Comparison of the 20-Hour Intravenous and 72-Hour Oral Acetylcysteine Protocols for the Treatment of Acute Acetaminophen Poisoning

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Study objective: To compare outcomes after acute acetaminophen poisoning in 2 large cohorts of patients treated with either the 20-hour intravenous or 72-hour oral acetylcysteine protocol.

Methods: We conducted a retrospective cohort study with historical control comparing patients treated with one of 2 acetylcysteine regimens. Data for the 20-hour group were obtained from a medical record review of patients on whom the 20-hour intravenous protocol was initiated in Canadian hospitals from 1980 to 2005. The 72-hour group consisted of a historical cohort of patients treated in US hospitals with the 72-hour oral protocol from 1976 to 1985. The primary outcome was hepatotoxicity (aminotransferase levels >1,000 IU/L).

Results: Of the 4,048 patients analyzed, 2,086 were in the 20-hour group and 1,962 were in the 72-hour group. The incidence of hepatotoxicity was 13.9% in the 20-hour group and 15.8% in the 72-hour group (~1.9% absolute difference; 95% confidence interval [CI] 4.2 to 0.3). The relative risk of hepatotoxicity was lower in the 20-hour group when acetylcysteine was initiated within 12 hours of ingestion. The relative risk was lower in the 72-hour group when acetylcysteine was initiated later than 18 hours after ingestion. There was no significant risk difference between groups when acetylcysteine treatment was started 12 to 18 hours after ingestion. One patient in the 20-hour group received a liver transplant and died because of acetaminophen toxicity compared with no liver transplants and 3 deaths in the 72-hour group. Anaphylactoid reactions to intravenous acetylcysteine were reported in 148 of 2,086 patients (7.1%; 95% CI 6.1% to 8.3%). This study is limited by comparison of 2 separate data sets from different countries and study years.

Conclusion: The risk of hepatotoxicity differed between the 20-hour and 72-hour protocols according to the time to initiation of acetylcysteine. It favored the 20-hour protocol for patients presenting early and favored the 72-hour protocol for patients presenting late after acute acetaminophen overdose. [Ann Emerg Med. 2009;54:606-614.]
Editor's Capsule Summary

What is already known on this topic
N-acetylcysteine is an effective antidote for acetaminophen poisoning when administered in a timely manner.

What question this study addressed
Is the 20-hour intravenous or 72-hour oral N-acetylcysteine protocol more effective in preventing hepatotoxicity?

What this study adds to our knowledge
In this historically controlled retrospective study comparing 2 cohorts treated by different strategies in different countries in different decades, the 20-hour intravenous protocol (n = 2,086) was more effective when administered before 12 hours after acute overdose. The 72-hour oral protocol (n = 1,962) was more effective when given more than 18 hours after overdose. Both protocols were equally effective when administered 12 to 18 hours after ingestion.

How this might change clinical practice
The time to presentation after acute acetaminophen overdose may influence which N-acetylcysteine protocol to administer, but this finding would need to be confirmed in a prospective randomized trial.

See Editorial, P. 615.

Introduction

Background
Acetaminophen remains a leading cause of morbidity and mortality from poisonings, with more than 100,000 exposures and 300 deaths reported annually to North American poison centers. The United States Acute Liver Failure Study group reported an increase in the proportion of acute liver failure cases attributed to acetaminophen from 28% in 1998 to 51% in 2003, far exceeding all other causes. Hepatic injury after acute acetaminophen overdose may be averted by timely administration of acetylcysteine; however, the optimal dose, route, and duration of acetylcysteine therapy remain unknown despite more than 30 years of experience with this antidote.

In 1985, the US Food and Drug Administration (FDA) approved a 72-hour oral protocol, the efficacy of which was supported by the results of the US National Multicenter Study, a prospective cohort study of 2,023 patients treated with this regimen. Outside the United States, acetylcysteine has predominantly been administered by the 20-hour intravenous protocol, which the FDA approved in 2004 for use in the United States. Although no direct comparative study data exist, previous landmark studies suggested the 2 regimens yield comparable results when started within 8 to 10 hours postingestion but that the 72-hour protocol might be better after this time. Conversely, after pooling available data involving both 20-hour and 48-hour intravenous regimens, 2 systematic reviews concluded that intravenous and oral acetylcysteine are similar in effectiveness.

