CHAPTER 148

ACETAMINOPHEN

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PERSPECTIVE

Acetaminophen is one of the most commonly used antipyretic and analgesic agents throughout the world. Acetaminophen is found as an isolated product or in combination medications for the treatment of cold symptoms, pain, and headache. In 2010, an intravenous (IV) formulation was approved in the United States (an IV formulation was available in Europe and Australia previously) for the treatment of pain[1-3] and as an antipyretic.[4] Given the widespread use and availability of acetaminophen, toxicity is a concern in all intentional ingestions as well as with repeated supratherapeutic dosing and drug abuse. Acetaminophen toxicity is one of the leading causes of hospital admission, antidote use, and fatalities from oral poisonings in the United States.[5]

Protocols have been established for the assessment and management of acute acetaminophen ingestion through decades of research and experience. However, controversy continues to exist, and with new formulations recently approved, the management of acetaminophen exposures continues to evolve.

PRINCIPLES OF DISEASE

Acetaminophen is absorbed rapidly, with peak plasma concentrations generally occurring within 1 hour and complete absorption within 4 hours. Once it is absorbed, acetaminophen inhibits prostaglandin E_2 (PGE_2) synthesis, leading to antipyresis and analgesia. Inhibition of PGE_2 synthesis is by either direct cyclooxygenase-2 inhibition or inhibition of membrane-associated prostaglandin synthase.[6,7]

In therapeutic doses, acetaminophen is primarily metabolized by conjugation with glucuronide (40-67%) and sulfate (20-46%) into nontoxic metabolites that are excreted in the urine[8] (Fig. 148-1). A small percentage (<5%) is oxidized by cytochrome P_{450} 2E1 (CYP2E1) (and to a lesser extent 1A4 and 3A4) to a highly cytotoxic metabolic intermediary, *N*-acetyl-*p*-benzoquinone imine (NAPQI).[9,10] In therapeutic doses, NAPQI is short-lived, combining rapidly with glutathione and other thiol-containing compounds to form nontoxic metabolites that are excreted in the urine. With typical therapeutic acetaminophen dosing, glutathione stores and the ability to regenerate glutathione easily keep up with NAPQI production.

After large ingestions or repeated supratherapeutic ingestions, the amount of NAPQI produced begins to outstrip glutathione stores and the liver's ability to regenerate glutathione, leading to unbound NAPQI. The highly reactive electrophile NAPQI covalently binds to cell proteins in the liver, which initiates a cascade of events that lead to hepatic cell death. Renal injury may also occur with or without liver injury[11] and may be mediated by renal CYP enzymes or activation of prostaglandin synthase.

Acetaminophen-induced liver damage initially occurs in hepatic zone III (centrilobular) because oxidative metabolism is concentrated in this area. With severe toxicity, necrosis of the entire liver parenchyma may occur. The clinical effects of severe acetaminophen toxicity are the result of severe fulminant liver failure rather than a direct acetaminophen effect. These effects include multiorgan failure, systemic inflammatory response syndrome, hypotension, cerebral edema, and death.[12]

The principal therapy for acetaminophen toxicity is *N*-acetylcysteine (NAC), which is effective by two separate mechanisms. Soon after overdose, NAC serves as a glutathione precursor and a sulfur-containing glutathione substitute (see Fig. 148-1), binding to and thereby detoxifying NAPQI and avoiding subsequent hepatotoxicity. In addition, NAC may decrease NAPQI formation by enhancing acetaminophen conjugation with sulfate to nontoxic metabolites.

Even after acetaminophen hepatotoxicity is evident, NAC acts as a free radical scavenger and an antioxidant and alters hepatic microcirculation and oxygen delivery.[13] In patients with acetaminophen-induced hepatic failure, IV administration of NAC decreases the rates of cerebral edema, hypotension, and death even when no acetaminophen remains.[12]

