Antipyretic Therapy

Physiologic Rationale, Diagnostic Implications, and Clinical Consequences

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Various treatments have been used to suppress fever since antiquity. Surprisingly, few studies have been performed to ascertain the physiologic consequences of antipyresis and validate the rationale behind such therapy. More importantly, it has not been established conclusively that the benefits of antipyretic therapy outweigh its risks. The present review considers these issues in light of currently available data and formulates guidelines for antipyretic therapy based on these data.

Antipyretic agents have been used to lower febrile body temperature for well over two millennia. Ancient Assyrian, Egyptian, and Greek physicians all apparently knew of and exploited the antipyretic property of extracts of the bark of the willow (Salix alba). However, it was not until 1763 that the Reverend Edward Stone gave the first scientific description of the clinical benefits of willow bark to the Royal Society of London. Less than 80 years later, Piria succeeded in preparing salicylic acid from salicin, a glycoside component of willow bark. Salicylic acid was first synthesized by Gerland in 1852, some 8 years before Kolbe and Lautemann, who are frequently credited with this accomplishment, and just a year before von Gerhardt developed acetylsalicylic acid (aspirin) during efforts to find a more palatable form of salicylate. In 1899, the Bayer Company launched the modern era of antipyretic therapy with the introduction of aspirin as the world’s first commercially available antipyretic drug. During this same period, acetanilide and phenacetin were derived from para-aminophenol compounds in coal tar, and pyrazolon compounds such as amino-pyrine were developed.

A little less than a century later, the marketplace is replete with drugs capable of suppressing fever. Their widespread application by primary care physicians, emergency department nurses, pharmacists, parents, and other caregivers has, at least in part, been motivated by a general suspicion that fever is inherently noxious. This suspicion is reflected in the results of surveys reporting that approximately 40% of parents and other caregivers regard temperatures encountered during fever as harmful, and that 12% of physicians believe that fever has the capacity to cause brain damage. Perhaps most indicative of the medical profession’s inherent antipyretic therapy is the fact that an estimated 70% of nurses and 30% of physicians routinely use antipyretic drugs to suppress fever.

The present review critically evaluates the physiologic rationale, the diagnostic implications, and the clinical consequences of antipyretic therapy. The data reviewed are also used to formulate recommendations regarding the appropriate clinical application of such therapy.

DEFINITIONS

Fever is “a state of elevated core temperature, which is often, but not necessarily, part of the defensive response of multicellular organisms (hosts) to the invasion of live (microorganisms) or inanimate matter recognized as pathogenic or alien by the host.” The febrile response, of which fever is but 1 component, is a complex physiologic reaction to disease involving a cytokine-mediated rise in core temperature, generation of acute-phase reactants, and activation of numerous physiologic, endocrinologic, and immunologic systems. The rise in core temperature during fever is to be distinguished from the unregulated rise that occurs during hyperthermia, in which pyrogenic cytokines are not directly involved and
against which standard antipyretics are largely ineffective. Antipyretics block or reverse fever's cytokine-mediated rise in core temperature, but do not affect body temperature in the afebrile state. They are to be distinguished from hypothermia agents (cryogens), which are capable of lowering core temperature even in the absence of fever.

RATIONALE

Two critical assumptions are made when prescribing antipyretic therapy. One is that fever is, at least in part, noxious, and the other, that suppressing fever will reduce if not eliminate fever's noxious effects. Neither assumption has been validated experimentally. In fact, there is considerable evidence that fever is an important defense mechanism that contributes to the host's ability to resist infection.15,16 Moreover, it has never been shown in humans that increases in core temperature encountered during fever, which rarely exceed 41°C (105.8°F), are harmful per se.17 Nevertheless, many clinicians believe that even the relatively modest increases in core temperature encountered during fever are deleterious to certain patients and should therefore be suppressed.

