SECTION C

ANALGESICS

49

Acetaminophen

HOLLY PERRY, MD
MICHAEL W. SHANNON, MD, MPH

IDENTIFICATION AND HISTORY

Acetaminophen is the most widely used analgesic/antipyretic in the world today, partly because of its excellent safety profile. Acetaminophen (also known as paracetamol, *N*-acetyl-*p*-aminophenol, and APAP) was first used in 1893 but did not gain popularity until 1949, when its relationship to another widely used analgesic, phenacetin, was appreciated. Acetaminophen was made available without a prescription in the United States in 1955. Acetaminophen is currently available either singly or in combination with other pharmaceuticals in more than 100 preparations.

Acetaminophen is a member of the family of coal tar analgesics, which also includes acetanilid and phenacetin. Once very popular, acetanilid and phenacetin were found to have serious adverse reactions when continually used, including renal papillary necrosis, hemolysis, and methemoglobinemia. Although acetaminophen is a metabolite of both phenacetin and acetanilid, it does not share the renal or hematologic toxicity of its precursors. Its primary toxicity is hepatic, and it is toxic only when taken in overdose quantities.

EPIDEMIOLOGY

Toxicity due to acetaminophen overdose was not recognized until 1966, when the first case was reported in the British literature.[1,2] Since that time, morbidity and mortality from acetaminophen overdose have continued to climb steadily. Acetaminophen currently is one of the most frequent causes of poisoning due to a pharmaceutical agent worldwide. It was one of the most common overdoses reported to the American Association of Poison Control Centers Toxic Exposures Surveillance System (AAPCC-TESS) in 1994.[3] One hundred thirty-five deaths attributed to acetaminophen overdose were reported to the AAPCC-TESS in 1994, more deaths than from any other pharmaceutical agent. Acetaminophen-induced hepatic failure is the most common cause of hepatic failure necessitating liver transplant in Great Britain and is the second most common reason for liver transplantation in the United States.[4]

PHARMACOKINETICS AND TOXICOKINETICS

The kinetics and metabolism of acetaminophen are well understood. Absorption of acetaminophen tablets is rapid and usually complete by 1 hour after a therapeutic dose, with slightly faster absorption of the liquid preparations.[5] After ingestion of excessive doses of standard-release preparations, absorption is delayed but invariably is complete within 4 hours. Theoretically, acetaminophen absorption could be delayed by coingestion of agents that reduce gastric emptying. However, only three reported cases of a peak level occurred later than 4 hours after overdose; propoxyphene was a coingestant in all three cases.[6–8] A concern is that the extended-release acetaminophen preparation that was marketed in 1995 might have absorption that extends beyond 4 hours; in one reported case, the plasma acetaminophen level did not peak until 16 hours after overdose.[9]

Acetaminophen has noncomplex, noncumulative log linear kinetics of the first-order type. This means that acetaminophen is metabolized—in the absence of liver damage—at a steady rate (such that the level declines over time in a predictable fashion).

(Salicylates, in contrast, have cumulative kinetics of the zero-order type, and when metabolic capacity is exceeded, elimination is predominantly dependent on urine flow and urine pH.) Acetaminophen has a half-life of 2.5 to 4 hours; the half-life may be prolonged in cases of liver damage. Protein binding of acetaminophen is about 10%, and its volume of distribution is approximately 0.9 L/kg.[5]

Metabolism is the basis of toxicity. Acetaminophen is a rare example of drug toxification rather than detoxification by the liver; other examples include methanol and ethylene glycol. Approximately 2% is excreted unchanged in the urine.[10] More than 90% of acetaminophen is metabolized by either sulfation or glucuronidation, and the remainder is metabolized by the cytochrome P-450 mixed-function oxidase system (Fig. 49–1)[10]; the mixed-function oxidase system is distributed throughout the body, but the majority is in the hepatocytes. The metabolism of acetaminophen is age dependent, with a larger proportion of acetaminophen undergoing sulfation in infants and children.[11] This difference diminishes with age and essentially resolves by age 12. Neither unchanged acetaminophen nor the glucuronide or sulfate conjugates are toxic. However, the metabolite that is elaborated by the mixed-function oxidase system is toxic.[12–14] This metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), is very short lived, with a half-life of nanoseconds. It attaches to the hepatic cell membrane and injures the lipid bilayer if not neutralized