Importance
To our knowledge no trials have been published that directly compare the 20-hour intravenous and 72-hour oral acetylcysteine therapies. For patients in whom the 2 protocols are comparably effective, a potential advantage of the 20-hour regimen is reduction in hospital costs because of decreased length of stay. However, since the approval of intravenous acetylcysteine in the United States, there have been reports of hepatic injury attributed to premature discontinuation of the 20-hour protocol. Consequently, it is important to more accurately describe the relative effectiveness of these 2 regimens with respect to time to initiation of therapy after an acute single acetaminophen overdose.

Goals of This Investigation
The purpose of the Canadian Acetaminophen Overdose Study was to compare outcomes after acute acetaminophen overdose in a large cohort of patients treated with the 20-hour intravenous acetylcysteine protocol to outcomes in the National Multicenter Study data set of patients treated with the 72-hour oral acetylcysteine protocol. We hypothesized that there would be no difference between the 2 protocols in their ability to prevent hepatotoxicity (peak aminotransferase level > 1,000 IU/L) in patients with potentially toxic serum acetaminophen concentrations measured between 4 and 24 hours after an acute overdose. We also wished to determine how time to initiation of acetylcysteine therapy might affect the relative effectiveness of the 2 treatment regimens. Finally, we studied the incidence of death or referral for liver transplant as a result of acetaminophen toxicity, and the incidence of anaphylactoid reactions to intravenous acetylcysteine.

Materials and Methods

Study Design and Setting
We performed a retrospective cohort study comparing patients with an acute acetaminophen overdose for whom the 20-hour intravenous acetylcysteine protocol was initiated in 34 Canadian hospitals against patients treated with the 72-hour oral acetylcysteine regimen who were previously enrolled in the National Multicenter Study. The Canadian data were collected from July 1999 to November 2005 and included patients admitted between 1980 and 2005. Patient enrollment in the National Multicenter Study occurred from September 1976 to February 1985. The current study was approved by the research ethics boards of all participating Canadian hospitals, and the
need for informed consent was waived. Community, tertiary, adult, pediatric, and transplant centers were represented in both the 20- and 72-hour groups.

Selection of Participants

We performed a structured medical record review of all patients admitted between 1980 and 2005 for acetaminophen poisoning at participating hospitals in 8 Canadian cities. Patients with acetaminophen poisoning as their primary or secondary discharge diagnosis were identified with the International Classification of Diseases codes 965.4 (9th revision, poisoning by aromatic analgesic) and T39.1 (10th revision, poisoning by nonopioid analgesics, antipyretics, and antirheumatics [4-aminophenol derivatives]), as previously described in a secondary analysis involving the Canadian Acetaminophen Overdose Study data set.9

We used the same inclusion criteria used by the investigators of the National Multicenter Study.3 Patients with an acute acetaminophen overdose (ingestion during less than an 8-hour period) were eligible. Subjects were required to have a potentially toxic serum acetaminophen concentration, defined as a concentration obtained between 4 and 24 hours after ingestion that fell on or above the nomogram treatment line starting at 150 µg/mL (993 µmol/L) at 4 hours.10 Patients had to have the 20-hour intravenous protocol initiated between 4 and 24 hours after their ingestion and administered as a 150 mg/kg infusion over 15 to 60 minutes, 50 mg/kg over 4 hours, and 100 mg/kg over 16 hours. To ensure that we identified the presence or absence of hepatotoxicity, patients were required to have one of the following criteria, along with a known clinical outcome: an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level greater than 1,000 IU/L at any time, an AST or ALT level below 100 IU/L measured between 36 and 72 hours after ingestion, or any AST or ALT value measured between 72 and 96 hours postingestion.

