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Cyclooxygenase-2 Inhibitors

A Review of Celecoxib and Rofecoxib

Brief Summary

Indications: Both agents are indicated in the treatment of signs and symptoms of osteoarthritis. Celecoxib (Celebrex®) is also indicated in patients with rheumatoid arthritis. Rofecoxib (Vioxx®) is labeled for the treatment of acute pain as well as primary dysmenorrhea.

Monitoring Parameters: Clinical effectiveness should be assessed using both subjective and objective measures of pain and inflammation reduction. Monitor for signs and symptoms of gastrointestinal ulceration or bleeding. Signs and symptoms of renal or hepatic toxicity should be followed in patients receiving either drug for three months or longer.

Dose: Celecoxib: The recommended dose is 200 mg per day (200mg po QD or 100mg po BID) for osteoarthritis; for rheumatoid arthritis, the recommended oral dose is 100 or 200 mg twice daily.

Rofecoxib: For osteoarthritis, the recommended starting dose is 12.5 mg daily with a maximum recommended dose of 25 mg daily. The recommended starting dose for acute pain or primary dysmenorrhea is 50 mg once daily. Subsequent doses of 50 mg daily may be administered as needed.

Pregnancy Category: C. Celecoxib and rofecoxib should be avoided during late pregnancy to avoid premature closure of the ductus arteriosus. Neither has been studied in labor and delivery. In rabbits, doses equivalent to two-to-three times human doses did induce a slight increase in skeletal abnormalities.

Pediatrics: Neither agent has been studied in patients under 18.

Geriatrics: Elderly patients usually do not require dosing adjustments. However, therapy should be initiated at the lowest recommended dose.

Dosage Formulations: Celecoxib is available as 100 mg and 200 mg oral capsules. Rofecoxib is available as 12.5 mg and 25 mg oral tablets as well as 12.5 mg and 25 mg per 5 mL oral suspension.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) have been used widely to treat pain and inflammation for many years. For the majority of patients, these drugs are effective and well tolerated. However, their use is associated with a risk of gastrointestinal (GI) complications including mucosal erosion, bleeding, ulceration or perforation, and rarely, renal complications. Two new anti-inflammatory agents, celecoxib and rofecoxib, representing a new therapeutic class of drugs with reduced risks of toxicity, have been approved by the U.S. Food and Drug Administration (FDA). Both drugs have been compared to placebo as well as traditional NSAIDs in clinical trials.

Clinical Pharmacology

Prostaglandins function both to maintain homeostasis of some normal physiologic processes and also to mediate symptoms of inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs) exhibit anti-inflammatory, antipyretic, and analgesic effects through the reduction of prostaglandin synthesis via the inhibition of the enzyme, cyclooxygenase (COX). We now know that there are two distinct isoforms of the enzyme, cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2).¹ The constitutive form of the enzyme, COX-1, catalyzes the synthesis of prostaglandins with important physiologic functions like protection of gastric mucosa, and maintenance of renal blood flow and platelet integrity. The COX-2 isoform normally is not present in most tissues, but is induced by mediators expressed in inflammatory processes.² Traditional NSAIDs inhibit both isoforms of COX, so that their therapeutic benefits have to be counterbalanced against possible gastrointestinal and renal toxicity.

Both celecoxib and rofecoxib are selective COX-2 inhibitors. The effects of both drugs are mediated through COX-2 inhibition that reduces prostaglandin synthesis at sites of inflammation. In vitro studies with celecoxib indicate that it is approximately 375 times more selective for COX-2 versus COX-1.³ Rofecoxib is reported to be approximately 1000 times more selective for the COX-2 isozyme.⁴

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At therapeutic concentrations in humans, neither celecoxib nor rofecoxib inhibits COX-1.⁵ Selective inhibition should produce symptom relief without the risk of serious gastrointestinal or renal toxicity. Clinical studies have shown that both selective inhibitors have improved gastrointestinal safety compared to non-selective NSAIDs, but renal safety is still under study. Both celecoxib and rofecoxib package inserts contain warnings similar to traditional NSAIDs for patients with considerable dehydration or others at risk of renal failure induced by prostaglandin inhibition.^{5,6}

Pharmacokinetics

Most pharmacokinetic information is available in the package inserts of Celebrex™ or Vioxx™.^{5,6} Administration of either agent with food delays peak plasma concentrations by 1 to 2 hours, but does not alter the area under the curve. For this reason, celecoxib may be administered without regard to meals. At therapeutic doses, approximately 97% of celecoxib is bound to serum proteins, while rofecoxib is approximately 87% protein-bound. Binding is primarily to albumin and to a minor extent to alpha-1-acid glycoprotein.

