

AMERICAN ACADEMY OF PEDIATRICS

Committee on Drugs

Acetaminophen Toxicity in Children

ABSTRACT. Acetaminophen is widely used in children, because its safety and efficacy are well established. Although the risk of developing toxic reactions to acetaminophen appears to be lower in children than in adults, such reactions occur in pediatric patients from intentional overdoses. Less frequently, acetaminophen toxicity is attributable to unintended inappropriate dosing or the failure to recognize children at increased risk in whom standard acetaminophen doses have been administered. Because the symptoms of acetaminophen intoxication are nonspecific, the diagnosis and treatment of acetaminophen intoxication are more likely to be delayed in unintentional cases of toxicity. This statement describes situations and conditions that may contribute to acetaminophen toxicity not associated with suicidal intentions.

ABBREVIATIONS. NAC, *N*-acetylcysteine; NAPQI, *N*-acetyl-p-benzoquinone imine.

INTRODUCTION

The safety and efficacy of acetaminophen in children are well established, especially in comparison with aspirin. In general, the risk of developing toxic reactions to acetaminophen appear to be lower in children than in adults.^{1,2} Despite the very low incidence of toxic effects, acetaminophen toxicity remains a concern, because this drug is used very widely in children.³ Data collected in 1997 by 66 US regional poison control centers included more than 10 000 cases in which *N*-acetylcysteine (NAC), the antidote for acetaminophen, was used.⁴ Of 94 fatal acetaminophen overdose cases in which the reasons for exposure are known, most were associated with suicidal intentions. In 25% of the fatal cases, unintentional therapeutic error ($n = 10$) and intentional misuse without suicidal intent ($n = 14$) were the reasons for the exposure. This indicates a lack of understanding on the part of the patient or caretaker regarding acetaminophen therapy. Among the cases without suicidal intent, 3 deaths occurred in patients younger than 16 years. The perceived safety of acetaminophen may contribute to inappropriate dosing, failure to recognize children at increased risk, and delay in diagnosis and treatment of acetaminophen intoxication.

Recent reviews identified several factors associated with acetaminophen hepatotoxicity in children, including: age less than 10 years associated with

inappropriate dosing, delays in onset of symptoms after a potentially toxic ingestion, delays in initiation of NAC treatment, unintentional multiple overdosing, ingestion of acetaminophen along with another hepatotoxic drug (Table 1),⁵ and use of adult rather than pediatric preparations.⁶ Failure to read and understand the label instructions or use of an incorrect measuring device or preparation were cited as the usual causes of unintentional overdosing.⁵ Use of sustained-release preparations, particularly without appropriate increases in dosing intervals, coadministration of an over-the-counter, fixed-dose combination product without recognizing that it contains acetaminophen, or supervision of medication administration by another child may also contribute to such errors.⁵

Rectal administration of acetaminophen may also lead to toxicity, because this route of administration produces peak drug levels that may vary by as much as ninefold and often does not achieve therapeutic levels after the recommended doses are administered.⁷⁻⁹ The time to reach peak levels after rectal administration is substantially longer than that after oral administration,⁷ and the appropriate dose interval is longer (6-8 hours).⁸ Because the drug may not be equally distributed throughout the suppository, the practice of dividing a suppository may not provide a predictable dose. In addition, different rectal preparations have substantially different absorption characteristics that cause variation in bioavailability.⁹ These factors create the potential for inadequate therapeutic effect from poor absorption as well as cumulative toxic effects from excessive or too frequently repeated rectal doses.

TOXICITY

The toxicity of acetaminophen is closely linked to its metabolism. With therapeutic dosing, acetaminophen is predominantly metabolized by conjugation

TABLE 1. Concomitant Drug Therapy and Situations for Which There Are In Vivo Data, Either in Adult Humans or Animals, for Increased Susceptibility to Acetaminophen Toxicity

Human
Carbamazepine induction of CYP450 ^{32,33}
Ethanol ^{18,31}
Isoniazid ^{30,34,35}
Phenobarbital ³⁶⁻³⁸
Rifampin ³⁵
Prolonged fasting ^{5,18}
Animal
Dexamethasone ³⁹
Doxorubicin ⁴⁰
Prolonged fasting ¹⁹⁻²¹

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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with sulfate and glucuronide. Approximately 5% to 10% of the drug is oxidized by CYP450-dependent pathways (mostly CYP2E1 and CYP3A4) to a toxic, electrophilic metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI).¹⁰ NAPQI is detoxified by glutathione and eliminated in the urine or bile. The NAPQI that is not detoxified may bind to hepatocytes and produce cellular necrosis. Usually, because of the relatively small amount of NAPQI formed and the adequate supply of glutathione, acetaminophen has an excellent safety profile.