The 72-hour oral acetylcysteine group was obtained from the National Multicenter Study data set. This prospective cohort study occurred from September 1976 to February 1985 and was coordinated by the Rocky Mountain Poison and Drug Center in Denver, CO. Hospitals in all 50 states were involved. Patients were considered eligible if they had either a potentially toxic acetaminophen concentration between 4 and 24 hours after their ingestion (a concentration that fell on or above the nomogram treatment line starting at 150 µg/mL [993 µmol/L] at 4 hours) or had an estimated ingestion of 7.5 g (adult) or 140 mg/kg (child). A total of 2,023 of these patients had a potentially toxic serum acetaminophen concentration and were treated with the 72-hour oral protocol (140 mg/kg followed by 70 mg/kg every 4 hours for 17 doses) between 4 and 24 hours after their ingestion. Serum aminotransferase levels, electrolyte levels, and coagulation profile were followed at least once daily, according to the study protocol.10 Further details on the methodology of the National Multicenter Study have been described previously.3,10,11

Data Collection and Processing

For the 20-hour group, a 75-variable data collection form was pilot-tested for interobserver agreement on 50 randomly selected selected charts until agreements on continuous variables and κ coefficients exceeded 80% and 0.8, respectively. One investigator (M.C.Y.) trained 1 to 3 medical record reviewers (health record analysts or medical students) at each participating site until percentage agreements exceeded 80% and κ coefficients exceeded 0.8 on a random subset of at least 50 records per reviewer. In total, 19 reviewers were involved in data abstraction, and all were blinded to the study hypothesis. Performance monitoring was achieved by independent review of the first 100 charts for each data abstractor, followed by quarterly database assessment for the duration of data collection.

Explicit a priori definitions were used for all subjective variables. In the 20-hour group, time of ingestion was obtained by review of out-of-hospital, emergency department, and inpatient notes. In the event that multiple times or intervals were listed in the record, the earliest time was used as the time of ingestion. Acute ethanol ingestion was defined as consumption of ethanol within the same period as the overdose. Chronic ethanol ingestion was defined as the presence of any of the following terms in the record: chronic alcoholic, chronic alcohol intake, binge drinker, 2 or more drinks per day, repeated alcohol intake, or alcohol abuse. Anaphylactoid reactions were defined as any episodes of pruritus, urticaria, facial flushing, edema, stridor, shortness of breath, wheezing, cough, or low blood pressure associated with the acetylcysteine infusion. For the 72-hour group, acute ethanol ingestion was defined as consumption of ethanol within the same period as the overdose, and chronic ethanol ingestion was defined as the consumption of ethanol for longer than the period of the overdose.

Outcome Measures

The primary outcome was hepatotoxicity, defined in the traditional manner as a peak serum AST or ALT level greater than 1,000 IU/L and as defined in the National Multicenter Study.3,4 Secondary outcomes included death or referral for liver transplant as a result of acetaminophen toxicity and the incidence of anaphylactoid reactions to intravenous acetylcysteine. Anaphylactoid reactions to oral acetylcysteine had not been assessed in the National Multicenter Study. With established criteria,2 all deaths in the 20-hour group were reviewed by 3 independent medical toxicologists to judge whether the death was a result of acetaminophen-induced hepatic failure or other causes.

Primary Data Analysis

According to the previous publication of the National Multicenter Study data,3 we were aware that there were approximately 2,000 patients in the 72-hour group and a 15% rate of hepatotoxicity. We planned to identify an equal number of eligible patients treated with the 20-hour protocol, which
would provide 80% power to detect an absolute difference of 3.3% or greater in the incidence of hepatotoxicity between groups according to a 2-tailed test of proportions with a significance level of .05.

The analysis of the primary outcome was performed by binary regression for relative risk (RR) with adjustment for factors thought to influence the risk of hepatic injury. These prespecified factors were age, time from ingestion to treatment with acetylcysteine, acute and chronic ethanol ingestion, acetaminophen concentration, and sex. Acetaminophen concentrations obtained after 4 hours postingestion were extrapolated to a 4-hour concentration, assuming a 4-hour elimination half-life. The extrapolated 4-hour concentration was tested in the model both as a continuous and categorical variable; results were grouped into 5 mutually exclusive, ordered categories that corresponded to treatment lines of 150, 200, 300, 400, and 500 µg/mL (993, 1,324, 1,986, 2,648, and 3,310 µmol/L). The interaction between time to acetylcysteine therapy and treatment protocol was examined to assess whether the difference in efficacy between the 2 protocols changed with increasing delay to initiation of acetylcysteine therapy. For the purposes of the binary regression analysis, time to treatment was considered a continuous variable from 4 to 24 hours postingestion, and subjects with unknown age were excluded. The R Project for Statistical Computing (available at http://www.r-project.org/) was used for statistical analysis.

