

COXIBS: RECENT CONTROVERSIES

A summary of a discussion between clinicians and pharmacists

The recent public and press interest in the cyclo-oxygenase type 2 inhibitors (Coxibs) has led to discussions between primary care trusts, pharmacists in both primary and secondary care, and clinicians. Two years ago the Journal reported on the gastrointestinal (GI) safety of this new and potentially promising class of drugs⁽¹⁾, but more recent evidence has suggested a cardiovascular (CV) risk. With one manufacturer voluntarily withdrawing its product from the market, another issuing statements in defence of its product, and the Committee on Safety of Medicines weighing in with its own advice, it was felt that a meeting of interested parties was appropriate. The Journal asked Pauline Bourne, Pharmacist, Marwan Bukhari, Consultant Rheumatologist, and Andrew Vickers, Consultant in Pain Management, for their views.

Pauline Bourne

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Merck halts Vioxx sales

Pain reliever linked to heart attack, stroke

Merck estimates \$2.5B impact from pulling Vioxx plug – Vioxx is no more

These were the headlines on the front page of *USA Today* on Friday 1 October 2004, competing with Bush and Kerry for the lead story.

I was in Moab in the USA on 30 September. My husband was watching *CNN* when he asked, 'What's Vioxx?' I thought this a rather odd question, especially as work is strictly taboo on holiday, but replied, 'It's an anti-inflammatory drug, like ibuprofen, why?' 'It's been withdrawn' he said, 'something to do with colon polyps'. I was eager to find out exactly why it had been withdrawn; Vioxx was the preferred coxib and was widely prescribed in the Morecambe Bay area. The article in *USA Today* the following day stated that the decision had been made by Merck to withdraw Vioxx because, in a study to assess the effect of Vioxx on the recurrence of colon polyps, patients on Vioxx were twice as likely to suffer a heart attack or stroke as those on placebo. The risk was 3.5% with Vioxx compared to 1.9% with placebo; the difference became apparent only after 18 months of treatment.

Of the four drugs considered by NICE, and for which guidance was issued in July 2001, only celecoxib and rofecoxib had been investigated in large randomised controlled trials designed to show a reduced incidence of GI adverse side effects compared to traditional NSAIDs. In the CLASS study, celecoxib was reported to have caused fewer symptomatic ulcers plus complications than diclofenac and ibuprofen (as combined comparator) and in VIGOR, rofecoxib was reported to have caused fewer symptomatic ulcers plus complications than naproxen.

The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial⁽²⁾

VIGOR compared 50 mg of rofecoxib daily with 500 mg of naprosyn daily in patients with rheumatoid arthritis in order to assess the relative risk of gastrointestinal perforation or obstruction, upper gastrointestinal bleeding, and symptomatic gastroduodenal ulcers. Patients in the trial did not take aspirin.

VIGOR concluded that rofecoxib was associated with a lower risk of gastrointestinal complications than naprosyn.

The Celecoxib Long-term Arthritis Safety Study (CLASS) trial⁽³⁾

CLASS compared celecoxib 400mg twice daily with ibuprofen 800mg three times daily or diclofenac 75 mg twice daily in order to assess the relative risk of upper gastrointestinal ulcers and ulcer complications over a six month period.

CLASS concluded that celecoxib, at doses larger than clinically necessary, was associated with a lower risk of gastrointestinal complications than ibuprofen or diclofenac, and that this reduction in risk was most obvious if patients were not taking aspirin.

NICE recommended that coxibs should not be used routinely in patients with osteoarthritis (OA) and rheumatoid arthritis (RA) and should be used in preference to traditional NSAIDs only in those patients who may be at 'high risk' of developing serious gastrointestinal adverse effects.

Many patients, however, fitted NICE criteria for a coxib and these drugs soon became widely prescribed, not only in patients with OA and RA needing an anti-inflammatory agent but also in other patients in whom simple analgesia such as paracetamol or codeine may have been adequate. Patients on low dose aspirin and/or a gastro protective agent were also prescribed a coxib even though NICE stated that there was no evidence to justify the simultaneous prescription of a coxib with these agents.

Subsequent to the publication of NICE guidance, two other coxibs – etoricoxib and valdecoxib – were introduced. In one

NICE guidelines on the use of coxibs in OA and RA

Patients over 65 years of age

Patients taking medicines known to increase the likelihood of upper GI adverse events

Patients with serious co-morbidity

Patients requiring prolonged use of maximum recommended doses of standard NSAIDs

clinical trial, etoricoxib had shown superior efficacy to naproxen, although in other trials it only showed equal efficacy to standard NSAIDs. No trials had been reported where the incidence of peptic ulcers or bleeds associated with etoricoxib versus traditional NSAIDs was a primary endpoint; the only evidence for its safety came from a combined analysis of a number of trials in which the incidence of upper GI events was 50% lower with etoricoxib compared with traditional NSAIDs.

