

Strategies against NSAID-induced gastrointestinal side effects: part 2

In this second article on the gastrointestinal risks associated with anti-inflammatory drugs, **Fiona MacRae**, **Lisa MacKenzie**, **Kenneth McColl** and **David Williams** discuss how efficacy, cost, compliance, co-morbidities and concurrent medication affect the choice of risk minimisation strategy

Currently two evidence-based strategies exist to minimise the gastrointestinal risk associated with non-steroidal anti-inflammatory drugs (NSAIDs): the prescription of cyclo-oxygenase-2 inhibitors (coxibs) instead of gastroprotective agents (eg, acid suppressants and prostaglandin analogues) with NSAIDs. The comparative safety and tolerability of these strategies have been discussed in a previous article (*PJ*, 14 February, pp187–9).

Throughout this article, “NSAID” refers to traditional NSAIDs such as naproxen. The term “coxib” refers to both cyclo-oxygenase-2-selective (eg, meloxicam) and COX2-specific (eg, celecoxib) agents. This does not imply equivalent safety profiles within these groups.

Comparative efficacy

With respect to analgesic and anti-inflammatory efficacy, coxibs (even in higher than normal doses) appear as effective (but not more so) than traditional NSAIDs. Choosing a coxib over an NSAID on the basis of efficacy is, therefore, not evidence-based.

None the less, variation in individual response to particular agents is possible. The British National Formulary estimates that 60 per cent of patients will respond to any one NSAID or coxib. This suggests that most patients could, therefore, be treated with a limited formulary of three drugs. For low-risk individuals, on the basis of cost (see Table 1 on p220) and well-established safety profiles, these three agents could, logically, be ibuprofen, diclofenac and naproxen. In some situations, lack of response could be attributable to assessing efficacy too early on in therapy. The BNF observes that a full anti-inflammatory response may not be clinically assessable for the first three weeks, so it may be premature to assume treatment failure during this time.

Comparative cost

Acquisition costs of coxibs compared with NSAIDs plus a proton pump inhibitor (PPI)

are broadly comparable, depending on the agent and dose selected (see Table 1). However, cost savings can currently be made by selecting omeprazole 20mg as the gastroprotectant of choice, choosing COX2-selective agents over COX2-specific agents (see *PJ*, 14 February, pp187–9 for evidence of poorer outcomes) or prescribing the lowest dose of any chosen anti-inflammatory (although some coxibs have flat pricing agreements).

However, acquisition costs change and choosing between strategies or between particular agents within each group, should be based on available safety data rather than cost alone. In the long term, targeting coxibs or gastroprotection at people at high risk of GI complications is likely to be the most practical cost containment strategy.

Compliance

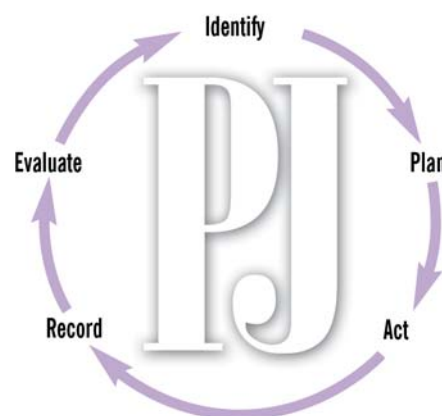
For some patients, choosing between one agent (ie, a coxib) and two agents (ie, an NSAID plus gastroprotectant) to lower GI risk may be influenced by concerns over polypharmacy and poor compliance. Without doubt, high-risk patients who take their NSAID regularly (but omit their gastroprotectant) will expose themselves to increased risk. Patient education in this regard is, therefore, paramount. None the less, despite the theoretical benefits of taking one tablet instead of two, to date, no published studies compare the impact of the two regimens on patient compliance.

It could be argued that before the introduction of coxibs, adding gastroprotectants to NSAIDs was considered acceptable clinical practice. In addition, some patients prescribed coxibs will still require a prescription for GI medicines, either for a separate clinical indication (eg, Barrett’s oesophagus) or as a result of coxib-induced dyspepsia. So, concerns about polypharmacy may be theoretical. The National Institute for Clinical Excellence estimates that between 17 and 34 per cent of patients receiving a coxib are likely to be co-prescribed a PPI.¹ A local audit in Paisley, Renfrewshire, revealed 43 per cent of the people over 65 years old were taking a coxib plus gastroprotection.

