Pediatric Pharmacotherapy

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Therapy Review: Antipyretics

Pharmacology Literature Reviews

In the past decade, we have seen major changes in over-the-counter antipyretic use in the pediatric population. With the potential link between Reyes' syndrome and aspirin given during viral illnesses, the use of aspirin-containing products to treat children has nearly disappeared in the United States. In its place, acetaminophen has become the mainstay of treatment. In recent years, the availability of nonsteroidal antiinflammatory drugs (NSAIDs) without a prescription has added more options for the treatment of the febrile child.[1-3]

The need to treat fevers remains controversial. Masking a clinical sign of infection may place young children at risk for delays in being brought to medical attention.[1,4,5] In both animal models and clinical trials in humans, the presence of fever has been associated with improvement in the morbidity and mortality

associated with infectious diseases. The use of antipyretics has also been associated with prolonged illness.[4,5] Despite these findings, clinicians and parents continue to use antipyretics in children to reduce discomfort.

Acetaminophen

Acetaminophen is believed to produce its antipyretic effect through central inhibition of the cyclo-oxygenase pathway, blocking the production of prostaglandins which stimulate elevation of the hypothalamic temperature set point. Unlike aspirin and other NSAIDs, acetaminophen has little or no effect on the peripheral formation of prostaglandins; and therefore, does not possess antiinflammatory activity.[1,3,6]

The pharmacokinetics of acetaminophen have been studied in several groups of children.[1,7] Peak serum concentrations occur 30 minutes to 1 hour after ingestion of liquid dosage forms. Maximum antipyretic effect usually lags behind the time of maximum concentration, occurring in most patients at 1-1.5 hours. The volume of distribution is similar to that of adults, approximately 0.8-1 L/kg, with minimal protein binding. Acetaminophen is primarily eliminated via hepatic metabolism to water-soluble compounds which are then excreted in the urine. The elimination half-life in neonates has been reported as 2.8-4.7 hours, and in older children 1.8-4 hrs. Metabolic pathways differ with age. Children rely on sulfate conjugation as the major pathway of metabolism; while in adults, glucuronide conjugates are the primary metabolites formed.[1-3,6,8]

Adverse reactions are rare following appropriate acetaminophen use. Hypersensitivity reactions, hematologic abnormalities, and impaired renal function have been reported. The most serious risk associated with acetaminophen use is hepatotoxicity associated with an overdose. Children appear to be less susceptible to acetaminophen toxicity than adults; this may be explained, in part, by the differences in metabolic paths described previously. Hepatic injury occurs as the result of accumulation of a toxic intermediary metabolite, N-acetyl-p-benzoquinonimine (NAPQI), and children appear to produce less of this metabolite than adults. In addition, glutathione, which is needed in the next step of this metabolic process to detoxify NAPQI, is present in greater quantities in young children. For those readers interested in further information on the management of acetaminophen toxicity, Kiebler and Mowry[6] provide a more in-depth review.

Acetaminophen is typically dosed at 10-15 mg/kg given every four hours.[1] The use of a higher dose given less frequently, 20 mg/kg given every six hours, has been recommended as an alternative. Accurate dosing by care providers is an area of concern. Gribetz and Cronley[9] found that 67% of parents interviewed in an inner-city clinic routinely gave less than the recommended dose of acetaminophen to their children. One of the most frequently cited sources for dosing errors was the use of the 0.8 ml dropper (designed for use with the infant drops but not the formulations for older children) to administer acetaminophen

syrup or suspension. Many parents desired the convenience of the dropper device and failed to compensate for the differences in the strengths between infant's and children's formulations.

