# COX-2 specific inhibitors
## safer anti-inflammatory therapy?

**A new class of anti-inflammatory agents that is as effective as conventional NSAIDs but carries less risk for the upper gastrointestinal tract has been released recently in Australia. The COX-2 specific inhibitors selectively block the formation of prostaglandins involved in inflammation and pain while sparing those involved in protecting the stomach from ulceration. What are these agents and when should we use them?**

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We would all feel better about prescribing NSAIDs if the risk of serious bleeding from the upper gastrointestinal tract was substantially lower. The new COX-2 specific inhibitors promise just this. But is this claim based more on hype than evidence? New NSAIDs used to be introduced with this same claim, and we were inevitably disappointed. If the claim is correct, should we now discard paracetamol and conventional NSAIDs for the treatment of musculoskeletal problems? Is the increased safety worth the extra money our patients or the taxpayer will have to pay? Are there subsets of our patients in whom prescribing these drugs is the right option? As with any new drug launched with impressive claims, healthy scepticism is usually an appropriate attitude.

### How do NSAIDs work?

Sir John Vane discovered how aspirin and the conventional NSAIDs worked in the early 1970s and won the Nobel Prize for medicine in the process. He found that aspirin blocked the production of prostaglandins. Prostaglandins

**IN SUMMARY**

- **The first COX-2 specific inhibitors – celecoxib (Celebrex) and rofecoxib (Vioxx) – have been registered in several countries. Celecoxib (Celebrex) is available in Australia.**
- **COX-2 specific inhibitors selectively block the formation of prostaglandins involved in inflammation and pain but spare those involved in protecting the stomach from ulceration.**
- **Although these new drugs are effective anti-inflammatory agents, they are no more effective than conventional NSAIDs.**
- **When compared with conventional NSAID treatment, COX-2 specific inhibitor treatment impressively reduces the incidence of endoscopically-proven peptic ulcers. Also, evidence to date suggests that the serious complications of peptic ulcers are significantly reduced.**
- **COX-2 specific inhibitors should not be given to people who are allergic to aspirin or NSAIDs, and should be used very cautiously in patients taking warfarin, with more intensive monitoring of prothrombin time initially being requested.**
- **These new agents are likely to be most useful for patients who need an anti-inflammatory drug but who have risk factors for upper gastrointestinal tract bleeding.**

turned out to be important promoters of inflammation and pain in osteoarthritis and rheumatoid arthritis (see Figures 1 to 4). They are synthesised by the enzyme cyclo-oxygenase, or COX for short, and it is this enzyme that is blocked by aspirin (by adding oxygen to substrates). However, prostaglandins also protect the stomach by blocking acid production and promoting more efficient removal of acid secreted into the stomach. Thus aspirin had both positive and negative qualities that seemed to be inseparable. Despite a plethora of NSAIDs that followed aspirin, such as ibuprofen, diclofenac, naproxen and piroxicam, none was free from the risk of serious upper gastrointestinal bleeding and they all inhibited prostaglandin production in the stomach.

## What are COX-1 and COX-2?

Brilliant research in the early 1990s led to a pivotal discovery. COX was found to be not one enzyme but two. These two forms were named COX-1 and COX-2 (see the box on page 33). The power of molecular biology allowed the full structure of COX-1 and COX-2 to be identified quickly along with the genes responsible. The groove in the centre of the two enzymes was slightly different, COX-1 having a bigger space. COX-2 also had a small side pocket.

The second exciting finding was that COX-1 constantly makes prostaglandins in the stomach, kidney and platelets. These prostaglandins were shown to be very important in maintaining normal stomach, kidney and platelet function. The prostaglandins responsible for the symptoms and signs of musculoskeletal inflammation and pain were found to be produced by COX-2. This form of COX was massively 'up-regulated' at sites of inflammation, such as an inflamed joint. In other words, there was much more COX-2 enzyme at sites of inflammation than would normally be expected.

