EDITORIAL

COX-2 Inhibitors — Lessons in Drug Safety

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Approximately six years after the cyclooxygenase-2 (COX-2) inhibitors were approved for use in the United States, the results of three randomized, placebo-controlled trials provide new evidence about the cardiovascular risks of rofecoxib, celecoxib, and valdecoxib.[1-3] The Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, a study of patients with a history of colorectal adenomas, was stopped early because rofecoxib doubled the risk of major cardiovascular events (relative risk, 1.92; 95 percent confidence interval, 1.19 to 3.11). These findings confirmed the increased risk of myocardial infarction previously seen in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial[4] and some observational studies.[5] The public announcement of the APPROVe results, which coincided with Merck's withdrawal of rofecoxib from the market in September 2004, prompted scientists to review the cardiovascular-safety results of a similar trial, the Adenoma Prevention with Celecoxib (APC) Study.[2] At either 200 or 400 mg twice a day, celecoxib in the APC trial was associated with a tripling of the risk of cardiovascular events (relative risk, 2.8; 95 percent confidence interval, 1.3 to 6.3). In the third COX-2 inhibitor trial reported in this issue of the *Journal*,[3] the short-term use of valdecoxib and its prodrug parecoxib was associated with increased cardiovascular risk in patients undergoing coronary bypass surgery.

After millions of Americans have used COX-2 inhibitors, which were intended to avert the gastrointestinal complications common to other nonsteroidal antiinflammatory drugs (NSAIDs), serious adverse cardiovascular events have now been reported for three members of the class. Physicians are dismayed, pharmaceutical companies are embarrassed and financially threatened, and patients are injured. Indeed, the integrity of the American drug-safety system has been questioned. How did such problems arise, and how can they be prevented in the future?

COX-2 inhibitors not only lack the antiplatelet effects of aspirin; by inhibiting the production of prostacyclin, they also disable one of the primary defenses of the endothelium against platelet aggregation, hypertension, and atherosclerosis.[6] COX-2 inhibitors also promote an imbalance in favor of vasoconstriction. These biologic actions, known since 1998, suggest that COX-2 inhibitors may increase the risk of cardiovascular events, including myocardial infarction, stroke, hypertension, and heart failure. To use COX-2 inhibitors wisely, patients and physicians need complete information about benefits and risks, including any cardiovascular risks.

Before rofecoxib was approved, 5435 patients received the drug, usually in small, short-term trials that were adequately powered to examine outcomes such as pain relief.[7] Adverse events, including cardiovascular ones, were identified incidentally, by self-report. Although only 371 and 381 patients received doses of 12.5 mg and 25 mg, respectively, for more than one year, safety signals were recognized by the medical officer of the Food and Drug Administration (FDA), who observed "that in 6-week studies, thromboembolic events are more frequent in patients receiving rofecoxib [12 (0.67%) of 1780] than placebo [1 (0.24%) of 412]."[7] Still, rofecoxib was approved in May 1999.

The tradeoff between gastrointestinal benefit and cardiovascular harm was highlighted in the VIGOR trial, which compared rofecoxib (50 mg daily) with naproxen (500 mg twice daily) in 8076 patients with rheumatoid arthritis.[4] Subjects with recent cardiovascular events were excluded, and so were those taking aspirin. Cardiovascular events were not a pre-

specified end point and were not adjudicated for the VIGOR trial itself. The occurrence of myocardial infarction, which was five times as high in the rofecoxib group as in the naproxen group, was reported only in preliminary form in the original article.[4,8] Revisions of the rofecoxib label took more than two years to complete.

In contrast, the Women's Health Initiative (WHI) study is an example of a trial designed to assess risks and benefits with equal scientific rigor.[9] In the evaluation of hormone-replacement therapy, the WHI treated the potential risks of breast cancer and venous thrombosis just as seriously as the hypothesized benefits with regard to myocardial infarction and stroke. Criteria for all these end points and the methods of case identification were defined in the protocol, and outcome data were collected prospectively and adjudicated blindly. Early on, the WHI's data and safety monitoring board considered how to handle potential scenarios of benefit or risk among the major end points.[10]

In the initial evaluation of the COX-2 inhibitors, the use of small, short-term trials, the exclusion of high-risk patients, and the methodologic inattention to cardiovascular events all minimized the possibility of uncovering evidence of cardiovascular harm. First, only a small number of events accrued in studies that were not designed to assess cardiovascular outcomes. Second, the adverse effects of a drug may differ between high-risk and low-risk patients. COX-2 inhibitors were not adequately evaluated in the large number of high-risk patients, 40 percent of users by some estimates,[11] who would eventually take them. Third, misclassification of study outcomes makes associations, if present, more difficult to detect. Even conventionally high levels of specificity, such as 99 percent, can have pronounced effects, biasing estimates of risk toward the null.

