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SAFETY AND EFFECTIVENESS OF ACETADOTE FOR ACETAMINOPHEN TOXICITY

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□ **Abstract—Background: Acetaminophen (APAP) toxicity is commonly encountered in the Emergency Department. Until 2004, treatment consisted of either oral N-acetylcysteine (NAC) or filtered oral NAC administered intravenously (i.v.). Intravenous acetylcysteine (Acetadote) is a new Food and Drug Administration-approved i.v. formulation of acetylcysteine manufactured by Cumberland Pharmaceuticals in Nashville, Tennessee. Little post-marketing data exists on the effectiveness and safety of i.v. acetylcysteine. Objectives: We evaluated the clinical presentations and outcomes of patients treated with i.v. acetylcysteine for APAP toxicity. Methods: We performed a retrospective chart review of patients treated with i.v. acetylcysteine for APAP ingestion. The primary outcome measures were: adverse reactions to and effectiveness of i.v. acetylcysteine, as defined by elevation of transaminases, liver failure, renal failure, death, and hospital length of stay (LOS). Data collected included: comorbidities, allergies, intentionality, timing and dosing of i.v. acetylcysteine, hospital LOS, transaminases > 1000 IU/L, development of liver failure requiring transplant, development of renal failure requiring hemodialysis, death, and anaphylactoid reactions. Results: Sixty-four patients met our study criteria. Overall, 16 (25%) patients developed transaminases > 1000 IU/L, 4 (6%) of them died and 2 (3%) received liver transplants. Of the 15 patients (23%) treated within 8 h, none died or developed liver or renal failure, and only 1 developed transient transaminase elevation > 1000 IU/L. In the patients treated outside of 8 h, the median LOS was 3 days, whereas the group treated within 8 h had a median LOS of only 1 day. Six (9%) patients developed anaphylactoid reactions, 2 of whom received the i.v. acetylcysteine bolus over 15 min. Five of these patients were treated pharmacologically and completed treatment, and one had treatment discontinued for undocumented reasons. Conclusion: Intravenous acetylcysteine seemed to be a safe and effective formulation of N-acetylcysteine. © 2010 Elsevier Inc.**

□ **Keywords—acetaminophen; i.v. acetylcysteine; N-acetylcysteine; anaphylactoid; toxicity**

INTRODUCTION

Acetaminophen (APAP) is one of the most frequent medications recognized in both accidental and intentional overdoses, with over 48,000 exposures treated in U.S. health care facilities in 2005 (1). Additionally, APAP is now recognized as the leading cause of acute liver failure in hospitalized patients (2).

Orally administered N-acetylcysteine (NAC) has traditionally been used in the United States in the treatment of APAP toxicity. Although demonstrating effectiveness and safety, oral NAC administration is often associated with several difficulties. As a result, oral NAC has been filtered to generate an intravenous (i.v.) solution. This preparation has been used openly and safely outside the United States, but only as an off-label product

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within the United States. Both i.v. and oral NAC, however, have demonstrated similar efficacy in treating APAP toxicity (3,4).

In 2004, the Food and Drug Administration (FDA) approved i.v. acetylcysteine, a sterile, pyrogen-free solution. To date, there have been few reported post-marketing data. Although an effective oral formulation of NAC already exists, more institutions are looking to use i.v. acetylcysteine due to the ease of administration and lack of noxious effects. As such, post-marketing evaluation of i.v. acetylcysteine is warranted. The primary objective of our study was to examine the effectiveness and safety of i.v. acetylcysteine administration for APAP toxicity.

MATERIALS AND METHODS

Study Design

This study was an institutional review board (IRB)-approved, retrospective review of patient records from March 2005 to June 2006 of consecutive patients admitted to the hospital receiving i.v. acetylcysteine for a known or suspected APAP overdose. The study start date was determined by the availability of i.v. acetylcysteine to our study facility.

None of the authors had any financial arrangements, connections, or obligations to the manufacturers of i.v. acetylcysteine. No financial support was provided for this study.

