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New Options for the Use of N-Acetylcysteine in Acetaminophen Overdose Marcia L. Buck, PharmD, FCCP, FPPAG

cetaminophen remains the most common cause of poisoning reported in the United States. In 2014, the American Association of Poison Control Centers reported 73,347 toxic acetaminophen exposures with 108 fatalities. Of those reports, 23,847 involved children and adolescents.<sup>1</sup> The antidote for acetaminophen overdose, N-acetylcysteine (acetylcysteine), was first approved by the Food and Drug Administration (FDA) in 1963 as a mucolytic to be delivered by nebulization. By the 1970s, it being widely used to was prevent acetaminophen-induced hepatotoxicity.<sup>2</sup> Oral administration of the 20% solution, however, was limited by nausea and vomiting resulting from the inability to mask the drug's odor and taste. An intravenous formulation was approved by the FDA on January 23, 2004 and has subsequently become the primary method for delivery of the antidote.<sup>3</sup>

A new formulation, effervescent tablets to be added to water to form a flavored oral solution, was approved by the FDA on February 9, 2016.<sup>4,5</sup> The solution is designed to be more palatable than the solution for inhalation and allow for rapid administration of acetylcysteine in settings where insertion of an IV catheter is not possible or may delay therapy. The tablets can also be carried by emergency medical personnel for administration in the prehospital setting for known acetaminophen overdoses. In addition to this new formulation, recent publications have described alternative dosing schedules for the IV formulation and the development of a modified form of acetylcysteine that may offer a more potent antidote with fewer adverse effects.

## Mechanism of Action

The hepatotoxicity associated with acetaminophen overdose is the result of overcoming the body's ability to metabolize and eliminate the drug.<sup>2,3,5-7</sup> At therapeutic doses, acetaminophen undergoes extensive glucuronidation and sulfation prior to excretion. Approximately 5-10% undergoes metabolism via

cytochrome P450 2E1 (CYP2E1) to N-acetyl-pbenzoquinone imine (NAPQI). This reactive intermediate metabolite then undergoes conjugation with glutathione and is excreted in the urine. In the presence of an overdose, acetaminophen saturates glucuronidation and sulfation pathways, resulting in a greater degree of metabolism via CYP2E1. The resulting increase in NAPOI can deplete available glutathione stores, leaving unconjugated NAPQI to bind to sulfhydryl groups on the cysteine of mitochondrial proteins within hepatocytes, leading to mitochondrial dysfunction, ATP depletion, and formation of reactive oxygen species within the mitochondria. This can result in collapse of the mitochondrial membrane potential and eventual hepatocellular necrosis.

Glutathione is synthesized from the amino acids cysteine, glutamate, and glycine. While glutamate and glycine are readily available in hepatocytes, the smaller quantities of cysteine make it the rate-limiting factor in glutathione synthesis. Acetylcysteine is the N-acetyl derivative of naturally occurring L-cysteine. It is readily absorbed and rapidly hydrolyzed to cysteine, providing the remaining amino acid needed for glutathione synthesis. The replenished glutathione stores provide substrate for conjugation of reactive NAPQI. In addition, L-cysteine serves as a precursor to cysteine, which is a substrate for the cystine-glutamate antiporter on astrocytes. Acetylcysteine has also been shown to have antioxidant and antiinflammatory properties.<sup>2,3,5-7</sup>

# Pharmacokinetics and Pharmacodynamics

Acetylcysteine is well absorbed after oral administration, with absorption directly into splanchnic blood flow resulting in higher levels of drug in the liver than seen with IV administration. Intravenous use results in higher blood concentrations. The volume of distribution at steady-state following a single IV dose in adults is 0.47 L/kg. Protein binding ranges from 66% to 87%. Acetylcysteine is metabolized in the liver to form cysteine, N,N-diacetylcysteine,

glutathione, and other metabolites. Following IV administration, the mean half-life of acetylcysteine in adults is 5.6 hours, with a clearance of 0.11 L/hr/kg. Pharmacokinetic studies in neonates have shown a longer half-life of approximately 11 hours. Hepatic impairment results in an increase in half-life of approximately 80%, but does not affect dosing. Renal clearance accounts for approximately 30% of total body clearance. There is no need to adjust dosing for renal impairment. Hemodialysis may remove acetylcysteine.<sup>5,7</sup>