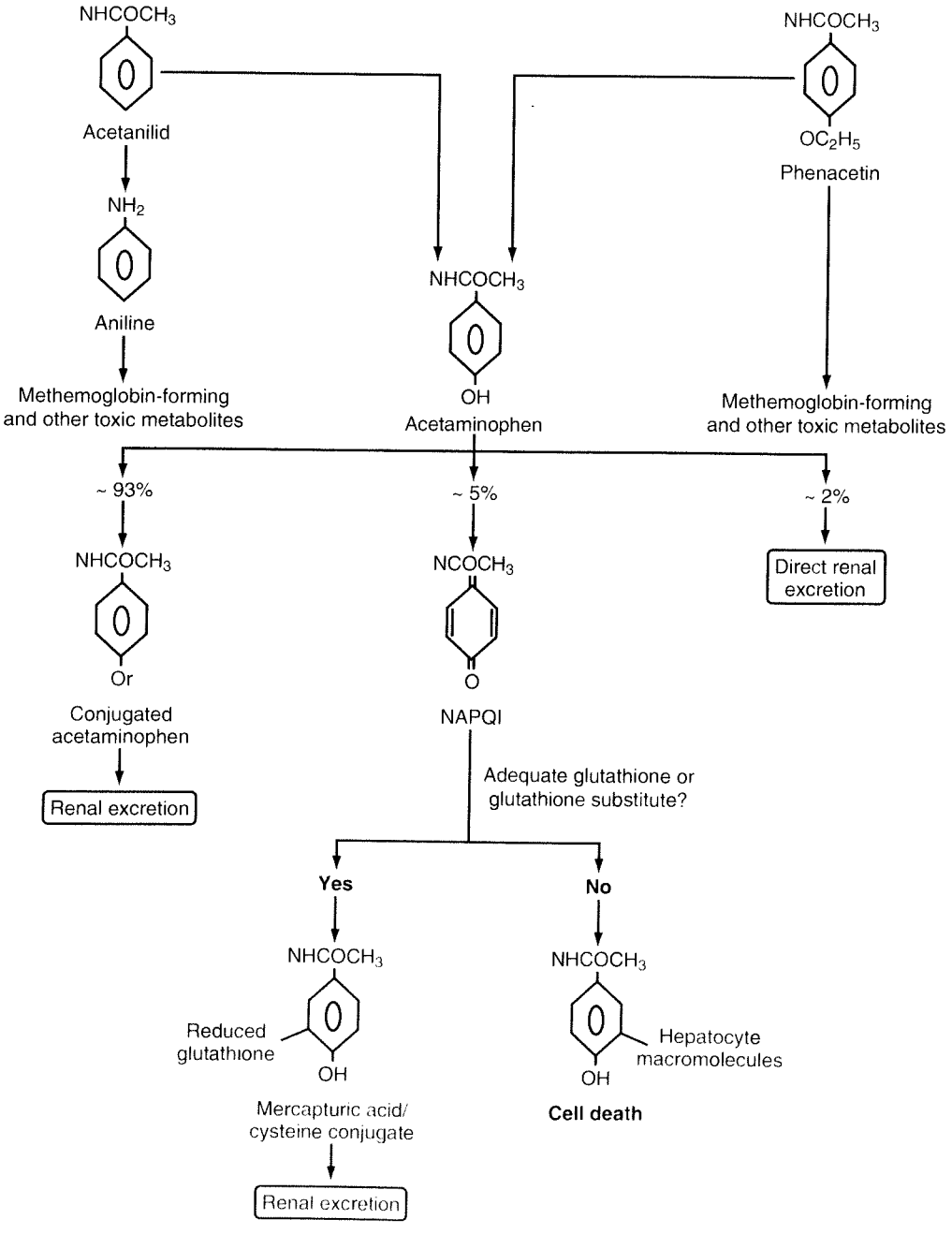

Figure 49–1. Metabolism of acetaminophen and other coal tar analgesics. R, glucuronide or sulfate; NAPQI, *N*-acetyl-*p*-benzoquinoneimine.

by an antioxidant. Hepatic glutathione appears to be the primary antioxidant that conjugates and neutralizes NAPQI.[10, 15-17]

At therapeutic doses, acetaminophen is a very safe drug with essentially no side effects. However, when hepatic glutathione stores have been depleted to less than 70% of normal values, such as after an acetaminophen overdose, NAPQI is not detoxified by glutathione but instead binds to hepatocytes, and arylation and cell death result.

MODULATORS OF TOXICITY

Acetaminophen toxicity results from an imbalance between hepatic glutathione stores and the amount of NAPQI formed by the hepatic mixed-function oxidase system, which is made up of several families of enzymes. Theoretically, any compound that affects the mixed-function oxidase system, specifically either the cyp2E1 or cyp1A2 enzymes, would be anticipated to affect the amount of NAPQI produced and thus to have an impact on the likelihood of developing hepatotoxicity after an acetaminophen overdose. The cyp2E1 enzyme is responsible for most NAPQI formation from acetaminophen, and the cyp1A2 enzyme produces a lesser amount. Probable inducers for cyp2E1 include ethanol, isoniazid, rifampin, phenytoin, and carbamazepine; probable inducers for cyp1A2 include cigarette smoke and charcoal-broiled foods.[18] Indeed, clinical series have demonstrated that patients who are continually ingesting substances that induce cyp2E1 such as anticonvulsants[19] and those who chronically abuse alcohol have poorer outcomes than the general population after acetaminophen overdose.[20-23] Several case reports describe patients' taking antituberculosis medications and subsequently developing hepatotoxicity after both acute single overdose and long-term excessive intake of acetaminophen.[24, 25] Patients with depleted glutathione stores, such as those with anorexia nervosa, may also be at higher risk for development of hepatotoxicity after an acetaminophen overdose.

Age may also be a potential modulator of toxicity. Children younger than 5 years appear to be more resistant to the toxic effects of acetaminophen. Very few deaths have been reported, and the incidence of hepatotoxicty is much lower than that observed in the general population.[26, 27] It is unclear why young children might be more resistant to large ingestions of acetaminophen, but a number of possibilities have been suggested, including early decontamination due to spontaneous or induced emesis, differences in the activity of the mixed-function oxidase system, increased glutathione stores, or a briefer delay before the antidote is administered. The amount of acetaminophen metabolized by the mixed-function oxidase system is difficult to ascertain because it is technically impractical to measure the glutathione-NAPQI complex. Inferences can be drawn from metabolic data for other drugs, such as phenytoin, which use the mixed-function oxidase system; kinetic analyses have shown the mixed-function oxidase systems to have greater activity in young children. Thus, young children would be expected to elaborate more NAPQI and be more susceptible to acetaminophen, which is opposite the clinical observation. Yet another possible explanation is that the lower incidence of severe hepatotoxicity is an effect of early treatment: most toddlers would be expected to present promptly to a health care provider after an accidental ingestion and thus receive treatment earlier than their adult counterparts. The largest reported series of young children with acetaminophen overdose did not address treatment delay.[26] One study that did investigate the role of treatment delay in children found that none who were younger than 6 years (n = 5) and who had acetaminophen levels in the probable or high toxicity range developed severe hepatotoxicity despite an average treatment delay of more than 15 hours.[27] Perhaps the lower incidence of severe hepatotoxicity is due to intrinsic differences in young children's ability to detoxify NAPQI, although there are no clear data to demonstrate this.

