Drug Therapy

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THE COXIBS, SELECTIVE INHIBITORS OF CYCLOOXYGENASE-2

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NONSTEROIDAL antiinflammatory drugs (NSAIDs) are widely used to treat arthritis, menstrual pain, and headache. Although they are effective, their long-term use is limited by gastrointestinal effects such as dyspepsia and abdominal pain and, less often, gastric or duodenal perforation or bleeding. Development of the coxibs, a new group of antiinflammatory drugs, represents a response to the unsatisfactory therapeutic profile of NSAIDs. Both groups of drugs inhibit prostaglandin G/H synthase, the enzyme that catalyzes the transformation of arachidonic acid to a range of lipid mediators, termed prostaglandins and thromboxanes (Fig. 1). However, whereas NSAIDs inhibit the two recognized forms of the enzyme, also referred to as cyclooxygenase-1 and cyclooxygenase-2, the coxibs are selective inhibitors of cyclooxygenase-2. The inhibition of cyclooxygenase-2 has been more directly implicated in ameliorating inflammation, whereas the inhibition of cyclooxygenase-1 has been related to adverse effects in the gastrointestinal tract. Therefore, it was hoped that coxibs would be better tolerated than nonselective NSAIDs but equally efficacious. This review will assess the evidence that has emerged in support of that hypothesis.

Prostaglandin G/H synthase has both cyclooxygenase and hydroperoxidase activity.[1] Neither coxibs nor NSAIDs inhibit the activity of hydroperoxidase. Aspirin inhibits the activity of cyclooxygenase by irreversibly acetylating a serine residue at position 529 in the only form of the enzyme expressed in platelets, cyclooxygenase-1.[2] There were several early suggestions of a second form of cyclooxygenase.[3-5] Analysis of unrelated genes identified one that was highly homologous to the gene for cyclooxygenase-1.[6-8] This isoform, termed cyclooxygenase-2, can be up-regulated by cytokines, growth factors, and tumor promoters,[6-10] suggesting its relevance to inflammation and cancer.

Although cyclooxygenase-1 has the structural features of a "housekeeping" enzyme, its expression may also be regulated.[11,12] The expression of both cyclooxygenase-1 and cyclooxygenase-2 is increased in the synovia of inflamed joints and in atherosclerotic plaques.[13,14] Although the catalytic activities and tertiary structures of cyclooxygenase-1 and cyclooxygenase-2 are also remarkably similar,[2,15,16] cyclooxygenase-2 has a broader affinity for substrates because the hydrophobic channel leading to the active site of this enzyme is more accommodating. However, distinguishing cyclooxygenase-1 as a constitutive enzyme and cyclooxygenase-2 as an inducible enzyme that accounts for the formation of prostanoid in disease is an oversimplification of the biologic reality.

SELECTIVE AND NONSELECTIVE INHIBITION OF CYCLOOXYGENASE ISOFORMS

Three broad classes of cyclooxygenase inhibitors have emerged: aspirin synthesized from salicylic acid; indomethacin and other NSAIDs, whose chemical modifications were based largely on findings in models of inflammation and gastric mucosal damage; and the first selective cyclooxygenase-2 inhibitors, the coxibs (e.g., celecoxib and rofecoxib). Other selective cyclooxygenase-2 inhibitors, such as valdecoxib[17] and etoricoxib,[18] are being developed.

Selectivity for cyclooxygenase-2 may be expressed at several levels. A compound may be biochemically selective for cyclooxygenase-2. Drug companies assess selectivity by in vitro assays during screening, because these assays are relatively rapid and simple. However, they do not necessarily reflect the complexity of the drug–enzyme interaction in vivo. To address this concern, whole-blood assays of cyclooxygenase-isoform activity have been developed.[19,20] These assays are based on the production of thromboxane B_2 during blood clotting (an index of platelet cyclooxygenase-1 activity) and the production of prostaglandin E_2 by bacterial lipopolysaccharide in whole blood (an index of monocyte cyclooxygenase-2 activity). Clinical selectivity has been based on either surrogates for clinical toxicity (e.g., endoscopically visualized gastroduodenal ulcers) or actual clinical end points at antiinflammatory doses of an inhibitor.

There are two basic requirements to test the hypothesis that cyclooxygenase-2 inhibitors are better tolerated than nonselective NSAIDs but just as efficacious. First, the drug must not inhibit cyclooxygenase-1 activity in clinically relevant targets (gastrointestinal mucosa and platelets) at therapeutic plasma concentrations. Second, the clinical end points assessed must reflect cyclooxygenase-1–dependent gastrointestinal toxicity. When symptoms are the end point, a limitation is that the dependence of cyclooxygenase-1 on the signal is uncertain, and symptoms may not correlate with lesions. When endoscopically visualized lesions are the end point, the situation is

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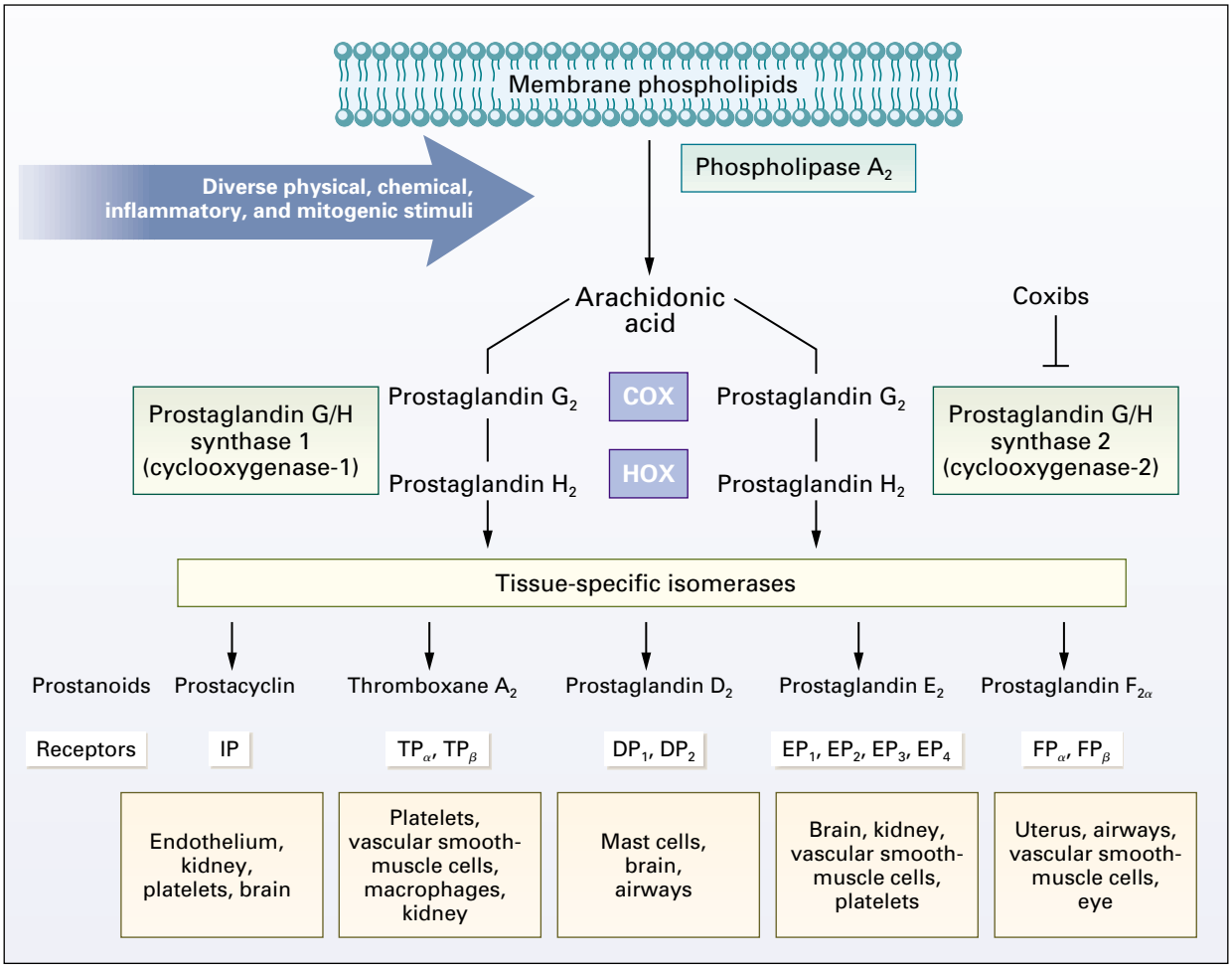