Celecoxib is metabolized primarily by the cytochrome P-450 (CYP) isoenzyme CYP2C9. Primary metabolites do not function as COX-1 or COX-2 inhibitors. Less than 3% of parent drug is excreted unchanged in the urine. Following single dosing, approximately 57% of the dose is excreted as metabolites in the feces and about 27% is excreted as metabolites in the urine. The terminal half-life of celecoxib is approximately 11 hours.

Rofecoxib is metabolized primarily by cytosolic hepatic enzymes, and the cytochrome P450 system does not play a major role in metabolism. The primary metabolites of rofecoxib do not inhibit COX-1 or COX-2. Less than 1% of parent drug is excreted unchanged in the urine. Following single oral dosing, approximately 14% of the dose is excreted in the feces as parent drug and 72% is excreted in the urine as metabolites.

Contraindications and Precautions

*Celecoxib*⁵

- Contraindications: Celecoxib is contraindicated in patients with hypersensitivity to celecoxib or any formulation component; patients with hypersensitivity to sulfonamides; and patients with allergic/urticarial/asthmatic reactions to aspirin or other NSAIDs.
- Precautions to celecoxib use include:
 - Pregnancy. Possible premature closure of the ductus arteriosus is possible.
 - History of gastric or duodenal bleeding, ulceration, or perforation
 - Liver dysfunction
 - Renal dysfunction

- Fluid retention, edema, or hypertension that may be aggravated by increased edema
- Patients with aspirin-sensitive asthma
- Signs or symptoms of anemia

*Rofecoxib*⁶

- Contraindications: Rofecoxib is contraindicated in patients with hypersensitivity to rofecoxib or any formulation component; patients with acute peptic ulcer disease; and patients with allergic/urticarial/asthmatic reactions to aspirin or other NSAIDs.
- Precautions to rofecoxib use include:
 - Patients with bleeding disorders.
 - Liver dysfunction
 - Severe renal dysfunction
 - Fluid retention, edema, or hypertension that may be aggravated by increased edema
 - Patients with aspirin-sensitive asthma
 - Signs or symptoms of anemia
 - History or predisposing conditions for gastrointestinal events (peptic ulcer disease, ulcerative colitis, smoking, elderly, stress, alcohol abuse, or concurrent systemic steroid use).

Clinical Trials

Celecoxib

Celecoxib has been studied internationally in large numbers of patients, but the clinical evidence is only gradually becoming available in published form.^{7,9} A preliminary publication evaluates one trial in osteoarthritis (OA) as well as one trial in patients with rheumatoid arthritis (RA).⁷ The article also details one gastrointestinal safety trial and one study evaluating the platelet effects of celecoxib. The final study presents results from Searle's multicenter US-Canadian clinical trial of 1149 patients with rheumatoid arthritis.⁸ Several trials have been published in abstract form. Additional data are available from unpublished trials appearing in the Celebrex™ package insert.

Efficacy in Osteoarthritis

A short-term pilot study of celecoxib was conducted in 293 patients with OA of the knee experiencing an NSAID withdrawal flare.^{9,10} In this two-week randomized, double blind, placebo-controlled trial, patients received either placebo or one of three doses of celecoxib [40 mg twice daily (BID), 100 mg BID, or 200 mg BID]. Efficacy parameters included patient withdrawal due to lack of efficacy, patient and physician global assessments, the Osteoarthritis Severity Index, and patient pain assessment using a visual analogue scale (VAS). Significantly more patients withdrew from the study due to lack of efficacy in the placebo group when compared to the celecoxib 100 mg twice daily BID and 200 mg BID groups.

Table 1¹¹ Efficacy Results in Pilot Study of Celecoxib

Parameter	Celecoxib 40 mg BID	Celecoxib 100 mg BID	Celecoxib 200 mg BID	Placebo
% Withdrawn due to lack of efficacy	8%	1%	4%	14%
Mean change in pain VAS (mm 1-100)	-23	-24*	-31*	-16
OA Severity Index (0-24)	-4.46*	-3.6	-4.07	-3.14
Physician Global Assessment (0-4)	-1.03	-1.03	-1.25*	-0.83
Patient Global Assessment (0-4)	-1.24*	-1.03	-1.29*	.079

* $p < 0.05$ versus placebo

Celecoxib was associated with significant reductions in severity scores in all dose groups compared to placebo. The 40mg BID dose was less effective than the higher doses (see Table 1).

