COX-2 inhibitors

Peter M Brooks and Richard O Day

ceuticals, with a world market in excess of $13 billion per annum.[1] Although primarily used to treat pain and inflammation in musculoskeletal disease, NSAIDs may also have a role in the management of such widely differing conditions as chronic pain associated with conditions other than musculoskeletal disorders, Alzheimer disease and colorectal cancer.[2] Although NSAIDs have been extraordinarily useful in controlling signs and symptoms of musculoskeletal disease, it is now appreciated that their use is associated with significant morbidity, primarily because of gastrointestinal toxicity,[3] but also because of renal dysfunction[4] and cardiac failure.[5]

Until 10 years ago, it was accepted that NSAIDs acted by reducing prostaglandin synthesis through inhibition of cyclooxygenase (COX). Over the last decade the finding that cyclooxygenase activity increases in inflammation led to the identification of a new COX isoform, and the elucidation of its molecular structure.[6] Recognition that cyclooxygenase consisted of two isoforms, COX-1 and COX-2, spawned an active, molecular-based drug development program for specific inhibitors of COX-2. The isoforms differ in that glucocorticoids inhibit synthesis of COX-2, but not COX-1, and COX-2 has a larger active site and a side pocket into which the new specific inhibitors fit.[7]

Inhibition by traditional NSAIDs and the selective COX-2 inhibitors (now classified as a separate class of NSAIDs — the coxibs) is compared in Box 1. Coxibs should have the same efficacy as a traditional NSAID, but without the effects on haemostasis and gut mucosa.

Adverse gastrointestinal events and NSAID therapy

Indigestion, mucosal erosion, ulceration, bleeding and perforation of the stomach are all associated with NSAID use, and serious side effects can be asymptomatic. The risk of adverse gastrointestinal events increases with age and dose. Other risk factors for gastrointestinal adverse effects include the simultaneous use of two or more NSAIDs, a history of peptic ulcer or gastrointestinal bleeding, comorbid conditions such as cardiac and renal dysfunction, and concomitant use of corticosteroids or anticoagulants.[8] Up to 2% of patients who take an NSAID for 12 months develop an ulcer or a significant gastrointestinal bleed, and this imposes a significant burden on individuals and the community.[3]

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- Cyclooxygenase-2 (COX-2) inhibitors constitute a new group of non-steroidal anti-inflammatory drugs (NSAIDs) which, at recommended doses, block prostaglandin production by cyclooxygenase-2, but not by cyclooxygenase-1.
- Two COX-2 inhibitors are currently available in Australia — celecoxib, which is taken twice daily, and rofecoxib, which is taken once daily. Both drugs act rapidly in providing pain relief and their anti-inflammatory analgesic effect in osteoarthritis and rheumatoid arthritis is equivalent to standard doses of non-selective NSAIDs.
- Celecoxib and rofecoxib show significantly lower incidences of gastrotoxicity (as measured by endoscopic studies and gastrointestinal ulcers and bleeds) than non-selective NSAIDs.
- There is Level 2 evidence that COX-2 inhibitors:
  - reduce pain in classic pain models — third-molar extraction, dysmenorrhoea and after orthopaedic surgery;
  - reduce pain and disability in osteoarthritis of the hip and knee; and
  - reduce pain and disability in rheumatoid arthritis.

Other adverse effects, such as interference with antihypertensive agents and the potential to produce renal dysfunction in patients with compromised renal function by COX-2 inhibitors, seem similar to those of non-selective NSAIDs.

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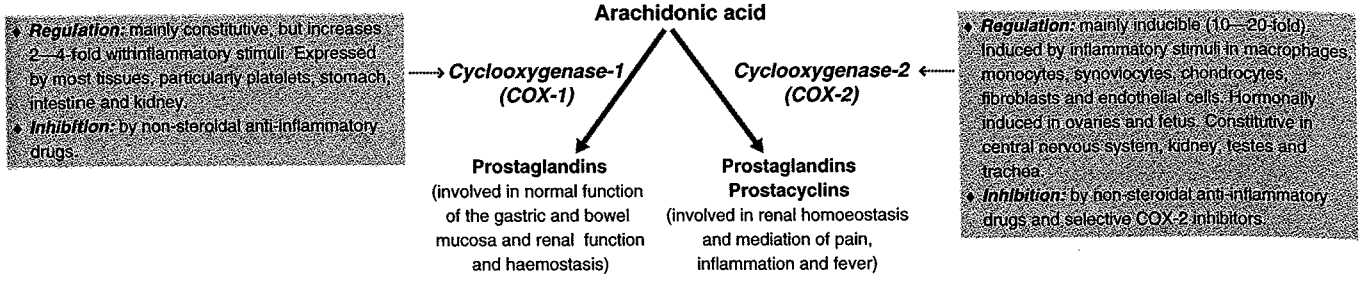
Coxibs

