Journal of
Medicinal
Chemistry

Volume 48, Number 7 April 7, 2005

Miniperspective

Adverse Cardiovascular Effects of the Coxibs

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Received November 22, 2004

The identification and characterization of an inducible form of cyclooxygenase (COX-2) in inflammatory cells in the early 1990s were the start of a race to the development of more selective nonsteroidal antiinflammatory drugs (NSAIDs), with reduced side effects (essentially gastro-intestinal toxicity) compared to classical NSAIDs. The development and the use of these specific inhibitors, collectively called coxibs, were immediately considered as a real breakthrough in antiinflammatory therapy. Thus, the development of the "coxibs" was based on the hypothesis that this isoform mediates inflammation in several organs via the biosynthesis of prostaglandins E_2 and I_2 (or prostacyclin) and that COX-1 was the source of the same prostaglandins in the gastric epithelium, where they would act as cytoprotective mediators (Figure 1.). Celecoxib (Celebrex) and rofecoxib (Vioxx) were the first two coxibs approved by the FDA and launched in 1999 by Pfizer and Merck & Co., respectively. A second generation of coxibs emerged later onto the market. Valdecoxib (Bextra, Pfizer-Pharmacia) was approved by the FDA and launched in 2002. Two other coxibs approved by the European regulatory authority were marketed in the same year: etoricoxib (Arcoxia, Merck & Co.) and parecoxib sodium (Dynastat, Pfizer-Pharmacia), the prodrug of valdecoxib. Today, etoricoxib and a fifth coxib, lumiracoxib (Prexige) developed by the Novartis company, are under consideration for FDA approval.

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At the end of September 2004, Merck & Co announced the voluntary withdrawal of rofecoxib worldwide from the market after a 3-year randomized, placebo-controlled, double-blind clinical trial enrolling 2600 patients called APPROVe (adenomatous polyp prevention on Vioxx) was halted later that month. The study, which was conducted to evaluate the efficacy of rofecoxib in preventing the recurrence of colorectal polyps among patients with a history of colorectal adenomas, revealed a 3.9-fold increase in serious thromboembolic adverse events beginning after 18 months in patients receiving 25 mg of rofecoxib per day compared with patients receiving placebo. Surprisingly, the potential cardiovascular risks of rofecoxib were already reported because it was launched onto the market. Thus, shortly after the drug was approved by the FDA, the results of a clinical study were published, that is, results from the Vioxx gastrointestinal outcomes research (VIGOR) trial.[1] In the VIGOR trial, rofecoxib and naproxen revealed 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 per 100 patient-years compared to 4.5, respectively). However, the comparison of both groups also revealed a significant 5-fold increase in the incidence of myocardial infarction in the rofecoxib group. This observation was first attributed to cardioprotection of naproxen rather than a 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.[2] The authors of this analysis showed that the unacceptable cardiovascular