In conclusion, compliance and polypharmacy concerns are best assessed on an individual patient basis.

Co-morbidities

When choosing between coxibs and NSAIDs plus gastroprotectants, consideration must be



Identify knowledge gaps

1. How do NSAIDs and coxibs compare in terms of analgesic and anti-inflammatory efficacy?
2. What is the current guidance on the use of coxibs in patients with cardiovascular disease?
3. Which strategy to minimise the gastrointestinal risk associated with anti-inflammatory drugs should be chosen for a patient taking low-dose aspirin?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society’s areas of competence for pharmacists are listed in “Plan and record”, (available at: www.rpsgb.org/education). This article relates to “drug therapies” and “adverse drug reactions (see appendix 4 of “Plan and record”).

given to any other illnesses the patient may suffer from.

Cardiovascular disease Current consensus guidelines state that coxibs should be avoided in patients with cardiovascular disease.¹ These recommendations are based primarily on the VIGOR study, which compared rofecoxib 50mg daily with naproxen 500mg twice a day. VIGOR found that myocardial infarctions were more common in patients treated with rofecoxib than in those treated with naproxen. This is supported by case reports, laboratory-based studies and a meta-analysis by Mukherjee *et al.*^{2,3}

Several explanations for these findings have been postulated. First is the suggestion that coxibs themselves (specifically rofecoxib) may be pro-thrombotic. The pharmacological basis of these claims is that coxibs inhibit

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prostacyclin (a vasodilator and platelet antagonist), but not thromboxane (a vasoconstrictor and platelet agonist). Second is the suggestion that naproxen (and potentially other NSAIDs) are cardioprotective. This theory is supported by some studies and disputed by others.⁴

Several studies and editorials argue against a link between coxibs and thrombotic complications.⁵ Notably, the validity of the Mukherjee meta-analysis has been fiercely contested. Also, the CLASS⁶ (comparing celecoxib with ibuprofen or diclofenac) and VIGOR studies (although not primarily

designed as cardiovascular outcome studies) reveal no apparent difference in overall myocardial infarction rates for celecoxib, rofecoxib, diclofenac or ibuprofen. Furthermore, three papers published since VIGOR have questioned the link between normal doses of rofecoxib and an increased risk of myocardial infarction.^{5,7,8}

The datasheet for celecoxib does not list a caution in ischaemic heart disease but those for rofecoxib and etoricoxib do. The datasheet for valdecoxib advises caution following coronary artery bypass surgery.

Even if claims relating to the pro-thrombotic potential of coxibs are put aside, three other issues serve to cause confusion. First, coxibs (like NSAIDs) can worsen hypertension, peripheral oedema and heart failure. Second, the use of low-dose aspirin in patients suffering from these conditions and the subsequent impact on GI safety (see below) must also be considered.

Most confusingly, other work has suggested a potentially positive role for coxibs (and perhaps all anti-inflammatories) in cardiovascular disease.⁹ The rationale for the latter is that atherosclerosis has features of an inflammatory disease and the presence of COX2 in atherosclerotic lesions promotes inflammation.⁹

In conclusion, it is difficult to give clear guidance in this area. As a minimum, discussion is required to agree a local strategy, and avoiding rofecoxib (in particular long-term use of doses >25mg) in patients with cardiovascular disease may be pertinent until the issue is resolved.

Concurrent medication

When choosing between the two strategies to minimise the GI risk associated with NSAIDs, any other medicines that a patient is taking must also be considered.

Low-dose aspirin Current consensus guidelines state that in patients taking low-dose aspirin, the preferential use of coxibs over traditional NSAIDs is not justified.¹ These recommendations are based, primarily, on celecoxib trials (no or limited data exist for other agents), which demonstrate that concurrent aspirin therapy reduces (if not negates) the GI benefits (reduced ulcers and ulcer complications) of selective COX2 inhibition. Pharmacologically, this could be predicted because aspirin irreversibly inhibits both COX1 and COX2 enzymes, thus negating the COX1-sparing effects of the coxibs on the GI mucosa.