CLINICAL FEATURES

Early after acute acetaminophen ingestion, patients may be asymptomatic or have mild nonspecific symptoms (e.g., nausea, vomiting, anorexia, malaise, diaphoresis) (Table 148-1). Liver injury becomes evident after a period of 8 to 36 hours as an elevation in aspartate transaminase (AST).[14] Once liver injury has begun, patients may have right upper quadrant pain or tenderness, vomiting, and jaundice. AST concentrations continue to rise rapidly[14] and usually peak in 2 to 4 days, corresponding to maximal liver injury. Alanine transaminase (ALT), prothrombin time, and bilirubin typically begin to rise and peak shortly after AST values. With severe toxicity, AST, ALT, and the prothrombin time may all be elevated within 24 hours (Fig. 148-2).[14] With maximal liver injury, patients have signs and symptoms consistent with fulminant liver failure, including metabolic acidosis, coagulopathy, and hepatic encephalopathy. Death may occur from hemorrhage, adult respiratory distress syndrome, sepsis, multiorgan failure, or cerebral edema. The risk of renal injury increases with the severity of hepatic injury; renal injury occurs in less than 2% of patients without hepatotoxicity and in 25% of patients with severe hepatotoxicity.

If patients recover, transaminases return to baseline concentrations during a 5- to 7-day period, although complete histologic resolution of liver injury may take months. Once histologic recovery is complete, there are no long-term sequelae to the

liver, and patients are not at increased risk for chronic hepatic dysfunction.

DIAGNOSTIC STRATEGIES

The goals of patient assessment after acetaminophen ingestion are the determination of the patient's risk, diagnostic testing, and treatment with the antidote NAC when appropriate.

Acetaminophen exposures may be classified as acute or chronic, and each type requires different testing and risk assessment. An acute ingestion is a single ingestion or a series of ingestions that are arbitrarily defined to occur within an 8-hour period. All other ingestions, including accidental repeated supratherapeutic ingestions and intentional ingestions spread for longer than 8 hours, can be considered to be chronic.

Risk Assessment with Acute Acetaminophen Ingestion

The initial diagnostic strategy of an acute ingestion is well established. The first step is to determine the patient's risk of acute acetaminophen exposure. Patients who report an acute intentional ingestion of acetaminophen should have laboratory risk stratification regardless of the reported amount ingested. It is likely that significantly more than 150 mg/kg must be acutely ingested before significant liver toxicity occurs; however, history alone may not be reliable. A serum acetaminophen concentration should be considered in all intentional overdoses because approximately 1.4 to 8.4% of patients with intentional ingestions who deny acetaminophen ingestion actually have a detectable but usually subtoxic concentration.[15-17]

Once a suggested exposure to acetaminophen is established, the next step is to establish a time of ingestion. If possible, this information should be corroborated by others. If no accurate time of ingestion can be determined, a worst-case scenario should be considered (e.g., the last time the patient was seen before the ingestion).

Once a patient is determined to be at risk and a time of ingestion has been established or estimated, the next step is to determine a serum acetaminophen concentration 4 hours after ingestion or as soon as possible after 4 hours. The serum acetaminophen concentration and the time of ingestion determine the need for antidotal therapy by plotting of the serum acetaminophen concentration against the time since ingestion on the treatment nomogram (Fig. 148-3), an adaptation of the Rumack-Matthew nomogram. If the serum acetaminophen concentration is on or above the treatment line (that starts at 150 µg/mL (990 µmol/L) at 4 hours and decreases to 4.7 µg/mL (31 µmol/L) at 24 hours), treatment with NAC should be initiated. If the serum acetaminophen concentration is below the treatment line and the most severe possible scenario has been taken for the time of ingestion,

