JPPT

Editorial

Acetylcysteine and Acetaminophen Overdose: The Many Shades of Gray

Peter A. Chyka, PharmD

Department of Clinical Pharmacy, College of Pharmacy, the University of Tennessee Health Science Center, Knoxville, Tennessee

INDEX TERMS: acetaminophen overdose, acetaminophen toxicity, acetylcysteine, pediatrics

J Pediatr Pharmacol Ther 2015;20(3):160–162

Although the use of acetylcysteine by oral or intravenous administration for the treatment of acetaminophen overdose is generally effective and safe,[1–3] there are aspects of its administration

see related article on page 178

that may be "gray" and less than optimal for several reasons. The paper by Pauley et al[4] in the current issue of *The Journal* describes an off-label regimen for the intravenous administration of acetylcysteine for treating acetaminophen overdose in pediatric patients. The authors' experience complements those of several other recent reports of alternative intravenous (IV) regimens administered to adult[5–7] and pediatric[8] patients.

The current US Food and Drug Administration-approved package insert for intravenous acetylcysteine (Acetadote; Cumberland Pharmaceuticals, Nashville, TN) describes a "3-bag method" of administration in which a loading dose of 150 mg/kg in 200 mL of 5% dextrose is infused over 1 hour, followed by a second dose of 50 mg/kg in 500 mL infused over 4 hours, and a third dose of 100 mg/kg in 1000 mL infused over 16 hours.[9] This regimen delivers 300 mg/kg acetylcysteine over 21 hours. The current 21-hour regimen in the United States is similar to the 20.25-hour regimen developed in the United Kingdom in 1979, except that the first dose is administered over 15 minutes in the UK instead of 60 minutes.[10] Some reasons for alternative regimens are to reduce treatment interruption resulting from adverse effects, to reduce drug administration errors resulting from complexity of the standard regimen, to reduce utilization of hospital resources and staff, and to tailor duration of therapy to patient-specific factors.[3,10]

Case series studies of the use of acetylcysteine for acetaminophen overdoses in pediatric patients, particularly patients who are preteenaged, preschool, and neonates, are sparse. The assessment and treatment of acetaminophen overdose is based principally on experiences in adults. Evidence from a 2015 Australian study of acetaminophen overdose indicated that adolescents (12-17 years of age) are different than adults in several meaningful ways, for example, adolescents are more likely to ingest acetaminophen alone, without other drugs or alcohol; will take an acute overdose rather than use supratherapeutic doses chronically; and experience a histamine-release anaphylactoid reaction to IV acetylcysteine.[11] A study performed in the 1970s showed the proportion of acetaminophen metabolites following therapeutic doses of acetaminophen in newborn infants differed from that in children ages 3 to 9 and from those in 12 year olds and adults (which did not differ from each other).[12] The serum elimination half-life of acetylcysteine in preterm neonates is 11 hours compared to 2.5 to 5.6 hours in adults.[9,13,14] Pharmacokinetic data for acetylcysteine in children and adolescents are lacking. In the largest multicenter, open-label trial of oral acetylcysteine in the United States to date, 2540 patients were prospectively studied, 3.3% of whom were less than 5 years of age, but no subgroup analysis was reported.[15] The small percentage of young children in that trial may portend the difficulties in enrolling sufficient numbers of patients to study acetylcysteine and

Table. Clinical Issues that Should Be Considered in the Study of the Administration of Acetylcysteine for Acetaminophen Overdose in Children

