COX-2 inhibitors

TRADITIONAL NON-STEROIDAL anti-inflammatory drugs (NSAIDs) constitute one of the largest groups of pharmaceuticals, 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 dysfunction4 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.9

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 β-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 furosemide 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

Peter M Brooks and Richard O Day

ABSTRACT

- Cycloxygenase-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.

MJA 2000; 173: 433-436

University of Queensland, Royal Brisbane Hospital, Brisbane, Qld.
Peter M Brooks, MB, BS, FRACP, FRCPA
University of New South Wales, St Vincent's Hospital, Sydney, NSW.
Richard O Day, MB, BS, FRACP, FRCPA

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

- Regulation: mainly constitutive, but increased by 2-4 fold extramurally stimuli; expressed by most tissues, particularly platelets, stomach, kidneys and salivary glands.
- Inhibition: by non-steroidal anti-inflammatory drugs.

Arachidonic acid → Cyclooxygenase-1 (COX-1)
Prostaglandins (involved in normal function of the gastric and bowel mucosa and renal function and haemostasis)

Cyclooxygenase-2 (COX-2) ← Prostaglandins
Prostacyclin (involved in renal haemostasis and mediation of pain, inflammation and fever)

- Regulation: mainly inducible (10-20 fold).
- Induced by inflammatory stimuli in macrophages, monocytes, lymphocytes, polymorphs, leukocytes and endothelial cells.
- Hormonally induced in ovaries and kidney. Constitutive in central nervous system, kidney tissues and testes.
- Inhibited by non-steroidal anti-inflammatory drugs and selective COX-2 inhibitors.

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 effective.

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.

Drug interactions

<table>
<thead>
<tr>
<th>Drug interaction</th>
<th>Celecoxib</th>
<th>Rofecoxib</th>
<th>Effect</th>
<th>Clinically significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Yes</td>
<td>Yes</td>
<td>Increased prothrombin time</td>
<td>Yes</td>
</tr>
<tr>
<td>Methotrexate</td>
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<td>Yes</td>
<td>Increased methotrexate levels</td>
<td>Probably not</td>
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<tr>
<td>Lithium</td>
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<td>Yes</td>
<td>Increased lithium levels</td>
<td>Yes</td>
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<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Yes</td>
<td>Yes</td>
<td>Reduced antihypertensive effects (potential for renal impairment)</td>
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</tr>
<tr>
<td>Inhibitors of CYP2C9*</td>
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<td>Increased plasma concentrations of celecoxib</td>
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<tr>
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<td>Increased plasma concentration of substrate</td>
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<tr>
<td>Furosemide and thiazides</td>
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<td>Yes</td>
<td>Reduced diuretic effect</td>
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<td>Cocodeine and oxycodone</td>
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<td>No</td>
<td>Potential for reduced pain efficacy of substrates</td>
<td>Possibility</td>
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<tr>
<td>Antacids</td>
<td>Yes</td>
<td>?</td>
<td>Reduced celecoxib plasma concentrations</td>
<td>Probably</td>
</tr>
</tbody>
</table>

* Amiodarone, cimetidine, fluoxetine, fluconazole, metronidazole, fluvastatin.
† β-Blockers, antidepressants (amitryptiline, desipramine, clomipramine, fluoxetine), antipsychotics (haloperidol, thioridazine), perhexiline.
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 naproxen14 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 kidney19 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 (PGL) 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 (PGE2),20 thus influencing PGI2 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
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. 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.

**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.

The release of COX-2 inhibitors in Australia appears to be good news for sufferers of musculoskeletal conditions. 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.

**References**