Two COX-2 inhibitors are currently available in Australia, and their drug profiles are given in Box 2. Rofecoxib has a longer half-life than celecoxib and is suitable for once-daily dosing, while celecoxib usually needs to be given twice daily. These two drugs also have significantly different effects on the cytochrome P450 (CP450) enzyme system, which is important in the metabolism of drugs. Celecoxib inhibits CP450 (CYP2C9) enzymes and thus may cause elevation of plasma concentrations of any drug metabolised by this isoenzyme, such as some ß-blockers, antidepressants and antipsychotics. Rofecoxib does not inhibit this enzyme system and has fewer potential metabolic interactions. Like conventional NSAIDs, both rofecoxib and celecoxib may diminish antihypertensive effects of angiotensin-converting enzyme (ACE) inhibitors and diuretic effects of frusemide and thiazides. Both coxibs have the potential to increase plasma lithium levels. Warfarin levels and, more importantly, prothrombin times can be increased by both drugs. Plasma concentrations of methotrexate were increased by just over

1: Action, regulation and inhibition of cyclooxygenase-1 and cyclooxygenase-2



20% when coadministered with rofecoxib, while celecoxib did not significantly increase methotrexate levels.[9] The clinical significance of this interaction is unclear, but increased care with methotrexate monitoring is appropriate after introducing a coxib.

Efficacy

Pain relief: Rofecoxib (50 mg) has been shown to be superior to placebo and equivalent to naproxen sodium (550 mg) in the 12 hours after being taken for orthopaedic surgical pain relief (E2) (see Box 3 for an explanation of level-of-evidence codes) and for dysmenorrhoea (E2), and equivalent to ibuprofen (400 mg) after third-molar tooth extraction (E2). Celecoxib in a dose of 100 mg or 200 mg was significantly better than placebo for pain after third-molar extraction, and no different than ibuprofen 400 mg or naproxen sodium 550 mg (E2).[10]

Osteoarthritis of hip and knee: In a 12-week trial of more than 1000 patients comparing 50 mg, 100 mg and 200 mg celecoxib twice daily with 500 mg naproxen twice daily or placebo, the 100 mg and 200 mg doses of celecoxib were as effective as the naproxen. Although 50 mg celecoxib twice daily was better than placebo, it was not as effective as the higher doses.[11]

Rofecoxib in doses of 12.5 mg and 25 mg once daily has been shown to be significantly better than placebo, as effective as 2.4 g of ibuprofen daily (over six weeks)[12] and as effec-

2: Drug profiles of celecoxib and rofecoxib

Action
At therapeutic plasma concentrations, coxibs block COX-2 but do not significantly interfere with COX-1.

Onset of action
Analgesia: 1 hour.
Anti-inflammatory effect: less than 2 weeks after starting therapy.

Dosing
Celecoxib, 200–400 mg, orally, twice daily.
Rofecoxib, 12.5–50 mg, orally, once daily.

Metabolism
Celecoxib: by cytochrome P450; half-life, 12 hours; protein binding, 97%.
Rofecoxib: by metabolic reduction; half-life, 17 hours; protein binding, 85%.

Adverse effects
Reduction in gastrointestinal events (ulcers, bleeds and erosions) compared with non-selective non-steroidal anti-inflammatory drugs (NSAIDs).
Effects on renal function (potential for mild fluid retention, renal insufficiency in renally compromised patients and those taking ACE inhibitors) similar to those of non-selective NSAIDs.

