

Do Cyclooxygenase-2 Inhibitors Provide Benefits Similar to Those of Traditional Nonsteroidal Anti-Inflammatory Drugs, with Less Gastrointestinal Toxicity?

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Two forms of cyclooxygenase, cyclooxygenase-1 (COX-1) and cyclooxygenase 2 (COX-2), act as rate-limiting enzymes in prostaglandin and thromboxane synthesis. Discovery of these compounds led to the development of drugs that selectively or specifically inhibit the COX-2 isoform. Although the COX-1 isoform is expressed at fairly constant levels in cells, including the gastrointestinal mucosa and platelets, expression of COX-2 varies greatly. In many cells, low expression of COX-2 can be upregulated by various stimuli, including inflammatory cytokines, bacterial toxins, and growth factors; this suggests that COX-2 plays a role in inflammation, infection, and cellular proliferation.

It was thought that newly developed drugs designed to block COX-2 but not COX-1 would have anti-inflammatory properties and would avoid inhibiting the synthesis of gastrointestinal prostaglandins (thereby avoiding ulcers) and platelet thromboxane (thereby avoiding bleeding). Gastrointestinal ulcers and bleeding are side effects of traditional nonsteroidal anti-inflammatory drugs (NSAIDs) that block COX-1 and COX-2. Meloxicam and nimesulide, selective COX-2 inhibitors available outside the United States, are as effective as traditional NSAIDs but have similar gastrointestinal side effects. Celecoxib (Celebrex, G.D. Searle and Co., Chicago, Illinois) and rofecoxib (Vioxx, Merck and Co., Inc., West Point, Pennsylvania), selective COX-2 inhibitors approved in the United States in the past year, are also as effective as traditional NSAIDs. However, celecoxib and rofecoxib have no antiplatelet activity and lead to fewer endoscopically detected gastric and duodenal ulcers than traditional NSAIDs, such as ibuprofen or naproxen.

Preliminary analyses of data pooled from several trials suggest that celecoxib and rofecoxib are associated with fewer clinically symptomatic ulcers and ulcer complications than traditional NSAIDs are. Postmarketing surveillance should help clarify the actual risk for serious ulcer complications with these new COX-2 inhibitors and reveal other potential nongastrointestinal toxic reactions that can result from their use.

A new family of nonsteroidal anti-inflammatory drugs (NSAIDs), referred to as cyclooxygenase-2 (COX-2) inhibitors, has been developed (1–3). Two of these drugs, celecoxib (Celebrex, G.D. Searle & Co., Chicago, Illinois) and rofecoxib (Vioxx, Merck & Co., Inc., West Point, Pennsylvania), are available for use in the United States in patients with osteoarthritis (**Figure 1**). Celecoxib is also approved for treatment of rheumatoid arthritis (2), and rofecoxib is also approved for treatment of acute pain and menstrual pain (3). Two other COX-2 inhibitors, meloxicam and nimesulide, are available outside the United States.

Background

Cells use cyclooxygenase to convert arachidonic acid to prostaglandin G_2 (PGG_2) and then to prostaglandin H_2 (PGH_2), which in turn is converted to physiologically active prostaglandins and thromboxanes (**Figure 2**). Although cyclooxygenase was once thought to be one enzyme, it is now known that two different cyclooxygenases—cyclooxygenase-1 (COX-1) and COX-2—can produce PGH_2 . Cyclooxygenase-1 is expressed at a fairly constant level in most cells, including the gastrointestinal mucosa and platelets. In the gastrointestinal mucosa, COX-1 plays a particularly important physiologic role: Prostaglandins, such as prostaglandin E_2 (PGE_2), that are produced from COX-1–derived PGH_2 protect the gastrointestinal epithelial lining against ulceration. Platelets use COX-1–derived PGH_2 to generate thromboxane A_2 , which assists in hemostasis. Because traditional NSAIDs and aspirin inhibit COX-1 and COX-2 (4), they decrease gastrointestinal synthesis of prostaglandins (predisposing patients to gastrointestinal ulceration) and production of platelet thromboxane A_2 (predisposing patients to bleeding). Persons who receive long-term therapy with traditional NSAIDs have more hemorrhages and other ulcer-related complications, hospitalizations, and deaths than those who do not receive such therapy (5).

In animals, COX-2 is constitutively expressed in

Ann Intern Med. 2000;132:134-143.

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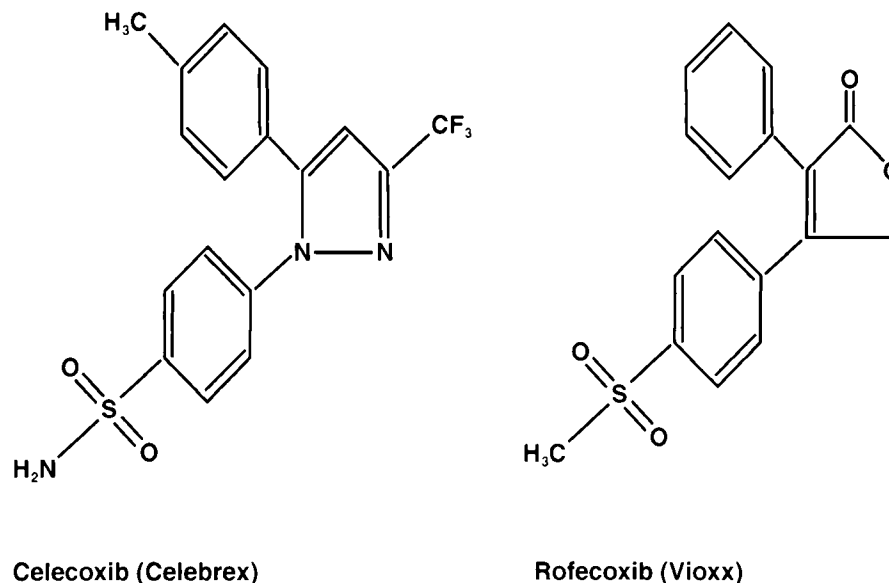


