Chapter 190: Acetaminophen

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INTRODUCTION AND EPIDEMIOLOGY

Acetaminophen (N-acetyl-p-aminophenol or paracetamol) is the most popular over-the-counter analgesic and is one of the most common toxic exposures reported to poison centers. Acetaminophen is available as a sole agent or combined with a variety of other medications prepared in many different forms, such as tablets, capsules, gels, and liquids. Poisonings often occur because of the erroneous belief that this medication is benign or because the victim was unaware that acetaminophen was an ingredient in the ingested preparation.\(^1\) The U.S. Acute Liver Failure Study Group found that acetaminophen poisoning was the cause of acute liver failure in 18% of cases initially judged to be of unknown cause.\(^2\) Acetaminophen–opioid combination products have been implicated in chronic overuse, likely due to an increasing opioid requirement leading to concomitantly increasing acetaminophen exposure. In response to these safety concerns, the U.S. Food and Drug Administration recently limited the prescription acetaminophen–opioid combination preparation strength to 325 milligrams per dosage unit and now requires a boxed warning to notify consumers of the potential risk for serious liver toxicity.\(^3\)

During 2010, the American Association of Poison Control Centers received reports of 66,473 exposures to acetaminophen–opioid combinations and 73,307 exposures to acetaminophen alone.\(^4\) There were 65 deaths attributed to isolated ingestions of acetaminophen combinations and 60 deaths attributed to isolated acetaminophen ingestions.\(^4\) Combining ED, hospital, and poisoning databases, an estimated 450 deaths occur each year in the United States due to acetaminophen overdose, and approximately 100 of them are unintentional, primarily due to supratherapeutic dosing of child preparations.\(^5\)

PHARMACOLOGY AND DOSING

ORAL ACETAMINOPHEN

The recommended maximum total daily dose is 3900 milligrams in adults using 325-milligram acetaminophen (regular strength) and 3000 milligrams when using the 500-milligram acetaminophen (extra strength) preparation. Adults should not use acetaminophen for more than 10 consecutive days unless directed by their physician. For children, the recommended acetaminophen dose is 10 to 15 milligrams/kg every 4 to 6 hours as needed, with a maximum daily dose of 75 milligrams/kg or five doses in a 24-hour
period. In 2011, the infant acetaminophen formulation (80 milligrams/0.8 mL concentration) was discontinued to minimize the risk for medication error. All pediatric, both infant and child, acetaminophen liquid preparations are now standardized to a concentration of 160 milligrams/5 mL.

Patients with insufficient glutathione stores (e.g., alcoholics and acquired immunodeficiency syndrome patients) and patients with induced cytochrome P-450 enzymatic activity (e.g., alcoholics and those taking concurrent anticonvulsant or antituberculous medications) may be at greater risk for developing acetaminophen-induced hepatotoxicity following overdose (as opposed to therapeutic dosing described earlier). Although the evidence supporting this risk is not definitive, it may be prudent to reduce acetaminophen dosage for this population. In contrast, children, because of their greater ability to metabolize acetaminophen through hepatic sulfation, may be at decreased risk for developing hepatotoxicity following a moderate overdose.\(^6,7\)

After ingestion of therapeutic doses, acetaminophen is rapidly absorbed from the GI tract, and peak serum concentrations are usually achieved within 30 minutes to 2 hours. In an overdose, peak serum concentrations are usually achieved within 2 hours, but delayed absorption of acetaminophen occurs following overdoses of preparations in which acetaminophen is combined with propoxyphene or diphenhydramine, as well as those with altered-release kinetics such as extended-release preparations.\(^8,9,10,11\) In therapeutic amounts, acetaminophen has nearly 100% bioavailability, is approximately 20% bound to serum proteins, has a volume of distribution of around 0.85 L/kg, and has an elimination half-life of approximately 2.5 hours. The therapeutic concentration for the antipyretic effect of acetaminophen is between 10 and 20 micrograms/mL (66 to 132 micromoles/L), but therapeutic concentrations for analgesia are not established.