The aim of preventing NSAID-induced gastrointestinal effects is to avoid ulcer complications, such as bleeding

With respect to ulcer complications, both the CLASS⁶ and SUCCESS¹⁰ studies failed to demonstrate a statistically significant difference between patients receiving celecoxib plus aspirin and those receiving NSAIDs (with or without aspirin).

In addition, although a systematic review¹¹ of GI safety with celecoxib showed a reduction in ulceration rates (compared with NSAIDs), irrespective of the presence of aspirin (51 per cent reduction in the aspirin cohort and 73 per cent reduction in those not taking aspirin), the importance of the review was subsequently questioned. MeReC pointed out that the results related to 55 ulcers (rather than ulcer complications) in a relatively small population (290 people) while CLASS demonstrated no benefit of celecoxib over NSAIDs with respect to serious GI complications in 1,645 aspirin users.¹² Also, in a letter published in the *BMJ*,¹³ it was commented that the review related only to the favourable (and incomplete) six-month data from CLASS.

Many authors have indicated that further work is required to establish whether or not concurrent aspirin reduces or negates the GI benefits of the coxibs. Until this issue is resolved, practitioners face the dilemma of what to do for the estimated 20 per cent of anti-inflammatory users requiring low-dose aspirin. Combining low-dose aspirin with an NSAID automatically places patients at increased risk of GI problems and is likely, therefore, to justify the addition of a gastroprotectant. Unfortunately, a direct comparison of a coxib plus aspirin with an NSAID plus aspirin and gastroprotection in terms of GI toxicity has not been undertaken. Nor is there evidence that switching to a coxib plus clopidogrel (a platelet adenosine diphosphate receptor antagonist) offers improved GI safety. Most

Table 1: Costs of 28 days' treatment at licensed doses of coxibs, NSAIDs and gastroprotectants

Regimen	Acquisition cost for 28 days' treatment*
COX2-specific agents	
Rofecoxib (Vioxx) 12.5–25mg <i>od</i> †	£20.99–£24.17
Celecoxib (Celebrex) 100–200mg <i>bd</i>	£20.11–£40.23
Etoricoxib (Arcoxia) 60–90mg <i>od</i>	£22.96
Valdecoxib (Bextra) 10–20mg <i>od</i> †	£21.58
COX2-selective agents	
Meloxicam (Mobic) 7.5–15mg <i>od</i>	£9.33–£12.97
Etodolac (Lodine SR) 600mg <i>od</i>	£14.47
Etodolac (Eccoxolac – non SR) 600mg daily (as single or divided doses)	£8.17
NSAIDs	
Ibuprofen 400–800mg <i>tid</i>	£1.92–£3.84
Diclofenac 25–50mg <i>tid</i>	£2.57–£3.71
Naproxen 250–500mg <i>bd</i>	£2.58–£5.42
Proton pump inhibitors (PPIs)‡	
Omeprazole 20mg <i>od</i>	£13.04
Lansoprazole (Zoton) 30mg <i>od</i>	£23.75
Misoprostol	
Misoprostol (Cytotec) 800µg daily	£18.72
Cheapest NSAID + PPI	
Ibuprofen 1.2g + omeprazole 20mg daily	£14.96
Most expensive NSAID + PPI	
Naproxen 1g + lansoprazole 30mg daily	£29.17
Cheapest NSAID + misoprostol	
Ibuprofen 1.2g + misoprostol 800 µg daily	£20.64
Most expensive NSAID + misoprostol	
Naproxen 1g + misoprostol 800µg daily	£24.14

* Prices for branded products taken from EMIMS January 2004. Prices for generic products taken from the Scottish Drug Tariff December 2003

† Price data on rofecoxib 50mg tablets (for acute pain) and valdecoxib 40mg tablets (for primary dysmenorrhoea) are not included because they are unlikely to be prescribed on a long-term basis

‡ Price data on pantoprazole (the only other PPI licensed for NSAID prophylaxis) and lansoprazole 15mg are not included on the basis of lack of evidence of a reduction in NSAID-induced ulcer complications (ie, perforations or bleeds)

local guidelines currently appear to favour the NSAID plus aspirin plus PPI combination.¹⁴