Figure 1. Chemical structures of celecoxib (Celebrex, G.D. Searle and Co., Chicago, Illinois) and rofecoxib (Vioxx, Merck and Co., Inc., West Point, Pennsylvania). Celecoxib has a sulfonamide side group, and rofecoxib has a methylsulfonyl side group. Celecoxib is contraindicated in patients who are allergic to sulfonamides.

the macula densa region of the kidney (6, 7) and in neurons in the cerebral cortex and the limbic region of the brain (8, 9). In many other cells, COX-2 is expressed at very low levels, but its expression can be dramatically upregulated by many stimuli. These stimuli include inflammatory cytokines, such as tumor necrosis factor- α and interleukin-1; mitogens, such as platelet-derived growth factor and epidermal growth factor; and bacteria-derived lipopolysaccharide (an endotoxin).

Selective COX-2 inhibitors and dual COX-1–COX-2 inhibitors result in similar reductions of cytokine-mediated, COX-2–derived prostaglandin production at sites of inflammation. However, the COX-2 inhibitors also reduce the risk for gastrointestinal ulcer formation and bleeding. Therefore, morbidity and mortality associated with use of traditional NSAIDs could be decreased by use of COX-2 inhibitors. In addition, prophylaxis of ulcers could become unnecessary in some patients receiving COX-2 inhibitors.

Cyclooxygenase-2 seems to play a vital role in ovulation, fertilization, embryo implantation, and decidua formation in mice (10, 11). Although it is not known whether COX-2 inhibitors would affect these functions in humans, they should not be used in late pregnancy because they could theoretically lead to premature closure of the ductus arteriosus (12, 13).

Traditional NSAIDs may cause renal sodium retention with weight gain and edema formation; potassium retention with hyperkalemia; and, rarely, acute renal failure. Because COX-1 and COX-2 are expressed in the kidney (6, 7), it was not clear at first whether selective COX-2 inhibitors would share

these effects. Rossat and colleagues (14) reported that in normotensive, salt-depleted persons, celecoxib resulted in decreased urinary outputs of sodium, potassium, and water that were similar to those seen with naproxen. In clinical trials, edema occurred in 2.1% (95% CI, 1.7% to 2.5%) of patients who received celecoxib and 1.1% (CI, 0.6% to 1.6%) of patients who received placebo (12). In rofecoxib trials, edema occurred in 3.7% (CI, 3.0% to 4.4%) of patients in the treatment group and 1.1% (CI, 0.4% to 1.9%) of patients in the placebo group. Because edema may result from therapy with

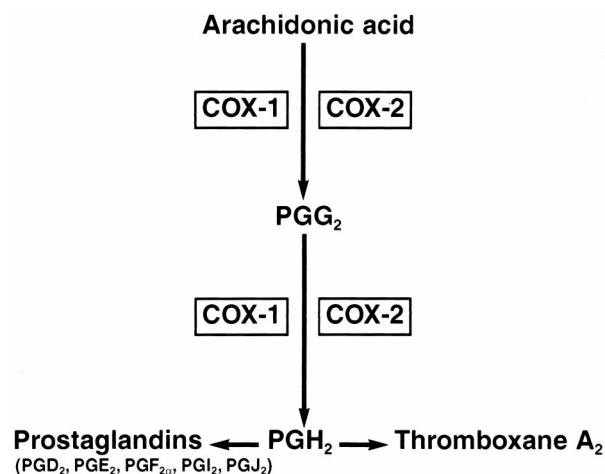


Figure 2. Reactions catalyzed by cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). These cyclooxygenases convert arachidonic acid (20:4), a fatty acid constituent of membrane phospholipids, to prostaglandin G₂ (PGG₂) (cyclooxygenase reaction) and then to prostaglandin H₂ (PGH₂) (peroxidase reaction). Prostaglandin H₂ is then converted by cells to prostaglandins or thromboxane A₂. Cyclooxygenase-1 is also known as PGH₂ synthase-1, and cyclooxygenase-2 is also known as PGH₂ synthase-2. PGG₂ = prostaglandin D₂; PGE₂ = prostaglandin E₂; PGF_{2 α} = prostaglandin F_{2 α} ; PGI₂ = prostaglandin I₂; PGJ₂ = prostaglandin J₂.