CLINICAL MANIFESTATIONS

The minimal single acute toxic dose is 7.5 g for an adult or 150 mg/kg for a child. Symptoms and laboratory abnormalities are predictable after an acetaminophen overdose and have traditionally been divided into four phases (Table 49–1). Symptoms may initially be minimal, although patients who are severely poisoned generally have nausea, vomiting, and occasionally lethargy. These symptoms tend to resolve by 12 to 18 hours and possibly reflect direct effects of the parent compound (because resolution occurs with declining acetaminophen levels). Evidence of hepatic injury as reflected by elevations in aspartate aminotransferase (AST) and alanine ami-

Table 49–1. Phases of Acetaminophen Poisoning

Phase I (0.5–24 h)
Anorexia, nausea, and vomiting are frequently present.
Malaise and diaphoresis may be present.
Transaminases may be elevated.
Patients may appear normal.
Phase II (24–72 h)
Anorexia, nausea, and vomiting become less pronounced.
Right upper quadrant pain may be present.
Transaminase levels continue to increase.
Bilirubin level may be elevated.
Prothrombin time may be prolonged.
Renal function may deteriorate.
Phase III (72–96 h)
Characterized by the sequelae of hepatic necrosis: jaundice, coagulation defects, renal failure, and hepatic encephalopathy.
Liver biopsy reveals centrilobular necrosis.
Death due to multiorgan failure may result.
Phase IV (4–14 d)
If patients survive, complete resolution of hepatic dysfunction occurs and the liver heals without evidence of fibrosis.

notransferase (ALT) may appear as early as 8 hours after overdose, and more than half of all patients with liver injury develop some elevation in transaminase levels within 24 hours after overdose.[28] (In patients who recover, transaminase levels peak between 48 and 72 hours, with peak values as high as 50,000 IU/L). Transaminases gradually return to normal levels during the ensuing 2 weeks. Patients who develop an elevation of AST or ALT level greater than 1000 IU/L commonly demonstrate other evidence of liver dysfunction by 24 to 72 hours after overdose, including elevations in prothrombin time and bilirubin. Patients who ultimately die or require liver transplantation progress to demonstrate the sequelae of hepatic necrosis, including jaundice, coagulation defects, hepatorenal syndrome, and hepatic encephalopathy. Death results from multiorgan failure and generally occurs 72 to 96 hours after overdose.

The liver is the primary target for toxicity after acetaminophen overdose because the hepatocytes elaborate NAPQI. Because NAPQI has such a short life span, it can damage only cells that elaborate it. The histopathologic signs following acetaminophen overdose are characteristic: centrilobular necrosis (which is where NAPQI is elaborated) with periportal sparing.

Organ systems other than the liver are rarely affected immediately after acute overdose. Multiorgan failure may occur several days after acetaminophen poisoning but only in the setting of severe hepatotoxicity. The mechanism of acute injury to other organs besides the liver is unclear. Isolated case reports describe acute nephrotoxicity[29–31] and altered mental status.[32] Elevation of pancreatic enzyme levels has been reported in as many as 22% of unselected cases.[33, 34] The clinical importance of these laboratory abnormalities is unknown. Although acetaminophen is a metabolite of phenacetin, it does not have the capacity to regenerate phenacetin, and consequently, neither the papillary necrosis nor the methemoglobinemia characteristic of phenacetin toxicity is observed in human beings with acetaminophen toxicity.

All outcome studies have defined severe hepatotoxicity due to acetaminophen overdose as either AST or ALT level greater than 1000 IU/L. Approximately 3.5% of patients who develop severe hepatotoxicity eventually suffer fulminant hepatic failure,[33] and slightly fewer than half of patients with fulminant hepatic failure die or require liver transplantation.[35] Death is most frequently caused by cerebral edema or sepsis. There are several early indicators of decreased survival for patients with fulminant hepatic failure: arterial pH less than 7.30,[35] peak prothrombin time greater than 100 seconds in combination with a serum creatinine level greater than 3.4 mg/dL, and a prothrombin time continuing to rise on day 4 after overdose.[36] In the subset of patients who develop severe hepatotoxicity, initial acetaminophen level and treatment with *N-acetylcysteine (NAC)* have no value for predicting which of those patients will progress to fulminant hepatic failure. Similarly, peak AST and ALT values have no prognostic significance. In one large study of patients who died of acetaminophen overdose, mean peak AST level was less than 3000 IU/L.[35] Patients who do not die have complete recovery of their liver with no evidence of scarring within 30 days.[37]