Children, primarily between ages 3 months and 5 years, are 1 such category of patients. In these children, seizures have occurred during episodes of fever at a frequency of from 2% to 5% in the United States and Western Europe18,19 to as high as 14% in other selected countries.20 Although most children have temperatures of 39.0°C or lower at the time of their seizure,21 many tolerate higher fevers at later dates without convulsing.22 Unfortunately, antipyretic therapy has not been shown to protect against recurrences of febrile seizure in the few controlled trials conducted thus far.23

It has also been suggested that patients with underlying cardiovascular or pulmonary disorders might be especially susceptible to the adverse effects of fever because of the increased metabolic demands imposed by the elevated temperature.24 Such demands, which peak during the chill phase, largely as a result of shivering, include increases in sympathetic tone,25 oxygen consumption, respiratory minute volume, and respiratory quotient.26 Although these have been proffered as prima facie justification for antipyretic therapy in patients with underlying cardiopulmonary disorders, the risk-benefit ratio of such therapy has yet to be determined.

Antipyretic therapy might also be justified, at least in theory, if fever's metabolic cost exceeded its physiologic benefit, if the treatment provided symptomatic relief without adversely affecting the course of the febrile illness, and/or if the toxicologic costs (adverse effects) of the antipyretic regimen were appreciably lower than its beneficial effects. Unfortunately, although clinicians have long argued the validity of each of these propositions as justification for antipyretic therapy, few experimental observations exist to support any of these arguments.27

ANTIPYRETIC DRUGS

The essential elements of the fever physiologic pathway are release of pyrogenic cytokines by inflammatory cells in response to some exogenous pyrogen (eg, infection), induction of cyclooxygenase (COX) 2 activation of the arachidonic acid cascade, and enhanced biosynthesis of prostaglandin E2 (PGE2) by hypothalamic vascular endothelial cells.28 Through its effect on thermoregulatory neurons located in the preoptic area of the anterior hypothalamus, PGE2 acts to raise the hypothalamic thermal set point (Figure) and thereby induce peripheral and thermogenic mechanisms to increase core temperature. Theoretically, antipyretic agents might interrupt the fever response at any step along this pathway.29

The drugs most commonly used today to suppress fever are the salicylates (eg, sodium salicylate and acetylsalicylic acid), ibuprofen, and the other nonsteroidal anti-inflammatory drugs (NSAIDs), and the para-aminophenol derivative acetaminophen. Until the 1970s, little was known about mechanisms responsible for the antipyretic activity of any of these compounds. In 1970, Milton and Wendlandt30 demonstrated both that prostaglandins of the E series cause rapid onset of fever when injected into the cerebral ventricles of cats and rabbits, and that PGE2 is released within the brain during fever. These observations, in conjunction with those of Vane31 showing that aspirin and other antipyretic drugs inhibit synthesis of prostaglandins, suggest that antipyretic drugs reduce fever primarily by inhibiting the formation of PGE2 in the brain. However, not all experimental data obtained since the early work of Milton and Wendlandt30 and Vane31 have supported this hypothesis. Injection of PGE2 into appropriate brain regions of animals capable of mounting a febrile response to endotoxin, for example, does not consistently cause fever in the animals.32 Moreover, salicylate infusions into the ventral septal area of experimental animals blocks the febrile response caused by intraventricular injection of PGE2,33 suggesting that the mechanisms of action of at least some antipyretic drugs might...
involve more than simple inhibition of PGE synthesis.

Acetaminophen, aspirin, and the other NSAIDs all seem to block conversion of arachidonic acid to PGE₂ by inhibiting COX. 21 Production of PGE₂ at key sites within the hypothalamus is widely regarded as a critical step in the process by which the physiologic cascade responsible for raising core temperature during the febrile response is activated. 34 Cyclooxygenase has at least 2 distinct isoforms: a constitutive isoform, COX-1, and a predominately inducible isoform, COX-2, which is undetectable in most resting cells. 1 The former initiates production of prostacyclin, which has both antithrombogenic and cytoprotective properties, whereas the latter is a principal mediator of the inflammatory response. The anti-inflammatory activity of NSAIDs is believed to result from inhibition of COX-2, and the unwanted adverse effects, such as gastric irritation, from inhibition of COX-1.

