Are All COX-2 Inhibitors Created Equal?

Ingrid J. Chang, Raymond C. Harris

Prostaglandins (PGs) are biologically active lipids derived from the cyclooxygenase (COX)-mediated metabolism of arachidonic acid. They are constitutively produced in certain tissues (eg, brain, gut, and kidney), and their synthesis is increased at sites of inflammation. Prostaglandins function as important mediators of inflammation and modulate a variety of physiological processes, including maintenance of gastric mucosal integrity, renal hemodynamic regulation, renin synthesis and release, and tubular reabsorption of salt and water.\(^1\) Cyclooxygenase, or PG synthase \(G/H_2\), is the rate-limiting enzyme responsible for the initial conversion of arachidonic acid to \(PGG_2\) and subsequently to \(PGH_2\). \(PGH_2\) is then metabolized by tissue-specific isomerases to produce prostaglandins and thromboxanes.

There are 2 distinct isoforms of cyclooxygenase, COX-1 and COX-2, which share 66% homology in amino acid sequence\(^2\)–\(^4\) but have different patterns of expression and regulation. COX-1, traditionally termed the “constitutive” enzyme, is widely distributed in tissues, and its level of activity is not dynamically regulated. COX-2, the glucocorticoid-sensitive “inducible” enzyme, is more restricted in its basal expression and is upregulated in response to inflammation, resulting in increased prostanoid production at the site of inflammation.

NSAIDs, which block both isoforms COX-1 and COX-2, have been widely used in the treatment of inflammatory conditions. However, the adverse effects of NSAIDs, especially gastrointestinal toxicity, have limited their long-term use in clinical settings. The hypothesis that NSAID-induced gastrointestinal toxicity was related to the inhibition of gastric COX-1, whereas the anti-inflammatory properties caused by COX-2 inhibition\(^5\) led to the development of the new anti-inflammatory agents, the coxibs, which were designed to inhibit COX-2 selectively. It was anticipated that these selective COX-2 inhibitors would be as effective as the nonselective NSAIDs in the treatment of inflammatory diseases but would be better-tolerated with fewer gastrointestinal side effects.

Rofecoxib (Vioxx) and celecoxib (Celebrex) were the first COX-2–selective inhibitors to be marketed as effective anti-inflammatory agents without serious gastrointestinal toxicity, based on the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial\(^6\) and the Celecoxib Long term Arthritis Safety Study (CLASS) trial,\(^7\) respectively. The VIGOR trial reported that patients with rheumatoid arthritis receiving rofecoxib (50 mg daily) had fewer gastrointestinal events compared with those taking naproxen (500 mg twice daily) (2.1\% versus 4.5\%; \(P<0.001\)), but there was similar efficacy between the drugs. However, the incidence of myocardial infarction was increased by a factor of 5 in the rofecoxib-treated group compared with the naproxen group. In the CLASS trial, celecoxib (400 mg twice daily) was compared with ibuprofen (800 mg thrice daily) or diclofenac (75 mg twice daily) in patients with osteoarthritis or rheumatoid arthritis. Celecoxib had a lower gastrointestinal side effect profile compared with other NSAIDs, and there was no difference in the incidence of cardiovascular events between celecoxib and NSAIDs regardless of aspirin use. Questions regarding the cardiovascular risk of the various coxibs remained, and on September 30, 2004 rofecoxib was withdrawn from the market based on the data from the Adenomatous Polyp Prevention On Vioxx (APPROVe) study.\(^8\) This trial was prematurely discontinued after it was discovered that 3.5\% of the patients treated with rofecoxib (25 mg once daily) had serious thromboembolic adverse events compared with 1.9\% of patients in the placebo group (\(P<0.001\)).\(^9\) The increase in thromboembolic cardiovascular events associated with selective COX-2 inhibitors has been hypothesized to be the result of the COX-2 inhibition of endothelial-derived prostacyclin formation with unopposed platelet production of COX-1–mediated thromboxane \(A_2\).\(^{10,11}\) In light of the recent withdrawal of rofecoxib, an important question remains whether the adverse effects of rofecoxib represent a class effect applicable to all COX-2 inhibitors, or whether there are differential effects of selective COX-2 inhibitors.

Although both rofecoxib and celecoxib are considered selective COX-2 inhibitors, they differ in several ways—chemical structure, potency, specificity of COX-2 inhibition, pharmacokinetics, and metabolism. The distinctive characteristics between these 2 compounds are not elaborated on further because they have been comprehensively reviewed elsewhere;\(^12\)–\(^15\) however, the Table summarizes a few clinically relevant differences.

In this issue of Hypertension, Hermann et al\(^16\) examined the differential effects of 2 COX-2–selective inhibitors (celecoxib and rofecoxib) compared with a nonselective NSAID (diclofenac) and placebo in a rat model of salt-sensitive hypertension. Dahl salt-sensitive rats were fed high-salt diets for a total of 8 weeks. At 6 weeks, the animals were treated with rofecoxib, celecoxib, diclofenac, or placebo. Significant hypertension was seen in all groups, although hypertension was somewhat attenuated in the celecoxib-treated group.