The tendency of conventional NSAIDs to cause peptic ulcers and increase the risk of bleeding relates to their inhibition of COX-1 (see Figures 5a to c). Conventional NSAIDs also block COX-2, thus providing anti-inflammatory analgesic activity. Some conventional NSAIDs are better at blocking COX-2 than COX-1. Diclofenac is a good example of this;

Figure 1. Osteoarthritis affecting both knees.

Figure 2. X-ray showing osteoarthritis of the knee.

Figure 3. Osteoarthritis affecting the hand.

Figure 4. Rheumatoid arthritis of the hands.

however, at usual clinical doses there is still some COX-1 blockade. Thus, although the risk of gastrointestinal bleeding is less than that with piroxicam, for example, there is still a measurable risk.

## What are COX-2 specific inhibitors?

It was obvious that blocking COX-2 but not COX-1 should inhibit inflammation and the associated pain without affecting the production of prostaglandins in the stomach and platelets. If this was possible, it was likely that the risk of peptic ulcers would be much lower with anti-inflammatory therapy. Also, the bleeding tendency seen with aspirin and NSAIDs, caused by their ability to block platelet function, should no longer be a problem.

The first job was for the synthetic chemists to make molecules that would fit snugly into COX-2 but not COX-1. The side pocket in the COX-2 enzyme allowed molecules with side chains to fit the COX-2 groove very well but not access the COX-1 groove. Blocking the groove of COX-2 stopped the precursor of prostaglandins, arachidonic acid, entering the groove of the COX-2 enzyme and being converted to prostaglandins.

The first representatives of this new class of drugs – celecoxib (Celebrex) and rofecoxib (Vioxx) – have been registered in several countries, and celecoxib has been released recently in Australia. These drugs do not inhibit COX-1 at the doses used clinically. In addition, whole blood measurements of prostaglandin production in people taking these drugs, even at doses well above clinical doses, shows blockage of COX-2 but not COX-1.

## How effective are COX-2 specific inhibitors?

As mentioned above, conventional NSAIDs block COX-1 and COX-2, and COX-2 is responsible for producing the prostaglandins that are key to inflammation and related pain. Thus COX-2 specific inhibitors should be as effective as conventional NSAIDs in relieving the symptoms and signs of inflammation, such as pain, swelling and stiffness of joints in rheumatoid arthritis. Both celecoxib and rofecoxib are effective anti-inflammatory drugs; however, they are no more effective than conventional NSAIDs (Figure 6).

In Australia, celecoxib is registered for the treatment of osteoarthritis and rheumatoid arthritis; rofecoxib is registered for osteoarthritis. Expect the registered indications for both drugs to eventually include acute pain, osteoarthritis, rheumatoid arthritis and other inflammatory rheumatic conditions, such as gout and ankylosing spondylitis.

## What about gastrointestinal safety?

Comparisons between COX-2 specific inhibitors and conventional NSAIDs in volunteers and in patients with osteoarthritis and rheumatoid arthritis have been made in short term studies and those lasting up to one year. They reveal an impressive reduction in the incidence of endoscopically-proven peptic ulcers following treatment with these new drugs (Figure 7). However, whether finding fewer cases of peptic ulcers at endoscopy means that there will be fewer cases of serious bleeding with these new drugs remains to be finally proven. There is evidence from the clinical studies conducted so far that the serious complications of peptic ulcers are significantly reduced;[3] however, we await publication of the outcomes of large, controlled trials to test this hypothesis comprehensively. These studies are almost completed for celecoxib and rofecoxib. Furthermore, since the release of celecoxib in the USA there

