New Drugs and Technologies

Selective Cyclooxygenase-2 Inhibitors Development in Cardiovascular Medicine

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At the end of September 2004, Merck & Co announced the voluntary withdrawal of rofecoxib (Vioxx) worldwide because of an increased risk of cardiovascular events. Since its approval in 1999, Vioxx, a selective cyclooxygenase-2 (COX-2) inhibitor, has been Merck & Co’s leading drug for control of acute pain and chronic pain associated with osteoarthritis, rheumatoid arthritis, and menstruation. Last year, worldwide sales of rofecoxib reached US $2.5 billion, and it is estimated that the drug was prescribed ~10 million times per month in the United States. Thus, given the number of patients involved and the serious nature of the side effects, the withdrawal raised serious concerns about the safety of other selective COX-2 inhibitors, collectively called coxibs, that are on the market and those currently under development. Celecoxib (Celebrex) and rofecoxib were the first 2 coxibs approved by the US Food and Drug Administration (FDA) and launched in 1999 by Pfizer and Merck & Co, respectively. Since then, a second generation of these drugs has emerged onto the market. Valdecoxib (Bextra) was approved by the FDA and launched in 2002. In that same year, the European regulatory authority approved 2 other coxibs: etoricoxib (Arcoxia) and parecoxib sodium (Dynastat), the prodrug of valdecoxib. Today, etoricoxib and a fifth coxib, lumiracoxib (Prexige), are under consideration for FDA approval. In view of the rapid development in this area, the main concern is whether the reported cardiovascular effects of rofecoxib are a class effect applicable to all coxibs that were initially designed to reduce the gastric toxicity of nonselective COX inhibitors. Although most of the data accumulated so far would suggest a class effect related to the general mode of action of all coxibs and the physiological role of COX-2, recent in vitro data would theoretically support the hypothesis that the cardiovascular side effects of some coxibs could also be linked to their specific pharmacokinetic properties.

Clinical Outcome Data

Rofecoxib Story

The data that resulted in the withdrawal of rofecoxib stemmed from a 3-year randomized, placebo-controlled, double-blind clinical trial enrolling 2600 patients called Adenomatous Polyp Prevention on Vioxx (APPROVe). The study evaluated the efficacy of the drug in preventing the recurrence of colorectal polyps among patients with a history of colorectal adenomas. It was prematurely halted after the investigators found that patients taking 25 mg/d rofecoxib had twice the risk of thromboembolic events compared with those receiving placebo (15 versus 7 per 1000 patients annually). The increased risk of serious thrombotic events, including heart attack and stroke, was statistically significant after 18 months. Interestingly, several years earlier, warning signs about the potential cardiovascular risks of rofecoxib were noted by the scientific community. Thus, in 2000, the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial revealed unexpected evidence of increased myocardial infarction and stroke. This study, a double-blind, randomized, prospective clinical trial, included 8076 patients with rheumatoid arthritis and compared the occurrence of gastrointestinal toxicity of rofecoxib (50 mg/d) and another nonsteroidal antiinflammatory drug (NSAID), naproxen (1000 mg/d). The trial, during which patients were allowed to use aspirin, revealed that rofecoxib and naproxen had a similar efficacy against rheumatoid arthritis. The rate of serious gastrointestinal events among those receiving rofecoxib was significantly less than in patients treated with naproxen (2.1 compared with 4.5 per 100 patient-years, respectively). However, comparison of both groups also revealed a significant 5-fold increase in the incidence of myocardial infarction in the rofecoxib group. At that time, the increased risks were attributed to the cardioprotection of naproxen rather than a more direct cardiotoxic effect of rofecoxib. Nevertheless, recent results from a cumulative meta-analysis revealed that the cardioprotective effect of naproxen was small and could not have explained the findings of the VIGOR trial. Just days before the publication of this report, the FDA posted on its own Web site a detailed study on the incidence of cardiovascular events in >1.39 million patients who used rofecoxib, celecoxib, or other traditional NSAIDs. The authors found that rofecoxib but not celecoxib increased the risk of heart attack and sudden cardiac death and showed that naproxen was not heart protective.