After a single dose of 11 grams, prepared by dissolving the effervescent tablets in 300 mL water, in 29 healthy adults, the median time to maximum concentration  $(T_{max})$  was 2 hours (range 1-3.5 hrs), with a mean maximum plasma concentration  $(C_{max})$  of 26.5 (CV 29%). The median area under the concentration-time curve (AUC) value was 186 (29%) hr•mcg/mL. The mean half-life was 18.1 (22%) hours.<sup>3</sup>

#### Warnings and Precautions

Hypersensitivity reactions have been reported with acetylcysteine. If a reaction occurs, therapy should be discontinued if possible. Oral acetylcysteine may aggravate vomiting after acetaminophen overdose and increase the risk for gastrointestinal bleeding in patients with underlying esophageal varices or ulcers.<sup>3,5</sup>

Acetylcysteine effervescent tablets contain sodium bicarbonate. The 500 mg tablet contains 88 mg (3.8 mEq) sodium and the 2.5 gram tablet contains 438 mg (19 mEq) sodium. The average 60 kg adult would receive a total 7 grams (304 mEq) of sodium on day 1 of treatment, 5.3 grams (230 mEq) on day 2, and 4.4 grams (191 mEq) on day 3 of the standard regimen. The sodium content for a pediatric patient is approximately 5 mEq/kg on day 1, 3.8 mEq/kg on day 2, and 3.2 mEq/kg on day 3. Exposure to this additional sodium load should be considered prior to use in patients with heart failure, hypertension, or renal impairment.<sup>5</sup>

#### Adverse Effects

The most commonly reported adverse effects following oral acetylcysteine administration include nausea, vomiting, and rash with or without fever. The IV preparation has a similar adverse effect profile, but with the addition of acute flushing and erythema during the first hour of administration in 1-7% of patients. Approximately 1-3% of patients receiving IV acetylcysteine develop symptoms of an anaphylactoid reaction, with rash, pruritus, bronchospasm, angioedema, and/or hypotension. with higher acetaminophen Patients concentrations when acetylcysteine is given are less likely to have a hypersensitivity reaction, possibly due to blunting of the symptoms. These reactions appear to be histamine-mediated; it has been suggested that patients with a history of asthma or atopy may be more prone to hypersensitivity reactions.<sup>3,5,8-10</sup>

There is a single case report of acute severe respiratory distress secondary to the erroneous swallowing of an acetylcysteine effervescent tablet.<sup>11</sup> The case occurred in a 72-year-old Turkish man who had attempted to swallow a 1,200 mg acetylcysteine effervescent tablet, available without a prescription in that country for respiratory infections. The tablet became stuck in his throat and began foaming. He aspirated the drug while attempting to breathe. Upon arrival at the hospital, he was conscious, but lethargic and had an oxygen saturation of 84%. Imaging revealed a narrowing of the subglottic region, suggestive of edema. He was initially managed with oxygen, epinephrine, nebulized albuterol, and prednisone. Additional therapies included theophylline and both esmolol and nitroglycerin to control his hypertension. Symptoms were largely resolved by day 3 of admission and he was discharged on day 7.

#### Dosing and Administration

Acetylcysteine should be initiated as soon as possible following acetaminophen overdose. Following assessment and review of the patient's laboratory values, the decision to administer acetylcysteine is typically based on the level of risk determined from the Rumack Matthew nomogram.<sup>12,13</sup> The nomogram uses plasma acetaminophen levels obtained 4 hours after ingestion or later, to account for complete absorption of the ingested drug. A level of 150 mcg/mL or greater at 4 hours indicates probable risk for hepatotoxicity, defined as an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 1000 IU/L.