Drug interactions

	Celecoxib	Rofecoxib	Effect	Clinically significant
Warfarin	Yes	Yes	Increased prothrombin time	Yes
Methotrexate	No	Yes	Increased methotrexate levels	Probably not
Lithium	Yes	Yes	Increased lithium levels	Yes
Angiotensin-converting enzyme inhibitors	Yes	Yes	Reduced antihypertensive effects (potential for renal impairment)	Yes
Inhibitors of CYP2C9*	Yes	No	Increased plasma concentrations of celecoxib	Yes
Substrates of CYP2D6†	Yes	No	Increased plasma concentration of substrate	Probably
Frusemide and thiazides	Yes	Yes	Reduced diuretic effect	Yes
Codeine and oxycodeine	Yes	No	Potential for reduced pain efficacy of substrates	Possibly
Antacids	Yes	?	Reduced celecoxib plasma concentrations	Probably

*Amiodarone, cimetidine, fluoxetine, fluconazole, metronidazole, fluvastatin.
†ß-Blockers, antidepressants (amitryptyline, desipramine, clomipramine, fluoxetine), antipsychotics (haloperidol, thioridazine), perhexiline.

3: Level-of-evidence codes

Evidence for the statements made in this article is graded according to the NHMRC system[7] for assessing the level of evidence:

E1	Level I: Evidence obtained from a systematic review of all relevant randomised controlled trials.
E2	Level II: Evidence obtained from at least one properly designed randomised controlled trial.
$E3_1$	Level III-1: Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
$E3_2$	Level III-2: Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case–control studies, or interrupted time series without a parallel control group.
$E3_3$	Level III-3: Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
E4	Level IV: Evidence obtained from case-series, either post-test, or pre-test and post-test.

tive as 150 mg of diclofenac daily (over one year) for osteoarthritis of the knee (E2).[13]

Rheumatoid arthritis: A three-month, double-blind, placebo-controlled study comparing naproxen 500 mg twice daily, placebo and celecoxib in doses of 100 mg, 200 mg or 400 mg twice daily in more than 1100 patients with rheumatoid arthritis showed that all celecoxib doses and naproxen were effective for pain and inflammation throughout the 12 weeks (E2).[14] Interestingly, only 60% of patients completed this study. The reasons for failure to complete were not different between the active treatment groups, although those taking placebo showed a higher treatment failure rate. These patients also underwent endoscopy within a week of commencing treatment and at the end of the three months. The peptic ulceration rate (defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth) was 4% for those taking placebo, and 6%, 4% and 6% for those taking 100 mg, 200 mg and 400 mg celecoxib, respectively; these incidences were not significantly different. However, the rate was significantly higher (26%) for those taking 500 mg naproxen (E2).[14] A six-month study comparing 200 mg celecoxib twice daily with 75 mg diclofenac twice daily in 655 patients with adult-onset rheumatoid arthritis showed that celecoxib had similar efficacy to diclofenac, with a significantly lower incidence of gastrointestinal side effects. In this study 430 patients underwent endoscopy within seven days of the last treatment, and gastroduodenal ulcers (defined as any break in the mucosa of at least 3 mm in diameter with unequivocal depth) were found in 33 patients (15%) treated with diclofenac and eight (4%) in the celecoxib group. In this study, the rate of withdrawal for any gastrointestinal-related adverse event (most commonly abdominal pain, diarrhoea and dyspepsia) was nearly three times higher in the diclofenac-treated group than in the celecoxib group, and this was significant at $P < 0.001$ (E2).[15]

In an eight-week study, 648 patients with rheumatoid arthritis were randomly assigned to groups receiving either placebo or 5 mg, 25 mg or 50 mg of rofecoxib once daily. In this study the 5 mg dose was no different to placebo, while both larger doses were significantly better than placebo. No clinically significant oedema, hypertension or serious gastrointestinal effects were reported.[16]

Adverse events

Gastrointestinal: Carefully conducted endoscopy studies show a significantly lower incidence of endoscopically proven ulcers with up to 12 months of treatment with COX-2-specific agents. In patients with rheumatoid arthritis, celecoxib is associated with significantly less gastroduodenal ulceration than naproxen[14] or diclofenac (E2).[15] In a combined analysis of eight trials in patients with osteoarthritis, treatment with rofecoxib was associated with a significantly lower incidence of perforations, ulcers or bleeds than treatment with ibuprofen, diclofenac or nabumetone (E1).[17] An endoscopic study in osteoarthritis showed an ulcer incidence at 12 weeks for rofecoxib equivalent to that for placebo and significantly lower than for ibuprofen.[18] Large studies of gastrointestinal outcomes with both celecoxib and rofecoxib are currently in progress, and these data should be available in the next few months. There are also data suggesting that small bowel permeability is not affected by COX-2-specific agents, whereas it is increased with non-selective NSAIDs.