The structure and catalytic activity of the two COX isoforms are similar. 35 Both contain approximately 600 amino acids, of which 63% are in identical sequence. Their active sites are located at the apex of a long, narrow, hydrophobic channel. The amino acids forming the channel, as well as catalytic sites and neighboring residues, are identical in the 2 isoforms with 2 exceptions. Valine in COX-1 is substituted for isoleucine at positions 434 and 523 in COX-2. These variations account for many but not all of the differences in the-reactivities of the 2 isoforms. Aspirin, for example, acetylates serine 530 of both isoforms. In COX-1, this blocks access of arachidonic acid to the catalytic site, causing irreversible inhibition of the enzyme. Because of the wider hydrophobic channel of COX-2, access of arachidonic acid to the active site persists after acetylation of serine 530 by aspirin.

Acetaminophen and the NSAIDs differ with respect to their relative potencies as inhibitors of peripheral and central nervous system COX. Acetaminophen, for example, is nearly as effective as aspirin and 10% as effective as indomethacin in inhibiting central COX, but only 5% as effective as aspirin and 0.02% as effective as indomethacin in inhibiting peripheral COX. 35-37 The relatively weak activity of acetaminophen against peripheral COX most likely accounts for its poor anti-inflammatory activity.

The duration of action of an antipyretic drug depends on both its concentration at the site of action and whether it inhibits COX reversibly or irreversibly. Because aspirin inhibits COX irreversibly, 38 its antipyretic effect persists until new enzyme is generated at the site of action. Other NSAIDs are reversible inhibitors of COX, and as such would be expected to have activities that vary directly with their concentration at the site of action. 38 However, many of the NSAIDs (eg, the 2-arylpropionic acid derivatives, ibuprofen and ketoprofen) are chiral compounds—that is, they exist as both S- and R-enantiomers. The R-enantiomer, which is 100- to 500-fold less active against COX-2 than the S-enantiomer, functions as a drug depot by being converted to the S-enantiomer in vivo. As a result, racemic mixtures of the 2 enantiomers, the form in which many NSAIDs are marketed, exhibit longer durations of action than might be expected based on the pharmacokinetics of the S-enantiomer alone. 39-41

Because it takes time for the fever cascade (Figure) to effectuate heat retention and production mechanisms, there is a necessary delay between the release of endogenous pyrogens and pyrogen-induced increases in core temperature. For similar reasons, there is a delay between the time an antipyretic drug reaches its site of action and core temperature begins to fall. This antipyretic latency period might also be influenced by the capacity of arachidonic acid metabolites, such as PGE₂, to down-regulate production of at least some pyrogenic cytokines. 32 By suppressing PGE₂ production, COX inhibitors cause a paradoxical increase in translation of pyrogenic cytokines.

Studies of the relative potencies of the various classes of antipyretic drugs have involved diverse clinical settings, numerous dosages and formulations of the antipyretic agents, and differing measures of clinical efficacy. As a result, a comprehensive meta-analysis of the accumulated data set is not possible. Nevertheless, several studies comparing ibuprofen with acetaminophen in children with fever are instructive. 41,43-51 In the aggregate, they suggest that orally administered ibuprofen is a more potent antipyretic than oral acetaminophen. However, the difference in potency is small, and the antipyretic effects of the 2 agents follow a similar time course, with both drugs exhibiting maximal activity 3 to 4 hours after oral administration. 41,43-51

Pediatric studies of the relative activity of other NSAIDs are sparse. In those comparing oral (5 mg/kg per day) and rectal (100-400 mg/d) nimesulide with oral placebo and rectal acetaminophen (200-800 mg/d), 52,53 the 2 formulations of nimesulide were nearly equivalent. Moreover, 100 mg of rectal nimesulide seemed to be at least as effective as 200-mg acetaminophen suppositories when given in doses varying between 1 and 4 suppositories per day, depending on individual needs. 53

Few studies have compared the antipyretic activity of NSAIDs in adults. In endotoxin-challenged adult volunteers, ibuprofen (800 mg orally) is an effective antipyretic if given just before or simultaneously with the endotoxin challenge. 45,54 and is superior to acetaminophen in lowering the temperature of patients with sepsis. 55 Intramuscular ketorolac (30 mg) was shown to be as effective as acetaminophen (650 mg orally) in suppressing fever in endotoxin-challenged adult volunteers. 56 In a single-dose crossover trial involving patients with various febrile disorders, oral nimesulide (200 mg) and dipyridone (500 mg) were more effective than oral aspirin (500 mg) in lowering fever. 57 Finally, in clinical trials comparing rectal nimesulide (200 mg) with acetaminophen (500 mg rectally) 58 and diclofenac (100 mg rectally) with placebo, 59 the 3 agents exhibited similar antipyretic activity.