Rheumatologists and pain specialists were keen to have etoricoxib available on the local formulary and a request was submitted to the Medicines Management Committee (MMC). This prompted a review of the available coxibs and their usage both in primary and secondary care.

Since publication of the NICE guidance further information on celecoxib and rofecoxib had been published, including a complete review of CLASS and VIGOR by the Federal Drugs Agency (FDA).

The CLASS study, published in the Journal of the American Medical Association (JAMA), and upon which NICE had based its guidance, only reported the first six months of data from two separate trials, one a 15 month study comparing celecoxib with ibuprofen and the other a 12 month study comparing celecoxib with diclofenac. The full data showed that by week 65 celecoxib was associated with a similar number of ulcer complications as the combined comparator diclofenac and ibuprofen and although there was a statistically significant relative risk reduction in favour of celecoxib when compared to ibuprofen there was no difference between celecoxib and diclofenac. This was in keeping with the fact that celecoxib was found to be only marginally more selective for COX-2 than diclofenac in in-vitro assays.

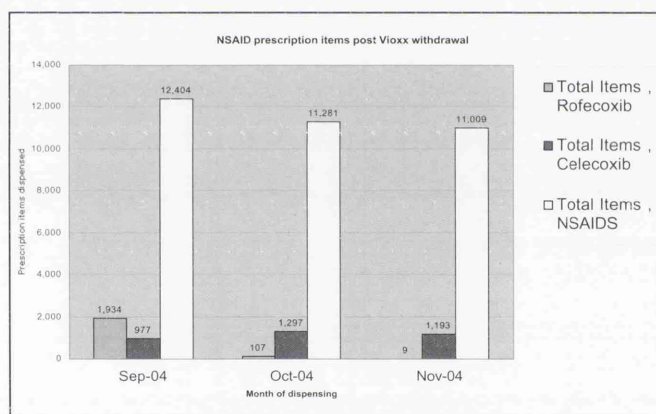
The review of VIGOR confirmed that rofecoxib caused approximately 50% fewer complicated ulcers than naproxen but highlighted the increased incidence of cardiovascular events with rofecoxib. It was unclear whether rofecoxib was the cause of the increase in cardiovascular events or whether it was due to the fact that in the VIGOR study patients were not allowed to take aspirin and the possibility that naproxen provided some protection against cardiovascular events.

Following the sudden, voluntary withdrawal of rofecoxib from the market separate advice was issued locally for prescribers in primary and secondary care. In both cases the advice very sensibly included a recommendation to reassess patients and to decide whether a NSAID was still necessary; if a NSAID was definitely needed prescribers were advised to choose a standard NSAID such as diclofenac. The advice differed however with regard to patients at 'high risk' of developing serious gastrointestinal adverse events and the prescription of alternative coxibs. The advice issued in primary care recommended the prescription of omeprazole with a standard NSAID and refrained from advising on an alternative coxib whereas the advice issued in secondary care recommended celecoxib. This led to enormous confusion between primary and secondary care and a surge in prescriptions for celecoxib.

At the time there was no evidence that the cardiovascular risk associated with rofecoxib is a class effect but there was evidence that celecoxib was not a cost-effective alternative to rofecoxib. There is some evidence that proton pump inhibitors (PPIs) reduce NSAID-associated dyspeptic symptoms and endoscopic gastric and duodenal ulcers but there is no direct evidence that PPIs prevent NSAID-associated serious upper GI complications.

Not surprisingly the manufacturers of celecoxib were keen to reassure customers that there was 'No increased cardiovascular risk associated with CELEBREX compared to traditional NSAIDs'. However, they were not able to claim that celecoxib was any safer than diclofenac with respect to upper GI events. When I raised my concern with the rep at the price of celecoxib (ie £21.55 for 200mg a day and £43.10 for 400mg a day compared to £3.23 for diclofenac 150mg a day) he reassured me that 93% of patients on celecoxib were on doses up to 200mg a day. So I, along with many others I am sure, was being hounded by reps who were opportunistically trying to corner the market with a product that they could not claim was any safer than diclofenac, that was being prescribed at a dose that was no more effective than paracetamol, and whose only selling point was that it had no increased cardiovascular risk compared to traditional NSAIDs! The reason for the development of coxibs seemed to have been totally forgotten.

On 17 December 2004, the Medicines and Health Regulatory Authority (MHRA) issued a statement that new clinical trial data for celecoxib showed an increased risk of heart attack, stroke and death relative to placebo. On 21 December, they issued interim advice on prescribing of all COX-2 inhibitors that stated that patients treated with any COX-2 inhibitor who have established ischaemic heart disease or cerebrovascular disease should be switched to alternative (non-COX-2 selective) treatments as soon as is convenient. We are awaiting definitive advice.