PREDICTION OF HEPATOXICITY

The natural history of cases treated with supportive care alone was known to be related to plasma acetaminophen concentration as a function of time since ingestion. The outcome measure chosen was elevation in the serum levels of transaminases, with severe hepatotoxicity being defined as either AST or ALT level greater than 1000 IU/L. Transaminases were chosen as a measure of liver injury because of ease of standardization and accessibility. Sixty per cent of patients with plasma acetaminophen concentration above a line connecting the points where plasma acetaminophen concentration is 200 μg/mL 4 hours after overdose to the point where plasma acetaminophen concentration is 100 μg/mL 8 hours after overdose developed severe hepatotoxicty. This percentage increased to 90% in patients with plasma acetaminophen concentration above a line connecting the points where plasma acetaminophen concentration is 300 μg/mL 4 hours after overdose to a point where plasma acetaminophen concentration 150 μg/mL 8 hours after overdose.[38]

Before antidotal therapy with NAC was evaluated in a national study in the United States, a treatment nomogram was devised by Rumack and colleagues using the foregoing data (Fig. 49–2). According to this nomogram, which remains a treatment standard, three levels of risk for development of severe hepatotoxicity following acetaminophen overdose are delineated: possible, probable, and high. Patients are at high risk if the 4-hour (or equivalent) plasma acetaminophen concentration is 300 μg/mL and at probable risk if the 4-hour (or equivalent) plasma acetaminophen concentration is 200 μg/mL. A third level was added to the nomogram to give a 25% margin of safety to allow for variations in measurement of acetaminophen levels among laboratories as well as uncertainty in time of ingestion.[39] The earliest time after ingestion that can be plotted on the nomogram is 4 hours, because this is when absorption of acetaminophen is complete and acetaminophen levels peak; levels obtained sooner than 4 hours after ingestion are uninterpretable. Acetaminophen levels obtained later than 20 hours after the overdose may be difficult to interpret if they are nondetectable. The lower limit of detection of acetaminophen for many laboratories is 10 μg/mL, which represents a toxic concentration if obtained more than 20 hours after acetaminophen overdose.

ANTIDOTE THERAPY

Several drugs have been evaluated as antidotes for acetaminophen overdose, including cysteamine,

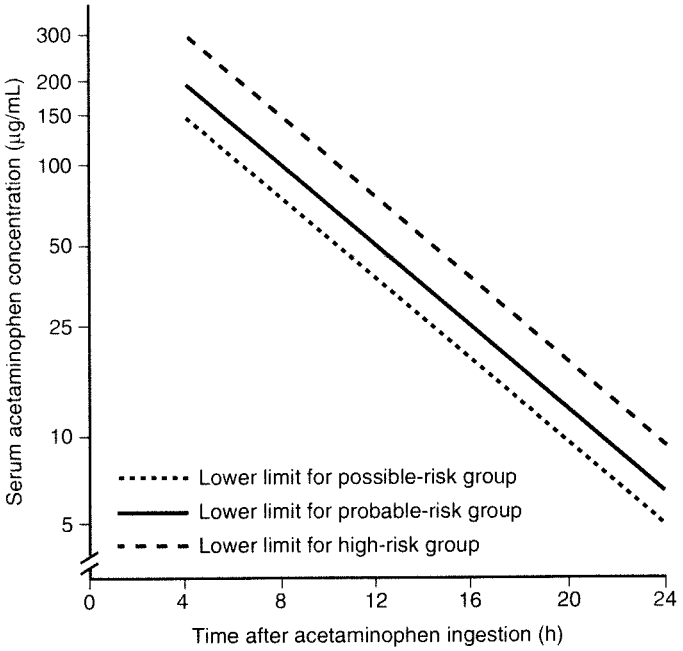

Figure 49–2. Acetaminophen (APAP) overdose treatment nomogram. Adapted from Smilkstein MJ, Knapp GL, Kully KW, et al: Efficacy of oral *N*-acetylcysteine in the treatment of acetaminophen overdose: Analysis of the National Multicenter Study (1976 to 1985). N Engl J Med *319*:1557, 1988.

methionine, and NAC. Each of these antidotes can serve as either a glutathione precursor or substitute. Glutathione itself has not been studied because it does not penetrate cell membranes. Cysteamine, although effective, has unacceptable adverse effects including nausea, vomiting, drowsiness, and cardiotoxicity.[40] Methionine, although safe, has not been very effective. In contrast, NAC is both safe and effective. In addition to serving as a glutathione substitute, NAC is thought to act as an antidote by enhancing glutathione synthesis and increasing the amount of acetaminophen that is metabolized by sulfation.[15] Other compounds such as cimetidine[41, 42] and 4-methylpyrazole,[43] which block the mixed-function oxidase system, have also been postulated to ameliorate the toxic effects of acetaminophen overdose, although no extensive clinical trials using these drugs have been conducted to date. Three different NAC protocols are currently in use worldwide. In the United Kingdom, Canada, Australia, and other countries, NAC is administered continuously for 20 hours by intravenous (IV) infusion. This regimen consists of a loading dose of 150 mg/kg over 15 minutes, followed by 50 mg/kg over the next 4 hours, followed by 100 mg/kg over the next 20 hours (total dose of 300 mg/kg). *In the United States, the only Food and Drug Administration–approved protocol is 72 hours of oral NAC, which consists of a 140 mg/kg loading dose followed by 17 maintenance doses of 70 mg/kg (total dose of 1330 mg/kg).* Although the 72-hour oral NAC regimen is effective, therapy is complicated by the frequent incidence of emesis; this has a negative impact on the usefulness of NAC as an oral antidote. Therefore, an IV regimen of NAC that is as efficacious as the oral regimen is being sought. In the United States, an on-going clinical trial of IV NAC is currently being conducted. The protocol is based on a modification of the oral regimen: a 140 mg/kg loading dose followed by 12 maintenance doses of 70 mg/kg (total dose of 980 mg/kg).