A threshold acetaminophen dose associated with hepatic toxicity in children has been difficult to establish because of inaccurate recollection of the ingested dose, doses administered during several days, and prolonged release products. Rumack and Matthew¹¹ in their landmark 1975 study did not indicate a minimum dose for toxicity, but emphasized prolongation of the half-life of acetaminophen from liver toxicity. Reports of liver toxicity in pediatric patients have suggested a minimal, single acetaminophen dose of 120 to 150 mg/kg of body weight may be associated with hepatotoxicity.^{12,13} Two reports of hepatotoxicity in association with dosages reported to be in the therapeutic range^{6,14} may represent inaccurate memory of the administered doses or a narrower acetaminophen therapeutic window because of associated conditions. Such conditions might include inherited differences in hepatic enzyme activity, malnutrition, ethanol ingestion, drug interactions, or concomitant medical disorders. Theoretically, an inherited increased activity of CYP2E1 could increase conversion of acetaminophen to its toxic metabolite, NAPQI.^{15,16} Individuals who are heterozygous for glutathione synthetase deficiency (a rare disorder) may have a limited capacity for detoxification of NAPQI through conjugation with glutathione.¹⁷ Children with a family history of hepatic toxicity to acetaminophen have an increased risk of developing a toxic reaction.

Nutritional and drug-drug interactions are more likely than genetic differences in metabolism to contribute to toxicity at conventional doses of acetaminophen. Fasting is associated with increased acetaminophen hepatotoxicity in humans¹⁸ and animals¹⁹ apparently because of increased metabolism to NAPQI.^{20,21} The contribution of fasting to acetaminophen toxicity in humans is unclear, because the interruption of feeding is not quantified and is associated with chronic alcohol intake, vomiting, or diarrhea.^{18,22} Protein-calorie malnutrition,^{23,24} obesity,²⁵ and poorly controlled diabetes^{26,27} are associated with increased activity of CYP2E1 that may increase formation of NAPQI. Detoxification may be reduced in patients with chronic protein-calorie malnutrition, who also have low glutathione levels.²⁸ Numerous drugs may affect acetaminophen elimination or NAPQI detoxification and some of their effects on CYP2E1 activity are variable (Table 1). Isoniazid first inhibits then enhances NAPQI formation as it is cleared.^{18,29,30} Ethanol ingested chronically increases CYP2E1 activity and depletes glutathione, which enhances susceptibility to acetaminophen toxicity,^{1,18,31} whereas acute ethanol ingestion reduces

acetaminophen toxicity through competitive inhibition of CYP2E1.³¹ Concurrent treatment with 1 or more of the medications in Table 1 may be likely among children with chronic illnesses, which should be considered in decisions to treat with acetaminophen.^{5,18–21,30–40} Finally, clinical signs of liver disease, such as fever or abdominal pain, are often treated with acetaminophen. Whether hepatic injury from underlying conditions, such as viral infections or metabolic diseases, is exacerbated by acetaminophen remains uncertain. Many reported cases of severe hepatotoxicity in children have been attributed to cumulative toxicity from repeated doses rather than acute intoxication from a single massive overdose.⁵ Severe toxicity has been observed despite apparently reassuringly low acetaminophen levels.^{3,6} The Rumack and Matthew nomogram of acetaminophen levels and time after dose was developed for prediction of risk in acute intoxications so that a low level does not eliminate the possibility of toxicity caused by chronic ingestion of acetaminophen.¹¹ The health care provider should consider acetaminophen toxicity in any child who has received acetaminophen who has signs of acute hepatic dysfunction, even if acetaminophen levels are not in the toxic range. If the levels are in the toxic range after long-term treatment with acetaminophen, it is an ominous finding associated with a high risk of mortality.⁶

Acetaminophen intoxication typically includes 4 phases.⁴¹ The first consists of anorexia, nausea, vomiting, malaise, and diaphoresis, which may provoke administration of additional doses of acetaminophen. In the second phase, those first-phase signs resolve and are replaced by right upper quadrant pain or tenderness, liver enlargement, and oliguria in some patients. Bilirubin and hepatic enzyme levels become elevated, and the prothrombin time becomes prolonged. In the third phase, usually 3 to 5 days into the course, anorexia, nausea, vomiting, and malaise reappear, along with signs of hepatic failure, including jaundice, hypoglycemia, coagulopathy, and encephalopathy. Renal failure and cardiomyopathy may also develop. The fourth phase is associated with recovery or progression to death from complete liver failure. Acetaminophen poisoning also may present as central nervous system depression, shock, hypothermia, and metabolic acidosis.⁴² Because delays in treatment with NAC are associated with worse outcomes,^{43,44} early treatment is indicated when acetaminophen hepatotoxicity is considered likely. Even delayed therapy may be beneficial.⁴⁵ Therefore, treatment should be considered even if 24 hours or more has elapsed since the last dose of acetaminophen was given.⁶

TREATMENT

Several treatment regimens for acetaminophen overdose have been proposed, but those best studied involve NAC.^{43–47} Treatment instituted within 6 to 8 hours after an acute ingestion should begin with a dose of activated charcoal; however, later treatment does not include charcoal unless a second toxin was ingested.⁴⁷ Intravenous administration of NAC over a 10-hour period (rapidly) is associated with a higher

frequency of allergic and anaphylactoid reactions (angioedema, hypotension, bronchospasm)⁴³ than is oral administration. Longer infusion periods (48 hours or longer) of NAC result in improved tolerance and reduced adverse effects.^{44,46} The treatment of hepatotoxicity in children caused by subacute overdosing of acetaminophen is difficult. Therefore, consulting a toxicologist or another expert should be considered.