Acetylcysteine is most effective when administered within 8 hours of an acetaminophen overdose, but has been shown to be effective when given as long as 16 to 18 hours after ingestion.<sup>7</sup> The nomogram does not apply in patients with acetaminophen toxicity secondary to repeated supratherapeutic doses where hepatotoxicity may occur in spite of lower acetaminophen levels. Administration of acetylcysteine in these cases should be guided by plasma levels and indicators of hepatic function.

## Dosing for Intravenous Administration

The manufacturer recommends a total IV acetylcysteine dose of 300 mg/kg be administered over 21 hours using a 3-dose regimen beginning with a loading dose of 150 mg/kg given over 1 hour, followed by a dose of 50 mg/kg given over 4 hours, and then a dose of 100 mg/kg given over 16 hours.

The 20% (200 mg/mL) injection is available in 30 mL single dose vials and should be diluted with 5% dextrose, 0.45% sodium chloride, or sterile water. The final dilution varies by weight

to prevent fluid overload. For patients  $\geq 40$  kg, the three doses are administered in 200 mL, 500 mL, and 1000 mL respectively. In patients weighing between 21 and 39 kg, the doses are given in 100 mL, 250 mL, and 500 mL. Weight-based dilutions are recommended for children  $\leq$  20 kg: 3 mL/kg for the 150 mg/kg loading dose, 7 mL/kg for the 50 mg/kg second dose, and 14 mL/kg for the 100 mg/kg third dose.

## Dosing for Oral Administration

The recommended oral dosing regimen for acetylcysteine (using either the 200 mg/mL inhalation solution or the oral solution prepared from the effervescent tablets) is a 140 mg/kg loading dose of acetylcysteine, followed by maintenance doses of 70 mg/kg beginning 4 hours after the loading dose. This dose is continued every 4 hours for a total of 17 maintenance doses. If the time of the overdose is unknown, or if the overdose occurred more than 8 hours prior to admission, the length of therapy should be guided by acetaminophen levels. In cases of a massive overdose, an overdose of a sustained-release product, in patients with preexisting liver disease, or in cases where plasma concentrations of ALT, AST, and INR remain elevated, acetylcysteine may be continued until resolution.

## Preparation of the Effervescent Tablets

Acetylcysteine effervescent tablets are available in 500 mg and 2.5 gram strengths. The calculated dose should be rounded to the nearest number of complete tablets. The tablets for each dose should be dissolved in 300 mL of water for patients weighing at least 60 kg or 150 mL of water for patients 20 to 59 kg. For children weighing less than 20 kg, two 2.5 gram tablets should be dissolved in 100 mL of water to make a 50 mg/mL solution. The dose should be drawn up and administered with an oral syringe. The effervescent tablets may be stored at room temperature. Once dissolved, the lemon mint solution should be used within 2 hours.

# Alternative Acetylcysteine Regimens

An alternative method of delivering IV acetylcysteine as a 150 mg/kg loading dose given over 1 hour followed by an infusion of 14 mg/kg/hr for 20 hours was shown to be safe and effective in adults by Johnson and colleagues in 2011.<sup>14</sup> This method reduces the potential for medication errors by eliminating the need to change doses, dilutions and infusion rates between the second and third maintenance infusions.

In 2015, Pauley and colleagues conducted a review of this regimen in pediatric patients.<sup>15</sup> Fifty-nine patients (mean age  $13.4 \pm 4.3$  years) were included in the analysis. The patients received an IV acetylcysteine regimen consisting of a 150 mg loading dose over 1 hour followed by a 15 mg/kg/hr infusion continued until

termination criteria (acetaminophen level < 10 mcg/mL and ALT/AST levels normal or decreasing) were met. Fifty-six patients had an acute acetaminophen overdose, with an estimated mean dose of 249 mg/kg; 49 were intentional overdoses. Forty-three patients (73%) were categorized as being at possible or probable risk of hepatotoxicity based on the Rumack Matthew nomogram.

The mean duration of treatment with IV acetylcysteine was  $30 \pm 17.7$  hours. At the time of discontinuation, 44 patients (76%) had ALT levels within the normal range, with the remaining 15 patients' levels trending downward. Two patients (3.4%) developed hepatotoxicity (ALT levels > 1000 units/L) following late presentations after intentional ingestions. No patients developed hepatic failure or required intubation, dialysis. or transplantation. There were no deaths. Two patients developed anaphylactoid reactions. Based on their findings, the authors concluded that this alternative regimen was effective and well tolerated among the pediatric patients evaluated.

