Alternating Acetaminophen with Ibuprofen for Fever: Is this a Problem?

Alvin A. Miller, MD

Fever is probably the most common reason parents seek the advice of healthcare providers. This is a symptom that causes fear, even panic, in some parents. The treatment of the child with fever has gone from blankets, to ice-water baths, to aspirin, to acetaminophen, to ibuprofen, and now we find children with fever getting two antipyretics — acetaminophen alternating with ibuprofen. This regimen for treating fever has been studied in a few clinical trials, but insufficient evidence has surfaced to accept this as an evidence-proved method of management of fever. This regimen has crept into the treatment of fever by caregivers and providers with very few studies or evidence that it is more effective than a single antipyretic, or more importantly, that it is safe.

FEVER PHOBIA

After an interview of 70 caregivers or parents, Schmitt in 1980 called attention to the prevailing attitude toward fever in children. It was considered by many to be harmful, to cause brain damage, to go up to 120 if not lowered, to cause convulsions and even death. These pervasive attitudes have created the concept of “fever phobia,” which has led to fears, myths, and to unusual, sometimes drastic, methods of lowering fevers. These fears and myths were prevalent in 2000 when Crocetti revisited the issue of “fever phobia” by interviewing 340 caregivers and pointing out that nothing had changed in 20 years. In 2007, Wright and Liebelt surveyed 256 caregivers and concluded that this “unfounded” phobia was passed down to parents from pediatricians.

Many believe that instruction, as well as education of caregivers, is necessary to eliminate these attitudes, myths, and fears in treating a child with fever. Such instruction will have to come from healthcare providers, as well as from the media and pharmaceutical companies, whose ads promote fever phobia. Magazines and the media contribute to fear of fever with comments such as, “if you love your child,” “if you care about his comfort,” or “if his illness needs rapid cure and comfort, use this product!”

MEASURING FEVER

Fever has been a concern in healthcare for many years and continues to create anxiety in parents and sometimes in providers. The role of temperature in humans has also been debated. Some may also believe that the survival of a species depends on fever, because it protects the host from moderate disease. If an infection becomes lethal, doesn’t this protect the species from an epidemic? Fever therapy (artificial hyperthermia) has been used in the past to treat malaria, syphilis, gonorrhea, and encephalitis. These thoughts regarding the benefits of fever are of little comfort to a parent of a febrile child and generate fear, myths, and result in the “fever phobia” coined by Schmitt in 1980. Measuring temperature has become complicated by the availability of so many methods used to measure temperature. Evaluation of these instruments...
with comments were reviewed by Rideout and are as follows:6
1. Tactile evaluation: Sensitivity ranges from 74% to 88% (negative predictive value up to 99%).
2. Glass mercury thermometer: Objections are breakage, mercury toxicity, and reading the scale.
4. Pacifier instrument: Takes 3 minutes, need to add 0.5 degrees to equal core temp.
5. Tympanic temperature: Takes 60 seconds, is variable with only 76% sensitivity and has high false elevation.

It is therefore recommended that for patients younger than 3 months, a rectal temperature should be taken; from 3 months to 5 years, digital, rectal, or axillary (+1 degree); and greater than 5 years, oral digital.

HISTORY OF ANTIPYRETICS: ACETAMINOPHEN AND IBUPROFEN

In ancient and medieval times, antipyretic agents were compounds in willow bark (salicins, which led to aspirin), and compounds in cinchona bark. Efforts to refine salicin and salicylic acid took place in the 19th century, and this was accomplished by Felix Hoffman (a Bayer chemist). The cinchona tree became scarce in the 1880s. Two antipyretic agents, acetanilide in 1886 and phenacetin in 1887, were common choices for antipyresis. Paracetamol was synthesized in 1873 and discovered in the urine of people taking phenacetin. Paracetamol was found to be a metabolite of acetanilide in 1899. This was ignored until 1948 when paracetamol was recommended for analgesia and antipyresis, because it did not have the toxic effects of acetanilide (methemoglobinemia). Paracetamol went on the market in the United States in 1955 under the name Tylenol and in the United Kingdom as Panadol. This was produced as an elixir and gained favor in the pharmacopoeia of the United Kingdom. Panadol is marketed in Europe, Africa, Asia, Central America, and Australia. In North America, paracetamol is sold in generic form as acetaminophen and under the brand names of Tylenol, Anacin, Tempra, and Datrex.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) marketed originally as Nurofen and since then under the names of Advil, Brufen, Dorval, Panafen, Motrin, Nuprin, Iprem, or Ibu- pron. Low doses (200 mg or sometimes 400 mg) are available over the counter (OTC). Ibuprofen’s action peaks at 4 to 8 hours. A child’s dose is 5 to 10 mg/kg every 4 to 6 hours. The drug works through the inhibition of cyclo-oxygenase (COX), thus inhibiting prostaglandin synthesis, which is how it exerts its antipyretic action.7 Toxic effects are mainly gastrointestinal and are because of continued usage or large doses of the drug. It became available by prescription in 1969 in the United Kingdom and in the United States in 1974. Ibuprofen was approved as an OTC drug in the United States in 1984. Its easy availability has led to its current use in combination with acetaminophen in the treatment of fever.

