

## Evaluation of an Alternative Intravenous N-Acetylcysteine Regimen in Pediatric Patients

Kathryn A. Pauley, PharmD,<sup>1</sup> Tracy L. Sandritter, PharmD,<sup>2</sup> Jennifer A. Lowry, MD,<sup>2</sup> and D. Adam Algren, MD<sup>2</sup>

<sup>1</sup>Department of Pharmacy, Children's Mercy Hospital, Kansas City, Missouri, <sup>2</sup>Division of Clinical Pharmacology and Therapeutic Innovations, Children's Mercy Hospital, Kansas City, Missouri

**OBJECTIVE:** Conventionally, intravenous N-acetylcysteine (IV-NAC) administration is a 3-bag regimen administered over the course of 21 hours, which increases the risk of reconstitution and administration errors. To minimize errors, an alternative IV-NAC regimen consists of a loading dose (150 mg/kg) followed by a maintenance infusion (15 mg/kg/hr) until termination criteria are met. The aim was to determine the clinical outcomes of an alternative IV-NAC regimen in pediatric patients.

**METHODS:** A retrospective review of pharmacy dispensing records and diagnostic codes at a pediatric hospital identified patients who received alternative IV-NAC dosing from March 1, 2008, to September 10, 2012, for acetaminophen overdoses. Exclusion criteria included chronic liver disease, initiation of oral or other IV-NAC regimens, and initiation of standard IV-NAC infusion prior to facility transfer. Clinical and laboratory data were abstracted from the electronic medical record. Descriptive statistics were utilized. Clinical outcomes and adverse drug reaction incidences were compared between the alternative and Food and Drug Administration (FDA)-approved IV-NAC regimens.

**RESULTS:** Fifty-nine patients (mean age  $13.4 \pm 4.3$  years; range: 2 months-18 years) with acetaminophen overdoses were identified. Upon IV-NAC discontinuation, 45 patients had normal alanine transaminase (ALT) concentrations, while 14 patients' ALT concentrations remained elevated (median 140 units/L) but were trending downward. Two patients (3.4%) developed hepatotoxicity (aspartate transaminase/ALT > 1000 units/L). No patients developed hepatic failure, were listed for a liver transplant, were intubated, underwent hemodialysis, or died. Two patients (3.4%) developed anaphylactoid reactions. No known medication or administration errors occurred. Clinical outcome incidences of the studied endpoints with the alternative IV-NAC regimen are at the lower end of published incidence ranges compared to the FDA IV-NAC regimen for acetaminophen overdoses.

**CONCLUSIONS:** This alternative IV-NAC regimen appears to be effective and well tolerated among pediatric patients when compared to the FDA-approved regimen. It may also result in fewer reconstitution and administration errors, leading to improved patient safety.

**INDEX TERMS:** acetaminophen, anaphylactoid, hepatotoxicity, N-acetylcysteine, pediatrics

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### INTRODUCTION

Acetaminophen, which is available in hundreds of single-ingredient and combination products, is the most common drug taken in overdoses around the world as a result of its

*see Editorial on page 160*

extensive availability and low cost.<sup>1</sup> Intravenous N-acetylcysteine (IV-NAC) is approved by the Food and Drug Administration (FDA) for the treatment of acetaminophen overdoses. The

FDA-approved IV-NAC dosing regimen consists of a loading dose of 150 mg/kg infused over 60 minutes, followed by a second dose of 50 mg/kg infused over 4 hours (12.5 mg/kg/hr), and finally, a third dose of 100 mg/kg infused over 16 hours (6.25 mg/kg/hr).<sup>2</sup> Each administered dose has different mg/kg dosing, additive volumes, and infusion rates.

Although the FDA-approved dosing regimen is effective and safe, the complex 3-step process is associated with an increased risk of medication errors.<sup>3,4</sup> In a retrospective chart review, Hayes et

al<sup>3</sup> reported 84 medication errors in 74 patients (33%), including incorrect dose (1.4%), greater than 1 hour of interruption in therapy (18.6%), incorrect infusion rate (5%), and unnecessary administration (13.1%). Another study<sup>4</sup> collected samples of IV-NAC–reconstituted solutions before and after infusion of acetylcysteine in 66 patients and analyzed the samples by lab assay; the chance of dosing calculations was estimated to be 5%, measurement of acetylcysteine was estimated to be 3%, and inadequate mixing was estimated to be 9%.