Setting

The study site is a tertiary care academic center caring for adult patients and a regional toxicology referral center.

Selection of Participants

IRB-approved, non-study-related personnel queried the electronic medical record system using International Classification of Diseases (9^{th} Revision) codes to identify all patients receiving NAC during the study period at any time during their hospitalization and provided data to the investigators. This query resulted in a total of 142 patients for possible inclusion. Patients were excluded if they received only oral or non-i.v. acetylcysteine preparation or i.v. acetylcysteine for any reason other than known or suspected APAP poisoning.

As defined by the Toxicology service at the study site, patients were considered to have been treated appropriately with i.v. acetylcysteine if they had at least one of the following: a treatable APAP level on the Rumack-Matthew nomogram, elevated transaminases with either a detectable or undetectable serum APAP level with high suspicion of APAP toxicity, or an elevated APAP level with unknown time of ingestion.

Data Collection and Processing/Methods of Measurement

Data collected included: gender, age, pre-existing liver or renal disease, allergies, intentional or accidental overdose, co-ingestions, timing and dosing of i.v. acetylcysteine, development of anaphylactoid reaction, transaminases $>$ 1000 IU/L at any time during hospital stay, hospital length of stay (LOS), development of liver failure requiring transplant, development of renal failure requiring hemodialysis, and death. Investigators independently reviewed all records. There was 89% agreement on all collected data, and differences were resolved by consensus opinion.

Intravenous acetylcysteine initiation time was defined as $<$ 8 h or $>$ 8 h from time of ingestion. If time of ingestion was unknown, initiation time was assumed to be $>$ 8 h. The dose of i.v. acetylcysteine was documented. If the loading dose was delivered at another facility, the loading dose data were not included.

Outcome Measures

The primary outcome measures were occurrence of organ damage and adverse effects of i.v. acetylcysteine in treating APAP toxicity. Organ damage was assessed by the following patient outcome measures: transaminase elevation $>$ 1000 IU/L at any point during hospital stay, liver failure requiring transplant, renal failure requiring hemodialysis, or death. We also described the LOS information. Transaminase elevation $>$ 1000 IU/L was used as a marker for hepatotoxicity, as it has historically been done in other NAC studies (5–7).

Adverse effects were defined as minor anaphylactoid reaction manifesting as rash, flushing, pruritus, or gastrointestinal reactions such as nausea or vomiting. Severe adverse reactions were defined as hypotension with or without respiratory distress.

Primary Data Analysis

Patient demographic and baseline clinical information were summarized with means and ranges for continuous variables, and frequencies and proportions for categori-

cal variables. We also reported the 95% confidence intervals for the dichotomous events. Adverse events from i.v. acetylcysteine and other patient outcomes were described with frequencies and proportions overall as well as stratified by timing of i.v. acetylcysteine administration.

RESULTS

Between March 2005 and June 2006, 142 patients were identified as potential cases. Of these, 78 patients were excluded because they: 1) had received NAC but not i.v. acetylcysteine, 2) received i.v. acetylcysteine for a reason other than APAP ingestion, or 3) did not receive the full FDA-approved i.v. acetylcysteine treatment regimen.

With the exception of alcohol co-ingestion, the baseline characteristics of those treated within and outside of 8 h were similar (Table 1). Of the 64 cases included, 34 (53%) were female. The mean age was 32 years (range 15–62 years). Five (8%) of the cases had pre-existing liver disease, and none had pre-existing renal disease. Forty-six (72%) of the cases were the result of an intentional overdose.

Fifty-seven (89%) received the recommended initial bolus dose of 150 mg/kg at our institution. The remainder received the bolus dose at a transferring facility. Of those receiving initial treatment at our facility, 47 (82%) received the bolus dose over the manufacturer-recommended 60 min. The remainder received the first dose in < 60 min, with a range of 15–30 min. Eleven (17%) patients received additional doses beyond the 21-h dosing regimen for continued hepatotoxicity. Of the 64 cases, only 15 (23%) were treated within 8 h of APAP ingestion. The remaining patients were treated after 8 h or at an unknown time from time of ingestion.

