CARDIOLOGY Rounds®

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Cardiovascular Risks of Cyclooxygenase-2 inhibitors

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Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat chronic pain and inflammation in patients with osteoarthritis and other musculoskeletal disorders. In the United States, these disorders affect 15 to 30 million people, aged between 50 to 60 years of age.[1] The use of NSAIDs is generally intermittent and fluctuates with the intensity of the disease state. Nonetheless, success of the therapy is frequently limited by gastrointestinal (GI) toxicity and complications such as bleeding, ulceration, or perforation. The development of a new class of anti-inflammatory drugs, the selective cyclooxygenase-2 (COX-2) inhibitors (coxibs), which inhibit the enzyme catalyzing the transformation of arachidonic acid to a range of lipid intermediates, was a direct response to the unsatisfactory side-effect profile of NSAIDs. On May 29, 1999, Merck was granted approval by the Food and Drug Administration (FDA) of the United States to market the coxib, rofecoxib (Vioxx®). However, on September 30, 2004, the company withdrew the drug because of excess cardiovascular risk. This represents the largest prescription drug withdrawal noted to date. There has been much debate about the evidence surrounding the withdrawal and this issue of *Cardiology Rounds* reviews the currently available literature.

Case example

A 75-year-old woman with debilitating osteoarthritis is sent by her family doctor to a specialist for cardiac assessment. Her risk factors include diabetes for 20 years, hypertension for 10 years, hyperlipidemia, and a 40-pack year history of smoking that is 20 years remote. There is no family history of cardiovascular disease (CVD). She denies symptoms of angina, but has poor functional capacity due to the longstanding osteoarthritis and has not undergone noninvasive cardiac testing. She is otherwise well. Her medications include aspirin, atorvastatin, metoprolol, celecoxib, and furosemide. Her physical examination is unremarkable and her resting electrocardiogram (EKG) shows evidence of left ventricular hypertrophy.

This case illustrates the following dilemma faced by clinicians treating patients who take coxibs:

- defining the patient's risk for a cardiac event while taking coxibs may be difficult
- convincing patients of increased cardiac risk may not necessarily alter their medication choices
- debilitating disease can make patients depend on certain classes of medications, while placing them at increased risk of serious adverse events

Mechanisms of action of COX-2 inhibitors

The primary effect of NSAIDs is to inhibit cyclooxygenase, thereby impairing the ultimate transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes (Figure 1).[2] The extent of enzyme inhibition varies among the different NSAIDs. Two related isoforms of the COX enzyme have been described: COX-1 and COX-2. They possess 60% homology and the most important differences between them are the regulation and expression of enzymes in various tissues.

