Naproxen and Risk of Heart Attack and Stroke

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Recent news included yet another distressing finding about a popular pain medication. Naproxen, a drug available for decades that was considered so safe it has been sold over-the-counter for the last ten years under the brand name Aleve®, was reported to cause an increase in heart attacks and strokes compared to placebo. The news came out of the ADAPT (Alzheimer's Disease Anti-Inflammatory Prevention Trial) clinical trial sponsored by the National Institute on Aging and conducted by the National Institutes of Health (NIH). On December 20, the NIH suspended the ADAPT trial, and the FDA issued a warning about the use of naproxen, one of the drugs used in the ADAPT trial, stating that patients taking naproxen 220 mg twice daily had a 50 percent greater risk of heart problems - including heart attack and stroke - than patients taking placebo. Among the 2,500 patients participating in the the trial, there were 70 heart attacks and strokes overall, and 23 deaths. The director of the NIH has suspended the study and the manufacturer of Aleve®, Bayer AG, has advised consumers to follow the label directions regarding dose and duration of therapy; current labeling recommends a maximum of 10 days of continuous use.

There are a number of difficulties associated with news reports surrounding suspension of the ADAPT. There is no statistical analysis of the outcomes, and the data are described as "preliminary." There is little information on the demographic makeup of the study participants, other than that they are older than 70 years at the time of enrollment and that they have a parent or sibling with Alzheimer's disease. More specific information on the age of the participants, for example, would be important as the incidence of heart attack and stroke increases significantly from age 65 to 75 years. Sex, race and family history are also important influences on the rate of cardiovascular events, yet we know nothing of the breakdown of these and other cardiac risk factors in this study.

A further problem with the ADAPT finding is that it is in conflict with previously reported study results. Naproxen has been reported to be cardioprotective compared with other non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), or at least to have no detrimental effects on cardiovascular risk.[1-5]

It is important to realize that other NSAIDs, such as ibuprofen, also have been associated with increased cardiovascular risk; however again, the data are inconsistent and derived from observational studies with significant design limitations.[2,6] All NSAIDs can cause fluid retention, worsen congestive heart failure, worsen hypertension and, in some circumstances, cause kidney failure. They also can cause gastrointestinal bleeding in susceptible individuals (*e.g.*, over 65 years old, history of peptic ulcer, use of corticosteroids, or use of anticoagulant medications).

Unfortunately, there has yet to be a well-designed, adequately controlled study of the cardioprotective potential of non-aspirin NSAIDs. Increasing data over the past decade have suggested that many commonly used classes of anti-inflammatory pain relief medications may increase cardiovascular risk. This includes our most powerful drugs, the corticosteroids (e.g., prednisone), the non-steroidal drugs (e.g., ibuprofen and naproxen), and the newer COX-2 drugs (e.g., rofecoxib, celecoxib and valdecoxib). We do not know the magnitude of the increased risk and whether or not certain drugs within a class are better than or worse than others, or if there is a major interaction with aspirin. While the detrimental effects of the COX-2 inhibitors* on cardiovascular risk are beginning to become known, at this time the balance of influences of non-aspirin NSAIDs on platelet aggregation, inhibition of prostacyclin synthesis and inflammation is complex. The true effect of non-aspirin NSAIDs in cardiovascular events remains uncertain. Further confusing the picture is the publication of one study reporting an increased risk of myocardial infarction after NSAIDs are discontinued.[7]

Recommendations for patients with pain due to arthritis, musculoskeletal injuries, or other causes for which NSAIDS or COX-2 inhibitors usually are used include:

1. Use non-pharmacological therapy when possible (ice, rest, stretching, etc.). Explore complimentary techniques such as meditation, biofeedback and acupuncture.
2. Use acetaminophen at recommended doses if you do not have liver problems or drink more than 2 alcohol-containing beverages a day.
3. If 1 and 2 are not effective, NSAIDS may be used with the following guidelines:
    a. use the lowest effective dose possible
    b. try to use intermittent rather than continuous therapy
    c. control your cardiac risk factors (achieve an ideal body weight, blood pressure and cholesterol values, stop smoking, exercise regularly and eat properly)
4. Speak with your physician about safe use of pain medications and other alternatives, if necessary. Patients with congestive heart failure, kidney disease, hypertension, or those at high risk of gastrointestinal bleeding also should contact their physician before using NSAIDS.

**COX-2 inhibitors include Vioxx (rofecoxib), Bextra (valdecoxib), and Celebrex (celecoxib), among others.*

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