The median LOS was 2 days, with an interquartile range of 1–6 days. Among those patients treated within 8 h of ingestion, the median LOS was 1 day, with an interquartile range of 1–2 days. Of those treated beyond 8 h, the median LOS was 3 days, with an interquartile range of 2–7 days.

Table 1. Baseline Characteristics of Study Patients

Characteristic	Treated < 8 h (n = 15)	Treated > 8 h (n = 49)
Male	6 (40%)	24 (49%)
Female	9 (60%)	25 (51%)
Mean age (years)	27	34
Pre-exiting liver failure	1 (7%)	4 (8%)
Alcohol co-ingestion	4 (27%)	7 (14%)
Other co-ingestions	7 (47%)	27 (55%)

Table 2. Comparison of Patients Treated Within or Outside of 8 Hours from Time of Ingestion

Outcome	Treated < 8 h (n = 15)	Treated > 8 h (n = 49)
Transaminases > 1000 IU/L	1 (7%) [0.2–32%]	15 (31%) [18–45%]
Liver transplant	0 (0%) [0–22%]*	2 (4%) [0.5–14%]
Renal failure	0 (0%) [0–22%]*	6 (12%) [5–25%]
Death	0 (0%) [0–22%]*	4 (8%) [2–20%]

* 97.5% confidence interval.
Values given are number of cases (%) [95% confidence intervals].

Of the 64 cases, 47 (73%) never developed transaminase elevation > 1000 IU/L, liver failure, renal failure, or death. Sixteen (25%) had transaminase elevations > 1000 IU/L. Of these, 4 (6%) patients died and 2 (3%) patients received liver transplants. All of the patients that died or required a liver transplant received i.v. acetylcysteine after 8 h from the time of ingestion. Only 1 of the 15 patients treated within 8 h of ingestion had transaminase elevation > 1000 IU/L; this patient fully recovered. None in this group required liver transplant or died. Of all the patients with transaminase elevations > 1000 IU/L, only 1 patient had pre-existing liver disease; this patient died during hospitalization (Table 2).

Overall, 6 (9%) patients developed acute renal failure requiring hemodialysis; none was treated within 8 h of ingestion. Of these 6 patients, 2 were among the reported deaths, 1 received a liver transplant, and the remaining 3 patients received hemodialysis that was discontinued before discharge. None had pre-existing renal disease.

Only 6 (9%) patients developed anaphylactoid reactions due to i.v. acetylcysteine administration. Three patients developed a skin reaction, 2 patients experienced gastrointestinal upset, and 1 patient developed both. None developed a severe adverse reaction. The i.v. acetylcysteine infusion was discontinued completely only in the patient who had both skin and gastrointestinal effects. The other 5 patients were treated pharmacologically and completed the infusion. In 2 of the 4 patients who developed skin reactions, the initial bolus dose had been

Table 3. Adverse Reactions Relative to Loading Dose Delivery Time

Outcome	Loading < 60 min (n = 10)	Loading > 60 min (n = 47)
Adverse reaction	2 (20%) [3–56%]	4 (8%) [2–20%]

Values given are number of cases (%) [95% confidence intervals].

infused over 15 min instead of the currently manufacturer recommended 60 min (Table 3).

DISCUSSION

Intravenous acetylcysteine was FDA approved primarily based on pre-existing data on oral NAC formulated as a filtered i.v. preparation. It is now the drug of choice at our institution for treatment of toxic APAP ingestions. However, there has been a paucity of post-marketing data on the safety and effectiveness of i.v. acetylcysteine (Acetadote; Cumberland Pharmaceuticals Inc., Nashville, TN).

