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Rational Use of Analgesic and Antiinflammatory Drugs

"TAKE two aspirin and call me in the morning"? Clinical decision making is no longer so straightforward. Millions of patients take analgesic and antiinflammatory medications regularly. The reasons are simple: these drugs are effective in relieving pain and inflammation,[1] and aspirin provides protection from cardiovascular thrombosis.[2,3] Osteoarthritis and other painful chronic conditions occur in a population of patients who often have coexisting medical conditions, including conditions associated with an increased risk of cardiovascular disease. Thus, aspirin is frequently prescribed for patients taking other analgesic and antiinflammatory agents. Since the mechanism of action of all these drugs is the inhibition of the cyclooxygenase (COX) enzymes, their adverse-event and efficacy profiles may change when they are used in combination.

The discovery of cyclooxygenase-2 (COX-2) represented an enormous conceptual advance in prostaglandin biology and provided new therapeutic options.[1,4,5] Acetaminophen, traditional nonsteroidal antiinflammatory drugs (NSAIDs), and specific COX-2 inhibitors (coxibs) are all currently recommended for the treatment of osteoarthritis.[5] When prescribing these drugs, physicians must consider their efficacy, but their toxicity and cost have appropriately become major considerations as well.[1,4] Although the relative effect of these drugs on gastrointestinal ulcers and bleeding has attracted the most attention,[6-8] cardiovascular and renal complications have recently assumed importance in the evaluation of their side effects, since the COX enzymes have prominent biologic roles in the vasculature and the kidneys.[9,10] In this issue of the *Journal*, Catella-Lawson et al.[11] address the potential for a competitive interaction between aspirin and other analgesic and antiinflammatory agents, and Fored et al.[12] examine the role of acetaminophen and aspirin in the progression of renal disease to chronic renal failure.

There are important distinctions among the mechanisms of action of aspirin, NSAIDs, coxibs, and acetaminophen. Aspirin remains unique among NSAIDs as an irreversible inhibitor of the activity of the COX enzymes. Low-dose aspirin acts as a selective inhibitor of platelet cyclooxygenase-1 (COX-1) activity by virtue of the fact that platelets, in contrast to nucleated cells, cannot recover COX activity.[4,11] Nonaspirin NSAIDs inhibit the activity of both COX-1 and COX-2 by reversibly blocking the access of arachidonic acid to the active site at the apex of a hydrophobic channel within these enzymes. The pharmacodynamic properties of the different NSAIDs with respect to the COX enzymes vary with their chemical structures.[4] Coxibs achieve specificity by virtue of a structure that is accommodated more efficiently by COX-2, which has a larger hydrophobic channel.[1] Acetaminophen is a weak, nonselective inhibitor of both COX enzymes. The precise mechanism of action of acetaminophen remains elusive, but acetaminophen does not appear to block the hydrophobic channel.[13] It was recently proposed that acetaminophen acts to reduce the active, oxidized form of the COX enzymes, which would make it more potent at sites, such as the brain and spinal cord, that have low peroxide concentrations.[13]

Catella-Lawson et al.[11] proposed the interesting and important hypothesis that by occupying the hydrophobic channel of platelet COX-1, NSAIDs could interfere with the antiplatelet effect of aspirin. The investigators demonstrated that prolonged dosing with ibuprofen blocked the inhibitory effect of low-dose aspirin on the release of thromboxane by platelets and platelet aggregation. This competitive interaction could not, however, be generalized to all NSAIDs, since experiments in which delayed-release diclofenac, rather than ibuprofen, was used failed to yield similar results. Acetaminophen and the specific COX-2 inhibitor rofecoxib, which do not block the COX-1 hydrophobic channel, did not interfere with the effect of low-dose aspirin on platelet function.

