EXPERIMENTAL AND CLINICAL PHARMACOLOGY

# COX-2 inhibitors

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## SYNOPSIS

**There are two cyclo-oxygenase enzymes: COX-1 regulates physiological function in the gut and kidney, while COX-2 is induced in inflammation and repair.**

**Selective COX-2 inhibitors are now available. In early clinical trials their efficacy in arthritis was equivalent to that of less selective non-steroidal anti-inflammatory drugs and they had a significantly lower incidence of gastrointestinal adverse effects. Larger and longer outcome studies are awaited to address issues such as a possible delaying effect of COX-2 inhibitors on ulcer healing and the potential for adverse cardiovascular effects.**


**Index words: anti-inflammatory drugs, arthritis, adverse effects.**

*(Aust Prescr 2000;23:30–2)*

## Introduction

The inhibition of prostaglandin synthesis by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) was first described over 20 years ago.[1] The NSAIDs are now one of the most commonly used medications worldwide, with annual sales in the order of US$13 billion. These drugs are frequently used for the management of musculoskeletal diseases and for other causes of acute and chronic pain. Despite their clear efficacy in the management of inflammation, NSAIDs are a significant cause of adverse events, particularly gastrointestinal ulceration[2] and altered renal function.

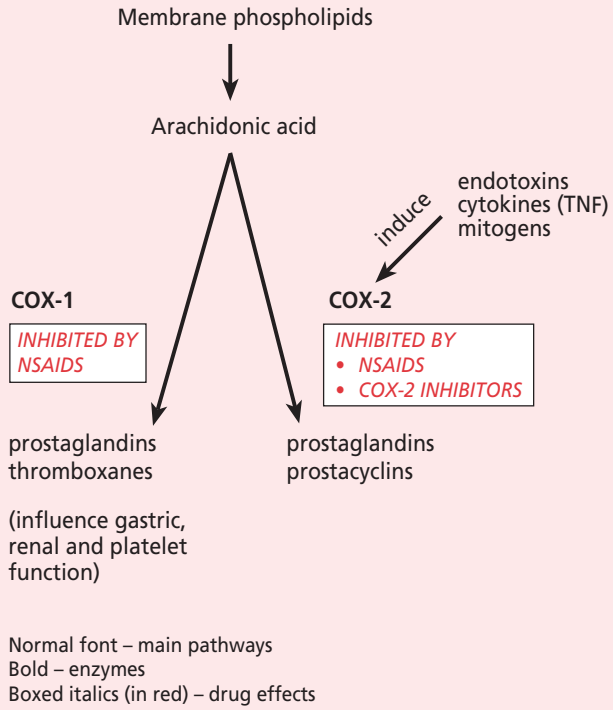
The enzyme responsible for prostaglandin synthesis is cyclo-oxygenase (COX). Following the observation that dexamethasone inhibits the increase in COX activity induced in macrophages, but has no effect on basal production of prostaglandins, it was proposed that there were two enzymes, COX-1 and COX-2.[3] The COX-1 enzyme seems to have primarily a 'housekeeping' role, subserving normal physiological function in the gut and kidney and being involved with platelet activation. The COX-2 enzyme is induced during inflammation and tissue repair and also has significant physiological roles to play in reproduction and in renal function (Fig. 1). The molecular function and protein structures of the COX isoforms were rapidly identified. This led to the development of a number of selective COX-2 inhibitors. These drugs should provide the same efficacy as the non-selective NSAIDs with fewer gastrointestinal adverse reactions.

There is a huge potential market for these drugs. In the first few months following its launch in the USA sales of one COX-2 inhibitor exceeded those of sildenafil.

*Fig. 1*

Cyclo-oxygenase enzymes.

COX-1 is involved in normal physiological functions including the production of protective prostaglandins in the stomach. COX-2 is induced by inflammation. Both enzymes are inhibited by non-steroidal anti-inflammatory drugs (NSAIDs). COX-2 inhibitors have little effect on COX-1 activity and so do not inhibit prostaglandin synthesis.