One of the most important characteristics separating the various antipyretic drugs relates to toxic effects. Aspirin, for example, has a unique capacity for causing Reye syndrome. 60,61 A children’s disorder characterized by hepatic failure and encephalopathy due to inhibition of mitochondrial oxidative phosphorylation. 62 A welter of other adverse effects have been attributed to NSAIDs (Table 1), 53 the most important of
which, renal dysfunction and gastrointestinal bleeding, derive from their capacity to inhibit COX.\textsuperscript{63} Nonselective COX inhibitors are especially prone to cause such toxic effects.\textsuperscript{35,64} Subjects who use piroxicam, a drug with a high affinity for COX-1, for example, are approximately 11 times more likely to experience an adverse gastrointestinal event than subjects not using NSAIDs.\textsuperscript{35,64} By comparison, those who use naproxen, a drug with a greater affinity for COX-2, have only a 3 times higher risk of serious gastrointestinal toxic effects than non-users of NSAIDs.\textsuperscript{35,64} Other factors that seem to increase the risk of gastrointestinal toxic effects in users of NSAIDs include being older than 60 years, a history of a gastrointestinal disorder, concomitant corticosteroid therapy, and duration of NSAID consumption. Toxic effects occur most often during the initial month of therapy.\textsuperscript{64} Findings of longitudinal endoscopic evaluation of subjects treated with long-term aspirin suggest that resistance of the gastric mucosa to the toxic effects of NSAIDs increases with time.\textsuperscript{65} As a result, rates of adverse reactions associated with chronic ingestion of nonselective COX inhibitors might underestimate the risk of serious complications associated with sporadic use of such agents. Volunteers receiving low-dose aspirin (650 mg twice daily) have been shown to repair aspirin-induced mucosal ulcers substantially faster (median time to healing, 1 week) than those receiving high-dose aspirin (650 mg 4 times daily; median time to healing, 5 weeks).\textsuperscript{56}

In a large survey examining antipyretic drug toxic effects, Lesko and Mitchell\textsuperscript{57} randomized over 84,000 children (aged 8 months to 10 years) to oral ibuprofen (5 mg/kg or 10 mg/kg) or acetaminophen (12 mg/kg) every 4 to 6 hours, later querying parents about adverse medical events. The median duration of treatment in their subjects was 3 days, during which a median of 6 to 10 doses of antipyretic drugs were administered. Approximately 1\% of subjects in each group were hospitalized during the study, most for treatment of infectious diseases. Four children, however, were hospitalized with gastrointestinal bleeding. All had been treated with ibuprofen, 2 at each dose. The risk of hospitalization for acute gastrointestinal bleeding in those receiving ibuprofen was 7.2 per 100,000. Although no child had to be hospitalized for acute gastrointestinal bleeding in the acetaminophen group, hospitalization rates in the 2 treatment groups were not significantly different. There were no episodes of Reye syndrome, anaphylaxis, or acute renal failure among the 55,785 children receiving ibuprofen.\textsuperscript{67}

Because acetaminophen has little activity against peripheral COX,\textsuperscript{35,37} it causes little gastric or renal toxicity. While acetaminophen is metabolized predominantly by glucuronidation and sulfation, it is also metabolized to a lesser extent via the p450 2E1 pathway to a highly electrophilic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). When the primary pathways are exceeded, NAPQI accumulates and binds covalently to cell proteins and DNA.\textsuperscript{68} When such binding is extensive and involves hepatocytes, acute hepatotoxicity ensues. Under normal circumstances, NAPQI is detoxified by conjugation to glutathione. If glutathione stores are depleted, eg, during chronic ethanol abuse or starvation, the risk of acetaminophen-induced hepatotoxicity increases markedly.\textsuperscript{68,69}