To minimize errors, alternative dosing regimens with simpler reconstitution and mixing processes as well as easier administration steps have been utilized. A retrospective chart review evaluated an alternative dosing regimen in adult patients that consisted of a 150 mg/kg loading dose administered over 60 minutes followed by an infusion of 14 mg/kg/hr for 20 hours.<sup>5</sup> This study found the alternative dosing regimen safe and effective; however, this regimen has not been studied in the pediatric population.

An alternative IV-NAC dosing regimen at a pediatric hospital consists of a loading dose of 150 mg/kg over 60 minutes followed by a maintenance infusion of 15 mg/kg/hr until the serum acetaminophen concentration measures less than 10 mg/L and the serum concentration of liver enzymes remain normal or are trending downward. The main difference between the FDA-approved IV-NAC regimen and the alternative IV-NAC dosing regimen at the pediatric hospital is the maintenance infusion dose. The purpose of the study was to determine the clinical outcomes of an alternative IV-NAC regimen in the treatment of acetaminophen overdoses in pediatric patients.

## METHODS

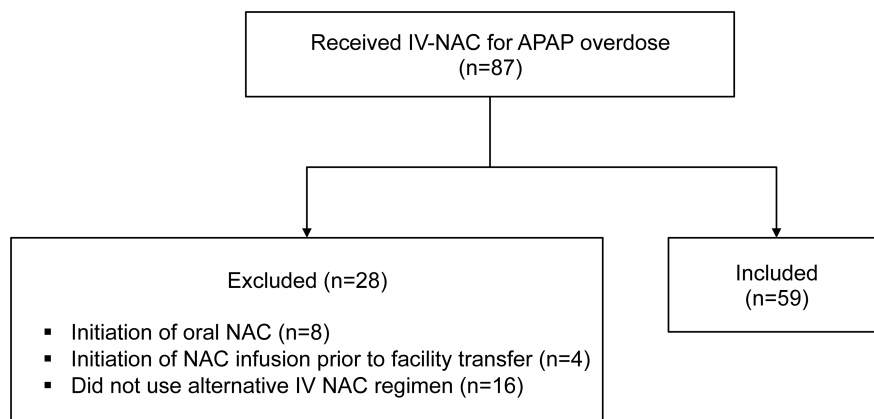
### Study Design

This study is a retrospective chart review of pediatric patients who received IV-NAC according to the dosing regimen recommended by the Section of Clinical Toxicology at a pediatric institution. All pediatric patients (newborn to 18 years) who received the alternative IV-NAC dosing regimen for the treatment of acute and chronic acetaminophen overdoses from March 1, 2008, to September 10, 2012, were eligible for inclusion. Indications for administration

of NAC were determined by the nature of the overdose. Acute acetaminophen overdoses received IV-NAC treatment if the serum acetaminophen concentration plotted above the lower treatment line of the Rumack Matthew Nomogram.<sup>6,7</sup> Chronic overdoses, defined as ingestions occurring over more than 8 hours, were assessed for risk based on the American Association of Poison Control Centers' consensus guideline.<sup>6,7</sup> Patients who were considered at risk underwent laboratory testing and were treated with IV-NAC if the serum aspartate transaminase (AST) or serum alanine transaminase (ALT) were abnormal or if the serum acetaminophen concentration was greater than 10 mg/L. This criterion was chosen because it has been shown to be safe and sensitive in determining the development of hepatotoxicity in chronic ingestions.<sup>8</sup> Exclusion criteria included the presence of chronic liver disease, initiation of oral or other IV-NAC regimens, and initiation of the standard 4- or 16-hour NAC infusion prior to facility transfer. Reasons for patient exclusion were collected. Patients were identified by pharmacy dispensing records and International Classification of Diseases, Ninth Revision (ICD-9), codes. Institutional Review Board approval was obtained.

The traditional NAC maintenance dosing of 6.25 mg/kg/hr may not be adequate in all overdose patients. There is evidence that the plasma concentration of NAC continues to decline even on maintenance dosing.<sup>9,10</sup> Thus, in patients with large ingestions the typical dosing may be inadequate to detoxify ongoing N-acetyl-*p*-benzoquinone imine (NAPQI) production and replenish glutathione stores. The Section of Medical Toxicology therefore chose to use only a larger dose of NAC (15 mg/kg/hr) for acetaminophen overdoses. This was done to eliminate situations in which individual physicians have to decide when the NAC dose should be increased, thereby attempting to limit the risk of inadequate NAC dosing.