Table 1. Cyclooxygenase Selectivity of 25 Nonsteroidal Anti-Inflammatory Drugs*

Nonsteroidal Anti-Inflammatory Drug	Ratio†	Reference‡
Flurbiprofen	10.27	4, 20, 21
Ketoprofen	8.16	4
Fenoprofen	5.14	4
Tolmetin	3.93	4, 20
Aspirin	3.12	4
Oxaprosin	2.52	4
Naproxen	1.79	4, 20, 21
Indomethacin	1.78	4, 20, 21
Ibuprofen	1.69	4
Ketorolac	1.64	4, 20, 21
Piroxicam	0.79	4, 20, 21
Nabumetone, 6-MNA	0.64	4, 21
Etodolac	0.11	4, 25
Celecoxib	0.11	Cryer B, Feldman M. Unpublished data
Meloxicam	0.09	21
Mefenamic acid	0.08	4
Flurbinitroxybutylester	0.08	22
NS-398	0.07	4, 20
Diclofenac	0.05	4, 20, 21
DuP-697	0.05	20
Rofecoxib	0.05	19
Nimesulide	0.04	4
Flosulide (CGP 28238)	0.02	20
SC-58125	0.007	20, 21
L-745,337	0.004	23

* Modified from reference 4.

† Expressed as the ratio of the 50% inhibitory concentration of cyclooxygenase-2 to the 50% inhibitory concentration of cyclooxygenase-1 in whole blood. Nonsteroidal anti-inflammatory drugs with a ratio <1 indicate selectivity for cyclooxygenase-2.

‡ If more than one study determined a ratio, the median ratio was used.

COX-2 inhibitors, they, like dual COX-1–COX-2 inhibitors, should be used with caution in patients with fluid retention, heart failure, and hypertension (12, 13).

Because prostaglandins synthesized from COX-2–derived PGH₂ may mediate some of the mitogenic effects of several growth factors, COX-2 inhibitors (and dual COX-1–COX-2 inhibitors) could also prove to have a suppressive effect in certain neoplasms. For example, COX-2 messenger RNA is overexpressed in most colorectal tumors and in some colon polyps (15). Cyclooxygenase-2 inhibitors are being evaluated in patients with colon polyps and polyposis syndromes (16). Dual COX-1–COX-2 inhibitors, such as aspirin and sulindac, have been reported to be beneficial in reducing the risk for colorectal adenoma and carcinoma (17) and the number of polyps in patients with familial adenomatous polyposis (18).

Determination of Cyclooxygenase Selectivity

A drug's selectivity in inhibiting COX-2 activity is usually determined by observing a reduction in the products of the reaction catalyzed by the enzyme. When leukocytes are exposed to bacterial lipopolysaccharide, COX-2 catalyzes the reaction that results in synthesis of PGE₂. The 50% inhibitory con-

centration (COX-2 IC₅₀) of a particular drug relative to PGE₂ production is often used as a COX-2 assay. Cyclooxygenase-1 assays estimate the drug concentration that reduces generation of platelet-derived thromboxane by 50% during clotting (the COX-1 IC₅₀). Cyclooxygenase-2 selectivity is reflected by a ratio of COX-2 IC₅₀ to the COX-1 IC₅₀ that is less than 1 (4, 19–25). For NSAIDs, such ratios can vary more than 1000-fold (Table 1). New COX-2 inhibitors (meloxicam, nimesulide, flosulide, celecoxib, and rofecoxib) have high COX-2 selectivity and have IC₅₀ ratios of approximately 0.1 or less (Table 1).

Role of Cyclooxygenase-1 and Cyclooxygenase-2 in Inflammation, Pain, and Fever

Several controlled clinical trials suggest that specific suppression of COX-2 (sparing COX-1) relieves joint inflammation, pain, and fever. However, this issue is not yet entirely clear because some selective COX-2 inhibitors also inhibit COX-1 at therapeutic doses (4, 24, 25). For example, the therapeutic dosage of nimesulide (100 mg/d), a powerful COX-2 inhibitor, results in plasma levels that are high enough to inhibit COX-1, thereby reducing platelet thromboxane production (24). In addition, the experimental COX-2 inhibitor L-745,337 inhibits prostaglandin generation in inflamed bursa tissue in vitro only at concentrations that also inhibit COX-1 (26).

In rodents, COX-2 inhibition alone may be insufficient to resolve inflammation and pain, although the relevance of these studies to humans is uncertain. For example, 0.1 mg of the COX-2 inhibitor SC-58125 per kg of body weight produced a 50% inhibition of COX-2 activity in rats. However, a dose 100 times greater was required to reduce inflammation and pain (27). In another study, carrageenan was injected into the paws of rats to induce inflammation. The lowest doses of nimesulide or NS-398 that reduced the inflammation also inhibited COX-1 activity, reduced gastric mucosal prostaglandin synthesis, and damaged the gastric mucosa (28). Furthermore, NS-398 did not reduce inflammation of the paw in COX-2–deficient mice. However, indomethacin, a dual COX-1–COX-2 inhibitor, reduced the inflammation presumably by blocking COX-1 (28). Carrageenan-induced inflammation of the paw also subsided more slowly in untreated, COX-2–deficient mice than in normal mice; this suggests that COX-2 also generates anti-inflammatory prostanoids. Similarly, COX-2–derived prostaglandin D₂ and 15-deoxy^Δ¹²⁻¹⁴PGJ₂ produced

by monocytes have a late-acting anti-inflammatory effect on carrageenan-induced pleurisy in rats (29).

