

Strategies against NSAID-induced gastrointestinal side effects: part 1

In the first in a series of three articles on minimising the gastrointestinal risk associated with anti-inflammatory drugs, **Fiona MacRae**, **Lisa MacKenzie**, **Kenneth McColl** and **David Williams** outline the available safety and tolerability data supporting the main risk-minimisation strategies

Anti-inflammatory drug-induced adverse effects on the gastrointestinal (GI) tract range from dyspepsia to ulceration and, most seriously, ulcer complications (haemorrhage, perforation and death). Ulcer complications (occurring in 1.5 per cent of patients a year) are the prime concern, so should be the endpoint of any strategy designed to minimise GI risk associated with anti-inflammatories. Dyspepsia is a poor predictor of GI risk. Symptoms correlate poorly with the presence of erosions or ulceration and only 15 per cent of ulcers induced by non-steroidal anti-inflammatory drugs (NSAIDs) become clinically apparent. Less than half of ulcer complications present with any warning signs.

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.

Pathogenesis

NSAIDs cause GI injury primarily through the inhibition of cyclo-oxygenase. The discovery of two COX isoenzymes (COX1 and COX2) led to the development of the group of drugs known as COX2 inhibitors or coxibs. COX1 is needed for maintaining gastric mucosal integrity. COX2 isoenzymes mediate pain and inflammation (see Figure 1, p188).

Coxibs inhibit COX2 while NSAIDs inhibit both isoenzymes. Thus coxibs are claimed to be as efficacious as NSAIDs, but less harmful on the GI tract. However, dyspepsia is still the most common adverse effect of coxib therapy. Furthermore, coxibs reduce but do not eliminate the risk of ulcer complications in "high-risk" individuals. The pathogenesis of these continuing adverse effects is not understood.

Identifying "high-risk" patients

The incidence of GI complications resulting from NSAID therapy depends on a variety of risk factors. Despite a vast literature describing

these factors, there is no national tool allowing objective quantification of overall GI risk for individuals. For some factors, the evidence is conflicting and some of the terms used (eg, "prolonged" therapy) are poorly defined.

Panel 1 (p188) summarises the factors identified as increasing GI risk. The more factors present, the greater the risk. Some factors pose a greater risk than others. A meta-analysis of 18 studies identified age and previous peptic ulcer disease, particularly if complicated, as the strongest predictors of absolute risk.⁴ In practice definitions of high risk need to be agreed locally. Using existing risk assessment tools is an option and will be covered in a later article.

Choosing the best strategy

Two main strategies to minimise GI risk exist: the preferential prescription of coxibs over NSAIDs and the combination of an NSAID with a gastroprotective drug (eg, acid suppressants, such as omeprazole, or prostaglandin analogues, such as misoprostol).

Guidance from the National Institute for Clinical Excellence recommends targeting risk reduction strategies at patients at highest baseline risk.⁵ This recommendation is based on cost. In high-risk groups (ie, baseline risk of a GI complication ≥ 10 per cent in any one year), the number needed to treat with a coxib to prevent one GI complication is in the region of 10–20.⁵ This increases to 100–200 for "typical" patients (baseline risk about 2 per cent per year) and may be as high as 500 for low risk patients.^{6,7} Not surprisingly, a cost-effectiveness analysis of gastroprotection with misoprostol showed that the cost per averted GI complication was lowest for high-risk patients (>75 years old with a history of peptic ulcer disease).⁸ Cost-effectiveness data for low to moderate risk groups are lacking.

NICE does not recommend one strategy over the other. Therefore, in order to choose the most appropriate strategy for a patient, several factors must be considered, including safety, tolerability, efficacy, cost, compliance, co-morbidities and concurrent medication.

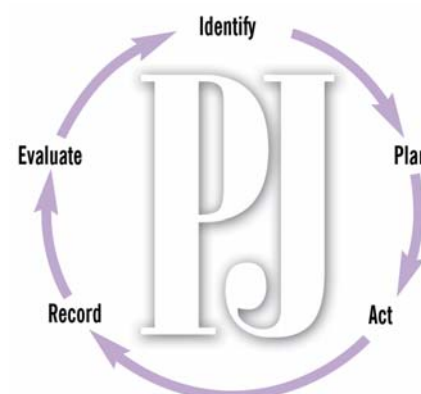
GI safety To date, only two small studies allow direct comparison of coxibs with gastroprotectants (specifically proton pump inhibitors — PPIs) in terms of their ability to reduce ulcer complications.^{9,10} Both concluded that the strategies were equally effective with respect to preventing recurrent GI bleeding.

