

A Monthly Newsletter for Health Care Professionals Children's Medical Center at the University of Virginia

Volume 6 Number 3

March 2000

Preventing Acetaminophen Overdose

In Recognition of Poison Prevention Week: March 19th-25th

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Acetaminophen is currently the most frequently used antipyretic in children in the United States. While the relative safety of acetaminophen has been well established over the past decades, there remains a significant risk for toxicity associated with excessive doses.¹⁻³ In this issue of *Pediatric Pharmacotherapy*, the mechanism of acetaminophen toxicity will be briefly reviewed, several case reports of toxicity in children discussed, and recommendations for preventing overdoses of this popular over-the-counter (OTC) drug presented.

Mechanism of Toxicity

Acetaminophen is well absorbed after oral administration. In children and adults, the elimination half-life ranges from 1 to 3 hours. With normal dosing, acetaminophen primarily undergoes sulfation and glucuronidation in the liver prior to elimination. Only 6% of the ingested dose is conjugated with glutathione. When an overdose is ingested, the normal conjugation pathways become saturated, and the glutathione pathway becomes one of the primary methods of clearing the parent compound.^{2,3}

The glutathione conjugation pathway involves a series of intermediate steps. A by-product of this pathway, N-acetyl-p-benzoquinoneimine (NAPQI), is of particular importance. The formation of NAPQI is the last step prior to glutathione conjugation, which produces mercaptopuric acid and other nontoxic metabolites. With a large single overdose, this pathway becomes the predominant route of clearance and glutathione stores quickly become depleted. Accumulation of NAPQI soon follows, with subsequent covalent binding to hepatocyte proteins resulting in cellular necrosis.^{2,3} The mechanism for toxicity associated with repeated smaller overdoses, such as those often seen in children, is less clear.

Accidental Ingestions

Although many people assume that the majority of acetaminophen overdoses result from curious toddlers, toxicity from this type of exposure is relatively rare. In the most recent data from the American Association of Poison Control Centers, less than 8% of all pediatric exposures resulting in contact with a poison center during 1998 involved an analgesic.⁴

Similar results have recently been published from New Zealand.⁵ Gee and coworkers reviewed 88 cases of acetaminophen toxicity presenting to their emergency department over a one year period. Eighty-five of the cases resulted from accidental ingestion, what the authors term "exploratory ingestions." The mean age of the patients was 35 months. In all of the cases, serum acetaminophen concentrations at 4 hours were well below toxic levels. None of the children developed hepatotoxicity.

Improvements in safety packaging and increasing education of caregivers have had a significant impact on reducing accidental acetaminophen poisonings. Prompt implementation of N-acetylcysteine therapy, which acts as a glutathione substrate and promotes nontoxic metabolic pathways, has also decreased the number of cases that result in death or hepatic failure.^{3,6} Zed and Krenzelok have recently published a thorough review of the management of these patients.³

Despite these advances, there is still a need to educate families about the risk of accidental poisonings. Any accidental ingestion should be thoroughly investigated. In children, single acetaminophen exposures exceeding 140 mg/kg are considered severe, and patients who may have ingested this amount or more should be referred to immediate medical care.

Dose Calculation and Administration Errors

There is a growing body of literature describing cases of acetaminophen toxicity resulting from inadvertent overdosage of children by parents and other caregivers.^{7,9} In 1997, Rivera-Penera and colleagues reviewed the records of 73 children admitted to five hospitals between 1985 and 1995 for an acetaminophen overdose.⁷ Of this group, 28 children (38%) had abnormal liver tests and progressed to severe hepatotoxicity. Six children required liver transplantation. In the subset of children 10 years of age and younger, all cases of severe hepatotoxicity were associated with chronic unintentional overdosage by caregivers. None of the cases were linked to accidental ingestions. The authors concluded that excessive doses given with therapeutic intent were more likely to result in severe morbidity than predicted and that delays in recognizing dosing errors and seeking medical care placed children at even greater risk.

The following year, Heubi, Barbacci, and Zimmerman compiled the cases of another 42 children (age range 5 weeks to 10 years) with hepatotoxicity resulting from errors in acetaminophen dose preparation.⁹ The total daily doses used in these patients ranged from 60 to 420 mg/kg/day for a period ranging from 1 to 42 days. In over half the cases, the children had received adult acetaminophen dosage forms, despite clear product labeling. Of the cases reviewed, 24 (55%) died as a result of acetaminophen toxicity. It is important to note that in both of these reviews, some of the children with significant hepatotoxicity received considerably less than the proposed toxicity threshold of 140 mg/kg set for a single exposure.