Celecoxib (100 mg/d to 200 mg/d) was more effective than placebo but less effective than dual COX-1–COX-2 inhibitors, such as ibuprofen (400 mg/d) or naproxen (550 mg/d), in relieving pain after dental surgery (2). Rofecoxib (50 mg/d) was effective in controlling acute pain in adults and menstrual pain in women (3, 13). Rofecoxib (25 mg/d) was also as effective as ibuprofen (400 mg/d) in reducing fever associated with an acute viral syndrome in adults. Both rofecoxib and ibuprofen were superior to placebo (30).

Role of Cyclooxygenase-2 in the Gastrointestinal Tract

Some evidence suggests that COX-2, like COX-1, may be present in normal gastric mucosa (31, 32), although not every study has found this (33). If COX-2 is present in the normal gastric mucosa, it could play a physiologic role there. For example, when the normal gastric mucosa of rats is exposed to a mild gastric irritant (for example, dilute ethanol), it is protected against subsequent injury by a stronger irritant, such as absolute ethanol (34). This protection is mediated by an increase in endogenous prostaglandin synthesis (34). In animals, selective COX-2 inhibitors (and dual COX-1–COX-2 inhibitors, such as indomethacin) abolish this protective response; this suggests that prostaglandins derived from COX-2 play a critical role in the defense reactions of the gastric mucosa (35).

Evidence also suggests that prostaglandins derived from COX-2 may be important in the healing of gastric ulcers (36–38). In experimental gastric erosions or ulcers in rodents, COX-2 (but not COX-1) messenger RNA and protein accumulated in the ulcer margin as a consequence of increased tumor necrosis factor- α and interleukin-1 β activity (38). Several COX-2 inhibitors and some dual COX-1–COX-2 inhibitors, such as indomethacin, impair the healing of these experimental lesions (36). The relevance of these observations to humans is uncertain.

Ulcers Caused By Nonsteroidal Anti-Inflammatory Drugs: Endoscopic Compared with Symptomatic

Many patients receiving long-term therapy with traditional NSAIDs have a gastric or duodenal ulcer that is visible on endoscopy (5, 39). The clinical significance of endoscopic ulcers is not clear be-

cause they usually cause no gastrointestinal symptoms. Although 10% to 20% of persons receiving NSAID therapy develop abdominal pain, dyspepsia, or nausea, ulcers are usually not found on endoscopy in such persons (5, 39). Therefore, these symptoms are poor indicators of whether an NSAID-related ulcer is present.

The most clinically relevant definition of an ulcer in persons who receive NSAID therapy is the combination of ulcer symptoms and the presence of an ulcer documented by endoscopy, barium study, or surgery (symptomatic upper gastrointestinal ulcer). The U.S. Food and Drug Administration (FDA) has placed a class warning on the labels of NSAIDs that states "... symptomatic upper GI [gastrointestinal] ulcers appear to occur in approximately 1% of patients treated for 3–6 months, and in about 2–4% of patients treated for one year."

It is uncertain whether all NSAIDs currently in use confer the same risk for gastrointestinal ulcers. It is difficult to adjust for differences in doses when comparing NSAIDs. In one analysis, 1200 mg of ibuprofen per day or less resulted in a lower incidence of complicated ulcers that required hospitalization than did several other NSAIDs (for example, ketoprofen, tolmetin, and diclofenac); this difference, however, was not seen at higher doses of ibuprofen (40). Certain NSAIDs that are mildly selective for COX-2, such as etodolac and nabumetone (**Table 1**), may confer a somewhat lower risk for ulcers than traditional NSAIDs (41, 42).

Clinical Trials with New Selective Cyclooxygenase-2 Inhibitors

We searched the MEDLINE database for articles that mentioned NSAID and COX (plus variations or derivatives of these terms) and any articles mentioning clinical trials and COX or any of the newer COX-2 inhibitors. We obtained copies of all 32 articles involving clinical trials. We eliminated 3 open-label studies (2 of meloxicam and 1 of nimesulide) and 3 additional studies in healthy volunteers (2 of meloxicam and 1 of nimesulide). The remaining 26 studies were all double-blind, controlled studies with placebo or positive (NSAID) controls.

Meloxicam

Meloxicam has been evaluated in several clinical trials in patients with arthritis or acute low back pain (43–51). All but one trial found that meloxicam and the NSAID being compared had similar clinical efficacy (**Table 2**). One 6-month study in patients with rheumatoid arthritis (51) found that naproxen