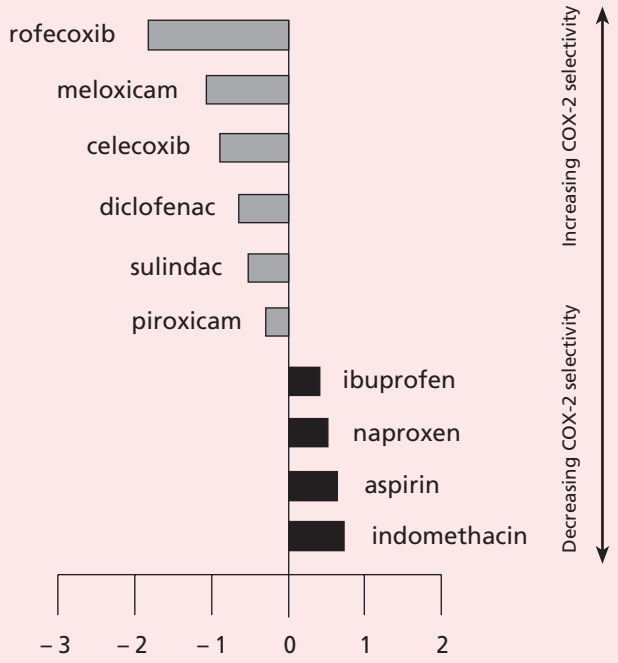

## Assessment of COX-2 selectivity

There is a wide variety of assays to assess COX-1 and COX-2 selectivity.[4] This has led to confusion in the reporting of the relative effects of some of the new selective inhibitors depending on which assay system is used. The Human Whole Blood Assay is probably the best available currently to assess inhibition of COX-1 and COX-2.

This assay has recently been modified slightly as the William Harvey Human Modified Whole Blood Assay (WHMA). A

*Fig. 2*

Selectivity of COX-2 inhibitors and non-steroidal anti-inflammatory drugs[5] given as log inhibitory concentration ($IC_{80}$) ratio. The '0' line indicates equipotency.




Log [$IC_{80}$ ratio (William Harvey Human Modified Whole Blood Assay (WHMA) COX-2/COX-1)]

wide range of COX-2/COX-1 ratios has been reported for currently available and experimental NSAIDs.[5] These data are summarised in Fig. 2 with rofecoxib being greater than 50-fold COX-2 selective, and celecoxib being 5-to-50 fold COX-2 selective. Diclofenac, sulindac and piroxicam have less than 5-fold COX-2 selectivity.

Measuring COX inhibition in gastric mucosa by using gastric biopsies may also provide important additional information. Although these investigations may define COX selectivity, they do not necessarily imply that COX-2 selective drugs will have improved safety profiles – this can only be shown by randomised controlled clinical trials.

## Clinical studies

When comparing the adverse effects of COX-2 inhibitors with those of NSAIDs appropriate doses must be used. It is essential to compare doses which have similar efficacy.

Although the new COX-2 inhibitors had significantly lower incidences of gastric injury in the short term, 12-month anti-inflammatory and gastrointestinal outcome studies against standard NSAIDs are required to fully assess their efficacy and adverse effects.

***Celecoxib***

In single dose studies celecoxib (100 mg and 400 mg) was superior to placebo and as effective as aspirin (650 mg) in relieving the pain of dental extraction. Phase II and III studies of up to six months in doses of 100–400 mg/day for osteoarthritis and 200–800 mg/day for rheumatoid arthritis showed equivalence to naproxen 1 g daily or diclofenac 150 mg daily in terms of efficacy. In normal volunteers, endoscopic studies with celecoxib 100 mg or 200 mg twice daily for seven days revealed levels of gastric mucosal injury similar to those of placebo. Larger three-[6] or six-month studies showed the incidence of ulcers was similar to placebo and significantly reduced compared to naproxen and diclofenac.