Oral acetaminophen appears to be nontoxic when administered following therapeutic dosing guidelines. Both retrospective and prospective studies have yielded inconsistent results concerning the risk of acute liver injury with repeated use of therapeutic acetaminophen doses.\(^12\) The prospective studies, which are better controlled than the retrospective ones, find a slight increase in liver injury but no evidence of increased hepatic failure or death when using therapeutic acetaminophen doses for sustained periods.\(^13\) For alcoholic patients, no evidence of liver injury was seen when treated with the recommended maximal daily dose of acetaminophen for 3 consecutive days.\(^14,15\)

**IV ACETAMINOPHEN**

An IV acetaminophen formulation was approved by the U.S. Food and Drug Administration in 2010 for adults and children 2 years of age or older. The recommended dosing of IV acetaminophen for adults or children weighing more than 50 kg is 650 milligrams every 4 hours or 1000 milligrams every 6 hours, with a maximum total daily dose of 4 grams. For adults or children weighing less than 50 kg, the recommended dosing is 12.5 milligrams/kg every 4 hours or 15 milligrams/kg every 6 hours (maximum individual dose of 750 milligrams), with a maximum total daily dose of 75 milligrams/kg or 3750 milligrams. Peak concentrations following IV administration occur at the end of the 15-minute infusion period.\(^16\) Compared to a similar dose of oral
acetaminophen, IV acetaminophen achieves a 70% greater maximum concentration but provides a similar total drug exposure. 16

ACETAMINOPHEN METABOLISM

In therapeutic amounts, acetaminophen is primarily metabolized by the liver through sulfation (20% to 46%) and glucuronidation (40% to 67%), with <5% undergoing direct renal elimination. Normally, a small percentage is also oxidized by the cytochrome P-450 system to a reactive metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). This is quickly detoxified by hepatic glutathione to a nontoxic acetaminophen-mercapturate compound that is renally eliminated (Figure 190-1). After acetaminophen overdose, hepatic metabolism through glucuronidation and sulfation may be saturated, and a larger proportion of acetaminophen is therefore metabolized by cytochrome P-450 to NAPQI, depleting intracellular glutathione. When hepatic stores of glutathione decrease to <30% of normal, NAPQI binds to other hepatic macromolecules, and hepatic necrosis ensues. Although the clinical manifestations of acetaminophen toxicity are classically delayed, hepatic injury actually occurs early, within 12 hours of exposure.

FIGURE 190-1.
Acetaminophen metabolism. A. After ingestion of therapeutic amounts, predominant metabolism is via glucuronidation and sulfation. The small amount of N-acetyl-p-benzoquinoneimine (NAPQI) generated is conjugated with glutathione to a nontoxic compound. B. After ingestion of large amounts, glucuronidation and sulfation are saturated, and an increased amount of NAPQI is generated. Detoxification of NAPQI to a nontoxic compound soon depletes glutathione stores, leaving excess NAPQI to bind to intracellular proteins, causing cell death. APAP = N-acetyl-p-aminophenol (acetaminophen).
Within the hepatic lobule, cytochrome P-450 is concentrated within hepatocytes surrounding the terminal hepatic vein and is least concentrated within hepatocytes surrounding the portal triad. As a result, acetaminophen-induced hepatic injury develops in the characteristic pattern of centrilobular necrosis. Hepatic injury can be identified by microscopic evidence as well as immunofluorescent staining of NAPQI-hepatic protein adducts within hepatocytes. Observed hepatocyte damage typically progresses with cell lysis on the second day after an acute toxic exposure, releasing hepatic enzymes, such as transaminases, and
NAPQI-hepatic protein adducts into the circulation where they are detectable in the serum. This corresponds generally to the development of overt clinical toxicity.

**CLINICAL FEATURES OF ACETAMINOPHEN TOXICITY**

The initial clinical findings of acetaminophen toxicity are nonspecific and delayed in onset.

