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A world without Vioxx: To COX-2 or not to COX-2?

LIKE MANY OTHER health care providers, we were surprised when Merck announced it was removing the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib (Vioxx) from the market worldwide. This leaves two selective COX-2 inhibitors available in the United States: celecoxib (Celebrex) and valdecoxib (Bextra).

Merck's announcement came with news that the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, not yet published, found that patients with colon polyps who received rofecoxib 25 mg per day had a twofold greater risk of thromboembolic cardiovascular events (myocardial infarctions or strokes) during 18 months of treatment compared with patients receiving placebo. An earlier study had also found a small but increased risk with rofecoxib (see below).

We are familiar with the science and controversies surrounding the selective COX-2 inhibitors, having participated as investigators and advisors in the design and interpretation of clinical trials of celecoxib and as observers of the regulatory process. Merck's announcement and the many phone calls and e-mails it prompted from patients reminded us of the history of the approval of the first two selec-

tive COX-2 inhibitors—rofecoxib and celecoxib—and raised two key questions:

- Are all selective COX-2 inhibitors associated with an increased risk (albeit small) for thromboembolic cardiovascular events?
- What should we tell patients who must now stop taking rofecoxib?

■ NO CLEAR EVIDENCE OF A CLASS EFFECT

To date, there is no clear evidence that the increased risk for thromboembolic cardiovascular events observed with rofecoxib is a class effect of selective COX-2 inhibitors.

Although we do not have long-term data in as many patients with the other selective COX-2 inhibitors as we do with rofecoxib in the APPROVe trial, we have accumulated a significant amount of relevant data since rofecoxib and celecoxib were approved almost 5 years ago.

VIGOR: Increased cardiovascular risk with rofecoxib in rheumatoid arthritis patients

The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial¹ was designed to investigate the gastrointestinal (GI) safety of rofecoxib in patients with rheumatoid arthritis. Patients taking low-dose aspirin were excluded. The total exposure to rofecoxib was about 3,947 patient-years vs 3,078 patient-years of exposure to the active comparator. The mean patient exposure was 9 months.

After about 80 days of treatment and continuing throughout the trial, statistically more thromboembolic cardiovascular events occurred in those receiving rofecoxib 50 mg daily compared with naproxen 500 mg twice a day; the incidence of myocardial infarction was 0.5% vs 0.1%.²

**Do all COX-2
drugs increase
the risk of
myocardial
infarction?**

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Why did more patients have a myocardial infarction with rofecoxib than with naproxen? A possible explanation is that rofecoxib induced a prothrombotic state by inhibiting the vasodilating effects of endothelial prostaglandin I₂ without affecting thromboxane A₂ (a product of platelet COX-1), resulting in an unbalanced prothrombotic state in patients at risk. Another hypothesis is that naproxen, which has a long half-life, inhibited platelet thromboxane A₂ synthesis by COX-1 sufficiently to be cardioprotective. A third possibility is that bad luck accounted for these findings, particularly in view of the low overall risk in the study population. Or a combination of these factors may have been responsible.

CLASS: No increased risk with celecoxib in mostly osteoarthritis patients

The CLASS trial (Celecoxib Long-term Arthritis Safety Study)^{3,4} compared three treatments: celecoxib 400 mg twice a day, diclofenac 75 mg twice a day, and ibuprofen 800 mg three times a day. Total exposure to celecoxib was 2,320 patient-years (mean patient exposure duration was 9 months). Of the patients, 72% had osteoarthritis and 28% had rheumatoid arthritis. Twenty-one percent of patients were considered by their physicians to be at high risk for cardiovascular events and were taking low-dose aspirin.

No differences in cardiovascular or cerebrovascular event rates were observed between the celecoxib and the nonselective nonsteroidal anti-inflammatory drug (NSAID) treatment groups (diclofenac 75 mg twice a day with 1,081 patient-years of exposure; and ibuprofen 800 mg three times a day with 1,123 years of patient exposure), regardless of aspirin use.

Why was celecoxib *not* associated with more events, even at a dosage (400 mg twice a day) two to four times the recommended daily dose? A suggested explanation was there were fewer patient-years of exposure in CLASS than in VIGOR; another was that the CLASS population had lower risk for thromboembolic cardiovascular events overall, as most patients had osteoarthritis.

Epidemiologic studies and meta-analyses

These observations prompted the makers of both celecoxib and rofecoxib to support mul-

multiple epidemiologic studies and reanalyses of the new drug application and postmarketing study databases for evidence of increased cardiovascular risk with COX-2 selective agents.

Meta-analyses of the new drug application databases did not reveal increased risk, although the trials were typically of short duration, had multiple comparator NSAIDs (also short exposure), had no placebo group, were conducted in more patients with osteoarthritis than rheumatoid arthritis, and used COX-2 agents at recommended doses rather than those used in CLASS and VIGOR.^{5,6}

During this time, celecoxib was approved for use in the treatment of familial adenomatous polyposis at a dose of 400 mg twice a day. Both sponsors, Pfizer and Merck, then began long-term studies designed to compare either rofecoxib 25 mg daily (APPROVe) or celecoxib 200 to 400 mg daily vs placebo for prevention of subsequent polyp formation. In view of the accumulated data above, as these trials included long-term exposure and large enrollment populations, the incidence of thromboembolic cardiovascular events was a predefined secondary end point.

