

EDITORIAL



COX-2 Inhibitors — A Lesson in Unexpected Problems

Jeffrey M. Drazen, M.D.

This issue of the *Journal* contains three articles about the adverse cardiovascular effects of agents that selectively inhibit one form of prostaglandin endoperoxide synthase, commonly known as cyclooxygenase-2 (COX-2).¹⁻³ This is part of a long bench-to-bedside story with an adverse outcome that was not widely anticipated at its start. Unfortunately, as the evidence began to suggest unexpected toxicity of this group of agents, the same zeal that had driven the clinical investigation to show their gastrointestinal safety was not evidenced by studies designed to show their cardiovascular safety.

In 1987, evidence emerged⁴ that there were probably two enzymes — cyclooxygenase-1 (COX-1) and COX-2 — with the capacity to catalyze the transformation of arachidonic acid to prostaglandin H₂; this is the step committing the substrate arachidonic acid to emerge as a member of the prostaglandin-thromboxane family. This family contains many molecular entities, including molecules with both prothrombotic (thromboxane A₂) and antithrombotic (prostacyclin) properties. Within a few years, it had been established that COX-2 was selectively expressed in tissues that had been exposed to certain inflammatory mediators and that it was possible to selectively inhibit COX-2. As the science advanced, it seemed likely that the adverse gastrointestinal effects of common pain relievers whose mechanism of action was cyclooxygenase inhibition were attributable to the inhibition of COX-1. The idea emerged that selective inhibitors of COX-2 could relieve pain without gastrointestinal side effects; if true, this would be a major advance.

A number of pharmaceutical companies developed and tested selective inhibitors of COX-2 with the idea of developing agents for the relief of inflammatory pain that would be as effective as non-steroidal antiinflammatory drugs but without one

of their major side effects, gastrointestinal bleeding. Although the basic science was logical, the actual proof of enhanced safety turned out to be more elusive. When the first two drugs in this class were approved by the Food and Drug Administration in 1999, the lack of evidence of a clear benefit with respect to gastrointestinal safety prevented the manufacturers from making the very claim that had been the reason for developing these agents in the first place. Two large studies of the drugs were published in 2000. In the Celecoxib Long-Term Arthritis Safety Study (CLASS), the apparent gastrointestinal protective effect of celecoxib noted at the 6-month analysis⁵ had evaporated at the 12-month analysis.⁶ Some have speculated that this lack of a demonstrable benefit might have been due to the fact that patients were allowed to continue the use of low-dose aspirin. In contrast, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study⁷ prohibited the use of low-dose aspirin and demonstrated a reduced incidence of gastrointestinal lesions after long-term use of rofecoxib, as compared with naproxen.

An unexpected problem arose. In the VIGOR study, there was a higher incidence of myocardial infarction in the rofecoxib group than in the control group treated with naproxen. Because the study lacked a placebo group, it was unclear whether the effect was due to an increased cardiovascular risk with rofecoxib or a protective effect of naproxen, or whether this was merely a chance finding. At the time, the science was not sufficiently advanced to give the adverse cardiovascular effects clear biologic plausibility; however, preliminary evidence published near the time of completion of the trial supported the plausibility of COX-2-induced adverse cardiovascular events by suggesting that COX-2 inhibitors reduced the production of the antithrombotic product, prostacyclin, without changing the

production of the prothrombotic product, thromboxane.⁸ Unfortunately, no randomized, controlled trials were initiated to address primarily the question of cardiovascular toxicity. Instead, efficacy trials designed to investigate the prevention of recurrent colonic polyps and the management of postoperative pain were launched, with monitoring of cardiovascular events for safety. From early on both drugs were marketed intensively, with massive direct-to-consumer advertising. Before withdrawal, the combined yearly sales of COX-2 inhibitors exceeded \$5 billion.

In September 2004, Merck withdrew rofecoxib from the market because its trial, designed to test the hypothesis that COX-2 inhibitors could prevent recurrent colonic polyps, showed increased cardiovascular toxicity (one of the articles in this issue of the *Journal* presents the cardiovascular data from this study³). The National Cancer Institute stopped a similar trial of celecoxib when an independent panel of cardiovascular experts reviewed the data and also found a greater risk of cardiovascular events among patients treated with celecoxib; the data on cardiovascular events from that trial are reported in this issue of the *Journal*.¹ Also reported in this issue are the cardiovascular toxicity data from a trial of another COX-2 inhibitor, valdecoxib (and its intravenous prodrug, parecoxib).² This trial, which examined pain relief in patients recovering from coronary-artery bypass surgery, showed an increased incidence of cardiovascular end points at 30 days among patients who had received a total of only 10 days of COX-2 inhibition.

Taken together, these three large, randomized, controlled trials designed to test the efficacy of different COX-2 inhibitors for a variety of indications confirmed the cardiovascular toxicity that had been suggested five years earlier. Since three different COX-2 inhibitors were all found to be associated with cardiovascular complications, it appears that this is a class effect. Because there are well-established options for treatment of all the approved indications for these drugs, it is reasonable to ask whether the use of the drugs can now be justified.

There is a lesson from all this. The spontaneous reporting systems we have in place to track adverse drug reactions make it possible to detect an increased incidence of rare events, such as fulminant liver failure or rhabdomyolysis, after the introduc-

tion of a new drug into the market. In contrast, the detection of an increased incidence of a common event, such as heart attack or stroke, is much more difficult. The uncomfortable conundrum is that the latter has a much bigger impact on the public health than the former. Because epidemiologic studies with cardiovascular end points are subject to major confounding, ascertainment of the true risk associated with treatment requires randomized controlled trials specifically designed to look for such a risk.

When the CLASS and VIGOR trials were started, the cardiovascular adverse events were not foreseen. However, when these clinical trials showed an increased risk of myocardial infarction, rather than consider this finding a major danger signal, the manufacturers designed trials to show efficacy for other indications and enhanced the cardiovascular safety monitoring in these subsequent trials. It is a sobering thought that although the number of deaths and cardiovascular events attributable to COX-2 inhibitors remains in dispute, had trials designed to test the question of cardiovascular toxicity directly been launched in 1999 and executed with urgency, substantial morbidity and perhaps a substantial number of deaths could have been prevented. As we apply new science to develop new medicines, we must not forget that our first job is to do no harm.

1. Solomon SD, McMurray JVV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;352.
2. Nussmeier NA, Whelton AA, Brown MT, et al. Cardiovascular complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005;352.
3. 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.
4. Tanaka Y, Ward SL, Smith WL. Immunochemical and kinetic evidence for two different prostaglandin H-prostaglandin E isomerases in sheep vesicular gland microsomes. *J Biol Chem* 1987;262:1374-81.
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;284:1247-55.
6. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;286:954-9.
7. 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.
8. 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. [Erratum, *Proc Natl Acad Sci U S A* 1999;96:5890.]

Copyright © 2005 Massachusetts Medical Society.