Figure 1. Production and Actions of Prostaglandins and Thromboxane.

Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is liberated from the *sn*2 position in membrane phospholipids by phospholipase A_2, which is activated by diverse stimuli. Arachidonic acid is converted by cytosolic prostaglandin G/H synthases, which have both cyclooxygenase (COX) and hydroperoxidase (HOX) activity, to the unstable intermediate prostaglandin H_2. The synthases are colloquially termed cyclooxygenases and exist in two forms, cyclooxygenase-1 and cyclooxygenase-2. Coxibs selectively inhibit cyclooxygenase-2. Prostaglandin H_2 is converted by tissue-specific isomerases to multiple prostanoids. These bioactive lipids activate specific cell-membrane receptors of the superfamily of G-protein–coupled receptors. Some of the tissues in which individual prostanoids exert prominent effects are indicated. IP denotes prostacyclin receptor, TP thromboxane receptor, DP prostaglandin D_2 receptor, EP prostaglandin E_2 receptor, and FP prostaglandin $F_{2\alpha}$ receptor.

different. The dependence of the lesions on cyclooxygenase-1 has been established, but it is uncertain whether the finding of lesions on endoscopy is actually predictive of the likelihood of serious gastrointestinal complications, such as perforation, obstruction, and bleeding. Indeed, the hemorrhagic nature of most serious gastrointestinal end points makes it likely that they primarily reflect the inhibition of cyclooxygenase-1 activity in platelets, rather than in gastric mucosa. Finally, the low incidence of these events means that many patients must be studied for prolonged periods of treatment to detect the differences between drugs reliably.[21,22]

The biochemical selectivity of a particular drug, as assessed in vitro, is critically dependent on its concentration. One can summarize such selectivity profiles by plotting the drug concentrations necessary to inhibit the activity of cyclooxygenase-2 and cyclooxygenase-1 by 50 percent (Fig. 2).[23-26] However, given the concentration dependence of these estimates, it is not useful to attempt to discriminate between existing NSAIDs on the basis of small differences in biochemical selectivity with the use of terms such as "preferential cyclooxygenase-2 inhibitor."

How well do the results of these in vitro assays predict selectivity when the measurements are per-

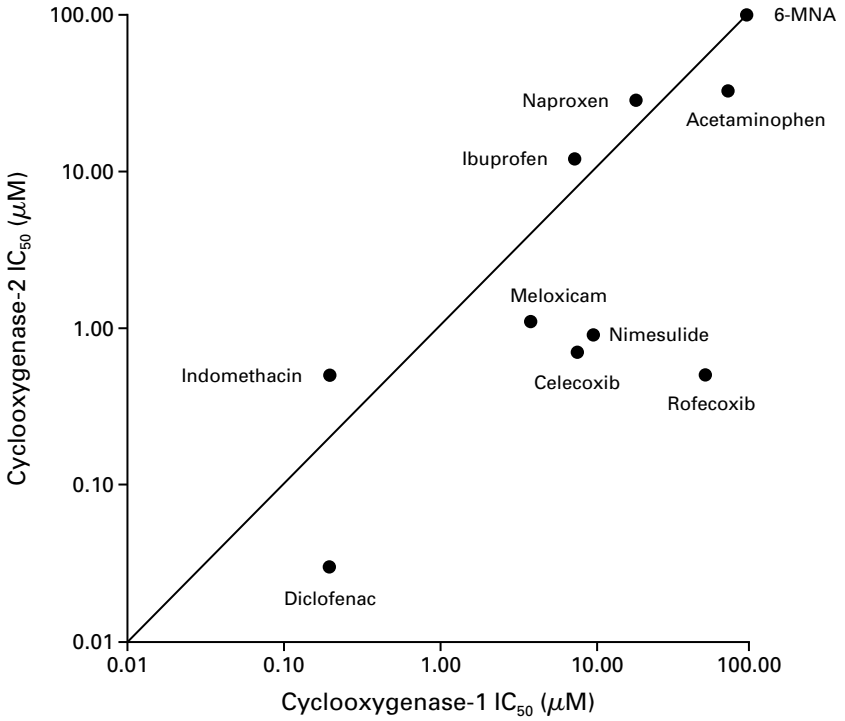

Figure 2. Concentrations of Various Drugs Required to Inhibit the Activity of Cyclooxygenase-1 and Cyclooxygenase-2 by 50 Percent (IC_{50}) in Assays of Whole Blood.

Each point is the mean of three or four values.[23-26] Drugs plotted below the diagonal line indicating equivalence are more potent inhibitors of cyclooxygenase-2 than drugs plotted on or above the line. 6-MNA denotes 6-methoxy-2-naphthylacetic acid.

formed in blood samples obtained from patients given cyclooxygenase inhibitors? Although the curves plotted from the in vitro data fit the plasma data well, the variance of the latter assays is much greater (Fig. 3). This variance reflects substantial variability between patients in plasma concentrations of the cyclooxygenase inhibitor after oral administration of a standard therapeutic dose and in the degree of inhibition of cyclooxygenase isoforms corresponding to any given concentration of inhibitor. Indeed, many factors determine the clinical response to a cyclooxygenase-2 inhibitor (Fig. 4). Thus, genetic variability in the target protein or metabolizing enzymes, interactions between drugs, and the characteristics of the patient, such as a history of peptic ulcer,[29,30] may all influence both the efficacy and the adverse effects of cyclooxygenase-2 inhibitors in clinical trials.

PHARMACOKINETICS AND DRUG INTERACTIONS

The pharmacokinetics, metabolism, and drug interactions of celecoxib[31-34] and rofecoxib[35-39] are summarized in Table 1. The clinically important differences between the two drugs are related to oral bioavailability, half-life, and main pathways of hepatic metabolism. Differences in the pathways of hepatic metabolism may have smaller effects on the pharmacokinetics of rofecoxib than on those of celecoxib.

