

Management of acetaminophen toxicity

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According to 1993 data, over 94,000 exposures to acetaminophen-containing medications in the United States necessitated contact with poison control centers.[1] Such cases represented approximately 70 percent of poison control center inquiries in the United States and do not include patients who ingested toxic doses of acetaminophen and did not contact a poison control center. Fifty percent of exposures were in children less than six years of age, although no acetaminophen-related deaths occurred in this age group. Sixty-three percent of all acetaminophen poisonings were accidental, resulting in a total of 92 deaths. The actual number of exposures to potentially toxic amounts of acetaminophen is probably much higher than that reported.

Therapeutic Use of Acetaminophen

Acetaminophen is a synthetic derivative of para-aminophenol that is considered therapeutically equivalent to aspirin for the treatment of mild to moderate pain and fever; however, acetaminophen has minimal anti-inflammatory activity compared with aspirin. Acetaminophen is available as the sole ingredient in liquids, tablets, capsules and rectal suppositories and is used in numerous cold and analgesic preparations. Pediatric doses (Table 1) usually are given three to four times daily (maximum of five doses per day). Alternatively, dosing can be based on weight (10 mg per kg, or 5 mg per kg if the patient has jaundice). Usual adult doses are 0.5 to 1.0 g given every four to six hours, up to a maximum of 4 g per day. For chronic administration, the maximum dose for adults is 2.6 g per day.[2]

TABLE I

Patients with depleted glutathione stores may have hepatotoxicity after taking therapeutic doses of acetaminophen.[13-15] These patients include those who regularly drink large amounts of alcohol and those who are chronically malnourished. Serum acetaminophen levels may be normal or slightly elevated in such cases.

Treatment

Patients with apparent acetaminophen poisoning should have a complete evaluation and physical examination, including an evaluation for ingestion of other toxic substances. Following evaluation and examination, patient management has three goals: (1) preventing absorption of ingested acetaminophen from the gastrointestinal tract; (2) appropriate use of the antidote N-acetylcysteine, and (3) supportive care. Absorption of acetaminophen from the gastrointestinal tract is prevented by emptying the stomach within two hours of the ingestion or by binding the acetaminophen to activated charcoal within the gastrointestinal tract. Alert patients may benefit from syrup of ipecac taken within two hours of the toxic ingestion, including treatment at home if the patient is unable to travel to a health care facility within one hour. Gastric lavage is generally

preferred and should be considered for untreated patients arriving at a suitably equipped health care facility within four hours after ingestion. Gastric emptying more than four hours after ingestion is not considered helpful.

The use of activated charcoal in acetaminophen overdose is problematic because charcoal adsorbs the antidote N-acetylcysteine. Delaying administration of N-acetylcysteine for at least one hour after charcoal administration minimizes this potential problem and may be appropriate, providing N-acetylcysteine may be initiated within eight hours of the ingestion. Regardless of the timing of N-acetylcysteine administration, a single dose of activated charcoal should be given as part of the initial management of most patients with acute acetaminophen overdose (dose: 1 g per kg). If ipecac was used to empty the stomach and emesis has stopped, charcoal should be given one to one and one-half hours after administration of the ipecac. This delay in administration will minimize the risk of aspiration if vomiting recurs. Charcoal should not be given if ipecac-induced emesis persists.

Use of N-acetylcysteine is essential in managing potentially toxic acetaminophen overdoses. Toxic doses include acute ingestions of 140 to 150 mg per kg in children or 7.5 g in adults. Similar guidelines for chronic or multiple ingestions have not been established.[16] N-acetylcysteine is believed to prevent accumulation of toxic metabolites by replacing depleted glutathione stores. N-acetylcysteine should be used if serum acetaminophen concentrations obtained four or more hours after ingestion are at the "possible risk" or higher levels on the Rumack-Matthew nomogram (Figure 1). For optimal therapeutic effect, N-acetylcysteine should be given as soon as possible following ingestion (within eight to 10 hours), particularly in pregnant women.[17-19] Recommendations to increase the bioavailability of N-acetylcysteine following administration of charcoal have included increasing the oral loading dose of N-acetylcysteine by 40 to 68 percent (as high as 235 mg per kg), doses generally well tolerated by patients.[20,21] However, others feel the standard loading dose is adequate in such cases.[16,22,23]

If serum acetaminophen levels are not readily available, N-acetylcysteine should be given empirically and may be effective up to 36 or more hours after ingestion, particularly in patients with fulminant hepatic failure.[16,24,25] If the initial serum concentration is found to be in the nontoxic range, N-acetylcysteine should be discontinued. The usual oral loading dose is 140 mg per kg, followed by doses of 70 mg per kg every four hours for 17 doses over three days (72 hours). If a dose is vomited within one hour of administration, it should be repeated. N-acetylcysteine has an offensive odor and should be diluted to a 5 percent concentration in fruit juices or carbonated beverages to diminish vomiting.