Ibuprofen

Ibuprofen has been available in the United States since 1974, and was transferred to over-the-counter status for adults in 1984. In 1989, ibuprofen was first marketed for children as a prescription product and last year, pediatric ibuprofen became available without a prescription. Although there are many NSAIDs on the market, only ibuprofen carries an FDA-approved indication for fever reduction in children. Ibuprofen is one of the propionic acid NSAIDs, and inhibits prostaglandin synthesis both centrally and peripherally. As a result, ibuprofen has antiinflammatory properties in addition to being an antipyretic and analgesic.[1,3]

Ibuprofen is a racemic mixture of R and S isomers. The S-isomer is the pharmacologically active form. The R-form is slowly converted *in vivo* to the S-isomer. Ibuprofen is rapidly absorbed from the gastrointestinal tract.[7,10,11] A pharmacokinetic study by Brown et al[7] performed in 93 children documented peak serum concentrations occurring at one to two hours after oral administration. The average volume of distribution of 0.2 L/kg is slightly higher than adults. Ibuprofen is extensively metabolized in the liver, primarily via oxidation to inactive compounds. Elimination half-life in older children (as well as adults) ranges from 1-3 hours, with a more rapid elimination in infants.

The most common adverse effects associated with ibuprofen use are nausea, stomach upset and skin rashes, occurring in 3 to 9% of patients (both adults and children).[1,3] A recent clinical trial involving 55,785 children receiving ibuprofen revealed few serious adverse effects. Based on their patient population, the authors estimated a risk of 5.4 per 100,000 patients for the development of acute renal failure, anaphylaxis, or Reyes' syndrome with routine out-patient ibuprofen use.[12] As with other NSAIDs, the risk of renal toxicity may be enhanced in dehydrated patients. Other rare adverse effects include: anaphylactic reactions, hepatic impairment, gastrointestinal bleeding, mental status changes, and blood dyscrasias.

Symptoms of ibuprofen overdose are generally mild, with gastric upset and CNS depression being most prominent. However, seizures, hypotension, renal failure, and coma have all been reported following ingestion of large quantities.[3] Parents should be informed that both acetaminophen and ibuprofen should be stored safely out of the reach of children in containers with child-proof caps to minimize the risk of accidental poisonings.

The recommended dosing schedule for ibuprofen is 5 mg/kg every 6 to 8 hours for baseline temperatures $\leq$ 39.2 C (102.5 F) and 10 mg/kg every 6 to 8 hours for higher fevers. The maximum recommended daily dose is 40 mg/kg. Children

more than 12 years of age or weighing over 40 kg should be dosed as adults, using 200-400 mg every four to six hours.[1,3]

Comparison Studies

Measurement of the pharmacodynamic response to antipyretics is complex. Factors such as the age of the child and the degree of elevation of temperature can influence a patient's response to acetaminophen or ibuprofen. For example, several investigators have found that children younger than 5 to 6 years of age appear to elicit a greater response to a standard, weight-based, antipyretic dose than older children.[7,11,13]

Several studies have been published comparing the efficacy and safety of acetaminophen and ibuprofen in the pediatric population.[13-16] In 1989, Walson and colleagues[14] performed a double-blind, triple-dummy-designed trial of single doses of ibuprofen (both 5 mg/kg and 10 mg/kg), 10 mg/kg acetaminophen, and placebo in 127 children between 2 and 11 years of age. Both antipyretics were more effective than placebo. A dose response relationship was found for ibuprofen, and the results of this study formed the basis for the current dosing recommendations. For fevers greater than 102.5 F, ibuprofen was found to be more effective than acetaminophen. All treatments were well tolerated and no adverse effects were reported. Similar results were reported by Kauffman et al[15] in a trial of 37 children randomized to the same dosing strategies.

The equivalency of the dosing regimens used in these earlier studies has been called into question. In a subsequent paper[16], Walson's group found that when administering multiple doses over a period of 24 to 48 hours, doses of 10 mg/kg ibuprofen were equivalent to 15 mg/kg acetaminophen.

Product Availability and Cost

Both acetaminophen and ibuprofen are available without a prescription. Most parents are familiar with the Tylenol® brand of acetaminophen, but less expensive generic brands also exist. Acetaminophen can be purchased in many dosage forms, including suppositories, infant drops, suspensions, elixirs, chewable tablets, as well as "junior-strength" and adult strength tablets and capsules. Ibuprofen is available as oral drops, a liquid suspension dosage form, and chewable tablets (Children's Motrin®) as well as numerous tablet and capsule dosage forms for adult use.

The following chart lists average retail prices for a sample of different brand name and generic products, rounded to the nearest half dollar. These values are based on prices obtained from four Charlottesville-area pharmacies.