Three large studies investigate the impact of coxibs or gastroprotectants on complication

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Identify knowledge gaps

1. Describe the pharmacological difference between traditional NSAIDs and "coxibs" in terms of gastrointestinal injury.
2. List five risk factors for NSAID-induced adverse effects on the gastrointestinal tract.
3. Which coxibs are the safest?

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 reactions" (see appendix 4 of "Plan and record")

rates: CLASS,¹¹ MUCOSA¹ and VIGOR.² CLASS (celecoxib 400mg *bd* versus ibuprofen 800mg *tds* or diclofenac 75mg *bd*) called into question the impact of celecoxib on ulcer complications. Twelve-month data accessible on the US Food and Drug Administration website (www.fda.gov) contradict the six-month conclusions from the published study. In particular, FDA data show no significant difference between celecoxib and comparator NSAIDs with respect to ulcer complications alone. Some authors attribute the negative findings to trial design deficiencies since other work suggests celecoxib is associated with reduced ulcer complication rates.¹²

In contrast, the MUCOSA (NSAIDs plus misoprostol 800µg *od* versus NSAIDs plus placebo) and VIGOR (rofecoxib 50mg *od* versus naproxen 500mg *bd*) trials provide strong evidence that effective gastroprotection or coxibs reduce ulcer complications. In MUCOSA, misoprostol achieved a relative risk reduction (RRR) in GI complications of 40 per cent compared with NSAIDs alone. In patients with a history of peptic ulcer disease or GI bleeding,

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misoprostol conferred RRRs of 52 and 50 per cent, respectively. In VIGOR, rofecoxib achieved a 57 per cent RRR in GI complications compared with naproxen.

Although the data suggest that both strategies provide comparable protection with respect to NSAID-induced ulcer complications (reducing relative risk by half), neither eliminates risk completely.

Data to support a positive impact of other gastroprotectants or coxibs on ulcer complications are sketchy. Doses of misoprostol less than 800µg/day (as in usual dose regimens of Arthrotec and Napratec) and the use of H₂ antagonists (which have been associated with increased rates of ulcer bleeding) or PPIs (other than omeprazole 20mg or lansoprazole 30mg) require review on the basis of lack of outcome data. Although both lansoprazole (15 mg *od*) and pantoprazole (20mg *od*) are licensed for gastroprotection, data to support this are based on reductions in ulceration and not ulcer complications. With respect to coxibs, only celecoxib and rofecoxib have been investigated in large, long-term trials designed to assess their effects on GI complications.

Clinical outcome data for etodolac and meloxicam are far from comparable.¹³

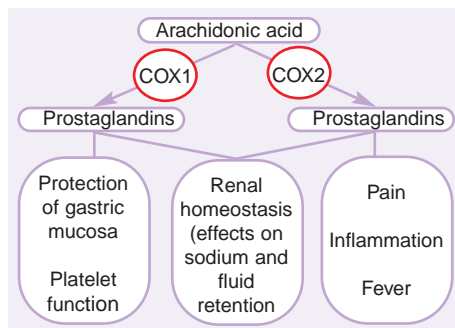


Figure 1: Functions of COX isoenzymes

Shorter, uncontrolled or descriptive data for these agents are consistent with reduced GI damage, but the evidence is far weaker.

The safety profiles of the newer coxibs (valdecoxib and etoricoxib) continue to emerge, but data are currently limited. The Scottish Medicines Consortium, which has recently approved etoricoxib and valdecoxib for general use within Scotland, has suggested these agents have no advantages or disadvantages compared with other coxibs. Health professionals need to decide whether or not they consider the outcome data for etodolac, meloxicam, etoricoxib and valdecoxib suffi-

ciently robust to justify preferential prescription over celecoxib or rofecoxib. NICE guidance does not differentiate between rofecoxib, celecoxib, etodolac and meloxicam.⁵

The impact of concurrent aspirin on GI safety will be discussed in the next article.

Overall safety Coxibs, like NSAIDs, can cause or worsen hypertension, oedema, heart failure and renal or hepatic dysfunction. Coxibs have also been shown to interact with anticoagulants (although lack of antiplatelet effect is postulated as a reason for using them in patients on anticoagulants), cause adverse skin reactions and display cross-sensitivity in aspirin-sensitive asthmatics (evidence for the latter is conflicting).

