THE IMPORTANCE OF TAKING A SECOND LOOK AT NEW MEDICATIONS

Your editor has been looking forward to the approval of the new injectable cyclooxygenase 2 (COX-2) nonsteroidal anti-inflammatory drug (NSAID) parecoxib for use in the perioperative period as a substitute for the non-selective injectable NSAID ketorolac, which inhibits platelet aggregation. Additionally, I have taken comfort that as I grow older and eventually may need pain relief for my stiff joints, I could depend on the oral COX-2 NSAIDs for safe and effective pain control. Now both of those options appear to be clouded.

The Food and Drug Administration (FDA) has issued an advisory opinion because of recently released data from controlled clinical trials that show that COX-2 selective agents (rofecoxib, celecoxib, and valdecoxib) may be associated with an increased risk of serious cardiovascular events, such as myocardial infarction and stroke, especially when they are used for long periods or perhaps in very high-risk settings, such as immediately after heart surgery. Rofecoxib (Vioxx) was voluntarily removed from the market by its manufacturer after data from a long-term gastrointestinal cancer prevention study indicated an increased risk of cardiovascular morbidity and mortality that may not have been apparent in its original premarketing short-term analgesic studies. It may ultimately return to the marketplace with limited indications if it can be determined that its risks are no greater than those of the other selective COX-2 inhibitors.

Preliminary data from a clinical trial suggest that long-term use of the nonselective NSAID naproxen might be associated with an increased cardiovascular risk compared with a placebo. However, these results are preliminary and conflict with other data from studies of the same drug. Until scientifically proven otherwise, we should consider nonselective NSAIDs to be no problem in this regard.

The FDA recommends that practitioners who prescribe celecoxib (Celebrex) or valdecoxib (Bextra) should consider this emerging information when weighing the benefits against risks for individual patients. Patients who are at high risk of gastrointestinal bleeding, have a history of intolerance to nonselective NSAIDs, or are not doing well with nonselective NSAIDs may be appropriate candidates for COX-2 selective agents. The individual patient risk for cardiovascular events and other risks commonly associated with NSAIDs should be taken into account for each prescribing situation. I believe the

practitioner must thoroughly discuss the benefits and risks with each patient before prescribing COX-2 NSAIDs. There should be written documentation similar to informed consent in the medical record attesting to the fact that the patient is willing to accept the drug under those circumstances.

The FDA also advises consumers that all over-the-counter pain medications, including NSAIDs, should be used in strict accordance with the labeled directions. If an over-the-counter NSAID is needed for longer than 10 days, the FDA suggests that a physician should be consulted.

As with all drugs, the ratio of the benefits compared with the risks must be considered when prescribing to individual patients. A huge body of data shows that long-term use of nonselective NSAIDs, such as ibuprofen, increases the risk of death from gastrointestinal bleeding, and this was the primary impetus for developing COX-2 inhibitors. The practitioner must now weigh that risk of death from gastrointestinal bleeding from nonselective NSAIDs against the risk of myocardial infarction or stroke with the COX-2 selective NSAIDs when deciding which analgesic to prescribe. It may turn out that the COX-2 inhibitors are much less likely to cause adverse cardiovascular events than life-threatening gastrointestinal bleeding associated with nonselective NSAIDs. Unfortunately, those studies may be much more difficult to conduct, particularly in the wake of all the television advertisements from trial lawyers who hope to get rich on their excessively large share of class action suit settlements while thousands or hundreds of thousands of individuals who claim harm from the drug each receive only a few dollars from perhaps a couple of million dollars that a court might award.

In the meantime, it is important for the FDA-required postmarketing studies on the safety and efficacy of newly marketed drugs to be conducted. Drug companies are often vilified in the press for making huge profits, yet imagine how much money, time, and effort the company spent to get rofecoxib on the market, only to lose it all before its investment could be returned as profit. The manufacturer pays for many of the postmarketing studies. Of course, independent research by academic scientists is also valuable in discovering new information, both good and bad, about these drugs. Taking a second look at new drugs and techniques is as important as performing the original investigations, and both companies and independent scientists should be applauded for their efforts.

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