Acetaminophen and Ibuprofen Overdosage

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In Brief

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Author Disclosure

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Fever is one of the most common symptoms managed by pediatricians. Many parents fear that fever is harmful to their children, leading to an estimated 30% of illness visits. Acetaminophen and ibuprofen remain the most common antipyretic medications, with numerous over-the-counter and prescription preparations available in the United States. Studies have reported that as many as one-half of parents administer the incorrect dose of acetaminophen and ibuprofen.

Acetaminophen is metabolized mainly in the liver by conjugation with sulfate and glucuronide. When an excessive amount of acetaminophen is present, it overwhelms the normal conjugation pathway, and metabolism is channeled to the cytochrome P-450 pathway, which produces the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is detoxified by glutathione; however, when gluthathione becomes depleted, NAPQI binds directly to hepatocytes, causing cellular necrosis.

A therapeutic dosage of acetaminophen is 75 mg/kg per 24-hour period, not to exceed 4 g in 24 hours. Single dosages of 10 to 15 mg/kg given every 4 to 6 hours orally generally are regarded as safe and effective. Liver toxicity in children has been reported after one dose of 120 to 150 mg/kg, with a higher risk of toxicity associated with fasting, liver disease, a history of excessive alcohol use, or the coadministration of medications that induce the cytochrome P-450 pathway.

Clinical manifestations of acetaminophen overdose can be gradual and nonspecific. Four clinical stages of acetaminophen toxicity have been described. The first stage occurs during the initial 12 to 24 hours after ingestion, during which time the patient may experience anorexia, malaise, diaphoresis, nausea, and vomiting. The second stage, or latent phase, begins during the subsequent 12 to 24 hours. During this phase, the clinical presentation may vary and include elevation of liver enzyme levels, liver enlargement, or right upper quadrant abdominal pain. Patients also may be asymptomatic. The third stage occurs 3 to 5 days after ingestion and is characterized by recurrence of anorexia, nausea, vomiting, and malaise. Liver enzyme levels may worsen and be accompanied by signs of liver failure, including jaundice, hypoglycemia, coagulopathy, and encephalopathy. The fourth stage is associated with either complete recovery or progression to liver failure.

If acetaminophen toxicity is suspected, a serum acetaminophen level should be obtained and plotted on the Rumack-Matthew nomogram, which can be found in standard references as well as the *New England Journal of Medicine* citation provided here. Given the acetaminophen level and the number of hours postingestion, the nomogram stratifies the patient's risk into one of three categories: no risk, possible risk, or probable risk of hepatotoxicity. If the serum acetaminophen level plots above the possible risk threshold for the time postingestion, treatment should be initiated. In addition, liver enzyme levels, coagulation profile, serum electrolytes, and complete blood count should be obtained before therapy as well as after treatment is completed.

The main therapy for acetaminophen toxicity is administration of *N*-acetylcysteine (NAC). The therapeutic effect of NAC occurs via multiple mechanisms within the liver, including increasing glutathione and directly detoxifying NAPQI.

Hepatotoxicity is minimized if NAC is started within 8 hours of the ingestion, but the treatment has therapeutic benefit if given within 24 to 48 hours. NAC is available in oral and intravenous preparations, and studies have shown similar efficacy between the two forms. In 2004, the US Food and Drug Administration approved a 20-hour, continuous intravenous infusion protocol that has efficacy similar to previous protocols.

Intravenous NAC has been associated with anaphylactoid reactions, including shortness of breath, wheezing, rash, and pruritus. In most cases, these reactions have been transient and relieved with antihistamine therapy. Oral NAC is bitter in taste and can be irritating to the gastrointestinal tract. The practitioner should weigh the risks and benefits of the two preparations in deciding which is best for the patient. Activated charcoal also has been shown to be effective in adsorbing acetaminophen, especially in the first 2 hours after ingestion. This therapy is particularly beneficial if multiple substances have been ingested.

Studies in children have shown that, at standard doses, ibuprofen is as safe as acetaminophen and is at least as effective at relieving pain and fever. The dosage of ibuprofen recommended for children is 5 to 10 mg/kg per dose, given every 6 to 8 hours orally. Ibuprofen is absorbed rapidly after oral administration, reaching peak concentration levels within 2 hours. As a nonsteroidal anti-inflammatory drug, ibuprofen inhibits cyclooxygenase, an enzyme in the prostaglandin synthetic pathway, thereby decreasing pain, fever, and inflammation. Ibuprofen is metabolized primarily in the liver, with urinary excretion as well. At standard doses, the drug is well tolerated by most children and has a low risk of complications. It should be noted, however, that currently there are insufficient data on the safety of ibuprofen in infants younger than 6 months of age.

Most adverse effects of ibuprofen, as with all nonsteroidal antiinflammatory drugs, result from prostaglandin inhibition. The most common adverse effects of ibuprofen are gastrointestinal: nausea, vomiting, abdominal pain, gastric ulcers, and gastrointestinal bleeding. The likely mechanism is decreased gastric cytoprotection resulting from prostaglandin inhibition. Ibuprofen also can have mild central nervous system effects, such as headache, confusion, disorientation, and dizziness. Ingestions of $>$400 mg/kg of ibuprofen have been associated with an increased risk of serious complications, including metabolic acidosis, liver or renal dysfunction, apnea, seizures, coma, and, rarely, death.

Concern has been raised over the potential nephrotoxicity of ibuprofen, which interferes with the renal effects of prostaglandins, thus reducing blood flow to the kidneys and potentially decreasing renal function. Particular caution should therefore be taken in children who have dehydration or underlying cardiac or renal disease.

When a child presents with an ibuprofen overdose, the practitioner should consider obtaining a laboratory evaluation that includes serum electrolytes, blood urea nitrogen, creatinine, coagulation studies, liver enzyme levels, and a complete blood count. Patients suspected of intentional overdose also should be tested for coingestion with acetaminophen and salicylates. Studies on ibuprofen serum levels have shown poor correlation between serum drug concentrations and toxicity. Although a nomogram exists, it is not useful in the management of ibuprofen overdose, and serum drug levels do not need to be checked routinely.

Because the risk for serious complications is low, treatment of ibuprofen overdose generally involves no more than supportive care. Activated charcoal can be given within 1 to 2 hours of ingestion to help decrease absorption of the ibuprofen. Clinical symptoms typically present within 4 hours of ingestion. Children who have ingested $<$100 mg/kg of ibuprofen and are asymptomatic may be observed at home. Symptomatic patients and those who have ingested $>$400 mg/kg should be observed at a health care facility for a minimum of 4 to 6 hours.

Comments: Given the ubiquity of acetaminophen and ibuprofen usage, we are fortunate that these drugs are relatively low risk for toxicity. One study estimated that the English, for example, administer 68 million child-days of antipyretic drugs each year. In Barton Schmitt's classic study of fever phobia, two-thirds of parents worried "lots" about the harm fever might cause their children, and more than one-half reported using an antipyretic drug for temperatures within the normal range. If parents are phobic regarding fevers, so too, apparently, are many of us. In a survey of American Academy of Pediatrics' members in Massachusetts, 2 of 3 responding pediatricians believed fever itself can pose a danger to children, and routinely recommended an antipyretic drug for temperatures under 102˚ F. Into the mouths of little children go the agents of our anxiety.

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Editor, In Brief

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