Patients were classified as early or late presentations. Early presentations were defined as patients who received the loading dose of IV-NAC less than or equal to 8 hours from the acute overdose, while late presentations were defined as patients who received the loading dose of IV-NAC more than 8 hours after the acute overdose.<sup>7</sup> Major clinical outcomes included the



**Figure 1.** Study sample.

development of hepatotoxicity, hepatic failure, kidney failure, referral for liver transplant, and mortality rate. Hepatotoxicity was defined as serum AST or ALT concentrations greater than 1000 units/L. Monitoring parameters to evaluate the clinical outcomes of the alternative regimen included serum AST concentrations, serum ALT concentrations, encephalopathy grade, ammonia concentrations, international normalized ratios (INR) values, administration of blood products or vitamin K, serum creatinine concentrations, and initiation of hemodialysis. All documented adverse reactions and their treatment were recorded and reviewed.

#### **Data Collection and Analysis**

Clinical and laboratory data were abstracted by a single investigator from the electronic medical record using a standardized data collection tool and were imported into Excel; all patient information was deidentified. Any discrepancies regarding the data were adjudicated by 2 of the other authors until a consensus was reached. Baseline demographic characteristics, length of the IV-NAC continuous infusion, and length of stay were collected.

Descriptive statistics were used to analyze the data. Clinical outcomes were assessed based on comparison to published literature that utilized the FDA-approved IV-NAC regimen. Additionally, the clinical outcomes of the alternative IV-NAC dosing regimen in the pediatric population were compared to those in the published literature of the alternative IV-NAC dosing regimen in the adult population.

## **RESULTS**

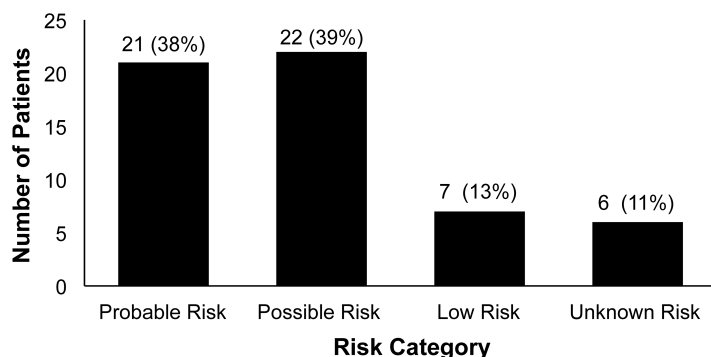
### **Patient Characteristics**

Intravenous N-acetylcysteine was dispensed to 87 patients from March 1, 2008, through September 10, 2012, at the pediatric hospital. Of the patients who received this IV-NAC, 28 were excluded, while 59 patients met the inclusion criteria (Figure 1). The mean

age was  $13 \pm 4.3$  years and the median age was 14 years (range, 2 months-18 years), with 49 females and 10 males.

Three patients (5.1%) presented with chronic overdoses and 56 patients (94.9%) presented with acute overdoses. In the acute overdoses, the reported average dose ingested was  $13.5 \pm 11.0$  g (median 10 g; range, 2-50 g), or 248.8 mg/kg. In children less than 12 years old, the reported average dose ingested was  $3.8 \pm 1.5$  g (median 3.75 g; range, 2-6 g), or 229 mg/kg, while in children greater than 12 years old, the reported average dose ingested was  $14.8 \pm 11.2$  g (median 10 g; range, 2.5-50 g), or 248 mg/kg. Doses were based on patient-reported information, with the highest maximum possible dose recorded. In 16 patients doses were unknown; therefore, these patients were not included in the data analysis of the dose ingested.

Of the 59 patients, 49 patients were intentional overdoses and 10 patients were unintentional overdoses. Other medications were ingested in addition to acetaminophen in 35 patients, with 4 of these being unintentional overdoses. These medications included ibuprofen, diphenhydramine, caffeine, aspirin, dextromethorphan, chlorpheniramine, pyrilamine, antidepressants (sertraline, citalopram, and paroxetine), anti-psychotics (quetiapine and risperidone), benzodiazepines, hydrocodone, and oxycodone. Diphenhydramine was a co-ingested medication in 11 patients. Diphenhydramine was separated from other co-ingested medications since it is an anticholinergic and has been associated with delayed absorption of acetaminophen.<sup>11,12</sup>



**Figure 2.** Number of patients by risk category (n = 56).

### Patient Severity

Risk of hepatic injury was assessed using the Rumack Matthew Nomogram in the 56 patients with acute overdoses (Figure 2). Of the patients categorized as low risk, 4 patients had IV-NAC discontinued following toxicology consults, and 3 patients had extended treatment as a result of elevations in serum ALT or AST concentrations, although the serum acetaminophen concentration was less than 10 mg/L. Of the 6 patients with unknown risk, 4 patients had unknown ingestion times, 1 patient presented after 36 hours, and 1 patient would not state the time of the ingestion until the following day.