Whereas acute liver failure in the setting of an attempted suicide with acetaminophen is well recognized, only recently has attention been focused on the risk of hepatic injury due to acetaminophen administered in doses within or slightly above the recommended range (4 g in 24 hours). In a recent series of 71 cases of acetaminophen-induced hepatotoxicity, 30\% of the cases were shown to result from accidental overdoses in patients using the drug for pain relief.\textsuperscript{68} Reasons for excessive dosing included too frequent dosing, simultaneous ingestion of multiple acetaminophen-containing compounds, and ingestion of cough and cold remedies not recognized to contain acetaminophen.

### Table 1. Adverse Effects Associated With Nonsteroidal Anti-inflammatory Drug Therapy

<table>
<thead>
<tr>
<th>System</th>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Peptic ulceration</td>
</tr>
<tr>
<td></td>
<td>Esophagitis and strictures</td>
</tr>
<tr>
<td></td>
<td>Small- and large-bowel erosions</td>
</tr>
<tr>
<td>Renal</td>
<td>Reversible acute renal failure</td>
</tr>
<tr>
<td></td>
<td>Fluid and electrolyte disturbances</td>
</tr>
<tr>
<td></td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td></td>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Exacerbation of hypertension</td>
</tr>
<tr>
<td></td>
<td>Exacerbation of congestive cardiac failure</td>
</tr>
<tr>
<td></td>
<td>Exacerbation of angina</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Elevated transaminases</td>
</tr>
<tr>
<td></td>
<td>Fulminant hepatic failure (rare)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Drowsiness</td>
</tr>
<tr>
<td></td>
<td>Confusion and behavior disturbance</td>
</tr>
<tr>
<td></td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td></td>
<td>Agranulocytosis and aplastic anemia</td>
</tr>
<tr>
<td>Other</td>
<td>Exacerbation of asthma and nasal polyposis</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
</tr>
</tbody>
</table>

**Physical Methods of Antipyresis**

External cooling has been used since antiquity to treat fever. Alexander the Great received external cooling in the form of repeated cool baths as his principal therapy for the febrile illness to which he succumbed in 323 BC.\textsuperscript{70} External cooling continues to be used, most often in combination with antipyretic medications, to treat children with fevers refractory to such medications and adults in intensive care units.\textsuperscript{71}

A variety of techniques are used to cool patients by physical means. These include sponging with vari-
ous solutions (eg, tepid water or alcohol), application of ice packs or cooling blankets, and exposure to circulating fans (most often in conjunction with sponging). In contrast to antipyretic drugs, external cooling lowers the temperature of febrile patients by overwhelming effector mechanisms that have been evoked by an elevated thermoregulatory set point, rather than by lowering that set point. Therefore, unless concomitant therapy with antipyretic agents has lowered the thermal set point or shivering is inhibited by other pharmacologic means, external cooling is vigorously opposed in the febrile patient by thermoregulatory mechanisms trying to maintain the elevated body temperature.

Physical methods promote heat loss by conduction (eg, during immersion in cold water), convection (eg, during passage of cool air over body surfaces), and evaporation (eg, during water or alcohol sponge baths). Evaporative methods have traditionally been touted as the most effective physical means of promoting heat loss in febrile patients because such methods are deemed to be the least likely method to induce shivering.7 However, carefully designed comparative trials have not yet established any 1 physical method of antipyresis as superior.

Direct comparisons of pharmacologic and physical methods of antipyresis are likewise all but nonexistent. In the only controlled study, Wenzel and Werner72 reported that salicylates reduced the second phase of pyretic responsiveness in rabbits, whereas abdominal skin cooling increased heat production and did not lower core temperature unless animals were simultaneously exposed to a warm environment. Neither antipyretic modality abolished the initial phase of the febrile response.

