Over-the-Counter Pain Management Gone Awry
Acetaminophen Poisoning
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Stephanie N. Baker, PharmD

ABSTRACT
Acetaminophen is one of the most popular nonnarcotic analgesic–antipyretic agents available. Inappropriate use of this agent can lead to significant morbidity and mortality secondary to hepatic necrosis. Several patient-specific factors impact its metabolism and the subsequent production of its toxic metabolite when consumed in excess. Rapid diagnosis and treatment with N-acetylcysteine in the first few hours following overdose is imperative in preventing permanent hepatic damage and death. It is essential for all health care providers to be familiar with the etiology and progression of this poisoning, as well as the necessary steps in treatment, to provide the highest level of care for this often-treatable condition. Key words: acetaminophen, acetadote, APAP, N-acetylcysteine, paracetamol

INTRODUCED IN 1955, acetaminophen (N-acetyl-para-aminophenol or APAP), also known as paracetamol outside the United States, is one of the most popular non-narcotic analgesic–antipyretic agents in the world. This agent is perceived by the public to be remarkably safe and it is, if taken appropriately. In addition, it is included in many over-the-counter and prescription cough, cold, and analgesia preparations—a fact that laypeople may not appreciate. Despite its widespread appeal, inappropriate use can lead to significant morbidity and mortality from hepatic necrosis. Easy accessibility and an array of product formulations mean that acetaminophen toxicity should be considered in the differential diagnosis when it is identified as a potential exposure and when it may just be a possibility. Fortunately, with the development of N-acetylcysteine (NAC), the impact of these poisonings on patient outcomes has been greatly diminished. The intent of this review is to discuss the toxicity associated with acetaminophen as well as its management.
EPIDEMIOLOGY

Acetaminophen is available in a wide variety of both prescription and nonprescription products, including in combination with opioid analgesics. On the basis of data reported in 2007 via the Toxic Exposure Surveillance System, this agent was involved in 50,758 single and combination exposures and associated with 348 fatalities in the United States (Bronstein et al., 2008). Approximately half of these exposures were classified as unintentional overdoses and close to 14,000 were in children younger than 6 years. Although generally safe, significant liver injury and hepatic necrosis can occur when doses are consumed in excess of those that can be metabolized safely by endogenous systems. These metabolic processes can be influenced by several patient-specific factors; however, generally liver injury and hepatic necrosis have been associated with doses in excess of 10 g or 150 mg/kg per day (Buckley, Whyte, O’Connell, & Dawson, 1999; Vale & Kulig, 2004).

METABOLISM

A functional understanding of the metabolism of acetaminophen is essential to comprehending the ensuing toxicity of this otherwise fairly innocuous agent (Figure 1). Following acute ingestion of large quantities of the immediate-release preparation, the time to peak concentrations in the bloodstream may be delayed for up to 4 hr (Rumack & Matthew, 1975). Food and coingestion of other agents, opioids, and anticholinergic agents, in particular, can also delay the time to peak concentration (Divoll, Greenblatt, Ameer, & Abernathy, 1982; Halcomb, Sivilotti, Goklaney, & Mullins, 2005). Metabolism of acetaminophen occurs through two separate pathways, the cytochrome P450 (CYP) system of mixed-function oxidases and conjugation by way of transferases (Bessems & Vermeulen, 2001). In adults, approximately 30% of acetaminophen is metabolized by direct sulfation, 55% by glucuronidation, and 5%-10% by the CYP system. The remaining 5% is excreted unchanged in the urine. Metabolism by the CYP system is responsible for the production of the toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI), that has the potential to covalently bind to protein (Mitchell, Jollow, Potter, Gillette, & Brodie, 1973). Under normal circumstances, NAPQI is detoxified by glutathione (GSH) to nontoxic metabolites that are eliminated in
the urine. However, following a toxic ingestion of acetaminophen, GSH stores are depleted resulting in the accumulation of NAPQI (Mitchell et al., 1973).