Table 2. Clinical Trials of Meloxicam or Nimesulide

Daily Dosage (Duration)	Agent Being Compared	Disorder	Patients	Gastrointestinal Adverse Events*		Withdrawals Due to Gastrointestinal Adverse Events*	
				<i>n</i>	%		%
Meloxicam							
15 mg/d (8 d)	Diclofenac (75–100 mg/d)	Acute back pain	183	Meloxicam group: 3.3 Diclofenac group: 6.5†		–	
15 mg/d (8 d)	Piroxicam (20 mg/d)	Acute back pain	169	Meloxicam group: 1.2 Piroxicam group: 7.0†		–	
15 mg/d, suppository (3 wk)	Piroxicam (20 mg/d), suppository	Osteoarthritis	325	Meloxicam group: 9.2 Piroxicam group: 11.9†		Meloxicam group: 1.4 Piroxicam group: 2.8†	
7.5 mg/d compared with 15 mg/d (3 wk)	Placebo	Rheumatoid arthritis	468	7.5-mg/d meloxicam group: 11 15-mg/d meloxicam group: 16 Placebo group: 11†		7.5-mg/d meloxicam group: 2 15-mg/d meloxicam group: 1 Placebo group: 2†	
7.5 mg/d compared with 15 mg/d and 30 mg/d (3 wk)	Placebo	Osteoarthritis	513	7.5-mg/d meloxicam group: 12.9 15-mg/d meloxicam group: 12.7 Placebo group: 12.4†‡		–	
15 mg/d (6 wk)	Diclofenac (100 mg/d)	Osteoarthritis	258	Meloxicam group: 16.4 Diclofenac group: 26.2†		–	
15 mg/d (6 wk)	Piroxicam (20 mg/d)	Osteoarthritis	256	Meloxicam group: 20.9 Diclofenac group: 22.8†		–	
7.5 mg/d (6 mo)	Diclofenac (100 mg/d)	Osteoarthritis	336	Meloxicam group: 26.6 Diclofenac group: 27.7†		Meloxicam group: 12.4 Diclofenac group: 18.7†	
7.5 mg/d (6 mo)	Naproxen (750 mg/d)	Rheumatoid arthritis	379	Meloxicam group: 26 Naproxen group: 35.6†		Meloxicam group: 6 Naproxen group: 12.2§	
Nimesulide							
200 mg/d (8 d)	Placebo	Ankle sprain	60	Nimesulide group: 13.3 Placebo group: 6.7†		–	
200 mg/d (2 wk)	Naproxen (1100 mg/d)	Tendonitis, bursitis	201	Nimesulide group: 15.8 Naproxen group: 22†		Nimesulide group: 2 Naproxen group: 4†	
200 mg/d (2 wk)	Placebo	Osteoarthritis	60	Nimesulide group: 6.7 Placebo group: 10†		Nimesulide group: 3.3 Placebo group: 3.3†	
200 mg/d (1 mo)	Diclofenac (150 mg/d)	Osteoarthritis	88	Nimesulide group: 25 Diclofenac group: 25†		Nimesulide group: 11.4 Diclofenac group: 11.4†	
100 mg/d compared with 200 mg/d and 400 mg/d (1 mo)	Placebo	Osteoarthritis	392	–†		100-mg/d nimesulide group: 6.2 200-mg/d nimesulide group: 11.2 400-mg/d nimesulide group: 13.4 Placebo group: 3	
200 mg/d (2 mo)	Ketoprofen (200 mg/d)	Osteoarthritis	60	Nimesulide group: 19.2 Ketoprofen group: 15.4†		Nimesulide group: 3.8 Ketoprofen group: 7.7†	
200 mg/d (3 mo)	Etodolac (600 mg/d)	Osteoarthritis	200	Nimesulide group: 39 Etodolac group: 34†		Nimesulide group: 6 Etodolac group: 9.1†	

* In some studies (references 50, 55, and 57), most but not all events were gastrointestinal.

† Difference is not statistically significant.

‡ Events in the 30-mg/d meloxicam group were not reported.

§ $P = 0.046$.

|| $P = 0.036$.

was slightly more efficacious than meloxicam but led to more withdrawals because of adverse gastrointestinal events; naproxen also caused two symptomatic ulcers (1% [95% CI, 0% to 2.6%]). Meloxicam did not differ from diclofenac or piroxicam in the incidence of adverse gastrointestinal events or withdrawals because of these events. In a comparative trial of 256 patients with osteoarthritis of the hip (49), 15 mg of meloxicam per day resulted in one perforated duodenal ulcer (1% [CI, 0% to 2.3%]), and 20 mg of piroxicam per day led to three symptomatic ulcers (2.4% [CI, 0% to 5.0%]), including a perforated gastric ulcer and a bleeding duodenal ulcer (49).

Nimesulide

Nimesulide has been evaluated in several clinical trials in patients with osteoarthritis or other musculoskeletal disorders (52–57). All trials found that nimesulide and the NSAID being compared had similar clinical efficacy and resulted in a similar

incidence of adverse gastrointestinal events (Table 2). In a 1-month trial involving patients with osteoarthritis (55), researchers found endoscopic ulcers in three patients who received diclofenac (7% [CI, 0% to 15%]) and in one patient who received nimesulide (2% [CI, 0% to 7%]), a nonsignificant difference. The same study reported endoscopic erosions in four patients taking nimesulide and two patients taking diclofenac, also a nonsignificant difference. No symptomatic gastrointestinal ulcers were reported.

Flosulide

Flosulide was compared with naproxen in a small 2-week crossover study in 19 patients with osteoarthritis (58). Endoscopic gastric erosions occurred in 2 patients receiving 40 mg of flosulide per day (11% [CI, 0% to 24%]) and in 10 patients receiving 1000 mg of naproxen per day (53% [CI, 30% to 75%]). No endoscopic or symptomatic ulcers occurred in either group.

