

# 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.<sup>1,2</sup> Despite the very low incidence of toxic effects, acetaminophen toxicity remains a concern, because this drug is used very widely in children.<sup>3</sup> 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.<sup>4</sup> 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),<sup>5</sup> and use of adult rather than pediatric preparations.<sup>6</sup> 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.<sup>5</sup> 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.<sup>5</sup>

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.<sup>7-9</sup> The time to reach peak levels after rectal administration is substantially longer than that after oral administration,<sup>7</sup> and the appropriate dose interval is longer (6-8 hours).<sup>8</sup> 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.<sup>9</sup> 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 <sup>32,33</sup>
Ethanol <sup>18,31</sup>
Isoniazid <sup>30,34,35</sup>
Phenobarbital <sup>36-38</sup>
Rifampin <sup>35</sup>
Prolonged fasting <sup>5,18</sup>
Animal
Dexamethasone <sup>39</sup>
Doxorubicin <sup>40</sup>
Prolonged fasting <sup>19-21</sup>

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.

PEDIATRICS (ISSN 0031 4005). Copyright © 2001 by the American Academy of Pediatrics.

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).<sup>10</sup> 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 Matthew<sup>11</sup> 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.<sup>12,13</sup> Two reports of hepatotoxicity in association with dosages reported to be in the therapeutic range<sup>6,14</sup> 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.<sup>15,16</sup> Individuals who are heterozygous for glutathione synthetase deficiency (a rare disorder) may have a limited capacity for detoxification of NAPQI through conjugation with glutathione.<sup>17</sup> 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 humans<sup>18</sup> and animals<sup>19</sup> apparently because of increased metabolism to NAPQI.<sup>20,21</sup> 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.<sup>18,22</sup> Protein-calorie malnutrition,<sup>23,24</sup> obesity,<sup>25</sup> and poorly controlled diabetes<sup>26,27</sup> 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.<sup>28</sup> 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.<sup>18,29,30</sup> Ethanol ingested chronically increases CYP2E1 activity and depletes glutathione, which enhances susceptibility to acetaminophen toxicity,<sup>1,18,31</sup> whereas acute ethanol ingestion reduces

acetaminophen toxicity through competitive inhibition of CYP2E1.<sup>31</sup> 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.<sup>5,18–21,30–40</sup> 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.<sup>5</sup> Severe toxicity has been observed despite apparently reassuringly low acetaminophen levels.<sup>3,6</sup> 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.<sup>11</sup> 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.<sup>6</sup>

Acetaminophen intoxication typically includes 4 phases.<sup>41</sup> 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.<sup>42</sup> Because delays in treatment with NAC are associated with worse outcomes,<sup>43,44</sup> early treatment is indicated when acetaminophen hepatotoxicity is considered likely. Even delayed therapy may be beneficial.<sup>45</sup> Therefore, treatment should be considered even if 24 hours or more has elapsed since the last dose of acetaminophen was given.<sup>6</sup>

## TREATMENT

Several treatment regimens for acetaminophen overdose have been proposed, but those best studied involve NAC.<sup>43–47</sup> 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.<sup>47</sup> Intravenous administration of NAC over a 10-hour period (rapidly) is associated with a higher

frequency of allergic and anaphylactoid reactions (angioedema, hypotension, bronchospasm)<sup>43</sup> than is oral administration. Longer infusion periods (48 hours or longer) of NAC result in improved tolerance and reduced adverse effects.<sup>44,46</sup> 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.<sup>48</sup> 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])<sup>49</sup> and every 4 hours up to 5 doses per day for acetaminophen (Tylenol [McNeil Consumer Products Co, Fort Washington, PA]).<sup>49</sup> 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,<sup>2,50-53</sup> consider different antipyretics or adjunctive treatment, such as tepid water sponge bathing<sup>54-56</sup> (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 toxification 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 <sup>26,27</sup>
Obesity <sup>25</sup>
Chronic undernutrition <sup>24</sup>
Prolonged fasting <sup>25</sup>
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.

