAP concentration exceeding an adjusted massive nomogram starting at 300 mcg/mL at 4 h post-ingestion [9]. The time of ingestion was determined by patient history as recorded during the consultation with the Virginia Poison Center. If a time interval was provided wherein an APAP ingestion occurred, the earliest exposure time was used to plot the APAP concentration on the nomogram. Cases were excluded if a time of ingestion was not available (i.e., no plottable concentration) if the overdose was not due to single, acute ingestion (i.e., repeat supratherapeutic APAP ingestion), APAP concentrations plotting below the 300 mcg/mL nomogram line, if intravenous NAC dosing greater than 300 mg/kg in 21 h was utilized, or if oral NAC was used during treatment. Our standard NAC intravenous protocol is a "three bag" protocol that includes an initial 150 mg/kg bolus infused over 1 h, followed by a 50 mg/kg bag infused over 4 h, and lastly, a 100 mg/kg bag infused over 16 h (total NAC dose 300 mg/kg over 21 h). If repeat lab work prior to completion of the last 16-h bag showed an APAP level $>$ 20 mcg/mL or up-trending aspartate transaminase and alanine transaminase (AST and ALT), then the 100 mg/kg infusion over 16 h was continued until APAP level was $<$20 mcg/mL and AST and ALT were down-trending. Demographic data including age, sex, and type of exposure were recorded. Additional data included APAP concentration, time of ingestion, time to initiate NAC treatment, total NAC dose, peak AST and ALT concentrations, and final clinical outcome. If multiple APAP concentrations were reported, the highest concentration was recorded for plotting. Given the objective nature of our primary outcome, interrater reliability measures were not performed.

Measures

The primary outcome of interest was the clinical outcome for cases meeting inclusion criteria. Final clinical outcomes were categorized as no acute liver injury, acute liver injury, hepatoxicity, death, or liver transplant. Acute liver injury was defined as an AST or ALT $>$150 U/L, but less than 1000 U/L. Hepatoxicity was defined as AST or ALT $>$1000 U/L.

Data analysis

Univariate analysis was conducted using standard statistical tests on available variables of interest to describe the cohort. Analysis of independent continuous variables was conducted via Student's *t*-test for parametric data or Wilcoxon Rank Sum Test for non-parametric data. Testing of independent categorical variables was conducted via Pearson's Chi-square test. Two-tailed significance was set at a *p*-value less than 0.05. Data were presented as medians and interquartile ranges (IQR) or number and percentage. Independent variables associated with the development of hepatotoxicity were included in a simple multivariate logistic model to calculate adjusted odds ratios for risk of hepatoxicity. All data analysis was conducted using Excel 2013 (Microsoft, Redmond, WA) or Stata/MP Version 15.1, (StataCorp, College Station, TX) and statistical significance was set at $p < 0.05$.

Results

The initial data search returned 1425 cases of APAP overdose for review. Of these, 104 cases met the inclusion criteria of massive APAP overdose for analysis (Figure 1). Table 1 provides demographic information for study subjects. The median age was similar across all groups. Females made up the majority of cases and this was consistent across all groups. Use of activated charcoal was limited across the cohort, occurring in less than a quarter of all cases ($n = 22$, 21%). A slightly larger proportion (28.5%, $n = 18$) of the cases were between the 300–449 mcg/mL line received activated charcoal as compared to those cases that exceeded the 600 mcg/mL line (14.8%, $n = 4$). This is most likely a