Many parents have difficulty measuring and administering a correct dose of medication for their child. In a mock scenario in which 100 caregivers were asked to determine the correct dose of acetaminophen for their children, only 30% of participants were able to demonstrate both accurate dose calculation and preparation. These same caregivers were also asked to complete a questionnaire about OTC use. Interestingly, while 66% of the respondents reported using Tylenol[®] in their children, only 8% reported acetaminophen use, showing that the majority of caregivers failed to associate generic and brand names.¹⁰ This highlights the basis for another common error, the failure to identify multiple sources of acetaminophen, leading to excessive cumulative doses when more than one product is used.

While the errors occurring in the home have become more well known, there are also reports of acetaminophen dose calculation and administration errors occurring in hospitals. Dunlevy and Wall reported a case of acetaminophen toxicity occurring in a 6 year old boy admitted to their institution with cervical adenitis and inflammatory torticollis.¹¹ Orders were written for acetaminophen (160 mg) or acetaminophen (also 160 mg) with codeine to be given every 4 hours. Unfortunately, both forms were given on regular basis over the next 30 hours until the error was detected. The patient developed emesis, was diaphoretic, and had elevated liver function tests. Prompt therapy with N-acetylcysteine was initiated, and the patient recovered without incident.

Dosing Limitations

Several reports of acetaminophen toxicity in children relate to its use in patients with impaired hepatic function. Last year, Pershad and colleagues described a case of an 18 month old child, born prematurely, who died after chronic acetaminophen exposure.¹² The child had received a dose of 20 mg/kg every 4 hours for a period of 4 days. The authors speculated that the patient's underlying hepatic changes resulting from administration of parenteral nutrition during the neonatal period may have placed the patient at risk.

Viral infections, dehydration, and underlying metabolic disease can also produce liver dysfunction which may exacerbate acetaminophen toxicity.⁷ Fasting or inadequate protein intake, commonly seen in children with infections who suffer a loss of appetite, can worsen the degree of toxicity by depleting glutathione stores.⁸

In addition to these patients, children receiving concomitant therapy with drugs that induce hepatic cytochrome P450 enzyme function may be at greater risk. Stimulating enzyme function may result in greater production of the toxic NAPQI metabolite. Children taking phenobarbital, phenytoin, rifampin, and isoniazid should be considered to be at greater risk for acetaminophen toxicity. Doses should be reduced in these patients and the duration of therapy kept to a minimum.²

Intentional Overdose by Adolescents

Acetaminophen overdoses continue to claim the lives of many adolescent suicide victims each year. Another group of teens survive their

suicide attempt, but suffer significant morbidity from their exposure. While attempts to identify and treat those patients at risk is the primary method to reduce teen suicide, it is also valuable for teens to understand the potential severity of an acetaminophen overdose.

In 1996, Gilbertson and colleagues reported the results of a questionnaire completed by 1,147 American and British adolescents. More than 90% of the teens surveyed recognized that an acetaminophen overdose could be fatal, but most overestimated the amount of drug that would be required. They likewise overestimated the amount of drug needed to cause significant harm, believing that more than twenty 500 mg tablets would have to be ingested to cause any adverse effects. This amount, 10 grams, is significantly more than the actual lower limit of toxicity, approximately 4 grams.

It is likely that this lack of awareness of the severity of acetaminophen toxicity by adolescents has led to many suicide gestures resulting in actual suicide or severe morbidity. In the retrospective review by Rivera-Penera described earlier, the primary reason for acetaminophen toxicity in children older than 10 years was intention to commit suicide.⁷ Like Gilbertson, these authors suggest that most teens are unaware of the potential severity of acetaminophen-induced hepatotoxicity and downplay the risk that a suicide gesture might actually result in death.

Recommendations for Reducing the Risk

All caregivers should be educated about the potential for acetaminophen toxicity. Dosing guidelines based on age and weight should be reviewed during well child visits. The recommendation to use a single acetaminophen product for all children in the family will help to reduce the likelihood of errors resulting from confusion about the differences in dosing cups, spoons, and droppers. Health care providers should clarify in which situations they should be contacted prior to the child being given acetaminophen. Caregivers should also know to report any potential error in dose preparation and to call the nearest Poison Control Center immediately after any significant exposure.