Notably, before the publication of this FDA report, conflicting data on the cardiovascular adverse events of rofe-
coxibs were released. Some reports showed no difference in cardiovascular risks between rofecoxib; NSAIDs such as diclofenac, ibuprofen, and nabumetone; and placebo.\(^6\) On the other hand, epidemiological studies confirmed the concern about the risk of serious cardiovascular events associated with rofecoxib.\(^7\)–\(^11\)

**Celecoxib Story**

Celecoxib was launched on the market in 1999 on the basis of the results of the Celecoxib Long-Term Arthritis Safety (CLASS) Study outcomes.\(^12\) That double-blind, randomized, controlled trial was conducted in 8059 patients with osteoarthritis or rheumatoid arthritis. The primary end point was upper gastrointestinal toxicity. Patients were treated with celecoxib (400 mg twice daily), ibuprofen (800 mg 3 times daily), or diclofenac (75 mg twice daily). Interestingly, the trial was not placebo controlled, and naproxen was not used as a comparative drug. Moreover, aspirin in daily doses up to 325 mg for cardioprotection was permitted in each group (used by 21% of the patients), but aspirin use was a reason for exclusion from the VIGOR trial. In the original report, celecoxib induced less bleeding than the other nonselective NSAIDs. In terms of cardiovascular events, results obtained from this study are divergent from the results of VIGOR. In the CLASS trial, there was no statistically significant difference among groups in the incidence of major cardiovascular events, although the celecoxib group had more myocardial infarctions. No differences in cardiovascular events were detected among groups of patients taking aspirin. However, it is still not known how this risk relates to arthritis patients chronically treated with parecoxib or valdecoxib. The first study used 40 mg parecoxib or valdecoxib for 14 days; the second study used 20 mg of the same drugs but for 10 days.\(^19\),\(^20\) In both cases, compared with placebo, an increased incidence of coronary and cerebrovascular events was observed. It is still not known how this risk relates to arthritis patients chronically treated with parecoxib or valdecoxib or to patients with low risk of cardiovascular disease.

**Mechanistic Explanations: Is There a Class Effect for the Coxibs?**

The data described so far raise some legitimate concerns about the mechanism(s) responsible for the cardiovascular toxicity of coxibs. Thus, is there a plausible mechanism that could explain the increased cardiovascular risks of rofecoxib? Is this risk associated with its selective COX-2 inhibition, and if so, is it applicable to other coxibs? The answers to these questions could lie in the current knowledge of the physiological role of COX-2 and the mode of action and specificity of coxibs.

The identification and characterization of the inducible form of COX, the COX-2, in inflammatory cells in the early 1990s led to the development of the coxibs; rofecoxib and celecoxib represent the first generation of coxibs.\(^21\) Such specific inhibitors were immediately considered a real breakthrough in antiinflammatory therapy. The rationale behind their development was based on the hypothesis that COX-2 expression is associated with the biosynthesis of prostanoids involved in pathological conditions such as inflammation or cancer progression, and in contrast, COX-1–derived prostanoids are involved in platelet aggregation, gastrointestinal mucosa homeostasis, and renal perfusion.\(^22\) Unfortunately,
since the launch of rofecoxib and celecoxib, it became obvious that this distinction is not so strict. Thus, COX-2 is not an exclusively proinflammatory inducible enzyme; its expression is also observed in tissues such as vascular endothelium, kidney, and brain under normal conditions, suggesting its involvement in physiological processes.23 Some recent studies also pointed out that COX-1 could be upregulated in particular cell types.24