Analysis was by intention to treat, meaning any patient for whom the 20-hour protocol was initiated was included, regardless of duration of treatment or conversion to the 72-hour protocol. This was done to avoid excluding patients for whom intravenous acetylcysteine infusions were continued for more than 20 hours because of increasing aminotransferase concentrations.

Baseline characteristics are reported as median with interquartile range or mean with SD, as appropriate, with 95% confidence intervals (CIs) for the difference. In the case of medians, the CIs were calculated with the method of Bauer. Differences between groups were analyzed with Wilcoxon’s test, χ² test, or Fisher’s exact test, as appropriate. Outcome measures are reported as point estimates with 95% CI. Binary regression results are reported as RR with 95% CI. For clarity, times from ingestion to treatment with acetylcysteine are rounded to the nearest hour.

Sensitivity Analyses

The definitions of acute and chronic ethanol ingestion in both the 20- and 72-hour groups involved subjective interpretation. Because of the qualitative nature of these definitions and the differences in the definition of chronic ethanol ingestion between groups, we performed a sensitivity analysis on the effects of removing acute or chronic ethanol use from the model.

RESULTS

Characteristics of Study Subjects

There were 11,987 hospital admissions retrieved during the Canadian chart review and 11,195 patients enrolled in the National Multicenter Study. A total of 2,086 patients in the 20-hour intravenous and 1,962 patients in the 72-hour oral groups met inclusion criteria. Of the 2,086 patients in the 20-hour intravenous group, 2,073 were admitted after February 1985, the enrollment termination date for the National Multicenter Study. Of the 2,023 patients reported in the primary publication from the National Multicenter Study, 61 were treated with acetylcysteine before a 4-hour acetaminophen concentration was obtained and were excluded from this analysis (Figure 1).

Table 1 summarizes the characteristics of the patients in each group. There were statistically significant differences between the groups for age, time to treatment with acetylcysteine, median extrapolated 4-hour acetaminophen concentration, and reported acute and chronic ethanol use.

Main Results

Table 2 shows the outcomes for patients in both groups. The unadjusted incidence of hepatotoxicity was 13.9% in the 20-hour intravenous group and 15.8% in the 72-hour oral group, a difference that was not significant (−1.9% absolute difference; 95% CI −4.2% to 0.3%). One (20-hour) and 3 (72-hour) deaths were attributed to acetaminophen-induced hepatic failure. The patient who died and was in the 20-hour group had acetylcysteine therapy initiated 20.5 hours after ingestion. The infusion continued for 100 hours, and the patient received a...
liver transplant for persistent coagulopathy and encephalopathy. The 3 deaths in the 72-hour group were patients for whom acetylcysteine was initiated 19.5, 20, and 24 hours after ingestion.

**Figure 2** displays the RRs for hepatotoxicity after adjusting for treatment protocol, age, sex, time from ingestion to treatment with acetylcysteine, acute and chronic ethanol ingestion, and acetaminophen concentration. In the final regression model, acetaminophen concentration was represented categorically as previously described in the “Materials and Methods.” Two patients in the 20-hour group and 6 in the 72-hour group were of unknown age and were excluded from this analysis. An interaction between time to treatment and protocol group on hepatotoxicity was observed. For patients treated with acetylcysteine before 12 hours postingestion, the risk of hepatotoxicity was significantly lower in the 20-hour group (RR 0.54, 95% CI 0.38 to 0.75 at 4 hours; RR 0.84, 95% CI 0.71 to 1.00 at 12 hours 12 minutes). No significant difference was observed when treatment was initiated from 12 to 18 hours postingestion. When acetylcysteine was commenced beyond 18 hours postingestion, a significantly greater risk of hepatotoxicity was observed in the 20-hour group (RR 1.19, 95% CI 1.00 to 1.40 at 18 hours 27 minutes; RR 1.61, 95% CI 1.22 to 2.12 at 24 hours). Although both acute and chronic ethanol ingestion were significant predictors of hepatotoxicity, removing them from the