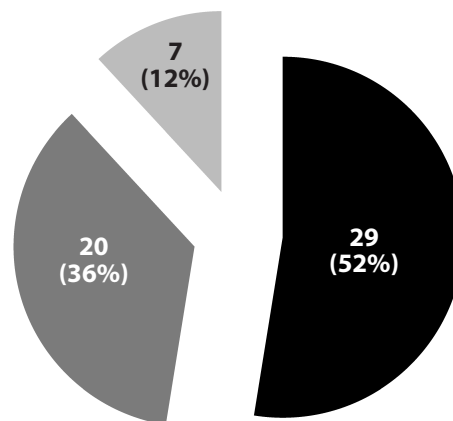
Patients with acute acetaminophen overdoses were classified as early or late presentations (Figure 3). Seven patients were not classified since 4 patients had unknown ingestion times and the time of the loading dose of IV-NAC could not be located in 3 patients' charts. Average IV-NAC infusion start time for patients with early presentations was  $5.2 \pm 2.7$  hours (median 5 hours; range, 2-8 hours), compared to  $13.6 \pm 8.6$  hours (median 12 hours; range, 8.25-26 hours) for patients who presented late. The mean duration of the IV-NAC continuous infusion was  $30 \pm 17.7$  hours (median 27 hours; range, 4.25-89 hours) (Figure 4). The mean duration of IV-NAC continuous infusion for acute overdoses was  $30.3 \pm 18.1$  hours (median 26.3 hours; range, 4.25-89 hours). Average time until serum acetaminophen concentrations reached less than 10 mg/L was  $31.5 \pm 9.7$  hours (median 32 hours; range, 0-58.5 hours).

Since co-ingesting diphenhydramine slows absorption of acetaminophen, serum acetaminophen concentrations may cross the hepatotoxicity line plotted on the Rumack Matthew Nomogram

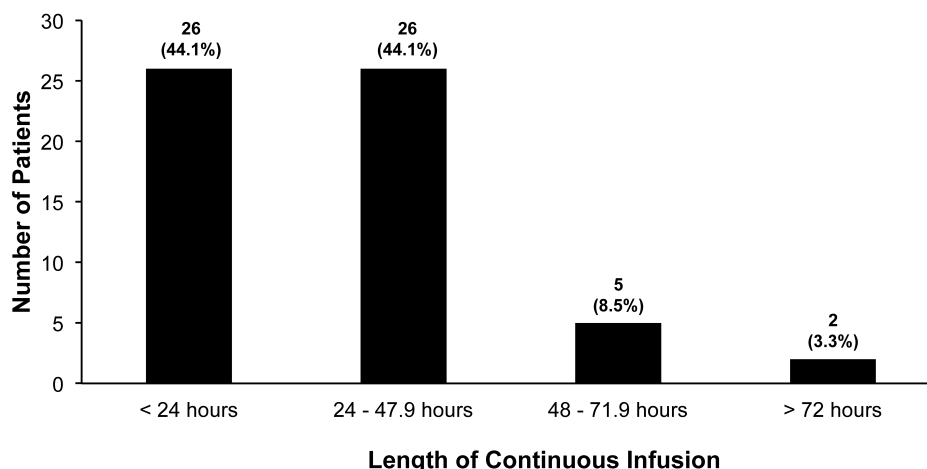
after the first 4-hour serum acetaminophen concentration; therefore, it is recommended that a second serum acetaminophen concentration be drawn 4 to 6 hours after the first 4-hour concentration. If the second serum acetaminophen concentration is still elevated, additional IV-NAC may be required.<sup>11,12</sup> The mean duration of the IV-NAC continuous infusion in patients who co-ingested diphenhydramine was  $36 \pm 23.6$  hours (median 31.75 hours; range, 10.75-89 hours). Of the 11 patients who co-ingested diphenhydramine, 9 patients did not experience an increase in serum acetaminophen concentrations following the initial concentration; 2 patients could not be assessed since they only had 1 serum acetaminophen concentration documented.