Initial studies by Rahme et al⁷ and Solomon et al⁸ failed to show differences in risk for cardiovascular events with rofecoxib and suggested⁸ that this was due to the protective effects of naproxen. However, other epidemiologic studies failed to show a protective effect for naproxen or other NSAIDs.²

Two subsequent large observational cohort studies found doses of rofecoxib higher than 25 mg daily to be associated with increased risk for cardiovascular events. Ray et al⁹ studied the Tennessee Medicaid database and found an odds ratio of 1.7 for acute myocardial infarction with doses of rofecoxib larger than 25 mg daily compared with ibuprofen. This risk was observed specifically in new users, ie, patients taking rofecoxib for less than 90 days—a predetermined outcome. Solomon et al¹⁰ analyzed a Medicare database from New Jersey and Pennsylvania and identified an increased relative risk for acute myocardial infarction with rofecoxib doses greater than 25 mg daily compared with celecoxib and traditional NSAIDs, again over the first 90 days of use, but not thereafter.

Recently, a collaborative study by the US Food and Drug Administration and Kaiser

More data are available with rofecoxib than with other COX-2 drugs

Permanente examined cardiovascular outcomes in approximately 1.4 million patients receiving nonselective NSAIDs or selective COX-2 inhibitors. Doses of rofecoxib higher than 25 mg/day were associated with a more than threefold higher incidence of acute myocardial infarction and sudden cardiac death compared with nonselective NSAIDs or other selective COX-2 inhibitors.¹¹

Of interest, in both the Medicaid and Kaiser Permanente databases the incidence of acute myocardial infarction with celecoxib treatment was lower than with the other agents.^{10,11} And in the Kaiser Permanente analysis,¹¹ naproxen was associated with an increased risk of thromboembolic cardiovascular events (relative risk [RR] 1.18, 95% confidence interval [CI] 1.04–1.35; $P = .01$), as was indomethacin (RR 1.33, 95% CI 1.09–1.63; $P = .005$).

In addition to these epidemiologic analyses, more robust data sets from clinical trials and new drug application summaries of both celecoxib and rofecoxib demonstrate a dose-related effect of rofecoxib on raising blood pressure and causing edema, not apparent with celecoxib at any dose. Therapeutic doses of both celecoxib and rofecoxib are associated with approximately a 2% incidence of hypertension and edema, not different from that observed with nonselective NSAIDs. However, a dose response for increased hypertension and edema is particularly evident with rofecoxib at 50 mg daily.

Two studies comparing these effects of rofecoxib and celecoxib^{12,13} have recently been confirmed in a randomized controlled trial using continuous ambulatory blood pressure monitoring.¹⁴ In hypertensive patients (treated with various antihypertensive drugs including angiotensin-converting enzyme inhibitors) who have osteoarthritis, both agents cause an increase in systolic and diastolic blood pressure, which is more pronounced with rofecoxib.

The subsequent ambulatory blood pressure monitoring trial was a trial that compared the effects of celecoxib 200 mg, rofecoxib 25 mg, and naproxen 500 mg twice a day in hypertensive diabetic patients with osteoarthritis on treatment for high blood pressure. At 6 weeks, there was a sustained increase in systolic blood pressure of about 4.2 mm Hg

with rofecoxib, but no rise with naproxen or celecoxib.

Although there is no evidence that these increases in blood pressure are associated with short-term increases in risk for acute myocardial infarctions, there is clear evidence that sustained increases in blood pressure are associated with ischemic cardiac events and stroke.

Trials of other COX-2 inhibitors

During this same time another selective COX-2 inhibitor was approved: valdecoxib (Bextra). Treatment with valdecoxib, approved for use at 10 and 20 mg/day, appears to be associated with a higher incidence of hypertension and edema at doses of 40 and 80 mg/day. The new drug application database has not revealed an increased risk for thromboembolic cardiovascular events, although it is smaller and does not include a large outcome trial similar to CLASS or VIGOR.¹⁵

Paracoxib, a parenteral prodrug form of valdecoxib, was studied in patients undergoing coronary artery bypass surgery, who subsequently received oral valdecoxib; a control group received placebo with 2:1 randomization. More cardiovascular events occurred in the active treatment group than in the placebo group, but whether the treatment caused the events cannot be determined: some events occurred during surgery, before paracoxib was given, or more than five half-lives after the valdecoxib was stopped.¹⁶ Furthermore, there were more cases of chest wall infections and pleuritis in the COX-2-treated group than in the placebo group. A second trial in the same type of patients is under way, but the results are yet unknown.