CLINICAL VERIFICATION OF THE CYCLOOXYGENASE-2 HYPOTHESIS

Both celecoxib and rofecoxib are superior to placebo in the relief of both subjective and objective measurements of pain and inflammation in patients with osteoarthritis of the hip and knee[40-45] and in the relief of symptoms in patients with rheumatoid arthritis.[22,46] Moreover, analgesic efficacy has been demonstrated in clinical models of acute pain, such as that after dental surgery, after orthopedic surgery, and during dysmenorrhea. On the basis of the results of various phase 3 studies, the Food and Drug Administration (FDA) approved celecoxib for the treatment of patients with osteoarthritis and rheumatoid arthritis, and rofecoxib for the treatment of patients with osteoarthritis and acute musculoskeletal pain.

Similar indications have now been approved worldwide. However, whether rofecoxib and celecoxib are equally efficacious is not known. In all of these stud-

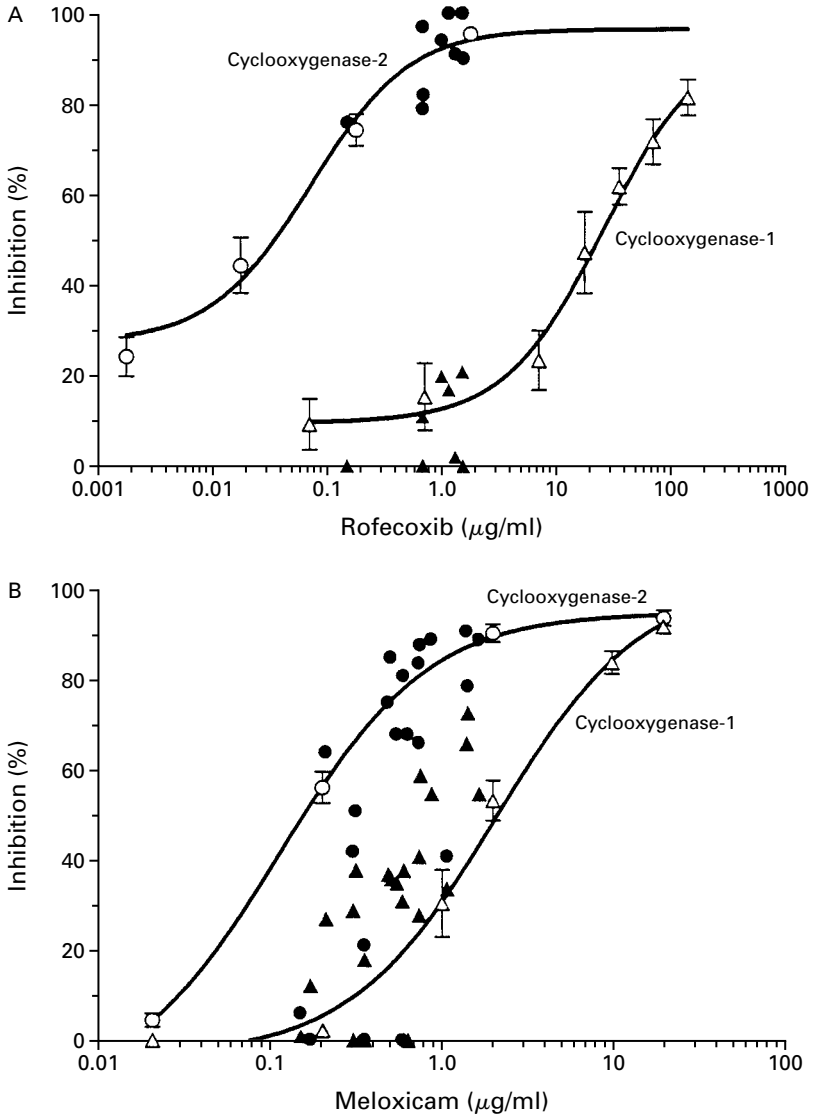

Figure 3. Relations between Mean (±SE) Steady-State Plasma Concentrations of Rofecoxib (Panel A) and Meloxicam (Panel B) and Inhibition of Cyclooxygenase-1 and Cyclooxygenase-2, as Measured in Vitro.

Data were obtained from 9 patients with rheumatoid arthritis who were given 50 mg of rofecoxib once daily for seven days[27] and from 21 normal subjects who received 7.5 or 15 mg of meloxicam once daily for seven days.[28] Blood was drawn 4 hours after the last dose of rofecoxib and 24 hours after the last dose of meloxicam. Superimposed on the same graphs are concentration–effect curves for the degree of inhibition of cyclooxygenase-2 and cyclooxygenase-1 induced by rofecoxib and meloxicam in vitro. In these studies, increasing concentrations of rofecoxib or meloxicam were incubated with 1-ml samples of heparin-treated whole blood in the presence of lipopolysaccharide for 24 hours, and plasma prostaglandin E_2 was measured as an index of cyclooxygenase-2 activity in monocytes. Rofecoxib or meloxicam was also incubated with 1-ml samples of whole blood that had been allowed to clot for 60 minutes, and serum thromboxane B_2 was measured as an index of cyclooxygenase-1 activity in platelets. Sigmoidal concentration–response curves fitting the experimental data were generated by ALLFIT analysis.[28]

ies,[22,40-46] a nonselective NSAID — that is, a drug that nonselectively inhibits cyclooxygenase-1 and cyclooxygenase-2 at therapeutic plasma concentrations — was included. However, the trials were designed to detect equivalence of efficacy between the NSAID and the coxib, rather than any small, but potentially important, difference between the treatments. Thus, although cyclooxygenase-1 may be a minor source of the prostaglandins produced in response to inflammation in humans,[47] and although both cyclooxygenase isoforms are expressed in inflamed synovia,[13] the studies of the efficacy of coxibs were not designed to de-

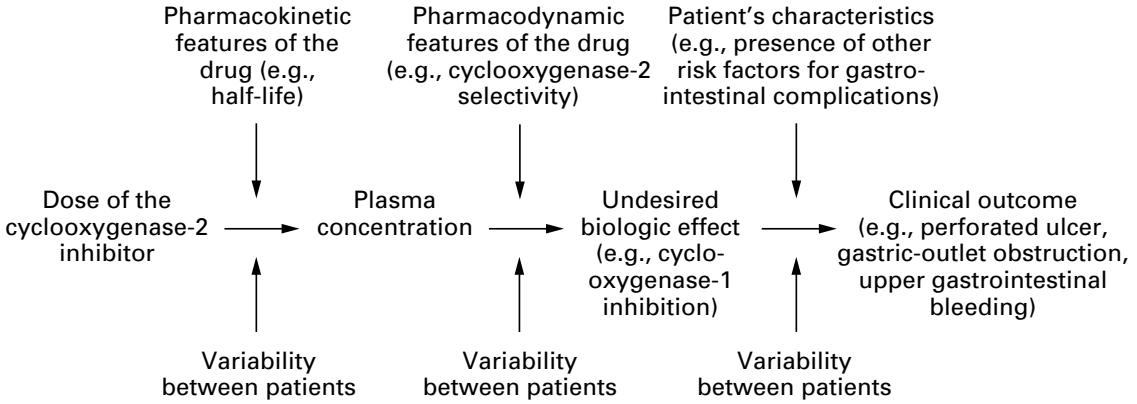

Figure 4. Factors That May Influence the Clinical Selectivity and Safety of a Cyclooxygenase-2 Inhibitor in an Individual Patient. These factors include pharmacokinetic and pharmacodynamic variables, as well as the interaction of the drug with preexisting risk factors for drug-dependent adverse effects. All these factors are subject to variability from patient to patient.