Zhao et al. assessed quality of life scores in the same 293 patients.¹⁰ The assessment instruments were eight domains of the SF-36 Health Survey concerning patient quality of life as well as the Arthritis-Specific SF-36 Health Index. Surveys were conducted at the end of the 2-week study and compared to baseline surveys. Patients in the 200mg celecoxib group showed significant ($p < 0.05$) improvement in nearly all survey scores when compared to placebo. The 40mg celecoxib group showed significant ($p < 0.05$) improvement in two of the SF-36 survey scores.

Celecoxib has also been compared with naproxen and placebo in a double-blind, randomized trial.¹¹ In this study, 1044 patients with OA of the knee were randomly assigned to one of five groups: placebo, celecoxib 50 mg, 100 mg, or 200 mg, each given BID, or naproxen 500 mg BID. Efficacy assessments included patient and physician global assessments, as well as patient pain assessments. Evaluations at 2, 6, 12 weeks, or at time of early termination were assessed. The celecoxib 100 mg, 200 mg, and naproxen groups were significantly superior to placebo in both patient and physician assessments. They did not, however, differ significantly from one another. The 50mg celecoxib group was superior to placebo but inferior to the three other treatment groups in terms of global assessments. The investigators concluded that celecoxib is effective when administered orally at doses of 100 to 200 mg BID.

Efficacy in Rheumatoid Arthritis

Patients with RA have also been treated with celecoxib. The initial study assessing this indication for celecoxib was a 4-week randomized, double-blind, placebo-controlled, dose-ranging study conducted in 330 patients with RA in a flare state.^{8,12} Any current NSAID administration was discontinued at entry into the study. Patients were then randomized to receive placebo or one of three celecoxib doses: 40 mg, 200 mg, or 400 mg BID. Efficacy parameters included withdrawal due to lack of efficacy, patient and physician global assess-

ment, arthritis pain using a VAS, duration of morning stiffness, serum C-reactive protein level, and numbers of painful or tender joints. Assessments were recorded at week 1, week 2, and week 4 of the study. Patients receiving placebo withdrew from the study at a significantly higher rate than either the 200-mg or 400-mg celecoxib groups ($p < 0.03$). At all assessments, the number of painful or tender joints were significantly ($p < 0.005$) fewer versus placebo for the 200 mg and 400 mg celecoxib groups. At study end, patients presented with 10 to 15 fewer tender joints vs baseline in these celecoxib groups.

Celecoxib has been compared to diclofenac and placebo in a multicenter, double-blind study.¹³ This trial investigated 655 patients with RA who had at least a 6-month history of the disease. Patients randomly received celecoxib 200 mg BID or diclofenac sustained-release 75 mg BID for up to 24 weeks. At 4-week intervals, efficacy parameters (undefined patient and physician assessments of arthritis severity) were assessed. The investigators state that celecoxib was highly efficacious and statistically comparable to diclofenac but do not present complete efficacy data. The efficacy of celecoxib was also compared with naproxen and placebo in a large, randomized, double-blind, multicenter study comprised of 1149 patients with active rheumatoid arthritis.^{7,14} Study patients received placebo, naproxen 500 mg BID, or celecoxib at doses of 100 mg, 200 mg, or 400 mg BID. Clinical assessments were performed at baseline and at weeks 2, 6 and 12. Efficacy was based on an analysis of American College of Rheumatology preliminary criteria for improvement in rheumatoid arthritis (ACR 20) plus other measures such as duration of morning stiffness. The ACR 20 are defined by the following responses:

- a reduction of 20% in swollen joints and tender joints
- an improvement of 20% in at least three of the following parameters:
 - the patient's assessment of pain
 - the physician's global assessment of disease status
 - the patient's global assessment of disease status
 - the patient's assessment of disability
- values for acute-phase reactants, c-reactive protein and erythrocyte sedimentation rate

The percentage of patients who were ACR-20 responders was 29% for placebo, 39% to 44% on the three doses of celecoxib, and 36% for naproxen. The responses for all four active drug groups were comparable, and all were significantly better than for placebo ($p<0.05$). Withdrawals from the study due to treatment failure comprised 45% of the placebo group, significantly higher than for any of the active drug groups ($p<0.001$). Efficacy in the active drug groups was evident and sustained from 2 weeks onward.