**FOUR STAGES OF ACETAMINOPHEN TOXICITY**

The clinical presentation of human acetaminophen poisoning can be roughly divided into four stages (Table 190-1). During the first 24 hours after exposure (stage 1), patients often have minimal and nonspecific symptoms of toxicity, such as anorexia, nausea, vomiting, and malaise. Hypokalemia and metabolic acidosis may be seen during the first 24 hours and correlate with a high 4-hour acetaminophen concentration.\(^1^7,1^8,1^9,2^0\) By days 2 to 3 (stage 2), symptoms seen in stage 1 often improve, but clinical signs of hepatotoxicity may occur, including right upper quadrant abdominal pain and tenderness, with elevated serum transaminases. Even without treatment, most patients with mild to moderate hepatotoxicity recover without sequelae. However, by days 3 to 4 (stage 3), some patients will progress to fulminant hepatic failure.\(^2^1,2^2\) Characteristic stage 3 findings include metabolic acidosis, coagulopathy, renal failure, encephalopathy, and recurrent GI symptoms. Patients who survive the complications of fulminant hepatic failure begin to recover over the next 2 weeks (stage 4), with complete resolution of hepatic dysfunction in survivors after 1 to 3 months.
TABLE 190-1
Clinical Stages of Acute Acetaminophen Toxicity

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>First 24 h</td>
<td>Days 2–3</td>
<td>Days 3–4</td>
</tr>
<tr>
<td><strong>Clinical manifestations</strong></td>
<td>Anorexia</td>
<td>Improvement in anorexia, nausea, and vomiting</td>
<td>Recurrence of anorexia, nausea, and vomiting</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Abdominal pain</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Hepatic tenderness</td>
<td>Anuria</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td><strong>Laboratory abnormalities</strong></td>
<td>Hypokalemia</td>
<td>Elevated serum transaminases</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elevated bilirubin and prolonged prothrombin time if severe</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coagulopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal failure</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Pancreatitis</td>
</tr>
</tbody>
</table>

Acetaminophen may also cause acute, extrahepatic toxic effects, presumably because of the presence of cytochrome P-450 or similar enzymes (e.g., prostaglandin H synthase) in other organs. Ingestion of massive doses of acetaminophen (e.g., 4-hour acetaminophen concentrations >800 micrograms/mL or >5300 micromoles/L) is associated with the altered sensorium and a metabolic acidosis with an elevated lactate that can occur in the absence of either liver failure or hypotension. Renal insufficiency occurs in 1% to 2% of patients following acetaminophen overdose, usually after hepatic failure is evident. In rare cases, isolated renal injury, cardiac toxicity, and pancreatitis may occur.

**DIAGNOSIS**

Acute acetaminophen poisoning is diagnosed by the serum acetaminophen concentration and estimating the time since ingestion.

A toxic exposure to acetaminophen is suggested when a patient ≥6 years old ingests (1) >10 grams or 200 milligrams/kg as a single ingestion, (2) >10 grams or 200 milligrams/kg over a 24-hour period, or (3) >6 grams or 150 milligrams/kg per 24-hour period for at least 2 consecutive days. For children <6 years old, ingestion of 200 milligrams/kg or more of acetaminophen as a single ingestion or over an 8-hour period, or of 150 milligrams/kg per 24-hour period for the preceding 48 hours is considered a toxic exposure. These values are
empiric and not validated in human trials, but they are widely used as recommendations for emergency evaluation. Even though a patient's history of the amount ingested may be unreliable, a patient report of >10 to 12 grams ingested was associated with a 4-hour acetaminophen concentration above 150 micrograms/mL (1000 micromoles/L) in 40% to 70% of toxic exposures.29,30

Due to the widespread availability of acetaminophen-containing products, the delayed clinical manifestations after overdose, and the serious complications of acute toxicity without antidotal therapy, measurement of a serum acetaminophen concentration is recommended for all patients presenting to the ED with an intentional overdose.31,32 Potentially toxic acetaminophen levels have been seen in ED overdose patients who denied ingesting acetaminophen.33,34 Empirical testing of all patients with intentional overdoses may be cost-effective, as the estimated cost of treating a single patient for complications of acetaminophen-induced hepatotoxicity is judged to outweigh the cost of routine laboratory testing all intentional overdose patients. A qualitative acetaminophen urine screen can also be used to identify potential acetaminophen overdose patients.35