In terms of cardiovascular physiology, COX-1 and thromboxane synthase are constitutively expressed within platelets. COX-1 is responsible for the oxygenation of arachidonic acid into prostaglandin endoperoxide H₂, which is subsequently metabolized by thromboxane synthase into thromboxane A₂ (TXA₂), a potent inducer of vasoconstriction and platelet aggregation25 (Figure 1). Besides, it was initially assumed that COX-1 was the only isoform expressed constitutively in endothelial cells, which led to prostacyclin synthesis via the prostacyclin synthase. Unfortunately, this hypothesis was later found to be incorrect. Studies performed in mice and humans revealed that COX-2 and not COX-1 was the predominant source of prostacyclin in vivo.26 It also appears that platelet-derived TXA₂ can act in a paracrine manner to upregulate endothelial COX-2 expression and prostacyclin synthesis27,28 (Figure 1). This is a key point because prostacyclin inhibits platelet aggregation, prevents vascular smooth muscle cell proliferation in vitro, and induces vascular smooth muscle relaxation. Thus, at low doses, aspirin preferentially inhibits COX-1 in platelets, resulting in a reduction in TxA₂ with little effect on COX-2–derived prostacyclin. This explains the antiplatelet effect of this drug and its beneficial use at low doses for secondary prevention in patients at high risk of cardiovascular diseases such as heart attack and stroke. Nonspecific NSAIDs block both COX isoforms and therefore have a balanced effect of reducing the prothrombotic actions of TXA₂ and the antithrombotic properties of prostacyclin.24,25

Both rofecoxib and celecoxib suppress the endogenous formation of prostacyclin in healthy volunteers without affecting TxA₂ generation in vivo,14 potentially creating an alteration of such a delicate vascular homeostasis. The shift of the thromboxane/prostacyclin balance is a strong theoretical basis for an association between coxib use and the occurrence of thrombotic phenomena.

Recent experimental studies further support the importance of the thromboxane/prostacyclin balance. Thus, it was demonstrated that injury-induced vascular proliferation and platelet activation are enhanced in mice that are genetically deficient in the prostacyclin receptor (IP) but depressed in mice deficient in the TxA₂ receptor (TP) or treated with a TP antagonist.29 Moreover, pharmacological inhibition of COX-1–derived TxA₂ formation and genetic deletion of TP retard atherogenesis,30,31 whereas the absence of IP accelerates atherosclerotic plaque growth.32 Although the clinical relevance of these experimental results remained uncertain, from a biochemical point of view, the suppression of prostacyclin formation might theoretically elevate blood pressure, increase prothrombotic risk associated with the rupture of an atherosclerotic plaque, and facilitate myocardial infarction.

If the shift of the thromboxane/prostacyclin balance induced by coxibs is at the basis of the cardiovascular toxicity of rofecoxib, a class effect would be expected. If so, what kind of information can the COX-2/COX-1 inhibitory ratios,
specific for each coxib, give us to predict this adverse effect? Indeed, not all coxibs have the same pharmacological profile, but they differ in terms of COX-2/COX-1 selectivity ratios. Riendeau and collaborators\textsuperscript{33} compared the potency and selectivity of different COX inhibitors. Selectivity ratios (COX-1/COX-2 IC\textsubscript{50}) for the inhibition of COX-2 of 106, 35, 30, 7.6, and 7.3 were obtained for etoricoxib, rofecoxib, valdecoxib (and parecoxib), celecoxib, and nimesulide, respectively. In contrast, lower ratios were observed for diclofenac, etodolac, and meloxicam (2- to 3-fold). Lumiracoxib, which was not evaluated in this study, has recently emerged as one of the most selective COX-2 inhibitors to date in another in vitro study.\textsuperscript{34} From that study, it appears that there is a substantial overlap in COX-2 selectivity between celecoxib and nimesulide, a more traditional NSAID with “preferential” COX-2 inhibitory activity. Although these in vitro data would suggest that celecoxib can also partially inhibit COX-1, no effects on TxA\textsubscript{2} production or antiplatelet activity were reported in healthy volunteers given this drug at supratherapeutic doses (600 to 800 mg), whereas suppression of urinary excretion of prostacyclin was observed.\textsuperscript{35,36} The same effect is observed with all coxibs at therapeutic dosages. In contrast, naproxen or ibuprofen produced a statistically significant reduction in platelet aggregation and serum TxB\textsubscript{2} levels (TxA\textsubscript{2} metabolite) and increased bleeding time. Consequently, it clearly appears that at therapeutic dosage all coxibs, even celecoxib, the weakest coxib in vitro, are equal in depressing prostacyclin biosynthesis while having no significant impact on thromboxane production.\textsuperscript{34} In such a condition, an exaggeration of the vascular effects of TxA\textsubscript{2} would be anticipated, which could predispose to serious vascular events.\textsuperscript{20} From the available data, there currently is enough evidence for a cardiovascular hazard for at least 3 structurally distinct coxibs: rofecoxib, celecoxib, and parecoxib. This fact would strongly support the hypothesis that the adverse cardiovascular events of these drugs are related to a class effect.