Gastrointestinal Toxicity

Celecoxib was developed to decrease gastrointestinal (GI) mucosal toxicity. Serious GI adverse effects of NSAIDs such as perforation, ulcers and bleeding are rare, and consequently difficult to study prospectively. Fortunately, previous clinical trials have provided evidence that the early development of NSAID-induced endoscopically detectable gastric or duodenal ulcers may serve as a surrogate marker of serious GI toxicity. Most of these ulcers are painless and have no clinical significance in themselves. To investigate the GI effects of celecoxib, an initial one-week double blind study was conducted in 128 healthy volunteers.^{8,14} The subjects, all with endoscopically normal GI mucosa, were randomized to receive placebo or NSAID treatment with either naproxen 500 mg BID, or celecoxib 100 mg BID or 200 mg BID for 7 days. Repeat upper GI endoscopies were performed on day 7 of the trial. No resultant duodenal ulcers (DU) were seen in any group. Nineteen percent of the subjects receiving naproxen did develop gastric ulcers (GU) ranging from 0.4 to 1.5 cm in diameter, while no patients in the celecoxib or placebo groups developed a GU. No clinical consequences were reported.

Two studies evaluated the GI safety profile of celecoxib as well as its efficacy in RA patients.^{13,14} In an early trial versus diclofenac, investigators reported cumulative GU incidences of 2% for celecoxib patients compared to 11% for diclofenac patients ($p=0.002$).¹⁵ Similarly, the DU incidence was lower with celecoxib than with diclofenac (2% vs 7% respectively,

$p=0.003$). The investigators then compiled these data and reported total rates of GI ulcers. Again, GI ulcers occurred in significantly fewer celecoxib patients than in patients taking diclofenac (4% vs 15%). No clinical or detailed endoscopic descriptions of ulcer size or severity were noted.

Safety was evaluated in the large study of 1149 rheumatoid arthritis patients. When compared to naproxen in patients with active RA, frequencies of endoscopically-documented gastroduodenal ulcers (GDU) were compared.^{7,13} The naproxen group had a GDU rate of 26% compared to 6% in the celecoxib 400 mg BID group, 4% in the celecoxib 200 mg BID group, 6% in the 100 mg BID group, and 4% in the placebo group. A single clinically significant ulcer complication occurred in one patient in the naproxen arm of the study. The authors state that the overall GI tolerability of celecoxib was intermediate between placebo and naproxen. The incidence of dyspepsia, diarrhea, abdominal pain, flatulence and nausea combined were 31% for naproxen, 25 to 28% for the celecoxib groups and 19% for placebo. No adverse renal effects, such as edema or hypertension, occurred more frequently in any of the treatment groups. Detailed information on the endoscopic studies appears in the prescribing information (see Tables 2 and 3).

Table 2⁵ Cumulative Gastroduodenal Ulcers in OA and RA Patients

	"STUDY 1" (N=1108)	"STUDY 2" (n=1049)
Placebo	2.3%	2%
Celecoxib 50 mg BID	3.4%	—
Celecoxib 100 mg BID	3.1%	4%
Celecoxib 200 mg BID	5.9%	2.7%
Celecoxib 400 mg BID	—	4.1%
Naproxen 500 mg BID	16.2%*	17.6%*

* $p<0.05$ vs all other treatments

Table 3 Cumulative Gastroduodenal Ulcers in OA and RA Patients⁵

	Week 4	Week 8	Week 12	Final
"STUDY 3" (N=523)				
Celecoxib 200 mg BID	4%*	2.2%	1.5%*	7.5%*
Naproxen 500 mg BID	19%	14.2%	9.9%	34.6v
"STUDY 4" (N=1062)				
Celecoxib 200 mg BID	3.9%#	2.4%#	1.8%#	7%#
Diclofenac 75 mg BID	5.1%	3.3%	2.9%	9.7%
Ibuprofen 800 mg TID	13%	6.2%	9.6%	23.3%

* $p<0.05$ celecoxib vs. naproxen based on interval and cumulative analyses

$p<0.05$ celecoxib vs. ibuprofen based on interval and cumulative analyses
In these studies, serial endoscopies were performed.

The manufacturer of celecoxib states that clinically significant upper GI bleeding has occurred in patients receiving this drug.⁵ In a letter to the *New England Journal of Medicine*, Mohammed and Croom reported a case of gastropathy due to celecoxib.¹⁶ This patient had received celecoxib 100 mg BID for about 6 weeks when she presented with persistent and severe epigastric pain. Endoscopic and histologic evaluation was consistent with NSAID-induced gastropathy and symptoms resolved within a week of celecoxib discontinuation.