Cost Comparison of Oral Antipyretic Products

Product	Brand	Generic

Acetaminophen		
Drops (100mg/ml; 15 ml)	$4.50	$3.00
Elixir (160mg/5ml; 4 oz)	5.50	3.00
Suspen. (160mg/5ml; 4 oz)	6.00	3.00
Chewable Tab. (80mg; 30)	4.00	2.00
Jr. Stren. Tab. (160mg; 30)	4.00	3.00
Ibuprofen		
Suspen. (100mg/5ml; 4 oz)	$6.50	---

Despite the continued controversy over their appropriate role, antipyretics continue to be widely used. When used appropriately, they are effective and safe for most children. Information on choice of agent, safe dosing, and storage practices will help parents to best utilize these products.

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Pharmacology Literature Review

Cefuroxime Axetil Review

A comparison of the oral cephalosporins was featured in the last issue of *Pediatric Pharmacotherapy*. For those readers interested in a more in-depth review, this article contains the latest information on the antibacterial activity, pharmacokinetics, adverse effects, and dosing regimens for oral cefuroxime. The authors include an extensive review of the clinical trials demonstrating the efficacy of this second generation cephalosporin in treating a variety of infections. Perry CM, Brogden RN. Cefuroxime axetil: A review of its antibacterial activity, pharmacokinetic properties, and therapeutic efficacy. **Drugs 1996;52:125-58.**

Leading Dollar Volume Pharmaceuticals

The medications demonstrating the greatest monetary growth during 1995 have been tabulated from an annual survey of drug wholesalers and a panel of hospitals representing direct purchasing. The top twenty-five medications/chemical entities for which the most money was spent by hospitals are (from largest amount to smallest): erythropoietin alfa, ceftriaxone, filgrastim (G-CSF), alteplase, immune globulin (all producers combined), midazolam, paclitaxel, ciprofloxacin, propofol, ranitidine, ondansetron, urokinase, albumin, clavulanic acid (in Timentin® and Augmentin®), ampicillin, fluconazole, ceftazidime, isoflurane, imipenem-cilastatin, acyclovir, vecuronium, diltiazem, ticarcillin, ketorolac, and nifedipine. Of note, the antiifectives continue to be the

most heavily represented therapeutic class in the survey. Ramspacher S. 1995 hospital pharmacy review: Leading dollar volume pharmaceuticals. **Hospital Pharmacy 1996;31:624-42.**

Management of Gestational Diabetes

The authors of this brief review provide the current recommendations regarding management of women with insulin-dependent diabetes mellitus in pregnancy. In addition to information about insulin use and monitoring glucose control, the authors include a discussion of the use of antenatal monitoring techniques as well as guidelines for managing both mother and infant throughout the perinatal period. Steel JM, Johnstone FD. Guidelines for the management of insulin-dependent diabetes mellitus in pregnancy. **Drugs 1996;52:60-70.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 6/28/96:

1. Abciximab (ReoPro®), a platelet receptor blocker, was added to the formulary. Pending the development of usage guidelines, it is restricted to use during cardiac catherization.
2. A class review of ophthalmic products was initiated. This review will be completed at the next meeting.

Editors' Note

Welcome to Our New Readers!

The editorial staff of *Pediatric Pharmacotherapy* would like to welcome all new members of the Children's Medical Center staff. This newsletter is provided free of charge to all CMC personnel. If you are interested in submitting material for publication or serving on the editorial board, please contact Dr. Marcia Buck at the address listed below.

For assistance with questions related to medication use in children currently admitted to the CMC, you may contact the pediatrics pharmacy at 982-0920. For more in-depth consultations, you can contact Dr. Buck by phone at 982-0921 or by paging 971-6222, or one of the pediatrics pharmacy team, Clara Jane Snipes, R.Ph. or Doug Paige, R.Ph. by paging PIC 1775. For questions concerning out-patients, please contact Dr. Buck.

The University of Virginia Drug Information Center is also available to assist you with medication questions. Dr. Anne Hendrick is the program director. You can contact the Center by phone at 924-8034, Monday through Friday between the

hours of 8:00AM to 4:30 PM. The Drug Information Center can also provide assistance with requests for additions to the formulary.

If you have comments, questions, suggestions, or would like
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