TABLE 1. PHARMACOKINETICS, METABOLISM, AND DRUG INTERACTIONS OF ROFECOXIB AND CELECOXIB.*

FEATURE	ROFECOXIB	CELECOXIB
Oral bioavailability (%)	92–93	22–40
Effect of food	Minimal	None
Time to maximal plasma concentration (hr)	2–3	2–4
Elimination half-life (hr)	10–17	Approximately 11
Volume of distribution (liters)	86–91	455±166
Extent of binding to plasma proteins (%)	86	>97
Main pathway of liver metabolism	Cytosolic reduction	Oxidation by cytochrome P-450 2C9, 3A4
Interaction with cytochrome P-450 inhibitors	No	Yes
Interaction with digoxin	No	Not tested
Interaction with warfarin	Causes 10% increase in INR	No
Interaction with methotrexate	At supratherapeutic doses	No
Interaction with antihypertensive drugs	Increases blood pressure	Increases blood pressure
Influence of renal insufficiency	Has little effect	AUC 43% lower
Influence of hepatic impairment	AUC 30–70% higher	AUC 40–180% higher
Approved daily doses (mg)		
For osteoarthritis	12.5–25	100–200
For rheumatoid arthritis	Not approved	200–400
For acute pain	Up to 50	Not approved

*INR denotes international normalized ratio, and AUC area under the curve. Plus–minus value is the mean ±SD.

tect a small difference in efficacy that might result from the coincidental inhibition of both isoforms, rather than from the inhibition of cyclooxygenase-2 alone. Moreover, it should be emphasized that the clinical-efficacy end points used in these trials have a rather poor ratio of signal (the drug effect) to noise (the placebo effect), making detection of moderate differences in efficacy between drugs an unrealistic exercise. Furthermore, although the efficacy of coxibs is similar to that of nonselective NSAIDs in animal models of acute inflammation,[48] they may exacerbate a late phase of inflammation characterized by the generation of antiinflammatory prostaglandins by cyclooxygenase-2.[49]

Two large trials have addressed the efficacy of coxibs and the associated risk of gastrointestinal complications, the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial and the Celecoxib Long-Term Arthri-

tis Safety Study (CLASS) trial. In the VIGOR trial,[22] a daily dose of 50 mg of rofecoxib was compared with a twice-daily dose of 500 mg of naproxen in 8076 patients with rheumatoid arthritis who were treated for a median of nine months. The mean age of the patients was 58 years, and 80 percent were women. Almost 60 percent were receiving long-term glucocorticoid therapy, and 8 percent had a history of gastrointestinal perforation, gastrointestinal hemorrhage, or symptomatic peptic ulcer. Both drugs were similarly effective, according to either the patient's or the investigator's Global Assessment of Disease Activity scores or the Modified Health Assessment scores. The rates of discontinuation of treatment owing to a lack of efficacy were low in both groups (6.3 percent in the rofecoxib group and 6.5 percent in the naproxen group). The incidence of gastrointestinal perforation, gastrointestinal hemorrhage, or symptomatic peptic ulcer was 4.5 per 100 patient-years in the naproxen group and 2.1 per 100 patient-years in the rofecoxib group, a difference of 54 percent ($P<0.001$). The results in these patients with rheumatoid arthritis were consistent with those of an overview analysis of gastrointestinal side effects in patients with osteoarthritis treated with rofecoxib or nonselective NSAIDs.[50]

The CLASS trial[21] consisted of two separate studies. In one, celecoxib (400 mg twice daily) was compared with diclofenac (75 mg twice daily); in the other, celecoxib was compared with ibuprofen (800 mg three times daily). In contrast to ibuprofen, which is a nonselective NSAID, the selectivity of diclofenac for cyclooxygenase-1 and cyclooxygenase-2 was similar to that of celecoxib (Fig. 2). Seventy-two percent of the patients had osteoarthritis, and 68.5 percent were women. The study lasted 13 months, but only the data from 6 months of follow-up have been published. The patients in the CLASS trial were permitted to take aspirin in doses of up to 325 mg per day. There was no statistically significant difference between the groups in the incidence of the primary end point of ulcer perforation, gastric-outlet obstruction, or upper gastrointestinal bleeding (0.8 percent in the celecoxib group vs. 1.5 percent in either NSAID group, $P=0.09$). The CLASS study was not designed to compare the efficacy of the drugs, and the choice of dosing regimens was based on an analysis of prescription patterns, rather than evidence of similar efficacy.[21] More patients withdrew from the combined NSAID groups than from the celecoxib group (14.8 percent vs. 12.6 percent, $P=0.005$) because of lack of efficacy. The reasons for the higher withdrawal rates in the CLASS trial than in the VIGOR trial are unclear.

Despite the evidence that a coxib is safer than a nonselective NSAID, there are some caveats. The likelihood of a gastrointestinal complication in patients who are taking NSAIDs depends on preexisting risk factors, including age and a history of peptic ulcer and gastrointestinal bleeding, which are likely to be relevant to the gastrointestinal effects of cyclooxygenase-2 inhibitors. Patients with a history of peptic ulcer and gastrointestinal bleeding who are given an NSAID have a risk of a complicated ulcer of about 5 percent per year, in contrast to an incidence of 0.4 percent in patients with no such history.[51] Although patients with peptic ulcers were excluded from both the VIGOR and the CLASS trials, many of those enrolled still had risk factors for gastrointestinal events. Analysis of the VIGOR results revealed an absolute reduction in the risk of peptic ulcers or gastrointestinal bleeding of 2.4 percent in the patients treated with rofecoxib, suggesting that 41 patients needed to be treated for one year to prevent one such event.