COMMITTEE ON DRUGS, 1999–2000

Robert M. Ward, MD, Chairperson  
Brian A. Bates, MD  
William E. Benitz, MD  
David J. Burchfield, MD  
John C. Ring, MD  
Richard P. Walls, MD, PhD  
Philip D. Walson, MD\*

LIAISONS

John Alexander, MD  
Food and Drug Administration *Alternate*  
Donald R. Bennett, MD, PhD  
American Medical Association/US Pharmacopeia  
Therese Cvetkovich, MD  
Food and Drug Administration  
Owen R. Hagino, MD  
American Academy of Child and Adolescent Psychiatry  
Stuart M. MacLeod, MD, PhD  
Canadian Paediatric Society  
Siddika Mithani, MD  
Bureau of Pharmaceutical Assessment/Health Protection Branch, Canada  
Joseph Mulinare, MD, MSPH  
Centers for Disease Control and Prevention  
Laura E. Riley, MD  
American College of Obstetricians and Gynecologists  
Sumner J. Yaffe, MD  
National Institutes of Health

SECTION LIAISONS

Charles J. Coté, MD  
Section on Anesthesiology  
Eli O. Meltzer, MD  
Section on Allergy and Immunology

CONSULTANTS

Gregory L. Kearns, PharmD  
D. Gail McCarver, MD  
Daniel A. Notterman, MD  
Stephen J. Spielberg, MD, PhD

STAFF

Raymond J. Koterak, MHA

\* Did not vote because of declared conflict.

REFERENCES

1. Rumack BH. Acetaminophen overdose in young children. Treatment and effects of alcohol and other additional ingestants in 417 cases. *Am J Dis Child.* 1984;138:428–433
2. Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics.* 1999;104(4). Available at: <http://www.pediatrics.org/cgi/content/full/104/4/e39>
3. Kearns GL, Leeder JS, Wasserman GS. Acetaminophen overdose with therapeutic intent. *J Pediatr.* 1998;132:5–8
4. Litovitz TL, Klein-Schwartz W, Dyher KS, Shannon M, Lee S, Powers M. 1997 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med.* 1998;16:443–497
5. Rivera-Penera T, Gugig R, Davis J, et al. Outcome of acetaminophen overdose in pediatric patients and factors contributing to hepatotoxicity. *J Pediatr.* 1997;130:300–304
6. Heubi JE, Barbacci MB, Zimmerman HJ. Therapeutic misadventures with acetaminophen: hepatotoxicity after multiple doses in children. *J Pediatr.* 1998;132:22–27
7. Birmingham PK, Tobin MJ, Henthorn TK, et al. Twenty-four-hour pharmacokinetics of rectal acetaminophen in children: an old drug with new recommendations. *Anesthesiology.* 1997;87:244–252
8. van Lingen RA, Deinum HT, Quak CM, Okken A, Tibboel D. Multiple-dose pharmacokinetics of rectally administered acetaminophen in term infants. *Clin Pharmacol Ther.* 1999;66:509–515
9. Cullen S, Kenny D, Ward OC, Sabra K. Paracetamol suppositories: a comparative study. *Arch Dis Child.* 1989;64:1504–1505