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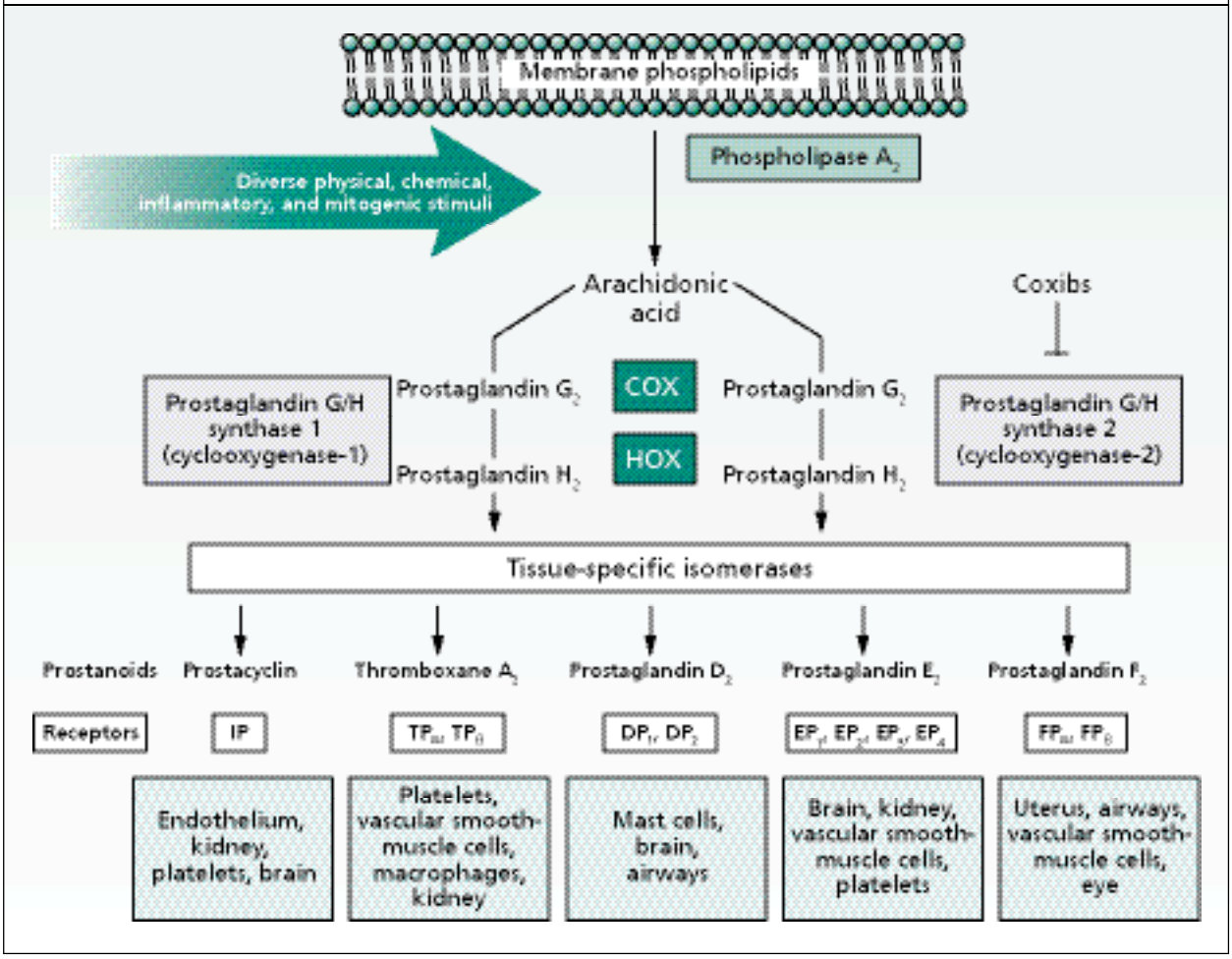
Figure 1: Mechanisms of action of NSAIDs[1]



• COX-1 is expressed in most tissues, but variably. It is described as a "housekeeping" enzyme, regulating normal cellular processes (eg, gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function) and is stimulated by hormones or growth factors.

• COX-2 is constitutively expressed in the brain, kidney, bone, and probably in the female reproductive system. Its expression at other sites is increased during states of inflammation or, experimentally, in response to mitogenic stimuli.

It has been proposed that the ideal NSAID would inhibit the inducible COX-2 isoform, thereby decreasing inflammation, without exerting any effects on the constitutive COX-l isoform and, thus, minimizing toxicity. Such an agent would maximize effectiveness, without inducing toxicity, particularly gastroduodenal erosions. As a result, it was hoped that the coxibs would be better tolerated than nonselective NSAIDs, while being equally efficacious.

Various coxibs received approval from the FDA in the United States for use in rheumatoid arthritis and osteoarthritis, including celecoxib (Celebrex®), rofecoxib (Vioxx®), and valdecoxib (Bextra®). Other coxibs were approved for use in acute pain and dysmenorrhea as well.