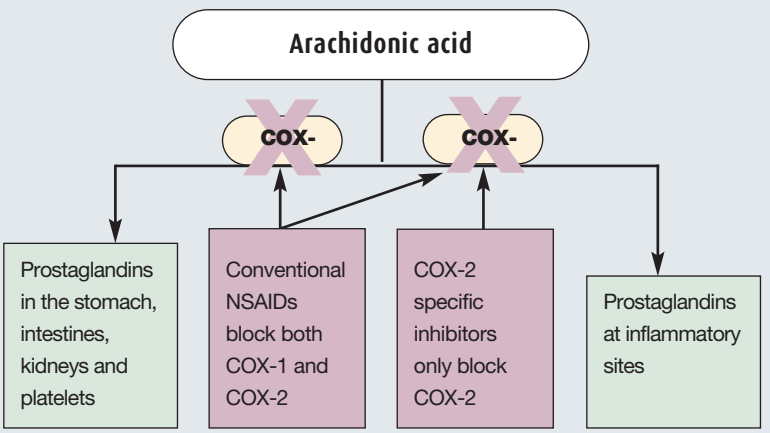
### Site of action of anti-inflammatory agents

Arachidonic acid is converted to prostaglandins by the enzyme cyclo-oxygenase (COX). There are two forms of this enzyme, COX-1 and COX-2.

COX-1 converts arachidonic acid to the prostaglandins that are responsible for maintaining normal stomach, kidney, intestine and platelet function. Low levels of these prostaglandins are usually produced constantly by COX-1.

COX-2 converts arachidonic acid to prostaglandins found at inflammatory sites. These prostaglandins are produced in high levels when the COX-2 enzyme is induced.

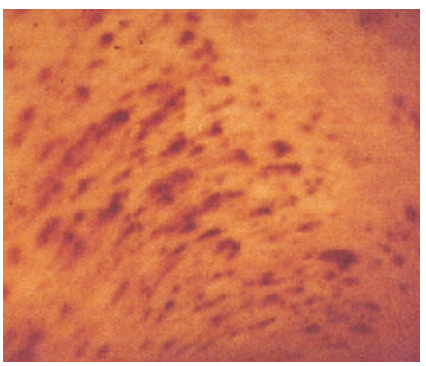
Conventional NSAIDs block both COX-1 and COX-2, thus they inhibit the production of both types of prostaglandins. COX-2 specific inhibitors block only COX-2, thus they inhibit only those prostaglandins responsible for inflammation.

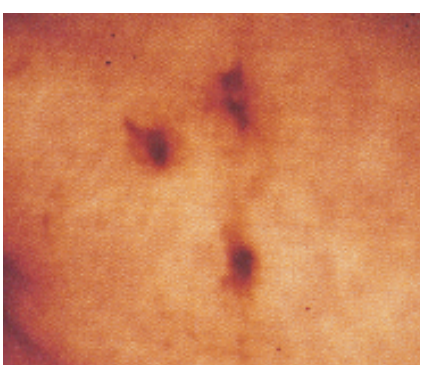


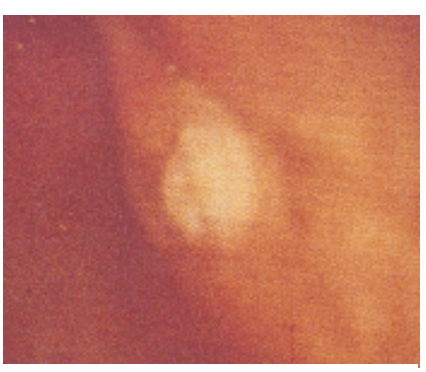
has been a substantially lower rate of serious upper gastrointestinal adverse effects than that expected with conventional NSAIDs. Similar experience has been noted in Australia since the release of celecoxib in 1999.

## What about renal and other effects?

It had been hoped that the renal adverse effects, well known with NSAIDs, would not be a problem with the COX-2 specific drugs. However, COX-2 is expressed in the kidney tubule, and it appears that salt and water retention, at least, can occur. Thus we can expect some cases of oedema, raised blood pressure and worsening of cardiac failure. Rofecoxib may be slightly more likely than celecoxib to be associated with peripheral oedema depending on the dose used. The acute reduction in glomerular filtration rate seen with conventional NSAIDs, especially in patients with pre-existing renal impairment, seems to be less of a problem with the COX-2 specific inhibitors.