THE RUMACK-MATTHEW NOMOGRAM

The implication of a measured acetaminophen concentration is determined by plotting the value on the Rumack-Matthew nomogram (Figure 190-2).36 This nomogram was derived from a retrospective analysis of oral acetaminophen overdose patients and their clinical outcomes. The original nomogram line separating possible toxicity from unlikely toxicity was based on a 4-hour acetaminophen concentration of 200 micrograms/mL (1300 micromoles/L), but was subsequently modified by moving the line to a 4-hour acetaminophen concentration of 150 micrograms/mL (1000 micromoles/L) to increase the safety margin for treatment decisions. The nomogram only directly applies to an acetaminophen concentration obtained after a single oral exposure and during the window between 4 hours and 24 hours postingestion. Outcome prediction using this nomogram cannot be applied to acetaminophen concentrations obtained outside this 20-hour window or with chronic or recurrent exposures. Obtaining multiple acetaminophen concentrations following acute overdose is rarely indicated in the absence of hepatotoxicity.37,38 An initial concentration below the nomogram line may rarely "cross the line" in patients who ingest acetaminophen preparations known to have prolonged absorption kinetics.11 However, the clinical significance of "crossing the line" in this fashion is unknown. Similarly, because the nomogram was constructed and verified by using only a single serum concentration, the clinical implications of a concentration above the line that falls below it on repeat analysis are unknown.

FIGURE 190-2.
Rumack-Matthew nomogram.
Based on data obtained before the widespread use of antidotal therapy, patients with serum acetaminophen concentrations above the original line (4-hour postingestion concentration >200 micrograms/mL or >1300 micromoles/L) were observed to have a 60% risk of developing hepatotoxicity (defined as alanine aminotransferase >1000 IU/mL), a 1% risk of renal failure, and a 5% risk of mortality. In addition, patients with extremely high serum acetaminophen concentrations (above a parallel line coinciding with a 4-hour
postigestion concentration of 300 micrograms/mL or 2000 micromoles/L) were observed to have a 90% risk of developing hepatotoxicity. The prediction of a safe outcome below the nomogram line corresponding to a 4-hour postigestion concentration of 150 micrograms/mL (1000 micromoles/L) was confirmed in patients who did not receive antidotal therapy; the incidence of hepatotoxicity in patients with acetaminophen concentrations below this nomogram line was 1%, and all patients recovered without complications.38

A method to determine potential toxicity from IV acetaminophen overdose has not been established. Fortunately, the European experience with IV acetaminophen suggests that these overdoses appear to be rare in-hospital occurrences that are likely to occur following an error in calculating the acetaminophen dose in pediatric patients.40,41,42 However, the available clinical data for evaluating IV acetaminophen overdose remain limited to several published case reports.42 Because the Rumack-Matthew nomogram was solely derived from oral acetaminophen overdose patients, strictly applying the nomogram to determine toxicity following IV acetaminophen overdose may not be appropriate at this time.

TREATMENT

GI DECONTAMINATION

Treatment of acetaminophen poisoning consists primarily of the timely use of the antidote acetylcysteine and supportive care.1,36,37 For most cases of acetaminophen poisoning, adequate GI decontamination consists of the early administration of activated charcoal orally or through a nasogastric tube.1,43,44 Inducing emesis by administering ipecac syrup is undesirable because it delays the administration of the oral antidote. In addition, more aggressive forms of decontamination, such as gastric lavage or whole-bowel irrigation, are unnecessary because of the rapid GI absorption of acetaminophen and the great success of treating acetaminophen poisoning with acetylcysteine.

ACETYLCYSTEINE

The mainstay for the prevention or treatment of acetaminophen toxicity is the administration of acetylcysteine.1,45,46,47 The current "standard" acetylcysteine protocols were developed from primarily observational trials, and it is not clear if they represent the most effective regimens.48

Although its mechanisms of action are not fully understood, acetylcysteine is thought to have two important beneficial effects.47,48 In early acetaminophen poisoning (<8 hours after ingestion), acetylcysteine averts toxicity by preventing the binding of NAPQI to hepatic macromolecules. Acetylcysteine may do this by acting as a glutathione precursor or substitute, or a sulfate precursor, or it may directly reduce NAPQI back to acetaminophen. In established acetaminophen toxicity or >24 hours after acetaminophen ingestion, acetylcysteine diminishes hepatic necrosis by acting as an antioxidant, decreasing neutrophil infiltration, improving microcirculatory blood flow, or increasing tissue oxygen delivery and extraction.
If acetylcysteine is given within 8 hours of an acute acetaminophen ingestion, it is nearly 100% effective in preventing the development of hepatotoxicity.\textsuperscript{39} The longer the initiation of acetylcysteine therapy is delayed beyond 8 hours after ingestion, the greater the risk of developing hepatotoxicity.\textsuperscript{49} Even up to 24 hours following acetaminophen ingestion, however, acetylcysteine treatment is associated with a lower risk of hepatotoxicity than historical controls.\textsuperscript{39}