The cardiovascular harm associated with COX-2 inhibitors became apparent in trials, such as APPROVe, APC, and the cardiac-surgery studies,[1-3,12] that were conducted for other indications. Even with the evidence from these trials, we lack adequate information to make confident statements about the exact levels of risk for each drug, the time course of the risk during therapy, and the populations of patients, if any, in whom the benefits might exceed the known risks.

Medicines that will be used by millions of Americans for long periods, especially when their biologic mechanisms suggest a risk, are best evaluated in large, long-term clinical trials that begin as early as possible in the drug-approval process.[13] If manufacturers do not on their own address the potential risks, then in the interests of public health the FDA must insist that they do so. In some instances, observational studies will be the most efficient and timely method of assessing drug safety.

In 2000, Pfizer completed a randomized trial of celecoxib in patients with Alzheimer's disease but never published the unfavorable cardiovascular results and only made them publicly available in January 2005.[14] Human subjects agree to participate in studies to contribute to science and public health. Failure to publish the findings of these studies not only violates their trust, but also misrepresents the evidence about risks and benefits for patients and physicians. All randomized clinical trials should be registered, and their results should be made public in a timely fashion.

For an approved drug, the FDA currently engages in protracted negotiations with manufacturers rather than mandating manufacturers (1) to change a product label, (2) to conduct patient or physician education, (3) to limit advertising to patients or physicians, (4) to modify approved indications, (5) to restrict use to selected patients, (6) to complete post-marketing studies agreed on at the time of approval, (7) to conduct additional post-marketing studies or trials, and (8) to suspend marketing or immediately withdraw a drug. The FDA has recently claimed to lack adequate authority in these areas. We believe that to protect the health of the public, Congress needs to provide the FDA with the necessary authority and also to create an independent Center for Drug Safety with new authority and funding. Civil penalties should be commensurate with the scale of drug sales. Provisional approval and regular repeated review would provide opportunities to reevaluate risk and benefit. In addition, ongoing congressional oversight of the FDA would afford an important forum for the public discussion of drug safety.

Without the efficacy results from the colorectal-polyp prevention studies, it is not possible to assess the balance of risk and benefit. Although the cardiovascular risks of COX-2 inhibitors are now more clearly documented,[1-3] they have not been adequately evaluated in long-term studies in low-risk populations or high-risk populations. The absence of evidence here is not evidence of safety. In clinical trials, NSAIDs, aspirin, and acetaminophen are just as effective in relieving pain as the COX-2 inhibitors.

If a COX-2 inhibitor were necessary, patients would have to be informed of the potential risks, and the lowest possible dose should be used for the shortest possible time.

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1. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352.
2. Solomon SD, McMurray JJV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352.
3. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005;352.
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;343:1520-8.
5. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet 2005;365:475-81.
6. McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci U S A 1999;96:272-7.
7. Villalba ML. FDA medical officer review of VIOXX (rofecoxib), NDA 21-042 (capsules) and NDA 21-052 (oral solution). (Accessed February 12, 2005, at http://www.fda.gov/cder/foi/nda/index.htm.)
8. Targum SL. Consultation on NDA 21-042, S-007: review of cardiovascular safety database (on Vioxx or rofecoxib). FDA memorandum, February 1, 2001. (Accessed February 12, 2005, at http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.doc.)
9. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
10. Freedman L, Anderson G, Kipnis V, et al. Approaches to monitoring the results of long-term disease prevention trials: examples from the Women's Health Initiative. Control Clin Trials 1996;17:509-25.
11. Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-flammatory drugs and risk of serious coronary heart disease. Lancet 2002;360:1071-3.
12. Ott E, Nussmeier NA, Duke PC, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg 2003;125:1481-92.
13. Psaty BM, Weiss NS, Furberg CD, et al. Surrogate end points, health outcomes, and the drug-approval process for the treatment of risk factors for cardiovascular disease. JAMA 1999;282:786-90.
14. Pfizer. A double-blind randomized placebo-controlled comparative study of celecoxib (SC-58635) for the inhibition of progression of Alzheimer's disease, protocol IQ5-97-02-001. (Accessed February 12, 2005, at http://www.clinicalstudyresults.org/documents/company-study_76_0.pdf.)