The mechanism of toxicity of NAPQI begins with covalent binding to cysteine groups on protein, forming acetaminophen–protein adducts (Mitchell et al., 1973). Although less well understood, several theories have been proposed regarding the subsequent events that lead to eventual hepatocellular death (James, Mayeux, & Hinson, 2003). One such theory is that it is the binding to mitochondrial proteins or to protein ion channels leading to a loss of energy production or ion control that results in cell death and lysis. Other theories have been described involving excess oxidative stress, nitrotyrosine formation, and cytokine and inflammatory mediator production. The actual toxicity of NAPQI is impacted by several individual patient factors, including age, genetics, alcohol use, concomitant medications, nutritional status, and tobacco use, as indicated in Table 1.

**STAGES AND SYMPTOMS OF TOXICITY**

Following acute acetaminophen overdose, the ensuing clinical processes can be categorized into several unique stages that are described in Table 2. Although not subjectively intuitive, the kidney is also susceptible to acetaminophen toxicity similar to the liver. The incidence of adverse renal effects is between 2% and 50% (Curry, Robinson, & Sughrue, 1982; Jones & Vale, 1993). Even though they differ somewhat, CYP enzymes in the kidney function in much the same way as their counterparts in the liver do. When their supply of GSH becomes depleted, NAPQI accumulates, and the result is acetaminophen-induced acute tubular necrosis (Blakely & McDonald, 1995; Mour, Feinfeld, Caraccio, & McGuigan, 2005).

**THERAPEUTIC DRUG MONITORING/LABORATORY EVALUATION**

As previously discussed, it is somewhat challenging to define the severity of an

<table>
<thead>
<tr>
<th>Table 1. Factors affecting acetaminophen hepatotoxicity</th>
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<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>&lt;5 years</td>
</tr>
<tr>
<td>Juveniles</td>
</tr>
<tr>
<td>Older adults</td>
</tr>
<tr>
<td>Genetics</td>
</tr>
<tr>
<td>Alcohol</td>
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<tr>
<td>Acute ingestion</td>
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<td>Chronic ingestion</td>
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<tr>
<td>Drugs</td>
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<tr>
<td>Isoniazid</td>
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<td>Halothane</td>
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<td>Phenytoin</td>
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<td>Carbamazepine</td>
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<td>Phenobarbital</td>
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<td>Zidovudine</td>
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<td>Trimethoprim/ sulfamethoxazole</td>
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<tr>
<td>Cimetidine</td>
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<td>Malnutrition</td>
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<td>Tobacco use</td>
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Table 2. Clinical stages of acetaminophen-induced hepatotoxicity

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Stage 1: 24 hr following ingestion</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain, anorexia, lethargy, malaise, and diaphoresis</td>
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<tr>
<td></td>
<td>Pallor and mild hepatic tenderness</td>
</tr>
<tr>
<td></td>
<td>Typically normal laboratory values</td>
</tr>
<tr>
<td>Stage 2: 24–72 hr following ingestion</td>
<td>Serum aspartate aminotransferase elevation</td>
</tr>
<tr>
<td></td>
<td>Serum alanine aminotransferase elevation</td>
</tr>
<tr>
<td></td>
<td>Elevations in total bilirubin and prothrombin time may occur</td>
</tr>
<tr>
<td></td>
<td>Right upper quadrant pain and jaundice</td>
</tr>
<tr>
<td></td>
<td>Nephrotoxicity and oliguria</td>
</tr>
<tr>
<td>Stage 3: 72–96 hr following ingestion</td>
<td>Hepatocellular necrosis and death</td>
</tr>
</tbody>
</table>


