Toxicities of Drugs Used in the Management of Fever

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Fever is frequently managed outside the purview of medical professionals, and antipyretic therapy, on the whole, is generally considered safe. However, each of the drugs used in the management of fever has significant toxicities. The purpose of this review is to examine the relative safety of such agents with a focus on the nonsteroidal anti-inflammatory drugs and acetaminophen. Toxicity to the gastrointestinal, renal, and hepatic systems are considered; the comparative safety profile of acetaminophen and ibuprofen as antipyretics are highlighted; and specific recommendations to improve the safe use of these therapies are advanced.

The treatment of fever is often undertaken in the absence of supervision from medical professionals, in no small part because multiple antipyretic agents are available without a prescription. Although aspirin and acetaminophen have been used medically for a century, and acetaminophen has been available as a nonprescription drug since 1960, the past decade has seen the transition of nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofen, naproxen and ketoprofen from prescription-only to nonprescription status. This multibillion-dollar industry offers $>300$ products containing aspirin, acetaminophen, or NSAIDs, either alone or in combination with other active drugs [1]. Although episodic use of these agents at appropriate doses for the treatment of fever or analgesia is relatively safe, this safety profile may be compromised in certain at-risk populations. In addition, because many products contain several active drugs, the label must be inspected carefully to prevent inadvertent overdosing.

Much of the toxicity associated with the NSAIDs and aspirin arises because of well-known effects on constitutive isoforms of cyclooxygenase (COX), especially COX-1. However, NSAIDs and aspirin can also cause non–COX-mediated side effects. When minor side effects lead to the discontinuation of one agent, another class is frequently empirically substituted [1]. Figure 1 summarizes both the COX- and non-COX-mediated toxicities of drugs commonly used to treat fever.

Inhibition of COX is responsible for the more serious toxic effects of these agents, particularly renal and gastrointestinal (GI) toxicity. Although data pertaining to the incidence, severity, and risk factors for the occurrence of these COX-mediated adverse events have been obtained largely in patients receiving prescription, anti-inflammatory doses for long periods of time, there is concern that these observations also apply to antipyretic regimens.

In addition to COX-mediated effects, there is a well-known epidemiologic association between aspirin use in children with viral infections (influenza and varicella) and the development of Reye’s syndrome—a disorder characterized by encephalopathy, fatty degeneration of the liver, and metabolic dysfunction. This association resulted in public admonitions against use of aspirin in children, culminating in warning labels mandated in 1986. The decline in the use of aspirin in children in the United States has been associated with a parallel decline in the incidence of Reye’s syndrome. Indeed, from 1994 to 1997, no more than 2 cases of the syndrome per year have been reported through the National Reye’s Syndrome Surveillance System [2].

Acetaminophen is generally regarded as the safest antipyretic drug; it has minimal activity against peripheral COX-1 and has not been linked to Reye’s syndrome. Nevertheless, liver failure is a well-recognized consequence of acetaminophen overdose. Moreover, recent series and case reports have suggested that administration of multiple doses of the drug at just slightly higher than the recommended maximum dose can also cause liver failure [3]. In addition, recent evidence suggests that the metabolic pathways involved in the production of metabolites responsible for acetaminophen’s liver toxicity are also present in the kidney. If acetaminophen has a role in analgesic-associated nephropathy, as some have suggested, generation of such toxic metabolites by the kidney would be the likely mechanism [4].

GI Toxicity

Antipyretic-induced GI toxicity can be divided into 3 categories: mucosal lesions that are visible radiographically or endoscopically, GI discomfort (such as dyspepsia, nausea, and heartburn), and severe GI complications, such as perforated ulcers and GI bleeding. Endoscopic lesions are common and seen in a majority of people treated with NSAIDs [5]. Such lesions are usually asymptomatic, healing and reappearing, despite continued NSAID therapy. Although gastric injury is a general side effect of NSAIDs, there are differences in the incidence of such toxicity among the various over-the-counter agents. Analysis of data from a single endoscopist suggests that the mean gastric injury scores are greatest with aspirin (3.07) and ketoprofen (2.38), lower with naproxen (1.17), and insignificant with ibuprofen (0.46) and acetaminophen (0.25) [6].
However, these observations must be interpreted with caution, because, in as many as 50% of patients with serious GI hemorrhages, endoscopy fails to identify an active ulcer. Furthermore, a reduction in the incidence of endoscopic ulcers in clinical trials has not translated into a concomitant decrease in clinically significant GI events. Therefore, endoscopic evidence of mucosal damage is not a reliable predictor of NSAID-induced serious GI complications [5].