***Rofecoxib***

Rofecoxib has a long half-life and is suitable for once-daily dosing in osteoarthritis and rheumatoid arthritis. A single dose of 50 mg is superior to placebo and equivalent to ibuprofen 400 mg or naproxen 550 mg for relieving acute pain after dental extraction. Gastric mucosal injury at seven days is similar to placebo, but less than ibuprofen 2.4 g daily or aspirin 2.6 g daily. A recent analysis of eight double-blind randomised controlled trials, including two one-year efficacy studies versus diclofenac 150 mg daily, in over 5000 osteoarthritis patients has reported a significantly lower 12-month cumulative incidence of perforations, ulcers and upper gastrointestinal tract bleeding with rofecoxib than with other NSAIDs (1.3% versus 1.8%).[7]

## Future directions

Significant interest has now been shown in the role that inflammation (driven by COX-2) plays in conditions such as Alzheimer's disease and colonic carcinoma.[8] COX-2 is certainly induced around the inflammatory plaques seen widely throughout the central nervous system in Alzheimer's disease, and COX-2 expression is upregulated dramatically in colonic carcinoma. Epidemiological data support the argument that patients taking NSAIDs have a lower incidence and a slower rate of progression of Alzheimer's disease. NSAIDs also reduce the growth rate of colonic polyps in humans[9] and the incidence of colonic tumours in animals.

The selective COX-2 inhibitors seem to have similar effects, increasing blood pressure and reducing renal function, as the non-selective COX inhibitors. Selective COX-2 inhibitors should not be given to people with aspirin sensitivity as there are no published studies to show that this is safe for these patients. Although there is some theoretical concern relating to the potential for an increased risk of thrombosis with COX-2 inhibitors this does not seem to have been borne out by studies to date. Larger and longer-term studies are however required to answer these and other issues such as whether or not ulcer healing might be impaired by a selective COX-2 inhibitor. Since these drugs have the potential for widespread use in the community it is important that cost-effectiveness studies are carried out, although it would seem that the selective COX-2 inhibitors may be cost-effective for those patients at high risk of ulcer complications.[10]

## Conclusion

The efficacy of the new drugs is not greater than that of the NSAIDs. However, if the current large outcome studies of celecoxib and rofecoxib confirm the reduced gastrointestinal toxicity then these drugs will increase the options for the treatment of arthritis.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FURTHER READING

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*Professor Brooks has acted as a consultant to Searle and is on advisory boards for Merck Sharpe and Dohme.*

(A summary of all clinical trials of the COX-2 inhibitors appears on the National Prescribing Service web site at www.nps.org.au under Topics)

### Self-test questions

*The following statements are either true or false (answers on page 47)*

1. The efficacy of COX-2 inhibitors is greater than the efficacy of non-steroidal anti-inflammatory drugs.
2. It is currently unknown if an inhibitor with high selectivity for COX-2 will be safer than a less selective COX-2 inhibitor.

# Your questions to the PBAC

## Brand premiums

A number of years ago, benchmark pricing was introduced to the Pharmaceutical Benefits Schedule, whereby a drug company would be allowed to introduce a brand surcharge for their particular product. My understanding of the operation of this scheme was that it would follow the guidelines of the Australian Competition and Consumer Commission with respect to collusive pricing and price fixing. This would not appear to be the case, as many products today are obviously manufactured by the same company, their logo and name appearing on both the generic and premium-priced product (despite having a 'different' manufacturing code on the Pharmaceutical Benefits Schedule). An explanation of how brand price premiums are allowed, and calculated, would be appreciated.

Michael D. Rumpff
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*The Secretary of the Pharmaceutical Benefits Pricing Authority comments:*

The Brand Premium Policy was introduced in December 1990 to reduce price controls where possible by allowing pharmaceutical suppliers to set their own price on multi-branded and therapeutically interchangeable brands listed on the Pharmaceutical Benefits Scheme, provided one brand was available at the subsidised price. This also encourages the development of the generic pharmaceutical industry in Australia.

Under the policy, suppliers of multi-branded items are able to set their own prices at a level they think the market will bear. At the same time, prescribers, pharmacists and patients can decide whether it is necessary to pay more for a particular brand when a cheaper equivalent and therapeutically interchangeable brand is available.

As the brand premium is not a government charge, it does not count towards a patient's safety net. The premium arises from the supplier's price setting and the majority of it goes to the supplier, with wholesalers and pharmacists receiving a percentage.

Under the competitive environment, it is up to the sponsor of the product to set the price at which it sells its brand. The government only sets the subsidised price. The pricing freedom that applies is similar to that of many other commodities such as food, clothing and cosmetics.

As of February 2000 there were 236 benefit items with a brand premium that could be therapeutically interchanged. The average brand premium was $1.45 and premiums ranged from $0.23 to $43.28.