Acetaminophen overdose, largely secondary to the multiple patient-specific factors involved. Although the quantity of acetaminophen ingested does give health care providers a starting point with regard to the anticipated risk of toxicity from this agent, it is often challenging to ascertain the exact quantity consumed. One method of combating this problem has been the development of a nomogram to assess an individual’s risk of hepatotoxicity and the need to initiate antidote therapy based on serum acetaminophen concentration; this is commonly referred to as the Rumack–Matthew nomogram (Figure 2). Three different lines are often depicted on the nomogram, but only two of those are actually utilized in clinical practice because treatment is started anywhere above the lowest line (number 3). The lines are (1) a high risk line that joins plots of 300 mg/L of acetaminophen at 4 hr and 10 mg/L at 24 hr on semilogarithmic graph (this line is not shown on Figure 2); (2) a probable risk line that joins plots of 200 mg/L of acetaminophen at 4 hr and 7 mg/L at 24 hr; and (3) a possible risk line that joins plots of 150 mg/L of acetaminophen at 4 hr and 5 mg/L at 24 hr (Prescott et al., 1979; Rumack & Matthew, 1975; Smilkstein et al., 1991).

Those patients who present with concentrations above any of these lines or those who present greater than 24 hours postexposure are considered at risk of developing hepatic necrosis and should be treated. This nomogram does not apply for those who have had long-term exposure, consumed the acetaminophen overdose, largely secondary to the multiple patient-specific factors involved. Although the quantity of acetaminophen ingested does give health care providers a starting point with regard to the anticipated risk of toxicity from this agent, it is often challenging to ascertain the exact quantity consumed. One method of combating this problem has been the development of a nomogram to assess an individual’s risk of hepatotoxicity and the need to initiate antidote therapy based on serum acetaminophen concentration; this is commonly referred to as the Rumack–Matthew nomogram (Figure 2). Three different lines are often depicted on the nomogram, but only two of those are actually utilized in clinical practice because treatment is started anywhere above the lowest line (number 3). The lines are (1) a high risk line that joins plots of 300 mg/L of acetaminophen at 4 hr and 10 mg/L at 24 hr on semilogarithmic graph (this line is not shown on Figure 2); (2) a probable risk line that joins plots of 200 mg/L of acetaminophen at 4 hr and 7 mg/L at 24 hr; and (3) a possible risk line that joins plots of 150 mg/L of acetaminophen at 4 hr and 5 mg/L at 24 hr (Prescott et al., 1979; Rumack & Matthew, 1975; Smilkstein et al., 1991).

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extended-release acetaminophen preparations, have an unknown time point of ingestion, or consume alcohol on a chronic basis because the time of ingestion (x-axis) is no longer a simple variable that is easy to determine. The patient scenarios in which the nomogram cannot be applied are more challenging and must be evaluated on a case-by-case basis (Dargan & Jones, 2002; Rumack & Matthew, 1975).

ACUTE MANAGEMENT

Once it has been determined via serum levels that a patient has had a toxic exposure to acetaminophen, several different therapies exist for treatment, some more effective than others. These therapies are intended to interrupt various steps in the toxicologic process of acetaminophen overdose. Initially attempts can be made to inhibit absorption of acetaminophen through various methods, most notably activated charcoal. The most successful treatment has been the use of NAC, which helps detoxify acetaminophen through different routes (Brok, Buckley, & Gluud, 2006).

Various agents have been used to help alter the absorption of acetaminophen into the bloodstream following a toxic ingestion. To date, the most common agents/strategies used include syrup of ipecac, gastric lavage, and activated charcoal. Although the first two have shown some benefit, it has been determined by the American Academy of Clinical Toxicology and the European Association of Poison Centers and Clinical Toxicologists that the risk of these interventions outweigh the benefits (Vale & Kulig, 2004). The therapy yielding the best results in preventing absorption and with the least toxicity is activated charcoal. When administered within the first 2 hr following ingestion, activated charcoal has been shown to significantly reduce serum concentrations (Buckley et al., 1999). In a randomized, controlled trial that assessed the efficacy of activated charcoal, gastric lavage, and syrup of ipecac administered within 4 hr of acetaminophen ingestion, activated charcoal was found to be significantly more effective in lowering serum concentrations than other therapies (Underhill, Greene, & Dove, 1990). No significant difference was noted between gastric lavage and syrup of ipecac ($p = .08$), but both were noted to be more effective than supportive care alone.

