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COX-2 INHIBITORS AND CARDIOVASCULAR RISK

Point and counterpoint

DO THE NONSTEROIDAL anti-inflammatory drugs (NSAIDs) that selectively inhibit cyclo-oxygenase 2 (COX-2) increase the risk of cardiovascular events? And if we do not know with certainty, what is a practicing physician to do?

See related articles, pages 961–962 and 963–964.

Recently, Drs. Mukherjee, Nissen, and Topol,[1] who are cardiologists and experienced clinical trialists, performed a meta-analysis of several large trials and implicated COX-2 inhibitors as possibly causing cardiovascular events via a putative prothrombotic effect. They concluded by calling for a randomized trial to settle this issue and, in the interim, urging caution in prescribing these drugs to patients at risk.

In this issue of the *Journal* we offer a point-counterpoint discussion of this topic. Dr. John Lipani,[2] who is a rheumatologist and clinical trialist, points out some problematic aspects of the study by Mukherjee et al[1] and concludes that, until a clear cause-and-effect relationship can be proved, we should go on using these useful drugs. Dr. Debabrata Mukherjee and colleagues[3] defend their data and conclusions.

BACKGROUND TO THE CONTROVERSY

The background issues surrounding this controversy are myriad.

Aggressive marketing by the manufacturers and distributors of these medications (celecoxib [Celebrex] and rofecoxib [Vioxx]) and ardent academic support resulted in inflated public expectations that these drugs would be more effective and safer than traditional nonselective NSAIDs. These strategies also resulted in several letters from the Food and Drug Administration (FDA) to the distributors requesting that certain potential toxicities of these drugs not be underemphasized.

Sober reflection and review of the detailed published data (and data provided by the FDA on its website) provides a more reasonable perspective: these drugs are no more effective than traditional NSAIDs, have no renal safety advantages, and can interfere with the pharmacodynamics of warfarin. They do not affect platelet function in clinically utilized doses, and thus are likely safer in the perioperative setting with regard to bleeding. But this lack of antiplatelet effect is at the heart (pun intended) of the issue surrounding the potential for thrombotic risk of these medications.

A possible thrombotic effect must be taken seriously

The COX-2 selective NSAIDs were designed in the hope that they would pose less risk for gastrointestinal bleeding and ulcer development than do typical NSAIDs.

The risk of these gastrointestinal complications developing in the average patient taking nonselective NSAIDs is small. Yet the huge numbers of patients who take these medications magnify the societal impact of this problem. Additionally, certain patients are at higher risk of developing these problems, including those with cardiovascular disease (especially if taking aspirin), those with rheumatoid arthritis, those with any prior gastrointestinal bleeding or ulcers, those on anticoagulants, and the aged.

The COX-2 selective NSAIDs do indeed seem to pose less of a risk of endoscopic ulcerations and clinical bleeds in patients not taking aspirin. But these adverse events are infre-

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A theoretic concern may not translate into clinical reality

quent enough that it took relatively large studies to document a statistically significant safety difference compared with traditional NSAIDs. Depending on the actual end point assessed, the differences have not always reached what I would consider clinical significance. Nonetheless, the continued demand for these medications is almost unprecedented.

Thus, concern over a possible prothrombotic effect of these medications must be taken seriously. And it has been, by FDA advisory panels and by the FDA.

THE META-ANALYSIS

Mukherjee et al[1] examined the rates of cardiovascular events in two large trials:

The VIGOR study (Vioxx Gastrointestinal Outcomes Research),[4] which was designed to compare the gastrointestinal adverse effects of the COX-2 inhibitor rofecoxib (Vioxx, 50 mg/day) with those of the nonselective NSAID naproxen (1,000 mg/day) in 8,076 patients with rheumatoid arthritis who were not taking aspirin; and

The CLASS study (Celecoxib Long-term Arthritis Safety Study),[5] which compared the adverse effects of celecoxib (800 mg/day) with those of the nonselective NSAIDs ibuprofen (2,400 mg/day) and diclofenac (150 mg/day) in 7,968 patients with rheumatoid arthritis or osteoarthritis, 21% of whom were taking aspirin.

They also examined the data from two smaller, unpublished studies, designated study 085 and study 090,[6] which compared rofecoxib (12.5 mg/day), nabumetone (1,000 mg/day), and placebo in a total of 2,020 patients with osteoarthritis (TABLE 1).

Findings

In the VIGOR study, 98 patients had cardiovascular events—65 (1.6%) of 4,047 patients in the rofecoxib group and 33 (0.8%) of 4,029 patients in the naproxen group. The events were judged to be "serious" (myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, or transient ischemic attack) in 65 patients. Mukherjee et al[1] calculated the relative risk of a serious cardiovascular event in the rofecoxib group to be 2.38 (95% confidence interval 1.39–4.00, $P = .002$).

On the other hand, in the CLASS study, there was no significant difference in the rate of cardiovascular events between the COX-2 and the NSAID groups. No difference was noted in the two smaller rofecoxib trials either. But the number of events was small.

What could account for the divergent findings? A possible explanation is that the different nonselective NSAIDs that were used as comparators had different effects on coagulation parameters and thrombosis. Naproxen, used in the VIGOR study, has antiplatelet activity, and perhaps more sustained antiplatelet activity than the other NSAIDs. Rofecoxib's manufacturer interpreted the results of the VIGOR study as being due to the salubrious effect of naproxen, not to a deleterious effect of rofecoxib. As emphasized at the FDA advisory panel discussions, without a matched placebo (or alternative NSAID) control group in the trial, it is not possible to determine with certainty that this is the correct interpretation. Since this is a safety issue, the FDA has wisely chosen not to downplay the potential significance of this finding, and not to simply accept comparisons with thrombosis rules from other trials.