10.1021/jm0402059 CCC: $30.25
Published on Web 03/09/2005

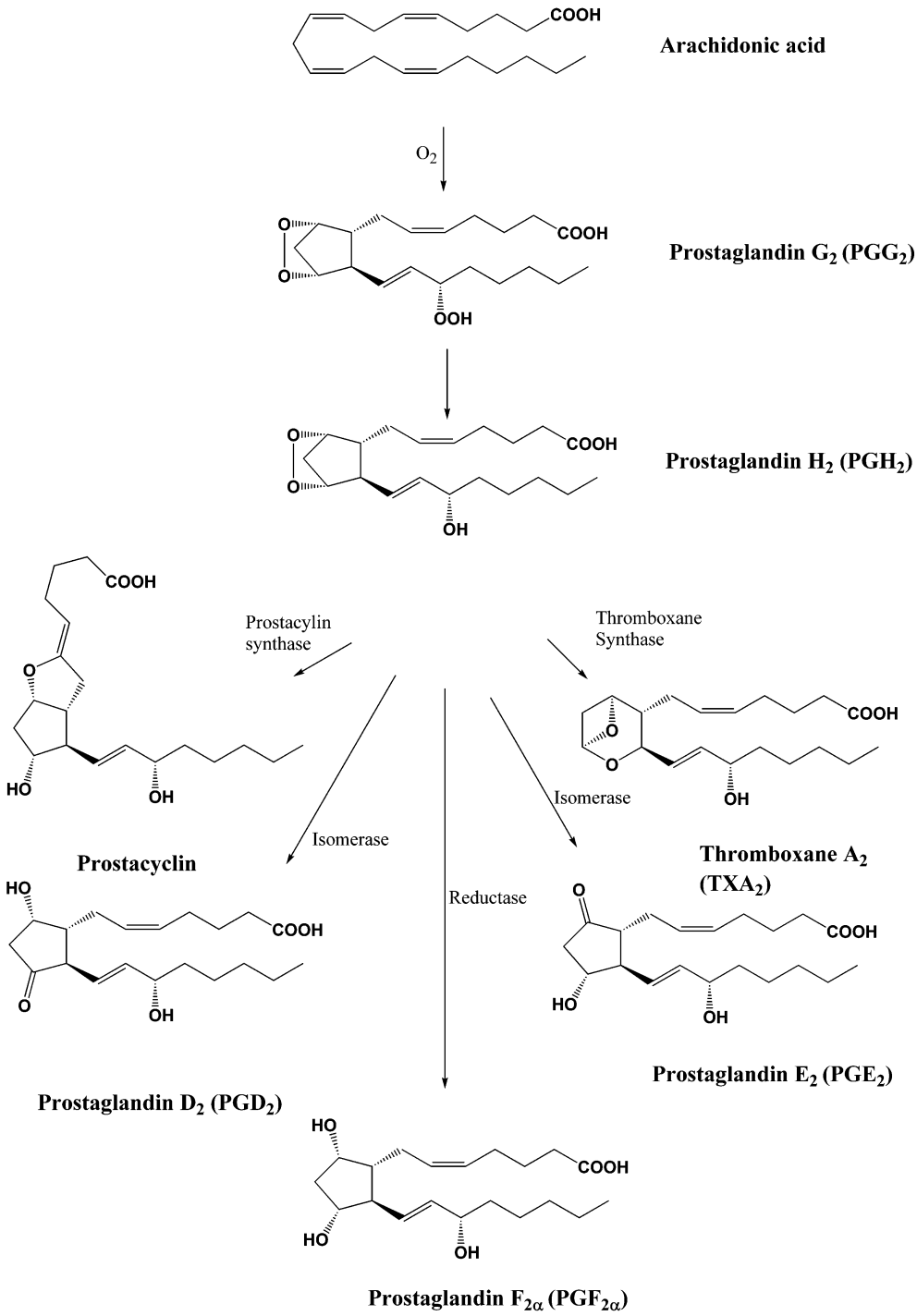

Figure 1. Cyclooxygenase pathway and chemical structures of arachidonic acid, prostaglandins endoperoxides (PGG_2 and PGH_2), prostaglandins (PGE_2, PGD_2, $PGF_{2\alpha}$), prostacyclin (PGI_2), and thromboxane A_2 (TXA_2).

risks of vioxx were evident as early as 2000, a full 4 years before the drug was ultimately withdrawn. Just days before publication of this *Lancet* report, the FDA had posted a detailed internal study (Memorandum from David J. Graham) about rofecoxib side effects on its own Web site. In this study over 1.39 million patients who used rofecoxib, celecoxib, or other traditional NSAIDs were analyzed. The authors found that, compared to the other NSAIDs, rofecoxib increased the risk of heart attack and sudden cardiac death. The second important finding from this study also revealed that naproxen was not protective against serious coronary heart disease.

Rofecoxib has been the 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 $2.5 billion (U.S. dollars), and overall sales of "coxibs" accounted for a global estimated sale of more than $10 billion.[3] The recent withdrawal of rofecoxib has raised serious concerns about the safety of the other COX-2 inhibitors being actively marketed today and "me too" COX-2 inhibitors currently under development by pharmaceutical companies. In other words, the main concern is whether the cardiovascular effects of rofecoxib are a class effect applicable to all COX-2 inhibitors and, if so,

what the limits are in terms of selectivity to have or expect this adverse effect. This concern is of particular interest for medicinal chemists and pharmacologists who are developing novel COX-2 specific inhibitors. Indeed, while the answer could lie in the specificity and the general mode of action of COX-2 inhibitors, differences in chemical structures could also explain some additive effects of certain coxibs.

