

The COX-2 Dilemma

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The recent controversy regarding the safety of cyclo-oxygenase 2 (COX-2) inhibitors has highlighted the inadequacies of reporting programmes¹ and post-marketing surveillance of new classes of drugs. In order to explain the controversy, this article will review the history and development of COX-2 inhibitors and present the evidence that prompted the widespread withdrawal of many of these agents.

The cyclooxygenase gene was cloned in 1988² and since then, two isoforms of the enzyme have been identified. COX-1 is expressed throughout the body and plays important roles in physiological homeostasis such as gastro-intestinal (GI) protection, renal blood flow regulation and platelet function.³ COX-2 is expressed in inflammatory cells and is involved in mediating pain and inflammation. It has also been shown to have a significant role in carcinogenesis.⁴ Recently, another isoform, COX-3, has been suggested; proposed as the site of action of paracetamol.⁵

The development of COX-2 inhibitor drugs was designed to provide the obvious advantages of non steroidal anti-inflammatory drug (NSAID) use without one of their more significant side effects, GI haemorrhage. In fact, NSAID induced GI toxicity is one of the most common drug related adverse effects in the Western world.⁶ The theoretical basis behind COX-2 inhibitors is the selective inhibition of COX-2 isoenzyme, without affecting COX-1 isoenzyme. However, this view may be overly simplistic and misrepresent the true in vivo functions of these enzymes. Both COX-1 and 2 have been found in apparently normal GI mucosa⁷ and may play roles in mucosal homeostasis. COX-2 has been found expressed in the edges of healing ulcers and may be involved in the healing process.

Two large trials (CLASS and VIGOR) published in 2000 demonstrated the efficacy and lack of GI side effects of COX-2 inhibitors. The CLASS (Celecoxib Long-term Arthritis Safety Study)⁸ trial compared celecoxib 400 mg twice daily with diclofenac (relatively selective for COX-2) 75 mg twice daily and ibuprofen (non selective) 800 mg three times daily. In this trial, 8059 patients, predominantly with osteoarthritis, were recruited and treated for 13 months. The incidence of symptomatic and/or complicated upper GI ulceration was 0.8% in the celecoxib group vs 1.5% in either of the other NSAID groups ($P=0.09$). The VIGOR (Vioxx GI Outcomes Research)⁹ trial compared rofecoxib 50 mg daily with naproxen 500 mg twice daily in 8076 patients with rheumatoid arthritis, for a period of 9 months. Patients who were on aspirin were excluded from the trial. The incidence of GI complications (symptomatic ulceration, perforation and haemorrhage) was again lower in the rofecoxib group (2.1% vs 4.5% in the naproxen group).

However, it was in the VIGOR trial that the controversy began in June 2000. It was noted that the incidence of myocardial infarction (MI) was 0.1% in the naproxen group and 0.4% in the rofecoxib group ($P < 0.01$). The overall cardiovascular complication rate (including nonfatal MI, non-fatal stroke and death from any vascular event) was again higher in the rofecoxib group (0.8% vs 0.4%, $P < 0.05$). The reason for this difference was unclear at the time and provoked considerable controversy. Neither VIGOR nor CLASS, were powered to assess cardiovascular adverse events and, in retrospect, 4% of those patients developing adverse events in VIGOR were those who would have been candidates for low dose aspirin for the prevention of vascular events.

In the CLASS trial, patients were not excluded if they were taking aspirin. In fact, they were allowed to have aspirin up to doses of 325 mg/day. This subgroup constitutes a large proportion of the study patients (21%). In this study, there were no differences in the incidence of cardiovascular events between the two groups, but the presence of aspirin negated the GI-sparing effects of celecoxib in this subgroup.

These two conflicting reports were scrutinized and there were a number of issues which confounded a clear interpretation. Firstly, the study population was different: VIGOR enrolled patients with rheumatoid arthritis which promotes thrombosis,¹⁰ whereas CLASS predominantly enrolled patients with osteoarthritis. Secondly, it was unclear whether the adverse effects seen were class specific or drug-specific. Thirdly, the use of aspirin in the two groups was different. Lastly, the median follow-up time in the CLASS study is only 6 to 12 months, which may not have been sufficient to detect further adverse events.