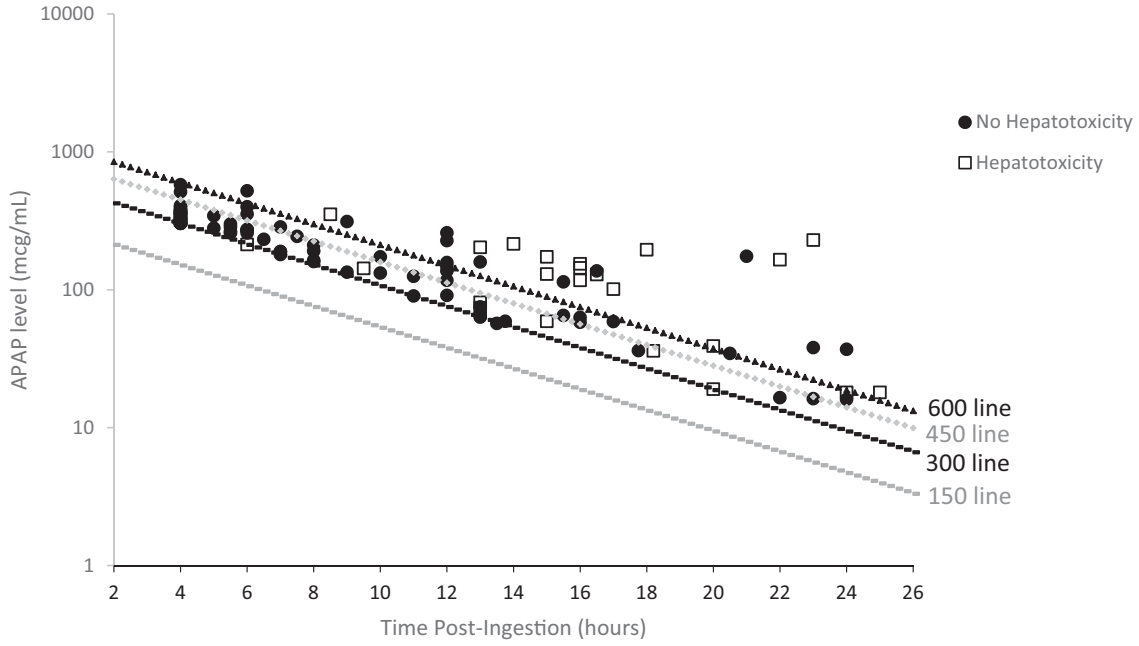

Figure 1. Acetaminophen (APAP) concentration versus time post-ingestion for single, acute "massive" overdoses. "Massive" ingestions were defined as those concentrations by plotting at or above the 300 mcg/mL nomogram line. Sloped lines represent extensions of the Rumack–Matthew 150 mcg/ mL nomogram line corresponding to 300, 450, and 600 mcg/mL at 4 h post-ingestion. White squares represent cases that developed hepatotoxicity (AST or ALT > 1000). Black dots represent cases that did not develop hepatotoxicity.

Table 1. Demographic information for study cases.

	Total cases	Time to NAC < 8 h	Time to NAC > 8 h	*p*-Value
Total, *n* (% of total)	*n* = 104 (100%)	*n* = 44 (42.3%)	*n* = 60 (57.7%)	
Female, *n* (%)	72 (69.2)	32 (72.7)	40 (66.7)	0.35
Age in years, median (IQR)	22 (17, 37)	23 (17, 36)	22 (17, 38)	0.66
Hepatoxicity, *n* (%)	25 (24.0)	4 (9.0)	21 (35.0)	<0.001
NAC Duration in hours, median (IQR)	21 (21, 53)	21 (21, 37)	21 (21, 84)	0.12
Activated Charcoal, *n* (%)	22 (21)	16 (36.3)	6 (10.0)	0.001
Nomogram Group, *n* (%)				
300–449 mcg/mL	62 (59.6)	36 (81.8)	26 (43.3)	
450–599 mcg/mL	15 (14.4)	5 (11.3)	16.7)	
>600 mcg/mL	27 (25.9)	3 (6.8)	24 (40.0)	<0.001

