

Acetylcysteine for Acetaminophen Overdose

Introduction

Acetylcysteine (NAC) is FDA approved to reduce the extent of liver injury after acetaminophen overdose. Acetadote® (acetylcysteine) was approved by the FDA January 23, 2004¹ and is the only parenteral formulation of acetylcysteine available in the United States. An intravenous (IV) formulation has been used for more than 20 years outside of the US. Prior to the availability of Acetadote®, the oral formulation of NAC was filtered and administered IV when the oral route of administration was not feasible. Introduction of the FDA approved IV formulation in the US is an important addition to antidote therapy for acetaminophen overdose since oral therapy is often poorly tolerated due to vomiting. An additional advantage of the IV formulation is that the FDA-approved dosing schedule is reduced from 72 hours to 20 hours. Distribution of Acetadote® (IV NAC) to pharmacies began in June 2004.

Pharmacology

The primary toxic effect of acetaminophen is hepatotoxicity caused by the formation of the toxic metabolite N-acetyl-p-benzoquinonimine (NAPQI). NAPQI is conjugated by glutathione at therapeutic dosages.² In an overdose, the normal pathways of metabolism are overwhelmed and NAPQI is formed in greater quantities, resulting in depletion of glutathione and hepatic injury. Administration of NAC is beneficial in preventing or mitigating hepatic injury through stimulation of glutathione synthesis, enhancing nontoxic routes of acetaminophen metabolism, detoxifying the toxic metabolite and free radical scavenging³.

Pharmacokinetics

Absorption of NAC is rapid following oral administration, but the bioavailability is only 6-10% due to extensive first-pass metabolism. In addition, oral administration is often limited by nausea and vomiting which results in delayed or ineffective administration of NAC. Intravenous administration of NAC results in 100% bioavailability. The mean terminal half-life is approximately 6 hours³.

Clearance is not reduced and plasma concentrations are not increased in patients with severe liver damage. Currently there is no dosage adjustment recommended for patients with renal or hepatic insufficiency.

Indications for antidotal therapy

Acute ingestion of 200 mg/kg in children or 6.5g in adults of acetaminophen may cause hepatotoxicity. Chronic ingestion of acetaminophen often occurs in adults with ongoing pain syndromes or children with febrile illnesses and can also result in hepatotoxicity if the recommended daily dose is exceeded. Chronic toxicity can develop at doses of greater than 75 mg/kg/day in children and more than 4-6 g/day in adults, especially when taken for several consecutive days³. The decision to initiate antidotal therapy following acute ingestion is based on the serum acetaminophen concentration. The Rumack-Matthew nomogram compares the acetaminophen concentration with the time since ingestion to provide guidance on which patients should be considered for antidotal therapy. The nomogram can not be used to evaluate chronic ingestions. The decision to treat following a chronic ingestion is based on the hepatic transaminases, an acetaminophen concentration and the clinical presentation.

Oral NAC

The FDA approved oral dosing regimen is 140 mg/kg as the loading dose, then 70 mg/kg every 4 hours for 17 doses starting 4 hours after the loading dose. Oral NAC is irritating to the gastrointestinal track and should be diluted to a final concentration of no more than 5% to reduce the risk for vomiting. The oral form of NAC has an unpleasant odor and taste that can also affect compliance with administration.

It is important to monitor patient's ability to tolerate therapy. Shorter courses of therapy may be used when no elevations in transaminases are noted at 36 hours post ingestion and there is no longer acetaminophen detected in the blood. In patients with chronic overdoses, NAC is administered for at least 24 hours and discontinued when the transaminases are trending downward.

IV NAC

The recommended adult dosage regimen for the IV formulation is a loading dose of 150 mg/kg in 200 mL of 5% dextrose given over 15 to 30 minutes. The maintenance dose follows at 50 mg/kg in 500 mL of 5% dextrose given IV over 4 hours then 100 mg/kg in 1000 mL of 5% dextrose given IV over 16 hours². Adjustments are required for children and patients at risk for fluid overload. In patients weighing less than 30kg, 20% NAC should be diluted to a final concentration of 40 mg/mL. This can be accomplished by adding 50 mL (10 g) of

20% NAC (Acetadote®) to 200 mL of D5W (remove 50 mL from a 250 mL bag). This single bag can be used for the entire infusion. The loading dose should be infused at 3.75 mL/kg (150 mg/kg) over 15 to 30 minutes, followed by a maintenance dose of 1.25 mL/kg (50 mg/kg) over 4 hours (0.31 mL/kg/hr); then 2.5 mL/kg (100 mg/kg) over the next 16 hours (0.16 mL/kg/hr)4.