10. Corcoran GB, Mitchell JR, Vaishnav YN, Horning EC. Evidence that acetaminophen and N-hydroxyacetaminophen form a common arylating intermediate, N-acetyl-p-benzoquinoneimine. *Mol Pharmacol.* 1980;18:536–542
11. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics.* 1975;55:871–876
12. Henretig FM, Selbst SM, Forrest C, et al. Repeated acetaminophen overdosing causing hepatotoxicity in children. Clinical reports and literature review. *Clin Pediatr (Phila).* 1989;28:525–528
13. Alander SW, Dowd D, Bratton SL, Kearns GL. Pediatric acetaminophen overdose: risk factors associated with hepatocellular injury. *Arch Pediatr Adolesc Med.* 2000;154:346–350
14. Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987–1993). *Gastroenterology.* 1995;109:1907–1916
15. Critchley JAJH, Nimmo GR, Gregson CA, Woolhouse NM, Prescott LF. Inter-subject and ethnic differences in paracetamol metabolism. *Br J Clin Pharmacol.* 1986;22:649–657
16. Ueshima Y, Tsutsumi M, Takase S, Matsuda Y, Kawahara H. Acetaminophen metabolism in patients with different cytochrome P-4502E1 genotypes. *Alcohol Clin Exp Res.* 1996;20(suppl 1):25A–28A
17. Spielberg SP. Acetaminophen toxicity in lymphocytes heterozygous for glutathione synthetase deficiency. *Can J Physiol Pharmacol.* 1985;63:468–471
18. Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA.* 1994;272:1845–1850
19. Miller MG, Price VF, Jollow DJ. Anomalous susceptibility of the fasted hamster to acetaminophen hepatotoxicity. *Biochem Pharmacol.* 1986;35:817–825
20. Brown BL, Allis JW, Simmons JE, House DE. Fasting for less than 24 h induces cytochrome P450 2E1 and 2B1/2 activities in rats. *Toxicol Lett.* 1995;81:39–44
21. Price VF, Jollow DJ. Effect of glucose and gluconeogenic substrates on fasting-induced suppression of acetaminophen glucuronidation in the rat. *Biochem Pharmacol.* 1989;38:289–297
22. Eriksson LS, Broome U, Kalin M, Lindholm M. Hepatotoxicity due to repeated intake of low doses of paracetamol. *J Intern Med.* 1992;231:567–570
23. Zhang W, Parentau H, Greenly RL, et al. Effect of protein-calorie malnutrition on cytochromes P450 and glutathione S-transferase. *Eur J Drug Metab Pharmacokinet.* 1999;24:141–147
24. Gregus Z, Kim HJ, Madhu C, Liu Y, Rozman P, Klaassen CD. Sulfation of acetaminophen and acetaminophen-induced alterations in sulfate and 3'-phosphoadenosine 5'-phosphosulfate homeostasis in rats with deficient dietary intake of sulfur. *Drug Metab Dispos.* 1994;22:725–730
25. O'Shea D, Davis SN, Kim RB, Wilkinson GR. Effect of fasting and obesity in humans on the 6-hydroxylation of chlorzoxazone: a putative probe of CYP2E1 activity. *Clin Pharmacol Ther.* 1994;56:359–367
26. Song BJ, Veech RL, Saenger P. Cytochrome P450IIIE1 is elevated in

