

COX-2 Inhibitors – The Evidence

The enzyme cyclooxygenase (COX), responsible for the production of prostaglandins, exists as two isoforms, COX-1 and COX-2. COX-1 plays a major role in normal functioning of the gastrointestinal (GI) mucosa, kidneys and platelets. COX-2 is expressed primarily in response to inflammation, but is also found in other tissues such as kidney and brain. Traditional non-steroidal anti-inflammatory drugs (NSAIDs) are non-selective and inhibit both COX-1 and COX-2. COX-2 inhibitors may be selective inhibitors, such as celecoxib (Celebrex[®]) and rofecoxib (Vioxx[®]), or preferential inhibitors of COX-2 (none yet marketed in Australia). Theoretically, COX-2 inhibitors should retain efficacy in inflammation and pain, but be less likely to cause serious gastrointestinal bleeding than traditional NSAIDs.

This summary of research evidence is intended to help inform decision-making regarding the appropriate place in therapy for these new agents and to aid clinicians in developing a balanced approach to this issue. It summarises what is currently known (but also what is as yet unknown) regarding the efficacy, safety and cost-effectiveness of selective COX-2 inhibitors.

EFFICACY

The efficacy of selective COX-2 inhibitors is equivalent to that of non-selective NSAIDs for the relief of pain and inflammation in adults with rheumatoid arthritis (RA) and osteoarthritis (OA)¹, which to date are the two indications which have been approved by the TGA in Australia. (Rofecoxib has been approved for OA and celecoxib has been registered for both OA and RA.)

The following points should be borne in mind regarding COX-2 inhibitors:

- They are no more efficacious than traditional NSAIDs.
- There are currently no published data on efficacy in non-RA, non-OA chronic non-inflammatory pain models. However, studies demonstrating efficacy in acute pain (dental surgery², dysmenorrhoea³) have been published.
- Evaluable data regarding efficacy and safety in children have not been published, although studies are in progress.
- Published studies have included elderly patients. However, data regarding efficacy and safety in elderly patients with co-morbidities are limited.

SAFETY

- In comparative clinical trials with non-selective NSAIDs, selective COX-2 inhibitors have demonstrated a safety advantage with respect to a lower rate of endoscopically detected ulcers, symptomatic ulcers and ulcer complications (upper gastrointestinal perforations, obstructions, bleeding)^{4 5 6 7}.

The following points should be borne in mind:

- Endoscopically detected ulcers correlate with the risk of upper gastrointestinal bleeding, perforation and obstruction. However, only a small proportion of endoscopically detected peptic ulcers (PU) become symptomatic.
- Two recent large clinical trials^{6 7} have evaluated the important clinical outcomes of symptomatic ulcers, upper GI perforations and bleeding in patients with OA or RA. A difference in these outcomes in favour of COX-2 inhibitors was observed for significant upper GI events (symptomatic peptic ulcer, bleeding, perforation or obstruction) in both studies. (For celecoxib⁶, relative risk (RR) = 0.59 (95% CI 0.38-0.94, p=0.02); absolute risk reduction (ARR) = 1.46%; number needed to treat (NNT) = 68. For rofecoxib⁷, RR = 0.5 (0.3-0.6, p<0.001); ARR = 2.4%; NNT = 42). These events were reduced irrespective of age, *H. Pylori* status, underlying condition or history of previous peptic ulcer. Low dose aspirin removed the protective effect in the celecoxib study⁶.
- These major outcome trials (CLASS⁶ and VIGOR⁷) excluded patients with active peptic ulcer (PU) disease but not those with a history of peptic ulcer disease. There is some evidence that COX-2 may have a physiological role in healing of GI inflammation or ulcers.¹ Therefore, the safety of COX-2 inhibitors in patients with silent PU disease needs further study before they can be confidently recommended for this high risk (but not easily identified) group. It

is worth noting that the risk of upper GI bleeding due to ulceration is reduced but not eliminated with COX-2 inhibitors.