Perhaps of most concern is that analysis of the complete FDA trial data for CLASS and VIGOR show no benefit in terms of GI mortality, a trend toward greater all-cause mortality, and a significant increase in total serious adverse events (ie, death, hospital admission, any life threatening event, or event causing serious disability). It has been calculated that for every 78 patients treated for nine months with a coxib instead of an NSAID, one patient will experience a serious adverse event.¹⁴ Whether

Panel 1: Comments on risk factors for NSAID-induced adverse events on the gastrointestinal tract

Increasing age It is undisputed that risk of GI adverse effects increases with age. Arbitrary cut-offs of over 60, 65 and 75 years of age have been described in the literature. *Bandolier* estimates that 1 in 570 NSAID-treated patients aged 65–74 will have a GI bleed in any one year. This increases to 1 in 110 in those over 75 years.

Previous peptic ulcer or GI bleed Most papers agree that a clinical history of peptic ulcer disease, GI bleeding or perforation is a significant predictor of future GI adverse effects.

Increasing dose Increasing NSAID dosage within accepted ranges can triple the risk of ulcer complications. Aiming for the lowest possible dose to control symptoms is, therefore, desirable. Of note, it is suggested that ≤ 1,200mg of ibuprofen per day has a similar level of risk to a placebo.

Type of anti-inflammatory Committee on Safety of Medicines data identify ibuprofen as the NSAID posing the lowest GI risk, with 50 per cent lower complication rates than other NSAIDs. Diclofenac and naproxen are of intermediate risk and piroxicam and azapropazone appear particularly likely to cause ulcer complications. Limited data prevent some of the less frequently used NSAIDs being ranked in terms of safety.

Combining anti-inflammatories Combinations of NSAIDs are associated with increased GI risk and should generally be avoided. Yellow card data relating to ulcers and ulcer complication reveal that 6 per cent of patients were receiving two NSAIDs and 28 per cent were taking aspirin. Concurrent aspirin is claimed to more than double GI risk.

Concurrent warfarin Concomitant treatment with an anticoagulant is likely to increase the risk of haemorrhage from NSAID-induced ulcers. In most cases, combined use of warfarin and an NSAID is best avoided.

Duration of therapy Previous studies suggest the risk of NSAID-induced GI toxicity is greatest in the first three months of therapy and that thereafter the GI mucosa adapts to the adverse effects. Other work, however, indicates that the risk of toxicity is constant over time and no users (whether intermittent, short-term or chronic) are immune to problems. Never the less, the likelihood of any one individual developing problems is higher over prolonged periods of exposure. NICE guidance identifies “prolonged” maximum dosing with NSAIDs as a risk factor.

Dyspepsia and concurrent GI medicine The consensus is that dyspeptic symptoms correlate poorly with ulcers or GI complications. However, some studies suggest that dyspepsia or antacid, H₂ antagonist or proton pump inhibitor use are predictors of higher risk. This might be because GI medicines mask early warning symptoms or are generally prescribed in populations of higher baseline risk. New onset dyspepsia in a previously asymptomatic NSAID user needs attention.

Concurrent corticosteroid use There is conflicting evidence for the effect of corticosteroids on the risk of ulcer disease. Neither MUCOSA¹ nor VIGOR² showed a significant correlation between corticosteroid use and GI events. However, work by the ARAMIS group suggests a link.³ Whether steroids

are an independent risk factor or an NSAID-specific risk magnifier remains uncertain.

Helicobacter pylori The link between *Helicobacter pylori* and NSAIDs is controversial. Some reports suggest infection raises the chances of NSAID associated ulcers, others the reverse. MeReC suggests that (in addition to stopping the NSAID) it may be reasonable to eradicate *H pylori* in patients who develop an NSAID-related ulcer. It also suggests eradicating the organism before starting NSAID treatment in patients with a history of peptic ulcer disease (although it acknowledges this is not evidence-based). In all other NSAID users, eradication is not currently recommended but, in practice, most clinicians do eradicate *H pylori* in dyspeptic patients.

Serious co-morbidities or disability The only serious co-morbidities defined in randomised controlled trials as influencing risk of ulcer complications are cardiovascular disease and rheumatoid arthritis. Some studies suggest CVD increases risk. Others dispute this. MeReC observes that providing gastroprotection to all CVD patients would be a huge undertaking. Some studies suggest rheumatoid arthritis may increase risk of NSAID-related complications. Others have found no evidence that the upper GI tract is intrinsically abnormal in patients with rheumatic disease. There is more support for the finding that arthritis-related disability, or decreased functional ability is an important risk factor for NSAID-associated GI problems.