- lymphocytes from poorly controlled insulin-dependent diabetics. *J Clin Endocrinol Metab.* 1990;71:1036-1040
27. Dong ZG, Hong JY, Ma QA, et al. Mechanism of induction of cytochrome P-450ac (P-450j) in chemically induced and spontaneously diabetic rats. *Arch Biochem Biophys.* 1988;263:29-35
  28. Sauerwein RW, Mulder JA, Mulder L, et al. Inflammatory mediators in children with protein-energy malnutrition. *Am J Clin Nutr.* 1997;65:1534-1539
  29. Chien JY, Peter RM, Nolan CM, et al. Influence of polymorphic N-acetyltransferase phenotype on the inhibition and induction of acetaminophen bioactivation with long-term isoniazid. *Clin Pharmacol Ther.* 1997;61:24-34
  30. Murphy R, Swartz R, Watkins PB. Severe acetaminophen toxicity in a patient receiving isoniazid. *Ann Intern Med.* 1990;113:799-800
  31. Altomare E, Leo MA, Lieber CS. Interaction of acute ethanol administration with acetaminophen metabolism and toxicity in rats fed alcohol chronically. *Alcoholism.* 1984;8:405-408
  32. Bray GP, Harrison PM, O'Grady JG, Tredger JM, Williams R. Long-term anticonvulsant therapy worsens outcome in paracetamol-induced fulminant hepatic failure. *Hum Exp Toxicol.* 1992;11:265-270
  33. Smith JA, Hine ID, Beck P, Routledge PA. Paracetamol toxicity: is enzyme induction important? *Hum Toxicol.* 1986;5:383-385
  34. Moulding TS, Redeker AG, Kanel GC. Acetaminophen, isoniazid, and hepatic toxicity. *Ann Intern Med.* 1991;114:431
  35. Nolan CM, Sandblom RE, Thummel KE, Slattey JT, Nelson SD. Hepatotoxicity associated with acetaminophen usage in patients receiving multiple drug therapy for tuberculosis. *Chest.* 1994;105:408-411
  36. Wilson JT, Kasantikul V, Harbison R, Martin D. Death in an adolescent following an overdose of acetaminophen and phenobarbital. *Am J Dis Child.* 1978;132:466-473
  37. Laskin DL, Robertson FM, Pilaro AM, Laskin JD. Activation of liver macrophages following phenobarbital treatment of rats. *Hepatology.* 1988;8:1051-1055
  38. Douidar SM, Ahmed AE. A novel mechanism for the enhancement of acetaminophen hepatotoxicity by phenobarbital. *J Pharmacol Exp Ther.* 1987;240:578-583
  39. Madhu C, Maziasz T, Klaassen CD. Effect of pregnenolone-16 alpha-carbonitrile and dexamethasone on acetaminophen-induced hepatotoxicity in mice. *Toxicol Appl Pharmacol.* 1992;115:191-198
  40. Wells PG, Boerth RC, Oates JA, Harbison RD. Toxicologic enhancement by a combination of drugs which deplete hepatic glutathione: acetaminophen and doxorubicin (adriamycin). *Toxicol Appl Pharmacol.* 1980;54:197-209
  41. McClain CJ, Holtzman J, Allen J, Kromhout J, Shedlofsky S. Clinical features of acetaminophen toxicity. *J Clin Gastroenterol.* 1988;10:76-80
  42. Flanagan RJ, Mant TG. Coma and metabolic acidosis early in severe acute paracetamol poisoning. *Hum Toxicol.* 1986;5:179-182
  43. Prescott LF, Illingworth RN, Critchley JA, Stewart MJ, Adam RD, Proudfoot AT. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. *Br Med J.* 1979;2:1097-1100
  44. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). *N Engl J Med.* 1988;319:1557-1562
  45. Keays R, Harrison PM, Wendon JA, et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *Br Med J.* 1991;303:1026-1029
  46. Perry HE, Shannon MW. Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label, clinical trial. *J Pediatr.* 1998;132:149-152
  47. Perry H, Shannon MW. Acetaminophen. In: Haddad LM, Shannon MW, Winchester JF, eds. *Clinical Management of Poisoning and Drug Overdose.* Philadelphia, PA: WB Saunders; 1998:664-674
  48. Kauffman RE. Drug therapeutics in the infant and child. In: Yaffe SJ, Aranda JV, eds. *Pediatric Pharmacology: Therapeutic Principles in Practice.* 2nd ed. Philadelphia, PA: WB Saunders; 1991:216
  49. *Physicians' Desk Reference for Nonprescription Drugs.* 17th ed. Montvale, NJ: Medical Economics Company; 1996
  50. Wilson JT, Brown D, Kearns GL, et al. Single-dose placebo-controlled comparative study of ibuprofen and acetaminophen antipyresis in children. *J Pediatr.* 1991;119:803-811
  51. Walson PD, Galletta G, Braden NJ. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharm Ther.* 1989;46:9-17
  52. Walson PD, Galletta G, Chomilo F, Braden NJ, Sawyer LA, Scheinbaum ML. Comparison of multidose ibuprofen and acetaminophen therapy in febrile children. *Am J Dis Child.* 1992;146:626-632
  53. Kauffman RE, Sawyer LA, Scheinbaum ML. Antipyretic efficacy of ibuprofen vs acetaminophen. *Arch Pediatr Adolesc Med.* 1992;146:622-627
  54. Steele RW, Tanaka PT, Lara RP, Bass JW. Evaluation of sponging and of oral antipyretic therapy to reduce fever. *J Pediatr.* 1970;77:824-829
  55. Friedman AD, Barton LL. Efficacy of sponging vs acetaminophen for reduction of fever. Sponging study group. *Pediatr Emerg Care.* 1990;6:6-7
  56. Mahar AF, Allen SJ, Milligan P, et al. Tepid sponging to reduce temperature in febrile children in a tropical climate. *Clin Pediatr (Phila).* 1994;33:227-231