Following absorption, acetaminophen overdose still remains a very treatable condition. If NAC is administered within 8 hours of an acute ingestion, hepatotoxicity is exceedingly rare (Smilkstein, Knapp, Kulig, & Rumack, 1988). Although different theories have been proposed regarding its mechanism of action, it is generally agreed that this agent prevents hepatic damage by substituting for glutathione in NAPQI metabolism and serving as a precursor in the production of glutathione (Bessem & Vermeulen, 2001; Larson, 2007). It has also been proposed that this agent may enhance sulfate conjugation and preserve hepatic function through anti-inflammatory, antioxidant, inotropic, and vasodilating effects.

The NAC is available in the United States as both an intravenous and an oral liquid preparation. The approved dosing for each agent is listed in Table 3 (Smilkstein et al., 1991; Smilkstein et al., 1988). Various authors have proposed different criteria for the use of this agent, but the following are some of the more generally accepted criteria: serum acetaminophen concentration above "possible" line, estimated single ingestion of more than 150 mg/kg, abnormal liver biochemistry, or fulminant hepatic failure after reported acetaminophen ingestion (Brok et al., 2006; Larson, 2007). Treatment should also be considered in patients who present with an unknown time of ingestion, a repeated ingestion, or the ingestion of extended release formulations with a detectable acetaminophen serum concentration.

Irregardless of the formulation used, an acetaminophen concentration and aspartate aminotransferase should be measured after the patient has completed the treatment course. If evidence of liver injury is present, aspartate aminotransferase is elevated, or acetaminophen is not completely metabolized
(i.e., serum concentration is greater than 10 mg/L), NAC therapy should be continued. The treatment duration in these scenarios will be determined on the basis of the patient’s condition (Kociancic et al., 2003).

Currently, neither the intravenous nor liquid preparation has been shown to be more beneficial or effective than the other (Brok et al., 2006). Intravenous administration would be preferred in patients who are intolerant to the oral preparation or who have a concomitant corrosive ingestion, gastrointestinal obstruction, or perforation (Brok et al., 2006; Heard, 2008; Larson, 2007). Concerns surrounding the administration of both activated charcoal and oral NAC are unfounded. Activated charcoal should be given prior to 4 hr postingestion because gastrointestinal absorption is complete after this time. The NAC is usually not administered until after the 4-hr mark, so a decrease in effectiveness is not seen as the two agents are given at different times. There are in vitro data that suggest that binding occurs between charcoal and NAC, but there is no clinical evidence that this interaction impacts patient outcomes (Spiller, Krenzelok, Grande, Safir, & Diamond, 1994). In addition, there is substantial debate over whether different preparations might be more advantageous in the situations of delayed presentation, pregnancy, or those with higher risk of toxicity. In 2007, an equivalent number of toxic ingestions received the intravenous and oral formulation (11,895 and 11,764, respectively). These data are reflective of information reported from 60 of 61 poison-control centers in the United States. Unfortunately, no outcomes data were released in the report (Bronstein et al., 2008). At present no conclusive data exist and therefore these decisions are left to individual prescriber preference.

Other less successful interventions have been evaluated in human trials. These measures involve targeting the removal of the agent from the systemic circulation after absorption through charcoal hemoperfusion and preventing conversion of the parent acetaminophen to the toxic NAPQI with the CYP inhibitor cimetidine. Neither of these has been demonstrated to be effective and is not recommended.

The vast majority of patients who have a toxic ingestion of acetaminophen will have a relatively uneventful clinical course and will recover completely (Makin, Wendon, & Williams, 1995). In those who present at high risk of hepatotoxicity, the survival rate was originally less than 50%; however, following the increase in the use of NAC, this number rose to 78%. If NAC therapy is initiated in patients at risk for severe hepatotoxicity within 8 hours of ingestion, it is almost completely protective against hepatic damage.