Clinical experience suggests that patients with poor glutathione reserves, such as alcoholics and the chronically ill, have similar excellent clinical outcomes when the standard treatment guidelines are applied to their care. As such, there is no need to alter the use of the acetaminophen treatment nomogram or modify the dosing of acetylcysteine for these patients.

The weight of evidence suggests that \textbf{acetylcysteine therapy is both safe and efficacious during pregnancy} and that the approach to treating a pregnant patient following an acetaminophen overdose should remain the same. Although an ovine model demonstrated that acetylcysteine is unable to cross the placenta, there are data in humans establishing that it does.\textsuperscript{50} Acetylcysteine treatment has never been associated with fetal malformations in humans, but fetal demise and malformations have been described following delayed acetylcysteine treatment after acetaminophen overdose in first-trimester pregnant women.\textsuperscript{51}

\textbf{IV Acetylcysteine}

IV acetylcysteine has been used to supplant oral administration due to its greater ease of administration, greater patient acceptance, equivalent efficacy, and shorter duration of treatment for many cases of acetaminophen poisoning.\textsuperscript{52,53,54,55} The major limitation of IV acetylcysteine is the occurrence of drug-related anaphylactoid reactions (occurring during the first 2 hours of administration), which in mild cases is treated with diphenhydramine and in severe cases is treated by temporarily slowing/stopping the acetylcysteine infusion.\textsuperscript{56} The risk of anaphylactoid reaction from IV acetylcysteine ranges from 4% to 17%.\textsuperscript{57,58,59,60} Asthmatics appear to have a greater risk of anaphylactoid reactions during IV acetylcysteine therapy, whereas overdose patients with high acetaminophen concentrations appear to have a lower risk of developing anaphylactoid reactions.\textsuperscript{59,60,61,62} Approximately 13% of patients treated with IV acetylcysteine develop nausea and vomiting.\textsuperscript{63} Rare complications, including status epilepticus, hemolytic uremic syndrome, cerebral edema, and death, have been reported following massive overdose of IV acetylcysteine.\textsuperscript{64,65,66,67}

The standard regimen for IV acetylcysteine utilizes a 20-hour protocol with a loading dose of 150 milligrams/kg over 15 minutes to 1 hour, followed by a first maintenance dose of 50 milligrams/kg infused over 4 hours, and then followed by a second maintenance dose of 100 milligrams/kg infused over 16 hours (\textbf{Table 190-2}). Administering the initial dose over an hour appears to minimize the incidence of drug-related adverse effects, particularly anaphylactoid responses, although this belief has not been substantiated when prospectively studied.\textsuperscript{58} Because the three-phase dosing regimen for IV acetylcysteine may result in dosing
errors and produce side effects due to the initial high infusion rate, alternative dosing regimens are being explored. 68,69,70
<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>IV Adult</th>
<th>IV Pediatric (&lt;40 kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preparation</strong></td>
<td>Available as 10% and 20% solutions. Dilute to 5% solution for oral administration.</td>
<td>Available as 20% solution.</td>
<td>Available as 20% solution. Dilute to 2% solution by mixing 50 mL in 450 mL 5% dextrose in water.</td>
</tr>
<tr>
<td><strong>Loading dose</strong></td>
<td>140 milligrams/kg.</td>
<td>150 milligrams/kg in 200 mL 5% dextrose in water infused over 15–60 min.</td>
<td>150 milligrams/kg (7.5 mL/kg) infused over 15–60 min.</td>
</tr>
<tr>
<td><strong>Maintenance dose</strong></td>
<td>70 milligrams/kg every 4 h for 17 doses.</td>
<td>50 milligrams/kg in 500 mL 5% dextrose in water infused over 4 h (12.5 milligrams/kg per hour). <em>followed by</em> 100 milligrams/kg in 1000 mL 5% dextrose in water infused over 16 h (6.25 milligrams/kg per hour).</td>
<td>50 milligrams/kg (2.5 mL/kg) infused over 4 h (12.5 milligrams/kg per hour). <em>followed by</em> 100 milligrams/kg (5 mL/kg) infused over 16 h (6.25 milligrams/kg per hour).</td>
</tr>
<tr>
<td><strong>Duration of therapy</strong></td>
<td>72 h.</td>
<td>20 h.</td>
<td>20 h.</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Dilute with powdered drink mix, juice, or soda. Serve chilled. Drink through a straw to reduce disagreeable smell.</td>
<td>Monitor for drug-related adverse effects and anaphylactoid reactions.</td>
<td>Monitor for drug-related adverse effects and anaphylactoid reactions. 500 mL of the 2% solution prepared as described above is enough to treat a 33-kg child for the full 20-h course.</td>
</tr>
</tbody>
</table>
IV acetylcysteine is commercially available as a 20% solution and requires dilution to a 2% solution for infusion into a peripheral vein. Both 5% dextrose in water and half-normal saline can be used as diluents.\textsuperscript{71} Given the volume and hypotonicity of fluid required, children and small adults should be carefully monitored to avoid fluid overload and hyponatremia during treatment.\textsuperscript{52}

