REVIEW ARTICLE

Cyclooxygenase-2 Inhibitors

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Cyclooxygenase (COX) catalyzes the initial step of arachidonic acid metabolism and prostaglandin production. COX activity has been found to be associated with two distinct isoenzymes, COX-1 and COX-2. COX-1 was hypothesized to be involved in the maintenance of physiologic functions such as gastric protection and hemostasis, whereas COX-2 was thought to be involved in pathophysiologic processes such as inflammation, pain, and fever. This compelling hypothesis led to the development of the currently available selective COX-2 inhibitors celecoxib, rofecoxib, and valdecoxib. These drugs have analgesic efficacy comparable with that of conventional nonsteroidal antiinflammatory drugs (NSAIDs). In addition, they have no antiplatelet activity at therapeutic dosages and may be associated with reduced gastrointestinal (GI) side effects compared with conventional NSAIDs such as ibuprofen.

COX Expression and Function

NSAIDs are a commonly used group of medications with a number of advantageous features (Table 1). NSAIDs were discovered to act by inhibition of the enzyme COX, which catalyzes the synthesis of prostaglandins from arachidonic acid (1–3). The COX gene was cloned by three separate research groups in 1988 (4–6), and two isoforms of COX have since been identified: COX-1 and COX-2 (7–14). The 2 isoforms have an approximate 60% amino acid homology, similar tertiary structures, and similar, but not identical, active sites (15–17).

COX-1 is expressed constitutively throughout the body (18–21) and is only slightly upregulated (two- to fourfold) in some cells in response to hormones or growth factors (22). It plays an essential role in homeostatic processes such as platelet aggregation, GI protection, and renal function.

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In contrast, COX-2 is expressed predominantly in inflammatory cells and is involved in the synthesis of prostaglandins mediating pathologic processes such as pain, inflammation, fever, and carcinogenesis (23–25). Expression of COX-2 may facilitate several oncogenic processes, including tumor invasion, angiogenesis, and metastasis (26–28). However, COX-2 has also been detected in the brain, testes, kidney, and trachea (29–32). COX-2 induction within the spinal cord may play an important role in central sensitization (33–38). Indeed, the acute antihyperalgesic action of NSAIDs has been shown to be mediated by the inhibition of constitutive spinal COX-2 (39). In response to inflammation and other stressors, COX-2 expression is markedly upregulated (10- to 20-fold) by a variety of mediators (40).

These distinct expression patterns have led to the theory that COX-1-derived prostaglandins are largely responsible for physiologic (housekeeping) functions (41), whereas COX-2-derived prostaglandins mediate pathophysiologic and inflammatory processes, including pain (Fig. 1). Conventional NSAIDs inhibit both COX-1 and COX-2 (42–48). It was hypothesized that selective COX-2 inhibitors would have the advantages of conventional NSAIDs but would not interfere with GI protection or hemostasis (49,50). However, it may be overly simplistic to view the efficacy and safety of NSAIDs only in terms of their effects on prostaglandin synthesis (51). Physicochemical and pharmacokinetic factors may also be important (52–54).

It is interesting to note that the existence of a COX-3 enzyme has been postulated. In a rat carrageenan pleurisy model, there was a second increase in COX-2 protein at 48 h that produced antiinflammatory prostanoids (55). It was suggested that this protein, which was formed during the resolution phase of inflammation, may represent a third COX isoform, COX-3. COX-3 has been proposed as a possible site of action for acetaminophen (56–58).

COX-2-Selective Drugs

Celecoxib (Celebrex®; Pharmacia, Peapack, NJ; Pfizer, New York, NY) was approved by the Food and Drug Administration in December 1998 (56), rofecoxib

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Table 1. Features of Conventional Nonsteroidal Antiinflammatory Drugs

Reduce the activation and sensitization of peripheral nociceptors
Attenuate the inflammatory response
May have a central effect
No dependence/addiction potential
Synergistic effects with opioids
Opioid-sparing effect (20%–50%)
Used as part of multimodal analgesia
Used for preemptive analgesia (decreased neuronal sensitization)
Used for pain prophylaxis (decreased postoperative pain)
Do not cause respiratory depression
Cause less nausea and vomiting than opiates
Long duration of action
Less dose variability than opiates
Cover some pain types better than opiates (bone pain, pain during movement)
No pupillary changes
No cognitive impairment

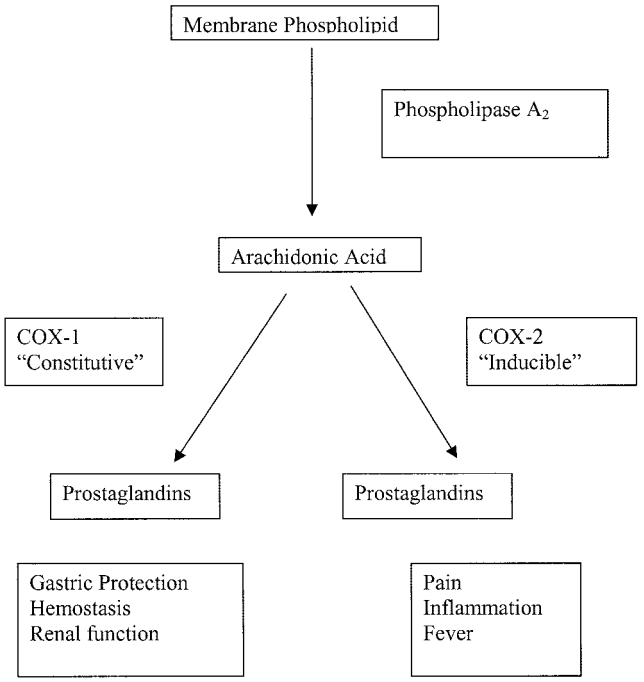

Figure 1. Cyclooxygenase (COX) pathways.

(Vioxx®; Merck, Whitehouse Station, NJ) in May 1999, and valdecoxib (Bextra®; Pharmacia) in November 2001 (59) (Fig. 2). Parecoxib is an injectable prodrug of valdecoxib that has yet to be approved by the Food and Drug Administration (60,61).

Although the biochemical selectivity of COX-2 inhibitors may be analyzed in several different *in vitro* assays, the most relevant evaluate the drug-enzyme interaction in whole-blood assays (62,63). Thromboxane B2 generated in clotting whole blood is a validated measure for COX-1 activity, and prostaglandin E_2 (PGE_2) production after incubation of whole blood with lipopolysaccharide is a validated measure of COX-2 activity (64,65). Whole-blood assays have shown the following COX-2/COX-1 selectivity ratios: ibuprofen, 0.2; indomethacin, 0.4; meloxicam, 2.0; etodolac, 2.4; diclofenac, 3; celecoxib, 7.6; valdecoxib, 30; rofecoxib, 35; and etoricoxib, 106 (66,67). However, the clinical relevance of whole-blood assays has been questioned, and the relationship of COX-2 selectivity to patient outcome remains to be established (68–70).

The currently available COX-2 inhibitors are chemically distinct compounds (Table 2). Celecoxib is a sulfonamide that is extensively distributed into tissues (volume of distribution is 400 L for the 200-mg dose) and is metabolized by the cytochrome P450 2C9/3A4 system. Indeed, interaction with other P450 inhibitors has been observed. Its half-life is 11 h. Rofecoxib, however, is a sulfone that is not as well distributed into tissues (volume of distribution is 86 L for the 25-mg dose) and is metabolized principally by cytosolic reduction. Cytochrome P450 plays only a minor role; thus, no important interaction with other P450 inhibitors has been observed. Its half-life is 17 h. These differences may result in variations in the degree of COX-2 versus COX-1 inhibition or in additional effects unrelated to COX-2 inhibition at the tissue level. This might also explain the differences in blood pressure increases and edema frequency reported by Whelton et al. (71).