Platelet Effects

In order to further evaluate selectivity of celecoxib for the COX-2 isozyme, investigators studied its effects on platelet aggregation.¹⁷ Higher than therapeutic doses of celecoxib (600 mg) were given to healthy subjects for 10 days. The effects on platelets were compared to that of placebo as well as naproxen 500 mg. Subjects received their study medication once on day 1 and day 10, and twice daily during days 3 through 9. Platelet aggregation, bleeding time, and serum thromboxane B₂ were determined on days 1 and 10. In all measures concerning platelet function, celecoxib showed no statistical difference versus placebo, whereas naproxen significantly reduced platelet aggregation, increased bleeding time, and reduced thromboxane B₂ levels. The investigators concluded that celecoxib, even at high doses does not inhibit COX-1 activity in platelets.

Rofecoxib

A limited number of clinical trials evaluating rofecoxib have been published, although pre-marketing experience included over 5000 patients. Two clinical trials report rofecoxib utility in dental pain. One recent article and several abstracts describe the use of rofecoxib in osteoarthritis and primary dysmenorrhea. As with celecoxib, additional unpublished data are available from the manufacturer's package labeling.

Analgesic and Antipyretic Efficacy

In a paper detailing both *in vitro* and *in vivo* analysis of COX-2 selectivity, Ehrlich, et al reported a pilot study investigating the efficacy of rofecoxib in postoperative dental pain.¹⁸ In this double-blind trial, 104 patients with moderate to severe pain following molar extraction were randomized to receive a single dose of rofecoxib 50 mg, rofecoxib 500 mg, ibuprofen 400 mg, or placebo. The patients then recorded pain intensity and pain relief (on a scale of 0 to 4) for the following 6 hours. Both rofecoxib groups as well as the ibuprofen treatment group experienced significant ($p < 0.01$) pain relief versus placebo. There was no significant difference between any of the three active treatment groups ($p > 0.2$).

In a subsequent double-blind, randomized study, rofecoxib was again compared to placebo and ibuprofen.¹⁹ Following dental surgery (similar procedures for all groups), a single oral dose of rofecoxib 50 mg, ibuprofen 400 mg, or placebo was given to each of 151 adult patients. No analgesics were allowed

within 6 hours of surgery. Following the procedure, patients evaluated efficacy for at least 8 hours. Follow-up pain assessments were also performed at 24 hours post-dose. Efficacy was assessed using pain relief and pain intensity scales, both of which utilized numerical 0 to 4 scales. Pain relief scores in both treatment groups attained significance compared to placebo within 1 hour post-dose ($p < 0.05$). Compiled pain intensity and pain relief scores throughout the evaluation period were significantly superior to placebo for both treatments ($p < 0.01$). No statistical significance was noted between the treatment groups in either onset of relief or peak relief. However, at both 12 and 24 hours after dosing, pain relief was statistically superior in the rofecoxib group as compared to the ibuprofen group ($p < 0.05$). The authors concluded that rofecoxib provides similar peak pain relief with an extended duration of action versus ibuprofen.

Two additional studies investigating the analgesic properties of rofecoxib have been conducted in patients with primary dysmenorrhea.²⁰⁻²² Both studies were double-blind, randomized trials comparing rofecoxib to placebo and naproxen. In the first study, 63 patients received rofecoxib 50 mg followed by 25 mg daily (QD) prn, naproxen 550 mg Q12H prn, or placebo. The primary endpoint, overall pain relief at 8 hours, showed rofecoxib to be superior to placebo ($p < 0.002$) and statistically similar to naproxen. In a subsequent study, 127 patients were randomized to placebo, or rofecoxib 25 mg and 25 mg every 24 hours as needed, rofecoxib 50 mg plus 25 mg every 24 hr as needed, or naproxen every 12 hours as needed up to 3 days.²² Rofecoxib at both doses was more effective than placebo ($p < 0.006$) and indistinguishable from naproxen. The primary endpoint was total pain relief over the first 8 hours, calculated as summed, time-weighted pain relief scores to 8 hours. In other efficacy endpoints such as global evaluation, peak pain relief, change in peak pain intensity and time to remedication, celecoxib and naproxen were equally effective.

The antipyretic efficacy of rofecoxib was assessed in a trial consisting of 93 patients.²³ In this single dose, placebo and active controlled trial, patients with fever due to upper respiratory tract infections received placebo, ibuprofen 400 mg, or rofecoxib 12.5 or 25 mg. The mean temperature decrease for the ibuprofen group was 2.17°F, compared to a decrease in the rofecoxib 12.5 and 25 mg groups of 1.74 and 2.13°F, respectively. These differences were all statistically superior to placebo but not statistically different from one another. This study provides evidence that rofecoxib exhibits similar antipyretic efficacy to the NSAIDs.