The few clinical studies done of the efficacy of physical methods of antipyresis have differed in their conclusions. Interpretation of these data has been difficult because pharmacologic agents have almost invariably been administered concomitantly with external cooling. Steele et al73 found oral acetaminophen (in age-adjusted dosages ranging from 80 to 320 mg) and sponging with ice water or with alcohol in water to be equally effective in reducing fever in children. While less effective in lowering febrile temperatures, sponging with tepid water has been reported to afford greater comfort than sponging with either ice water or alcohol in water.73 When acetaminophen was combined with sponging, more rapid cooling occurred than with either modality alone. Newman,74 on the other hand, reported that tepid-water sponging in combination with 5 to 10 mg/kg of oral acetaminophen is no more effective than acetaminophen alone in lowering the temperature of children with fever. In a prospective observational study of adults with fever being treated in intensive care units, O’Donnell et al75 concluded that while hypothermia blanket therapy added little to the action of pharmacologic agents in lowering temperature, it induced wider temperature fluctuations and more episodes of hypothermia.

### Table 2. Studies in Children of the Oral Temperature Response of Bacteremic vs Nonbacteremic Infections to Antipyretic Agents

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study Design</th>
<th>Antipyretic Agent</th>
<th>Age of Subjects, y</th>
<th>Temperature Response, °C</th>
<th>Bacteremic</th>
<th>Nonbacteremic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torrey et al</td>
<td>1985</td>
<td>Prospective/observational</td>
<td>Acetaminophen/aspirin</td>
<td>2</td>
<td>40.1 1.3 239</td>
<td>39.9</td>
<td>1.0 1.4</td>
</tr>
<tr>
<td>Baker et al</td>
<td>1987</td>
<td>Prospective/observational</td>
<td>Acetaminophen</td>
<td>6</td>
<td>40.1 1.5 225</td>
<td>39.6</td>
<td>1.0 NG</td>
</tr>
<tr>
<td>Yamamoto et al</td>
<td>1987</td>
<td>Prospective/observational</td>
<td>Acetaminophen</td>
<td>6</td>
<td>40.5 1.6 216</td>
<td>40.4 1.6</td>
<td>.85</td>
</tr>
<tr>
<td>Weisse et al</td>
<td>1987</td>
<td>Prospective/observational</td>
<td>Acetaminophen</td>
<td>17</td>
<td>40.1 1.4 16</td>
<td>39.9</td>
<td>1.0 1.2  .37</td>
</tr>
<tr>
<td>Baker et al</td>
<td>1989</td>
<td>Prospective/observational</td>
<td>Acetaminophen</td>
<td>2</td>
<td>40.1 1.7 135</td>
<td>40.6 1.6</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Mazur et al</td>
<td>1989</td>
<td>Retrospective/case control</td>
<td>Acetaminophen</td>
<td>6</td>
<td>34 39.8 1.0 68</td>
<td>39.8 1.5</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Mean number of subjects studied.
†Mean initial temperature (T) (ie, T just prior to administration of antipyretic agent).
‡Mean decrease in T 60 to 120 minutes following treatment with antipyretic agent.
§Comparison of T in “bacteremic” vs “nonbacteremic” subjects by t test.

### Diagnostic Implications

Numerous investigators have observed a direct correlation between the height of fever and the rate of serious bacterial infections in children, with the likelihood of such infections increasing sharply in children febrile to greater than 40°C.7–8 It has also been suggested that the response of a fever to antipyretic therapy might be important diagnostically, in that a drop in temperature and/or improvement in the general appearance of a febrile child indicate that the fever is not due to a serious illness.7 This conclusion, however, is not supported by several investigations comparing the response of children to antipyretics (primarily oral acetaminophen) during bacteremic and nonbacteremic infections80–85 (Table 2). Of 6 such investigations published in recent years, only 185 found a difference in the antipyretic responsiveness of bacteremic and nonbacteremic fever. In that study, bacteremic fevers responded substantially less well to acetaminophen than nonbacteremic fevers. However, unlike the other prospective investigations that showed no such difference, this investigation was a retrospective study. Thus, with 1 retrospective exception, published investigations suggest that in children, fevers due to serious infections (ie, bacteremic) are as responsive to antipyretic therapy as less serious infections.