Initial comparative trials with NSAIDs demonstrated the analgesic efficacy of selective COX-2 inhibition with a decreased incidence of GI side effects in patients with arthritis. These data and the high commercial value of the market, along with extensive marketing programs, have led to wide-ranging use for a number of indications (Table 3).

Analgesic Efficacy

Each trial has been assessed for quality by using a 1–5 scale (72) (Table 4). One point each was given if the report was described as randomized and double-blinded and if there was a description of withdrawals or dropouts. An additional point each was given if the method of randomization was described and adequate and if the method of blinding was adequate and appropriate.

Osteoarthritis. A 6-wk trial evaluated the efficacy of two doses of celecoxib (100 mg twice daily [BID] and 200 once daily [QD]) in patients with osteoarthritis (OA) of the knee in flare (73). Celecoxib was more effective than placebo, with comparable benefits for both dosages. Another study of patients with OA of the knee showed that patients treated with celecoxib 100 mg BID had significantly greater improvements in pain scores than with either naproxen 500 mg BID or placebo (74). In a large study of patients with OA of

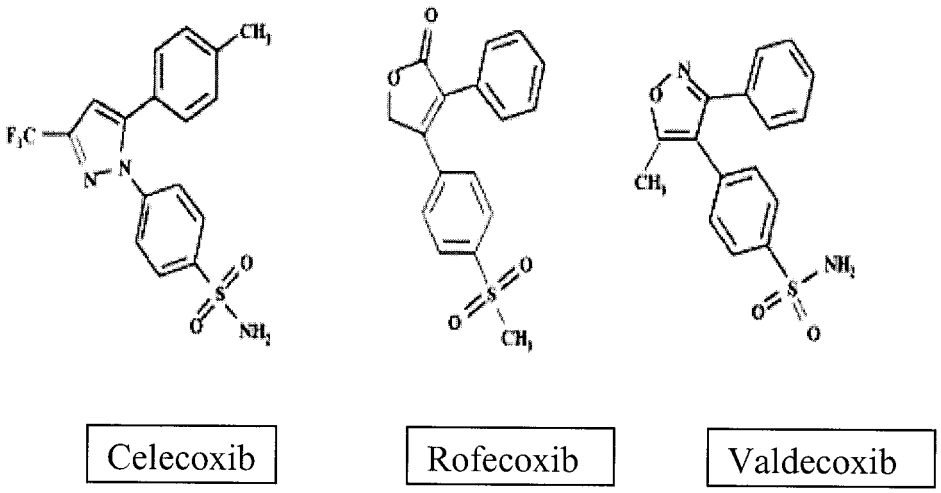

Figure 2. Structure of cyclooxygenase-2 inhibitors.

Table 2. Comparison of Currently Available Cyclooxygenase-2 Inhibitors

Variable	Celecoxib	Rofecoxib	Valdecoxib
Molecular weight	381.38	314.36	314.36
Elimination $t_{1/2}$ (h)	12	17	8–11
VD (L)	400	86–89	86
Protein binding	98%	87%	98%
Metabolism	Cytochrome P450 (2C9)	Cytosolic enzymes	Cytochrome P450 (3A4 and 2C9) Noncytochrome pathway (glucuronidation)
Metabolite	Inactive	Active	Active

VD = volume of distribution.

Table 3. Indications and Dosage Recommendations for Cyclooxygenase-2 Inhibitors

Drug	Indication	Dosage
Celecoxib	Osteoarthritis	200 mg QD or 100 mg BID
	Rheumatoid arthritis	100–200 mg BID
	Familial adenomatous polyposis	400 mg BID
	Acute pain and primary dysmenorrhea	400 mg initially, followed by an additional 200 mg if needed, then 200 mg BID PRN
Rofecoxib	Osteoarthritis	12.5–25 mg QD
	Rheumatoid arthritis	25 mg QD
	Acute pain	50 mg QD
	Primary dysmenorrhea	50 mg QD
Valdecoxib	Osteoarthritis	10 mg QD
	Rheumatoid arthritis	10 mg QD
	Primary dysmenorrhea	20 mg BID PRN

QD = once daily; BID = twice daily; PRN = as needed.

the knee, Bensen et al. (75) found celecoxib 100 mg BID, celecoxib 200 BID, and naproxen 500 mg BID to be equally effective.

In a 6-wk study of patients with OA of the knee, rofecoxib 25 mg and 125 mg were found to be equally effective, and both were more effective than placebo (76). In another study of patients with OA of the hip or knee in flare, subjects were randomized to receive rofecoxib 12.5 mg QD, rofecoxib 25 mg QD, ibuprofen 800 mg three times daily (TID), or placebo (77). Both doses of rofecoxib and ibuprofen were equally effective and were more effective than placebo.

Saag et al. (78) conducted two studies in patients with OA of the knee or hip. A 6-wk study compared rofecoxib 12.5 mg QD, rofecoxib 25 mg QD, and ibuprofen 800 mg TID, and a 1-yr study compared rofecoxib 12.5 mg QD, rofecoxib 25 mg QD, and diclofenac 50 mg TID. Rofecoxib 12.5 mg and 25 mg demonstrated efficacy comparable with that of ibuprofen. Both rofecoxib doses and ibuprofen provided significantly greater efficacy than placebo at 6 wk. Both rofecoxib doses and diclofenac showed similar efficacy over 1 yr. Another 1-yr randomized study of patients with OA of the hip and knee assessed the

Table 4. Analgesic Efficacy

Author/study population	Quality score	Groups	Efficacy
Williams et al. (73)/718 patients with osteoarthritis of the knee	3	Placebo Celecoxib 100 mg BID Celecoxib 200 mg BID	Celecoxib 100 mg BID = celecoxib 200 mg BID > placebo
Zhao et al. (74)/1004 patients with osteoarthritis of the knee	3	Placebo Celecoxib 50 mg BID Celecoxib 100 mg BID Celecoxib 200 mg BID Naproxen 500 mg BID	Celecoxib 100 mg BID > celecoxib 200 mg BID = naproxen 500 mg BID > celecoxib 50 mg BID > placebo
Bensen et al. (75)/1003 patients with osteoarthritis of the knee	4	Placebo Celecoxib 50 mg BID Celecoxib 100 mg BID Celecoxib 200 mg BID Naproxen 500 mg BID	Celecoxib 100 mg BID = celecoxib 200 mg BID = naproxen 500 mg BID > celecoxib 50 mg BID > placebo
Ehrich et al. (76)/219 patients with osteoarthritis of the knee	5	Placebo Rofecoxib 25 mg QD Rofecoxib 125 mg QD	Rofecoxib 25 mg QD = rofecoxib 125 mg QD > placebo
Day et al. (77)/809 patients with osteoarthritis of the knee or hip	5	Placebo Rofecoxib 12.5 mg QD Rofecoxib 25 mg QD Ibuprofen 800 mg TID	Rofecoxib 12.6 mg QD = rofecoxib 25 mg = ibuprofen 800 mg TID > placebo
Saag et al. (78)/736 patients with osteoarthritis of the knee or hip	5	Placebo Rofecoxib 12.5 mg QD Rofecoxib 25 mg QD Ibuprofen 800 mg TID	Rofecoxib 12.5 mg QD = rofecoxib 25 mg QD = ibuprofen 800 mg TID > placebo
Cannon et al. (79)/784 patients with osteoarthritis of the knee or hip	3	Rofecoxib 12.5 mg QD Rofecoxib 25 mg QD Diclofenac 50 mg TID	Rofecoxib 12.5 mg QD = rofecoxib 25 mg QD = diclofenac 50 mg TID
McKenna et al. (80)/182 patients with osteoarthritis of the knee	5	Placebo Celecoxib 200 mg QD Rofecoxib 50 mg QD	Celecoxib 200 mg QD = rofecoxib 50 mg QD > placebo
Geba et al. (81)/382 patients with	5	Rofecoxib 12.5 mg QD Rofecoxib 25 mg QD Celecoxib 200 mg QD Acetaminophen (APAP) 4000 mg	Rofecoxib 25 mg QD > rofecoxib 12.5 mg QD = celecoxib 200 mg QD > APAP 4000 mg
Fiechtner et al. (82)/642 patients with osteoarthritis of the knee	2	Placebo Valdecoxib 0.5 mg BID Valdecoxib 1.25 mg BID Valdecoxib 5 mg BID Valdecoxib 10 mg BID Valdecoxib 10 QD Naproxen 500 mg BID	Valdecoxib 5.0 mg BID = valdecoxib 10 mg BID = valdecoxib 10 mg QD = naproxen 500 mg BID > valdecoxib 1.25 mg BID > placebo = valdecoxib 0.5 mg BID
Kivitz et al. (83)/1019 patients with osteoarthritis of the knee	5	Placebo Valdecoxib 5 mg QD Valdecoxib 10 mg QD Valdecoxib 20 mg QD Naproxen 500 mg BID	Valdecoxib 10 mg QD = valdecoxib 20 mg QD = naproxen 500 mg BID > valdecoxib 5 mg QD = placebo
Makarowski et al. (84)/467 patients with osteoarthritis of the hip	3	Placebo Valdecoxib 5 mg QD Valdecoxib 10 mg QD Naproxen 500 mg BID	Valdecoxib 10 mg QD = naproxen 500 mg BID > valdecoxib 5 mg QD = placebo
Simon et al. (85)/1149 patients with rheumatoid arthritis	5	Placebo Celecoxib 100 mg BID Celecoxib 200 mg BID Celecoxib 400 mg BID	Celecoxib 100 mg BID = celecoxib 200 mg BID = celecoxib 400 mg BID = naproxen 500 mg BID > placebo
Emery et al. (86)/655 patients with rheumatoid arthritis	3	Celecoxib 200 mg BID Diclofenac 75 mg BID	Celecoxib 200 mg BID = diclofenac 75 mg BID