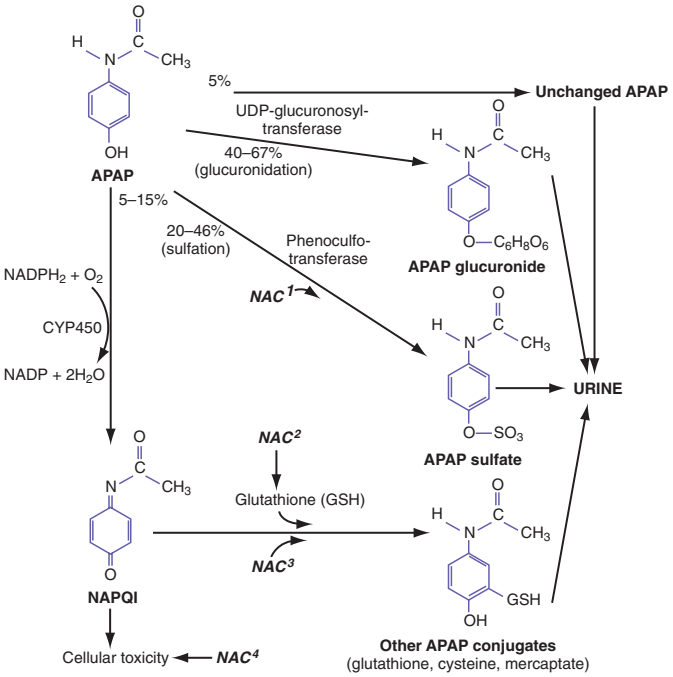

Figure 148-1. Acetaminophen (APAP) metabolism and *N*-acetylcysteine (NAC) mechanisms of action. NAC^1 enhances sulfation; NAC^2 serves as a glutathione (GSH) precursor; NAC^3 is a GSH substitute; NAC^4 may reduce systemic toxicity. *NAPQI, N*-acetyl-*p*-benzoquinone imine. (Modified from Smilkstein MJ: Acetaminophen. In Goldfrank LR, et al (eds): Goldfrank's Toxological Emergencies, ed 6. Stamford, Conn, Appleton & Lange, 1998, p 547.)

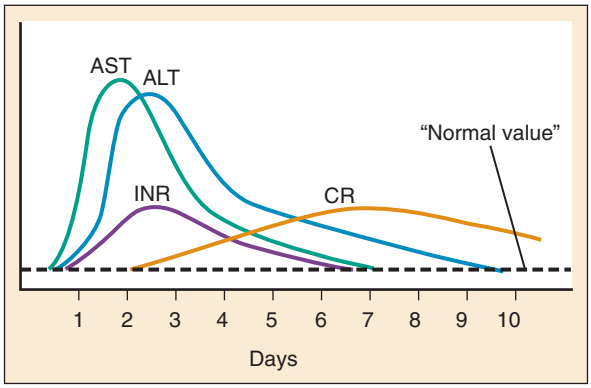

Figure 148-2. A typical time course of rise, peak, and fall of laboratory values in patients with acetaminophen-induced hepatic dysfunction who survive. Peaks are not proportional. Not all laboratory abnormalities occur in all patients, and significant individual variation may occur. *ALT,* alanine transaminase; *AST,* aspartate transaminase; *CR,* creatinine; *INR,* international normalized ratio. (Modified from Robert G. Hendrickson, MD. ©)

Table 148-1 Time Course and Clinical Stages of Acetaminophen Toxicity

STAGE	TIME COURSE	NAME	SYMPTOMS	SIGNS
1	0-12 (up to 24-36) hr	Preinjury	Nausea, vomiting, anorexia, malaise	Elevated serum acetaminophen concentration
2	8-36 hr	Liver injury	Nausea, vomiting, right upper quadrant abdominal tenderness	Transaminitis (AST begins to rise 8-36 hr after ingestion)
3	2-4 days	Maximum liver injury	Liver failure (encephalopathy, coagulopathy, hemorrhage, acidosis)	Hemorrhage, ARDS, sepsis/SIRS, multiorgan failure, cerebral edema
4	>4 days	Recovery	None	Complete hepatic histologic recovery

ARDS, acute respiratory distress syndrome; *AST,* aspartate transaminase; *SIRS,* systemic inflammatory response syndrome.