Cases were divided into categories based whether intravenous N-acetylcysteine (NAC) was received less than 8 h from ingestion or greater than 8 h from ingestion. The categories included cases that plotted between 301–449 mcg/mL, 450–599 mcg/mL, and cases exceeding 600 mcg/mL on the modified Rumack–Matthew nomogram. Analysis of independent continuous variables was conducted via Student's *t*-test for parametric data or Wilcoxon Rank-Sum test for non-parametric data. Testing of independent categorical variables was conducted via Pearson's Chi-square test. Two-tailed significance was set at *p*-value less than 0.05. Data were presented as medians and interquartile ranges (IQR), or number and percentage.

reflection, however, of a trend toward cases with higher APAP concentrations presenting late after APAP ingestion when activated charcoal may no longer be considered. Overall, 79 cases (76%) had no acute liver injury or hepatotoxicity. Only 6 (6%) showed acute liver injury. Of the total 104 cases, 25 cases (24%) developed hepatoxicity. Of those 25 cases that developed hepatoxicity, nine cases (14%) were in the 300–449 mcg/mL nomogram group, one case (7%) was in the 450–599 mcg/mL nomogram group, and 15 cases (56%) were in the nomogram group exceeding 600 mcg/mL. Among all cases that received NAC within 8 h of ingestion (*n* = 44), four cases (9%) developed hepatotoxicity despite early NAC. In contrast, 60 cases did not receive NAC within 8 h and of these 21 cases (35%) developed hepatoxicity. No deaths or liver transplants were noted among the entire cohort. The crude odds ratio for hepatoxicity across the entire cohort was 5.4 times higher (OR = 5.4; 95% CI 1.7–17.1) for cases who received NAC later than 8 h compared to those cases who received NAC sooner than 8 h after APAP ingestion. A simple multivariate logistic model was developed including the nomogram line exceeded as a surrogate for dose, the administration of activated charcoal, and time to NAC administration as a continuous variable. The adjusted odds ratio for hepatoxicity was 3.8 times higher (OR 3.8; 95% CI 1.2–12.0) in the cases that exceeded the 600 mcg/mL nomogram line compared to those cases that were in the 300–449 mcg/mL nomogram group, even after controlling for time to NAC administration, or activated

charcoal administration. After adjusting for the nomogram group, and activated charcoal administration, we found an ~12% increase (OR 1.12; 95% CI 1.03–1.22) in risk for hepatotoxicity for every 1-h delay in NAC administration. The administration of activated charcoal did not seem to have an impact on the risk for hepatotoxicity in this series (OR 0.71; 95% CI 0.15–3.33).

Discussion

APAP overdose is the most common cause of acute liver failure in the Western world [10]. The FDA approved standard intravenous NAC dosing includes a three-bag regimen providing a total dose of 300 mg/kg over a 21-h infusion. This regimen was reportedly created to treat a 16-g APAP ingestion in a 70 kg patient [2]. While it is effective in treating early APAP overdoses, questions remain as to whether massive overdoses require a higher dose of NAC. Recent studies have demonstrated that APAP concentrations plotting above a 300 mcg/mL nomogram line may be at increased risk of hepatotoxicity despite receiving standard NAC dosing initiated within the first 8 h [5,6,11]. These studies demonstrated that additional data is needed to determine if standard intravenous NAC is adequate to prevent hepatotoxicity in massive APAP overdoses.