On the Mode of Action of COX-2 Inhibitors

Cyclooxygenases catalyze the conversion of free arachidonic acid into endoperoxide PGH_2 as the first step in the biosynthesis of prostanoids, potent lipidic mediators involved in both physiological and pathological processes. Since the early 1990s, the existence of two distinct COX isoforms (COX-1 and COX-2) is well established.[4] Recently, a third isoform, COX-3, whose functions are still unknown, has also been described.[5]

Initially, in contrast with COX-1 whose expression is ubiquitous, COX-2 seemed mainly expressed during pathological processes. High levels of COX-1 are found in platelets, stomach, and kidney. Furthermore, prostanoids derived from the COX-1 catalytic activity are involved in platelet aggregation, gastrointestinal homeostasis, and renal perfusion. On the other hand, COX-2 expression is associated with the biosynthesis of large amounts of prostanoids observed during pathological conditions such as inflammation or cancer progression. These initial observations represented the rationale basis for the enormous effort that pharmaceutical companies undertook to develop specific COX-2 inhibitors, of which rofecoxib and celecoxib constituted the first generation. Unfortunately, since the launch of these drugs, it became obvious that the distinction between COX-1 and COX-2 is not so strict and that COX-2 is not an exclusively proinflammatory inducible enzyme. Thus, COX-2 expression is also observed in some tissues such as vascular endothelium, kidney, or brain under normal conditions, suggesting the involvement of COX-2 in the regulation of physiological processes.[6,7] Consequently, the dichotomy between "good guy, bad guy" roles of COX-2 and COX-1, at least in cardiovascular and renal physiology, was completely reconsidered. Moreover, some recent studies also pointed out that COX-1 could also be up-regulated in particular cell types.[8]

In terms of cardiovascular function, the COX-1 is constitutive within platelets and is associated with the production of thromboxane A_2 (TXA_2), a potent inducer of vasoconstriction and platelet aggregation.[9] On the other hand, initially it was assumed that prostacyclin was derived mainly from COX-1, the only cyclooxygenase isoform expressed constitutively in endothelial cells. Unfortunately, this hypothesis was later found to be incorrect because studies performed in mice and humans revealed that COX-2, and not COX-1, was the predominant source of prostacyclin in vivo.[10,11] This is of particular importance because prostacyclin is responsible for inhibition of platelet aggregation and induction of vascular smooth muscle vasodilation.[6] Thus, at low doses aspirin, a nonselective NSAID, preferentially inhibits COX-1 in platelets, reducing thromboxane A_2 with little effect on COX-2 derived prostacyclin. This explains the beneficial use of low-dose aspirin in patients at high risk of cardiovascular conditions to protect against heart attack and stroke.[12] Nonspecific NSAIDs block both COX isoforms and therefore have balanced effects of reducing the prothrombotic effects of TXA_2 and the antithrombotic prostacyclin.

In 1999, the year of the approval of rofecoxib and celecoxib, it was reported that both drugs suppressed the formation of prostacyclin in healthy volunteers without affecting thromboxane A_2 generation.[7] The lack of inhibition of thromboxane A_2 synthesis with coxibs was also correlated with the absence of antiaggregatory properties of COX-2 inhibitors demonstrated by ex vivo aggregometry studies performed in human. Accordingly, this shift of the thromboxane/prostacyclin ratio toward thromboxane by selective COX-2 inhibition is a strong theoretical basis for an association between coxib use and the occurrence of thrombotic phenomena. Later, we and others reported that while selective pharmacological inhibition of COX-1 had a protective effect during atherogenesis, inhibition of COX-2 did not.[13] Furthermore, the 2002 publication of Cheng et al. demonstrated that injury-induced vascular proliferation and platelet activation are enhanced in mice that are genetically deficient in the prostacyclin receptor but depressed in the thromboxane A_2 receptor (TP) deficient mice or that are treated with a TP antagonist.[14] Consequently, from a biochemical point of view, for highly selective COX-2 inhibitors, an effect that is opposite to aspirin is anticipated. This is the paradox of the coxibs that were first termed by the media as the new "super-aspirin".

The same type of discussion underlies the potential renal toxicity of coxibs. Indeed, both COX isoforms are present constitutively in the human kidney. Thus, prostaglandins produced by COX-2 have diuretic and natriuretic effects while COX-1 derived prostaglandins induce renal vasodilation and increase renal perfusion.[15,16] However, the potential renal toxicity of specific COX-2 inhibitors (sodium retention, edema, and the closely related risk for arterial hypertension) is still under debate.