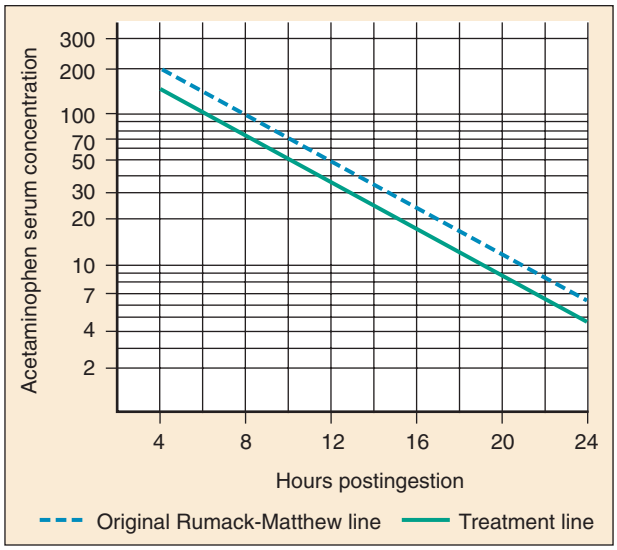

Figure 148-3. Treatment nomogram for acute overdose. The lower treatment line should be used for treatment decisions. (Modified from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. Pediatrics 55:871, 1975.)

the patient requires no antidote.[18] The treatment nomogram is a highly sensitive approach and may be used for all acute ingestions. Alternative approaches in patients with alcoholism,[19] in patients with coingestions of antimuscarinic agents,[20,21] in patients with unknown ingestion times,[22] and after the administration of IV formulations[23] have been suggested, but these remain controversial and unvalidated. Strict adherence to the approach described here is recommended.

Measurement of serum acetaminophen concentration before 4 hours is typically not necessary. It is likely that a serum acetaminophen concentration less than 10 µg/mL (66 µmol/L) between 1 and 4 hours after ingestion excludes significant ingestion of acetaminophen; however, there are few data on which to base this conclusion. Absorption of acetaminophen may not be complete before 4 hours, and any serum acetaminophen concentration greater than 10 µg/mL (66 µmol/L) is difficult to interpret. Finally, serum acetaminophen concentrations measured before 4 hours cannot be plotted on the treatment nomogram. Fortunately, there is little need to treat patients before 6 to 8 hours after ingestion; patients treated with NAC up to 6 hours after ingestion, even after very large doses, have no increased risk of hepatotoxicity regardless of their serum acetaminophen concentration.[24] For most overdose patients, the risk of hepatotoxicity does not significantly increase unless NAC is delayed for 8 hours or longer after ingestion.[24] This is generally enough time for a serum acetaminophen concentration to be determined at 4 hours and the laboratory evaluation to be completed. For patients at risk whose serum acetaminophen concentration cannot be obtained before 8 hours after ingestion, a loading dose of NAC should be considered.

There are few data for development of a strategy of risk assessment after a large IV acetaminophen overdose. Several pharmacokinetic factors suggest that some alteration of the typical nomogram-based assessment may be necessary. After infusion, IV acetaminophen generates serum concentrations that are significantly higher than an equivalent oral dose. In addition, the nomogram that is used for acute ingestions takes into account an absorptive period that is not necessary for an IV infusion. These and other factors suggest that an alternative approach may be necessary, but experience is limited. We adhere to a conservative approach, which suggests that patients be treated with NAC if they either (1) are treated with more than 60 mg/kg IV acetaminophen in one dose or (2) they have a serum acetaminophen concentration that is above 50 µg/mL (330 µmol/L) at 4 hours after the infusion stops.[25]

Table 148-2 Indications to Initiate Testing for Serum Acetaminophen Concentration and AST in Chronic Acetaminophen Ingestions[26]

Age ≥6 years	Ingestion of >10 g/day or >200 mg/kg/day (whichever is smaller) during a 24-hr period
or	Ingestion of >6 g/day or >150 mg/kg/day (whichever is smaller) during a 48-hr period or longer
or	Symptomatic (e.g., RUQ pain or tenderness, jaundice, vomiting)
Children <6 years	Ingestion of >200 mg/kg/day during a 24-hr period
or	Ingestion of >150 mg/kg/day during a 48-hr period
or	Ingestion of >100 mg/kg/day during a 72-hr or longer period
or	Symptomatic (e.g., RUQ pain or tenderness, jaundice, vomiting)

AST, aspartate transaminase; *RUQ,* right upper quadrant.

Risk Assessment with Chronic Ingestion

If the ingestion is a repeated or chronic exposure, risk assessment is more complex, and the treatment nomogram cannot be used. The initial steps include determining whether the patient is at risk for hepatotoxicity, evaluating the patient by measuring a serum acetaminophen concentration and AST, and initiating therapy with NAC.