Our results demonstrate that hepatotoxicity due to massive APAP overdose is more likely due to delay in NAC treatment as opposed to insufficient NAC dosing when the standard 300 mg/kg over 21 h regimen is utilized. This is most evidenced by the small proportion of cases developing hepatotoxicity despite receiving NAC within 8 h of ingestion. This finding has been noted in prior studies as well. Smilkstein found that 2–5% of all cases that receive NAC within 8 h of ingestion develop hepatotoxicity, and this finding held even with increasing APAP concentrations [1]. It is important to note here, however, that the NAC protocol utilized in Smilkstein's landmark study was the historical American oral NAC protocol of a 140 mg/kg loading dose followed by 70 mg/kg every 4 h for 17 doses. The total amount of NAC received in the first 20 h of this protocol is 490 mg/kg, significantly greater than the dose received with the current standard intravenous NAC dosing utilized in our study. Chiew's study of massive APAP ingestions is more similar to our current study in that the standard 300 mg/kg NAC dosing utilized in some cases, and also noted a small proportion of cases (roughly 3%) with massive APAP ingestion will develop hepatotoxicity even if NAC is started before 8 h with one case progressing to requiring liver transplant [6]. Chiew's study also demonstrated that most cases of hepatoxicity had a delay in treatment compared to those who did not (13.9 vs. 6 h) [6]. Another series demonstrated an increased incidence of acute liver injury (defined as ALT doubling or >150 U/L) in massive APAP overdoses despite NAC treatment within 8 h, but there were too few cases who developed hepatotoxicity (defined as ALT >1000 U/L) for a meaningful analysis [5]. In their study, 5 cases (6%) in the 301–500 mcg/mL nomogram group and 8 cases (18%) in the >500 mcg/mL nomogram group developed hepatotoxicity, but the mean times to NAC treatment were notably 7.42 and 16.42 h, respectively. The delay to NAC treatment in these groups makes it difficult to interpret the significance of hepatotoxicity in the setting of massive APAP overdose. Our data clearly demonstrated a dose-response risk for hepatotoxicity directly related to the plot of the serum APAP concentration above the nomogram line, in a manner similar to what Cairney showed for risk for acute liver injury in his study. Although the total cases of hepatotoxicity in Cairney's study were small, there seemed to be a significant increase in the proportion of cases resulting in hepatotoxicity once the 500 mcg/mL nomogram line was crossed. We noted a similar trend in our data, but again the case counts are too small to draw any conclusions. Additional data is needed to determine the clinical outcomes of massive APAP overdose using current intravenous NAC dosing. However, this raises the question that perhaps the real benefit of increased dosing of NAC lies somewhere within those cases with an initial APAP concentration within the 500–600 mcg/mL range.

Our study, while small, does possess some notable strengths. First, it reflects current practice patterns in many areas of the world and is likely generalizable to poison center consultations for APAP overdoses in many areas. Second, it adds a sizeable number of cases ($n = 104$) to the growing body of literature on massive APAP overdoses, emphasizing that in most cases traditional NAC dosing is sufficient to treat these cases. Third, while some recent studies have proposed that a larger dose of NAC is indicated for massive overdoses, our study demonstrates that the standard intravenous NAC regimen adequately prevented hepatotoxicity in the vast majority of massive APAP overdoses if administered within 8 h. Even those cases that developed hepatotoxicity despite receiving NAC within 8 h recovered without sequelae.

Limitations

As with all observational studies, our study has limitations worth mentioning. Most notably, our data were obtained from poison center charts that are generated passively through voluntary discussions with healthcare providers by poison center specialists. This process can result in the omission of certain data including important historical features or laboratory values. The assessment and plotting of APAP concentrations on a modified nomogram rely on historical information obtained from the patient that could be inaccurate. It is also physically difficult to ingest a "massive" amount of APAP within a short period of time, making it more difficult to obtain an accurate time of ingestion. However, obtaining accurate historical information regarding overdose ingestions is a "real life" and "real time" issue that occurs with almost all poison center consultations. Thus, while this is a limitation, it also reflects the reality of poison center practice day to day and will be found in any other similar study involving poison center data. The consistency of our results with those of other recent studies suggests that any inaccuracies are minimal.

Conclusion

Standard dosing of NAC adequately prevented hepatoxicity in 91% ($n = 40$) of massive APAP overdose patients who received NAC within 8 h. No deaths or hepatic transplants occurred in this cohort with standard NAC dosing. While our data suggest that hepatoxicity due to massive APAP overdose is more likely secondary to delay in treatment, our samples size is small and larger studies are needed to determine the clinical outcomes of these massive overdoses with current intravenous NAC dosing. We also hope that future prospective studies will be performed to determine the efficacy of higher intravenous NAC dosing for massive APAP overdoses.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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