Table 4. *Continued*

Author/study population	Quality score	Groups	Efficacy
Schnitzer et al. (87)/658 patients with rheumatoid arthritis	3	Placebo Rofecoxib 5 mg QD Rofecoxib 25 mg QD Rofecoxib 50 mg QD	Rofecoxib 50 mg QD = rofecoxib 25 mg QD > rofecoxib 5 mg QD = placebo
Bensen et al. (88)/1089 patients with rheumatoid arthritis	2	Placebo Valdecoxib 10 mg QD Valdecoxib 20 mg QD Valdecoxib 40 mg QD Naproxen 500 mg BID	Valdecoxib 40 mg QD = valdecoxib 20 mg QD = valdecoxib 10 mg QD = naproxen 500 mg BID > placebo
Dougados et al. (90)/246 patients with ankylosing spondylitis	3	Placebo Celecoxib 100 mg BID Ketoprofen 100 mg BID	Celecoxib 100 mg BID = ketoprofen 100 mg BID > placebo
Ekman et al. (91)/443 patients with acute ankle sprain	3	Placebo Celecoxib 400 mg/d Ibuprofen 2400 mg/d	Celecoxib 400 mg = ibuprofen 2400 mg > placebo
Petrella et al. (92)/397 patients with acute ankle sprain	2	Celecoxib 200 mg BID Naproxen 500 mg BID	Celecoxib 200 mg BID = naproxen 500 mg BID
Bertin et al. (93)/202 patients with acute shoulder pain	2	Celecoxib 200 mg BID Naproxen 500 mg BID	Celecoxib 200 mg BID = naproxen 500 mg BID
Reuben and Connelly (94)/60 patients undergoing spinal fusion	2	Placebo Rofecoxib 50 mg Celecoxib 200 mg	Rofecoxib 50 mg > celecoxib 200 mg > placebo
Bekker et al. (95)/61 patients undergoing lumbar disk surgery	4	Placebo Rofecoxib 50 mg	Rofecoxib 50 mg > placebo (morphine requirement decreased 37%)
Reicin et al. (96)/218 patients undergoing major orthopedic surgery	5	Placebo Rofecoxib 25 mg Rofecoxib 50 mg Naproxen 550 mg	Rofecoxib 50 mg = naproxen 550 mg > rofecoxib 25 mg > placebo
Reuben et al. (97)/60 patients undergoing arthroscopic knee surgery	4	Placebo Rofecoxib 50 mg before surgery Rofecoxib 50 mg after surgery	Rofecoxib 50 mg before surgery > 50 mg after surgery > placebo
Issioui et al. (98)/68 patients undergoing orthopedic surgery	3	Placebo Celecoxib 200 mg Rofecoxib 50 mg Ibuprofen 800 mg	Celecoxib 200 mg = rofecoxib 50 mg = ibuprofen 800 mg > placebo
Gimbel et al. (99)/418 patients undergoing ambulatory orthopedic surgrey	3	Placebo Celecoxib 200 mg TID Hydrocodone 10/1000 TID (10 mg/APAP 100 mg)	Celecoxib 200 mg TID > hydrocodone 10/1000 TID > placebo
Desjardins et al. (100)/223 patients undergoing bunionectomy	5	Placebo Valdecoxib 20 mg Valdecoxib 40 mg Valdecoxib 80 mg	Valdecoxib 80 mg = valdecoxib 40 mg > valdecoxib 20 mg > placebo
Camu et al. (101)/217 patients undergoing hip arthroplasty	2	Placebo Valdecoxib 20 mg BID Valdecoxib 40 mg BID	Valdecoxib 40 mg BID = 20 mg BID > placebo (morphine requirement decreased 40%)
Issioui et al. (103)/112 patients undergoing ear-nose-throat surgery	3	Placebo Acetaminophen 2 g Celecoxib 200 mg Celecoxib 200 mg/ acetaminophen 2 g	Celecoxib 200 mg/APAP 2 g > celecoxib 200 mg = APAP 2 g = placebo
Issioui et al. (104)/68 patients undergoing ear-nose-throat surgery	3	Placebo Aetaminophen (APAP) 2 g Rofecoxib 50 g Aetaminophen 2 g/ rofecoxib 50 mg	Rofecoxib 50 mg = rofecoxib 50 mg/APAP 2 g > APAP 2 g = placebo