The hypothesis that some NSAIDs are competitive inhibitors of aspirin with respect to platelet function requires further clinical evaluation. The platelet-aggregation studies reported by Catella-Lawson et al. were performed ex vivo and tested platelet function in isolation. Other factors may well contribute to the overall vascular effects of these drugs. For example, in an experimental model of thrombosis in animals, inhibition of COX-2 significantly decreases the coronary vasodilator response to infused arachidonic acid, irrespective of whether COX-1 activity is inhibited by aspirin. In the same model, inhibition of COX-2 prevents the antithrombotic effect of aspirin.[14] Whether concurrent treatment with analgesic and antiinflammatory agents blunts the cardiovascular protective effects of aspirin has not been determined in human studies. Thus, in vivo and clinical studies assessing the combination of low-dose aspirin with NSAIDs, coxibs, or acetaminophen will be required to determine the cardiovascular implications of the interactions among these drugs.

The article by Fored et al.[12] also addresses the use of analgesics and antiinflammatory drugs; it examines the relation between the use of such drugs and the development of chronic renal failure. This case–control study involved controls who were randomly selected from the Swedish Population Register, which included all persons born in Sweden, 18 to 74 years of age, who were living in the country between 1996 and 1998. Underlying disease and analgesic use were assessed in men whose creatinine level exceeded 3.4 mg per deciliter (300 μmol per liter) for the first time and women whose creatinine level exceeded 2.8 mg per deciliter (250 μmol per liter) for the first time; patients with a prerenal or postrenal cause of chronic renal failure were excluded, as were those who had received transplants. The authors demonstrate that regular use of acetaminophen, aspirin, or both was associated, in a dose-dependent manner, with an increased risk of chronic renal failure. Subjects who took 1.4 g or more of acetaminophen per day had an odds ratio for chronic renal failure of 5.3 (95 percent confidence interval, 1.8 to 15.1), whereas the doses of aspirin associated with the highest risk were in the range used for analgesic purposes rather than the lower doses generally used for cardiovascular prophylaxis. Another important result of this study is that preexisting renal or systemic disease was a necessary precursor to analgesic-associated chronic renal failure. In this and other studies, subjects without preexisting renal disease who used analgesics had only a small risk of end-stage disease.[12]

Important questions remain unanswered regarding the association of analgesic and antiinflammatory drugs with chronic renal failure. Whether COX inhibition by acetaminophen or aspirin is necessary for progression to renal failure is unclear. In this study, nonaspirin NSAIDs did not confer an increased risk of chronic renal failure when the data were adjusted for acetaminophen use and aspirin use.[12] Nevertheless, acute and chronic nephrotoxic effects can clearly occur as a result of the inhibition of renal prostaglandin production by NSAIDs and coxibs.[10] On the basis of the data, clinicians should consider carefully whether acetaminophen or aspirin should be avoided in their patients with chronic renal disease.

How are medical practitioners to synthesize information regarding the efficacy and toxicity of these analgesic and antiinflammatory agents to arrive at selections appropriate for their patients with coexisting medical conditions? Certainly, each patient must be considered individually with respect to the risk of cardiovasular events, gastrointestinal side effects, and progressive renal failure. In making such clinical decisions, physicians must first consider whether or not the patient has an indication for primary or secondary cardiovascular prophylaxis with aspirin. NSAIDs and coxibs do not provide the same protective effect as low-dose aspirin.[11,15] The hypothesis that coxibs may promote cardiovascular thrombosis remains plausible but unproved.[9,16,17] If the findings of Catella-Lawson et al. are confirmed as clinically important, drug interactions may also need to be considered when aspirin and NSAIDs are combined. Given the gastrointestinal side effects of aspirin,[2] patients who are at risk for such effects should receive prophylaxis against ulcers regardless of which other analgesic or antiinflammatory agents they use.[18] When aspirin is not indicated, side effects can be minimized in patients with risk factors for adverse gastrointestinal events by treatment with lower doses of acetaminophen, coxibs, or traditional NSAIDs along with a protective agent, such as misoprostol or a proton-pump inhibitor.[6-8,18] A recent study demonstrated an increased risk of ulcers and bleeding that is equivalent to that associated with NSAIDs in patients taking acetaminophen at doses of 2 g or more per day[8] — a potentially relevant finding that needs to be confirmed. In patients with progressive renal disease, all these drugs, with the exception of low-dose aspirin, are best avoided if possible.

