Antipyretic Therapy's Future

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There is little doubt that clinicians will continue to seek new and, one hopes, more intelligent ways to suppress fever. In the process, new agents will be developed, new uses will be identified for existing antipyretic agents, new measures will be designed to maximize the benefits of antipyretic therapy while minimizing its adverse effects, and a concerted effort will be made to define more clearly and to promote appropriate indications for such therapy.

An estimated $6 billion is spent worldwide each year on antipyretic drugs [1, 2]. Because such drugs are also analgesics, anti-inflammatory agents, or both, it is uncertain how often they are used to suppress fever, as opposed to being used to alleviate pain and inflammation. Nevertheless, it is clear that clinicians and other caregivers have long had an inherent antipathy toward fever that continues to the present day [3]. This antipathy is reflected in the results of surveys showing that 40% of parents and other caregivers regard temperatures encountered during fever as harmful [4, 5], that 12% of physicians believe that fever can cause brain damage [6], and that an estimated 70% of nurses and 30% of physicians routinely use drugs to suppress fever [6, 7]. Thus there seems little doubt that clinicians will continue to seek new—and, one hopes, more intelligent—ways to suppress fever. In the process, new agents will be developed, new uses will be identified for existing antipyretic agents, new measures will be designed to maximize the benefits of antipyretic therapy while minimizing its adverse effects, and a concerted effort will be made to more clearly define and promote appropriate indications for such therapy.

With regard to new antipyretic agents, cyclooxygenase (COX)-2-selective inhibitors will likely dominate the attention of pharmaceutical research and development programs for the foreseeable future. Monsanto/Searle (Skokie, IL) has already developed and obtained US Food and Drug Administration approval for Celebrex (cecloxib), a nonsteroidal anti-inflammatory drug (NSAID) with some 400-fold greater potency against COX-2 than COX-1 [8, 9]. The only other COX-2-specific inhibitor available in the United States, Vioxx (rofeceoxib), was developed by Merck-Frosst (Kirkland, Quebec). Both companies are currently working on second- and third-generation derivatives, with more potent activity against COX-2, that can be administered parenterally. Several other companies, notably Novartis (East Hanover, NJ) and Johnson & Johnson (New Brunswick, NJ), are currently developing similar agents. Although analysis of preliminary data indicates that these agents have antipyretic as well as anti-inflammatory activity [10], these observations require verification. Whether there are additional COX isoforms not yet identified, as suggested by Vane and Botting [11], remains to be determined. If so, their particular function and potential therapeutic manipulation might be the subject of equally intensive future research efforts.

With regard to new uses for existing antipyretic drugs, the array of conditions treated with such agents will most likely continue to expand beyond the traditional confines of fever, pain, and inflammation. The ability of aspirin to irreversibly inhibit platelet thromboxane synthesis has led to its extensive use as prophylaxis against stroke and myocardial infarction [12–14]. It has also been recommended, in low doses, to prevent toxemia of pregnancy [15]. More recently, COX-2 expression has been shown to be involved in the deposition of β-amyloid protein in the neuritic plaques of Alzheimer’s disease [16]. More importantly, a 1995 study of 225 patients with Alzheimer’s disease showed that those who used NSAIDs or aspirin daily exhibited slower progression of their disease than those who did not [17]. Several subsequent investigations have identified similarly favorable effects of NSAIDs on both the incidence and course of Alzheimer’s disease [18–21]. In addition, promising results have been obtained in experimental models that used COX inhibitors to treat sepsis [22]. Unfortunately, such drugs have not yet been applied successfully in septic patients [23]. Aspirin has also been shown to diminish colon cancer incidence and mortality [24, 25], providing yet another reason to believe that the use of aspirin and the NSAIDs will continue to increase, as will efforts to develop more efficacious and less toxic derivatives of such drugs. Moreover, efforts to identify the specific mechanisms responsible for both the therapeutic and toxic effects of these agents should continue, as should those to verify the clinical relevance of observations obtained in animal models.

Efforts to reduce the toxicity of antipyretic and anti-inflammatory drugs have taken a number of different clinical approaches. These have included the use of prodrugs, such as sulindac and nabumetone, enteric coating, and parenteral and
rectal administration [26]. Other measures designed to reduce the gastrointestinal toxicity of such drugs have included concomitant administration of the prostaglandin E1 analog, misoprostol, H₂-receptor antagonists such as ranitidine and famotidine, and the proton pump inhibitor omeprazole. NSAIDs preassociated with zwitterionic phospholipids, pure enantiomers of clinical NSAIDs, and nitric oxide-releasing NSAIDs have likewise been used in an attempt to reduce the toxicity of this class of drugs [27]. Additional novel approaches to solving the problem of toxicity will no doubt continue to surface in the future.

Perhaps the most important task for the future will be to develop more intelligent criteria for the use of antipyretic therapy. To do so, outstanding questions regarding the relative risks and benefits of fever itself and the various modes of therapy directed against the response will have to be answered. In my opinion, the following are some of the most pressing of these questions. Should external cooling measures ever be used to treat fever? Does antipyretic therapy significantly reduce the metabolic demands of fever in debilitated patients or mental dysfunction in the elderly? Does such therapy really prolong the course of viral infections, even as it alleviates their signs and symptoms? Is vasoconstriction of diseased coronary arteries a significant side effect of NSAIDs and cooling blankets in patients with coronary artery disease?

**References**