- COX-2 inhibitors have in some cases been associated with life-threatening and fatal ulcer complications in clinical trials and in post-marketing surveillance data from the Australian Drug Reaction Advisory Committee (ADRAC).^{4,8} It is not clear at this time whether this reflects a background rate for these problems or whether there is preferential use of COX-2 inhibitors in a high-risk group of patients⁸.
- Although earlier trials were equivocal, the recent outcome studies have demonstrated a small (but statistically significant) reduction in GI symptoms such as dyspepsia, abdominal pain and nausea with COX-2 inhibitors. (31.4% of patients experienced such symptoms with celecoxib⁶ in comparison with 36.8% on ibuprofen or diclofenac. 3.5% of patients discontinued treatment with rofecoxib⁷ because of such symptoms vs 4.9% with naproxen). Whether the rates are greater than placebo is uncertain as placebos were not used in either trial.
- Concomitant glucocorticoid and NSAID therapy has been reported to be associated with a higher risk of clinically significant GI events than is NSAID therapy alone^{9, 10}. However, much of the data supporting this association comes from observational studies with inherent biases and wide estimates of possible risk. If there is an increased risk, the magnitude of such risk appears to be relatively small (Odds Ratio about 2) or perhaps limited to certain sub-populations, such as the elderly⁹. A systematic review of the literature in this area is currently under way¹¹.

➤ The development of COX-2 inhibitors was based on the hypothesis that COX-1 mediated uniquely physiological prostaglandin production while COX-2 mediated uniquely pathological prostaglandin production. This is now known to be an over-simplification.¹² Both COX-1 and COX-2 enzymes have physiological and pathological functions. The full clinical implications of selectively blocking the physiological or protective functions of COX-2 are not yet known. In particular, COX-2 appears to have a physiological function in the following^{12, 13}: kidney, brain, ovary and uterus, cartilage and bone, healing of GI inflammation or ulcers, and anti-thrombotic activities of endothelial cells. The consequences of abolition of these physiological functions by inhibition of COX-2 without inhibition of COX 1 is not yet clear¹².

➤ Since COX-2 is present in kidney and endothelial tissue, COX-2 inhibitors can cause peripheral oedema and other effects on kidney function, so care needs to be taken in patients with impaired glomerular filtration, hypertension or volume contraction (eg in the post-operative situation). Interactions with antihypertensives, diuretics and lithium should be expected with selective COX-2 inhibitors¹⁴.

➤ Inhibition of platelet aggregation is mediated through COX-1, so that use of COX-2 inhibitors might be expected to avoid precipitation of bleeding complications in those at risk. In one small trial of 24 healthy volunteers given celecoxib, naproxen or placebo for 10 days, there was no observed change in ex vivo platelet aggregation, serum thromboxane B₂ levels or bleeding time in the celecoxib group.¹⁵ However, clinical outcomes with chronic dosing in patients with co-morbidities and co-therapies are still awaited. Data from studies in healthy volunteers also indicate that both celecoxib and rofecoxib can decrease renal and systemic synthesis of prostacycline (PG I₂).¹⁶ Since PG I₂ is thought to have an important role in preventing thrombosis, the implications of this data for those who may be at risk for thromboembolic disease are currently unknown. Caution should be used in such patients and warnings to this effect are included in the Product Information.

The finding in the VIGOR study⁷ that naproxen was associated with a lower rate of myocardial infarction than rofecoxib requires confirmation in larger studies, but it may be unlikely that such studies will be undertaken. However data from the CLASS⁶ and VIGOR⁷ studies suggest that patients with a history of myocardial infarction should be treated with low dose aspirin. Because of the risk of aspirin-related GI toxicity, the lowest possible dose should be used (80-100mg). The need for ongoing COX-2 therapy should be carefully considered in these patients. The benefit of gastroprotective therapy in conjunction with COX-2 inhibitors has not been evaluated.

➤ Celecoxib is a sulfonamide and the drug therefore has not been studied in patients with sulfur hypersensitivity. Rofecoxib was studied in patients with sulfur allergies without the occurrence of adverse effects associated with hypersensitivity. Both drugs are contraindicated in patients with aspirin-sensitive asthma^{17, 18}.

COST-EFFECTIVENESS

Since the main rationale for using COX-2 inhibitors is a reduction in serious PU disease, it is worthwhile considering the magnitude of this benefit. The key clinical issue is whether the reduction in ulcer complications is great enough to warrant prescribing COX-2 inhibitors instead of traditional NSAIDs given the price differential. Furthermore, it is important to consider how the magnitude of any background risk may vary in different populations.