Figures 5a (top), b (middle) and c (bottom). NSAID-induced gastric ulceration in the early (a), middle (b) and late (c) stages.

There has been a substantial number of reports to the Adverse Drug Reactions Advisory Committee of adverse effects with celecoxib since its release. There has been the sort of adverse effects expected from an NSAID, except for a substantially lower rate of upper gastrointestinal bleeding.

## What are the important drug interactions?

COX-2 inhibitors should be used very carefully in patients who are taking warfarin. The prothrombin time is slightly longer in patients who are taking rofecoxib concurrently with warfarin, and there have been some cases of bleeding in patients taking warfarin who were started on celecoxib after its launch onto the US market in March 1999. Some of these patients had prolonged prothrombin times. As a result, the FDA required a warning to be put into the product information for celecoxib.

Because the COX-2 specific inhibitors do not block platelet function and because they are much less likely to cause peptic ulceration than conventional NSAIDS, their concurrent use with warfarin is likely to be safer than the concurrent use of conventional NSAIDs with warfarin. However, extra care is necessary in monitoring prothrombin time early during combined therapy.

## What if my patient is taking low dose aspirin?

Low dose aspirin is a common treatment today for cardiovascular disease. We know there is an increased risk of upper gastrointestinal bleeding with low dose aspirin and the bigger the dose the bigger the risk. People who take both aspirin and COX-2 specific inhibitors will have an increased risk of peptic ulcer bleeds, but this will be lower than in someone taking conventional NSAIDs with low dose aspirin where most of the increased risk can be attributed to the NSAIDs. If there is a good reason for prescribing low dose aspirin, it should be continued in patients started on COX-2 specific inhibitors.

## Are there special hazards or contraindications?

Before prescribing these drugs, carefully check that people are not allergic to aspirin or NSAIDs. Studies in this group have not yet been conducted. Sulfur allergy is a contraindication for celecoxib but not rofecoxib. The sulfur atom in the celecoxib molecule is reactive.

People taking some NSAIDs have been shown to have a lower risk of cardiovascular events, such as thrombotic stroke and myocardial infarct, as platelet function is inhibited by drugs that block COX-1.

The production of the vasodilator prostacyclins is also inhibited by drugs that block COX-1, but some inhibition comes from blocking COX-2.

There has been a theoretical concern that switching from treatment with conventional NSAIDs to treatment with COX-2 specific inhibitors might lead to a higher than usual incidence of cardio- and cerebrovascular conditions. The practical implication for this is that patients at risk for vascular thrombosis probably need to have their platelet function inhibited if treatment is being converted from conventional NSAIDs to COX-2 inhibitors.