The risk of hepatotoxicity from chronic ingestion of acetaminophen is increased with both an increasing total dose of acetaminophen and a longer duration in which it has been ingested in supratherapeutic quantities. With this in mind, laboratory testing for serum acetaminophen concentration and AST should be initiated in any patient who fits the criteria in Table 148-2.[26]

Ingestion of therapeutic amounts of acetaminophen appears to be safe.[27,28] However, rare reports of transaminitis and liver injury during therapeutic dosing suggest that some patients may be at increased risk for liver injury, possibly because of genetic variation or specific risk factors.[29] Patients who chronically ingest isoniazid or ethanol may have increased CYP2E1 activity and theoretically be at higher risk for chronic acetaminophen toxicity. Similarly, patients who have prolonged fasting (e.g., malnourished, AIDS, severe prolonged vomiting) and children with febrile illnesses[30-32] have reason to be at higher risk. All of these risk factors are controversial and require additional study. Given that we are unable to accurately predict the rare patient at high risk, patients who have symptoms consistent with liver injury (e.g., right upper quadrant pain or tenderness, jaundice) after taking acetaminophen merit risk determination regardless of the amount that they reportedly ingest.

Once serum acetaminophen concentration and AST are determined, further risk assessment is necessary. Conceptually, patients with chronic ingestions may benefit from antidotal therapy if they have evidence of liver injury *or* if they have evidence of acetaminophen excess that may lead to liver injury. With this in mind, patients with chronic supratherapeutic acetaminophen exposure with significant elevations of AST (e.g., >50 IU/L) should be treated with NAC regardless of their serum acetaminophen concentration.[33,34] A higher cutoff for AST (e.g., twice normal, or >120 IU/L) has been suggested but is unstudied.[35,36] In patients with an AST that is not elevated (e.g., <50 IU/L), NAC should be initiated if the serum acetaminophen concentration is higher than expected. After a typical therapeutic dose of acetaminophen, serum acetaminophen concentration peaks below 30 µg/mL (199 µmol/L) and is less than 10 µg/mL (66 µmol/L) at 4 hours.

All patients who do not require antidotal therapy should be instructed to return to the emergency department if they have signs of hepatotoxicity (e.g., right upper quadrant abdominal pain, vomiting, jaundice).

Risk Assessment in Pregnant Women

Fetal acetaminophen toxicity is rare, but adverse outcomes have been reported in all stages of pregnancy.[37] Acetaminophen crosses the placenta and may be present in concentrations in the fetus that are as high as or higher than those in the mother.[37] In the early gestational period, acetaminophen toxicity can be associated with fetal death.[37] CYP enzymes appear in the fetus during the second trimester, and activity increases with gestational age, which may put the maturing fetus (e.g., third trimester) or newborn at risk of toxicity.

The risk assessment for and diagnostic approach to pregnant women, however, are the same as those for nonpregnant women. In acute overdoses, a serum acetaminophen concentration should be determined and plotted on the treatment nomogram. NAC therapy should be initiated if the serum acetaminophen concentration plots above the treatment line. With chronic exposure, if either the AST is above 50 IU/L or the serum acetaminophen concentration is above expected, NAC therapy should be initiated.

MANAGEMENT

The mainstays of management are to provide supportive care and to initiate NAC therapy when it is indicated. Emergency physicians may consult with a regional poison center (1-800-222-1222) as the management of acetaminophen exposures is continually changing.

Limiting Gastrointestinal Absorption

Activated charcoal effectively binds acetaminophen in vitro[38] and limited studies have suggested some efficacy,[39,40] but there is no evidence that administration of activated charcoal to patients translates into improved clinical outcomes.

N-Acetylcysteine

When it is indicated, NAC should be administered as early as possible. Delay of NAC administration for more than 8 hours after ingestion increases the risk of hepatotoxicity (Fig. 148-4).