### Development of Hepatotoxicity

Hepatotoxicity (AST/ALT > 1000 units/L) developed in 2 patients (3.4%). One patient was a 14-year-old female who ingested 25 g of acetaminophen (213 mg/kg) and diphenhydramine with a serum acetaminophen concentration of 132 mg/L at 11 hours after ingestion. Her peak serum AST concentration was 746 units/L, and her peak serum ALT concentration was 1280 units/L. The second patient was a 17-year-old female who ingested 32 g of acetaminophen (319 mg/kg) with an unknown risk because her serum



**Figure 3.** Time from ingestion to treatment (n = 56). ■ = Late presentation (>8 hours); ■ = Early presentation (<8 hours); □ = Unknown presentation.



**Figure 4.** Intravenous N-acetylcysteine (IV-NAC) continuous infusion duration (n = 59).

acetaminophen concentration was less than 2 mg/L at 36 hours after ingestion. Her peak serum AST concentration was 1414 units/L, and her peak serum ALT concentration was 1428 units/L. Both patients were intentional acute overdoses and were classified as late presentations.

At the time of IV-NAC discontinuation, 44 patients had normal serum ALT concentrations, while in 15 patients serum ALT concentrations remained elevated but were trending downward. The median peak serum ALT concentration was 140 units/L (range, 64-1428 units/L). Hepatology was not consulted on any patient. No patients required liver transplantation.

#### **Documented Adverse Reactions**

Two patients (3.4%) developed minor anaphylactoid reactions, including flushing, facial redness, and itching. These reactions occurred at the end of the loading dose infusion of IV-NAC. Both patients were treated with intravenous diphenhydramine and completed the IV-NAC therapy without any further complications. One patient had asthma, with a serum acetaminophen concentration of less than 2 mg/L, while the other patient did not have asthma, with a serum acetaminophen concentration of 187.9 mg/L. Patients diagnosed with asthma and a history of allergies appear to be at a higher risk for development of anaphylactoid reactions.<sup>13,14</sup> Seven patients had asthma and did not have a documented adverse reaction.

#### **Additional Outcomes**

No patients developed hepatic failure. No pa-

tients developed encephalopathy or experienced an active bleed or received fresh frozen plasma, packed red blood cells, or vitamin K. No patients were intubated or underwent hemodialysis. No patients died. No known medication or administration errors were document-

ed in the electronic medical record. Access to reports to view medication errors was not allowed by the pediatric hospital.

## **DISCUSSION**

The traditional FDA-approved IV-NAC regimen is a 21-hour protocol; however, various studies<sup>15,16</sup> have examined different IV-NAC dosing and therapy durations ranging in length from 21 to 48 hours. Patient-tailored NAC therapy individualizes the duration of treatment with NAC based on the patient's risk of toxicity. A retrospective case series<sup>17</sup> evaluated a patient-tailored protocol based on serum acetaminophen and AST concentrations in 27 patients. No hepatotoxicity developed in patients treated for less than 36 hours with IV-NAC; however, these patients had NAC initiated within 10 hours of the acetaminophen overdoses. There was a lower incidence of hepatotoxicity in patients who presented late (>10 hours) and who received IV-NAC treatment for 80 to 164 hours based on the patient-tailored protocol compared to the FDA-approved IV-NAC regimen for 72 hours. Continued use of IV-NAC is important in patients with persistently elevated serum acetaminophen and AST/ALT concentrations or signs of hepatic injury.

A retrospective study<sup>5</sup> of an alternative IV-NAC regimen in an adult population found 69 (99%) of 70 patients were discharged home, while 1 patient died. Hepatotoxicity, defined as an AST value of >1000 units/L, occurred in 16 patients. One adverse reaction was attributed to the IV-NAC; the patient developed facial and truncal

**Table 1.** Comparison to FDA IV-NAC Regimen

Primary Endpoints	FDA-Approved Regimen, % <sup>14,16-24</sup>	Alternative Regimen, %
Development of hepatotoxicity	0–27.1	3.4
Development of encephalopathy	0–3.4	0
Development of active bleed, elevated PT/INR	7.3–8	0
Development of acute kidney failure	0–50	0
Received liver transplant	0.6–21	0
Mortality rate	0.2–6	0
Documented adverse reactions	0.2–20.8	3.4

FDA, Food and Drug Administration; IV-NAC, intravenous N-acetylcysteine; PT/INR, prothrombin/international normalized ratio

flushing with respiratory difficulty. The duration of therapy was  $25.6 \pm 17.8$  hours (range, 1–76.5 hours) and the length of stay was  $2.99 \pm 3.85$  days. The severity of patients was not reported.