**Mechanistic Explanations: Is There a Single Molecule Effect for Different Coxibs?**

What is the evidence supporting a single molecule effect that could explain the cardiovascular events observed with different coxibs? In other words, is there a potential non-COX-2-dependent mechanism for these drugs that may provide mechanistic insights into the reported cardiovascular risks? Differences in chemical structures of coxibs could explain differences in their pharmacodynamic and/or pharmacological properties. From a chemical point of view, these compounds belong to 2 distinct classes: (1) the diaryl-substituted cycles class for celecoxib, rofecoxib, valdecoxib (and parecoxib sodium), and etoricoxib (2) the phenylacetic acid class for lumiracoxib (similar to diclofenac) (Figure 2). Within the first class, some interesting small chemical variations among coxibs have recently been proved responsible for different pharmacological properties. Thus, although rofecoxib and etoricoxib contain a methylsulfone moiety, celecoxib and valdecoxib possess a sulfonamide group common to many carbonic anhydrase inhibitors. A recent study demonstrated a high affinity of the sulfonamide coxibs celecoxib and valdecoxib for carbonic anhydrase I, II, IV, and IX, whereas the methylsulfone rofecoxib had no effect.\textsuperscript{37} This was confirmed in vivo; oral administration of celecoxib and valdecoxib to rabbits with glaucoma, a condition in which carbonic anhydrase has been involved, reduced the intraocular pressure, whereas rofecoxib had no effect.\textsuperscript{37}

Moreover, it has been shown that in vitro the methylsulfone coxibs increase the susceptibility of human LDL to oxidative modification through a nonenzymatic process, whereas other coxibs (celecoxib, valdecoxib, meloxicam) and nonselective COX inhibitors (ibuprofen, naproxen, diclofenac) had no effect.\textsuperscript{38} Besides, the authors demonstrated that the pro-oxidant activity of rofecoxib was dose dependent and that both methylsulfone drugs rofecoxib and etoricoxib caused a marked increase in nonenzymatic generation of isoprostanes, specific markers of lipid peroxidation.\textsuperscript{38}

Differences in the chemical structures of the coxibs can also be responsible for some of their different pharmacokinetic parameters.\textsuperscript{39} For instance, methylsulphonates (rofecoxib and etoricoxib) and sulfonamides (celecoxib and valdecoxib) are very different in some of these properties. Thus, in contrast to rofecoxib and etoricoxib, celecoxib and valdecoxib have a poor oral bioavailability and a short half-life. Moreover, the primary metabolism of rofecoxib is unique. Although the metabolism of all coxibs is oxidative, involving cytochrome P450 enzymes, rofecoxib is first metabolized by a cytoplasmic reductase.\textsuperscript{39}

Chemically, lumiracoxib is a very different member of the coxib family. It is a typical “phenylacetic acid” derivative such as diclofenac and indomethacin. For this reason, unlike other coxibs that distribute almost equally throughout the body, with the exception of celecoxib sequestered in body fat because of its extremely high lipophilicity, lumiracoxib could reach a high concentration in the synovial fluid and inflamed tissue.