Table 4. *Continued*

Author/study population	Quality score	Groups	Efficacy
Shen et al. (106)/25 patients undergoing lower abdominal surgery	2	Placebo Rofecoxib 25 mg Rofecoxib 50 mg	Rofecoxib 50 mg > rofecoxib 25 mg > placebo
Morrison et al. (107)/151 patients undergoing dental surgery	3	Placebo Rofecoxib 50 mg Ibuprofen 400 mg	Rofecoxib 50 mg = ibuprofen 400 mg > placebo
Ehrich et al. (108)/102 patients undergoing dental surgery	2	Placebo Rofecoxib 50 mg Ibuprofen 400 mg	Rofecoxib 50 mg = ibuprofen 400 mg > placebo
Chang et al. (109)/305 patients undergoing dental surgery	5	Placebo Rofecoxib 50 mg Diclofenac 50 mg TID	Rofecoxib 50 mg > diclofenac 50 mg > placebo
Chang et al. (110)/393 patients undergoing dental surgery	4	Placebo Rofecoxib 50 mg Codeine 60 mg/APAP 600 mg	Rofecoxib 50 mg > codeine 60 mg/APAP 600 mg > placebo
Malmstrom et al. (112)/272 patients undergoing dental surgery	4	Placebo Rofecoxib 50 mg Celecoxib 200 mg Ibuprofen 400 mg	Rofecoxib 50 mg = ibuprofen 400 mg > celecoxib 200 mg
Daniels et al. (113)/284 patients undergoing oral surgery	2	Placebo Valdecoxib 10 mg Valdecoxib 20 mg Valdecoxib 40 mg Valdecoxib 80 mg	Valdecoxib 80 mg = valdecoxib 40 mg > valdecoxib 20 mg = valdecoxib 10 mg > placebo
Daniels et al. (114)/406 patients undergoing dental surgery	5	Placebo Valdecoxib 20 mg Valdecoxib 40 mg Oxycodone 10 mg/APAP 1000 mg	Valdecoxib 40 mg = oxycodone 10 mg/APAP 1000 mg > valdecoxib 20 mg > placebo
Fricke et al. (115)/203 patients undergoing oral surgery	2	Placebo Valdecoxib 40 mg Rofecoxib 50 mg	Valdecoxib 40 mg > rofecoxib 50 mg > placebo
Morrison et al. (117)/127 patients	5	Placebo Rofecoxib 25 mg Rofecoxib 50 mg Naproxen 550 mg	Rofecoxib 50 mg = rofecoxib 25 mg = naproxen 550 mg > placebo
Daniels et al. (118)/120 patients with primary dysmenorrhea	4	Placebo Valdecoxib 20 mg Valdecoxib 40 mg Naproxen 550 mg	Valdecoxib 40 mg = valdecoxib 20 mg = naproxen 550 mg > placebo

BID = twice daily; QD = once daily; TID = three times daily.

efficacy of rofecoxib 12.5 mg QD, rofecoxib 25 mg QD, and diclofenac 50 mg TID. The three treatments were equally effective (79).

In a 6-wk study of patients with OA of the knee, celecoxib 200 mg QD and rofecoxib 25 mg QD were found to be equally effective and more effective than placebo (80). In another study, patients with symptomatic OA of the knee were randomly assigned to receive rofecoxib 12.5 mg QD, rofecoxib 25 mg QD, celecoxib 200 mg QD, or acetaminophen 4000 mg/d for 6 wk (81). Rofecoxib 25 mg QD was more effective than acetaminophen 4000 mg/d, celecoxib 200 mg QD, or rofecoxib 12.5 mg QD.

In a study by Fiechtner et al. (82), patients with OA of the knee were randomized to receive valdecoxib 0.5, 1.25, 2.5, 5, or 10 mg BID; valdecoxib 10 mg QD; naproxen 500 mg BID; or placebo. Valdecoxib demonstrated analgesic efficacy that was significantly better than that of placebo at every dose except 0.5 mg BID. The greatest improvements were observed at 5 mg BID, 10 mg QD, and 10 mg BID, compared with placebo. Valdecoxib doses of 5 mg BID, 10 mg QD, and 10 mg BID were also as effective as naproxen 500 mg BID. Kivitz et al. (83) randomized patients with osteoarthritis of the knee to receive valdecoxib 5, 10, or 20 mg QD; placebo; or naproxen 500 mg BID. Valdecoxib 10 and 20 mg and naproxen were similarly effective, and these treatments were all more effective than placebo. In addition, the incidence of endoscopically confirmed

gastroduodenal ulcers was significantly more frequent in the naproxen group than in all valdecoxib groups. In a study of patients with symptomatic OA of the hip, subjects were randomized to receive placebo, valdecoxib 5 mg QD, valdecoxib 10 mg QD, or naproxen 500 mg BID (84). Valdecoxib 10 mg QD and naproxen 500 mg BID demonstrated similar efficacy, and both were significantly more effective than placebo.

Rheumatoid Arthritis. In a study of patients with rheumatoid arthritis, patients were randomized to receive celecoxib 100, 200, or 400 mg BID; naproxen 500 mg BID; or placebo (85). All dosages of celecoxib and naproxen were more effective than placebo. Another study showed that celecoxib 200 mg BID was as effective as diclofenac 75 mg BID (86). In a study by Schnitzer et al. (87), 3 dosages of rofecoxib (5, 25, and 50 mg QD) were compared with placebo over 8 wk in patients with rheumatoid arthritis in flare. Patients receiving rofecoxib 25 and 50 mg showed significant clinical improvement compared with those taking placebo. Rofecoxib 5 mg did not differ significantly from placebo.

A 12-wk study compared the efficacy and tolerability of single daily doses of valdecoxib 10, 20, and 40 mg with naproxen 500 mg BID or placebo in patients with rheumatoid arthritis (88). All doses of valdecoxib and naproxen had similar efficacy and were significantly more effective than placebo. However, naproxen demonstrated an increased incidence of abdominal pain, dyspepsia, and constipation compared with the smaller doses of valdecoxib (10 and 20 mg QD). COX-2 inhibitors are now recommended as the drugs of choice by the American Pain Society for moderate to severe pain from both OA and rheumatoid arthritis because of their efficacy and infrequent GI side-effects (89).

Other Musculoskeletal Conditions. In a 6-wk study of patients with ankylosing spondylitis, celecoxib 100 mg BID demonstrated equal efficacy compared with ketoprofen 100 mg BID, and both were superior to placebo (90). In a 10-day trial, patients with ankle sprain were randomly allocated to receive celecoxib 400 mg/d, ibuprofen 2400 mg/d, or placebo (91). Celecoxib and ibuprofen were more effective than placebo, and celecoxib-treated patients demonstrated faster functional recovery. In a 7-day trial of patients with acute ankle sprain, celecoxib 200 mg BID and naproxen 500 mg BID were found to be of equal efficacy (92). In another study, patients with acute shoulder pain were randomized to receive celecoxib 200 mg BID or naproxen 500 mg BID for 14 days; both treatments were found to be equally effective (93).

Acute Postoperative Pain. Reuben and Connelly (94) studied the analgesic efficacy of a single dose of rofecoxib 50 mg, celecoxib 200 mg, or placebo given 1 h before spinal fusion surgery. Patients given placebo required an average of 117 mg of morphine per day after surgery; celecoxib patients, 107 mg (9% reduction); and rofecoxib patients, 71 mg (39% reduction). Although both rofecoxib and celecoxib produced similar analgesic effects in the first 4 h after surgery, rofecoxib demonstrated an extended analgesic effect that lasted throughout the 24-h study period. Bekker et al. (95) studied the analgesic efficacy of rofecoxib 50 mg or placebo before lumbar disk surgery. The first dose of medication was given on the night before surgery, and a second dose was given 30 min before the induction of general anesthesia. Patients given rofecoxib required less morphine in the immediate postoperative period while in the postanesthesia care unit (PACU) than the placebo group (5.0 vs 7.9 mg; $P < 0.05$). Patients in the rofecoxib group had fewer pain scores more than 7 out of 10 and had lower mean arterial blood pressures on arrival to the PACU compared with the placebo group.

In a study of patients undergoing major orthopedic surgery, rofecoxib 50 mg, naproxen 550 mg, or placebo was given on Day 1 after surgery (96). On Days 2 to 5, patients in the placebo and naproxen groups received placebo, and the rofecoxib group received rofecoxib 25 or 50 mg. Rofecoxib 50 mg was found to be superior to placebo and similar to naproxen for all measures of pain relief. On Days 2 to 5, the rofecoxib 50 mg group of patients used less supplemental narcotic analgesia and reported less pain on global evaluations compared with the placebo group.