MECHANISM OF ACTION

Paracetamol (acetaminophen) has similar action to aspirin, which is to inhibit COX enzymatic activity, thereby reducing production of prostaglandins that are active in producing fever via the hypothalamus and vasodilatation of vessels. Unlike aspirin, acetaminophen does not impair blood clotting or cause gastric irritation. It is also metabolized in the liver, its toxic metabolites being detoxified with glutathione and excreted by the kidneys.9 Toxicity to the liver in children is possible when doses of 200 mg/kg are reached. The inclusion of acetaminophen in many OTC cold remedies makes it necessary to be aware of drug combinations with acetaminophen when treating a child to avoid toxicity.9,10 Because ibuprofen has the same antipyretic action, namely inhibition of prostaglandin synthesis, it is possible that when this drug is used with acetaminophen in treating fever, the two act synergistically. The accumulation of acetaminophen toxic metabolites in the renal medulla when used with ibuprofen, along with reduced prostaglandin and glutathione, has been postulated in three cases of renal failure because ischemia occurs when prostaglandin synthesis is inhibited.10,11 Before Reye’s syndrome was recognized, aspirin was used with acetaminophen in managing fever, with some data showing that the reduction of fever was more sustained, although it was no greater than with monotherapy.16 When aspirin was implicated in Reye’s syndrome causation, ibuprofen was substituted, leading to the use of ibuprofen with acetaminophen to control fever, an unfounded practice passed down to parents from pediatricians.5

WHAT ARE PHYSICIANS DOING TO TREAT FEVER?

Mayoral interviewed and surveyed 161 healthcare providers, asking how they managed fever in children.17 He reported that alternating acetaminophen

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<tr>
<th>Antipyretic of Choice</th>
<th>Dosage</th>
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<tr>
<td>33% recommend acetaminophen</td>
<td>10 mg/kg every 4 hours</td>
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<tr>
<td>33% recommend acetaminophen</td>
<td>15 mg/kg every 4 hours</td>
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<tr>
<td>22% recommend ibuprofen</td>
<td>10 mg/kg every 6 hours</td>
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<tr>
<td>8% recommend ibuprofen</td>
<td>7.5 mg/kg every 6 hours</td>
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with ibuprofen was a common practice (50% of those surveyed were doing this). However, he reported significant differences in the “schedule” being used as well as the source of healthcare providers’ knowledge regarding this practice (see Table, page 385, and Sidebar). He concluded that providers did not all use the same regimen, that intervals of dosing and doses varied, and their source of education was “unusual.” He concluded that caution is necessary because of the potential toxicity from incorrect dosing, and that there was no evidence at that time that combination therapy was better or safer. The same caution was expressed by Shortridge after reviewing studies on alternating the two drugs in managing fever.21

**CLINICAL TRIALS REGARDING ALTERNATING DRUGS**

Three studies have attempted to evaluate the use of alternating acetaminophen and ibuprofen in children. Each study used differing regimes of dosing and/or intervals. Sarrell18 studied 464 children (6 months to 36 months) in a day care setting and separated these children into three groups:

- A) Tylenol 12.5 mg/kg every 6 hours,
- B) Motrin 5 mg/kg every 8 hours, and
- C) Tylenol 12.5 mg/kg and Motrin 5 mg/kg alternating the drugs every 4 hours.

All three groups received a loading dose of either Motrin 5 mg/kg or Tylenol 25 mg/kg at the start of treatment.

The results of these studies showed that group C had faster and lower mean temperatures on day 1 to day 3, and patients lost fewer days in daycare. The alternating drug group (C) had faster and lower mean temperatures on days 1 through 3 and fewer day care days lost. They concluded that this two-drug regime was superior to monotherapy.

**Criticism**

This study has been criticized in that intervals and dosages differed in each group, and are not the schedules used today.