Lifestyle factors Limited data suggest smoking or drinking increases the risk of NSAID-related upper GI complications. Based on existing evidence, the level of increased risk is modest.

the increased morbidity associated with rofecoxib and celecoxib is a manifestation of their COX2 selectivity or the high doses used in trials remains unproven. The use of coxibs in patients with cardiovascular disease will be discussed in the next article.

With respect to the long-term use of PPIs, concerns over an increased risk of gastric carcinoma appear unfounded. However, the suggestion that PPI use results in parietal cell proliferation and increased capacity to secrete acid requires further clarification.

GI tolerability Although coxibs have been shown to be associated with statistically significant reductions in upper GI symptoms (eg, abdominal pain, nausea and heartburn) compared with NSAIDs, these are still the most common side effects. In the VIGOR trial 3.5 per cent of patients taking rofecoxib experienced upper GI symptoms compared with 4.9 per cent of patients taking naproxen. In CLASS, 14.4 per cent of patients given celecoxib experienced dyspepsia compared with 16.1 per cent of patients given an NSAID.

In one meta-analysis involving 5,425 patients with osteoarthritis (prescribed rofecoxib, NSAID or placebo) the cumulative incidence of dyspeptic-type effects at six months was 23.5 per cent for rofecoxib and 25.5 per cent for the NSAID ($P=0.02$), after which the incidences converged.¹⁵ Incidence rates for placebo were not given but other work reports the risk ratio of dyspeptic-type adverse effects for rofecoxib vs placebo as 1.39 and 1.63 for NSAIDs vs placebo.¹⁶ Overall, it has been estimated that the use of coxibs instead of NSAIDs leads to a reduction in dyspepsia incidence of 2 or 3 per cent.¹⁷

In terms of concomitant gastroprotectants minimising NSAID-induced dyspepsia, MeReC recently reported that the evidence for these agents producing symptomatic relief was weak for H₂-antagonists, absent for misoprostol and strongest for PPIs.¹⁵ The superiority of PPIs is confirmed by other studies conducted over one to three months, where co-prescription of omeprazole 20–40mg daily resulted in reductions in dyspepsia ranging from 20 to 46 per cent compared with NSAID therapy alone.^{18,19}

Head-to-head data comparing coxibs with NSAIDs plus a gastroprotectant with respect to GI tolerability are lacking. Also, trials do not use the same definition of dyspepsia. However, one pharmacoeconomics paper reports that the risk ratio of GI discomfort with celecoxib is similar to that predicted for patients receiving NSAIDs plus H₂ antagonists or PPIs, and less than that experienced with concurrent misoprostol.²⁰ Although not surprising for misoprostol (a quarter of patients cannot tolerate 800µg doses), this is at odds with the reductions in dyspepsia claimed for coxibs or co-therapy with PPIs in other papers.^{17–19}

In relation to dyspepsia, four other points are noteworthy. First, dyspepsia occurs in placebo-treated patients. Second, dyspepsia is dose-related and can be minimised by reduc-

ing the dose of the anti-inflammatory. This has the added advantage of lowering overall GI risk (see Panel 1). Third, dyspeptic symptoms are poorly predictive of the risk of developing GI complications. Fourth, other strategies to minimise NSAID-induced dyspepsia exist. These include taking the NSAID with or after food and switching to an alternative NSAID (patient tolerability varies between agents).

Overall tolerability Much of the promotion of coxibs has centred around improved GI tolerability. This should be balanced against all other adverse effects and overall tolerability or drop-out rates. In VIGOR, overall drop-out rates were similar in both groups: 29.3 and 28.5 per cent for rofecoxib and naproxen patients, respectively. A systematic review of celecoxib trials showed a significant reduction in withdrawals due to GI adverse events compared with NSAIDs but no significant difference in withdrawals due to all adverse events (8.13 per cent versus 9.7 per cent, $P=0.15$).²¹

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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.

- Revise NSAIDs and coxibs — read section 10.1.1 of the British National Formulary.
- Summarise the evidence in this article.
- Do you have a local protocol for prescribing NSAIDs? On what evidence is it based?

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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Topics in this series

Further articles in this series on gastrointestinal risk associated with NSAIDs will look at:

- The effect of efficacy, cost, compliance, co-morbidities and concurrent medication on the choice of risk minimisation strategy
- Changing anti-inflammatory prescribing