In summary, it is clear that coxibs have different pharmacodynamic and pharmacokinetics properties. However, whether these specific characteristics of the coxibs are accountable for their efficacy and/or cardiovascular toxicity remains to be fully elucidated in future comparative studies, and no conclusions can be drawn at this moment.

**Conclusions: Implications for Future Therapy**

The outcomes of the VIGOR trial initially raised questions about the cardiovascular safety of rofecoxib and subsequently all coxibs. The original interpretation of the study was that the increased cardiovascular risk of rofecoxib was secondary to the cardioprotection of naproxen, but the gastrointestinal safety of rofecoxib and this class of agents in general prevailed over the potential cardiovascular risks. Later, conflicting conclusions from different studies emerged on the cardiovascular side effects of the coxibs. Thus, although VIGOR revealed an increased risk of thrombotic events with rofecoxib, CLASS and TARGET failed to demonstrate a significant difference in cardiovascular side effects between NSAIDs and coxibs. Unfortunately, the original clinical designs of these trials were not powered to study the cardiovascular toxicity of the coxibs as a primary end point. With the recent results of the APPROVe study, we now have
clear evidence of an increased cardiovascular risk with rofecoxib. Similar data are also accumulating for celecoxib and parecoxib. A mechanistic explanation supported by emerging consistent evidence has been proposed that would extend the risks to all coxibs. Indeed, at therapeutic dosage, all coxibs reduce prostacyclin production, whereas the COX-1–dependent TxA2 biosynthesis remains unchanged. This fact would result in an alteration of the delicate homeostasis between these 2 systems with a natural predisposition to thrombotic vascular events.40

Differences in chemical structures resulting in different pharmacological and pharmacokinetic properties among coxibs could also theoretically support a specific molecule effect rather than a cardiotoxic class effect of some coxibs. However, there have not been any direct comparative trials of one coxib versus another, which is the only way to test this hypothesis.

Because we are facing a worldwide public health issue and until more clear-cut data become available on this emerging class of drugs, providing useful recommendation about all the coxibs on the market is timely. It has been estimated that a total of 88 000 to 139 000 Americans had heart attacks and strokes as a result of taking rofecoxib. Indeed, given the findings of the APPROVe trial, in which >16 myocardial infarctions per 1000 patients were observed, there may be tens of thousands of patients who have had major events attributable to this drug in the United States alone. Parenthetically, rofecoxib has been available in >80 countries. Despite the evidence of cardiovascular toxicity of some coxibs, we remain convinced that selective COX-2 inhibitors, with certain restrictions, remain useful drug choices for treatment of inflammatory conditions.

Coxibs should not be prescribed in patients with concurrent cardiovascular diseases or at high cardiovascular risk. Prescription of these drugs should always be associated with a careful cardiovascular evaluation and simultaneous monitoring of the patient, particularly when a chronic use is indicated. The use of coxibs without the concomitant use of low-dose aspirin should be avoided. This could limit the prostacyclin/thromboxane A2 imbalance. The most suitable indication for prescription of coxibs would be for patients at low cardiovascular risk who have suffered from serious gastrointestinal events especially while taking traditional NSAIDs. The use of coxibs for acute indications should be
avoided when a simple analgesic such as acetaminophen would suffice.

Beyond these recommendations on the use of coxibs, lessons from the withdrawal of rofecoxib and from the available data on the other components of this family must be learned. On the basis of actual knowledge of the cardiovascular risk of coxibs, which is pointing more and more toward a class effect mechanism, it is appropriate that at this time all COX-2 inhibitors display a clear warning label about it. Large, long-term, randomized, controlled clinical trials with coxibs that are specifically powered to detect the cardiovasculat risks and benefits of these drugs and include patients suffering from both cardiovascular diseases and arthritis remain an urgent need.

In a recent hearing, external advisers to the US FDA recommended, by a narrow margin, that rofecoxib, celecoxib, and valdecoxib remain available to patients, despite the fact that they increase cardiovascular risk. It is anticipated that the agency will act on these recommendations in the near future.41

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