The results of clinical trials of these regimens are compared in Table 49–2.[38, 44, 45] Both the 20-hour IV protocol and the 72-hour oral protocol are efficacious when treatment is begun early, but the 72-hour oral protocol is clearly superior to the 20-hour IV protocol when patients present more than 15 hours after an overdose. The protocol of 72 hours of oral NAC is effective when used within the 24 hours after overdose, although its efficacy is a function of treatment delay. It is most effective when administered within the first 8 hours after acetaminophen overdose, but its effectiveness decreases incrementally every hour thereafter. Patients who are at probable risk for de-

Table 49–2. Comparison of Incidence of Hepatotoxicity After Treatment with Either Oral or Intravenous *N*-Acetylcysteine

Treatment Delay	20-h IV	72-h Oral	52-h IV
Probable Risk			
0–10 h	1/62 (1.6) [0–9%]	32/527 (6.1) [4–8%]	5/50 (10) [3–22%]
10–24 h	20/38 (52.6) [36–69%]	247/935 (26.4) [24–30%]	23/85 (27.1) [18–38%]
High Risk			
0–10 h	1/33 (3) [0–16%]	17/206 (8.3) [5–13%]	1/24 (4.2) [0–21%]
10–24 h	18/27 (67) [46–83%]	199/578 (34.4) [30–37%]	16/50 (32) [19–47%]
16–24 h	9/11 (82) [48–98%]	116/283 (41) [35–47%]	11/19 (57.9) [34–80%]

Values given are number of cases, percent (in parentheses), and 95% confidence intervals (in brackets) with AST or ALT of more than 1000 IU/L.

Adapted from Smilkstein MJ, Bronstein AC, Linden C, et al: Acetaminophen overdose: A 48-hour intravenous *N*-acetylcysteine treatment protocol. Ann Emerg Med *20*:1058, 1991.

veloping hepatotoxicity have a 6.1% incidence of hepatotoxicity if treatment is begun with oral NAC within 10 hours after ingestion; this incidence increases to 26.4% if treatment is initiated between 10 and 24 hours after ingestion. For patients at high risk for developing hepatotoxity, the incidence is 8.3% if treatment with oral NAC is initiated within 10 hours after overdose, 34.4% if treatment is initiated between 10 and 24 hours after overdose, and 41% if treatment is initiated between 16 and 24 hours. The 52-hour IV protocol appears to be equivalent to the 72-hour oral protocol.

Treatment with either the oral or IV forms of NAC is associated with some adverse effects. The incidence of nausea and vomiting associated with the administration of oral NAC is high, but the incidence of anaphylactoid reactions is only 2% to 3%.[45, 46] In contrast, IV infusion of NAC has been associated with a 3% to 14% rate of adverse reactions including erythema at the injection site, diffuse urticaria, bronchospasm, fever, and, rarely, anaphylaxis and death.[45, 47, 48] Anaphylactoid reactions typically respond to administration of antihistamines.[46, 48]

TREATMENT

Acetaminophen intoxication by itself does not typically produce cardiorespiratory compromise unless the patient presents late and is in severe hepatic failure. A patient's airway, breathing, and circulation should always be evaluated first, however, and stabilized if necessary. Decontamination should then be performed. Gastric lavage for an isolated acetaminophen overdose is rarely necessary. One dose of activated charcoal should be given if a patient presents less than 4 to 6 hours after ingestion. Thereafter, the only indication for activated charcoal is coingestion of another toxin. Although activated charcoal does adsorb NAC and reduce its peak serum levels by as much as 29%,[49] the loading dose of NAC does not need to be increased because the amount adsorbed is not considered clinically important.[50, 51] Past guidelines for gastrointestinal decontamination after acetaminophen overdose recommended that activated charcoal be lavaged from the stomach before administration of NAC, that NAC be alternated with activated charcoal, or that the loading dose of NAC be increased. None of these interventions is necessary.

Laboratory evaluation on arrival at a health care facility should include an acetaminophen level obtained 4 or more hours after ingestion, baseline AST level, ALT level, bilirubin level, prothrombin time, creatinine level, pregnancy test for women of childbearing age, and toxicologic screen as appropriate. Aspirin is a frequent coingestant, and a salicylate level should therefore be determined in every patient who presents with an acetaminophen overdose. Consideration should be given to obtaining amylase and lipase determinations, particularly in patients with protracted emesis.

Perhaps the most crucial piece of information required for making appropriate management decisions about a patient who has ingested a single overdose of acetaminophen is *time elapsed since ingestion* (Fig. 49–3). For a patient who has ingested a potentially toxic amount of acetaminophen and presents later than 8 hours after the overdose or in circumstances in which an acetaminophen determination is not available within 8 hours after the overdose, a loading dose of NAC should be administered immediately. If the acetaminophen level is found to be in the nontoxic range, further doses of NAC are unnecessary. Otherwise, a complete course of NAC should be given. For nonpregnant patients who present less than 8 hours after overdose, the decision to initiate NAC therapy may be delayed until an acetaminophen level is available and it is known whether or not the patient has a toxic level. A dose of activated charcoal should be given to these patients on presentation while awaiting the acetaminophen level. A pregnant woman should be administered a loading dose of NAC as soon as possible regardless of time since overdose, for reasons discussed later.

Acetaminophen level should be plotted on the nomogram as a function of time after ingestion. Patients who present within 24 hours of an acute single overdose and have an acetaminophen level above the possible toxicity line should be treated with NAC. The lines denoting probable and high toxicity are not used to make treatment decisions but rather may be used to estimate a patient's risk for development of severe hepatotoxicity.

