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# Rofecoxib, selective COX-2 inhibitors and cardiovascular risk

[1]N Dhaun, [2]SRJ Maxwell, [3]DJ Webb
*[1]Renal Research Fellow, [2]Senior Lecturer, Professor of Therapeutics and Pharmacology, [3]Clinical Pharmacology Unit, University of Edinburgh, Edinburgh, Scotland*

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**LIST OF ABBREVIATIONS** Adenomatous Polyp Prevention on VIOXX® (APPROVe), cyclo-oxygenase (COX), Food & Drug Administration (FDA), Medicines & Healthcare Products Agency (MHRA), myocardial infarction (MI), non-steroidal anti-inflammatory drugs (NSAIDs), prostacyclin (PGI2), thromboxane (TxA2), VIOXX® Gastrointestinal Outcomes Research (VIGOR)

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*Correspondence to* **N Dhaun, Clinical Pharmacology Unit, University of Edinburgh, Western General Hospital, Edinburgh, EH4 2XU**

*fax.* **+44 (0) 131 343 6017**

*tel.* **+44 (0)131 537 2008**

*e-mail* **bean.dhaun@ed.ac.uk**

On 21 May 1999 the US FDA granted Merck Pharmaceuticals (Whitehouse Station, NJ, USA) a licence to market rofecoxib (VIOXX®), a selective inhibitor of COX-2. Over the next five years more than 80 million patients would take this medicine and annual sales would top $2·5 billion (with sales of £11·1 million in Scotland in the last financial year). On 30 September 2004, the company withdrew rofecoxib because of an increased risk of MI and stroke. This represents the largest prescription drug withdrawal in history. Controversy, however, surrounding these once named 'wonder drugs' and the system that sanctioned their use rages on.

## THE JEKYLL AND HYDE NATURE OF SELECTIVE COX-2 INHIBITORS

The coxibs are a subclass of NSAIDs designed to selectively inhibit COX-2, an inducible enzyme involved in inflammation. Conventional NSAIDs, such as ibuprofen (used to manage chronic pain), inhibit both COX-1 and COX-2 isoenzymes. Unfortunately, their use is often limited by gastrointestinal toxicity. Selective inhibitors of COX-2 spare COX-1 which confers a degree of gastroprotection.

Although the effects of coxibs on prostaglandin synthesis are beneficial in countering inflammation there are some more concerning effects which may, in part, explain the increased cardiovascular risk observed with rofecoxib. Coxibs inhibit endothelial COX-2-derived $PGI_2$ synthesis. $PGI_2$ prevents platelet aggregation and causes vasodilatation. These effects contrast with platelet COX-1-derived $TxA_2$ which causes platelet aggregation, vasoconstriction and vascular proliferation. Thus, selective blockade of COX-2 tips the balance in favour of $TxA_2$ and potentially predisposes to hypertension, MI and stroke.

## POST-MARKETING SURVEILLANCE: A FAILURE IN THE SYSTEM?

There remain a number of unresolved issues. From the public's viewpoint, how could it have taken so long for the potential risk with rofecoxib to be recognised? Could this happen again with other medicines, and what can be done to prevent this? It remains unclear why the FDA did not act earlier. A number of reports were published during the first few years after rofecoxib became available expressing concern over the associated cardiovascular risk. The VIGOR study,[1] which compared over 8,000 patients with rheumatoid arthritis receiving either 50 mg of rofecoxib daily or 500 mg twice daily of the non-selective NSAID naproxen, showed at least a four-fold increased risk for cardiovascular events in the rofecoxib arm. A number of arguments were put forward accounting for these unexpected results other than risk attributable to rofecoxib. It was postulated, for example, that naproxen may be cardioprotective, or that patients included in the trial were of a particularly high-risk group. In 2002, the FDA requested a caution to be included on packaging of rofecoxib relating to cardiovascular risk. It was not until early results of the recently published APPROVe trial[2] emerged that rofecoxib was deemed unsafe. This study, designed to show the efficacy of rofecoxib in preventing the recurrence of colorectal polyps in patients with a history of colorectal adenomas, found a 3·9-fold increased incidence of thromboembolic adverse events in the rofecoxib group compared with placebo.