It is well established that early administration of NAC results in replenished stores of glutathione, resulting in decreased risk of hepatotoxicity secondary to the toxic APAP metabolite, N-acetyl-p-benzoquinoneimine (8,9). In our study, despite the fact that only 23% of patients received i.v. acetylcysteine within the recommended 8 h, the overall outcome of those treated was favorable. Of the patients who died or required a liver transplant, all were treated with i.v. acetylcysteine beyond 8 h from the time of ingestion. It is unclear why initiation of i.v. acetylcysteine therapy was delayed in such a large percentage of the study population. The most likely explanations are: unclear history, late presentation, and delayed diagnosis.

Our results are comparable to those of previous studies defining NAC as effective. Smilkstein et al. performed a non-randomized multi-center open trial using the traditional oral NAC formulated as i.v. (5). They reported transaminases $>$ 1000 IU/L in patients treated within 10 h and after 10 h as 10% and 27.1%, respectively. This compares to our results of patients treated within and after 8 h of 7% and 23%, respectively. Smilkstein et al. reported a mortality rate of 1.1%, which is lower than our reported 6%. This is most likely secondary to the fact that our institution is a tertiary care referral and liver transplant center admitting sicker patients, whereas their study sites ranged from community settings to university hospitals.

There has been a hesitancy to use i.v. formulations of NAC due to a reported increased risk of anaphylactoid reactions, especially during infusion of the loading dose (10). (Since the FDA approval of i.v. acetylcysteine, the package insert has changed to recommend a 60-min initial infusion, instead of 15 min, to decrease the risk of anaphylactoid reactions.) In our patient population, anaphylactoid reactions were noted in 9% of the patients treated with i.v. acetylcysteine, which is within the previously reported range of 3.2–48.4% (3,11–14). In our population, all of the adverse reactions were minor and no patient developed major side effects. Notably, 2 of the 4 patients with skin involvement received the initial i.v. acetylcysteine dose over 15 min rather than the newly recommended 60 min. This finding supports the longer initial infusion time. Only one patient had i.v. acetylcysteine discontinued completely; the circumstances surrounding this are unclear.

For comparison with a similar study design and study site, Kao et al. performed a retrospective review at a tertiary referral center with a Toxicology service, and they reported a total of seven (3.2%) adverse events (13). Of these, six were cutaneous and one was life-threatening. Our adverse event rate was higher at 9%. This is likely due to two factors. First, all of their patient population received the loading dose over 1 h. Second, we included in our adverse events those patients with gastrointestinal upset that may have been secondary to the APAP ingestion, not the i.v. acetylcysteine bolus.

Not only did the early administration of i.v. acetylcysteine for APAP toxicity result in a favorable outcome, but it also resulted in a decrease in LOS as well. When treated within 8 h of ingestion, there was an absolute reduction of 2 days in median hospital LOS. This finding suggests that administration of i.v. acetylcysteine within the recommended 8 h may result in the saving of significant hospital resources.

Limitations

There were several limitations in our study. Firstly, it is a retrospective chart review. Although we did review the entire patient chart including, but not limited to, nurse's notes, physician's notes, and medication records, it is possible that minor unreported adverse reactions were missed. However, these would have been reactions that did not require a rescue medication or disruption of the i.v. acetylcysteine infusion. Secondly, it was a small study including only 64 patients. Thirdly, there was no accurate way of quantifying each patient's ingestion. Therefore, it is possible that the group treated outside of 8 h did worse due to larger ingestions. However, historically, other studies have shown that treatment within 8 h results in a better outcome. Lastly, as our study was conducted at an academic liver transplant center, our study population likely included a greater proportion of higher acuity patients, therefore decreasing the external validity of our study. This higher acuity patient population may also make the effectiveness of i.v. acetylcysteine seem artificially lower.

CONCLUSIONS

Intravenous acetylcysteine seemed to be a safe and effective formulation of N-acetylcysteine in our retrospec-

tive chart review. Furthermore, the data support i.v. acetylcysteine administration over 60 min and within 8 h to achieve all of the following: low risk of anaphylactoid reaction, favorable outcome, and shorter hospital LOS. Larger studies, including examining the pediatric population, are indicated.

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