The distinct roles of the two cyclooxygenase enzymes in patients with peptic ulcers are unknown. For example, cyclooxygenase-2, as well as cyclooxygenase-1, has been detected in apparently normal gastrointestinal epithelium, and therefore, it may also help protect the gastric mucosa.[52] However, the results of both the VIGOR and the CLASS trials suggest that cyclooxygenase-1 has the main cytoprotective role. Perhaps of more concern is that the expression of gastrointestinal epithelial cyclooxygenase-2 is increased by traumatic and inflammatory stimuli, as well as by *Helicobacter pylori* infection.[53,54] Expression is increased in the margin of healing ulcers, and cyclooxygenase-2 inhibitors impair ulcer healing in mice.[55,56] We still have much to learn about the potential risks of the inhibition of cyclooxygenase-2 in the gastrointestinal tract. For example, cyclooxygenase-2 inhibitors impair tolerance of dietary antigens[57] and exacerbate experimental colitis in rodents.[58,59]

CYCLOOXYGENASE-2, COXIBS, AND CARDIOVASCULAR DISEASE

Cyclooxygenase-1 is constitutively expressed in cultured endothelial and vascular smooth-muscle cells. The expression of cyclooxygenase-2 is increased by cytokines, growth factors, phorbol esters, and lipopolysaccharide in both types of cells and by injury to smooth-muscle cells. These observations suggest that cyclooxygenase-2 has an important role in the increase in prostacyclin formation that occurs in clinical syndromes of platelet activation.[60] Expression of both cyclooxygenase-2 and cyclooxygenase-1 is upregulated in the foam cells and smooth-muscle cells of atherosclerotic plaques.[14] Cyclooxygenase-2 may well be important under physiologic conditions also. For example, cyclooxygenase-2 inhibitors decrease urinary excretion of prostacyclin metabolites in normal subjects,[61-63] indicating that the production of prostacyclin is also decreased.[64-66] Laminar shear forces increase the expression of cyclooxygenase-2 in endothelial cells in vitro[67] and may do so in endothelial cells in normal subjects.[61] Prostacyclin is thought to be part of a homeostatic defense mechanism that limits the consequences of platelet activation in vivo.[60]

In mice, deletion of the prostacyclin receptor increased the sensitivity to thrombotic stimuli but did not increase the risk of spontaneous thrombosis.[68]

What are the implications of these observations with respect to selective cyclooxygenase-2 inhibitors? If they are associated with a risk of thrombosis, the risk should be small, because of the presence of other endothelium-derived substances, such as nitric oxide, that protect against thrombosis. However, thrombosis would be expected to occur in patients who are already at increased risk because of other underlying conditions. In fact, arterial thrombosis occurred after the initiation of celecoxib therapy in four patients with lupus anticoagulant.[69]

In the VIGOR trial, 4 percent of the patients met the FDA criteria for the use of aspirin therapy for secondary prevention of major vascular events, but patients who were taking aspirin were excluded from the trial.[22] The rates of nonfatal myocardial infarction, nonfatal stroke, and death from any vascular event were higher in the rofecoxib group than in the naproxen group (0.8 percent vs. 0.4 percent, $P<0.05$). This difference was largely due to a difference in the incidence of myocardial infarction (0.4 percent in the rofecoxib group vs. 0.1 percent in the naproxen group, $P<0.01$). In contrast, in the CLASS trial, in which 21 percent of the patients took aspirin, there was no significant difference between the treatment groups in the incidence of major cardiovascular events.[21]

The difference in major cardiovascular events in the VIGOR trial may reflect the play of chance. The end point was prespecified, and the difference in the frequency of events was statistically significant, but the absolute number of cardiovascular events was small (less than 70). Although an effect of this magnitude would be surprising, it would be consistent with the formation of thromboxane in the absence of the concomitant generation of prostacyclin. This would be a drug-class–specific effect, but a difference in rates of cardiovascular events may not have been revealed in the CLASS trial because of differences in the study patients, the use of aspirin by some patients, or the nature of the nonselective NSAIDs used in the two trials. Patients with rheumatoid arthritis, such as those in the VIGOR trial, may have an increased risk of thrombotic events.[70,71] This is not true of patients with osteoarthritis, who constituted most of the patients in the CLASS trial. Naproxen, the nonselective NSAID used in the VIGOR trial, may be protective against cardiovascular events.[22] Naproxen has an extended half-life and may have completely suppressed the capacity of platelets to make thromboxane A_2 throughout its dosing interval,[72] although this feature of naproxen has been disputed.[73] There is no convincing evidence from epidemiologic studies that NSAIDs, including naproxen, protect against cardiovascular events.[74] Clearly, more information is needed on the cardiovascular effect of selective inhibitors of cyclooxygenase-2 and their combination with antiplatelet drugs.

In the interim, what approach to cardioprotection might be taken in patients with arthritis? Patients who have had a major cardiovascular event should be treated with low-dose aspirin.[75] For such patients who need antiarthritic therapy, the additional suppressive effect on the synthesis of prostacyclin of either a coxib or a nonselective NSAID should be indistinguishable,[61-63] whereas the profile of adverse gastrointestinal effects may favor the former. However, whether this combination maintains the advantage of a coxib over a nonselective NSAID with respect to gastrointestinal side effects remains to be tested. The incidence of serious gastrointestinal bleeding in patients taking low doses of aspirin, although low, is roughly double the incidence in those taking placebos.[76] Aside from potentially increasing the rate of acute events, such as myocardial infarction, cyclooxygenase-2 inhibitors may have relevance to other aspects of cardiovascular biology, such as cardiac function and atherogenesis.[77-79]

CYCLOOXYGENASE-2 AND RENAL FUNCTION

Cyclooxygenase-2–dependent prostaglandin formation is necessary for normal renal development. In mice, the complete absence of cyclooxygenase-2 results in severe renal dysplasia characterized by a postnatal arrest of maturation in the subcapsular nephrogenic zone and progressive deterioration with increasing age.[80] Antenatal exposure of both mice and rats to an inhibitor of cyclooxygenase-2, but not of cyclooxygenase-1, had similar effects.[81]

Cyclooxygenase-2 has been localized to the renal vasculature, the cortical macula densa, and the medullary interstitial cells of the kidney, and its content in these areas increases with age. By contrast, cyclooxygenase-1 is found in the vasculature, the collecting ducts, and the thin loops of Henle.[82] The presence of both isoforms in the vasculature raises the question of which is the predominant source of the increased production of vasodilator prostaglandins that are critical to the preservation of renal blood flow in the presence of volume depletion. Inhibition of this homeostatic response accounts for the most common renal side effects associated with nonselective NSAID therapy.[83]

Remarkably little information on the renal pharmacology of cyclooxygenase-2 inhibitors in humans is available. In normal salt-replete subjects who were 59 to 80 years of age, the administration of 50 mg of rofecoxib once daily or 50 mg of indomethacin three times daily transiently decreased urinary sodium excretion by approximately 20 percent but did not cause detectable edema or hypertension. The glomerular filtration rate, measured after 14 days, declined by an average of 5 percent in the indomethacin group but did not change in the rofecoxib group ($P=0.005$).[63]

By contrast, 12.5 or 25 mg of rofecoxib once daily and 50 mg of indomethacin three times daily reduced the glomerular filtration rate in salt-depleted elderly subjects, but to a similar degree.[84]

An analysis of the post-marketing data for celecoxib revealed that edema occurred in 2.1 percent of patients, hypertension in 0.8 percent, and exacerbation of preexisting hypertension in 0.6 percent — a profile and incidence similar to those of nonselective NSAIDs.[85] Similarly, post hoc analysis of the rofecoxib data base revealed that peripheral edema occurred in 3.8 percent of the patients who received a dose of 25 mg per day.[86] Controlled comparisons of the coxibs with each other and with nonselective NSAIDs are necessary to assess the risk of hypertension. These should be designed to match the degree and duration of cyclooxygenase-2 inhibition throughout the dosing interval.