Adverse events associated with IV NAC administration include anaphylactoid type reactions such as flushing, urticaria, rash, hypotension, and bronchospasm. Generally these events are associated with administration of the loading dose, and are thus dose dependent. The reactions may be more common in patients with history of asthma or reactive airway disease. Anaphylactoid symptoms can usually be managed with IV antihistamine therapy. In a study of 187 patients who received the oral form of NAC intravenously, 6 (3.2%) experienced a cutaneous adverse event (itching, rash, flushing, or urticaria).⁵ The rate of adverse events in this study was not significantly different in patients who were pretreated with an antihistamine and those who were not. One additional patient had life-threatening cardiovascular events following the administration of IV NAC that were felt to be unrelated to the administration of IV NAC

Serum transaminases should be obtained at the end of the 20 hour infusion period. Normal transaminases at completion of the infusion protocol suggest hepatotoxicity is unlikely. However, an elevation in transaminases warrants continued administration of IV NAC at the maintenance rate until they begin to trend downward.

Preparation of the oral formulation for intravenous administration is considered compounding. There are federal and state laws that govern compounding of pharmaceutical products. The Food and Drug Administration's Compliance Policy Guide (CPG) Sec 460.200 states that the FDA will consider enforcement action for compounding drug products that are commercially available in the market place or that are essentially copies of commercially available drug products.⁶

Pregnancy/Lactation

No well-controlled studies have been performed in pregnancy. The risk of not treating a pregnant woman with acetaminophen toxicity far exceeds the risk of any potential harmful effect from NAC. However, NAC should only be used when clearly indicated². NAC crosses the placenta. Both IV and oral NAC have been used safely in the management of pregnant woman with acetaminophen toxicity.

IV vs. PO: Treatment considerations

Because there are now two formulations of NAC available, the question arises, why use one over the other? The IV formulation provides an alternative method of administration when the oral route is not possible. No study has directly compared the efficacy of the oral versus

intravenous route. However, if NAC is administered within the first 8 hours both routes are associated with good outcomes. The advantages of the IV formulation include an FDA approved shorter course of therapy leading to possible shorter hospital stay, and delivery of the antidote despite persistent vomiting.

It has been shown that the optimal time to treatment is within 8-10 hours of ingestion⁸. However, some patients do not present within this time period. Patients who present after the ideal 8-10 hour period (late presenter) should still receive NAC. One study showed a mortality rate of 37% in late presenters receiving IV NAC compared to 58% in late presenters not receiving NAC⁹. Progression to coma was significantly less in those receiving the antidote (51% vs. 75%). A second study showed a higher survival rate in patients receiving the IV antidote (48%) compared to the control group (20%)¹⁰. However, the rate of deterioration and the recovery of liver function were similar in both groups. The mechanism by which acetylcysteine improves outcomes in hepatic failure may be that it increases oxygen delivery and consumption in patients with fulminant hepatic failure caused by acetaminophen¹¹. Late treatment of patients after acetaminophen exposure appears to be of benefit.

Summary

The IV formulation of NAC has been available in Europe for 20 years, and just recently became available in the US. The FDA approved oral regimen is 72 hours, while the FDA approved IV regimen is 20 hours. Oral administration is associated with vomiting which may limit NAC effectiveness. Anaphylactoid-type reactions may occur following IV administration and usually occur during the loading dose. If anaphylactoid reactions do occur, antihistamine therapy is usually effective and therapy can often be continued.

NAC can minimize liver toxicity associated with acetaminophen and should be administered within 8-10 hours of an acute exposure when possible. NAC can also be administered to patients who present greater than 8-10 hours after exposure. IV NAC is not contraindicated in any subset of patients, although patients with reactive airway disease may be more prone to adverse reactions during the loading dose.

Stephanie Barton, Pharm.D student

References

1. Acetadote® package insert. Cumberland Pharmaceuticals, Nashville, TN. Issued March 2004.
2. Bizovi KE, Smilkstein MJ. Analgesics and nonprescription medications. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS, eds. Goldfrank's Toxicologic Emergencies. 7th ed. New York, NY: McGraw-Hill; 2002, 480-501.
3. Howland MA. Antidotes in Depth, Acetaminophen. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS, eds. Goldfrank's Toxicologic Emergencies. 7th ed. New York, NY: McGraw-Hill; 2002, 502-506.

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4. Sung L, Simons JA, Dayneka NL. Dilution of intravenous N-acetylcysteine as a cause of hyponatremia. *Pediatr* 1997;100:389-391.
5. Kao LW, Kirk MA, Furbee RB, Mehta NJ, Skinner JR, Brizendine EJ. What is the rate of adverse events after oral N-acetylcysteine administered by the intravenous route to patients with suspected acetaminophen poisoning? *Ann Emerg Med*. 2003;42: 741-750.
6. FDA/CDER The FDA Compliance Policy Guide. Food and Drug Administration Web site. Available at: http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html. Accessed February 18, 2005.
7. Flanagan RJ, Meredith TJ. Use of N-acetylcysteine in clinical toxicology. *Am J Med*. 1991;91(3C): 131S-139S.
8. Smilkstein MJ, Knapp GL, 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 Dec 15;319(24):1557-62.
9. Harrison PM, Keays R, Bray GP, Alexander GJ, Williams R. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet*. 1990;336(8720): 948.
10. Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Aldexander GJ, Williams R. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *BMJ*. 1991;303(6809): 1026-1029.
11. Harrison PM, Wendon JA, Gimson AE, Alexander GJ, Williams R. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. *N Engl J Med*. 1991;324(26): 1852-57.

