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.
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 CLASS (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 data sheet for celecoxib does not list a caution in ischaemic heart disease but those for rofecoxib and etoricoxib do. The data sheet 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 reduces or negates the GI complications associated 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). 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, 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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Acquisition cost for 28 days’ treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX2-specific agents</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib (Vioxx) 12.5–25mg od†‡</td>
<td>£20.99–£24.17</td>
</tr>
<tr>
<td>Celecoxib (Celebrex) 100–200mg bd</td>
<td>£20.11–£40.23</td>
</tr>
<tr>
<td>Etoricoxib (Arcoxia) 60–90mg od</td>
<td>£22.96</td>
</tr>
<tr>
<td>Valdecoxib (Bextra) 10–20mg od†‡</td>
<td>£21.58</td>
</tr>
<tr>
<td>COX2-selective agents</td>
<td></td>
</tr>
<tr>
<td>Meloxicam (Mobic) 7.5–15mg od</td>
<td>£9.33–£12.97</td>
</tr>
<tr>
<td>Etoricoxib (Lodine SR) 600mg od</td>
<td>£14.47</td>
</tr>
<tr>
<td>Etoricoxib (Eccoxol non SR) 600mg daily</td>
<td>£8.17</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Naproxen 250–500mg bd</td>
<td>£2.57–£3.71</td>
</tr>
<tr>
<td>Ibuprofen 1.2g</td>
<td>£1.92–£3.84</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>£4.25–£5.16</td>
</tr>
<tr>
<td>Most expensive NSAID + PPI</td>
<td></td>
</tr>
<tr>
<td>Naproxen 250–500mg bd</td>
<td>£2.57–£3.71</td>
</tr>
<tr>
<td>Naproxen 1g + omeprazole 20mg daily</td>
<td>£18.72</td>
</tr>
<tr>
<td>Cheapest NSAID + PPI</td>
<td></td>
</tr>
<tr>
<td>Naproxen 1g + omeprazole 30mg daily</td>
<td>£14.96</td>
</tr>
<tr>
<td>Most expensive NSAID + misoprostol</td>
<td></td>
</tr>
<tr>
<td>Naproxen 250–500mg bd</td>
<td>£18.72</td>
</tr>
<tr>
<td>Naproxen 1g + misoprostol 800 µg daily</td>
<td>£24.14</td>
</tr>
</tbody>
</table>

† 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)
NICE states impact on GI toxicity.

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.2

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 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.18 Equally, other authors have argued that since neither coxibs nor NSAIDs plus gastroprotekants 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.19

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. This 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.

References


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:


Action: practice points

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

1. Read the NICE technology appraisal referred to in this article (see Reference 1).

2. Discuss with a colleague whether or not you think coxibs should be prescribed for patients with heart disease.

3. 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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