The current system set up by the FDA to monitor drug safety in the post-marketing period is clearly imperfect. Known as MedWatch, it has many inherent problems: reliance on voluntary reporting of adverse events by doctors and other healthcare professionals leads to

under-reporting, poor quality of submitted reports, often with inadequate detail, and difficulty in determining whether the adverse event resulted from the drug or the disease it was intended to treat, to name but a few. This system is similar to the MHRA 'yellow card' system in the UK. Improvements are clearly needed. It has been suggested that the drug approval process needs to be de-coupled from the post-marketing and surveillance system. Is it reasonable after all to expect the same authority that approved marketing of a drug to actively seek evidence questioning its safety? In response to this situation, the FDA has recently proposed the establishment of a Drug Safety Overview Board, independent of influence from the pharmaceutical industry and specifically charged to oversee post-marketing surveillance of drugs, and a new Drug Watch web page to improve communication of emerging data and risk information.[3]

Coxibs were introduced on the basis of short-term studies. Thus, at licensing there was inadequate long-term safety data in the target population. Initial provisional product licensing may be the way forward. Manufacturers should then be mandated to conduct adequately powered studies to assess safety of all new drugs. These should be completed within the first two years after drug marketing, ideally in the drug's target population. Progress of such studies would be under the watchful eye of the independent drug agency with further studies performed as they see necessary. If adverse events are noted, especially early after marketing, the manufacturer should be obliged to make these widely known, with clear information on drug packaging, and communication directly to the medical profession, mentioned in all product promotional materials. In the US, the additional problem of direct-to-consumer advertising would also need to be addressed. This rather worrying phenomenon allows drug manufacturers to advertise in the public arena without necessarily presenting a balanced view.

## FALL OF THE 'HOUSE OF COXIBS'?[4]

So can the deleterious cardiovascular outcomes associated with one coxib be extrapolated to a class effect or is this a structurally related phenomenon specific to rofecoxib? Examples exist of agents belonging to the same drug class that differ in their safety profile: cerivastatin was removed from the European and US markets in 2001 because of a higher rate of rhabdomyolysis compared with other statins. Meta-analysis of data relating to valdecoxib, a structurally distinct coxib, reveals a three-fold increase in MI and stroke.[5] Furthermore, a trial comparing placebo against celecoxib was prematurely terminated due to an excess of cardiovascular events in the coxib arm.[6] Valdecoxib and celecoxib are still available in the US as prescribable items; of these only celecoxib is available in Scotland and sales totalled £8·6 million last year.

Structural differences, it appears, are not the key, and a class effect is apparent. A putative explanation for the respective adverse events profile of coxibs is their differing affinities for the two COX isoenzymes. Rofecoxib inhibits COX-2 80 times more than COX-1, whereas celecoxib inhibits COX-2 only nine times more than COX-1. (The ratio of COX-2:COX-1 inhibition for the non-selective NSAIDs ibuprofen and naproxen is 0·4 and 0·3, respectively.) It can then be extrapolated that rofecoxib shifts the $PGI_2/TxA_2$ balance more significantly against $PGI_2$ than other coxibs. Trials further investigating the pharmacology of coxibs are in progress.

## THE PUBLIC MESSAGE

What should patients who are taking a coxib do? In making this decision it must be appreciated that the additional cardiovascular risk to those presently at low risk of heart disease is still low and the symptomatic benefit may be considered to outweigh possible risks. These patients should discuss continuation of treatment at their next GP appointment. Given new information available,[7] those who have heart disease or are considered at high risk should arrange to meet their GP and seek alternative treatment where possible.

What of the remaining available coxibs? One must ask if there is a continuing role for this class of drug. Only rofecoxib has been shown to reduce gastrointestinal complications compared with naproxen.[1] From the CLASS trial, comparing celecoxib with ibuprofen or diclofenac, it is clear that celecoxib does not differ from the traditional NSAIDs in its effect on the pre-defined gastrointestinal end-points.[8] While coxib superiority over NSAID for relief of arthritic pain has not been shown, a number of individuals report pain relief with a coxib but not an NSAID. With a considerably higher financial burden, no efficacy benefit, and known, or rather suspected, cardiovascular risk, it would seem prudent to avoid these agents entirely in individuals with established coronary or cerebrovascular disease. In others the use of coxibs should be limited to only short courses and only when all other treatments are exhausted.

### KEYPOINTS

- Conventional NSAIDs inhibit COX-1 and COX-2 isoenzymes which are involved in prostaglandin production.
- COX-2 inhibitors (coxibs), a sub-class of NSAIDs, preferentially inhibit the COX-2 isoenzyme which predisposes the vascular system to hypertension, MI and stroke.
- Coxibs generally appear to increase the incidence of MI and stroke three to four-fold when taken long-term, whereas they may reduce the frequency of gastrointestinal side-effects.
- Coxibs may provide better pain relief than NSAIDs in particular patients, but not in patients as whole.
- Patients at increased risk of vascular disease should not take coxibs, and other patients should take them on medical advice only.
- New independent agencies are needed to survey the long-term safety of drugs after they have been licensed.



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