Pediatric Unintentional Acetaminophen Ingestion Referral Guidelines

The pediatric acetaminophen referral guidelines established by the UPCC are only for children less than 6 years of age who unintentionally ingest acetaminophen products that contain acetaminophen only. Children are at risk for hepatotoxicity if they ingest more than 200mg/kg of acetaminophen. Children who ingest less and are otherwise healthy are managed at home with telephone follow-up unless there are mitigating circumstances to preclude home management.

Children who ingest an unknown amount or 200 mg/kg or more are referred to the emergency department for a 4-hour acetaminophen concentration. At one time, decontamination was performed at home with ipecac syrup prior to the referral to the emergency department. The UPCC no longer recommends decontamination for pediatric unintentional acetaminophen ingestions – just the 4-hour acetaminophen concentration.

Why no decontamination? The American Academy of Pediatrics published a position statement in 2003 recommending that ipecac syrup no longer be used in the routine management of pediatric poison exposures. One of the reasons for this policy change was the lack of data that the use of ipecac syrup improved outcomes. The same lack of information exists with activated charcoal. For this and other reasons, the UPCC does NOT advocate home use of activated charcoal to replace ipecac syrup. The UPCC also does not recommend routine decontamination in the ED for unintentional pediatric acetaminophen ingestions for the following reasons: 1) there is a very effective antidote for acetaminophen toxicity, 2) there is no data to show that decontamination improves outcome, and 3) children who reportedly ingest greater than 150 mg/kg rarely attain a potentially toxic serum acetaminophen concentration (<1%), even without decontamination.

When UPCC sends children to the ED The UPCC generally instructs caregivers to bring children who have ingested 200 mg/kg of acetaminophen or greater to the emergency

department in time for the 4 hour acetaminophen concentration. Why this delay? Acetaminophen when ingested alone is not associated with significant toxic effects in the first 12-24 hours. The antidote, acetylcysteine, is equally effective if given within the first 8 hours after the exposure. This provides plenty of time to draw blood for a 4-hour acetaminophen concentration and to obtain the results within 8 hours after the exposure. Most unintentional ingestions in children occur in the 12 month to 36 month age range. These children are usually very active and do not easily sit still while waiting for a 4-hour acetaminophen concentration. Our experience is that many ED's discharge children who present soon after an ingestion to return at 4 hours for a serum concentration. A serum concentration obtained prior to 4 hours is not helpful in determining which patient requires treatment and is therefore not necessary.

Products that contain other ingredients in addition to acetaminophen? There are a number of acetaminophen combination products available with and without a prescription containing antihistamines, decongestants, dextromethorphan, or opiate analgesics, to name just a few. In most situations, the risk for toxicity is greatest from the non-acetaminophen component. In these situations, the UPCC refers the patient immediately to the emergency department for decontamination, evaluation for toxicity from the co-ingestant and a 4-hour acetaminophen concentration. These children require monitoring in the emergency department for a minimum of 4-hours for signs of toxicity and should not be discharged to return for a 4-hour acetaminophen concentration.

In 2004, the UPCC responded to 703 calls involving children who unintentionally ingested acetaminophen products. Of these, 83% were managed at home with telephone follow-up; 15% were treated and released from the ED, 3 (0.4%) were admitted for treatment and 10 (1.4%) refused referral or were lost to follow-up.

We hope this information is useful to you. Please do not hesitate to contact the UPCC if you have any questions or concerns about these referral guidelines.

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*CSPI denotes Certified Specialist in Poison Information.

National Poison Prevention Week



National Poison Prevention Week is March 20 – 26. It was established in 1961 as a reminder that poisonings occur and they are preventable. The theme for this year's poison prevention week is "Children Act Fast, So Do Poisons". Poison Prevention week is an opportunity to remind caregivers of small children to take action to prevent unintentional poisonings in the home. Please contact us for educational materials to distribute to your patients.

Meet the UPCC Staff



Erlynn is a native of Utah, with the exception of a few years spent between Washington and California. She has worked at the Utah Poison Center since April 2003. Prior to that she worked as an LPN in CCU and a registered nurse in dialysis, ED and a telemetry monitoring unit. She received her ASN in 1981, officially from Fresno City College, although transcripts included 4 other institutions (a more mobile time period). Interests include playing in the dirt, cooking, a great teenage son and looking after a menagerie of pets—5 well-behaved cats and 2 spoiled dogs. She finds aspirin overdoses particularly interesting to follow and observe how the patient ultimately responds and improves with therapy. She enjoys the staff at UPCC and the opportunity to learn and integrate as part of the team.

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