On the Selectivity of COX-2 Inhibitors

Not all the COX-2 inhibitors have the same pharmacological profile and differ in terms of COX-2/COX-1 selectivity ratios. It is important to note that the selectivity ratio estimated by different research groups, even in the same test, can be quite different. Therefore, it seems essential to consider this kind of data only when other reference drugs are also evaluated in the same test, which permits us to rank at the same time classical NSAIDs and coxibs in term of selectivity. By using the human whole blood assay, which is generally accepted to be the gold standard for in vitro testing of COX inhibitors,[17] Riendeau recently compared the potency and selectivity of different COX inhibitors.[18] In particular, this group used the ratio of (COX-1 IC_{50})/(COX-2 IC_{50}) to calculate selective inhibitory potencies toward COX-2. Ratios of 106, 35, 30, 7.6, and 7.3 were obtained for etoricoxib, rofecoxib, valdecoxib (and parecoxib), celecoxib, and nimesulide, respectively. By contrast, lower selectivity ratios were observed for diclofenac, etodolac, and meloxicam (2- to 3-fold). Lumiracoxib, which was not evaluated in this study, has recently

emerged as the most selective COX-2 inhibitor to date in another study. Thus, lumiracoxib manifests a 700-fold COX-2 selectivity in the human whole blood assay, where rofecoxib and celecoxib had 100 and 50, respectively.[19]

It appears that there is a substantial overlap in COX-2 selectivity between celecoxib and some traditional NSAIDs such as nimesulide that should be considered as "preferential" COX-2 inhibitors. However, if celecoxib inhibits COX-2 to a lesser extent and can partially inhibit COX-1 at daily doses of 400 mg twice daily, which would reduce its potential cardiovascular activity, no effects on thromboxane A_2 production or antiplatelet effect in healthy volunteers were reported with this drug at supratherapeutic doses (600−800 mg) while a suppression of urinary excretion of the prostacyclin was observed.[7] In contrast, naproxen or ibuprofen produced statistically significant reductions in platelet aggregation and serum thromboxane B_2 levels (thromboxane A_2 metabolite) and increased bleeding time. In terms of cardiovascular events, results obtained from a CLASS (celecoxib long-term arthritis safety study) study are divergent from the results of the VIGOR study. In the CLASS trial, celecoxib was compared with ibuprofen or diclofenac.[20] Patients also taking aspirin were permitted to participate, while this was a reason for exclusion from the VIGOR trial. In the CLASS trial, in which 21% of patients took aspirin, there was no significant difference between the treatment groups in the incidence of major cardiovascular events. Thus, patients from the CLASS trial did not show an increased risk of thrombotic events. Moreover, other clinical studies did not revealed an increase of adverse cardiovascular events with celecoxib. However, on December 16, 2004, Pfizer received new information related to the cardiovascular safety of celecoxib. The company warned that one colon cancer study had shown that celecoxib might increase the chances of heart attack and stroke in some patients. The findings come from a National Cancer Institute (NCI) 5-year adenoma prevention with celecoxib (APC) trial enrolling 3600 patients. The NCI halted the study, designed to see whether celecoxib could prevent colon cancer in people who previously had colon polyps removed. Those who took 400 mg of celecoxib a day had 2.5 times as many heart deaths, heart attacks, and strokes as those who did not take the drug. Those who took 800 mg of celecoxib a day had 3.4 times more of these cardiovascular events. Surprisingly, no increased risk of heart problems were found in a second similar long-term cancer study called prevention of spontaneous adenomatopus polyps (PreSAP) comparing the regimen of 400 mg daily of celecoxib with placebo. Because of these unexpected results, the company is taking "immediate steps to fully understand the results and rapidly communicate new information to regulators, physicians, and patients around the world". As a consequence, the FDA advised doctors to consider "alternative therapy" to celebrex, and Pfizer has agreed to limit advertising of this coxib. Moreover, celecoxib sustained another blow in early February 2005 when Pfizer acknowledged that a 1999 clinical trial found that elderly patients taking the drug were far more likely to suffer heart problems than patients taking a placebo. The study, which was intended to examine whether celebrex could treat Alzheimer's disease, found that the number of patients taking celecoxib (400 mg daily) suffering heart attacks was almost 4 times that of those taking a placebo (22 out of 285 patients taking Celebrex suffered heart attacks, strokes, and other heart problems; only 3 of 140 patients taking a placebo had similar problems).