**Table 3. N-acetylcysteine dosing regimens**

<table>
<thead>
<tr>
<th>Route</th>
<th>Duration of therapy, hrs</th>
<th>Loading dose</th>
<th>Maintenance dose no. 1</th>
<th>Maintenance dose no. 2</th>
<th>Total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>72</td>
<td>140 mg/kg</td>
<td>70 mg/kg every 4 hours</td>
<td>N/A</td>
<td>1330 mg/kg</td>
</tr>
<tr>
<td>Intravenous</td>
<td>20</td>
<td>150 mg/kg over 60 min</td>
<td>50 mg/kg over 4 hr</td>
<td>100 mg/kg over 16 hr</td>
<td>300 mg/kg</td>
</tr>
</tbody>
</table>

However, if initiated outside of this timeframe, efficacy begins to decline significantly (41% risk of hepatotoxicity if initiated 16–24 hr after ingestion), although some level of protection exists. The importance of rapid diagnosis, risk stratification, and treatment in this clinical scenario cannot be underestimated.

**ADMINISTRATION CONSIDERATIONS**

The use of NAC for the treatment of acetaminophen overdose is relatively safe. However, side effects can be seen with both oral and intravenous formulations. Oral NAC has an odor analogous to rotten eggs and a bad taste due to the sulfur component. However, this agent may also be mixed with juice or soda to make it somewhat more palatable. Common side effects include nausea, vomiting, and diarrhea. If any dose is regurgitated, it must be repeated (Larson, 2007). Because of these gastrointestinal limitations, the placement of a nasogastric tube is often necessary for administration. Unfortunately, the intravenous preparation is not as benign. The incidence of side effects ranges dramatically from 0.2% to 21% and includes a wide spectrum of possible presentations from nausea and flushing to hemolysis, angioedema, and anaphylaxis (Dawson, Henry, & McEwen, 1989; Mant, Tempowski, Volans, & Talbot, 1984). The vast majority of these reactions are mild and resolve completely upon discontinuation of the drug. Although some authors have advocated slowing the infusion to decrease the incidence of these effects, this has been shown to have little impact (Kerr et al., 2005).

The majority of the administration issues regarding this agent involve the rather complex dosing strategies (Table 3) and their implementation in an already chaotic emergency department. To prevent errors, health care providers can verify that the doses are given on time for both oral and intravenous formulations, verify that the correct dose is infusing at the right time for the intravenous formulation, and ensure that future doses follow the patient when they are transferred to another area in the hospital. A recent retrospective analysis of Maryland Poison Center records of all patients treated with intravenous NAC over 1 year found that of the 221 cases recorded, 84 medication errors occurred in 74 patients (Hayes, Klein-Schwartz, & Doyon, 2008). The most common error (18.6%) was an interruption in therapy of greater than 1 hr followed by unnecessary administration in 13.1%. Errors occurred most frequently during third shift and more than half of them occurred in the emergency department. This study highlights the overall importance of educating all health care personnel regarding the treatment of acetaminophen overdose and vigilance during the use of NAC.

**FUTURE RESEARCH**

Several areas remain to be evaluated systematically regarding the use of different therapies for acetaminophen overdose. For example, an evaluation comparing the clinical efficacy and outcomes of patients randomized to NAC administered intravenously compared with orally as well as prolonging therapy in patients who present with existing liver dysfunction. In addition, the efficacy of different dosing strategies needs to be evaluated for both easing administration issues and reducing length of stay in those patients who could otherwise be discharged. Further research also needs to be conducted into areas of predisposing factors that may change an individual’s risk of hepatotoxicity following acetaminophen overdose.

**CONCLUSION**

Despite its widespread availability and popularity, acetaminophen remains a potentially lethal agent if used inappropriately. The danger of this agent is veiled beneath its complex metabolic process and the multiple patient-specific characteristics that factor into the heightened predisposition of some to develop this toxicity. If treated in a timely fashion with NAC, much of the ensuing hepatic damage...
associated with this agent can be avoided. A thorough understanding of this toxicologic emergency is necessary to provide optimal care to these individuals.

REFERENCES