The use of a standard duration of treatment has been questioned in several other papers. In a 2012 commentary published in *Clinical Toxicology*, Rumack and Bateman noted that the dosing scheme for IV acetylcysteine was done without consideration for massive overdose or patients presenting late after ingestion.<sup>7</sup> The authors summarized earlier studies that found greater efficacy with oral acetylcysteine in patients for whom therapy was started more than 16-18 hours after ingestion. They hypothesized that the longer duration of the oral schedule may provide higher acetylcysteine plasma concentrations lasting and а longer hepatoprotective effect.

The authors suggested that an approach tailored to the patient may be more effective.<sup>7</sup> Patients with less severe ingestions may not require a full treatment course. For patients with delayed treatment or a larger overdose, it may be appropriate to continue treatment beyond the typical 21-hour IV course. The appropriate dose for continuation in these cases has not been defined. Prolonged infusion of the third dose (6.25 mg/kg/hr) may not provide enough acetylcysteine to be effective. They provided a scenario based on the acetaminophen level taken after 20 hours of acetylcysteine administration, with the examples of a level of 13 mcg/mL requiring continued treatment at 6.25 mg/kg/hr, a level of 27 mcg/mL requiring treatment with 12.5 mg/kg/hr, and a level of 41 mcg/mL requiring treatment with 17.5 mcg/kg/hr.

The concept of discontinuing IV acetylcysteine prior to completion of the 21-hour course has recently been studied by Lucyk and colleagues.<sup>16</sup>

This multicenter collaborative research group, performed a secondary analysis of the Canadian Acetaminophen Overdose Study database. Patients with an acetaminophen ingestion who had a level of 150 mcg/mL or greater at 4 hours but were treated with less than the full 21-hour course were included. Fifty-nine patients met the inclusion criteria; in 18 of the cases (31%), therapy was discontinued early due to anaphylactoid reactions. Thirteen patients still had acetaminophen levels > 30 mcg/mL (above the therapeutic range) at the time acetylcysteine was discontinued, and another 12 had levels between 10 and 30 mcg/mL. Five of the 25 patients with elevated acetaminophen levels (20%) and four of the 34 patients with levels < 10 mcg/mL (12%) had evidence of hepatic injury. The authors concluded that hepatic injury was uncommon in patients treated with less than the full acetylcysteine regimen. They suggest that prospective studies be conducted with lowrisk patients to determine if a shorter course if adequate.

#### N-acetylcysteine Amide: A Future Alternative

While acetylcysteine has proven to be a safe and effective means of reducing the hepatotoxicity associated with acetaminophen overdose, work continues on further refining the antidote. In 2015, Khayyat and colleagues reviewed the studies conducted to date with N-acetylcysteine amide, a modified form of acetylcysteine that increases its lipophilicity.<sup>6</sup> The result of this change is a greater ability of the drug to cross cell membranes, resulting in a lower effective dose and a potential reduction in dose-related adverse effects.

In a study comparing the efficacy of rescue with the two drugs, mice given a 500 mg/kg acetaminophen dose followed by treatment with N-acetylcysteine amide had a 100% survival rate, compared to only 60% in those treated with acetylcysteine. Additional murine studies have demonstrated a greater protective effect of Nacetylcysteine amide on hepatic tissue compared to that seen with acetylcysteine, with increased intracellular and mitochondrial glutathione levels. as well as increased glutamate dehydrogenase and glutathione reductase activity, increased lipid peroxidation, and a reduction in centrilobular necrosis on macroscopic and microscopic inspection.<sup>7</sup>

#### Summary Summary

The availability of acetylcysteine has dramatically reduced the number of fatalities associated with acetaminophen overdose. While effective, the current 3-day regimen may not be the optimal method for treatment. New dosing strategies and new treatments, including Nacetylcysteine amide, may provide options that are easier to administer, better tolerated, and potentially more effective.

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