Several studies have suggested that neoplastic fevers are more responsive to NSAIDs than infectious fevers, and that this difference in antipyretic responsiveness can be used...
to distinguish fevers of infectious origin from those due to cancer.66-88 Unfortunately, because patients with obvious infections were excluded from analysis in these studies, the results may have been biased. Naproxen was one of the first such drugs to be studied in this regard.86 Subsequent randomized comparisons have reported naproxen, indomethacin, and diclofenac to be equally effective in inhibiting cancer-induced fever.86 No satisfactory explanation has been offered to date as to why NSAIDs might be more effective in reducing fever due to cancer than that due to infection.

RISK-BENEFIT CONSIDERATIONS

One of the reasons commonly given as justification for suppressing fever is that the metabolic cost of fever exceeds its clinical benefits. In fact, the metabolic and cardiovascular costs of fever are substantial, especially during the chill phase of the response with its shivering-induced increase in metabolic rate, norepinephrine-mediated peripheral vasoconstriction, and increased arterial blood pressure.72 Because of the potential adverse consequences of these metabolic effects on cardiovascular and pulmonary function, fever has been attacked with particular vigor in patients with underlying cardiovascular and/or pulmonary diseases.71 Although antipyretic therapy has theoretical merit in this regard (if it does not induce shivering86), neither the detrimental effects of fever nor the salutary effects of antipyretic therapy have been confirmed experimentally, even in patients with underlying cardiovascular and pulmonary diseases.

External cooling, which is widely used in such patients to suppress fevers unresponsive to antipyretic drugs, has been shown to decrease oxygen consumption by as much as 20% in febrile critically ill patients if shivering is prevented by therapeutic paralysis.89 If shivering is not inhibited, external cooling causes a rise in oxygen consumption.89 Perhaps more important to febrile patients with underlying cardiovascular disease, external cooling has the capacity to cause vasospasm of diseased coronary arteries by inducing a cold pressor response.90,91 For these reasons, it has been suggested that a more rational strategy for treating fevers unresponsive to antipyretic drugs is to warm rather than to cool selected skin surfaces, thereby reducing the vasoconstriction and shivering thresholds dictated by the elevated hypothalamic thermal set point, and, in this way, promoting heat loss.92

Unfortunately, certain antipyretic drugs also seem to cause coronary vasoconstriction in patients with coronary artery disease. Friedman et al33 observed significant increases in mean arterial pressure, coronary vascular resistance, and myocardial arteriovenous oxygen difference after administration of intravenous indomethacin (0.5 mg/kg) in such patients. Mean ± SEM coronary blood flow decreased simultaneously from 181 ± 29 to 111 ± 14 mL/min (P<.05). Thus, in this investigation, myocardial oxygen demand increased in the face of a fall in coronary blood flow following indomethacin administration. The authors speculated that indomethacin’s vasoconstrictor effect derives from its capacity to block the synthesis of vasodilatory prostaglandins.

Antipyretic therapy is also commonly administered to enhance patient comfort.94 General experience with antipyretic drugs, which are for the most part also analgesic agents, seems to support this rationale. However, carefully controlled efficacy studies have never quantified the degree to which antipyretic therapy enhances the comfort of patients with fever. Moreover, the relative cost of such symptomatic relief, in terms of drug toxicity and adverse effects of antipyretic agents on the course of the illness responsible for the fever, has never been determined. The importance of such information is underscored by reports that acetaminophen prolongs the time to crusting of skin lesions in children with chicken pox95 and that acetaminophen and aspirin increase viral shedding and nasal signs and symptoms while suppressing the serum-neutralizing antibody response in adults with rhinovirus infections.96,97 Findings of studies in human volunteers imply further that the capacity of antipyretic agents to prolong the course of rhinovirus and varicella infections might extend to viruses such as influenza virus as well (K.I.P., S. Kudaravalli, MD, S.S. Wasserman, MD, and P.A.M., unpublished data, 1999). Finally, paracetamol has recently been reported to prolong parasitemia in children infected with Plasmodium falciparum, presumably by decreasing production of tumor necrosis factor and oxygen radicals.98

Antipyretic therapy is also occasionally given to prevent febrile seizures in children and to prevent or to reverse fever-associated mental dysfunction in frail elderly patients. Beisel et al99 showed that aspirin (in combination with propoxyphene) ameliorates fever-associated decrements in mental work performance in young volunteers infected with sandfly fever virus, even in the face of only partial relief of either the fever or other symptoms of the illness. In view of these observations, antipyretic therapy might be expected to have a beneficial effect on fever-associated mental dysfunction in frail elderly patients. However, studies designed to test this hypothesis have not been conducted.