Despite the lack of randomized direct comparisons, IV acetylcysteine is as effective and safe as oral therapy for patients with early acetaminophen poisoning, as compared with retrospective cohorts and historical controls.\textsuperscript{54,72,73,74,75} IV acetylcysteine is the route of choice for patients with acetaminophen-induced fulminant hepatic failure, because oral acetylcysteine has not been adequately studied in this setting.\textsuperscript{76} There is the potential for delayed hepatic toxicity after the completion of acetylcysteine therapy, especially the 20-hour IV protocol.\textsuperscript{77}

**Oral Acetylcysteine**

The standard 72-hour oral acetylcysteine regimen used in the United States consists of a loading dose of 140 milligrams/kg followed by maintenance doses of 70 milligrams/kg every 4 hours for 17 additional doses (Table 190-2). It may still be appropriate in certain patients, such as those at high risk for anaphylactoid responses to the IV formulation and asthmatics. The taste is disagreeable, and some patients with persistent nausea and vomiting may require concomitant antiemetics such as ondansetron.

**EXTRACORPOREAL ELIMINATION**

Case reports describe the use of extracorporeal detoxification in patients presenting late after a serious acetaminophen overdose to both remove the drug and treat the hepatic encephalopathy.\textsuperscript{78,79} The role of such therapy in the overall management of serious acetaminophen toxicity remains to be defined.

**TREATMENT GUIDELINES BASED ON TIME TO ED PRESENTATION**

Treatment guidelines for oral acetaminophen poisoning are based on the time to presentation to the ED after ingestion: <4 hours, between 4 hours and 24 hours, and unknown time or >24 hours before presentation (Figure 190-3).\textsuperscript{37} In toxic overdoses, the risk of hepatotoxicity increases with the lag time between ingestion and initiation of acetylcysteine therapy.\textsuperscript{49} The optimal outcome with acetylcysteine therapy is seen if it is administered within 8 hours after ingestion, so the optimal "decision-time window" for treatment is between the 4-hour acetaminophen concentration measurement and 8-hour goal to initiate acetylcysteine.\textsuperscript{39} No further acetaminophen serum measurements are necessary once the need for acetylcysteine therapy has been determined until the completion of the course of therapy.

**FIGURE 190-3.**

Treatment guidelines for acetaminophen (APAP) ingestion. All times noted are postingestion. AC = acetylcysteine; ALT = alanine aminotransferase; AMS = altered mental status; AST = aspartate aminotransferase; Cr = creatinine; LFTs = liver function tests; PT = prothrombin time; Rx = treatment.
Presentation Within 4 Hours of Ingestion

For patients who present to the ED within 4 hours and are likely to have a significant acetaminophen overdose, treatment begins with GI decontamination (usually activated charcoal) while awaiting the 4-hour postingestion acetaminophen concentration. If the clinical laboratory can report an acetaminophen concentration within 8 hours post-ingestion, wait for the serum acetaminophen concentration and plot the result on the nomogram to determine whether acetylcysteine therapy is necessary. If the acetaminophen concentration will not be available by 8 hours post-ingestion, empirically initiate acetylcysteine therapy without waiting for the result. Subsequently, when the acetaminophen concentration is determined, the need for acetylcysteine therapy can be determined with the use of the nomogram.