EFFECTS OF OTHER CYCLOOXYGENASE-2 INHIBITORS

Two older drugs, nimesulide and meloxicam, the latter recently approved for use in the United States, exhibit cyclooxygenase-2 selectivity similar to that of celecoxib in vitro (Fig. 2). It is not clear whether their effects are similar to those of rofecoxib or celecoxib in clinical practice. Variability between patients in plasma drug concentrations is an important determinant of the selectivity of these agents for cyclooxygenase-2. Thus, in the case of nimesulide, a daily dose of 100 mg reduced cyclooxygenase-1 activity measured ex vivo in normal subjects in one study[87] but not in another.[62] Meloxicam caused dose-dependent inhibition of cyclooxygenase-2 and cyclooxygenase-1, but the extent of inhibition varied greatly among the subjects (Fig. 3).[28,88]

The clinical selectivity of these drugs has not been addressed in large trials with statistical power similar to that of the VIGOR and CLASS trials. Thus, although post hoc analyses of small studies have suggested that gastrointestinal side effects are less frequent with nimesulide than with nonselective NSAIDs,[89] prospective studies of the efficacy and gastrointestinal safety have been small, involving 60 to 392 patients who were treated for eight days to three months.[90-93] There was no significant difference in the incidence of serious gastrointestinal side effects among patients who were taking 7.5 mg of meloxicam daily, those who were taking 100 mg of slow-release diclofenac daily, and those who were taking 20 mg of piroxicam daily for 28 days in two large studies, the Meloxicam Large-Scale International Study Safety Assessment[94] and the Safety and Efficacy Large-Scale Evaluation of COX-Inhibiting Therapies.[95] A meta-analysis of six trials, including these two large trials, suggested a relative risk of serious upper gastrointestinal side effects of 0.5 for meloxicam as compared with NSAIDs, with the upper bound of the 95 percent confidence interval approaching 1.0.[96] In contrast, a small observational study suggested that the risk of upper gastrointestinal complications associated with meloxicam was similar to that of conventional NSAIDs.[30]

CONCLUSIONS

In less than a decade after the discovery of cyclooxygenase-2, clinical trials have demonstrated that treatment with highly selective cyclooxygenase-2 inhibitors causes significantly fewer serious gastrointestinal adverse events than does treatment with nonselective NSAIDs. More selective coxibs are already being developed. We must gather additional information on the pharmacology of the coxibs. Given the cardiovascular findings in the VIGOR trial and the association of both rofecoxib and celecoxib with small, but potentially clinically relevant, changes in blood pressure, elucidation of the cardiovascular and renal effects of these drugs and their interactions with potential adjuvant therapies, such as low-dose aspirin, is imperative.

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REFERENCES

1. Marnett LJ, Rowlinson SW, Goodwin DC, Kalgutkar AS, Lanzo CA. Arachidonic acid oxygenation by COX-1 and COX-2: mechanisms of catalysis and inhibition. J Biol Chem 1999;274:22903-6.

2. Loll PJ, Picot D, Garavito RM. The structural basis of aspirin activity inferred from the crystal structure of inactivated prostaglandin H_2 synthase. Nat Struct Biol 1995;2:637-43.

3. Pash JM, Bailey JM. Inhibition by corticosteroids of epidermal growth factor-induced recovery of cyclooxygenase after aspirin inactivation. FASEB J 1988;2:2613-8.

4. Sebaldt RJ, Sheller JR, Oates JA, Roberts LJ II, FitzGerald GA. Inhibition of eicosanoid biosynthesis by glucocorticoids in humans. Proc Natl Acad Sci U S A 1990;87:6974-8.

5. Masferrer JL, Zweifel BS, Seibert K, Needleman P. Selective regulation of cellular cyclooxygenase by dexamethasone and endotoxin in mice. J Clin Invest 1990;86:1375-9.

6. Xie W, Chipman JG, Robertson DL, Erikson RL, Simmons DL. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proc Natl Acad Sci U S A 1991;88:2692-6.

7. Kujubu DA, Herschman HR. Dexamethasone inhibits mitogen induction of the T1S10 prostaglandin synthase/cyclooxygenase gene. J Biol Chem 1992;267:7991-4.

8. O'Banion MK, Winn VD, Young DA. cDNA cloning and functional activity of a glucocorticoid-regulated inflammatory cyclooxygenase. Proc Natl Acad Sci U S A 1992;89:4888-92.

9. Lee SH, Soyoola E, Chanmugam P, et al. Selective expression of mitogen-inducible cyclooxygenase in macrophages stimulated with lipopolysaccharide. J Biol Chem 1992;267:25934-8.

10. Sheng H, Shao J, Dixon DA, et al. Transforming growth factor-β1 enhances Ha-*ras*-induced expression of cyclooxygenase-2 in intestinal epithelial cells via stabilization of mRNA. J Biol Chem 2000;275:6628-35.

11. Smith CJ, Morrow JD, Roberts LJ II, Marnett LJ. Induction of prostaglandin endoperoxide synthase-1 (COX-1) in a human promonocytic cell line by treatment with the differentiating agent TPA. Adv Exp Med Biol 1997;400A:99-106.

12. Rocca B, Spain LM, Pure E, Laugenbach R, Patrono C, FitzGerald GA. Distinct roles of prostaglandin H synthases 1 and 2 in T-cell development. J Clin Invest 1999;103:1469-77.