Table 2—Continued

Ulcers	Reference
Not reported	43
Not reported	44
Not reported	45
1 in the 15 mg/d meloxicam group (symptomatic, esophageal)	46
Not reported	47
1 in the diclofenac group (symptomatic)	48
1 in the meloxicam group, 3 in the piroxicam group (symptomatic)	49
Not reported	50
2 in the naproxen group (symptomatic)	51
Not reported	52
Not reported	53
Not reported	54
1 in the nimesulide group, 3 in the diclofenac group (endoscopic)	55
Not reported	56
Not reported	54
Not reported	57

Celecoxib

Celecoxib was approved for treatment of osteoarthritis at 200 mg/d and for treatment of rheumatoid arthritis at 200 mg/d or 400 mg/d (2, 12, 59–62). These dosages of celecoxib (and even higher dosages of up to 1200 mg/d) have no detectable antiplatelet effect (12, 59). Celecoxib dosages of up to 800 mg/d have been evaluated in several clinical trials (12) (**Table 3**). Celecoxib had clinical efficacy superior to that of placebo and efficacy similar to that of the NSAIDs being compared. Celecoxib resulted in fewer upper gastrointestinal symptoms than naproxen in one 12-week trial in patients with rheumatoid arthritis (62) but led to similar upper gastrointestinal symptoms in a second trial (60). Celecoxib had a rate of adverse gastrointestinal events similar to that seen with diclofenac in a study of patients with rheumatoid arthritis (61). However, celecoxib led to significantly fewer withdrawals due to adverse gastrointestinal events than did diclofenac (61). The pooled effects of celecoxib, selected

NSAIDs, and placebo on common gastrointestinal symptoms are summarized in **Table 4**. Celecoxib and selected NSAIDs were associated with more abdominal pain, dyspepsia, and diarrhea than placebo. However, celecoxib was associated with less abdominal pain than ibuprofen, diclofenac, and naproxen and with less dyspepsia than naproxen.

As shown in **Table 3**, celecoxib caused many fewer endoscopic ulcers than naproxen (1000 mg/d) or ibuprofen (2400 mg/d). In one trial in persons with rheumatoid arthritis, celecoxib led to fewer endoscopic ulcers than diclofenac (150 mg/d) (61); however, this result was not seen in a second trial in persons with osteoarthritis or rheumatoid arthritis (12, 62) (**Table 3**). Endoscopic ulcers were more common with celecoxib than with placebo, but the differences were small and not statistically significant (**Table 3**).

Recently, the manufacturer of celecoxib and its investigators pooled the results of 14 controlled clinical trials that were 2 to 24 weeks in duration and involved 11 007 patients. They compared celecoxib (regardless of dose, patient diagnosis, or duration of therapy) with selected NSAIDs (regardless of type, dose, patient diagnosis, or duration of therapy) (66). Upper gastrointestinal bleeding occurred in 2 patients who were receiving celecoxib and 7 patients who were receiving NSAIDs (3 who were receiving naproxen, 3 who were receiving diclofenac, and 1 who was receiving ibuprofen). Gastrointestinal complications (bleeding, obstruction, or perforation) occurred in 0.2% of patients per year of exposure to celecoxib and in 1.7% of patients per year of exposure to traditional NSAIDs (66). The 1.5% (CI, 0.4% to 2.6%) absolute risk reduction was statistically significant.

Rofecoxib

Rofecoxib is approved for treatment of osteoarthritis (single dosages of 12.5 mg/d or 25 mg/d) and for acute pain or menstrual pain (50 mg/d) (3, 13). In one study, 25 mg of rofecoxib per day did not affect gastric mucosal prostaglandin synthesis in humans, and 1000 mg of naproxen per day reduced gastric prostaglandin levels by 72% (67). Rofecoxib dosages of 25 mg/d or 250 mg/d did not affect platelet-derived serum thromboxane concentrations; in contrast, traditional NSAIDs markedly reduced them (67, 68). Rofecoxib (12.5 mg/d and 25 g/d) has been evaluated in two placebo-controlled and NSAID-controlled trials involving 1520 patients with osteoarthritis of the hip or knee. One study compared rofecoxib with diclofenac, 150 mg/d, and the other compared rofecoxib with ibuprofen, 2400 mg/d (63, 64). Compared with placebo, rofecoxib and the selected NSAIDs had equally superior clinical efficacy. In addition, rofecoxib, 25 mg/d, was as

Table 3. Clinical Trials with Celecoxib (Celebrex) or Rofecoxib (Vioxx)*

Daily Dosage <i>mg/d</i>	Duration of Trial <i>wk</i>	Agent Being Compared	Disorder	Patients <i>n</i>
Celecoxib 100, 200, 400	12	Placebo, naproxen (1000 mg/d)	Osteoarthritis, rheumatoid arthritis	1108
200, 400, 800	12	Placebo, naproxen (1000 mg/d)	Osteoarthritis, rheumatoid arthritis	1049
400	12	Naproxen (1000 mg/d)	Osteoarthritis, rheumatoid arthritis	523
400	12	Diclofenac (150 mg/d), ibuprofen (2400 mg/d)	Osteoarthritis, rheumatoid arthritis	1062
400	24	Diclofenac (150 mg)	Rheumatoid arthritis	430
Rofecoxib				
12.5, 25	26	Placebo, diclofenac (150 mg)	Osteoarthritis	784
12.5, 25	6	Placebo†, ibuprofen (2400 mg)	Osteoarthritis	736
25, 50	24	Placebo, ibuprofen (2400 mg)	Osteoarthritis	1427

* Celebrex is manufactured by G.D. Searle and Co., Chicago, Illinois. Vioxx is manufactured by Merck and Co., Inc., West Point, Pennsylvania.