➤ In adults with RA and no risk factors for NSAID induced ulcers, the risk of developing an ulcer complication related to NSAID use is only 0.4% pa¹⁹. Peterson and Cryer²⁰ have estimated that, assuming COX-2 inhibitors prevent complicated ulcers in about 50% of those treated, and assuming a reduction in complication risk to 0.2%, 500 low-risk patients would need to be treated with COX-2 inhibitors to prevent each complicated ulcer that might have developed if all of these patients had been taking traditional₂NSAIDs. The estimated cost of preventing one such

ulcer would be about US\$400,000 per 500 patients.

- In younger, otherwise healthy individuals without RA, the risk of NSAID induced ulcer complications is likely to be considerably lower than 0.4% and consequently the number needed to treat and cost to prevent 1 ulcer complication would be even greater than 500 and US\$400,000 respectively.
- In higher risk patients (eg age >75yrs and past history of ulcer and GI bleeding) the risk of developing an ulcer complication related to NSAIDs is estimated to be about 5%.¹⁹ Using similar assumptions as above, Peterson and Cryer²⁰ have estimated that about 40 high-risk patients would need to be treated with COX-2 inhibitors to prevent each complicated ulcer. The estimated cost of preventing one such ulcer would be about US\$30,000 per 40 patients.
- Calculations from the VIGOR⁷ study suggest that 42 high risk patients with RA would need to be treated with rofecoxib rather than naproxen to avert one clinically important upper GI event in a one-year period. The CLASS⁶ study suggests that 68 patients would need to be treated with celecoxib rather than non-selective NSAIDs to avert one clinically important GI event in a one-year period.

The accuracy of these estimated costs needs further evaluation with formal cost-effectiveness studies. Furthermore, whether such costs are justified involves value judgements, which will vary depending on the setting in which therapy is being considered.

DRUG INTERACTIONS

There are a number of actual or potential drug interactions with COX-2 inhibitors that should be borne in mind.^{21 22} The examples given below are illustrative but not exhaustive and to date are largely theoretical:

- Celecoxib is metabolised by CYP2C9:
 - Drugs which inhibit this enzyme may theoretically increase plasma levels of celecoxib eg amiodarone, cimetidine, fluoxetine, fluconazole, fluvastatin, fluvoxamine, metronidazole.
- Celecoxib inhibits CYP2D6:
 - Drugs which are metabolised by this enzyme may have increased levels eg. beta-blockers, some anti-depressants and anti-psychotics
 - Drugs which are metabolised to their active form by this enzyme may have reduced effect eg. codeine
- Interactions mediated through physiological effects of COX-2 inhibitors (both celecoxib and rofecoxib):
 - ACE inhibitors and angiotensin II receptor antagonists have the potential to induce renal impairment in those who are renally compensated. Caution is particularly required in patients receiving so-called 'triple-whammy' therapy (ACE inhibitor, diuretic and either COX-2 inhibitor or non-selective NSAID)⁸.
 - WarfarinIncreased prothrombin time (PT) and bleeding events have been reported. PT should be carefully monitored when starting or stopping either celecoxib or rofecoxib. Rofecoxib is noted to prolong the PT slightly. Since platelets are not inhibited with COX-2 inhibitors, bleeding is generally less likely.

RECOMMENDATIONS

NSW TAG hospitals have endorsed the following guidelines for use of these agents in hospitals:

1. In adult patients with RA or OA:

COX-2 inhibitors have a place in analgesic and anti-inflammatory treatment in those at high risk for peptic ulcer (PU) disease. This may include:

- Patients with a documented history of peptic ulcer disease.
- The elderly (> 65 years). In this group, risk may be further increased in those on concurrent corticosteroid therapy.

Note: Safety has not been demonstrated in patients with active PU disease who need to continue NSAID therapy. Alternative approaches with documented safety and efficacy include co-therapy with misoprostol¹⁹ or a proton pump inhibitor¹⁰.

2. In adult patients with non-RA, non-OA chronic pain

Efficacy and safety has not been clearly demonstrated to date. Use may be justified in very select circumstances in patients at high risk for PU disease.

3. In children

There are no data to support use in children at this time. Although GI symptoms occur commonly in children treated with traditional NSAIDs, the risk of significant peptic ulcer disease is negligible. Use of these agents in this age group outside of formal clinical trials should be discouraged until further data is available.

4. In all patients treated with COX-2 inhibitors

All adverse events which occur in patients being treated with COX-2 inhibitors should be reported to ADRAC.

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