On average, 10%–20% of patients experience dyspepsia while taking NSAIDs, and, within 6 months of beginning therapy with a NSAID, 5%–15% of patients with rheumatoid arthritis discontinue the drug because of dyspepsia. However, dyspepsia correlates poorly with both GI bleeding and endoscopically identified GI lesions. In a prospective cohort of 1921 patients with rheumatoid arthritis treated with NSAIDs, those with GI symptoms were only slightly more likely to have serious GI complications (2.7%) than were those without antecedent symptoms (2%). The majority (81%) of those developing major GI complications had no previous GI symptoms [7].

Over-the-counter use of both aspirin and NSAIDs is frequent among patients admitted for bleeding peptic ulcers. In one series, the overall prevalence of NSAID use among patients with bleeding peptic ulcers in the week before admission was 56% [8]. At the time this series was accumulated (1990–1992), ibuprofen was the only NSAID available without a prescription.

The annual relative risks of NSAID-induced GI complications serious enough to require hospitalization in patients with osteoarthritis and rheumatoid arthritis are 2.51 and 6.77, respectively [5]. The lower relative risk of such toxicity in patients with osteoarthritis probably reflects a lack of concomitant use of corticosteroids, as well as use of lower doses of NSAIDs, than by patients with rheumatoid arthritis. In the United States, NSAIDs are used chronically by as many as 13 million people with rheumatoid arthritis and osteoarthritis. At an estimated cost per NSAID-related hospitalization of $15,000–$20,000, such toxicity has a probable annual direct cost of >$2 billion [5]. Advanced age is the primary risk factor for serious NSAID-induced GI toxicity. Other risk factors are listed in table 1 [9].

Of these risk factors, one of the most relevant to episodic use for the treatment of fever is the shorter duration of therapy.

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**Figure 1.** Potential adverse effects of antipyretic agents. GI, gastrointestinal.
Table 1. Risk factors for serious gastrointestinal toxicity from non-steroidal anti-inflammatory drugs (NSAIDs).

<table>
<thead>
<tr>
<th>Risk factor(s)</th>
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<tr>
<td>Advanced age</td>
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<tr>
<td>High doses of NSAIDs</td>
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<tr>
<td>History of peptic ulcer disease or gastrointestinal bleeding</td>
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<tr>
<td>Concomitant corticosteroid use</td>
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<tr>
<td>Shorter duration of therapy</td>
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<td>Concomitant anticoagulant therapy</td>
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Longitudinal endoscopic evaluation of volunteers treated with aspirin (for \( \leq 8 \) weeks) suggests that the gastric mucosa adapts to the toxic effects of aspirin [10]. Studies have suggested that GI toxicity occurs most often during the initial month of therapy [11]. However, a cohort of 1600 patients followed for \( \leq 15 \) years after initiation of NSAID therapy revealed a constant risk of GI bleeding throughout the study period [5]. Although these data are conflicting, the duration of NSAID use remains a important risk factor for GI bleeding. The relative risk of such toxicity with episodic versus chronic use awaits further study.

In patients with rheumatoid arthritis, the crude death rate due to NSAID-induced GI toxicity is 0.22% per year, with an annual relative risk of death of 4.21 [5]. Given that 13 million patients with arthritis use NSAIDs, if the death rate attributed to NSAIDs in osteoarthritis is just half that observed in patients with rheumatoid arthritis, an estimated 16,500 arthritis patients die of NSAID-induced GI toxicity each year. This estimate would make NSAID-related mortality the 15th leading cause of death in the United States [5], even if deaths due to over-the-counter NSAIDs used for nonarthritic conditions are ignored.

Renal Toxicity

Four forms of renal toxicity have been associated with NSAIDs, aspirin, and acetaminophen: fluid and electrolyte disturbances, acute renal failure, acute interstitial nephritis, and analgesic-associated nephropathy. The first 3 are renal abnormalities most commonly associated with the use of nonselective COX inhibitors. Analgesic-induced nephropathy has been associated primarily with the habitual consumption of combination analgesic products that contain phenacetin.

The severe renal effects of NSAIDs are most evident in the setting of reduced intravascular volume, where prostaglandins are needed to moderate the adverse renal effects of circulating neurohumoral vasoconstrictors. Under such circumstances, the loss of vasodilatory prostaglandins can cause an abrupt decline in the glomerular filtration rate, resulting in oliguric renal failure. When this is due to a NSAID, discontinuing the drug usually results in the prompt resolution of the acute renal failure [12]. Risk factors for NSAID-induced acute renal failure include dehydration, New York Heart Association class III and IV heart failure, and liver failure with ascites [12].