13. Crofford LJ, Wilder RL, Ristimäki AP, et al. Cyclooxygenase-1 and -2 expression in rheumatoid synovial tissues: effects of interleukin-1β, phorbol ester, and corticosteroids. J Clin Invest 1994;93:1095-101.
14. Schonbeck U, Sukhova GK, Graber P, Coulter S, Libby P. Augmented expression of cyclooxygenase-2 in human atherosclerotic lesions. Am J Pathol 1999;155:1281-91.
15. Kurumbail RG, Stevens AM, Gierse JK, et al. Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents. Nature 1996;384:644-8. [Erratum, Nature 1997;385:555.]
16. Malkowski MG, Ginell SL, Smith WL, Garavito RM. The productive conformation of arachidonic acid bound to prostaglandin synthase. Science 2000;289:1933-7.
17. Talley JJ, Brown DL, Carter JS, et al. 4-[5-Methyl-3-phenylisoxazol-4-yl]-benzenesulfonamide, valdecoxib: a potent and selective inhibitor of COX-2. J Med Chem 2000;43:775-7.
18. Riendeau D, Percival MD, Brideau C, et al. Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. J Pharmacol Exp Ther 2001;296:558-66.
19. Patrono C, Ciabattoni G, Pinca E, et al. Low dose aspirin and inhibition of thromboxane B_2 production in healthy subjects. Thromb Res 1980; 17:317-27.
20. Patrignani P, Panara MR, Greco A, et al. Biochemical and pharmacological characterization of the cyclooxygenase activity of human blood prostaglandin endoperoxide synthases. J Pharmacol Exp Ther 1994;271: 1705-12.
21. 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.
22. 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.
23. Patrignani P, Panara MR, Sciulli MG, Santini G, Renda G, Patrono C. Differential inhibition of human prostaglandin endoperoxide synthase-1 and -2 by nonsteroidal anti-inflammatory drugs. J Physiol Pharmacol 1997; 48:623-31.
24. Chan C-C, Boyes S, Brideau C, et al. Rofecoxib [Vioxx, MK-0966; 4-(4′-methylsulfonylphenyl)-3-phenyl-2-(5H)-furanone]: a potent and orally active cyclooxygenase-2 inhibitor: pharmacological and biochemical profiles. J Pharmacol Exp Ther 1999;290:551-60.
25. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. Proc Natl Acad Sci U S A 1999;96:7563-8. [Erratum, Proc Natl Acad Sci U S A 1999;96:9666.]
26. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. Am J Med 1998;104:413-21.
27. Patrignani P, Panara MR, Santini G, et al. Biochemical selectivity of rofecoxib in rheumatoid arthritis. In: Proceedings of the 11th International Conference on Advances in Prostaglandin and Leukotriene Research: Basic Science and New Clinical Applications, Florence, Italy, June 4–8, 2000:19. abstract.
28. Panara MR, Renda G, Sciulli MG, et al. Dose-dependent inhibition of platelet cyclooxygenase-1 and monocyte cyclooxygenase-2 by meloxicam in healthy subjects. J Pharmacol Exp Ther 1999;290:276-80.
29. Garcia Rodríguez LA, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. Arch Intern Med 1998;158:33-9.
30. Garcia Rodriguez LA, Hernandez-Diaz S. The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combination of these agents. Arthritis Res 2001;3:98-101.
31. Tang C, Shou M, Mei Q, Rushmore TH, Rodrigues AD. Major role of human liver microsomal cytochrome P450 2C9 (CYP2C9) in the oxidative metabolism of celecoxib, a novel cyclooxygenase-II inhibitor. J Pharmacol Exp Ther 2000;293:453-9.
32. Davies NM, McLachlan AJ, Day RO, Williams KM. Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclo-oxygenase-2 inhibitor. Clin Pharmacokinet 2000;38:225-42.
33. Paulson SK, Hribar JD, Liu NW, et al. Metabolism and excretion of [^{14}C]celecoxib in healthy male volunteers. Drug Metab Dispos 2000;28: 308-14.
34. Karim A, Tolbert DS, Hunt TL, Hubbard RC, Harper KM, Geis GS. Celecoxib, a specific COX-2 inhibitor, has no significant effect on methotrexate pharmacokinetics in patients with rheumatoid arthritis. J Rheumatol 1999;26:2539-43.
35. Porras A, Ko A, Larson P, et al. Single and multiple dose pharmacokinetics (PK) of rofecoxib (R) in healthy subjects. Clin Pharmacol Ther 2000;67:137. abstract.
36. Depre M, Ehrich E, Van Hecken A, et al. Pharmacokinetics, COX-2 specificity, and tolerability of supratherapeutic doses of rofecoxib in humans. Eur J Clin Pharmacol 2000;56:167-74.
37. Schwartz J, Zhao P, Gertz B, et al. Pharmacokinetics of rofecoxib in mild to moderate hepatic insufficiency (H1). Clin Pharmacol Ther 2000; 67:137. abstract.
38. Schwartz JI, Larson PJ, Bugianesi KJ, et al. Effect of rofecoxib (R) on the pharmacodynamics and pharmacokinetics (PK) of warfarin (W). Clin Pharmacol Ther 2000;67:165. abstract.
39. Nicoll-Griffith DA, Yergey JA, Trimble LA, et al. Synthesis, characterization, and activity of metabolites derived from the cyclooxygenase-2 inhibitor rofecoxib (MK-0966, Vioxx). Bioorg Med Chem Lett 2000;10: 2683-6.
40. Hawkey C, Laine L, Simon T, et al. Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2000;43:370-7.
41. Simon LS, Lanza FL, Lipsky PE, et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. Arthritis Rheum 1998;41:1591-602.
42. Bensen WG, Fiechtner JJ, McMillen JI, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. Mayo Clin Proc 1999;74:1095-105.
43. Clemett D, Goa KL. Celecoxib: a review of its use in osteoarthritis, rheumatoid arthritis and acute pain. Drugs 2000;59:957-80.
44. Cannon GW, Caldwell JR, Holt P, et al. Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Arthritis Rheum 2000;43:978-87.
45. Day R, Morrison B, Luza A, et al. A randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. Arch Intern Med 2000;160:1781-7.
46. Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. JAMA 1999;282:1921-8.
47. McAdam BF, Mardini I, Habib A, et al. Effect of regulated expression of human cyclooxygenase isoforms on eicosanoid and isoeicosanoid production in inflammation. J Clin Invest 2000;105:1473-82.
48. Seibert K, Zhang Y, Leahy K, et al. Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. Proc Natl Acad Sci U S A 1994;91:12013-7.
49. Gilroy DW, Colville-Nash PR, Willis D, Chivers J, Paul-Clark MJ, Willoughby DA. Inducible cyclooxygenase may have anti-inflammatory properties. Nat Med 1999;5:698-701.
50. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999;282: 1929-33.
51. Silverstein FD, Graham DY, Senior JR, et al. Misoprostol reduced serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995;123:241-9.
52. Zimmermann KC, Sarbia M, Schror K, Weber AA. Constitutive cyclooxygenase-2 expression in healthy human and rabbit gastric mucosa. Mol Pharmacol 1998;54:536-40.
53. Sawaoka H, Kawano S, Tsuji S, et al. Helicobacter pylori infection induces cyclooxygenase-2 expression in human gastric mucosa. Prostaglandins Leukot Essent Fatty Acids 1998;59:313-6.
54. McCarthy CJ, Crofford LJ, Greenson J, Scheiman JM. Cyclooxygenase-2 expression in gastric antral mucosa before and after eradication of Helicobacter pylori infection. Am J Gastroenterol 1999;94:1218-23.
55. Mizuno H, Sakamoto C, Matsuda K, et al. Induction of cyclooxygenase 2 in gastric mucosal lesions and its inhibition by the specific antagonist delays healing in mice. Gastroenterology 1997;112:387-97.
56. Prescott SM. Is cyclooxygenase-2 the alpha and the omega in cancer? J Clin Invest 2000;105:1511-3.
57. Newberry RD, Stenson WF, Lorenz RG. Cyclooxygenase-2-dependent arachidonic acid metabolites are essential modulators of the intestinal immune response to dietary antigen. Nat Med 1999;5:900-6.
58. Morteau O, Morham SG, Sellon R, et al. Impaired mucosal defense to acute colonic injury in mice lacking cyclooxygenase-1 or cyclooxygenase-2. J Clin Invest 2000;105:469-78.
59. Reuter BK, Asfaha S, Buret A, Sharkey KA, Wallace JL. Exacerbation of inflammation-associated colonic injury in rat through inhibition of cyclooxygenase-2. J Clin Invest 1996;98:2076-85.
60. FitzGerald GA, Smith B, Pedersen AK, Brash AR. Increased prosta-