The oral preparation of NAC (Mucomyst) is available as a 20% solution and should be diluted to a 5% solution with either fruit juice or a carbonated beverage. A loading dose of 140 mg/kg should be administered, followed every 4 hours by 17 maintenance doses of 70 mg/kg. If a patient vomits within 1 hour of receiving NAC, that dose must be repeated. As an example, a 50-kg patient requires (50 × 140) 7000 mg, or 7 g, of NAC or 35 mL of 20% Mucomyst as a loading dose.

Aggressive antiemetic therapy is critical to successful treatment when the oral preparation of NAC is used because emesis of the antidote prevents effective therapy. Acetaminophen overdose by itself is associated with emesis, and NAC, which is foul smelling, only adds to the nausea and vomiting that may already be present. For a patient with emesis, although the usual dose is 10 mg (IV) we recommend metoclopramide (Reglan) at an initial dose up to 25 mg IV with additional doses if needed to a maximum of 1 mg/kg. Consideration should be given to coadministration of diphenhydramine (Benadryl) (25 mg IV) in order to decrease the risk of metoclopramide-induced dystonic reaction, which occurs most frequently in younger patients. If emesis persists, ondansetron (0.15 mg/kg IV) or droperidol (2 to 5 mg IV for adults; 0.15 mg/kg for children) may be useful adjuncts (Table 49–3). If emesis is still persistent, a nasogastric or duodenal tube should be inserted and the NAC dripped in over 30 minutes. If emesis continues despite aggressive antiemetic therapy, the pa-

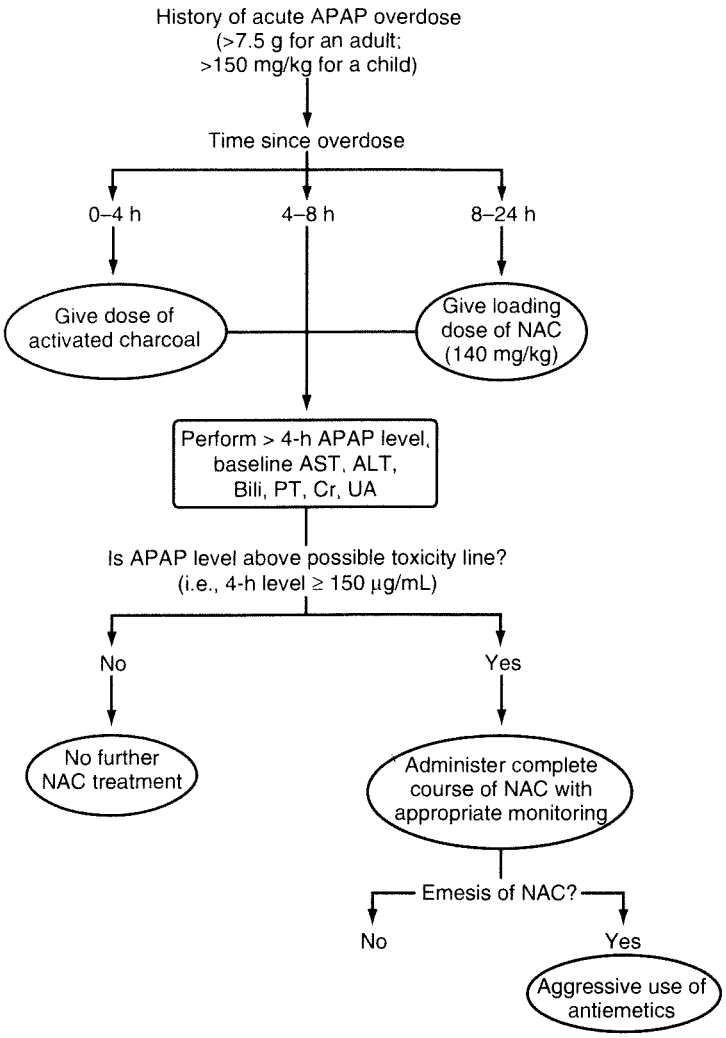

Figure 49–3. Management of acute acetaminophen overdose. NAC, *N*-acetylcysteine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Bili, bilirubin; PT, prothrombin time; Cr, creatinine; UA, urinalysis.

tient should be transferred to a center that has an IV preparation of NAC available. If this is not feasible, consideration should be given to IV administration of the oral form of NAC through a 25 μ millipore filter, which removes pyrogens and other contaminants. Although substantial experience has been gained with this, it is *not* routinely recommended and should only be done as a last resort; there is a high rate of anaphylaxis when the oral form of NAC is administered IV.