† Numbers in square brackets are 95% CIs.

‡ Given for 16 weeks only.

effective as ibuprofen, 400 mg/d, in reducing fever (30). Rofecoxib, 50 mg/d, was superior to placebo and was equal to traditional NSAIDs (ibuprofen, 400 mg/d, or naproxen, 550 mg/d) in relieving dental pain (69–71) and menstrual pain (72).

The pooled effects of rofecoxib, selected NSAIDs, and placebo on common gastrointestinal symptoms are summarized in **Table 4** (13). In general, symptoms caused by rofecoxib did not differ from those caused by placebo, ibuprofen, and diclofenac, except that diclofenac caused diarrhea more often than rofecoxib. Rofecoxib, 25 mg/d or 50 mg/d, caused many fewer endoscopic ulcers in patients with osteoarthritis than ibuprofen, 2400 mg/d, after 12 weeks and 24 weeks of treatment in two identical trials that were combined for analysis (72) (**Table 3**).

Recently, the manufacturer of rofecoxib and its investigators compared rofecoxib (regardless of dose or duration of therapy) with three traditional NSAIDs (regardless of type, dose, or duration of therapy) by pooling results of eight trials that were 6 to 86 weeks in duration and involved 5435 patients with osteoarthritis. Confirmed clinical ulcer events (including uncomplicated symptomatic and

endoscopic ulcers, perforations, and bleeding) occurred in 1.3% of patients during the first year of exposure to rofecoxib and in 1.8% of patients during the first year of exposure to traditional NSAIDs (73). The 0.5% absolute risk reduction was statistically significant.

Summary and Conclusions

Both COX-1 and COX-2 contribute to inflammatory responses in rodent models. Doses of COX-2 inhibitors that reduced inflammation in rodents were not specific for COX-2 and produced significant gastric damage through COX-1 inhibition. Studies in rodents also suggest that COX-2 plays a role in both the normal homeostasis of the stomach and in the healing of gastric erosions and ulcers. Accordingly, many COX-2 inhibitors slow ulcer healing in rodents. Whether these findings apply to humans is uncertain.

Substantial postmarketing clinical data are available for the selective COX-2 inhibitors meloxicam and nimesulide. Several controlled clinical studies of

Table 3—Continued

Patients with Ulcer† <i>n</i> (%)	<i>P</i> Value	Reference
67 endoscopic ulcers Placebo group: 5 (2.3 [0.3–4.3]) 100-mg/d celecoxib group: 8 (3.4 [1.1–5.8]) 200-mg/d celecoxib group: 7 (3.1 [0.8–5.3]) 400-mg/d celecoxib group: 13 (5.9 [2.8–9.0]) Naproxen group: 34 (16.2 [11.2–21.2])	≤0.05 for naproxen compared with all others	12
64 endoscopic ulcers Placebo group: 4 (2 [0–3.9]) 200-mg/d celecoxib group: 9 (3.9 [1.4–6.3]) 400-mg/d celecoxib group: 6 (2.7 [0.6–4.9]) 800-mg/d celecoxib group: 8 (4.1 [1.3–6.8]) Naproxen group: 37 (17.6 [12.5–22.8])	≤0.05 for naproxen compared with all others	12
109 endoscopic ulcers Celecoxib group: 20 (7.5 [4.4–10.7]) Naproxen group: 89 (34.6 [28.8–40.4])	<0.05	12
139 endoscopic ulcers Celecoxib group: 25 (7 [4.4–9.7]) Diclofenac group: 36 (9.7 [6.7–12.7]) Ibuprofen group: 78 (23.3 [18.8–27.9])	<0.05 for celecoxib compared with ibuprofen and diclofenac compared with ibuprofen	
Celecoxib group: (4) (endoscopic) Diclofenac group: (15) (endoscopic) Not reported	0.001	12 66
1 symptomatic ulcer Ibuprofen group: 1 (0.4)		67
150 endoscopic ulcers at 12 wk Placebo group: 16 (4.7 [2.5–7.0]) 25-mg/d rofecoxib group: 16 (4.3 [2.2–6.3]) 50 mg/d rofecoxib group: 27 (7.5 [4.8–10.2]) Ibuprofen group: 91 (25.7 [21.1–30.3])	<0.001 for placebo at 12 weeks, 25 mg of rofecoxib per day at 12 and 24 weeks, and 50 mg of rofecoxib per day at 12 and 24 weeks compared with ibuprofen	13, 72
At 24 wk: 25-mg/d rofecoxib group: (9.7) 50-mg rofecoxib group: (13.5) Ibuprofen group: (46.4)		

these two drugs have been published as full reports in peer-reviewed journals. Our analysis of adverse gastrointestinal events from clinical trials of meloxicam and nimesulide in thousands of patients reflects only a small reduction in adverse gastrointestinal events compared with traditional NSAIDs (**Table 2**). Symptomatic ulcers were rarely reported in these

trials, however, regardless of whether patients received COX-2 inhibitors or traditional NSAIDs.