cyclin biosynthesis in patients with severe atherosclerosis and platelet activation. N Engl J Med 1984;310:1065-8.
61. 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.]
62. Cullen L, Kelly L, Connor SO, Fitzgerald DJ. Selective cyclooxygenase-2 inhibition by nimesulide in man. J Pharmacol Exp Ther 1998;287: 578-82.
63. Catella-Lawson F, McAdam B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther 1999;289:735-41.
64. FitzGerald GA, Brash AR, Falardeau P, Oates JA. Estimated rate of prostacyclin secretion into the circulation of normal man. J Clin Invest 1981;68:1272-5.
65. Braden GA, Knapp HR, FitzGerald GA. Suppression of eicosanoid biosynthesis during coronary angioplasty by fish oil and aspirin. Circulation 1991;84:679-85.
66. Wennmalm A, FitzGerald GA. Excretion of prostacyclin and thromboxane A_2 metabolites during leg exercise in humans. Am J Physiol 1988; 255:H15-H18.
67. Topper JN, Cai J, Falb D, Gimbrone MA Jr. Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. Proc Natl Acad Sci U S A 1996;93:10417-22.
68. Murata T, Ushikubi F, Matsuoka T, et al. Altered pain perception and inflammatory response in mice lacking prostacyclin receptor. Nature 1997; 388:678-82.
69. Crofford LJ, Oates JC, McCune WJ, et al. Thrombosis in patients with connective tissue diseases treated with specific cyclooxygenase 2 inhibitors: a report of four cases. Arthritis Rheum 2000;43:1891-6.
70. Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in northern Sweden. J Rheumatol 1997;24:445-51.
71. Wallberg-Jonsson S, Cederfelt M, Rantapaa Dahlqvist S. Hemostatic factors and cardiovascular disease in active rheumatoid arthritis: an 8 year followup study. J Rheumatol 2000;27:71-5.
72. Van Hecken A, Schwartz JI, Depre M, et al. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. J Clin Pharmacol 2000;40: 1109-20.
73. Knijff-Dutmer EA, Martens A, vd Laar MA. Effects of nabumetone compared with naproxen on platelet aggregation in patients with rheumatoid arthritis. Ann Rheum Dis 1999;58:257-9.
74. Garcia Rodriguez LA, Varas C, Patrono C. Differential effects of aspirin and nonaspirin nonsteroidal antiinflammatory drugs in the primary prevention of myocardial infarction in postmenopausal women. Epidemiology 2000;11:382-7.
75. Antithrombotic Trialists' (ATT) Collaboration. Prevention of death, myocardial infarction and stroke by antiplatelet therapy: collaborative meta-analysis of 266 trials involving 200,000 patients at high risk of occlusive vascular events. BMJ (in press).
76. Patrono C, Coller B, Dalen JE, et al. Platelet-active drugs: the relationships among dose, effectiveness, and side effects. Chest 2001;119: Suppl:39S-63S.
77. Pratico D, Tillman C, Zhang ZB, Li H, FitzGerald GA. Acceleration of atherogenesis by COX-1-dependent prostanoid formation in low density lipoprotein receptor knockout mice. Proc Natl Acad Sci U S A 2001;98:3358-63.
78. Adderley SR, Fitzgerald DJ. Oxidative damage of cardiomyocytes is limited by extracellular regulated kinases 1/2-mediated induction of cyclooxygenase-2. J Biol Chem 1999;274:5038-46.
79. Shinmura K, Tang XL, Wang Y, et al. Cyclooxygenase-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning in conscious rabbits. Proc Natl Acad Sci U S A 2000;97:10197-202.
80. Dinchuk JE, Car BD, Focht RJ, et al. Renal abnormalities and an altered inflammatory response in mice lacking cyclooxygenase II. Nature 1995;378:406-9.
81. Komhoff M, Wang JL, Cheng HF, et al. Cyclooxygenase-2-selective inhibitors impair glomerulogenesis and renal cortical development. Kidney Int 2000;57:414-22.
82. Nantel F, Meadows E, Denis D, Connolly B, Metters KM, Giaid A. Immunolocalization of cyclooxygenase 2 in the macula densa of human elderly. FEBS Lett 1999;457:475-7.
83. Patrono C, Dunn MJ. The clinical significance of inhibition of renal prostaglandin synthesis. Kidney Int 1987;32:1-12.
84. Swan SK, Rudy DW, Lasseter KC, et al. Randomized evaluations of the effects of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet: a randomized, controlled trial. Ann Intern Med 2000;133:1-9.
85. Whelton A, Maurath CJ, Verburg KM, Geis GS. Renal safety and tolerability of celecoxib, a novel cyclooxygenase-2 inhibitor. Am J Ther 2000; 159-75.
86. Whelton A. Renal aspects of treatment with conventional nonsteroidal anti-inflammatory drugs versus cyclooxygenase-2 specific inhibitors. Am J Med 2001;110:Suppl 1:33-42.
87. Panara MR, Padovano R, Sciulli MG, et al. Effects of nimesulide on constitutive and inducible prostanoid biosynthesis in human beings. Clin Pharmacol Ther 1998;63:672-81.
88. Tegeder I, Lotsch J, Krebs S, Muth-Selbach U, Brune K, Geisslinger G. Comparison of inhibitory effects of meloxicam and diclofenac on human thromboxane biosynthesis after single doses and at steady state. Clin Pharmacol Ther 1999;65:533-44.
89. Feldman M, McMahon AT. Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional nonsteroidal anti-inflammatory drugs, with less gastrointestinal toxicity? Ann Intern Med 2000;132:134-43. [Erratum, Ann Intern Med 2000;132:1011.]
90. Singla AK, Chawla M, Singh A. Nimesulide: some pharmaceutical and pharmacological aspects — an update. J Pharm Pharmacol 2000;52:467-86.
91. Shah AA, Thjodleifsson B, Murray FE, et al. Selective inhibition of COX-2 in humans is associated with less gastrointestinal injury: a comparison of nimesulide and naproxen. Gut 2001;48:339-46.
92. Porto A, Almeida H, Cunha MJ, Macciocchi A. Double-blind study evaluating by endoscopy the tolerability of nimesulide and diclofenac on the gastric mucosa in osteoarthritic patients. Eur J Rheumatol Inflamm 1994;14:33-8.
93. Bourgeois P, Dreiser RL, Lequesne MG, Macciocchi A, Monti T. Multi-centre double-blind study to define the most favourable dose of nimesulide in terms of efficacy/safety ratio in the treatment of osteoarthritis. Eur J Rheumatol Inflamm 1994;14:39-50.
94. Hawkey C, Kahan A, Steinbruck K, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. Br J Rheumatol 1998;37:937-45. [Erratum, Br J Rheumatol 1998;37:1142.]
95. Dequeker J, Hawkey C, Kahan A, et al. Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies (SELECT) trial in osteoarthritis. Br J Rheumatol 1998;37:946-51.
96. Schoenfeld P. Gastrointestinal safety profile of meloxicam: a meta-analysis and systematic review of randomized controlled trials. Am J Med 1999;107:48S-54S.