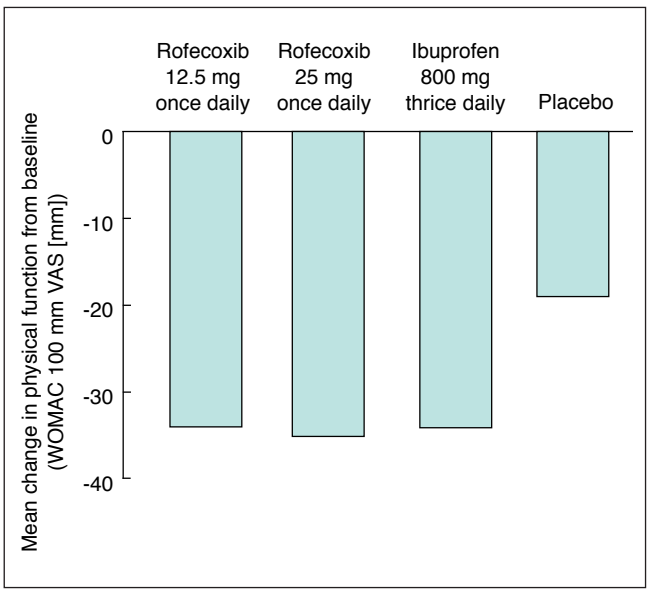



Figure 6. In a six-week study rofecoxib 12.5 mg and 25 mg daily were as effective as ibuprofen 800 mg three times daily in improving physical function in 809 patients with osteoarthritis ($p \leq 0.01$ *v.* placebo).[1] Physical function was measured using the WOMAC index (Western Ontario and McMasters Universities Osteoarthritis Index).

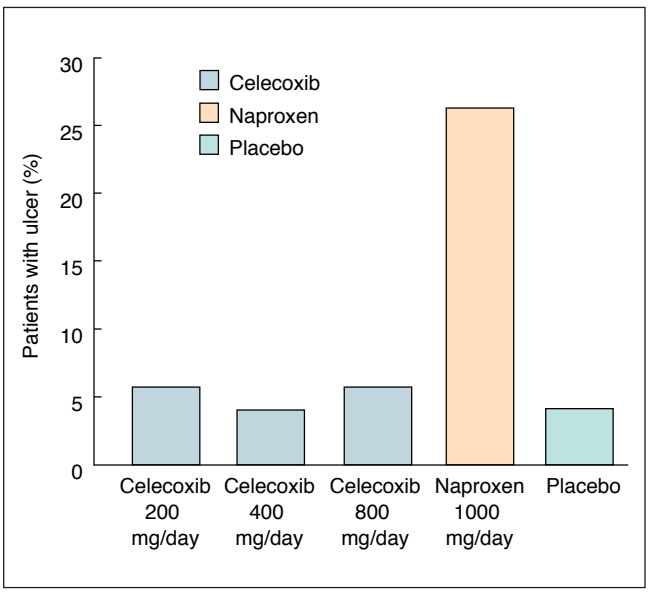



Figure 7. The incidence of endoscopically-proven gastroduodenal ulcer over 12 weeks' oral therapy with celecoxib in doses of 100, 200 and 400 mg twice daily was substantially less than that with naproxen 500 mg twice daily in 1149 patients with rheumatoid arthritis (60% of whom completed 12 weeks' therapy).[2]

## Which COX-2 specific inhibitor should I use?

Currently, there is only one direct comparison of rofecoxib and celecoxib, and that is in the single-dose treatment of acute dental pain. Rofecoxib 50 mg worked faster and had a longer analgesic effect than ibuprofen 400 mg and celecoxib 200 mg, but a higher dose of celecoxib might have been a fairer comparison.

Both COX-2 inhibitors can be given once daily, but celecoxib is registered to be given twice daily. As mentioned above, sulfur allergy is a hazard with celecoxib, but not rofecoxib. There is a suggestion that peripheral oedema is more common with rofecoxib. Comparisons in osteoarthritis and rheumatoid arthritis will certainly follow, but it might turn out that there is individual preference for one or the other agent just like there is with conventional NSAIDs.

## Should we change the way we treat osteoarthritis?

We have little trial evidence that compares COX-2 specific inhibitors with paracetamol in the treatment of simple noninflammatory rheumatic conditions, such as osteoarthritis. Early data, still in abstract form, suggest that COX-2 specific inhibitors (and also NSAIDs) are better in terms of quality of life and pain relief. However, there is still a substantial proportion of people who get a good result with paracetamol at appropriate dosage. Don't forget also the proven value of nondrug measures, such as targeted exercise therapy, orthotics for shoes, joint protection measures, etc.

The approach to the treatment of osteoarthritis and conditions like back and neck pain should remain the same, as noted below.