Table 49–3. Administration of Oral *N*-Acetylcysteine After Acetaminophen Overdose

How Supplied	
As 10% (10 g/100 mL) or 20% (20 g/100 mL) solution	
Dosing	
Loading	140 mg/kg
Maintenance	70 mg/kg every 4 h for 17 doses
Administration	
Dilute each dose with carbonated beverage or fruit juice to make a 5% solution.	
Repeat dose if patient vomits within 1 h of administration.	
Aggressive antiemetic therapy may be indicated.	
Antiemetics	
Metoclopramide: 0.5–1.0 mg/kg IV	
Droperidol: 2–5 mg IV (adult); 0.15 mg/kg IV (pediatric)	
Ondansetron: 0.15 mg/kg	

Monitoring in the hospital should include at least daily measurements of AST, ALT, bilirubin, blood urea nitrogen, creatinine, and prothrombin time, as well as urinalysis. Acetaminophen elimination half-life was previously thought to be the most reliable early guide to prognosis: A half-life exceeding 4 hours was almost always (16 of 17) associated with hepatotoxicity, and a half-life of less than 4 hours was practically never (12 of 13) associated with hepatotoxicity.[52] However, the correlation between acetaminophen half-life and development of hepatotoxicity has subsequently been demonstrated to have a low positive predictive value, and thus half-life determination is not helpful.[53] Furthermore, delaying treatment with NAC while awaiting determination of acetaminophen half-life is detrimental to patients who should receive NAC based on a single toxic acetaminophen level. Because acetaminophen itself is not toxic and will continue to be metabolized unless a patient has severe liver damage, no information is gained from serial acetaminophen determinations. It

is important to recognize that NAC has no effect on the elimination of acetaminophen from the serum; declining acetaminophen concentrations are not evidence of the efficacy of NAC. Only patients who have ingested an extended-release acetaminophen preparation or who are being considered for an abbreviated course of NAC therapy (discussed later) should receive serial acetaminophen determinations.

SPECIAL CIRCUMSTANCES IN MANAGEMENT

Pregnancy

Acetaminophen is the preferred analgesic/antipyretic for use during pregnancy because it is safe at therapeutic doses; there is no evidence that it is teratogenic.[54] However, there is potential for fetal toxicity after maternal overdose. Animal studies have shown that both acetaminophen[55] and NAC[56] freely cross the placenta. The fetal liver is capable of elaborating NAPQI by 14 weeks' gestation.[57] Little has been published about acetaminophen overdose in pregnancy, but overdose has been reported to result in fetal morbidity[58] and mortality.[59] *Treatment delay is significantly correlated with fetal wastage.* Therefore, it is recommended that any pregnant woman who has ingested a potentially toxic amount of acetaminophen receive a loading dose of NAC on presentation, regardless of time after ingestion. If the acetaminophen level is then found to be in the nontoxic range, further doses of NAC are unnecessary.

Acute Acetaminophen Overdose in Chronic Alcoholics

Several studies have demonstrated that patients who chronically abuse alcohol are more likely to develop hepatotoxicity after an acute acetaminophen overdose[20–22] and, having developed hepatotoxicity, have a higher mortality than the general population.[23] In contrast, Rumack and co-workers found no association between alcohol use and hepatotoxicity; however, only 11 patients in this series met criteria for chronic alcohol use.[39] Most toxicologists agree that patients who chronically ingest ethanol are at higher risk for development of hepatotoxicity than the general population after acetaminophen overdose. Some toxicologists have even recommended that the treatment line on the Rumack nomogram be lowered to a 4-hour or equivalent acetaminophen concentration of 100 μg/mL in the setting of an acute acetaminophen overdose in a chronically alcoholic patient.[60] The increased susceptibility of these patients to acetaminophen overdose is perhaps due to both lower than average glutathione stores as well as increased production of NAPQI due to induction of the cyp2E1 system.

Long-Term Acetaminophen Overdose

Four grams of acetaminophen for an adult and 90 mg/kg for a child are the maximum recommended daily doses of acetaminophen. Ingestion of larger quantities constitutes chronic excess, which may result in hepatotoxicity; a few case reports describe even smaller doses resulting in hepatotoxicity in adults. Young children who have received as little as 150 mg/kg per day have developed hepatotoxicity.[61, 62] Chronic acetaminophen excess is usually a therapeutic misadventure. Common scenarios include increased daily intake because patients believe it is safe, use of combination products such as acetaminophen and codeine along with acetaminophen, or the substitution of pediatric with adult suppositories in a young child. The incidence of hepatotoxicity after chronic excess is unknown. Certain populations appear to be at risk, however, including patients who are fasting or who have ingested alcohol in the preceding 5 days.[63] Additionally, numerous cases of hepatotoxicity have occurred in alcoholic patients after long-term acetaminophen excess, although the apparent frequency may in part be due to ascertainment bias.[64] Indeed, Benson and co-workers showed that alcoholic patients who were given 4 g/day of acetaminophen for 14 days did not develop hepatotoxicity.[65]

The basis of certain patients' sensitivity to long-term acetaminophen excess is not well understood. Fasting is known to decrease the amount of acetaminophen that undergoes glucuronidation; this may increase metabolism by the cyp2E1 system, which would result in elaboration of more NAPQI. Similarly, because ethanol use induces cyp2E1, NAPQI production may be increased in patients who ingest alcohol. Continual alcohol use may also result in glutathione depletion. Finally, patients who chronically abuse alcohol may be at a higher risk because abnormal transaminase values may be wrongly attributed to alcoholic hepatitis instead of acetaminophen toxicity. Chronically alcoholic patients frequently have abnormal transaminase levels; knowledge of the pattern of enzyme abnormalities is important to make an accurate diagnosis of the etiology of hepatitis in patients who continually abuse alcohol. In alcoholic hepatitis, AST level is less than 300 IU/L, ALT level is normal or marginally increased, and AST value is usually greater than twice the ALT. In contrast, chronic excess of acetaminophen in a chronically alcoholic patient leads to an elevation of AST greater than 300 IU/L, although the proportion between AST and ALT remains the same.[63, 66]

For patients who present with a history of chronic acetaminophen excess, with or without a history of long-term ethanol use, a modified treatment approach is necessary. On presentation to the health care facility, baseline values of acetaminophen, AST, ALT, bilirubin, and prothrombin time should be ob-

tained and a loading dose of NAC given pending the results. The nomogram cannot be used to determine which patients may benefit from treatment. In fact, no studies have been performed to prove that NAC provides benefit in the setting of long-term excess. However, it seems prudent to continue NAC if a plasma acetaminophen concentration is detectable or if either the AST or ALT value is abnormal.