Efficacy in Osteoarthritis

The pilot study of rofecoxib in patients with OA was conducted in 219 patients with OA of the knee in a flare state after NSAID withdrawal.²⁴ Patients were randomly assigned to receive rofecoxib 25 mg or 12.5 mg QD or placebo for 6 weeks.

Pain via 1 to 100 mm visual analogue scale (VAS) measurements, subjective stiffness scale measurements, and investigator and patient global assessments were used to evaluate patient progress. Both rofecoxib treatment arms were superior to placebo ($p < 0.001$). Both rofecoxib doses were equally effective.

This study was followed by a large multicenter 6-week trial including 672 patients with OA of the hip or knee in a flare state after NSAID withdrawal.²⁵ Treatment groups included rofecoxib 5 mg, 12.5 mg, 25 mg, and 50 mg QD. Efficacy (a VAS of pain walking on flat surface, as well as global patient and investigator assessments) was compared both to placebo and between-treatment groups. All treatment arms were significantly superior to placebo for each parameter ($p < 0.001$). The 5-mg rofecoxib dose was not as effective as the higher doses. The authors concluded that daily doses of 12.5 to 50 mg rofecoxib were clinically effective for the treatment of pain and associated symptoms of OA. This trial was also analyzed in terms of impact on quality of life, using the SF-36 Short Form Health Survey.²⁵ For all doses of rofecoxib, significant increases in survey scores assessing both physical and mental health were observed versus placebo.

Investigators have also compared rofecoxib to other NSAIDs in the treatment of the signs and symptoms of OA.²⁷ In a double-blind, comparator-controlled randomized trial, rofecoxib was compared to diclofenac and placebo in 784 patients with OA of the hip or knee in a flare state after NSAID withdrawal, or OA poorly controlled with acetaminophen. Treatment groups included once-daily rofecoxib, either 12.5 mg or 25 mg, and diclofenac 50 mg three times daily (TID). Treatment was compared to placebo for a period of 26 weeks. The primary efficacy endpoint was assessed via the WOMAC 100 mm VAS of pain walking on a flat surface, with additional secondary endpoints of patient and investigator global assessment. All three treatments were reported to be similar in terms of efficacy at all points during the study. However, no statistical analysis or detailed description of study results was provided. The investigators concluded that once-daily rofecoxib was generally well tolerated and was similar in effectiveness to diclofenac 50 mg TID.

In another trial comparing rofecoxib to conventional NSAIDs, 736 patients with OA were treated with either rofecoxib, ibuprofen, or placebo for 6 weeks.²⁸ Rofecoxib treatment doses were again 12.5 and 25 mg daily (QD). These groups were compared with ibuprofen 800 mg TID and placebo. This trial included the same efficacy parameters as the previous study and results were similar. All active treatment groups were superior to placebo but not statistically different in efficacy ($p > 0.05$). Again, the authors concluded that rofecoxib in doses of 12.5 to 25 mg daily are comparable to ibuprofen for the treatment of signs and symptoms of OA.

Gastrointestinal Toxicity

The gastrointestinal effects of rofecoxib have been investigated in several trials of varying size. Investigators have reported the effects of rofecoxib on in vivo GI prostaglandin and thromboxane B₂ synthesis.²⁹ Thirty-three healthy subjects with endoscopically proven normal GI mucosa were studied. These subjects, who were seronegative for H pylori, received either placebo, naproxen 500 mg BID, or rofecoxib 25 mg QD for 5 days. At the end of the treatment period, endoscopically-guided gastric mucosal biopsies were obtained. Prostaglandin E₂ (PGE₂) synthesis was reduced by 72.1% in the naproxen group compared to placebo ($p < 0.001$). In contrast, PGE₂ synthesis was increased 11.8% in the rofecoxib group, but the result was not statistically significant. The authors concluded that rofecoxib had no effect on gastric mucosal prostaglandin synthesis.

Studies have been carried out to determine the incidence of asymptomatic ulcers following NSAID use. In an initial study conducted in 167 healthy volunteers with endoscopically proven normal GI mucosa, investigators compared the GI effects of rofecoxib, ibuprofen, aspirin, and placebo.³⁰ Subjects were randomized to receive either a supratherapeutic dose, 250 mg QD of rofecoxib, ibuprofen 800 mg TID, or aspirin 650 mg QID for 7 days. Repeat upper GI endoscopies were performed on day eight. A pre-defined scale was used to assess the severity of GI mucosal damage. Significantly fewer patients with a score of greater or equal to 2 (multiple erosions or ulcer) on this scale were reported in the rofecoxib group compared with the aspirin and ibuprofen groups ($p < 0.001$ between rofecoxib and the two conventional NSAIDs).