Benefits of COX-2 inhibitors

The principal benefit with coxibs is that they produce analgesia and anti-inflammatory effects comparable to the nonselective NSAIDs, but with fewer symptomatic gastric and duodenal ulcers and GI symptoms. In addition, benefits have been described in patients with familial adenomatous polyposis, colon cancer, and breast cancer.[3]

Effect on colon cancer

Sandler et al[4] demonstrated that there is increased COX-2 expression in colon cancer as compared to adjacent colonic mucosa, which may also increase the metastatic potential of colon cancer cells and tumour growth.[5] There was significantly higher 10-year survival in patients with the lowest levels of COX-2 staining (68% versus 35%). In addition, when human colon cancer cells expressing high levels of COX-2 were implanted into nude mice, treatment with a coxib reduced tumour formation by 85%-90%, as well as colony formation potential.[6] In a case-controlled trial involving 83 patients with familial adenomatous polyposis (FAP), celecoxib (400 mg twice daily) was associated with a 28% reduction in rectal polyps.

These data led an FDA advisory panel to recommend the drug for approval in patients with FAP. However, a clinical trial of rofecoxib was halted early due to an increased rate of serious adverse cardiovascular events in those receiving rofecoxib.

Reduced risk of bleeding in anticoagulated patients

The lack of an inhibitory effect on platelet function by coxibs (see below) may be of value when an anti-inflammatory effect is needed in patients receiving ongoing anticoagulation. This was illustrated by a case-control study in 1491 patients where no increase in the number of bleeding episodes was demonstrated in patients anticoagulated with warfarin.[7]

Risks of COX-2 inhibitors

Gastrointestinal side-effects

The toxicity and/or adverse effects associated with coxibs, outside of the effects described for the GI tract, were limited until recently. A potential concern is the possibility of delayed healing for gastric erosions or ulcers seen in mouse models,[8] although this has not been observed clinically. The lack of clinical evidence is likely because approximately 40% of patients included in trials were required to be free of ulcers prior to study entry. Also, other studies excluded patients with active peptic ulcer disease. Thus, it is still unclear whether the coxibs induce damage to the GI tract, even though there may be no effects on COX-1 activity in vivo at any therapeutic dose. Instead, the observed GI effects of the coxibs may be due to their effect on the healing of ulcers induced through other pathologic mechanisms.

Acute renal failure

Multiple animal studies suggest that the COX-2 enzyme plays a significant role in renal development and function.[9,10] In COX-2 $^{-/-}$ knockout mice, there is evidence of aberrant kidney development after birth, resulting in marked diffuse tubular cysts, glomerular hypoplasia, interstitial fibrosis, and renal failure. In contrast, clinical trials with celecoxib and rofecoxib did not demonstrate significant changes in renal function associated with treatment at the approved doses for osteoarthritis and rheumatoid arthritis. Patients at risk include those with volume depletion, heart failure, cirrhosis, intrinsic renal disease (eg, diabetic nephropathy), and hypercalcemia. After discontinuation of coxibs and aggressive supportive therapy, renal function tends to return to baseline within 2 days to 3 weeks.[9,10]

Risk of ischemic heart disease with the coxibs

Coxibs are associated with reduced prostacyclin production by vascular endothelium with little, or no, inhibition of potentially prothrombotic platelet thromboxane A2 production. This relatively selective reduction in prostacyclin activity could predispose to endothelial injury. This may be an important factor, since it has been demonstrated that there are increased ischemic cardiovascular events with rofecoxib, an observation that has raised questions about the safety of other members of this class. In fact, on September 30, 2004, the manufacturer of rofecoxib, Merck, announced that the drug was being withdrawn from the market, worldwide. This decision was based upon data from an unpublished study of rofecoxib in the prevention of adenomatous colonic polyps – the Adenomatous Polyp Prevention On Vioxx trial (APPROVe) – in which 2568 patients were randomly assigned to rofecoxib (25 mg/day) or placebo with a 3-year follow-up (Merck news release). Safety monitoring after 18 months indicated an increased incidence of myocardial infarction (MI) and stroke in the patients taking rofecoxib (14.5/1000 patient-years), as compared to placebo (7.5/1000 patient-years) and a relative risk (RR) of 1.92 (95% confidence interval [CI], 1.19-3.11).