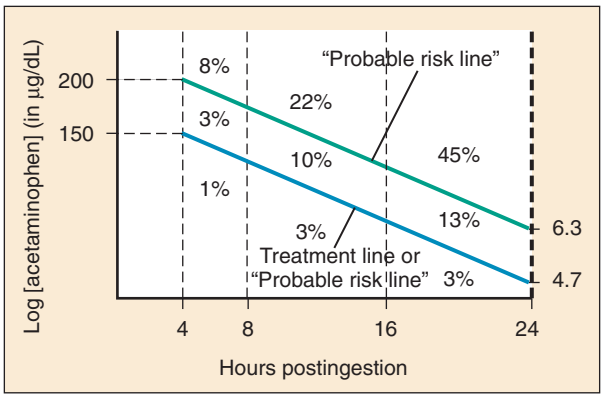

Figure 148-4. Risk of liver injury (alanine transaminase > 1000 IU) based on initial acetaminophen concentration and time to oral administration of *N*-acetylcysteine. (Modified from Rumack BH: Acetaminophen hepatotoxicity: The first 35 years. J Toxicol Clin Toxicol 40:3, 2002.)

NAC can be administered by the oral (PO) or IV route, with advantages and disadvantages for each. All formulations of NAC (PO and IV) are effective when they are started within 8 hours of ingestion.[24,41-44] The main role of early NAC administration is to prevent hepatotoxicity by detoxifying NAPQI and decreasing NAPQI production. The risk of liver injury (i.e., AST > 1000 IU/L) in this group with treatment with NAC is less than 4%, and the mortality rate approaches zero[41,44] (see Fig. 148-4).

Both PO and IV NAC are equally effective in treating patients who present 8 to 24 hours after ingestion, although the overall rate of liver injury (i.e., AST > 1000 IU/L) in this group is significantly higher (approximately 30%).[41,42,45]

Once liver failure (e.g., coagulopathy, encephalopathy) is evident, however, the IV route is the only route that has been systematically studied.[12] IV NAC decreases the risk of hypotension, cerebral edema, and death in patients with acetaminophen-related hepatic failure.[12] Oral NAC should be used only if IV NAC is not available.

The main differences between IV and PO NAC are in their side effect profiles (Table 148-3). Approximately 2 to 6% of patients treated with IV NAC have anaphylactoid reactions,[43,46-48] although rates of up to 30% have been reported in prospective trials.[49,50] The majority of these symptoms are mild and consist of transient skin rashes and flushing. More severe reactions have been reported in less than 1% of patients and include angioedema, bronchospasm, hypotension, and at least one death.[47-51] Symptoms typically occur within 30 minutes of the start of the loading infusion. These anaphylactoid reactions are dose, rate, and concentration dependent.[46,47]

Anaphylactoid reactions are much less frequent with PO NAC. Skin rash, serious systemic reactions, and anaphylactic reactions are rarely reported with the PO formulation. However, approximately 23% of patients receiving PO NAC vomit, delaying timely antidotal delivery.[52] PO NAC is extremely unpalatable, largely because of a "rotten egg" odor and taste. Palatability may be improved by administering NAC diluted with either soda or juice and serving it in a covered container through a straw. Any dose that is vomited within 1 hour of administration should be repeated. Antiemetics (e.g., ondansetron, metoclopramide) are advisable before PO NAC dosing, but there are few data about effectiveness of this approach.

Anaphylactoid reactions to IV NAC are typically mild (e.g., flushing) and occur during the initial 15- to 60-minute infusion. Mild reactions can be managed with antihistamines (e.g., IV diphenhydramine) without stopping the infusion. Serious reactions can be managed by slowing or pausing the infusion, giving a fluid bolus, and administering diphenhydramine or glucocorticoids intravenously if necessary.[53] Epinephrine is rarely required. Although these reactions require close observation and treatment as necessary, they do not preclude subsequent doses.[53]

Table 148-3 Side Effect Profile for *N*-Acetylcysteine Formulations

NAC FORMULATION	COMMON SIDE EFFECTS	SEVERE SIDE EFFECTS
PO NAC	Vomiting (23%)[52]	Very rare
IV NAC	Mild anaphylactoid reactions (e.g., rash, flushing, pruritus, vomiting), 2-18%[46-49,53]	Severe anaphylactoid reactions (e.g., hypotension), <1%[43,46-49]

IV, intravenous; *NAC, N*-acetylcysteine; *PO,* by mouth.