Etoricoxib has been approved in 47 countries, many of which require a label warning of the risk for cardiovascular events. The original US new drug application for this product was withdrawn owing to an increased risk for acute myocardial infarction.

The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)¹⁷ demonstrated no statistically significant increased risk for cardiovascular events with the selective COX-2 inhibitor lumiracoxib. Although numerically higher than in the group receiving naproxen, the overall incidence of these events was quite low.

Patients in VIGOR were at higher baseline cardiovascular risk than those in CLASS

Hypothetical reasons for apparent differences in outcomes

Potential differences in cardiovascular outcomes with the selective COX-2 inhibitors may be due to differences in the drugs' molecular structures, pharmacokinetics, and pharmacodynamics. Celecoxib and valdecoxib are sulfonamides; celecoxib has a halogenated side chain. Rofecoxib and etoricoxib are sulfones, one with a halogen-containing ring structure and the other a chlorine side component. The half-life of rofecoxib is more than 17 hours compared with approximately 11 hours for celecoxib and 8 hours for valdecoxib.

Much has been said about the "differential selectivity" of rofecoxib, celecoxib, and valdecoxib for inhibition of COX-2 vs COX-1 activity, although in vitro and ex vivo assays employing different molecular targets may not accurately reflect in vivo effects. Regardless, each of these agents effectively and selectively inhibits COX-2 activity when used in approved therapeutic doses, and none affects in vivo platelet thromboxane A₂ generation at any recommended dose.

Whether these differences in molecular structure and pharmacodynamics can translate into differences in clinical effects such as hypertension and edema is unknown. Furthermore, the exact biology that may explain the observed increased risk for thromboembolic cardiovascular events with at least some COX-2-selective inhibitors is unknown.

Conclusions: All COX-2 drugs are not alike

Weighing the available total evidence, it appears that, as with the nonselective NSAIDs, all selective COX-2 agents are not alike.

- Rofecoxib has demonstrated a dose-related risk for increased hypertension and edema and a clearly increased risk for cardiovascular complications, but it is unclear whether the two are related.
- Celecoxib does not appear to cause hypertension or edema over a broad range of doses (200 to 800 mg/day), and the available data have not shown an increased risk for acute thromboembolic cardiovascular events. Further analyses and prospective trials are under way.
- Valdecoxib appears to be associated with a dose-related increase in hypertension and edema at doses of 40 to 80 mg/day—higher

than the doses of 10 and 20 mg/day approved for chronic use. The limited evidence to date does not reveal a significant increase in cardiovascular thromboembolism. There are no large outcome trials; another trial in coronary artery bypass graft patients is pending. The first trial was adjudicated to have events.

- More large outcome trials will be required to definitively answer the question, but at present the conclusion that an increased risk for cardiovascular events is a class effect of all selective COX-2 inhibitors is premature.

WHAT TO TELL PATIENTS

Now that rofecoxib is gone, what should clinicians tell patients who have been taking it? The discussion should take into account the issues of need, safety, and cost.

Does the patient still need chronic anti-inflammatory therapy?

This may be a good time to review the patient's medications and eliminate those that are not needed. Would non-NSAID analgesic therapy be an option?

Is the patient at risk for GI bleeding?

Bleeding or other NSAID-induced GI complications such as perforation or obstruction are the major reason most patients receive a selective COX-2 inhibitor in many managed care environments. If the patient has no risk factors for GI complications, then perhaps a nonselective NSAID would suffice—and would be cheaper. These risk factors include age greater than 60 years, past history of a complication with or without past use of an NSAID, concomitant glucocorticoid use, combination use of NSAIDs (such as aspirin), higher doses of the NSAIDs, severe illness, and, for bleeding, concomitant use of an anticoagulant.

If the patient needs an anti-inflammatory drug and is at risk for GI complications, one option is to give the combination of a nonselective NSAID plus a proton pump inhibitor.¹⁸ Although adding a proton pump inhibitor to a nonselective NSAID will reduce the risk of upper GI adverse events to a level observed with COX-2 inhibitors, it will not protect the lower GI tract. Nonselective NSAIDs can cause mucosal ulcers throughout the GI tract.

A proton pump inhibitor will not protect the lower GI system



Bleeding from lower GI lesions has previously been underestimated.

Therefore, if the patient is at increased risk for GI complications, then one of the two remaining approved selective COX-2 inhibitors should be used. Evidence to date does not indicate that celecoxib is associated with an increased risk for thromboembolic cardiovascular events. Supportive epidemiologic studies and large prospective trials are available only for celecoxib, and not valdecoxib. As both share a sulfonamide structure, careful

screening for potential drug allergy is required.

Is the patient at high risk for a cardiovascular event?

If the patient is considered to be at high risk for cardiovascular events, then low-dose aspirin should be used. If the patient is frail, has multiple medical comorbidities, is at high risk for GI complications with nonselective NSAID use, and must take low-dose aspirin, then both a COX-2 inhibitor and a proton pump inhibitor should be prescribed.

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