A similar increase in risk of MI in those receiving rofecoxib was noted in a meta-analysis that included data from 18 randomized controlled clinical trials and 11 observational trials, in which a total of 20,742 patients were randomly assigned to rofecoxib or a control (placebo or comparison NSAID).[11] The incidence of MI in the control groups was 1.45/1000 patient-years and the relative risk of MI for those who received rofecoxib was 2.24 (95% CI, 1.24-4.02). The increase in risk may be greater with rofecoxib doses above 25 mg/day.[12,13]

In a series of other trials, the possible adverse effects of rofecoxib, as compared to naproxen and other NSAIDs, could not necessarily be distinguished from a possible beneficial effect of naproxen.[14-16] In a post-hoc analysis of the results of the Vioxx Gastrointestinal Outcome Research (VIGOR) trial, a randomized clinical trial that compared rofecoxib to naproxen in patients with rheumatoid arthritis, patients treated with rofecoxib (50 mg/day) had an increased incidence of MI (0.4% versus 0.1%).[14] In addition, a summary of the literature relating to the use of coxibs in 2001 also found an increased relative risk for cardiovascular events with use of rofecoxib compared to naproxen (RR 2.2, 95 % CI, 1.62-3.21).[15] There was no difference in rates among the groups being administered celecoxib, ibuprofen, and diclofenac.

Is this a class effect?

Celecoxib

There are 2 representative observational studies describing the currently available data on celecoxib and adverse cardiovascular events. In a study in 7968 patients with arthritis randomly assigned to receive celecoxib or a nonselective NSAID, there was no statistically significant difference in serious cardiovascular event rates.[17] During a 1-year follow-up, the rate of MI was 0.3 % in both groups.[18] The incidence of the composite endpoint of stroke, MI, and/or angina was also similar in both groups

(0.86% versus 1.06%, p=0.62). This analysis did not demonstrate a statistically significant increase in adverse cardiovascular events with celecoxib.

The possibility of increased cardiovascular risk during chronic use, particularly at higher doses of celecoxib, was raised by a review of safety data from 3 prevention studies that evaluated celecoxib.

One of the 3 studies, the Adenomatous Polyp Prevention (APC) trial,[13] randomly assigned 2035 patients to celecoxib or placebo. Analysis of cardiovascular safety after follow-up of at least 2.8 years revealed that:

- the placebo group had a 1% (7/679) incidence of cardiovascular events (MI, stroke, cardiovascular death)
- in patients receiving celecoxib, 200 mg twice daily, there were 16/685 events (2.3% incidence of cardiovascular events; hazard ratio 2.3, 95% CI, 0.9-5.5)
- in patients receiving celecoxib 400 mg twice daily, there were 23/671 events (3.4% incidence of cardiovascular events; hazard ratio 3.4, 95% CI,1.4-7.8).

Based on the similar trends for other composite endpoints, the data and safety monitoring board recommended early discontinuation of the study drug.

Valdecoxib

The cardiovascular safety of valdecoxib was also assessed in a study pooling results from 10 clinical trials that included nearly 8000 subjects and compared the incidence of cardiovascular events in patients with rheumatoid arthritis or osteoarthritis taking valdecoxib (10-80 mg/day) to those of controls taking nonselective NSAIDs (diclofenac, ibuprofen, or naproxen) or placebo.[18] The studies varied in duration (6 to 52 weeks) and there were no significant differences in serious thrombotic events between groups. In analyses of aspirin-using and nonaspirin-using subgroups, no significant differences in the risk of serious cardiovascular events were noted in those taking valdecoxib.[18] A recent meta-analysis of data from 2 trials in post-bypass graft surgery patients, however, found a significantly increased risk of cardiovascular events in those assigned to receive valdecoxib (RR 3.08, 95% CI,1.20-7.87).[19]