Presentation >4 and <24 Hours After Ingestion
For patients who present >4 hours but <24 hours following acetaminophen ingestion, determine the serum acetaminophen concentration as soon as possible. GI decontamination may be performed, particularly for suspected coingestants, but it may have limited effectiveness because of the delay in presentation. If the laboratory can determine the acetaminophen concentration within 8 hours postingestion, await the acetaminophen concentration and plot the result on the nomogram to determine if acetylcysteine therapy is necessary. Otherwise, empirically administer acetylcysteine.

**Presentation >24 Hours After Ingestion or Time of Ingestion Unknown**

For patients in whom the time of acetaminophen ingestion remains unknown or is >24 hours or for those with suggestive clinical findings of acetaminophen poisoning, a serum acetaminophen concentration and serum transaminase, bilirubin, and prothrombin time tests should be determined. Initiate acetylcysteine therapy as soon as possible while awaiting laboratory results. In this scenario, a detectable acetaminophen concentration (>10 micrograms/mL or >66 micromoles/L) suggests that the patient may be at risk for developing hepatotoxicity. Similarly, elevated serum transaminases suggest the possibility of ongoing hepatic toxicity. Therefore, continued acetylcysteine therapy is indicated if the acetaminophen concentration is measurable or if the serum transaminases are elevated. If serum acetaminophen concentration is <10 micrograms/mL (<66 micromoles/L) and the serum transaminases are not elevated, then acetylcysteine can be discontinued.

**DISPOSITION AND FOLLOW-UP**

Many experts recommend rechecking serum acetaminophen and transaminase levels at the completion of acetylcysteine therapy with continuation of acetylcysteine infusion at the rate of 6.25 milligrams/kg per hour until the serum acetaminophen concentration is not detectable or is less than 10 micrograms/mL (66 micromoles/L) and transaminase concentrations are normal or rapidly decreasing.\(^48,55\)

All patients requiring acetylcysteine therapy should be admitted to the hospital until the completion of the therapy. In general, admission to a hospital floor bed is adequate unless the coingestant is of concern, hepatotoxicity is severe, or the patient is suicidal and 24-hour direct observation cannot be arranged. Patients who are not at risk for developing acetaminophen-induced hepatotoxicity (e.g., acetaminophen concentration below the nomogram or unmeasurable acetaminophen concentration with normal hepatic transaminase concentrations) should be observed in the ED for 4 to 6 hours to exclude potentially toxic coingestants before disposition. Psychiatric evaluation should be considered for patients with intentional acetaminophen overdoses. Cases of acetaminophen ingestion or toxicity should be reported to the regional poison control center for both data collection purposes and assistance with management.

**SPECIAL CONSIDERATIONS**

**FULMINANT HEPATIC FAILURE**
Unfortunately, a small percentage of patients who overdose with acetaminophen will develop fulminant hepatic failure. Acetaminophen poisoning is the number one cause of acute liver failure, accounting for 39% to 46% of cases in the United States. The mortality rate for patients with acetaminophen-induced fulminant hepatic failure without acetylcysteine therapy is estimated to be between 5% and 80%. Most fatalities occur on days 3 to 5 after overdose and are attributed to hepatic complications such as cerebral edema, hemorrhage, shock, acute lung injury, sepsis, and multi-organ failure. Patients who eventually survive fulminant hepatic failure generally begin to show evidence of recovery by days 5 to 7. Survivors will eventually develop complete hepatic regeneration without any persistence of hepatic impairment.

Acetylcysteine treatment decreases the incidence of cerebral edema, reduces vasopressor requirements, and improves survival in acetaminophen-induced fulminant hepatic failure. Acetylcysteine also appears to be beneficial in the treatment of other forms of hepatic failure, including viral hepatitis and alcoholic cirrhosis.