**Table 1.** Patient characteristics by study group.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>20-Hour Intravenous (n=2,086)</th>
<th>72-Hour Oral (n=1,962)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (IQR)</td>
<td>21.0 (15.0)</td>
<td>20.0 (11.0)</td>
<td>1.0 (1.0 to 4.0)</td>
</tr>
<tr>
<td>Sex, female, No. (%)</td>
<td>1,497 (71.8)</td>
<td>1,365 (69.6)</td>
<td>2.2 (0.7 to 5.1)</td>
</tr>
<tr>
<td>Acute ethanol ingestion, No. (%)</td>
<td>525 (25.2)</td>
<td>31 (1.6)</td>
<td>23.6 (21.6 to 25.6)</td>
</tr>
<tr>
<td>Chronic ethanol ingestion, No. (%)</td>
<td>339 (16.1)</td>
<td>81 (4.1)</td>
<td>12.0 (10.2 to 13.9)</td>
</tr>
<tr>
<td>Reported acetaminophen dose ingested, g, median (IQR)</td>
<td>20.0 (22.5)</td>
<td>22.5 (15.0)</td>
<td>–2.5 (–4.0 to 1.0)</td>
</tr>
<tr>
<td>Median extrapolated 4-h acetaminophen concentration, μg/mL (IQR)</td>
<td>280.3 (217.1)</td>
<td>260 (198.7)</td>
<td>20.3 (12.1 to 31.7)</td>
</tr>
</tbody>
</table>

**Patients in categories based on extrapolated 4-h acetaminophen concentration, No. (%)**

<table>
<thead>
<tr>
<th>Concentration</th>
<th>20-Hour Intravenous</th>
<th>72-Hour Oral</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150-200 μg/mL</td>
<td>497 (23.8)</td>
<td>538 (27.4)</td>
<td>–3.6% (–6.3% to 0.9%)</td>
</tr>
<tr>
<td>200-300 μg/mL</td>
<td>653 (31.3)</td>
<td>659 (33.6)</td>
<td>–2.3% (–5.2% to 0.7%)</td>
</tr>
<tr>
<td>300-400 μg/mL</td>
<td>371 (17.8)</td>
<td>289 (14.7)</td>
<td>3.1% (0.7% to 5.4%)</td>
</tr>
<tr>
<td>400-500 μg/mL</td>
<td>182 (8.7)</td>
<td>155 (7.9)</td>
<td>0.8% (–0.9% to 2.6%)</td>
</tr>
<tr>
<td>&gt; 500 μg/mL</td>
<td>383 (18.4)</td>
<td>321 (16.4)</td>
<td>2.0% (–0.4% to 4.4%)</td>
</tr>
<tr>
<td>Median time from ingestion to start of acetylcysteine therapy, h (IQR)</td>
<td>8.8 (8.8)</td>
<td>11.5 (7.5)</td>
<td>–2.7 (–3.4 to –2.5)</td>
</tr>
</tbody>
</table>

**Outcome by study group.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>20-Hour Intravenous (n=2,086)</th>
<th>72-Hour Oral (n=1,962)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity, No. (%)*</td>
<td>289 (13.9)</td>
<td>310 (15.8)</td>
<td>–1.9% (–4.2% to 0.3%)</td>
</tr>
<tr>
<td>Median peak aminotransferase level, IU/L (IQR)</td>
<td>33.0 (66.5)</td>
<td>48.0 (275.0)</td>
<td>–15.0 IU/L (–21.0 to –13.0)</td>
</tr>
<tr>
<td>Death, No. (%)†</td>
<td>2 (0.1)</td>
<td>5 (0.3)</td>
<td>–0.2% (–0.5% to 0.2%)</td>
</tr>
<tr>
<td>Fatal exposure, No. (%)‡</td>
<td>1 (0.1)</td>
<td>3 (0.2)</td>
<td>–0.1% (–0.4% to 0.1%)</td>
</tr>
</tbody>
</table>

*AST or ALT level greater than 1.000 IU/L.
†All-cause mortality in both groups.
‡Death or liver transplant attributed to the acetaminophen exposure.
model did not affect these results. Of the 199 patients in the 20-hour group treated after 18 hours postingestion, 119 were treated for 20 hours, 7 for fewer than 20 hours (range 1 to 18 hours), and 73 for more than 20 hours (range 22 to 210 hours).