- Explain the condition to the patient and consider nondrug options.
- Recommend the use of paracetamol at an appropriate dosage (up to 4 g daily in otherwise well adults).
- If pain is not satisfactorily controlled consider local therapy, including liniments and local injections of corticosteroids with local anaesthetics.
- Prescribe a low dose NSAID, selecting from those known to be safer for the gastrointestinal tract – namely, ibuprofen and diclofenac. If this is used with paracetamol the dose of the NSAID can be kept lower. Intermittent therapy is fine – NSAIDs should be taken only if symptoms are present.

What if a patient needs an anti-inflammatory drug, especially for the long term, but has risk factors for NSAID-induced upper gastrointestinal bleeding – that is, a patient older than 65 years, with a history of peptic ulcer (especially if complicated) or taking concurrent chronic glucocorticosteroids? Before the

availability of COX-2 specific inhibitors we would have recommended coprescription of misoprostol (Cytotec), the prostaglandin analogue, which reduces the risk of serious bleeding from NSAIDs by at least half. Proton pump inhibitors, such as omeprazole (Acimax, Losec, Maxor), probably do just as well with fewer adverse effects but are not subsidised under the PBS for this indication. This is the setting in which the COX-2 specific inhibitors are likely to be most useful – they have the same efficacy as NSAIDs but significantly lower risk for serious upper gastrointestinal bleeding.

## Can we afford COX-2 specific inhibitors?

Whether we can afford COX-2 specific inhibitors is a dilemma. These drugs are more expensive than conventional NSAIDs but they deliver greater gastrointestinal safety. If everyone took COX-2 inhibitors instead of NSAIDs there would be a large increase in our national drug bill. If we restricted these drugs to those people with known risk factors for NSAID-induced gastrointestinal bleeding we could reduce the toll of serious bleeding and probably could afford these drugs. There would also be offsets:

- less coprescription of antiulcer therapies
- fewer endoscopies
- less hospitalisation for upper gastrointestinal bleeding.

One of the challenges will be to try to confine prescriptions to those people who really need COX-2 specific inhibitors – that is, those with risk factors. There is, and will be, much promotional pressure to prescribe these new drugs.

## Are there any other indications?

COX-2 is expressed in the brain in association with the inflammatory process of Alzheimer's disease. There is good evidence that NSAIDs can slow the onset and progress of this disease, and thus COX-2 specific inhibitors might be a good therapy given their safety.

Colon cancers express high levels of COX-2 and people taking NSAIDs are known to be less likely to develop this cancer. COX-2 specific inhibitors are being tested as prophylaxis, as well as treatment, for colon cancer.

## Conclusion

COX-2 specific inhibitors are an important advance for anti-inflammatory therapy. They have weakened the link between effective anti-inflammatory therapy and upper gastrointestinal adverse effects. For patients who have been unable to take NSAIDs because of this risk, effective anti-inflammatory therapy is a possibility.

The safety record of these drugs since their release early in 1999 is impressive with much less serious upper gastrointestinal toxicity than expected from a conventional NSAID. However, they are new chemical entities so the wise prescriber will be cautious and vigilant when considering using these drugs.

Issues of cost and value are important unresolved issues at present. Major gastrointestinal safety outcome studies comparing COX-2 specific inhibitors with conventional NSAIDs are eagerly awaited. These will finally tell us whether these drugs are the significant therapeutic advance that has been claimed. MT

## Consultant's comment

Compared with conventional NSAIDs, this new class of drugs offers greater protection from gastrointestinal bleeding due to peptic ulceration. They are likely to be similar to other NSAIDs with regard to efficacy and all other side effects. Patients who are elderly or have a history of peptic ulceration are the obvious candidates for these drugs. However, care should be taken because these patients were not well represented in the original clinical trials. As with all new medications, it is preferable to gain experience with cautious use in a few patients until the role of these drugs is established.

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## References

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## Further reading

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The author is on the steering committee of a multicentre trial involving COX-2 inhibitors and is an Advisory Board Member for the manufacturers of both celecoxib and rofecoxib.