Lumiracoxib

The cardiovascular safety of lumiracoxib was assessed in the Therapeutic Arthritis Research and Gastrointestinal Event (TARGET) trial, in which 18,325 patients with osteoarthritis were randomly assigned to lumiracoxib (400 mg once-a-day), naproxen (500 mg twice daily), or ibuprofen (800 mg 3 times a day) and followed for 1 year for composite cardiovascular events (MI, stroke, or cardiac death).[20] Event rates were not significantly different between the various groups (0.55% and 0.65%) NSAIDs vs lumiracoxib, respectively. Adjustment for cardiovascular risk factors did not show a significant increase in risk (hazard ratio 1.14, 95% CI, 0.78-1.66). The respective MI rates were not significantly different at 0.33 versus 0.26 per 100 patient years (hazard ratio 1.31, 95% CI, 0.70-2.45; p = 0.4012). Prior to randomization, patients in the TARGET trial were stratified for use of low-dose aspirin. Interestingly, preplanned analyses of non-aspirin and aspirin-using subgroups did not show any statistically significant differences in event rates or MI rates among those using lumiracoxib or NSAIDs in either subgroup. However, the absence of statistically significant differences in cardiovascular event or MI rates between the lumiracoxib and nonselective NSAID groups does not necessarily mean that the risks are, in fact, similar. There was a relatively small number of patients who were at high risk for MI (since patients with prior MI, stroke, coronary bypass grafting, angioplasty or stenting, angina, or significant heart failure were excluded) and there was a lower than expected number of events. As a result, the TARGET trial lacked statistical power to exclude or detect a potentially clinically important difference in risk of cardiovascular outcomes.

Heart failure

Nonselective NSAIDs may precipitate clinical heart failure or worsen already existing disease. Whether coxibs share this effect is uncertain. A population-based retrospective cohort study was conducted using a large administrative healthcare database to examine the incidence of heart failure among NSAID-naïve, older (>66 years) patients.[21] New prescriptions for rofecoxib, celecoxib, and nonselective NSAIDs were issued to 14,583, 18,908, and 11606 patients, respectively, and the outcomes in these groups were compared to those of 100,000 controls. The demographics and clinical characteristics of the treatment groups were similar. Interestingly, the risk of hospitalization with heart failure was significantly higher in those receiving rofecoxib than in those receiving celecoxib (adjusted RR, 1.8 versus 1.0, respectively). In view of these findings and the known increased risk of acute renal failure when NSAIDs or coxibs are given to patients with heart failure, this class of drugs should be used with great caution in patients with established heart failure. Conversely, patients without a prior history of heart failure should be suspected of having drug-induced disease if symptoms or signs of heart failure develop during use of a coxib.

Hypertension

NSAIDs, selective and nonselective, can raise blood pressure. In fact, the effects of celecoxib and rofecoxib were evaluated in 810 elderly patients with

osteoarthritis who were taking antihypertensive drugs.[22] After 6 weeks, rofecoxib produced a mean elevation in systolic pressure of 2.3 mm Hg, whereas celecoxib was associated with no change. In a recent meta-analysis of 19 randomized trials in 45,461 patients using coxibs, there was a statistically significant increase in the incidence of hypertension among those patients using rofecoxib (RR 2.63; 95% CI,1.42-4.85).[23] The greatest weighted mean difference in blood pressure was seen with rofecoxib, with a 5.6 mm Hg increase in systolic blood pressure. It was less for celecoxib (2.6 mm Hg increase in systolic blood pressure).

Similar relationships were noted in a retrospective case-control study evaluating the frequency of new-onset hypertension in elderly NSAID users.[24] There was increased risk with rofecoxib as compared to celecoxib (odds ratio 1.6), a nonselective NSAID (odds ratio 1.4), or no NSAID (odds ratio 1.6).