It is pointed out that these studies were initially not powered to detect rates of cardiovascular events between groups. Unfortunately, this is also the case with the recently published TARGET trial (therapeutic arthritis research and gastrointestinal event trial), the largest COX-2 clinical study to date (involving more than 18 000 patients for a year). TARGET compared lumiracoxib, the most selective COX-2 inhibitor, with naproxen or ibuprofen and also failed to demonstrate a statistically significant difference in cardiovascular side effects between groups even though it was evident that more people taking lumiracoxib had a myocardial infarction.

An interesting question is whether valdecoxib, with a selectivity similar to that of rofecoxib, is characterized by a similar risk for cardiovascular events. Unfortunately, no large-scale study of the gastrointestinal effects of valdecoxib has been reported yet. However, in a study of patients at high cardiovascular risk (treatment of postoperative pain in patients undergoing coronary artery bypass grafing), parecoxib, the prodrug of valdecoxib, was associated with a cluster of cardiovascular events. Consequently, the drug was not approved by the FDA. On the other hand, in patients at low cardiovascular risk suffering from rheumatoid arthritis or osteoarthritis, no increased cardiovascular side effects were reported in those taking valdecoxib for up to a year (Pfizer source).

Finally, Merck reported that etoricoxib showed no significant difference in the number of serious side effects in osteoarthritis patients compared with those treated with diclofenac.

On the Chemical Differences of COX-2 Inhibitors

The concept of COX-2 selective inhibition is based on the differences of amino acids sequence existing between COX-1 and COX-2. The differences in the amino acid sequence between COX isoforms are responsible for the differences in the enzyme structures and especially in the access to the COX catalytic site. Schematically, in comparison with the COX-1 isoform, the access to the COX-2 catalytic site is larger because of the presence of a secondary pocket side. This major structural difference led medicinal chemists to synthesize compounds interacting with the cyclooxygenase active site and possessing a "critical" size permitting a specific interaction with the COX-2 active site without inhibiting the COX-1 catalytic activity. Chemically, these compounds belong to distinct classes: the diaryl-substituted cycles class for celecoxib, rofecoxib, valdecoxib (and parecoxib sodium), and etoricoxib; the phenylacetic acid class for lumiracoxib (Figure 2).

Differences in the chemical structures of COX-2 inhibitors could explain the differences in their pharmacodynamic and/or pharmacological responses. Thus, within the diaryl-substituted cycles class, while rofe-

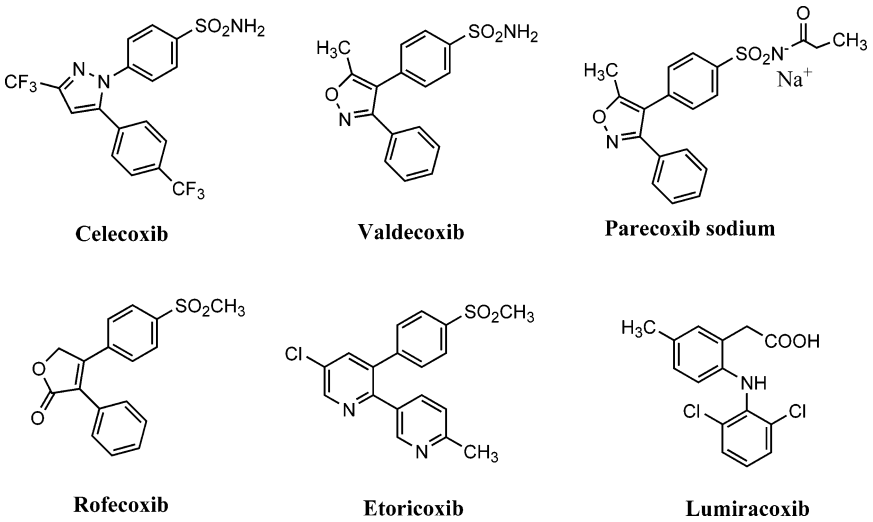

Figure 2. Chemical structures of selective COX-2 inhibitors (coxibs).