Mukherjee et al[1] compared the annualized rates of myocardial infarction in the COX-2 treatment groups in the VIGOR study (in patients with rheumatoid arthritis) and CLASS study (rheumatoid arthritis or osteoarthritis) and in the placebo group (without inflammatory disease) in studies of the use of aspirin as cardioprotection.[7] These were as follows:

- Placebo (aspirin studies)—0.52%
- Rofecoxib (VIGOR trial)—0.74% ($P = .04$)
- Celecoxib (CLASS trial)—0.80% ($P = .02$).

As Mukherjee et al point out, a prothrombotic effect of COX-2 selective NSAIDs is a theoretic concern. This was recognized before these trial results were published,[8] and this concern is consistent with results of the VIGOR trial and their meta-analysis.

CRITICISM OF THE META-ANALYSIS

In his critique of this analysis, Dr. Lipani[2] points out that a theoretic concern does not always translate into clinical reality. When interpreting infrequent events which arise in clinical trials, one must meticulously assess whether the trial had adequate statistical power and sample size to detect a difference in events, whether the trial was designed to assess the events under question, and whether the patient populations were appropriately randomized.

For a meta-analysis, it must be ascertained that the study populations being compared are in fact comparable. How reasonable is it to compare the placebo group from studies designed to assess the long-term impact of aspirin on cardiovascular events—in patients who did not have rheumatoid arthritis—with the patients in the VIGOR study (all of whom had rheumatoid arthritis and were therefore at an increased risk for cardiovascular events)? Additionally, if rofecoxib and celecoxib are different in their prothrombotic potential, is it appropriate conceptually to lump them together?

When comparing trials, the patients and design must be identical

Mukherjee et al,[3] however, marshal strong arguments as to why we should have concern with the use of these drugs in our patients who are at cardiovascular risk, especially if these patients are not taking aspirin.

SOME CONSENSUS

Both Lipani[2] and Mukherjee et al[3] point out the need for directed clinical trials to assess whether the COX-2 selective NSAIDs as a class or an individual COX-2 selective NSAID uniquely causes an increase in cardiovascular thrombosis. This trial may or may not ever be undertaken. The frequency of events is low enough that such a trial or trials will need to be of significant size and duration.

WHAT IS A PRACTICING PHYSICIAN TO DO?

As a practicing rheumatologist and internist, I realize I need to incorporate these concerns into my practice. What do I do?

I first assess whether all the patients who request or demand a COX-2 inhibitor actually need *any* NSAID on a *chronic* basis, and if there are any contraindications to NSAID use. If a patient truly needs to take an NSAID long-term for its analgesic and anti-inflammatory properties and cost is not a prohibitive issue, I generally suggest a COX-2 selective NSAID because of the slightly advantageous gastrointestinal safety profile, but I have true concern over loss of some of the gastrointestinal safety advantage of these drugs when used concomitantly with low-dose aspirin.

I always consider giving aspirin in low doses if the patient is at any increased cardiovascular risk. However, even in low doses, aspirin can cause macroscopic ulcerations, and a COX-2 selective NSAID can potentially (based on animal studies) slow the healing of these ulcerations and perhaps permit them to evolve into a true ulcer or bleed. The CLASS study suggests that some of the gastrointestinal-protective benefits of a COX-2 selective drug may be lost when given with low-dose aspirin. But I believe this combination may be safer than a traditional NSAID combined with aspirin.

First, I ask whether the patient needs any NSAID on a chronic basis

Ultimately, when the proton pump inhibitors become available as generic formulations and, hopefully, plummet in cost, the combination of low-dose aspirin, a generic non-selective NSAID, and a proton pump inhibitor may be the safest, cheapest, and most effective option for patients with significant cardiovascular risk who require long-term NSAID therapy. But I also hope this need for polypharmacy and concern over the theoretic risks of the alternative options will promote a continued reevaluation of our prescribing practices in general. Not all patients with arthritis *need* chronic NSAIDs. In a recent chart survey in our department, fewer than 45% of our rheumatoid arthritis patients were prescribed NSAIDs to be taken on a regular basis.

I also consider other effective measures for limiting cardiovascular disease, such as maximized lipid control, maximized blood pressure control, and angiotensin-converting enzyme inhibitors and beta-blockers following myocardial infarction. These measures are underutilized.

I applaud the willingness of Drs. Lipani, Mukherjee, Nissen, and Topol to put in print their thoughts on this thorny issue.

REFERENCES

1. **Mukherjee D, Nissen SE, Topol EJ.** Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286:954–959.
2. **Lipani J.** COX-2 inhibitors and cardiovascular risk. The data are inconclusive, and these drugs are needed. Cleve Clin J Med 2001; 68:961–962.
3. **Mukherjee D, Nissen SE, Topol EJ.** COX-2 inhibitors and cardiovascular risk. We defend our data and suggest caution. Cleve Clin J Med 2001; 68:963–964.
4. **Bombardier C, Laine L, Reicin A, et al.** Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000; 343:1520–1528.
5. **Silverstein FE, Faich G, Goldstein JL, et al.** Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. JAMA 2000; 284:1247–1255.
6. **Food and Drug Administration.** Cardiovascular safety review. Rockville, Md: Food and Drug Administration; 2001. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing 3677b2_06_cardio.pdf.
7. **Steering Committee of the Physicians' Research Study Group.** Final report on the aspirin component of the ongoing Physicians Health Study. N Engl J Med 1989; 321:129–135.
8. **Mandell BF.** And then there were two: the cyclooxygenase story. Can the expectations be fulfilled. J Clin Rheumatol 1996; 2:173–175.

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