- Time elapsed since acetaminophen overdose (early and late presenters) and the start of acetylcysteine therapy. Acetylcysteine is most hepatoprotective when started within 8 to 10 hours of acute exposure;
- Acute, one-time overdose versus staggered overdoses over several hours versus chronic supratherapeutic overdoses over several days and the outcome after acetylcysteine therapy, duration of therapy, and the use of the acetaminophen nomogram (intended only for acute overdoses with serum acetaminophen concentrations obtained within 4 to 24 hours after ingestion, preferably at 4 hours);
- Dosage formulation of acetaminophen, that is, oral regular-release (also referred to as immediate release), oral extended release, rectal, and IV 15-minute infusion, and use of the acetaminophen nomogram, which is intended to assess only oral regular-release dosage forms;
- The presence of other drugs as co-ingestants or concurrent therapy and their effects on the assessment of acetaminophen overdose, for example, delayed acetaminophen peak serum concentrations by anticholinergic drugs and use of acetylcysteine;
- Presence of fulminant hepatotoxicity and the extension of acetylcysteine therapy for longer duration than an a priori, fixed time period;
- The reliability and predictive value of currently available clinical laboratory data (e.g., concentrations of aspartate transaminase, alanine transaminase, bilirubin, and serum acetaminophen and international normalized ratio) to guide the cessation of acetylcysteine therapy.
- Define meaningful age sub-groups to assess acetylcysteine therapy instead of assigning all pediatrics patients into one group.

may reflect the prevalence of potential acetaminophen toxicity in this age group.

Notwithstanding these concerns, there may be a case to be made that children, particularly those 12 years old and younger, may be different in their responses to acetaminophen overdose and the administration of acetylcysteine. Because a case series of pediatric patients in sufficient number and description does not currently exist to inform decision making, pediatric patients are assessed and treated in the same manner as adults. The one exception is that the dilution of acetylcysteine in intravenous fluids is adjusted to reduce the total fluid volume administered to patients weighing less than 40 kg to guard against hyponatremia and fluid overload.[9] Based on considerations in the treatment of adults who have overdosed with acetaminophen,[1–3,10] several clinical issues should be considered in the study of the administration of acetylcysteine for acetaminophen overdose in children (Table).

The study by Pauley et al[4] addresses some of these issues, such as acute versus chronic overdose, early or late presenters for treatment, and the influence of co-ingested drugs, but falls short in describing pediatric patient-aged subgroups. The "2-bag" regimen used in their study appears to be an adaptation of regimens reported in a small number of adults (300 mg/kg, total dose over 20 hours in 1 IV bag)[5] and pediatric patients (350 mg/kg, total dose over 20 hours in 2 IV bags).[8] In place of a fixed 20-hour regimen, Pauley et al[4] used clinical laboratory endpoints of liver enzymes and serum acetaminophen concentrations, which led to treatment durations ranging from 4.25 to 89 hours. The corresponding total acetylcysteine dose was not reported. Due to the small number of patients, it is understandable that subgroup analysis is not practical, but categorical groupings by age groups and acute versus chronic acetaminophen exposure would be informative. Just as children are not small adults in terms of drug therapy and toxicity, not all pediatric patients (infants to teenagers) should be considered the same. In the case of acetaminophen overdoses and acetylcysteine therapy, clinically significant differences are not well studied.

The shades of gray even extend to the names of the drugs and the nomogram for assessment of acetaminophen toxicity. In the United States, the drug is called acetaminophen, but most of the rest of the world calls it paracetamol. Acetaminophen is sometimes abbreviated "APAP" in reference to its chemical name, *N*-acetyl-*p*-aminophenol. The official US name is acetylcysteine, but many refer to the drug as *N*-acetylcysteine or "NAC." In the United States, the acetaminophen nomogram is typically interpreted such that the "acetylcysteine-treatment line" starts at 150 mg/

mL at 4 hours after ingestion.[1,9] In September 2012, guidelines in the United Kingdom lowered the "treatment line" to start at 100 mg/mL to account for high-risk patients.[16,17] The effects on patient outcome, international harmonization, and historical comparison of acetylcysteine effectiveness in this more inclusive assessment have yet to be determined. Hopefully, good evidence from prospective studies with sufficient patient categorization will shed a brighter light on the optimal regimen for acetylcysteine for acetaminophen overdose in adults and children. In the interim, informed clinical judgement and expert opinion[1–3] will guide therapy for acetaminophen overdose in children and acetylcysteine will remain as one among many drugs that is administered "off-label" to pediatric patients.[18]