Fortunately, there has recently been a move to clarify dosing instructions on acetaminophen products. At a Food and Drug Administration advisory committee meeting on September 18, 1997, recommendations were made by the

American Academy of Pediatrics, the American Association of Poison Control Centers, and pharmaceutical manufacturers for improving dosing information. The committee subsequently approved revised labeling standards for these products in children. New standards clarify the difference between concentrated drops and the liquid suspension for older children and are easier to read. A more specific warning statement about the risk of toxicity from exceeding the recommended daily dose was also added to all product labeling.

In addition to the improvements in package labeling, a number of other educational materials are available to give to parents, including easily read materials for families with limited literacy skills.^{13,14} McNeil, the manufacturer of the Tylenol[®] brand of acetaminophen, has developed many educational tools for families, including a website at <http://www.tylenol.com>. Parents and health care providers may also contact the company at 1-800-962-5357.

Whether in the home, hospital, or office setting, all caregivers should follow appropriate dosing guidelines. The accepted acetaminophen dose for children is 10 to 15 mg/kg/dose given every 4 to 6 hours as needed. Patients should receive no more than 5 doses in a 24 hour period. In patients receiving "around-the-clock" dosing, a six-hour dosing interval should be used. A maximum total daily dose of 80 mg/kg/day is recommended; however, several of the studies discussed previously included cases of toxicity well below this limit. The duration of therapy should be kept to a minimum. In selected situations, such as analgesia following medical procedures, a single 20 mg/kg dose may be given to children with normal hepatic function.

Caregivers should also be aware that many OTC cough and cold preparations contain acetaminophen. Pharmacists can play an important role in assisting with the selection of OTC products for children and educating families about dose preparation and administration. Caregivers also should understand the need to look for the generic name "acetaminophen" in all products rather than rely on common brand names.

Anticipatory guidance for adolescents should incorporate a discussion of the safe use of OTC medications, including the risk of toxicity with acetaminophen overdose. Discussions about self-medication and acetaminophen toxicity should be encouraged in high school health

courses. The potentiating effect of ethanol on acetaminophen-induced hepatotoxicity should also be addressed in this population.

Summary

Acetaminophen remains the most popular, and one of the safest antipyretics available without a prescription in the United States. Educating families and instituting safe dosing practices can further reduce the risk of toxicity in the pediatric patient population.

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Literature Review

Acetaminophen-associated TEN

A 7 year old girl who developed toxic epidermal necrolysis (TEN) associated with the use of acetaminophen is presented in this report. The child received only three 10 mg/kg doses of acetaminophen for a fever and sore throat. Within 12 hours, an erythematous rash developed over her trunk and legs. Vesicle formation occurred soon afterwards. Abnormal laboratory values included a sedimentation rate of 30 mm/h

and elevated liver function tests. Creatine phosphokinase on admission was 1,660 U/L (normal 0-150). The patient received supportive care and was discharged after 10 days. Upon interview, the parents described a history of itching, erythema, and mild skin peeling after acetaminophen use, previously been ascribed to viral illnesses. A rechallenge performed with a single 10 mg/kg acetaminophen dose produced diffuse urticaria, erythema, fever, and blood pressure instability requiring rehospitalization. Halevi A, Ben-Amitai D, Garty BZ. Toxic epidermal necrolysis associated with acetaminophen ingestion. ***Ann Pharmacother* 2000;34:32-4.**

Levalbuterol assessment

The authors of this review question the need for levalbuterol to replace racemic albuterol for nebulization in patients with asthma. The studies comparing the two agents are reviewed, supporting their argument that levalbuterol is no more effective as a bronchodilator than albuterol and produces a similar incidence of adverse effects. The authors conclude that levalbuterol, at a cost five times that of generic albuterol, offers no significant advantage. Asmus MJ, Hendeles L. Levalbuterol nebulizer solution: Is it worth five times the cost of albuterol? ***Pharmacotherapy* 2000;20:123-9.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 2/18/00:

The restrictions applying to the use of infliximab (Remicade[®]; Centocor) were amended to include patients with rheumatoid arthritis.

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