Fluid and electrolyte disturbances are the most common renal side effects of NSAIDs. Most people treated with NSAIDs retain sodium, although this sodium retention is transient, diminishing over several days. Few people develop frank edema because of NSAID-induced sodium retention, and prompt natriuresis follows discontinuation of such drugs [12]. However, NSAID-induced sodium retention can interfere with the activity of both loop and thiazide diuretics and limit their effectiveness in the management of cardiovascular disease [1, 12]. Another major NSAID-induced electrolyte abnormality, hyperkalemia, rarely occurs in the absence of other factors that affect potassium homeostasis. NSAIDs suppress prostaglandin-mediated renin release, thereby inducing a state of hyporeninemic hypoaldosteronism [12]. Patients with insulin-dependent diabetes mellitus, particularly those with impaired renal function, and patients receiving concomitant therapy with beta blockers or potassium-sparing diuretics are at risk of acquiring NSAID-induced hyperkalemia. NSAIDs also cause water retention by enhancing the action of antidiuretic hormone [12].

Acute interstitial nephritis is a rare side effect of NSAIDs, generally occurring after 2–18 months of therapy. Although most cases are reversible, NSAID-induced nephritis may be severe enough to require dialysis. Reactive, non-COX by-products of arachidonic acid metabolism are the putative mediators of this adverse reaction [12].

Analgesic-associated nephropathy (AAN) was first recognized >40 years ago as a progressive disorder characterized by renal papillary necrosis and chronic interstitial nephritis in habitual overconsumers of phenacetin-containing combination products [13]. Although AAN has declined in incidence since the banning of phenacetin in many countries, it has not yet disappeared. This might be because acetaminophen is a major metabolite of phenacetin, and many products previously containing phenacetin have had acetaminophen substituted for phenacetin. Although epidemiologic data incriminating acetaminophen as a cause of AAN are inconclusive (largely because of confounding by other analgesics and recall bias) [13], case-control studies have suggested a weak association between habitual use of acetaminophen and chronic renal insufficiency and end-stage renal disease [14]. Renal papillary necrosis and chronic renal failure have also been associated with the daily use of prescription and over-the-counter NSAIDs, although the magnitude of the risk is uncertain [12, 15].

Hepatotoxicity

Acetaminophen is primarily metabolized by glucuronidation and sulfation, but also, to a lesser extent, via the p450 2E1 pathway to a highly electrophilic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). When primary pathways are saturated, NAPQI accumulates and binds covalently to cell proteins and DNA [16]. When such binding is extensive and involves hepatocytes, acute liver toxicity ensues. Under normal circumstances, NAPQI is detoxified by conjugation to glutathione. If glutathione stores are depleted (e.g., during chronic ethanol abuse or star-
the risk of acetaminophen-induced hepatotoxicity increases markedly [16, 17].

Whereas acute liver failure in the setting of attempted suicide with acetaminophen is well recognized, only recently has attention focused on the risk of hepatic injury due to acetaminophen administered in doses within or only slightly above the recommended range (4 g in 24 h). In recent series of 71 cases of acetaminophen-induced hepatotoxicity, 30% of the cases were due to accidental overdoses in patients using the drug for pain relief [16]. Reasons for excessive dosing included too frequent dosing, simultaneous ingestion of multiple acetaminophen-containing products, and ingestion of cough and cold remedies not recognized as containing acetaminophen.

Acetaminophen-induced hepatotoxicity has also occurred in children because of inadvertent administration of multiple supratherapeutic doses of the drug. Such overdoses occur because of simultaneous administration of several acetaminophen-containing products or of administration of acetaminophen-containing preparations geared to adults; overdoses may also occur as a result of simple dosage miscalculations. In the largest pediatric series reported to date [3], half of the children died (24 deaths), and 3 survived after orthotopic liver transplantation. Although 52% of the children had received adult formulations of acetaminophen, ~15% had received doses of acetaminophen within or only slightly above the approved dosage range (≤100 mg/kg/d). Children with comorbidities were likely be at increased risk of acquiring acetaminophen-induced hepatotoxicity, both because of drug-mediated perturbations of the metabolism of acetaminophen (induction of p450) and because of transient glutathione deficiency resulting from their acute illness [18]. Such data underscore the importance of detailed parental education in the appropriate use of acetaminophen-containing products.