Clinical data on the gastrointestinal toxicity of celecoxib and rofecoxib are limited and have been published mostly in abstract form and in product labels. However, these data are encouraging and show an approximately 1% absolute risk reduction

Table 4. Selected Gastrointestinal Symptoms in Pooled Celecoxib and Rofecoxib Trials*

Drug	Symptom	Persons Receiving Placebo	Persons Receiving COX-2 Inhibitors	Persons Receiving Ibuprofen, 2400 mg/d	Persons Receiving Diclofenac, 150 mg/d	Persons Receiving Naproxen, 1000 mg/d
		← % →				
Celecoxib, 200–400 mg/d†	Abdominal pain	2.8 (2.0–3.5)	4.1 (3.5–4.7)	9.0 (6.2–11.9)	9.0 (6.0–12.0)	7.7 (6.3–9.1)
	Dyspepsia	6.2 (5.1–7.3)	8.8 (7.9–9.7)	10.9 (7.8–14.0)	12.8 (9.2–16.3)	12.2 (10.5–14.0)
	Nausea	4.2 (3.3–5.1)	3.5 (2.9–4.1)	3.4 (1.6–5.2)	6.7 (4.0–9.3)	6.0 (4.7–7.3)
	Diarrhea	3.8 (2.9–4.7)	5.6 (4.9–6.3)	9.3 (6.4–12.2)	5.8 (3.3–8.3)	5.3 (4.1–6.5)
Rofecoxib, 12–25 mg/d‡	Abdominal pain	4.1 (2.7–5.5)	3.4 (2.7–4.1)	4.6 (3.2–6.0)	5.8 (5.8–7.9)	–
	Dyspepsia	2.7 (1.6–3.8)	3.5 (2.8–4.2)	4.7 (3.3–6.2)	4.0 (2.3–5.7)	–
	Nausea	4.7 (3.2–6.2)	5.2 (4.4–6.0)	7.1 (5.4–8.8)	7.4 (5.1–9.7)	–
	Diarrhea	6.8 (5–8.5)	6.5 (5.6–7.4)	7.1 (5.4–8.8)	10.6 (7.9–13.4)	–

* Data taken from references 12 and 13. COX-2 = cyclooxygenase-2.

† Trials involved a total of 8108 patients. Withdrawals due to adverse events occurred in 7.1% of celecoxib-treated patients in controlled celecoxib trials and in 6.1% of placebo recipients. Withdrawal due to abdominal pain or dyspepsia occurred in 0.7% and 0.8% of celecoxib-treated patients and in 0.6% and 0.6% of placebo recipients, respectively.

‡ Trials involved a total of 4957 patients. No published information is available on withdrawal rates.

for symptomatic ulcer disease. On the basis of these data, it seems that for every 100 patients treated with a COX-2 inhibitor instead of a traditional NSAID, one symptomatic ulcer may be prevented during the first year of exposure. Trials that directly compare celecoxib and rofecoxib have not yet been reported.

New COX-2 inhibitors available in the United States seem to be safer than traditional NSAIDs. However, life-threatening and fatal ulcer complications have been reported in patients receiving celecoxib (66) and rofecoxib (73), although a cause-and-effect relation has not been proven. The FDA requires that packaging for celecoxib and rofecoxib carry gastrointestinal ulcer warnings similar to those used for traditional NSAIDs. Such warnings remain appropriate for celecoxib and rofecoxib until post-marketing surveillance studies demonstrate that these drugs confer little or no risk for symptomatic gastrointestinal ulcers above the baseline risk, especially during long-term use. Whether use of COX-2 inhibitors in place of traditional NSAIDs will prove to be cost-effective by reducing ulcer-related morbidity, hospitalizations, and mortality—particularly with long-term use—remains to be demonstrated.

Note added in proof: The equal efficacy of celecoxib and naproxen in rheumatoid arthritis, with fewer endoscopic ulcers in the celecoxib groups, was reported in a recent paper (Simon LS, Weaver AL, Graham DY, Kivitz AJ, Lipsky PE, Hubbard RC, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA*. 1999;282:1921-8).

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Disclaimer: Dr. Feldman performed clinical studies of rofecoxib for Merck and Co., Inc., before the drug received FDA approval. He currently has no consulting or financial arrangements with any company that manufactures NSAIDs or COX-1–COX-2 inhibitors. Mr. McMahon and Salix Pharmaceuticals, Inc., have no current financial interest in the use of NSAIDs or COX-1–COX-2 inhibitors for the treatment of arthritis or other conditions and are not now involved in the manufacture of any related drugs or products.

Acknowledgments: The authors thank Drs. Byron Cryer, Ping Hsu, Lorin Johnson, and Salahuddin Kazi for their useful comments and Vicky Robertson for helping prepare the manuscript.

Grant Support: By the Veterans' Administration (Merit Award to Dr. Feldman).

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