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compared with the other 3 groups at week 8. Of note, celecoxib selectively reduced proteinuria, decreased morphological changes associated with glomerular and vascular injury, and reduced infiltrating cellular inflammatory cells in the vasculature compared with animals treated with either rofecoxib or diclofenac. Rofecoxib actually exacerbated proteinuria and was associated with worsening glomerular injury, increased cellular inflammatory infiltrate, and enhanced endothelial dysfunction with decreased levels of endothelial nitric oxide synthase (eNOS).

The differential effects of celecoxib and rofecoxib on blood pressure in the study from Hermann et al are consistent with previous animal studies in rodent models of hypertension and also parallel clinical findings seen in elderly patients treated with the different COX-2-selective inhibitors. Although celecoxib attenuated further increases in systolic blood pressure (SBP) in week 8 compared with the other treatment groups, the difference in mean SBP was still small (9 to 12 mm Hg) relative to the severe hypertension (mean SBP >200 mm Hg) found in these Dahl salt-sensitive animals. The more striking aspects of this study were the dramatic histological differences in renal injury between the treatment groups. Celecoxib treatment ameliorated vascular injury compared with diclofenac-treated and rofecoxib-treated animals, as noted by a relative reduction in endothelial proliferation, adventitial widening, and subintimal plasma insudation. Meanwhile, rofecoxib treatment actually worsened renal injury by enhancing smooth muscle necrosis in the renal vasculature.

Hermann et al also examined the role of coxibs in mediating inflammatory renal injury and endothelial dysfunction in this model of salt-sensitive hypertension. Celecoxib not only significantly reduced mesangial sclerosis and extracapillary proliferation but also reduced glomerular infiltration by cytotoxic T cells (CD8\(^+\) cells) and monocytes/macrophages (ED1\(^+\) cells) compared with rofecoxib-treated and diclofenac-treated animals. Again, rofecoxib had the opposite effect and, in fact, aggravated inflammatory cellular infiltration of the glomerulus by ED1\(^+\) cells. In addition, elevated expression of C-reactive protein (CRP) mRNA in hypertensive animals was normalized with celecoxib treatment but was unchanged with either rofecoxib or diclofenac treatment. CRP, a marker of chronic low-grade inflammation, has been linked to cardiovascular disease and endothelial dysfunction. CRP has been shown to be a strong independent risk factor for future cardiovascular events, and increased CRP mRNA expression has been found in atheromatous plaques. The in vitro role of CRP in endothelial dysfunction was described by Verma et al in a study that demonstrated that CRP directly inhibited endothelial nitric oxide (NO) production through posttranscriptional effects on eNOS mRNA stability. This resulted in decreased NO bioactivity and endothelial dysfunction. Therefore, the normalization of CRP mRNA levels in the hypertensive animals after celecoxib treatment suggests that the beneficial effects of celecoxib on endothelial function may be partially attributed to the reduction in CRP. Other studies have also investigated the beneficial role of celecoxib on endothelial dysfunction. In a previous study by Hermann et al, celecoxib was found to improve endothelial dysfunction and reduce oxidative stress in the same model of salt-sensitive hypertension, whereas rofecoxib and diclofenac had no effect. In addition, clinical studies in patients with coronary artery disease or hypertension have also suggested that celecoxib selectively improved NO-mediated endothelial function. In the current study, Hermann et al examined renal cortical eNOS mRNA levels. Although celecoxib treatment did not alter levels of eNOS mRNA, there was a significant reduction of eNOS mRNA levels after treatment with rofecoxib. These data implicate oxidative stress as a potential mechanism for the deleterious effects seen with rofecoxib. Therefore, it appears that celecoxib may potentially have renoprotective benefits related to its anti-

<table>
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<th>Chemical family</th>
<th>Celecoxib</th>
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<tr>
<td>COX-2 selectivity*</td>
<td>9</td>
<td>&gt;50</td>
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<td>Oral bioavailability, %</td>
<td>22–40</td>
<td>92–93</td>
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<tr>
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<td>~90</td>
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</tr>
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<td>Oxidation by CYP2C9, 3AA</td>
<td>Cytosolic reductase</td>
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*COX-2 selectivity based on the IC\(_{80}\) (80% inhibitory concentration) of COX-2 relative to COX-1 using the William Harvey human modified whole blood assay.
inflammatory actions that are unique compared with both another COX-2 selective inhibitor (rofecoxib) and a nonselective NSAID (diclofenac) and independent from celecoxib-mediated reductions in SBP. There is mounting evidence that there may be heterogeneity within the coxib class of anti-inflammatory agents. This study by Hermann et al raises several clinically relevant questions, especially in light of the recent withdrawal of rofecoxib from the market. Is the heterogeneity of the coxibs related to their relative COX-2/COX-1 binding specificity? Are the adverse cardiovascular effects of rofecoxib a class effect or unique to rofecoxib? Will the beneficial pleiotropic effects of celecoxib, or other coxibs, prove to have clinical relevance? Certainly, further studies will be needed to elucidate these and other unanswered questions.

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References

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