Reuben et al. (97) studied patients undergoing arthroscopic knee surgery under local anesthesia. Subjects were randomly allocated to receive rofecoxib 50 mg 1 h before surgical incision, rofecoxib 50 mg after the completion of surgery, or placebo 1 h before surgery. The administration of rofecoxib 50 mg before surgery provided a longer duration of postoperative analgesia, less 24-h opioid use, and lower pain scores during movement compared with patients given rofecoxib 50 mg after the completion of surgery. In a study of patients undergoing outpatient orthopedic surgery, patients were randomly allocated to receive placebo, ibuprofen 800 mg, celecoxib 200 mg, or rofecoxib 50 mg, 30–90 min before general anesthesia (98). Premedication with NSAIDs reduced the times to achieve fast-track eligibility. The NSAIDs also decreased the requirement for analgesic medication. In addition, rofecoxib was associated with a reduced time to home discharge.

Gimbel et al. (99) studied the efficacy and tolerability of celecoxib versus hydrocodone/acetaminophen in the treatment of pain after ambulatory orthopedic surgery. Patients were randomly allocated to receive celecoxib 200 mg, hydrocodone 10 mg/acetaminophen 1000 mg, or placebo within 24 h after the end the surgery, with pain assessments made for 8 h after the first dose of

medication. Over the subsequent 5 days, patients received either celecoxib 200 mg TID as needed or hydrocodone 10 mg/acetaminophen 1000 mg TID as needed. During the first eight postoperative hours, patients with moderate to severe pain after orthopedic surgery experienced comparable analgesia with single doses of celecoxib and hydrocodone. During the 5-day period, patients in the celecoxib group had superior analgesia and tolerability compared with patients in the hydrocodone/acetaminophen group. Most patients required no more than 2 daily doses of celecoxib 200 mg for the control of their postorthopedic surgical pain.

It should be noted that many of the acute-pain studies are flawed because they have not compared equipotent dosages of the different COX-2 inhibitors. For acute pain, rofecoxib 50 mg QD should be compared with celecoxib 400 mg followed by an additional 200 mg on the first day if necessary. The need for an initial loading dose of celecoxib is related to its large volume of distribution.

In another study, patients undergoing bunionectomy were randomly allocated to receive valdecoxib 20, 40, or 80 mg or placebo 45–75 min before surgery (100). Patients in the valdecoxib groups had superior analgesia compared with placebo and required less rescue medication. Time to the use of rescue medication was significantly longer in the valdecoxib 40 mg and 80 mg groups relative to the valdecoxib 20 mg and placebo groups.

In a more recent study of patients undergoing hip arthroplasty, subjects received placebo, valdecoxib 20 mg BID, or valdecoxib 40 mg BID (101). Study medication was first given 1 to 2 h before surgery, and the surgery was performed under spinal anesthesia. After surgery, patients received IV patient-controlled analgesia with morphine. Patients receiving valdecoxib 20 or 40 mg BID required on average 40% less morphine than those receiving placebo. Pain intensity levels and patient satisfaction were significantly improved in both valdecoxib groups compared with placebo.

There are data to support a synergistic effect when conventional NSAIDs and acetaminophen are combined (102). In one study, patients undergoing elective ear-nose-throat surgery were allocated to receive placebo, acetaminophen 2 g, celecoxib 200 mg, or celecoxib 200 mg together with acetaminophen 2 g. Only the combination of celecoxib and acetaminophen was significantly more effective that placebo (103). In a similarly designed study, patients were randomly allocated to receive placebo, acetaminophen 2 g, rofecoxib 50 mg, or rofecoxib 50 mg together with acetaminophen 2 g (104). The first dose of study medication was given 30 min before surgery, and a second dose of the same medication was given the morning after surgery. Premedication with rofecoxib 50 mg was significantly more effective than acetaminophen 2 g or placebo. In addition, rofecoxib reduced the requirement for fentanyl by 54%, improved patient satisfaction, and improved the quality of recovery.

Because of the lack of antiplatelet effects, COX-2 inhibitors may be continued throughout the perioperative period, thus avoiding an exacerbation of arthritic pain. This may be important because the intensity of preoperative pain has been shown to correlate directly with the severity of postoperative pain and the amount of opioid required after total joint arthroplasty (105).

In a study by Shen et al. (106), patients undergoing elective lower abdominal surgery were randomized to receive rofecoxib 25 mg, rofecoxib 50 mg, or placebo 1 h before surgery. Compared with placebo, patients receiving rofecoxib 50 mg required 44% less morphine during the first 24-h postoperative period, had less pain on effort, and had better pulmonary function 12 h after surgery.

The efficacy of COX-2 inhibitors has been well studied in the dental pain model. In one study, patients were randomized to receive placebo, rofecoxib 50 mg, or ibuprofen 400 mg after dental surgery (107). Rofecoxib was found to be more effective than placebo on all measures of analgesic efficacy. Rofecoxib and ibuprofen were not significantly different in terms of overall analgesic effects, onset of analgesia, or peak analgesic effect, but rofecoxib had a longer duration of action. In another study, rofecoxib 50 mg was again found to be as effective as ibuprofen 400 mg and superior to placebo in the treatment of dental pain (108). The analgesic efficacy of a single dose of rofecoxib 50 mg was also compared with that of three doses of enteric-coated diclofenac sodium 50 mg and placebo (109). The overall analgesic efficacy of rofecoxib 50 mg was superior to that of diclofenac 50 mg and placebo. Another dental pain study compared rofecoxib 50 mg, codeine 60 mg/acetaminophen 600 mg, and placebo (110). Compared with codeine 60 mg/acetaminophen (APAP), rofecoxib 50 mg demonstrated superior analgesia with a greater peak effect and a longer duration of action. Significantly more patients in the codeine/APAP group experienced adverse events, particularly nausea, compared with patients in the rofecoxib group. Thus, several studies have shown that rofecoxib 50 mg is effective in the management of postoperative dental pain (111). In a study of pain after the extraction of two or more molars, patients were given placebo, celecoxib 200 mg, rofecoxib 50 mg, or ibuprofen 400 mg after surgery (112). Compared with celecoxib, rofecoxib had superior analgesic effects on all measures of analgesic efficacy, including overall analgesic effect, time to onset of effect, peak pain relief, and duration of effect. In addition, rofecoxib's analgesic efficacy was similar to that of ibuprofen, but, again, its duration was longer.

In another study, patients scheduled to undergo extraction of two ipsilateral third molars were randomized to receive valdecoxib 10, 20, 40, or 80 mg or placebo, 60–75 min before surgery (113). All valdecoxib groups experienced greater analgesic efficacy than with placebo. Valdecoxib 40 mg provided better efficacy than 10 and 20 mg, but increasing the dose to 80 mg did not confer any additional benefits. A similar study compared a single dose of valdecoxib 20 or 40 mg, a combination of oxycodone 10 mg/APAP 1000 mg, or placebo (114). The efficacy of valdecoxib 40 mg was comparable to that of oxycodone/APAP. Both doses of valdecoxib had a significantly longer duration of action than oxycodone/APAP and had a tolerability profile similar to that of placebo.

A more recent study assessed patients undergoing extraction of two or more third molars (at least one of which was impacted) requiring bone removal. Patients were allocated to receive valdecoxib 40 mg, rofecoxib 50 mg, or placebo (115). Patients receiving valdecoxib 40 mg experienced a significantly quicker onset of analgesia, significantly improved pain relief, and decreased pain intensity compared with patients receiving rofecoxib 50 mg or placebo. The median time to perceptible pain relief was 34 min in the valdecoxib 40 mg group, 55 min in the rofecoxib 50 mg group, and >24 h in the placebo group.

It should be noted that local anesthetics such as lidocaine and bupivacaine have been shown to inhibit G protein-coupled signaling by interfering specifically with G-alpha (q) subunit (116). COX-1 effects are also mediated by the Gq transduction pathway. Therefore, attenuation of the effects of conventional NSAIDs may be a confounding variable in studies comparing analgesic efficacy.

