about ***Randomized placebo-controlled trial comparing efficacy and safety of valdecoxib with naproxen in patients with osteoarthritis*** *on page 530*

Right ballpark, wrong base: Assessing safety of NSAIDs

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The nonsteroidal anti-inflammatory drug (NSAID) class has become large enough to form 3 subgroups: aspirin, the traditional NSAIDs, and the cyloxygenase-2 (COX-2)–inhibiting NSAIDs. Although pharmacologically distinct, however, a clear advantage of the COX-2 inhibitors over the traditional NSAIDs remains to be demonstrated for typical short-term or long-term users of anti-inflammatory therapy.

Kivitz and colleagues[1] found that valdecoxib, a COX-2 inhibitor, produces similar pain relief to the older NSAID naproxen in the treatment of moderate to severe osteoarthritis of the knee. The effect on pain was dose related, with 20 mg daily producing results similar to those of naproxen at 500 mg twice daily.[1]

When the researchers evaluated the safety of the 2 NSAIDs, the results were not as straightforward. The investigators performed endoscopy before the study and after 12 weeks of treatment. At 12 weeks, more ulcers were found on endoscopy in the naproxen group (10%) than in the 5- and 10-mg valdecoxib groups (3% incidence in each group, $P \leq .05$). No difference was noted in the incidence of gastroduodenal ulcers between the naproxen and valdecoxib 20-mg groups. As in other studies of NSAIDs, most of these ulcers were asymptomatic. Ulcers caused by NSAIDs frequently are transient, and gastric symptoms correlate poorly with the presence of these ulcers.[2] Further, the Food and Drug Administration does not consider endoscopically proven ulcers to be a surrogate for clinically relevant events.[3]

The much more important safety outcome for NSAIDs is the incidence of POBs: perforation, gastric outlet obstruction, or gastric bleeding. These adverse effects may result in hospitalization and death. Fortunately for patients, these effects occur rarely, even in the worst offenders in the NSAID class.

Such is the case with another COX-2 inhibitor, celecoxib. Although data after 6 months of therapy showed a lower incidence of POBs as compared with ibuprofen or diclofenac,[4] unpublished data for the second 6 months of treatment showed, overall, similar rates among the 3 drugs.[5] Dropouts due to adverse effects were also similar in the ibuprofen- and celecoxib-treated patients.

Rofecoxib, another COX-2 inhibitor, produced a slightly lower rate of POBs than did other NSAIDs (1.3% vs 1.8%).[6] Given these statistics, 1 POB would be prevented for every 200 patients given rofecoxib rather than a traditional NSAID for a full year.

The study by Kivitz et al does not give us much guidance with regard to the role valdecoxib or, by implication, other COX-2 inhibitors should play in clinical care. At equivalent doses, all of the COX-2 inhibitors seemed to produce analgesia and inflammation reduction similar to that of the older NSAIDs. Current research, however, does not support a safety or tolerability advantage of this class of drugs for most patients over the nonspecific NSAIDs that have been around since the 1960s. Even if there is a small advantage of COX-2 inhibitors with regard to POBs, this advantage would be realized only in patients at high risk of complications who will be taking the drug for many months—the only group for whom COX-2 inhibitors should be considered a drug of choice. Although definitive work has not been done to identify high-risk groups, it may be reasonable to include patients for whom a bleeding complication would be devastating, such as the frail elderly and patients with a history of significant gastrointestinal bleeding.

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