The choice of therapeutic agent should otherwise be based on the preference of the patient with respect to efficacy and tolerability, but the cost of the drugs should be taken into account as well. Future studies should focus on the many important and unanswered questions regarding the effects of the different analgesic and antiinflammatory drugs, used alone or in combination with aspirin, in patients with cardiovascular and renal disease.

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Tragedy and Insomnia

In this issue of the *Journal,* Lavie points out the high frequency of sleep disturbances, primarily insomnia and nightmares, that occur after local or distant disasters.[1] This observation is supported by the recent article on stress reactions after the September 11 terrorist attacks.[2] Schuster et al. reported that 11 percent of randomly selected adults in the United States have had "trouble falling or staying asleep" since the attacks.[2] Lavie also stresses that such sleep disturbances may precede or even predict the development of more sustained sleep disturbances, psychiatric disorders, or physical symptoms. The question therefore becomes whether sleep disturbances related to severe stress of any type should be aggressively treated, and if so, how this can best be accomplished.

In answering these questions, several observations must be kept in mind. Most cases of insomnia resulting from the stress of daily life, even severe cases, usually resolve spontaneously without medical intervention. On the other hand, a subgroup of people with such cases will go on to have a chronic form of insomnia that is referred to as conditioned, or psychophysiologic, insomnia.[3] As these people become increasingly focused on their sleep problems, they become increasingly anxious about their inability to sleep. This anxiety frequently leads to maladaptive sleep behavior, including the use of alcohol to induce sleep, that, in the long run, will further decrease their ability to stay asleep. Thus, insomnia often becomes chronic despite resolution of the problem that initiated the sleep disturbance.

Current data do not provide any real means of identifying which patients with relatively acute sleep disturbances will go on to have chronic problems. Most clinicians believe that patients with depression or symptoms or disorders of anxiety are at greatest risk. This belief stems from the ample evidence that the development of insomnia may be an early marker of new or recurrent depression.[4] There are also no data indicating that treatment of the acute problem will prevent the disorder from becoming chronic, although this assumption seems logical. However, even acute insomnia can be distressing, potentially exacerbating a person's general level of anxiety and diminishing his or her ability to deal with whatever initiated the problem. Thus, therapy must be considered. Since only a relatively small percentage of patients with insomnia related to a specific stressful event ever seek a physician's advice, those who do may have more severe cases or a more prolonged course or may be less able to correct the problem on their own. They may also have preexisting subclinical anxiety or depressive disorders that are manifested by insomnia in response to a difficult situation. Thus, for these patients, treatment of the insomnia may prove particularly beneficial.

How should primary care physicians treat patients who have new-onset insomnia after a traumatic world or local event or a personal tragedy? A number of therapeutic approaches might be considered. First, clinicians should review the general principles of sleep hygiene, as outlined by Lavie, with all patients who have difficulty falling asleep or staying asleep. Following these guidelines may not only improve sleep quality immediately, but also avert the development of maladaptive sleep behavior. Any habit that is counterproductive to sleep should be identified and corrected. Such habits include drinking caffeinated beverages late in the afternoon or evening and drinking large amounts of alcohol in the evening.

Second, clinicians should consider the short-term use of a benzodiazepine or benzodiazepine-receptor agonist. Since all data indicate that these agents are effective when used for relatively short periods (one to two weeks)[5] and have a very low incidence of adverse reactions,[6] their use would seem appropriate in at least some patients with stress-related insomnia. In my mind, this group would include patients with signs of or a history of clinical or subclinical anxiety or depression, patients with good sleep hygiene but a brief history (three or four nights) of substantial insomnia, and patients with a previous episode of insomnia that responded well to a short course of hypnotic agents. On the other hand, patients with a history of alcohol or substance abuse are not good candidates for hypnotic therapy.

If the decision is made to begin treatment with a hypnotic agent, instructions to take this medication either every night or as needed over a period of one to two weeks will probably not cause rebound insomnia (increased difficulty sleeping after the medication is stopped) and thus a dependence on these drugs to induce or maintain sleep. Rebound insom-