When considering a change from a coxib plus aspirin to an NSAID plus aspirin and a PPI, practitioners may be concerned about recent reports that some NSAIDs negate the anti-platelet benefits of low-dose aspirin. The proposed pharmacological basis of this negative interaction is that aspirin and NSAIDs both bind to the same place on the COX1 enzyme, but NSAIDs bind first, thus blocking aspirin. Coxibs do not share the interaction because they have no effect on the platelet COX1 enzyme. However, closer examination of the data reveals that the evidence of an interaction appears to be restricted to (or more likely in) regular ibuprofen users, with structural differences and variations in COX2 selectivity being postulated as the possible explanation for differences between NSAIDs.^{15,16}

Some reviewers have pointed to methodological weaknesses in the work supporting the interaction, while others have provided evidence of no effect, notably a recent study published in the *BMJ*.^{17,18} To date, no published article has categorically suggested patients on aspirin and ibuprofen be actively searched for and their prescription changed. If patients are concerned, the strength of the evidence base should be discussed with them and any decision about change reached, with their involvement.

The ideal scenario involves reviewing the clinical need for aspirin and the anti-inflammatory and, if possible, avoiding concurrent therapy. With respect to aspirin, some authors suggest that a maximal risk to benefit ratio could perhaps be achieved by restricting aspirin use to those needing it for secondary cardiovascular prophylaxis. At a minimum, patients receiving aspirin for primary prevention with a coronary heart disease risk <15 per cent at 10 years require review. If discontinuation of either agent is unfeasible, reducing the dose of aspirin (to a maximum of 75mg daily), coxibs or NSAIDs (to as low a dose as possible) will also have a positive impact on GI toxicity.

Proton pump inhibitors NICE states that the combination of coxibs and PPIs is

“not justified” on the basis of lack of evidence of a further reduction in GI risk.¹ Equally, it could be stated that there is no evidence to indicate that the combination does not reduce risk. There are data from at least one observational study to suggest that the combination of a coxib and PPI (compared with a NSAID plus PPI) results in a lower incidence of gastroduodenal ulcers, but not complications.¹⁹ Equally, other authors have argued, that since neither coxibs nor NSAIDs plus gastroprotectants eliminate GI problems completely, then from a pharmacological perspective, it would be reasonable to hypothesise that the addition of a PPI to coxib therapy may reduce risk further.²⁰

It is known that some patients still develop ulcers if exposed to coxib therapy. Where ulcers exist, acid is known to produce a “second wave” of injury, deepening superficial erosions. Thus, in theory, co-prescribing a PPI with a coxib may reduce this risk further (as it does with traditional NSAIDs). Discontinuing PPI cover (according to NICE guidance) in high-risk patients receiving coxibs may therefore pose ethical dilemmas for clinicians and pharmacists. The best option in these patients may well be to discontinue the anti-inflammatory. If necessary, analgesia can be achieved with a simple or compound analgesic. The combination of a coxib and PPI is likely to cost in the region of £25–£60 per month, depending on the agents and doses used (see Table 1). This cost comes with an as yet unquantified clinical benefit.

In patients already established on PPI therapy before the introduction of an anti-inflammatory, based on evidence that NSAIDs plus PPIs offer comparable GI safety to coxibs and comparable (if not superior) reductions in dyspepsia incidence, it may be more practical to choose an NSAID in this patient group.

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Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

- Read the NICE technology appraisal referred to in this article (see Reference 1).
- Discuss with a colleague whether or not you think coxibs should be prescribed for patients with heart disease.
- Summarise the evidence presented in this article.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions:

What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?)

What will you do now and how will this be achieved?

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Further reading

Professor CJ Hawkey has written several thought provoking articles dealing, in some detail, with the issues addressed in this series. Pharmacists tackling this area in any detail may wish to read the following articles in full:

- Hawkey CJ. Cyclooxygenase inhibition: between the devil and the deep blue sea. *Gut* 2002;50(Suppl III):iii25–30.
- Hawkey CJ, Langman MJS. Non-steroidal anti-inflammatory drugs: overall risks and management. Complementary roles for COX2 inhibitors and proton pump inhibitors. *Gut* 2003;52:600–8.