coxib and etoricoxib contain a methylsulfone moiety, celecoxib and valdecoxib possess an unsubstituted arylsulfonamide group. The latter group being common to many carbonic anhydrase inhibitors, Weber et al. evaluated the effects of celecoxib, rofecoxib, and valdecoxib on different human carbonic anhydrase isoenzymes.[21,22] The authors demonstrated an unexpected nanomolar affinity of the arylsulfonamide COX-2 inhibitors celecoxib and valdecoxib for carbonic anhydrases I, II, IV, and IX, whereas the methylsulfone rofecoxib had no effect. This was confirmed in vivo because oral administration of celecoxib and valdecoxib to glaucomatous rabbits resulted in a reduction of intraocular pressure while rofecoxib had no effect. Cross-reactivity of celecoxib to COX-2 and human CA II has been demonstrated by enzyme kinetics and crystal structure analysis. A comparison of the binding cavities of both enzymes indicates some relationship of the exposed recognition properties. Elimination of the essential arylsulfonamide group as in rofecoxib leads to a loss of the cross-reactivity with CAs. The presence of a pharmacological effect in the absence of COX-2 suggests that the response to celecoxib is derived independently of prostanoid metabolism at least in some cases. A number of cancer cell lines are known to up-regulate expression of CA isoforms, and mainly CA IX and perhaps a celecoxib-mediated inhibition of CA are in part responsible for this type of pharmacological response. The cross-reactivity of celecoxib with CA II and COX-2 can be explained by structural similarities across the subsites of the binding pockets in both enzymes. This inhibition of type II carbonic anhydrase could also be responsible for a diuretic effect that could counteract the renal hypertension induced by a COX-2 inhibition. Moreover, interestingly, a recent study found that celecoxib, but not rofecoxib, inhibited growth of hematopoietic and epithelial cell lines that did not express COX-2. The celecoxib mediated type IX carbonic anhydrase inhibition could also be in part responsible for this difference because a number of cell lines are known to up-regulate expression of this isozyme.

Sulfone COX-2 inhibitors have also been shown to increase in vitro the susceptibility of human low-density lipoprotein (LDL) to oxidative modification through a nonenzymatic process, while other coxibs (celecoxib, valdecoxib, meloxicam) and nonselective COX inhibitors (ibuprofen, naproxen, diclofenac) had no effect.[23] 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. Other properties have been selectively attributed to celecoxib. Thus, celecoxib exhibits a weak 3-phosphoinositide-dependent kinase-1 (PDK-1) inhibiting activity. Structure-based optimization of celecoxib led us to develop PDK-1 inhibitors with greater potency in enzyme inhibition and growth inhibition. These analogues are of translational relevance for cancer prevention and therapy.[24] Finally, celecoxib can induce apoptosis in various cancer cell lines through a mechanism that is independent of its cyclooxygenase-2 inhibitory activity, maybe through the expression of death receptors.[25]

Chemically, lumiracoxib is different from other coxibs. It is a typical "phenylacetic acid" derivative such as diclofenac and indomethacin. This is of great importance from a pharmacokinetics point of view. Indeed, unlike other coxibs that are distributed almost equally throughout the body, with the exception of celecoxib sequestered in body fat because of its extremely high lipophilicity, lumiracoxib reaches a high concentration in the synovial fluid and inflamed tissue. Consequently, lumiracoxib has the profile of an ideal drug because it combines the tissue-specific distribution of acidic NSAIDs with COX-2 selectivity.[26]

Conclusions

In conclusion, the recent withdrawal of rofecoxib raised the question of the cardiovascular safety of the entire class of COX-2 inhibitors. We provided evidence that the differences in COX-1/COX-2 selectivity between coxibs are of minor clinical importance. Indeed, at therapeutic dosage, even celecoxib, the substance displaying the lowest degree of selectivity, inhibits COX-2 but not platelet COX-1 in humans. Nonetheless, the consequence of this selective COX-2 inhibition in vivo is the significant reduction of prostacyclin production, while the COX-1 dependent thromboxane A_2 biosynthesis by platelets remains unchanged. This theoretical mechanistic hypothesis would be in favor of an associa-