**Comparative Safety of Antipyretic Drugs**

From 1991 through 1993, a landmark, randomized, office-based, controlled clinical trial compared the risk of serious, but uncommon, adverse events due to ibuprofen (at 2 dose levels) with that due to acetaminophen. Children were excluded if they were significantly dehydrated or if they had known aspirin sensitivity. The primary outcomes assessed included hospitalization within 4 weeks of entry to the study for acute GI bleeding, acute renal failure, anaphylaxis, and Reye’s syndrome. More than 84,000 children participated in the study, of which the overall results were published in 1995 [19]. Subsequent analyses focused on specific areas of interest [20, 21]. The median duration of treatment was 3 days. Approximately 1% of study subjects in each of the 3 groups was hospitalized, generally for treatment of an infectious disease. Four children were hospitalized for acute GI bleeding. Interestingly, all had been treated with ibuprofen [19], and 3 of 4 were aged <2 years [21]. The risk of hospitalization for acute GI bleeding in those receiving ibuprofen was 7.2 per 100,000 (17 per 100,000 in children aged <2 years), which was not significantly different from acetaminophen. There were no episodes of Reye’s syndrome, anaphylaxis, or acute renal failure in any of the children receiving ibuprofen [19, 21]. A further analysis of relatively crude measures of renal function in hospitalized children suggested no greater risk of renal insufficiency among children treated with ibuprofen than among those receiving acetaminophen [20]. These studies verify the safety of both ibuprofen and acetaminophen, given individually in the appropriate doses, for the short-term management of fever.

Alternating acetaminophen with ibuprofen (with doses administered every 2–3 h) is sometimes recommended in cases of refractory fever. The practice most likely recalls the former use of the combination of aspirin and acetaminophen in the era before aspirin was recognized to cause Reye’s syndrome [22]. The time course of antipyretic effects of these agents, however, does not support such a strategy. Although temperature begins to decrease within 30 min of ingestion, the maximum drug-induced reduction in temperature is generally not achieved until after 3–4 h [23]. For this reason, and because of the increased potential for toxicity, such alternating antipyretic regimens are not recommended [24].

**COX-2 Inhibitors**

The Food and Drug Administration has recently approved 2 selective inhibitors of COX-2, celecoxib and rofecoxib. Because COX-2 is the primary COX isoform implicated in the febrile response, the antipyretic effectiveness of COX-2 inhibitors should be similar to the nonselective COX inhibitors. Indeed, analysis of data obtained using rofecoxib suggests that COX-2 inhibitors have antipyretic activity comparable with ibuprofen [25]. The major benefit from these agents relates primarily to their COX-1 sparing effect, which has the potential to reduce drug-related GI and renal toxicity [26]. The results of a multicenter randomized trial involving 1149 patients [27] and a combined analysis from 8 randomized clinical trials involving 5435 patients [28] suggest that COX-2 inhibitors do indeed cause fewer asymptomatic GI lesions than do the nonselective NSAIDs. However, several lines of evidence suggest that selective COX-2 inhibitors are not devoid of GI and renal toxicity [29] and that COX-2, like COX-1, is constitutively expressed in tissues such as the GI mucosa, where it has an important role in homeostasis [30]. Nevertheless, the COX-2 inhibitors appear to be cost-effective in certain high-risk patients receiving chronic high doses of these drugs as an alternative to nonselective NSAIDs combined with antiulcer prophylaxis [26].

**Conclusion**

Given the frequency of antipyretic use for the treatment of fever and the relative paucity of adverse events associated with
such therapy, treatment of fever with antipyretic agents should be considered safe. However the following caveats are in order. First, there are probably some populations at increased risk for adverse events, even with episodic treatment employing single agents [15]. Table 2 summarizes recommendations regarding the selection of agents in specific populations. Second, patients should receive clear instructions regarding formulation-specific dosing guidelines and the need to account for antipyretic content of combination multisymptom products. Finally, expectations regarding the response to antipyretic agents should be addressed. Attempts at achieving euthermia through aggressive pharmacotherapy should be modulated by the toxicities of the individual agents. Adherence to these principles should allow for even safer use of these agents in the management of fever.

Table 2. Recommendations regarding antipyretic selection in specific populations.

<table>
<thead>
<tr>
<th>Population, agent</th>
<th>Cautions</th>
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<tbody>
<tr>
<td>Children</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Follow dosing guidelines; avoid multisymptom products</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Avoid in view of Reye’s syndrome</td>
</tr>
<tr>
<td>Adults (especially those with hypertension or diabetes)</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Follow dosing guidelines; avoid multisymptom products</td>
</tr>
<tr>
<td>Reduced intravascular volume</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Avoid in hepatic failure</td>
</tr>
<tr>
<td>Dehydration</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Avoid and/or reduce dose if malnourished</td>
</tr>
<tr>
<td>Renal disease</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Avoid habitual use</td>
</tr>
<tr>
<td>Liver disease</td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>Avoid if intravascularly depleted</td>
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</table>

NOTE: NSAID, nonsteroidal anti-inflammatory drug.

References