Late Treatment of Acute Overdose

NAC, when given early (i.e., < 24 hours after ingestion when the oral protocol is used < 15 hours when the 20-hour IV protocol is used), is beneficial in all patients with a potentially toxic plasma acetaminophen level. Additionally, late administration of NAC is beneficial to patients with fulminant hepatic failure. Although late NAC use does not change the biochemical markers of liver function such as prothrombin time, it has been shown to improve survival and decrease the incidence of cerebral edema as well as the incidence of hypotension requiring inotropic support.[67, 68] In a prospective randomized study,[68] survival was improved from 20% for patients who received intensive liver care only as compared with 48% for patients who received late NAC treatment. Groups were well matched for age, sex, and time to presentation to a health care facility. Administration of NAC was continued until recovery from encephalopathy occurred or death ensued. Unlike methionine, NAC use is safe in patients with encephalopathy. The mechanism for the salutary effect of NAC is not completely understood but may in part be due to improvement of tissue oxygenation.[69]

Extended-Release Tylenol

Tylenol-ER is a new, unique formulation of acetaminophen released in 1995. It is a caplet consisting of 325 mg of immediate-release acetaminophen on one side and 325 mg in a matrix formulation designed for slow release on the other. At therapeutic doses, the manufacturer's *in vitro* studies have shown that 88% of the product is released within 3 hours and 95% within 5 hours. The figures are similar when 10-fold the therapeutic dose is ingested.[70] However, other investigators have shown a decreased rate of dissolution with increasing number of tablets.[71, 72] Therefore, because this formulation potentially changes the absorption kinetics *in vivo* and because experience to date is limited, plasma acetaminophen levels must be interpreted cautiously using the Rumack nomogram. One approach is to measure at least three serial plasma acetaminophen levels, with the first at least 4 hours after overdose and the following measurements at 2-hour intervals. Unequivocally, the full course of NAC should be given if any level is above the treatment nomogram line. NAC therapy should be considered if the second level is greater than the first level or if any level is more than half of the potentially toxic level on the nomogram. The factor of one half is conservative. It is derived from a prospective, randomized, double-blind crossover comparison study of volunteers ingesting 75 mg/kg of acetaminophen. This study showed that peak acetaminophen levels after a dose of Tylenol-ER were 57% of that after an immediate-release Tylenol preparation.[73] Management of any overdose involving Tylenol-ER should be discussed with a consulting toxicologist or poison control center.

NEW DIRECTIONS

Abbreviated Therapy

An increasingly popular view is that 72 hours of oral NAC is longer treatment than many patients require. Therefore, clinicians have begun to administer NAC for only 24 hours (a loading dose of 140 mg/kg and six maintenance doses of 70 mg/kg; total, 560 mg/kg) for selected patients. Two groups of patients appear to be ideal candidates for abbreviated therapy. The first group of patients who should be considered for abbreviated therapy are those with a history of long-term acetaminophen overdose who have transaminases less than 1000 IU/L and a nondetectable acetaminophen level. In the setting of acute overdose, the ideal patient to be considered for abbreviated therapy is otherwise healthy, has no history of chronic alcohol use, and is treated successfully with NAC within 8 hours of overdose. The patient should be re-evaluated after 24 hours of treatment; if the acetaminophen concentration is nondetectable and the transaminase levels are normal, NAC may be discontinued. The major concern with abbreviated therapy is that a minority of patients may not have abnormal transaminase values within 28 hours of ingestion and NAC would be prematurely terminated in these patients, before evidence of liver injury is manifested. Published clinical experience with abbreviated NAC therapy is sparse,[74] and a prospective trial with clinical follow-up is necessary before this approach can be endorsed. Therefore, unless a specific recommendation is made by a consulting toxicologist, the full course of NAC should be considered the standard of care.

Intravenous Therapy

The protocol of 52 hours of IV NAC appears to be as effective as the 72-hour course of oral NAC in reducing hepatotoxicity. Additionally, it has the advantage of assured delivery of treatment to patients who are vomiting. The IV form of NAC is safe, although it has a higher incidence of anaphylactoid reactions than does the oral form. Only a limited number of centers in the United States currently have access to the IV form of NAC on the basis of investigational drug status. It is hoped that the IV

form will gain Food and Drug Administration approval in the near future.

SUMMARY

Acetaminophen, although safe when taken at therapeutic doses, is hepatotoxic when taken as an acute single overdose or in continual excess. It is an important cause of morbidity and mortality worldwide.

Toxicity of acetaminophen is a result of its metabolism. Neither the parent compound nor the major metabolites are toxic. However, NAPQI, which is a minor metabolite elaborated by the mixed-function oxidase, is toxic when hepatic glutathione stores have been depleted.

Patients who have ingested overdose quantities of acetaminophen can be effectively treated with NAC. Treatment with NAC is beneficial for all patients with a massive single overdose when begun less than 24 hours after overdose but is most effective if started within 8 hours, and effectiveness declines incrementally for each hour after 8 hours. The Rumack nomogram is a reliable guide for determining which patients require antidote therapy after an acute overdose. The nomogram is not useful for patients who have continually ingested excessive amounts, and its usefulness after an overdose of the extended-release preparation of acetaminophen is untested.

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