Primary Dysmenorrhea. In a study of patients with primary dysmenorrhea, subjects were randomly assigned to receive placebo, rofecoxib 25 or 50 mg followed by 25 mg every 24 h as needed, or naproxen 550 mg every 12 h as needed for up to 3 days (117). Rofecoxib 25 and 50 mg provided analgesic efficacy more than placebo and equal to naproxen. In another study, women with moderate to severe menstrual pain were randomly assigned to receive valdecoxib 20 mg, valdecoxib 40 mg, naproxen 550 mg, or placebo (118). All active treatments were superior to placebo. Valdecoxib 40 mg was as effective as naproxen and more effective than valdecoxib 20 mg.

GI Toxicity

NSAID-induced GI toxicity is one of the most common drug-related serious adverse events in industrialized countries (119,120). It has been estimated that more than 100,000 patients are hospitalized and 16,500 die each year in the United States as a result of NSAID-associated GI events. Upper GI endoscopy studies have shown a 15%–30% prevalence of ulcers in the stomach or duodenum of patients taking NSAIDs regularly (121). Symptomatic ulcers and ulcer complications associated with the use of conventional NSAIDs may occur in approximately 1% of patients treated for 3 to 6 mo and in 2%–4% of patients treated for 1 yr (122–124). Most ulcers and ulcer complications in patients treated with traditional NSAIDs occur in patients with a small number or no risk factors (125), and 80% of patients may have no preceding symptoms (126). The risk of clinical GI events in NSAID users depends on their baseline risk, the added risk associated with the individual NSAID, and the protection conferred by co-therapy. Medical co-therapy with histamine-2 receptor blockers, proton pump inhibitors, or misoprostol reduces the incidence of endoscopic duodenal and gastric ulcers (127). Omeprazole may be more effective than ranitidine for reducing the incidence of NSAID-induced ulcers (128,129). The cost-effectiveness of these various strategies requires further study (130).

Because prostaglandins are involved in the maintenance of GI mucosal integrity and because only COX-1 is present in the normal GI mucosa, the GI toxicity of NSAIDs has been proposed to result largely from inhibition of COX-1 activity (131,132). Indeed, selective COX-2 inhibitors caused fewer GI side effects than conventional NSAIDs (133–141). COX-2-selective inhibitors with methyl or aminosulfonyl moieties have relatively high pKa values and other properties that are similar to those of traditional NSAIDs with low GI toxicity (53,54).

A 12-wk placebo-controlled trial compared the upper GI effects of celecoxib and naproxen in 1149 patients with symptomatic rheumatoid arthritis (85). The incidence of endoscopically confirmed ulcers was 6% in those patients randomized to receive celecoxib 100 mg BID, 4% in those receiving celecoxib 200 mg BID, and 6% in those receiving celecoxib 400 mg BID. In contrast, the incidence in patients taking naproxen 500 mg BID was 26%, which was significantly more than either placebo (4%) or celecoxib.

In the Celecoxib Long-Term Arthritis Safety Study (CLASS), 8059 patients were randomized to receive celecoxib 400 mg BID, diclofenac 75 mg BID, or ibuprofen 800 mg TID (142). Aspirin use for cardiovascular prophylaxis (≤325 mg/d) was permitted. The primary end-point was complicated ulcers, and the secondary end-point was complicated and symptomatic ulcers. Celecoxib was unable to demonstrate statistical superiority to either ibuprofen or diclofenac when the primary end-point was considered. The use of aspirin may have been an important factor. From their earlier experience in the misoprostol study, the CLASS investigators had expected 10% of patients to be taking small-dose aspirin as prophylaxis against ischemic heart disease: the actual percentage was 21%.

In this subgroup, the incidence of perforation, obstruction, and bleeding with celecoxib was similar to that with classic NSAIDs; i.e., the beneficial effect of celecoxib was negated. Celecoxib was able to demonstrate a less-frequent incidence of ulcer complications and symptomatic ulcers together compared with ibuprofen but not with diclofenac. Differential dropout rates between the celecoxib and diclofenac groups may also need to be considered. Celecoxib was also associated with smaller reductions in hematocrit, hemoglobin, or both compared with the other NSAIDs, despite the use of aspirin. However, concerns have been raised about the CLASS trial with regard to design, possible sources of bias, reporting of the data, and lack of clear superiority of celecoxib over diclofenac (143,144).

A pooled analysis of data from controlled arthritis trials with celecoxib demonstrated that it was associated with an annual incidence of serious upper GI complications of 0.20% (140). This was similar to the annual incidence observed in placebo-treated patients and was significantly less than the annual incidence of 1.68% observed in patients given conventional NSAIDs. In comparison, ulcer complication rates in patients not taking NSAIDs have been reported in epidemiologic studies to be 0.27% by the Arthritis, Rheumatism, and Aging Medical Information System (124) data bank and 0.25% in a study by Gutthann et al. (145).

Deeks et al. (146) recently reviewed 9 randomized trials that compared at least 12 wk of celecoxib treatment with another NSAID or placebo. In patients taking celecoxib, the rate of withdrawals was 46% less, the incidence of ulcers detectable by endoscopy was 71% less, and the incidence of symptoms of ulcers, perforations, bleeds, and obstructions was 39% less. Subgroup analysis of patients taking aspirin showed that the incidence of ulcers detected by endoscopy was reduced by 51% in those patients given celecoxib compared with other NSAIDs. The reduction was larger in those not taking aspirin (73%).

In the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial (147), 8076 patients with rheumatoid arthritis were randomly allocated to receive rofecoxib 50 mg QD or naproxen 500 mg BID for a median of 9 mo. Use of aspirin was not permitted. The incidence of confirmed clinical upper GI events, which include perforation, obstruction, symptomatic ulcers, and upper GI bleeding, was chosen as the primary end-point. The rate of clinically important upper GI events was significantly decreased in the rofecoxib group (2.09 events per 100 patient-years) compared with the naproxen group (4.49 events per 100 patient-years). This difference represented a 54% relative risk reduction in favor of rofecoxib. However, the incidence of myocardial infarctions was much more frequent in the rofecoxib group than in the naproxen group (although it was still very small in absolute terms: 0.4% versus 0.1%). There were significantly fewer dropouts in the rofecoxib group than the naproxen group because of GI side effects (307 versus 406). However, there was no overall safety superiority of rofecoxib over naproxen because of an excess of serious cardiovascular events in the rofecoxib group compared with the naproxen group, as well as more hospitalizations and deaths. The incidence of any serious adverse event was 9.3% in the rofecoxib group and 7.8% in the naproxen group (148). However, other comparative studies of rofecoxib and conventional NSAIDs have demonstrated fewer symptoms of gastroduodenal ulceration and upper GI tract perforation and bleeding (149–151).

A double-blinded, placebo-controlled study compared the effects of valdecoxib 40 mg BID, naproxen 500 mg BID, or placebo on the upper GI mucosa of healthy elderly (>65 yr old) subjects who were confirmed by endoscopy to have no ulcers at baseline (152). After 6.5 days, the incidence of ulcers with valdecoxib was similar to that with placebo (0% versus 3%) and significantly less than with naproxen (18%). In another study, patients were randomized to receive valdecoxib 10 mg QD, valdecoxib 20 mg QD, ibuprofen 800 mg TID, or diclofenac 75 mg BID. After 12 wk, the incidence of endoscopically confirmed gastroduodenal ulcers was similar in the valdecoxib and placebo groups (4%) and was significantly less than in patients receiving ibuprofen or diclofenac (14% and 13%, respectively) (153). Agrawal et al. (154) compared the incidence of gastroduodenal ulcers associated with the use of valdecoxib 20 mg BID, valdecoxib 40 mg BID, and naproxen 500 mg BID given for 14 wk to patients with OA and rheumatoid arthritis. The incidence of ulcers in the valdecoxib 20 mg BID and valdecoxib 40 mg BID groups was significantly less than that in the naproxen group (4%, 8%, and 18% respectively). It should be noted, however, that endoscopically diagnosed ulcers do not necessary correlate with significant clinical events. In another 12-wk study, 1052 patients with OA were randomized to receive valdecoxib 10 mg QD, valdecoxib 20 mg QD, ibuprofen 800 mg TID, or diclofenac 75 mg BID (155). The incidence of endoscopically diagnosed ulcers in the valdecoxib 10 mg QD and valdecoxib 20 mg QD groups was significantly less than in the ibuprofen and naproxen groups (5%, 4%, 16%, and 17%, respectively).