Two other studies had different protocols. Nabulsi19 studied 70 children (6 months to 14 years) in two separate groups. Group A received a single of ibuprofen (10 mg/kg) followed by acetaminophen (15 mg/kg) 4 hours later. Group B received the same dose of ibuprofen followed by a placebo at 4 hours. Temperatures were measured at 4, 5, 6, 7, and 8 hours after dosing. The investigators concluded that a single dose of ibuprofen alternating with acetaminophen was better than ibuprofen alone. The criticism with this study is that two drugs are being compared to single drug. In the United Kingdom, in a study done by Erlewyn on 123 children (6 months to 10 years), it was concluded by the authors that giving both drugs simultaneously (Tylenol 15 mg/kg with Motrin 5 mg/kg every 4 hours) was better than either monotherapy arm of the study (0.35°C lower 1 hour after administration). Design flaws in the studies performed to date limit conclusions other than alternating the two drugs provides little or no advantage over monotherapy.21 With the potential of toxicity when both drugs are used together, and possible toxic effects when overdosing occurs, it appears that monotherapy should be considered as first-line treatment. Alternating acetaminophen with ibuprofen provides little or no advantage over monotherapy and may prove to be dangerous.

**MONOTHERAPY**

Studies have evaluated monotherapy with either acetaminophen or ibuprofen. Some have shown that ibuprofen is a better antipyretic than acetaminophen, but there was no great difference of clinical importance. It seems from most studies that the antipyretic effect of ibuprofen alone is more prolonged, and it may be given every 6 hours instead of every 4 hours for acetaminophen. Sidle24 demonstrated that 7 mg/kg of ibuprofen had the same fever reduction effect as acetaminophen at 10 mg/kg. Perot25 compared one time single doses of ibuprofen (5 to 10 mg/kg) to acetaminophen (10 to 15 mg/kg) but did not study the effect of repeat dosing. The study concluded that the single dose of ibuprofen was “superior.” Wilson compared single dose placebo-controlled antipyresis in children and found similar results.26 Studies indicate that ibuprofen fever reduction appears to last longer than that of acetaminophen, but every study tested varying doses from 5 mg/kg to 7.5 mg/kg to 10 mg/kg. Pharmacologic investigators believe that ideal studies would compare equivalent doses of each drug rather than 10 mg/kg of one to 15 mg/kg of the other.27

**TOXICITY REPORTS**

What price normo-thermia?

Reversible renal failure has been reported when ibuprofen and acetaminophen are used in combination.3 3,13 It is suggested that this occurs because both acetaminophen and ibuprofen inhibit synthesis and release of prostaglandins, which produce glutathione as well as increase vasodilation of renal vasculature.9 When toxic metabolites of acetaminophen are left in the kidney, they need glutathione to be detoxified and excreted. If the patient is dehydrated and has low renal blood flow, these products have potential of causing acute tubular necrosis. Acetaminophen poisoning is a well-studied toxic illness, and with the confusion and potential of incorrect dosing, the possibility of liver tox-
ticity or encephalopathy is a real danger. In addition, hematemesis has been reported from ibuprofen treatment, with resultant gastric ulceration. Endoscopic lesions are commonly seen as a result of ibuprofen therapy, often asymptomatic. The problems of wrong drug preparation (children versus infant drops), the confusion caused by the huge number of OTC preparations of both of these drugs, and the difficulty with correct use of both drugs are a potential danger to the child.

AMERICAN ACADEMY OF PEDIATRICS STATEMENT

The American Academy of Pediatrics (AAP) stated that there is no evidence that alternating ibuprofen and acetaminophen achieves faster, safer, or more efficient reduction of fever in children compared to monotherapy. Utilizing two agents may be confusing to parents, and lethal consequences have resulted from incorrect dosing. Some children are at greater risk of untoward side effects, such as a dehydrated patient or a child with liver disease. In addition, many children are also receiving other OTC drugs containing these two drugs, Providers need to be realistic about the expected response to antipyretics, should avoid aggressive pharmacotherapy, and teach the caregiver proper management of fever. Use the optimal dose of the antipyretic and perhaps consider doubling the first dose.

EDUCATION REGARDING FEVER IN CHILDREN

Understanding fever and the management of the febrile child requires broader education of both caretakers as well as providers. The treatment of fever by alternating two potentially toxic drugs may lead to serious morbidity and possibly mortality because they are synergistic. Also, and there are no evidence-based studies to show the superiority of using two agents rather than a single agent. Poison control centers receive frequent calls from caregivers asking questions on how to alternate these drugs and what doses to use. We need not join the “fever phobia” panic when a child has a fever. We need to educate, inform, and guide our parents through this issue that is so worrisome to them. Choose and recommend one drug, give maximal dosage, and use caution and realism in managing fever in a child. The need for a change in how we approach and advise parents on treating fever in a child may avoid serious consequences when unfounded practices suddenly appear in pediatrics.

REFERENCES