Table 148-4 Inpatient Predictors of the Severity of Illness in Patients with Acetaminophen Toxicity

SCORE	PREDICTIVE VARIABLES	OUTCOME PREDICTED	NOTES
Modified King's College Criteria	pH < 7.3 *or* *All three:* Cr > 3.3 mg/dL (292 mmol/L) *and* INR > 5 (or PTT > 100s) *and* Encephalopathy > grade III (patient comatose)	Death or transplantation	Arterial pH is measured *after* fluid resuscitation.
APACHE II[56]	APACHE II score > 20	Death or transplantation	Confounders include coingested medications that may alter the APACHE II score.
Lactate[57]	Lactate > 3.5 mmol/L before resuscitation	Death or transplantation	A specimen for lactate measurement was drawn a mean of 55 hr after ingestion. The predictive ability of an early draw is unknown.

APACHE II, Acute Physiology and Chronic Health Evaluation II; *Cr,* creatinine; *INR,* international normalized ratio; *PTT,* partial thromboplastin time.

N-Acetylcysteine in Pregnancy

Treatment of the mother with NAC is safe and effective,[54] and NAC effectively crosses the placenta.[55] Administration of IV NAC to the mother has the theoretic advantage of increased NAC delivery to the fetus compared with PO NAC. IV administration circumvents first-pass metabolism, presumably exposing the fetal circulation to higher maternal serum concentrations. On the basis of large published studies, we recommend continuation of therapy for 72 hours.[37]

Duration of Therapy

There are two well-established protocols for NAC administration: a 72-hour PO protocol and a 21-hour IV protocol. At the completion of these protocols, NAC may be discontinued if the metabolism of acetaminophen is complete (i.e., serum acetaminophen concentration > 10 µg/mL [66 µmol/L]) and there is no evidence of liver injury (normal AST concentration). The endpoint does not rely solely on the predetermined length of a protocol, and all protocols should be extended if there is significant liver injury (AST concentration greater than normal) *or* acetaminophen metabolism is incomplete (serum acetaminophen concentration > 10 µg/mL [66 µmol/L]). If it is extended, NAC therapy may be discontinued once evidence of liver injury has resolved (e.g., encephalopathy and coagulopathy have resolved and AST is decreasing and is less than 1000 IU/L) and acetaminophen is undetectable.

Supportive Care

Supportive care includes management of coingestions and the nausea and vomiting, hepatic injury, and renal dysfunction related to acetaminophen poisoning. Treatment of these problems is based on general treatment principles and is not acetaminophen dependent (see Chapter 90).

DISPOSITION

Asymptomatic patients who fit the criteria for treatment should be treated with NAC and can be admitted to a medical inpatient unit or emergency department observation unit. The motivation behind any ingestion needs to be evaluated, and psychiatric consultation may be obtained when it is appropriate.

Patients showing evidence of severe hepatotoxicity and those at risk for fulminant hepatic failure may need to be admitted to a monitored bed, often in an intensive care unit. These patients require frequent neurologic checks, monitoring of vital signs, and laboratory studies.

If a patient presents with established hepatotoxicity, transfer to a higher level center that specializes in the care of patients with liver failure may be advisable, as is the case for any other patient presenting with liver failure. Clinical predictors of severe hepatic failure are listed in Table 148-4.[56,57]

KEY CONCEPTS

- Acetaminophen concentration should be measured in cases of unknown or mixed overdoses. Acetaminophen is relatively clinically silent until serious hepatotoxicity ensues.
- Repeated supratherapeutic dosing of acetaminophen can lead to life-threatening toxicity.
- The acetaminophen concentration on the nomogram at 4 hours or more after ingestion is used to determine whether NAC therapy is indicated for acute ingestions.
- For maximum benefit, NAC treatment should not be delayed beyond 8 hours after ingestion. If more than 8 hours has passed since ingestion, treatment should be started with ongoing assessment of the amount of ingestion and likelihood of hepatotoxicity.
- Late or prolonged administration of NAC is beneficial even with low acetaminophen concentrations if hepatotoxicity is evident.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

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