The Successive Celecoxib Efficacy and Safety Studies in OA trial was a large randomized, double-blinded trial designed to reflect standard clinical practice (156). A population of 13,274 patients were treated with celecoxib 200 mg/d or 400 mg/d, naproxen 1000 mg/d, or diclofenac 100 mg/d. Celecoxib was associated with significantly fewer ulcer complications and symptomatic ulcers compared with conventional NSAIDs, and these differences were associated

with smaller rates of health care utilization compared with conventional NSAIDs.

In a recent observational study of upper GI hemorrhage in elderly patients given selective COX-2 inhibitors or traditional NSAIDs, relative to controls there was an increased short-term risk of upper GI hemorrhage for users of nonselective NSAIDs (adjusted rate ratio, 4.0), diclofenac plus misoprostol (3.2), and rofecoxib (1.9) (157). The American College of Rheumatology has recommended COX-2-specific inhibitors for patients who are at increased risk for serious upper GI adverse events (158). Use of gastroprotective drugs such as misoprostol or a proton pump inhibitor with traditional NSAIDs in high-risk patients was also recommended even if the traditional NSAID is given at small dosage.

COX-2 is upregulated at sites of gastric injury, and both nonselective COX inhibitors and COX-2-specific inhibitors may similarly delay mucosal healing in animals (159,160). The clinical implication for humans is undetermined.

Hematological Effects

Platelet aggregation and hemostasis depend on the ability of platelets to generate thromboxane A_2 from prostaglandin H_2. Because platelets do not contain COX-2, all synthesis of thromboxane A_2 in the platelet is mediated by COX-1. By inhibiting COX-1, conventional NSAIDs impair the ability of platelets to aggregate (161). COX-2 inhibitors have no effect on platelet function at therapeutic dosages (162–164). Rofecoxib had no effect on platelet aggregation or bleeding time, even in doses of 1000 mg/d (76,165). Rofecoxib has also not interfered with the antiplatelet effects of aspirin, which can occur with concurrent use of ibuprofen (166–168). Perioperative administration of rofecoxib has not resulted in increased bleeding when administered before spinal fusion surgery or total joint arthroplasty (94,97,169).

A recent meta-analysis found increased cardiovascular risk with COX-2 inhibitors (170). However, such analyses have been criticized for combining results from different studies with differing patient populations, cardiovascular risk factors, protocols, study drug comparators, and use of concomitant medications. In the VIGOR study, the incidence of myocardial infarction was 0.1% in the naproxen group and 0.4% in the rofecoxib group. The reason for this difference remains a subject of controversy (171). The VIGOR study did not contain a placebo group and was not powered to assess cardiovascular events. Further analysis revealed that 35% of these infarctions occurred in the 4% of patients who in retrospect had been candidates for small-dose aspirin. Studies of patients in the United States (172), the United Kingdom (173), and Canada (174) have shown that patients treated with naproxen have a decreased incidence of myocardial infarction compared with patients receiving NSAIDs other than naproxen. However, naproxen offers less protection than aspirin, which is still the preferred drug for patients requiring cardioprotection (175). Celecoxib does not appear to be associated with an increased risk of serious cardiovascular thromboembolic events (176). Clearly, the risk of cardiovascular events with COX-2 inhibitors requires further study.

Cardiorenal Effects

Conventional NSAIDs cause hypertension and edema (177–180) and cause nephrotoxicity in patients who are at risk (181). Angiotensin-converting enzyme (ACE) inhibitors and β-blockers stimulate vasodilator prostaglandins, whereas conventional NSAIDS inhibit the production of such prostaglandins and thereby destabilize blood pressure control. The intrarenal distribution and regulation of renal COX-2 by sodium intake suggests a role for this enzyme in renal physiology and in the renal effects of NSAIDs (182,183). Renal and cardiovascular effects of the selective COX-2 inhibitors are similar to conventional NSAIDs (184–186).

In a 10-day crossover study, increasing doses of celecoxib (200 mg BID for 5 days and then 400 mg BID for 5 days) and naproxen 500 mg BID were compared in a group of healthy individuals aged 65–85 yr (187). Celecoxib had no effect on the glomerular filtration rate (GFR), whereas naproxen caused a slight, but statistically significant, reduction in GFR. Celecoxib and naproxen both caused a significant reduction in renal production of PGE_2 and urinary sodium. COX-2 may play more of a role in salt and water homeostasis, whereas COX-1 may play more of a role in the maintenance of GFR. However, there is considerable overlap in the renal functions of these two isoenzymes. In patients with severe, preexisting renal impairment, the use of a COX-2 inhibitor should be closely monitored, as is required for conventional NSAIDs.

Studies of celecoxib and rofecoxib in elderly cohorts have evaluated the stability of renal function as measured by GFR (187,188). These studies have identified a pattern of modest systemic sodium retention (100 to 150 mmol) during the fist few days of administration (189). By approximately 5 to 7 days of treatment, the typical individual returned to a pretreatment sodium balance state through renal elimination of the retained sodium by using homeostatic mechanisms that are independent of renal prostaglandin.

In a 6-wk study, patients with OA aged 65 yr or older and taking antihypertensive therapy were randomly allocated to receive either celecoxib 200 mg QD or rofecoxib 25 mg QD (71). The incidence of increased

systolic blood pressure was significantly more frequent in the rofecoxib group compared with the celecoxib group (17% versus 11%). At week six, the mean systolic blood pressure change from baseline was +2.6 mm Hg for rofecoxib compared with −0.5 mm Hg for celecoxib. Small increases in systolic blood pressure are now known to be both measurable and important determinants of cardiovascular risk (190–192). The incidence of edema was also significantly more frequent in the rofecoxib group compared with the celecoxib group (9.5% versus 4.9%). Patients taking antihypertensive therapy and receiving COX-2 inhibitors should be monitored for the development of cardiorenal events.

More recently, in a 6-wk study, Whelton et al. (193) assessed the effects of celecoxib (200 mg/d) and rofecoxib (25 mg/d) on blood pressure and edema in 1092 patients 65 yr of age or older with systemic hypertension and OA. Significantly more patients in the rofecoxib compared with the celecoxib group developed increased systolic blood pressure (change >20 mm Hg plus an absolute value of ≥140 mm Hg) at any time (14.9% vs 6.9%; $P < 0.01$). Rofecoxib caused the largest increase in systolic blood pressure in patients receiving ACE inhibitors or β-blockers, whereas those taking calcium channel antagonists or diuretic monotherapy who received either celecoxib or rofecoxib showed no significant increases in blood pressure. Clinically significant new-onset or worsening edema associated with weight gain developed in a larger percentage of patients in the rofecoxib group (7.7%) compared with the celecoxib group (4.7%) ($P < 0.05$). A recent retrospective study of the Tennessee Medicaid program found that use of rofecoxib at doses more than 25 mg was associated with an increased incidence of congestive heart failure (194).