tion between all coxibs and the occurrence of cardiovascular side effects. However, clinical and chemical differences among COX-2 inhibitors have been reported. Thus, the available data from different clinical trials are divergent in terms of cardiovascular safety. While APPROVe and VIGOR revealed an increased risk of thrombotic events with rofecoxib, CLASS and TARGET failed to demonstrate significant differences in cardiovascular side effects between nonselective and selective COX-2 inhibitors. Unfortunately, the original clinical designs of these trials were not powered to study the cardiovascular toxicity of COX-2 inhibitors as the primary end point. The increase of cardiovascular risks recently revealed from two studies (the interim analysis of the clinical trial adenoma prevention with celecoxib and a 1999 clinical trial in elderly patients suffering from Alzheimer's disease) casts a shadow over all COX-2 inhibitors. Consequently, a large double-blind study should be conducted to see whether each COX-2 inhibitor increases the risk of heart attack in osteoarthritis patients. From a chemical point of view, significant differences exist between coxibs even within the same subclass. This could also explain some differences in pharmacodynamic and pharmacokinetic parameters between these drugs.

The discovery of COX-2 initiated a race to the development of the most selective inhibitors. The approval of rofecoxib and celecoxib urged medicinal chemists to develop "me too" drugs with even higher selectivity. It is evident now that it is not obvious that a higher degree of selectivity confers any advantages. On the contrary, the design of a COX-2 "preferential" inhibitor keeping a slight effect on COX-1 at therapeutic dosage could theoretically limit the imbalance prostacyclin/thromboxane A_2. This situation is reproduced in patients taking both aspirin and a coxib. The question of the efficacy and the limitations of gastrointestinal side effects with these preferential inhibitors should be further evaluated. Another strategy in the design of COX-2 inhibitors would be to reduce the risk of increased cardiovascular side effects. Thus, the concept of combined COX-2 inhibitors/thromboxane receptor antagonists is seducing. Indeed, such compounds could block thromboxane and other thromboxane receptor agonists such as non-cyclooxygenase-dependent isoprostane from activating platelet aggregation. The antiinflammatory activity would be maintained by cyclooxygenase-2 inhibition.

Finally, from a clinical point of view, selective COX-2 inhibitors remain a rational choice for patients at high risk of serious gastrointestinal complications, especially while taking traditional NSAIDs. However, patients suffering from cardiovascular diseases or at high risk for them should not take COX-2 inhibitors.

Biographies

Jean-Michel Dogné was born in Belgium in 1973. He received his Pharm.D. degree from the University of Liège in 1996 and his Ph.D. degree in Pharmaceutical Sciences from the same University in 2000. After postdoctoral research in the Department of Bioorganic and Medicinal Chemistry at the University of Florence under the supervision of Dr. Claudiu Supuran, he was appointed a senior researcher in the Laboratory of Medicinal Chemistry of the University of Liège. His research interests are mainly in heterocyclic chemistry. He has made major scientific contributions in the discovery and development of modulators of the cyclooxygenase pathway of thromboxane and cyclooxygenase inhibitors. He is currently focusing his researches on the pharmacological application of thromboxane modulators in the cardiovascular field.

Claudiu T. Supuran received his B.Sc. in Chemistry from the Polytechnic University of Bucharest, Roumania (1987), and his Ph.D. in Chemistry at the same university in 1991. In 1990 he became Assistant Professor of Chemistry at the University of Bucharest. After a leave at the University of Florida in Gainesville, he returned to Bucharest where he became Associate Professor in the Department of Organic Chemistry. In 1995 he moved to the University of Florence, Italy, where he is currently a Research Fellow and Contract Professor of Chemistry. His major research interests in medicinal chemistry include design of enzyme inhibitors and activators, chemistry of sulfonamides, biologically active organoelement derivatives, X-ray crystallography of metalloenzymes, metal complexes with biologically active ligands, carbonic anhydrases, serine proteases, matrix metalloproteinases, and bacterial proteases.

Domenico Pratico received his M.D. from the University of Rome "La Sapienza". After finishing a residency program in internal medicine at the same university, he went to the University College, Dublin, Ireland, where he did a postdoctoral fellowship in clinical pharmacology at the Centre for Cardiovascular Science. In 1994 he moved to the University of Pennsylvania, Philadelphia, where he is now an Associate Professor in the Division of Experimental Therapeutics of the Department of Pharmacology. He has a long-standing interest in the analytical biochemistry and pharmacology of eicosanoids and isoeicosanoids.

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JM0402059