COX-2 inhibitors: managing comorbidities in primary care

The recent withdrawal of rofecoxib, a COX-2 inhibitor, has focussed attention on the use of COX-2 inhibitors and other non-steroidal anti-inflammatory drugs (NSAIDs) in patients with cardiovascular disease. Current guidance is to avoid COX-2 inhibitors in patients with established cardiovascular disease[1] but it is prudent to assume that similar caveats should also apply to patients at increased risk of cardiac events. The withdrawal of rofecoxib and a subsequent reluctance amongst general practitioners (GPs) to prescribe COX-2 inhibitors requires an appraisal of prescribing strategies for NSAIDs.

Many patients in primary care suffer from both osteoarthritis and cardiovascular disease, whilst the incidence of rheumatoid arthritis also increases with age. Rheumatoid arthritis is thought to be associated with an increased cardiovascular risk[2] while many patients with osteoarthritis will be at increased cardiovascular risk through advanced age and adverse lipid and blood pressure parameters that are not uncommon with advancing age. Additionally, there is conflicting evidence as to whether patients with cardiovascular disease represent a population at high risk for gastrointestinal events.[3,4]

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CSM advice

COX-2 inhibitors should not be prescribed routinely to patients at high cardiovascular risk, regardless of whether they are taking aspirin, according to existing guidance.[1] Hence, it is patients at high cardiovascular risk who potentially require both aspirin and further anti-inflammatory treatment that might present as a management dilemma to GPs. Advice from the Committee on Safety of Medicines (CSM) recommends that aspirin and non-aspirin NSAIDs (NANSAIDs) should not be co-prescribed unless absolutely necessary as co-prescribing confers an approximate doubling of the risk of gastrointestinal perforation, ulcers or bleeding events (PUBs).[5] Data from the yellow card scheme indicate that 28% of reports of gastrointestinal PUBs were in patients taking aspirin and another NSAID.[5]

Whilst aspirin has an antithrombotic effect with well established clinical benefits, the status of NANSAIDs is unclear. Evidence suggests that regular ibuprofen may impair the antiplatelet effects of aspirin,[6,7] rendering this unsuitable for regular administration with aspirin, while diclofenac[6] and naproxen[8] appear not to affect antiplatelet function when co-administered with aspirin. As ibuprofen is thought to cause fewer gastrointestinal side effects than either diclofenac or naproxen,[9] it follows that combinations of NANSAIDs and aspirin which do not impair the efficacy of aspirin are also likely to confer a higher risk of gastrotoxicity. Limited endoscopic (but not outcome) data[10,11] support the use of proton pump inhibitors (PPIs) in reducing 'later ulcer bleeding' in patients who have presented either with or without initial ulcer bleeding and continue to take NSAIDs – these patients need close monitoring. A weakness of PPIs is that they are unlikely to reduce the risks of lower gastrointestinal problems.

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There is trial evidence which indicates that co-administration of aspirin and COX-2 inhibitors might negate the relative gastroprotection afforded by the latter.[3] Although patients requiring non-selective NSAIDs and aspirin are often

Table 1. Risk factors for NSAID-induced GI events[12]

- Increasing age
- Previous GI bleed or peptic ulcer
- Type of NSAID
- Increasing dosage
- Duration of therapy
- Use of multiple NSAIDs
- Concurrent warfarin
- Dyspepsia and current GI medication
- Concurrent corticosteroid use
- *H. pylori* status
- Concurrent comorbidities (i.e. rheumatoid arthritis or CVD)
- Lifestyle factors (smoking, alcohol).

Key: NSAID = non-steroidal anti-inflammatory drug; GI = gastrointestinal; CVD = cardiovascular disease

at simultaneously high risk for cardiac and gastrointestinal events, evaluation of the effects of an aspirin, NANSAID and PPI combination on these end points requires a trial that has yet to be conducted. The evidence to guide therapeutic management in this area is weak and often conflicting.

My approach

In the midst of this uncertainty, my personal approach is based on assessing a patient's risk of both cardiovascular and gastrointestinal events. If a patient's cardiovascular risk status is high, there are two possible scenarios. Aspirin can be prescribed alone in the absence of any factors that increase the risk of gastrointestinal events (see table 1). Alternatively, if gastrointestinal risk status is also high, then coprescription of aspirin, a NANSAID only when necessary (but not ibuprofen) together with a PPI seems a reasonable approach although, admittedly, data to support this are lacking. The decision to prescribe aspirin and a NANSAID depends on the balance between clinical need and risk – if comorbidities such as rheumatoid arthritis are present, the opinion of the appropriate secondary care physician should also be sought. If a decision is made not to prescribe aspirin, then aggressive reduction of other risk factors would be required. In all cases, the lowest possible dose of NSAID and/or aspirin should be used and co-prescription of different NSAIDs avoided where possible.

GPs should be aware that NSAIDs can also increase blood pressure and worsen congestive heart failure, especially in patients receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers. Additionally, the risk of bleeding may be increased in patients who are receiving anticoagulation – there are numerous reasons to be cautious about using NSAIDs in patients at high risk of cardiovascular disease. It has been reported that NSAID treatment elevates blood pressure by an average of 3–5 mmHg and this might result in an increase in the annual risk of cardiovascular events by approximately 4/1,000 per 5 mmHg rise in blood pressure.[13] If extrapolated to the 1.5 million patients prescribed NSAIDs in the UK who are aged 60 years and over, it has been suggested that NSAIDs might cause as much cardiovascular disease as a result of drug-induced hypertension as they may be responsible for ulcer complications.[13]

Conflict of interest

None declared.

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