If the time of the ingestion is unknown, management decisions may be difficult. Careful consideration of the available history, serum acetaminophen level and AST elevation (if

present) is often helpful in such cases. Use of intravenous N-acetylcysteine is still being investigated in the United States.

Once absorption of the ingested acetaminophen has been minimized and N-acetylcysteine has been administered as indicated, attention should be directed to the reasons for the poisoning and the potential physiologic and psychological consequences. Psychiatric evaluation is indicated for all patients with intentional overdoses. Accidental overdose situations require counseling and patient education. Liver and renal function tests (AST, ALT, bilirubin, prothrombin time, creatinine) and complete blood counts should be performed daily until the patient is stable, and thereafter as indicated.

[1.] Litovitz TL, Clark LR, Soloway RA. 1993 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 1994;12:546-84. [2.] Acetaminophen. In: AHFS Drug information 94. Bethesda Md.: American Society of Hospital Pharmacists, 1994;1327-33. [3.] Letter to physicians. McNeil Consumer Products Company. January 23, 1955. [4.] Lewis RK, Paloucek FP. Assessment and treatment of acetaminophen overdose. *Clin Pharm* 1991;10:765-74. [5.] Rex DK, Kumar S. Recognizing acetaminophen hepatotoxicity in chronic alcoholics. *Postgrad Med* 1992;91(4):241-5. [6.] Crippin JS. Acetaminophen hepatotoxicity: potentiation by isoniazid. *Am J Gastroenterol* 1993;88:590-2. [7.] Rumack BH, Peterson RC, Koch GG, Amara IA. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med* 1981;141:380-5. [8.] Rumack BH, Peterson RG. Acetaminophen overdose: incidence, diagnosis, and management in 416 patients. *Pediatrics* 1978;62(5 Pt 2 Suppl):898-903. [9.] Zarro VJ. Acetaminophen overdose. *Am Fam Physician* 1987;35(4):235-7. [10.] Rumack BH. Acetaminophen overdose in children and adolescents. *Pediatr Clin North Am* 1986;33:691-701. [11.] Rumack BH. Acetaminophen: acute overdose toxicity in children. *Drug Intell Clin Pharm* 1985;19:911-2. [12.] Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med* 1994;331:1675-9. [13.] Benson GD. Hepatotoxicity following the therapeutic use of antipyretic analgesics. *Am J Med* 1983;75:85-93. [14.] Barker JD Jr, de Carle DJ, Anuras S. Chronic excessive acetaminophen use and liver damage. *Ann Intern Med* 1977;87:299-301. [15.] Prescott LF. Effects of non-narcotic analgesics on the liver. *Drugs* 1986;32(Suppl 4):129-47. [16.] Anker AL, Smilkstein MJ. Acetaminophen. Concepts and controversies. *Emerg Med Clin North Am* 1994;12:335-49. [17.] 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;319:1557-62. [18.] Flanagan RJ, Meredith TJ. Use of N-acetylcysteine in clinical toxicology. *Am J Med* 1991;91(Suppl):131S-9S. [19.] Riggs BS, Bronstein AC, Kulig K, Archer PG, Rumack BH. Acute acetaminophen overdose during pregnancy. *Obstet Gynecol* 1989;74:247-53. [20.] Ekins BR, Ford DC, Thompson MI, Bridges RR, Rollins DE, Jenkins RD. The effect of activated charcoal on N-acetylcysteine absorption in normal subjects. *Am J Emerg Med* 1987;5:483-7. [21.] Chamberlain JM, Gorman RL, Oderda GM, Klein-Schwartz W, Klein BL. Use of activated charcoal in a simulated poisoning with acetaminophen: a new loading dose for N-acetylcysteine? *Ann Emerg Med* 1993;22:1398-402. [22.] Brent J. Are activated

charcoal-N-acetylcysteine interactions of clinical significance? [Editorial]. *Ann Emerg Med* 1993;22:1860-2. [23.] Spiller HA, Krenzelok EP, Grande GA, Safir EF, Diamond JJ. A prospective evaluation of the effect of activated charcoal before oral N-acetylcysteine in acetaminophen overdose. *Ann Emerg Med* 1994;23:519-23. [24.] 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;335:1572-3. [25.] Keays RT, Gove C, Forbes A, Alexander GJ, Williams R. Use of late N-acetyl cysteine in severe paracetamol overdose [abstract]. *Gut* 1989;30:A1512.

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