NSAID prescriptions in the Morecambe Bay area have fallen by 11.2% between September and November 2004.

Source: Michael Cryan, MBPCT.

New Advice for Prescribers, Committee on Safety of Medicines

Patients treated with any COX-2 inhibitor who have established ischaemic heart disease or cerebrovascular disease should be switched to alternative (non-COX-2 selective) treatments as soon as is convenient

For all patients, alternative treatments should be considered in light of an individual assessment of risks and benefits of COX-2 inhibitors, in particular cardiovascular, gastrointestinal and other risk factors

Prescribers are reminded that for all NSAID (including COX-2 inhibitors), the lowest effective dose should be used, for the shortest duration necessary

For patients switched to chronic non-selective NSAIDs, consideration should be given to the possible need for gastroprotective treatments

Marwan Bukhari

Consultant Rheumatologist

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COX-2 inhibitors (Coxibs) reduce the incidence of serious events by between 30-70 %. This is an important therapeutic advance. The current issue with Coxibs is concern about cardiovascular safety. Information about CV risk is not new: a fourfold increase in risk was noticed in the 2000 VIGOR study. However, it was initially attributed to the fact that those patients in the VIGOR study had rheumatoid arthritis, which carries its own risks of cardiovascular disease. (Aspirin was not allowed in the trial protocol.)

More recent analysis has shown that a dose of rofecoxib as used in the VIGOR trial (50mg) had some pro-thrombotic tendencies^(4,5). Rofecoxib was withdrawn following a trial that involved 2950 patients with colon polyps who were randomised to rofecoxib or placebo and there was a twofold incidence of thrombotic events after 18 months treatment.

Recently, concerns have also been raised with celecoxib in one trial, but not another, and has prompted the drug company to issue concerns about thrombotic risk with celecoxib. Valdecoxib has had concerns raised about its dermatologic side effects including Stevens Johnson syndrome. There is still not much convincing evidence regarding cardiovascular disease with etoricoxib or lumiracoxib.

These concerns have prompted my personal view that if a coxib is needed for a prolonged period of time, cardiovascular risk should be assessed versus the benefit from reduced bleeding risk with coxibs. The emphasis should be the need for coxibs as there has been guidance from NICE about patients at risk. Patients with CV risk should not be offered coxibs for a prolonged period of time. Further work is needed to assess what a short term period of time would mean as the trials only uncovered increased risk after 12-18 months of treatment.

Andrew Vickers

Consultant in Pain Management

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Non-steroidal anti-inflammatory drugs (NSAIDs) are widely recognised as effective analgesics. For example, ibuprofen 400mg has a lower 'number needed to treat' (NNT) than morphine 10mg. The importance of mast cells in the generation of peripheral nociceptive signals and the presence of central prostaglandin mechanisms support the view that these drugs can provide analgesia in the absence of what would be regarded as a 'classic' inflammatory process, and this may explain their continuing popularity amongst prescribers and patients. NSAIDs are not without complications, however, and the risk of peptic ulceration and/or bleeding continues with every dose. The introduction of the coxib drugs offered the potential of NSAID-like analgesia without many of the important adverse effects. The recent demonstration of a pro-thrombotic effect of rofecoxib

is likely to be a class effect and has posed some difficult questions. When should coxibs be used? Are they safer than NSAIDs? Perhaps more importantly, in the field of pain management, we should ask, should these drugs be used at all?

Acute pain (including post-operative) is by definition short-lived and the complications of NSAIDs administered for 3-5 days are minimal in the majority of patients. Coxibs, by virtue of the fact they do not prolong bleeding time, may have advantages for procedures where bleeding may be an important issue (eg hip arthroplasty). There will be concern about using coxibs even for a few days despite the fact that increased risk was only demonstrated after months of use. This situation may or may not be clarified by the definitive advice we have been promised.

Chronic pain is a much more complicated phenomenon which may persist for many months or years. Is it appropriate to use NSAIDs or coxibs in the long term for these patients? The answer must always be based on a risk/benefit analysis with improved quality of life being the primary end point. I believe that for many of my patients NSAIDs and coxibs have little to offer when used continuously for more than a few weeks. We have safe alternatives in paracetamol, opioids and opioid-like analgesics. Pain reducing procedures such as nerve blocks can be very effective in some cases. Physical therapy can improve quality of life by improving mobility, and psychological input (if it is available) can develop coping strategies.

It is important that we look beyond the current arguments of efficacy, safety and cost with respect to NSAIDs and coxibs, and consider the needs as a whole of our chronic pain patients.

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