Renal: Although it was initially felt that COX-2-specific agents might be renal-sparing, there is COX-2 in the kidney[19] and it can be induced in circumstances such as sodium depletion or in patients taking ACE inhibitors. COX-2-specific inhibitors may affect renal function in much the same way as traditional NSAIDs, and particular care should be taken in prescribing these drugs to patients with renal dysfunction or in those taking diuretics or antihypertensive agents, particularly ACE inhibitors.

Cardiovascular: The inhibitory effect on platelet function by traditional non-selective NSAIDs may play a contributory role in gastric bleeding. However, prostacyclin (PGI_2) is also thought to play an important role as an antithrombotic and vasodilator, and COX-2 is thought to play a role in the biosynthesis of both systemic and renal prostaglandin (PGE_2),[20] thus influencing PGI_2 synthesis. This may have important connotations in vascular disease. The implications of specific COX-2 inhibition on thrombosis are not known, although there have been several case reports of thromboses in patients with the antiphospholipid syndrome treated with celecoxib.[21] As the COX-2 story unfolds it will be important to explore the effect of combinations of low-dose aspirin and specific COX-2 inhibitors in a wide range of patients.

Reproduction

COX-1 and COX-2 are both involved in various aspects of ovulation, implantation and parturition.[22] COX-2-deficient mice are infertile and COX-2-specific inhibitors should not be taken by women wishing to become pregnant.

The future of COX-2 inhibitors

Large studies of gastrointestinal outcomes are currently in progress with both these agents to further examine clinical

4: When to prescribe a COX-2 inhibitor

Prescribe for patients with rheumatoid arthritis or osteoarthritis who are:

- Not responding to conventional non-steroidal anti-inflammatory drugs (NSAIDs) and/or
- At risk of gastrointestinal (GI) toxicity because they:
  - have had previous NSAID-associated GI toxicity;
  - are aged over 65 years;
  - have severe arthritic disease;
  - are taking a high dose of NSAIDs.

gastrointestinal events. Patients with a previous history of peptic ulceration (although not in the previous six months) and patients up to and over the age of 90 years have been included in outcome studies so far completed. As COX-2 is involved in ulcer healing, it is important to know whether use of these agents will retard this process. It will also be important to see, in large clinical trials, whether coxibs will have any effect on the incidence of vascular disease.

With the knowledge that COX-2 is overexpressed in bowel cancer and in Alzheimer disease and that non-selective NSAIDs retard both of these conditions comes the tantalising prospect that coxibs may have potential for wider use in the future.[1,7] Celecoxib has been approved in the US for patients with familial polyposis coli after a randomised placebo-controlled trial showed a 28% reduction in the number of polyps in patients who took 400 mg celecoxib twice daily.[23]

Practical issues

An algorithm for prescribing specific COX-2 inhibitors is shown in Box 4, and important messages for patients are shown in Box 5. Cost-effectiveness studies (which are dependent on the local price of the drug), based on current US prices, suggest that use of COX-2 inhibitors would be cost effective in high risk patients — those with a history of peptic ulceration, those taking high doses of NSAIDs or corticosteroids, and those aged over 65.[24]

The release of COX-2 inhibitors in Australia appears to be good news for sufferers of musculoskeletal conditions.[25] As with the introduction of any new drug, doctors should assess patients carefully, asking whether there are specific reasons for changing therapy (such as ineffectiveness or adverse events), and review patients taking the new drug at frequent intervals. In this way these drugs can be introduced cost effectively and benefit the maximum number of patients.

5: Important messages for patients

- COX-2 inhibitors produce many effects of non-steroidal anti-inflammatory drugs (NSAIDs) but with a reduced incidence of gastrotoxicity.
- COX-2 inhibitors are no better than NSAIDS in reducing musculoskeletal pain and inflammation but are safer.
- COX-2 inhibitors may interfere with antihypertensive or diuretic medication.

Disclaimer: Peter Brooks serves on Advisory Boards for Merck Sharp and Dohme for rofecoxib, and in the past has consulted and been a member of Advisory Boards for Pfizer and Searle. Richard Day serves on Advisory Boards on rofecoxib for Merck Sharp and Dohme and on Advisory Boards for celecoxib for Pfizer and Searle.

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