ALTERNATING WITH IBUPROFEN

Some pediatricians recommend alternating administration of acetaminophen and ibuprofen every 2 hours, although no clinical trials of this treatment have been identified. The pathways of metabolism for acetaminophen and ibuprofen are quite different and do not affect each other. They have quite different half-lives in children, averaging 4.5 hours for acetaminophen and 1.0 to 2.0 hours for ibuprofen.⁴⁸ The *Physician's Desk Reference for Nonprescription Drugs* lists dosing intervals of 6 to 8 hours for ibuprofen oral suspension (Motrin [McNeil Consumer Products Co, Fort Washington, PA])⁴⁹ and every 4 hours up to 5 doses per day for acetaminophen (Tylenol [McNeil Consumer Products Co, Fort Washington, PA]).⁴⁹ Thus, the 2 drugs should not be administered in the same schedule (every 4 hours) on the basis of pharmacokinetics or current dosing recommendations. Alternating doses every 6 hours might be used so that 1 drug or the other is administered every 3 hours. Given the absence of published safety and efficacy data related to the practice of alternating acetaminophen and ibuprofen, it is prudent for health care providers to exercise discretion when considering this sequence of therapy.

RECOMMENDATIONS

1. Most acetaminophen therapy is begun without direct advice from health care providers; therefore, instruction regarding appropriate pain and fever therapy should be incorporated into well-child visits.
2. Optimally, written, specific information about acetaminophen is given to parents as part of well-child visits and reviewed with parents during subsequent visits. Appropriate information that would convey individualization of therapy for a specific child should:
 - a) include the dose, frequency, duration of therapy, and the specific strength and formulation for the individual child.
 - b) state clearly the danger of substituting alternative dosage forms, in particular, adult for pediatric preparations.
 - c) recommend that rectal acetaminophen therapy should be avoided unless specifically discussed with the health care provider and that directions be followed.
 - d) dispel the misconception that, even with over-the-counter drugs, "more is better."
 - e) warn that many preparations contain acetaminophen and that the simultaneous use of more than 1 product containing acetaminophen may be dangerous. Include a recommen-

ation that parents search the entire label of any over-the-counter product for acetaminophen content, especially those recommended for colds, cough, fever, headaches, or general aches and pains.

- f) recommend that parents inform the pharmacist that their child is taking acetaminophen when a new prescription is filled.
 - g) caution parents against allowing drug administration by children.
 - h) provide patient-specific advice regarding professional follow-up for children who continue to have fever and/or other signs or symptoms.
3. Sustained-release preparations should not be substituted for immediate-release preparations without changing the dosing interval.
 4. For children with refractory fever and for those at increased risk of developing acetaminophen toxicity,^{2,50-53} consider different antipyretics or adjunctive treatment, such as tepid water sponge bathing⁵⁴⁻⁵⁶ (although its effectiveness is controversial) with directions to avoid measures that induce shivering.
 5. Because early symptoms of acetaminophen toxicity are nonspecific, health care providers are advised to include acetaminophen toxicity in the initial differential diagnosis in many illnesses, especially those with unexplained hepatic dysfunction and obtain detailed information regarding acetaminophen therapy. A complete history would:
 - a) describe the exact drug formulation(s), the dose, the route, the dosage frequency, and the number of doses.
 - b) identify the individual(s) administering the drug.
 - c) seek information about "hidden" sources of acetaminophen in over-the-counter drug use, in particular all cold and pain preparations, as well as alternative or herbal remedies.
 - d) include information on concomitant drug therapy, particularly hepatotoxic drugs and drugs metabolized by the enzymes involved in acetaminophen toxicification or detoxification (Table 1).
 - e) include an assessment of dietary status, particularly whether there is chronic undernutrition or recent fasting.
 6. In caring for children whose differential diagnosis includes acetaminophen toxicity but whose acetaminophen blood concentration and history do not match, it is important to recognize that either piece of information may be misleading, particularly in cases of chronic, unintentional acetaminophen overdosage. Likewise, acetaminophen is often used to treat children who have symptoms of liver dysfunction caused by various conditions (eg, viral hepatitis, metabolic disease).
 7. Although the relative safety of acetaminophen has been clearly demonstrated and toxicity is infrequent, health care providers need to be aware that some children appear to be at increased risk of developing acetaminophen toxicity, including those with chronic diseases treated with several

TABLE 2. Conditions and Situations That May Increase the Risk of Acetaminophen Toxicity

Diabetes mellitus ^{26,27}
Obesity ²⁵
Chronic undernutrition ²⁴
Prolonged fasting ²⁵
Family history of hepatotoxic reaction
Concomitant viral infection

different medications or chronic undernutrition (Table 2).

8. Because of low toxicity and potential beneficial effects, consider early treatment with NAC when acetaminophen toxicity is a likely contributor of liver dysfunction.
9. Reassure parents that although some parental anxiety over fever is understandable, the primary reason to treat fever is for patient comfort and that complete normalization of the temperature is not necessary and may not be possible.

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