Another trial conducted in 67 healthy volunteers assessed fecal blood loss following study treatment.³¹ Subjects were injected with radiolabeled red blood cells. Subjects who had normal fecal blood losses were randomly assigned to receive either rofecoxib 25 mg or 50 mg QD, ibuprofen 800 mg TID, or placebo for a total of 28 days. The authors reported that fecal blood loss in the rofecoxib group was similar to placebo, but less than blood loss in the ibuprofen group. No statistical analyses of the results was reported.

Two trials investigated the ulcerogenicity of rofecoxib in OA patients.³⁰ Laine et al, reported that a total of 1516 OA patients without endoscopic ulceration at the baseline of the study were randomized to receive placebo, ibuprofen 800 mg TID, rofecoxib 25 mg QD or 50 mg QD in two identical trials. Baseline upper endoscopies were compared with repeat endoscopies at weeks 6, 12, and 24. Results were available for 1427 patients (see Table 4). The authors concluded that even at doses higher than recommended for OA, rofecoxib was associated with significantly less GI ulceration than ibuprofen.

Table 4 Cumulative Ulcer Incidence

	N	12-week Incidence (%)	24-week Incidence (%)
Placebo	340	7.3	*
Rofecoxib 25 mg QD	373	4.7	9.7
Rofecoxib 50 mg QD	360	8.1	13.5
Ibuprofen 800 mg TID	354	28.5	46.4

* Most patients in the placebo group were phased out of the study by week 16.

Langman et al looked at the incidence of serious adverse GI effects of rofecoxib on the GI mucosa of osteoarthritis patients.^{34,35} This prospectively-designed analysis of eight Merck-sponsored Phase II or III trials included a total of 5435 patients. Clinical investigators in the eight trials reported all potential upper GI tract perforations, symptomatic gastric or duodenal ulcers and upper GI bleeds (designated by the authors as PUBs) to an external, blinded committee for confirmation. Pooled data were then analyzed for PUBs during treatment or within 14 days following treatment. The time to first confirmed PUB was recorded and evaluated using survival analysis. Significantly fewer PUBs were recorded in patients receiving rofecoxib at any daily dose when compared to those receiving diclofenac 50 mg TID, ibuprofen 800 mg TID, or nabumetone 1500 mg daily. According to the abstract, cumulative incidence of confirmed PUBs over 12 months of therapy was 1.5% for rofecoxib compared to 2.68% for pooled NSAIDs ($p < 0.006$). The relative risk of PUBs for patients taking rofecoxib versus other NSAIDs was 0.45. The authors reported that sensitivity analyses confirmed the final results and conclude that celecoxib administration is associated with a lower risk of PUB than conventional NSAIDs. The final publication reported that for the same 5435 patients, the cumulative incidence of PUBs was 1.3% for rofecoxib and 1.8% for the other NSAID groups, but the difference was barely significant ($p = 0.046$).³³ The cumulative incidence of dyspeptic adverse reactions showed a non-significant trend in favor of rofecoxib for the first 6 months, but the differences were no longer detectable after six months.

Additional data are available from the rofecoxib package insert.⁶ The manufacturer reports that in 3357 patients on rofecoxib in controlled trials of six-week to one-year duration, four patients experienced a serious upper GI event. However, the manufacturer cautions that these study populations are not necessarily representative of the general population.

Antiplatelet Effects

The effects of rofecoxib on the antiplatelet activity of aspirin were investigated in a small trial consisting of 24 subjects.³¹ In this double-blind study, participants received either placebo or rofecoxib 50 mg daily for 10 days. On days

4 through 10, all subjects received aspirin 81 mg daily. Thromboxane-B2 inhibition, the main endpoint, was measured and reported. In subjects receiving aspirin therapy alone, inhibition was 98.4%. In subjects receiving both aspirin and rofecoxib, inhibition was also 98.4%. Similarly, arachidonic acid-induced platelet aggregation was inhibited in 93.7% of those receiving rofecoxib and aspirin as compared to 93.5% in patients receiving aspirin alone. The authors concluded that rofecoxib did not influence the antiplatelet effects of low-dose aspirin at steady state.