Unfortunately, antipyretic therapy has yet to prove effective in preventing febrile seizures.23 Camfield et al100 conducted a randomized double-blind study comparing single daily-dose phenobarbital plus antipyretic instruction with placebo plus antipyretic instruction in preventing recurrent febrile seizures following an initial simple febrile seizure. In children treated with phenobarbital and antipyretics, the febrile seizure recurrence rate was 5%, whereas in those receiving placebo and antipyretics, the rate was 25%, suggesting that a single daily dose of phenobarbital is more effective than counseling parents about antipyretic therapy in preventing recurrent febrile seizures. More recent studies in children have shown that whether given in moderate doses (10 mg/kg per dose, 4 times a day)101 or in relatively high doses (15-20 mg/kg per dose every 4 hours),102 acetaminophen fails to reduce the rate of recurrence of febrile seizures.

Finally, there has been considerable recent interest in the use of antipyretic drugs to modulate the activity of pyrogenic cytokines during bacterial sepsis.103 In certain animal models, antipyretic drugs that in-
hibit COX confer protection when given soon after bacterial challenge, presumably by blunting the adverse effects of tumor necrosis factor α and interleukin 1. In a recent large clinical trial, Bernard et al reported that 48 hours of intravenous therapy with the COX inhibitor ibuprofen lowered core temperature, heart rate, oxygen consumption, and lactic acid blood levels, but did not decrease the incidence of organ failure or 30-day mortality rate in patients with sepsis. Thus, in spite of promising results obtained in some experimental models, the antipyretic agent ibuprofen has not yet been shown to be of clinical value in treating bacterial sepsis.

CONCLUSIONS

Although clinicians have used various forms of antipyretic therapy since time immemorial, there is a dearth of data concerning the benefits and relative risks of such treatments. Nevertheless, several tentative conclusions regarding antipyretic therapy seem justified in light of the limited data available. It is clear, for instance, that short courses of approved doses of standard antipyretic drugs carry a low risk of toxic effects. Most of these drugs have analgesic as well as antipyretic properties. Therefore, if not otherwise contraindicated (eg, aspirin in young children because of the risk of Reye syndrome), such drugs can be used to provide symptomatic relief in patients with fever, to reduce the metabolic demands of fever in chronically debilitated patients, and possibly to prevent or alleviate fever-associated mental dysfunction in the elderly. To minimize antipyretic-induced fluctuations in temperature (and the risk of recurrent shivering and its increased metabolic demands) antipyretic agents should be administered to patients with fever at regular intervals to preclude abrupt recurrences of fever, rather than as needed for temperatures above some arbitrary level. When prescribing such medications, physicians must recognize that each carries its own risk of toxic effects, and might prolong the course of at least some infections. It should be noted further that there is no compelling evidence that a response to antipyretic medications is useful diagnostically in distinguishing serious from self-limiting illnesses, nor is there evidence that such medications are effective in suppressing febrile seizures, even if given prophylactically.

In view of the capacity of external cooling measures to induce a cold pressor response, it is questionable whether this form of antipyretic therapy should ever be administered to patients with fever (much less to patients in the intensive care unit, for whom it is most commonly prescribed). If external cooling is used to treat fever, care must be taken to prevent shivering because of its associated increase in oxygen consumption. Unfortunately, even if shivering is prevented, there is no guarantee that a cold pressor response will be averted. In view of indomethacin’s capacity to cause coronary vasoconstriction in patients with coronary artery disease, NSAIDs should be used with caution, if at all, to suppress fever in such patients.

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