The incidences of the studied endpoints with administration of the alternative IV-NAC dosing regimen are at the lower end of published incidence ranges with administration of the FDA IV-NAC regimen for acetaminophen overdoses. The incidences of outcomes between the alternative IV-NAC dosing regimen and the FDA IV-NAC regimen were compared (Table 1).<sup>16,18-25</sup> Published literature does not separate the data by pediatric and adult populations, and the ranges and comparison groups are widely variable.

Adverse drug reactions, mean duration of therapy, and length of stay were comparable between the adult and pediatric populations (Table 2). However, only 2 (3.4%) patients developed hepatotoxicity in the pediatric population at the pediatric hospital, which was lower than the number reported in the adult population. The average duration of the continuous infusion in the pediatric population was slightly longer than the duration in the adult population. It has been reported<sup>26</sup> that hepatotoxicity occurs less frequently

in young children; this finding is presumed to be secondary to increased sulfation in children. Long-term ethanol use, larger acetaminophen doses, or underlying hepatic disease may explain the differences in the rates of hepatotoxicity seen between children and adults.<sup>26</sup>

In pediatric patients, adverse reactions have occurred in 3% to 14% of patients with the FDA-approved IV-NAC regimen; adverse reactions include bronchospasms, injection site erythema, urticaria, fever, and rarely anaphylaxis and death. These adverse reactions are caused by the histamine-related response and more commonly occur when the largest dose of NAC is given, especially during the loading dose, and diminish with discontinued infusions or administration of antihistamines.<sup>16</sup> The incidence of adverse reactions with administration of the alternative IV-NAC regimen is at the lower end of the published incidence compared with administration of the FDA-approved IV-NAC regimen.

### Limitations

Limitations of the study include a retrospective study design, 13 patients classified as low or unknown risk on the Rumack Matthew Nomogram,

**Table 2.** Comparison to Alternative IV-NAC Regimen in the Adult Population

Primary Endpoints	Adults (n = 70) <sup>5</sup>	Alternative Regimen: Pediatrics (n = 59)
Hepatotoxicity	16 patients (22.8%)	2 patients (3.4%)
Adverse drug reaction	1 patient (1.4%)	2 patients (3.4%)
Death	1 patient (1.4%)	No patients (0%)
Duration of therapy	$25.6 \pm 17.8$ hr (range 1–76.5 hr)	$30 \pm 17.7$ hr (range 4.25–89 hr)
Length of stay	$2.99 \pm 3.85$ days	$2.7 \pm 1.2$ days (median 2 days)

IV-NAC, intravenous N-acetylcysteine

and unknown time of the NAC loading dose administration in 3 patients. These patients were inadvertently included initially and were only determined to be at low risk later in the course of treatment when further history or laboratory data became available. One implication of the inclusion of these patients is the increased risk of potential anaphylactoid reactions, since low serum acetaminophen concentrations have been shown<sup>27</sup> to be a risk factor for anaphylactoid reactions; high serum acetaminophen concentrations appear to stabilize mast cells. Additionally, these patients may have made the alternative IV-NAC regimen appear more effective when in reality these patients may have done well without treatment.

Since there were only 3 patients with chronic overdoses, the ability to generalize the assessments to this population is limited. Another limitation is that the alternative IV-NAC regimen was not prospectively compared to the traditional FDA-approved regimen. Although no known medication or administration errors were noted, access to reports to review errors was not allowed at the pediatric hospital.

## CONCLUSIONS

This alternative IV-NAC dosing regimen appears to be effective and well tolerated among pediatric patients when compared to the FDA-approved regimen. In addition, it may result in fewer compounding and administration errors, leading to improved patient care and patient safety.

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**Abbreviations** ALT, serum alanine transaminase; AST, serum aspartate transaminase; FDA, Food and Drug Administration; ICD-9, International Classification of Diseases, Ninth Revision; INR, international normalized ratio; IV-NAC, intravenous N-acetylcysteine; NAPQI, N-acetyl-p-benzoquinone imine

**Correspondence** Kathryn Pauley, PharmD, 1633 NW 97th Street, Clive, IA 50325, email: pauley.katie@gmail.com

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