Prognostic indicators associated with the highest risk of mortality from acetaminophen-induced fulminant hepatic failure include metabolic acidosis (arterial pH <7.30) despite fluid and hemodynamic resuscitation, or a combination of coagulopathy (prothrombin time >100 seconds), renal insufficiency (serum creatinine >3.3 milligrams/dL or >292 micromoles/L), and grade III or IV hepatic encephalopathy. Other predictors of a poor prognosis include an Acute Physiology and Chronic Health Evaluation II score >15, elevated serum lactate (>26 milligrams/dL or >3.0 mmol/L) after fluid resuscitation, and elevated serum phosphate (>3.71 milligrams/dL or >1.2 mmol/L) on the second day after ingestion. Multifactor scoring systems have also been developed to predict hepatotoxicity in single and staggered overdoses.

Treatment for acetaminophen-induced fulminant hepatic failure includes acetylcysteine therapy, correction of coagulopathy and acidosis, monitoring for and aggressive treatment of cerebral edema, and early patient referral to a liver specialty/transplant center. Unlike the treatment of early acetaminophen toxicity, IV acetylcysteine therapy should be continued past the 20-hour standard regimen until the patient recovers, receives a liver transplant, or dies.

**MULTIPLE-DOSE AND EXTENDED-RELEASE ACETAMINOPHEN INGESTIONS**

Patients with staggered acetaminophen ingestions and liver injury often have delayed presentation to the hospital and a higher rate of adverse outcomes. Multiple closely spaced acetaminophen ingestions and extended-release acetaminophen ingestions represent two unique aspects of acetaminophen poisoning for which the Rumack-Matthew nomogram cannot be readily applied because a single time of ingestion does not exist. A conservative approach is to assume that a single ingestion occurred at the earliest possible time stated by the patient, with the acetaminophen concentration plotted on the Rumack-Matthew nomogram based on this artificial time and treatment decisions made accordingly. For example, if the patient ingests five doses of 50 milligrams/kg of acetaminophen over a 4-hour period beginning 8 hours ago, a single acetaminophen ingestion is assumed to have occurred 8 hours ago, and the serum concentration accordingly is plotted on the nomogram.
Extended-release acetaminophen formulations consist of a bilayered tablet containing a 325-milligram immediate-release outer layer and a 325-milligram slow, continuous-release, highly compressed inner layer. Because there are little clinical data concerning overdose with these preparations, treatment guidelines remain conservative, and the manufacturer recommends obtaining a second acetaminophen concentration 4 to 6 hours after the first concentration in those situations in which the first measured concentration (4 to 8 hours postingestion) is elevated but below the nomogram line.92,93 A full course of acetylcysteine therapy should be instituted (or continued if already started) if the second acetaminophen concentration is above the nomogram line. If the initial concentration is above the nomogram line, standard therapy should be administered, and there is no need to obtain a second concentration.

**IV ACETAMINOPHEN OVERDOSE**

Accepted guidelines for treatment of IV acetaminophen overdose do not currently exist in the United States. The local poison center should be contacted for guidance following any suspected IV acetaminophen overdose.

**REFERENCES**


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**USEFUL WEB RESOURCES**

The American Association of Poison Control Centers (AAPC)—http://www.aapcc.org/DNN

The American Academy of Clinical Toxicology (AACT)—http://www.clintox.org/index.cfm

The European Association of Poisons Centres and Clinical Toxicologists (EAPCCT)—http://www.eapcct.org

The Asia Pacific Association of Medical Toxicology (APAMT)—http://www.asiatox.org
The South Asian Clinical Toxicology Research Collaboration (SACTRC)—http://www.sactrc.org

TOXBASE: The primary clinical toxicology database of the National Poisons Information Service—http://www.toxbase.org. (Free access for United Kingdom National Health Service hospital departments and general practices, National Health Service Departments of Public Health and Health Protection Agency Units. Available to hospital emergency departments in Ireland by contract. Available to European poison centers whose staff are members of the European Association of Poisons Centres and Clinical Toxicologists. Overseas users may be allowed access on payment of a yearly subscription, subject to approval of the Health Protection Agency.)


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