Anaphylactoid reactions to intravenous acetylcysteine were reported in 148 of 2,086 patients (7.1%; 95% CI 6.1% to 8.3%). Of these, 114 were only cutaneous reactions (urticaria, pruritus, edema, facial flushing), 7 were only systemic (respiratory symptoms, hypotension), 26 were both cutaneous and systemic, and 1 was documented as a reaction, but no clinical features were recorded in the medical record. Seventy-five patients had their infusion stopped (transiently or permanently). There were no deaths as a result of anaphylactoid reactions.

LIMITATIONS

Our study has several limitations. We compared retrospective hospital records to prospectively collected data collected from different times and jurisdictions. Improvements in both supportive care and the diagnosis and management of acetaminophen poisoning during the study periods and other confounders not accounted for in the analysis, such as preexisting liver disease, may have contributed to the observed differences between groups. By using enrollment criteria, definitions, and operating protocols that differed in both route and duration precludes comparison of which variable influences outcome. Finally, our definition of hepatotoxicity is a surrogate for more clinically important but rare outcomes such as fulminant hepatic failure or death.

DISCUSSION

The interval between ingestion and treatment is an important predictor of outcome after acetaminophen overdose, in part because the efficacy of acetylcysteine decreases if treatment is initiated after 8 hours postingestion. Our results suggest that the most effective acetylcysteine protocol varies with the time between ingestion and treatment. Specifically, our data support the initiation of the 20-hour intravenous protocol for patients who can be treated before 12 hours postingestion. Differences in outcome were not statistically significant between the 2 groups from 12 to 18 hours postingestion. Beyond 18 hours postingestion, our results support the initiation of the 72-hour oral protocol.

Differences in kinetics between intravenous and oral acetylcysteine may account for the apparent superiority of intravenous acetylcysteine when started before 12 hours postingestion. Although measuring total acetylcysteine serum concentrations is challenging given that acetylcysteine exists in both free and bound forms in serum, acetylcysteine concentrations peak earlier and are much higher after intravenous administration. Intravenous administration avoids the unpleasant smell and taste of oral acetylcysteine, which often results in vomiting and necessitates coadministration of antiemetics, possibly delaying acetylcysteine absorption. The critical serum and hepatic acetylcysteine concentrations required to protect against hepatotoxicity vary with both the absorbed acetaminophen dose and N-acetyl-p-benzo-quinone imine production. Because these variables were not measured in our study, the importance of antidote kinetics remains speculative.

Our data suggest that the 20-hour intravenous protocol is sufficient for some patients presenting early after their ingestion, a finding consistent with that of other reports. Oral
Acetylcysteine protocols shorter than 72 hours have been studied and also found to be effective in preventing hepatotoxicity after acute acetaminophen overdose. Whether intravenous acetylcysteine protocols shorter than 20 hours are effective in preventing hepatotoxicity and might obviate the need for hospital admission is a subject for future research.

In our study, the relative efficacy of the 20-hour intravenous protocol declined with increasing delay to treatment. Differences between protocols in treatment duration (20 versus 72 hours), total dose administered (300 mg/kg versus 1,330 mg/kg), and maintenance dose (6.25 mg/kg per hour versus 17.5 mg/kg per hour) may explain the apparent advantage of the 72-hour oral protocol after 18 hours postingestion. It has long been presumed that oral acetylcysteine would produce higher hepatic concentrations because of first-pass flow from the splanchnic circulation. However, it is unclear whether administration of acetylcysteine by the oral route also contributed to the improved outcomes in these late-presenting patients.