Disclosure The author declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Correspondence Peter A. Chyka, PharmD, College of Pharmacy, Knoxville Campus, University of Tennessee Health Science Center, 1924 Alcoa Highway, Box 117, Knoxville, TN 37920, email: pchyka@uthsc.edu

REFERENCES

1. Heard KJ. Acetylcysteine for acetaminophen poisoning. *N Engl J Med.* 2008;359(3):285-292.
2. Ferner RE, Dear JW, Bateman DN. Management of paracetamol poisoning. *BMJ.* 2011;342:d2218.
3. Hendrickson RG, Howland MA. Antidotes in depth: *N*-acetylcysteine. In: Hoffman RS, Howland MA, Lewin NA, et al, eds. *Goldfrank's Toxicologic Emergencies.* 10th ed. New York: McGraw Hill; 2014:465-472.
4. Pauley KA, Sandritter TL, Lowry JA, Algren DA. Evaluation of an alternative intravenous N-acetylcysteine regimen in pediatric patients. *J Pediatr Pharmacol Ther.* 2015:20(3):178-185.
5. Johnson M, McCammon C, Mullins M, Halcomb, S. Evaluation of a simplified *N*-acetylcysteine dosing regimen for the treatment of acetaminophen toxicity. *Ann Pharmacother.* 2011;45(6):713-720.
6. Shen F, Coulter C, Isbister G, Duffull S. A dosing regimen for immediate *N*-acetylcysteine treatment for acute paracetamol overdose. *Clin Toxicol*. 2011;49(7):643-647.
7. Bateman DN, Dear JW, Thanacoody HK, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomized controlled trial. *Lancet.* 2014;383(9918):697-704.
8. Oakley E, Robinson J, Deasy C. Using 0.45% saline solution and a modified dosing regimen for infusing *N*-acetylcysteine in children with paracetamol poisoning. *Emerg Med Australas.* 2011;23(1):63-67.
9. Acetadote [package insert]: Nashville, TN; Cumberland Pharmaceuticals; 2015.
10. Waring WS. Novel acetylcysteine regimens for treatment of paracetamol overdose. *Ther Adv Drug Saf*. 2012;3(6):305-315.
11. Graudins A. Paracetamol poisoning in adolescents in an Australian setting: not quite adults. *Emerg Med Australas.* 2015;27(2):139-144.
12. Miller RP, Roberts RJ, Fischer LJ. Acetaminophen kinetics in neonates, children and adults. *Clin Pharmacol Ther.* 1976;19(3):284-94.
13. Borgstrom L, Kagedal B, Paulsen O. Pharmacokinetics of N-acetylcysteine in man. *Eur J Clin Pharmacol.* 1986;31(2):217-222.
14. Aloha T, Fellman V, Laaksonen R et al. Pharmacokinetics of intravenous N-acetylcysteine in pre-term new-born infants. *Eur J Clin Pharmacol.* 1999;55(9):645-650.
15. Smilkstein MJ, Knapp JL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose: analysis of the national multicenter study (1976 to 1985). *N Engl J Med.* 1988;319(24):1557-1562.
16. Waring WS. Paracetamol (acetaminophen) overdose and acetylcysteine administration: should the United Kingdom adopt a single '150-line'? *Br J Clin Pharmacol.* 2012;74(6):1066-1067.
17. Freeman R. MHRA recommendations on the use of intravenous acetylcysteine in paracetamol overdose. *Arch Dis Child Educ Pract Ed.* 2014;99(1):37-40.
18. American Academy of Pediatrics Committee on Drugs. Off-label use of drugs in children. *Pediatrics*. 2014;133(3):563-567.