Plaisance Ketal 2000, Arch Intern Med Vol 160, Feb 28, 2000

92.

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to distinguish fevers of infectious origin from those due to cancer.[86-88] 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.[88] 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.[25] 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 shivering[89]), 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.

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 al[93] 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 pox[95] 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]

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 al[99] 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 al[100] 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-