The oral acetylcysteine treatment protocol for the National Multicenter Study was initially intended to be 20 hours in duration at a dose of 6 mg/kg per hour. This dose was determined with the following assumptions: a body weight of 70 kg, an average-sized (1.5 L) liver containing 6 mmol glutathione, 70% depletion of glutathione required to cause hepatic damage, a 4-hour acetaminophen elimination half-life, and an absorbed acetaminophen dose of 15.9 g. After safety discussions with the FDA, the oral acetylcysteine dose was increased to 17.5 mg/kg per hour and treatment duration extended to 72 hours. In our study, it is possible that late-presenting patients benefited from both the increased dose and treatment duration provided by the 72-hour oral protocol.

With intravenous acetylcysteine available in the United States since 2004, do our results mean that clinicians should administer acetylcysteine orally in late-presenting patients? Conceivably, other existing intravenous protocols may be comparable to the 72-hour oral protocol in late-presenting patients. Benefited from both the increased dose and extended to 72 hours. In our study, it is possible that late-presenting patients benefited from both the increased dose and treatment duration provided by the 72-hour oral protocol.

With intravenous acetylcysteine available in the United States since 2004, do our results mean that clinicians should administer acetylcysteine orally in late-presenting patients? Conceivably, other existing intravenous protocols may be comparable to the 72-hour oral protocol in late-presenting patients. Some clinicians recommend increasing either the dose or duration of the third infusion of the 20-hour protocol (6.25 mg/kg per hour) to provide longer therapy for patients with increasing aminotransferase levels, coagulopathy, ongoing measurable acetaminophen levels, or anticipated delayed absorption of acetaminophen. The 48-hour intravenous protocol provides the same dosing intensity as the first 48 hours of the 72-hour protocol, although hepatotoxicity may still be less likely with 72 hours of therapy. Finally, administering the 72-hour protocol intravenously is used anecdotally, although no data exist to support such a practice. Although our study was not designed to assess these other intravenous protocols, our results suggest that the 20-hour intravenous protocol may be less effective than the 72-hour oral protocol for patients presenting late after acute acetaminophen ingestion. Of note, the FDA approvals of both oral and intravenous acetylcysteine are silent on its use in patients who present more than 24 hours after their ingestion, although continuing the third infusion of the 20-hour intravenous protocol until recovery from encephalopathy or death has been recommended for patients with acetaminophen-induced fulminant hepatic failure. Further research is required to determine the optimal acetylcysteine dose and treatment duration for late-presenting patients.

We also observed that anaphylactoid reactions to intravenous acetylcysteine are primarily cutaneous and usually not life threatening. Our incidence of anaphylactoid reactions is higher than one report from the United States and lower than other reports from Australia, Denmark, the United States, and the United Kingdom, which may be due to the higher incidence of reactions observed with prospective studies, varying definitions of anaphylactoid reactions, and differences in the infusion rate of the first, or loading, dose of intravenous acetylcysteine. Because data on anaphylactoid reactions were not available for the 72-hour group, we were unable to compare rates of adverse outcomes between groups.

To our knowledge, this is the largest study reporting the effectiveness and safety of intravenous acetylcysteine and is the only direct comparison between these 2 treatment regimens ever performed. Other attempts to compare the 2 treatment regimens have pooled 20- and 48-hour intravenous data from multiple studies, limiting the conclusions that can be made about the effectiveness of the 20-hour intravenous protocol. Our study is unique in suggesting that the most appropriate acetylcysteine regimen may depend on the interval between ingestion and initiation of acetylcysteine therapy. This finding is consistent with our understanding of the pathophysiology of acetaminophen poisoning and its antidotal therapy.

In conclusion, the comparison of Canadian patients who began receiving the 20-hour intravenous acetylcysteine protocol with the historical cohort of US patients treated with the 72-hour oral protocol suggests that for individuals presenting early after an acute acetaminophen overdose, the risk of hepatotoxicity was lower when the 20-hour intravenous acetylcysteine protocol was initiated. With increasing delay to treatment, the risk of hepatotoxicity was lower when the 72-hour oral protocol was administered. No difference was observed between the groups with respect to death or liver transplant.

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