Adverse Drug Reactions

Adverse drug reactions associated with the administration of celecoxib have been similar to placebo for most reactions.⁵ Only headache, dyspepsia, upper respiratory tract infection, and diarrhea were recorded in more than 5% of patients. Adverse drug reactions associated with the administration of rofecoxib have been similar to placebo for most reactions.⁶ Only nausea, upper respiratory tract infection, and diarrhea were recorded in more than 5% of patients taking rofecoxib. Differences in adverse event rates between both agents and comparator NSAIDs were clinically insignificant.

Drug Interactions

Celecoxib

Since celecoxib is extensively metabolized via the isozyme CYP2C9, other substrates of this enzyme can potentially interact with celecoxib. Also, *in vitro* studies have suggested that celecoxib may inhibit the isozyme, CYP2D6. Post-marketing data have revealed that in elderly patients receiving warfarin and celecoxib concomitantly, increases in prothrombin time with associated bleeding events have occurred. The manufacturer states that close monitoring of warfarin anticoagulation should be instituted when initiating or withdrawing celecoxib therapy. In healthy subjects, celecoxib does not significantly affect the pharmacokinetics or pharmacodynamics of methotrexate.³⁴ The manufacturer states that clinical studies *in vivo* have shown possible interactions with

Table 5³⁸ Risk Factors for NSAID-Induced GI Complications

- History of peptic ulcer disease
- History of GI bleeding
- History of NSAID-induced GI adverse reactions
- Age >65
- Anticoagulant therapy
- Long-term or high-dose NSAID therapy
- *H pylori* positive status
- Concurrent H2 blocker or antacid utilization
- Smoking
- Alcohol overuse

fluconazole and lithium. The package labeling of Celebrex™ also states that interactions with furosemide and angiotensin converting enzyme inhibitors, analogous to those associated with traditional NSAIDs, are possible.⁵

Rofecoxib

Rofecoxib has not been shown to inhibit or induce any common CYP enzymes in early *in vitro* studies. Clinically insignificant interactions with methotrexate, rifampin, and warfarin have been noted.⁶ Rofecoxib given at 75 mg once daily resulted in an increase in the area under the curve of methotrexate of approximately 23%. However, therapeutic daily doses, 12.5 to 50 mg, have not been studied with concurrent methotrexate administration. In patients receiving concomitant warfarin, rofecoxib administration has increased INR by 8 to 11%. Possible interactions with furosemide, angiotensin converting enzyme inhibitors and lithium are mentioned in the package labeling of rofecoxib. Early *ex vivo* studies have indicated that no clinically significant interactions exist with cimetidine, digoxin, ketoconazole, prednisone, or oral contraceptives.^{6,37}

Summary/Recommendations

The specific COX-2 inhibitors have enjoyed much attention and have been prescribed widely in their first months on the U.S. market. Both celecoxib and rofecoxib are comparable, but not superior to conventional NSAIDs in terms of efficacy in analgesia, antipyretic and anti-inflammatory activity. In controlled trials, these medications have been shown to cause statistically fewer endoscopic GI erosions compared to traditional NSAID therapy, but these erosions are not clinically significant themselves, although there is good evidence that they function predictively as surrogate markers of possible serious GI toxicity. GI toxicity issues have not yet been resolved, both because patients at risk for GI toxicity were excluded from some trials, and also because many trials were concluded at the end of only 6 to 12 weeks. The cumulative 12-month incidence of serious GI adverse effects has been studied for rofecoxib, and so far, GI toxicity is lower for the COX-2 inhibitors compared to older NSAIDs, including nabumetone.³⁴ Renal complications over the short term look minimal for celecoxib.⁷ For patients at high risk of GI or renal complications, or for those who have not tolerated conventional NSAIDs, these drugs may be more suitable for long-term treatment of chronic illness than older NSAIDs. The use of COX-2 inhibitors in low-risk patients like healthy women with dysmenorrhea has no clinical advantage and is unjustifiably expensive.

Relative advantages in comparing the two drugs include the following:

- both drugs so far have shown comparable efficacy and lower toxicity than older NSAIDs
- rofecoxib has once daily dosing options
- rofecoxib does not have a sulfonamide group, but celecoxib does, a consideration in patients with sulfa allergies
- rofecoxib is available as an oral suspension
- the average wholesale price is comparable, but group purchasing discounts may be available in individual situations

The COX-2 inhibitors may cost up to 50 to 100 times as much as generically available NSAIDs. Prescribers should be reminded, in the face of direct consumer advertising that has made Celebrex® the all-time prescription leader after it surpassed Viagra® in June, that the COX-2 inhibitors are not more effective than other NSAIDs. Their one advantage is increased safety, and they should be reserved for patients at risk for serious GI adverse effects (see Table 5). ■

References

Available on request.