Edema

Coxibs have been associated with the development of lower extremity edema at rates similar to those for nonselective NSAIDs. The incidence of edema ranged from approximately 1% to 10% of patients.[14,24] In a randomized controlled trial comparing rofecoxib with celecoxib, the incidence of edema was significantly higher with rofecoxib (9.5% versus 4.9%).[22]

Summary

The safety of coxibs is uncertain. Although concurrent therapy with low-dose aspirin might mitigate some of the adverse cardiac effects of these drugs, data to support this hypothesis are not available. This concern was addressed in the TARGET trial, but the number of events was too small to have confidence in the results.[20] Parecoxib and valdecoxib should not be used for analgesia or anti-inflammatory effects in patients following coronary artery bypass grafting because of a significantly increased risk of adverse cardiovascular events when they are used in this setting. In addition, the need for an anti-inflammatory effect, as opposed to a simple analgesic, should be assessed in any patient for whom prescription of a coxib is being considered. A patient who requires an anti-inflammatory agent for a well-established indication and who is at high risk for gastroduodenal ulcer and complications, may be treated with one of the available coxibs. Celecoxib is probably the preferred choice at this time because there are greater amounts of available data supporting a lack of deleterious effects on cardiovascular outcomes; the lowest effective dose should be used.

However, patients should be informed of the potential concern. These recommendations are similar to those of the American Heart Association for patients with known, or at high risk of, cardiovascular disease. Doses of 400 mg twice daily of celecoxib are associated with an increased risk of stroke, MI, cardiovascular death, and heart failure and are typically reserved for patients with familial adenomatous polyposis, since it has been shown to decrease both the incidence and size of these polyps. In addition, patients beginning long-term treatment with a coxib may develop hypertension or experience worsening of established high blood pressure. This effect tends to be primarily associated with the use of rofecoxib, which has been withdrawn from the market. Periodic monitoring of blood pressure in patients treated with coxibs is prudent and use in patients with poorly controlled hypertension is discouraged.

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Abstract of Interest

Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis.

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AIMS: To determine the comparative risk of myocardial infarction in patients taking cyclo-oxygenase-2 and other non-steroidal anti-inflammatory drugs (NSAIDs) in primary care between 2000 and 2004; to determine these risks in patients with and without pre-existing coronary heart disease and in those taking and not taking aspirin.

DESIGN: Nested case-control study.

SETTING: 367 general practices contributing to the UK QRESEARCH database and spread throughout every strategic health authority and health board in England, Wales, and Scotland.

SUBJECTS: 9218 cases with a first ever diagnosis of myocardial infarction during the four year study period; 86 349 controls matched for age, calendar year, sex, and practice.

OUTCOME MEASURES: Unadjusted and adjusted odds ratios with 95% confidence intervals for myocardial infarction associated with rofecoxib, celecoxib, naproxen, ibuprofen, diclofenac, and other selective and non-selective NSAIDS. Odds ratios were adjusted for smoking status, comorbidity, deprivation, and use of statins, aspirin, and antidepressants.

RESULTS: A significantly increased risk of myocardial infarction was associated with current use of rofecoxib (adjusted odds ratio 1.32, 95% confidence interval 1.09 to 1.61) compared with no use within the previous three years; with current use of diclofenac (1.55, 1.39 to 1.72); and with current use of ibuprofen (1.24, 1.11 to 1.39). Increased risks were associated with the other selective NSAIDs, with naproxen, and with non-selective NSAIDs; these risks were significant at < 0.05 rather than < 0.01 for current use but significant at < 0.01 in the tests for trend. No significant interactions occurred between any of the NSAIDs and either aspirin or coronary heart disease.

CONCLUSION: These results suggest an increased risk of myocardial infarction associated with current use of rofecoxib, diclofenac, and ibuprofen despite adjustment for many potential confounders. No evidence was found to support a reduction in risk of myocardial infarction associated with current use of naproxen. This is an observational study and may be subject to residual confounding that cannot be fully corrected for. However, enough concerns may exist to warrant a reconsideration of the cardiovascular safety of all NSAIDs.

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