Hepatic Effects

Borderline increases of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable increases of alanine aminotransferase or aspartate aminotransferase (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, remain unchanged, or be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure (some with fatal outcome), have been reported with NSAIDs. A patient with symptoms or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while receiving therapy with COX-2 inhibitors. If clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur, COX-2 therapy should be discontinued. It should be noted that in the VIGOR study, rofecoxib-treated patients had increased numbers of liver-related adverse events compared with naproxen (10 vs 3) (148).

Effects on Bone and Wound Healing

NSAID compounds affect bone osteogenesis during bone repair (195,196). A retrospective study by Deguchi et al. (197) found that patients who continued to take NSAIDs for more than 3 mo after surgery showed smaller fusion success rates than controls (44% vs 37%) after posterolateral fusion for isthmic spondylolisthesis. In a rat model of posterior spine fusion, Dimar et al. (198) demonstrated a fusion rate of 10% if indomethacin was given for 12 wk after surgery versus 45% in controls. Glassman et al. (199) further demonstrated that even the short-term administration of NSAIDs can significantly affect spinal fusion. This retrospective study of 288 patients showed that nonunion was five times more likely to occur if ketorolac was administered after surgery compared with no use of NSAIDS. Recently it has been demonstrated that the COX-2 inhibitors do not have significant deleterious effects on the healing of intertransverse process fusions in the rabbit model (200). In this study, rabbits were randomly allocated to receive celecoxib (10 mg/kg), indomethacin (10 mg/kg), or placebo for 8 wk after single-level intertransverse posterolateral fusions with autogenous iliac crest bone. Gross inspection and palpation revealed that 64% of the 22 control spines and 45% of the 22 spines in the rabbits treated with celecoxib were fused. This difference was not statistically significant. Of the 22 spines in the indomethacin-treated rabbits, 18% were fused, and this percentage was significantly different from the control value. On radiographic assessment, the spine segment was judged to be fused in 82% of the 22 controls, 86% of the 22 rabbits treated with celecoxib, and 41% of the 22 indomethacin-treated animals. Only the difference between the indomethacin-treated and control groups was significant. A study in mice has suggested that selective inhibition of COX-2 may prevent or reduce bone loss in inflammation-induced bone disease (201). Using a rat closed femur fracture model, Simon et al. (202) showed that COX-2 inhibitors can have an effect on normal fracture healing, resulting in incomplete unions and nonunions. These findings cannot be extrapolated to the short-term perioperative use of COX-2 inhibitors in humans. There are no data from prospective randomized trials in humans.

It has been suggested that COX-2-mediated prostaglandins may have a role in wound healing (203,204). Although there is some evidence for impaired ligament healing in the rat (205), the effects of COX-2

inhibitors on human wound healing have not been fully studied.

Sulfonamide Allergy

The overall incidence of sulfonamide hypersensitivity in the general population is low, at approximately 3% (206). All sulfonamides can be regarded as belonging to one of two main biochemical categories: arylamines or nonarylamines (207). The key to sulfonamide allergenicity is thought to be related to the formation of a hydroxylamine metabolite that is unique to the arylamine structure. Celecoxib and valdecoxib belong to the nonarylamine group of medications and are contraindicated in patients allergic to sulfonamides.

Drug Interactions

NSAIDs may diminish the antihypertensive effect of ACE inhibitors and the natriuretic effect of furosemide and thiazides in some patients. Concomitant administration of fluconazole may result in an increase in plasma levels of celecoxib and valdecoxib (208). Concomitant administration of aspirin and COX-2 inhibitors increases the risk of GI ulceration, thus diminishing the beneficial effects of the COX-2 inhibitor. However, the combination of COX-2 inhibitors and aspirin is probably associated with fewer GI side effects than combinations of traditional NSAIDs and aspirin (142,209).

Rofecoxib 75 mg administered once a day for 10 days increased plasma levels of methotrexate by 23% in patients receiving 7.5 to 15 mg/wk for rheumatoid arthritis. However, recommended doses of rofecoxib (12.5–50 mg) have not increased methotrexate levels (210). Celecoxib and valdecoxib do not have a significant effect on the pharmacokinetics of methotrexate (211). The administration of antacids has led to a 20% decrease in maximal serum concentration of rofecoxib, and rifampicin may decrease plasma levels by 50%.

All the currently available COX-2 inhibitors may increase serum warfarin levels, and therefore anticoagulant therapy should be monitored, particularly in the first few days of initiating or changing therapy (212). Lithium levels may also increase with the administration of celecoxib, rofecoxib, and valdecoxib (213).

Contraindications

COX-2 inhibitors should not be given to patients with a known hypersensitivity to the medication or to patients who have experienced asthma, urticaria, or allergic-type reactions (the aspirin triad) after taking aspirin or other NSAIDs. Depletion of PGE_2, which is usually generated by COX-1, appears to be an important event in the generation of this reaction. However, COX-2 inhibitors have been given to such patients without deleterious results (214,215). Celecoxib and valdecoxib should not be given to patients who have demonstrated allergic-type reactions to sulfonamides.

Colorectal Cancer Prevention

In the normal GI tract, very little COX-2 or undetectable levels of COX-2 are expressed (20). COX-2 expression has been found to increase 2- to 50-fold in approximately 80% of human colorectal adenocarcinomas collected surgically or by endoscopic removal (216). These findings indicated that COX-2 isoenzymes might play an important role in the development of colorectal cancer. Indeed, in more than 50 population-based studies, chronic use of aspirin and other conventional NSAIDs that inhibit COX-1 and COX-, was associated with a 40%–50% reduction in the risk for colorectal cancer (217). Biologic activity of NSAIDs in the treatment of familial adenomatous polyposis (FAP) was demonstrated in a double-blinded, randomized, placebo-controlled trial that evaluated the effects of sulindac in patients with this condition (218). Over a 9-mo period, patients treated with sulindac showed a significant reduction in the number and size of adenomas compared with patients treated with placebo.

The effect of treatment with COX-2 inhibitors on tumor growth was first investigated in animal studies. Sheng et al. (219) grafted human colonic adenocarcinoma cells that had very high levels of COX-2 expression into immunocompromised mice. After these cells developed into tumors, a COX-2-specific inhibitor was added to the mice's diets, resulting in a significant inhibition of tumor growth. In another study, rats treated with celecoxib had a significant reduction in the number of adenomas and of noninvasive and invasive adenocarcinomas (220). Evidence that COX-2-specific inhibitors reduce tumor growth was also shown in a study involving the multiple intestinal neoplasia mouse, a genetic model for FAP (221).

In humans, 77 patients with FAP were treated with celecoxib 100 mg BID, celecoxib 400 mg BID, or placebo (222). At 6 mo, patients receiving celecoxib 400 mg BID demonstrated a significant reduction in polyp burden compared with placebo (30.7% vs 4.9%).

Future Directions

COX-2 inhibitors represent a significant therapeutic development because of their improved side effect profile compared with conventional NSAIDs (223). They are likely to be used increasingly for the treatment of pain and inflammation, and several other COX-2 inhibitors are currently under development. Future industry-independent analysis of published and unpublished data will reduce potential bias error. The Baltimore Longitudinal Study of Aging reported that the risk of developing Alzheimer's disease was

reduced among NSAID users, especially in those who had taken the medications for 2 yr or more (224). Other studies have confirmed this association (225,226). A possible mechanism for this effect is a reduction in inflammatory processes that may promote neuronal destruction. The use of COX-2-selective drugs to decrease the risk of Alzheimer's disease is being studied. Studies are also continuing to assess the use of COX inhibitors in the treatment of colorectal cancer, esophageal cancer (227), gastric cancer, and breast cancer (228,229). However, questions remain regarding the use of COX-2 inhibitors, such as restriction of their use to patients at increased risk for complications, cost-effectiveness, safety compared with conventional NSAIDs plus prostaglandin replacement or acid-reduction therapy, and safety in patients also taking aspirin for platelet inhibition (230).

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