The theory underpinning the apparent increase in cardiovascular complications remains unclear. While aspirin and conventional NSAIDs inhibit formation of platelet derived thromboxane and endothelial PGI₂ via COX-1 inhibition, COX-2 inhibitors selectively block both vasodilatory and platelet inhibitory prostaglandins, leaving an unopposed thromboxane A₂ prothrombotic effect. However, this prothrombotic effect may be attenuated by COX-2 mediated inhibition of vascular inflammation, improvement in endothelial function and changes in atherosclerotic plaque stability.¹¹

Despite the conflicting results, the US Food and Drug Administration (FDA) was sufficiently convinced to consult its Arthritis Advisory Committee in February 2001¹² regarding this new information. In April 2002, the FDA implemented changes in the drug labeling of rofecoxib (Vioxx®), warning of the increased risk of cardiovascular events. Since then, a number of studies have been conducted, mostly observational^{13, 14, 15} and meta-analyses.^{16, 17, 18} Unfortunately, they provided conflicting results or were unable to assign causality, especially in the observational studies.

Recently, Levesque et al¹⁹ conducted a population based, retrospective cohort study where 113,927 elderly patients without previous MI were commenced on treatment with a NSAID between 1 January 1999 and 30 June 2002. The authors found that concurrent use of rofecoxib is associated with a higher risk for an acute MI (relative risk [RR], 1.24, 95% CI 1.05 to 1.46). This increased further if on rofecoxib >25 mg/day. (RR 1.73, CI 1.09 to 2.76). There was no increased risk associated with celecoxib, naproxen or meloxicam. In another case control study by Kimmel et al,¹³ patients on rofecoxib had a statistically significant greater risk of myocardial infarction compared to patients taking celecoxib (Odds ratio 2.73 [CI 1.24 to 5.95]; $P = 0.01$).

On 30 September 2004, Merck & Co Inc announced a worldwide recall of rofecoxib²⁰ after the three year safety data from the APPROVe (Adenomatous Polyp Prevention on Vioxx) trial were analysed. In this long term multicentre double blind study, 2586

patients with a past history of colorectal adenomas were randomised to receive either placebo or rofecoxib 25 mg daily for 3 years. In the rofecoxib group, 46 patients had a confirmed thrombotic event (1.5 events per 100 patient-years) compared to 26 patients in the placebo group (0.78 events per 100 patient-years), giving a relative risk of 1.92 (CI 1.19-3.11; $P=0.008$). During the first 18 months, the cardiovascular complication rates attributed to thrombotic events were similar in both groups. However, in the subsequent 18 months, the increased relative risk emerged with patients in the rofecoxib group suffering more MI and ischaemic strokes. At five months, there was also separation of the two groups with respect to the incidences of congestive cardiac failure and pulmonary oedema, although both groups had similar cardiovascular and overall mortality.

This study prompted the FDA to announce their intention to carefully review the safety of all marketed COX-2 inhibitors.²¹ There was still uncertainty regarding whether this was an isolated drug effect, limited to rofecoxib, or a class effect which involves all COX-2 inhibitors. At this point, no evidence so far had implicated celecoxib as having significant cardiovascular toxicity. This event was soon followed by an announcement from the US National Institutes of Health in December 2004, that it was suspending a colorectal cancer prevention trial with celecoxib, on the basis of increased risk of cardiovascular morbidity and mortality. In this Adenoma Prevention with Celecoxib (APC) trial, 2035 patients with a history of colorectal adenomas were enrolled in a study comparing two doses of celecoxib with placebo for the prevention of colorectal neoplasia. All surviving patients had 2.8 to 3.1 years of follow up. A review of the cardiovascular safety²² revealed that 7 (1.0%) of 679 patients in the placebo group, 16 (2.3%) of 685 patients receiving 200 mg celecoxib twice daily (Hazard ratio [HR] 2.3; 95% CI 0.9 to 5.5) and in 23 (3.4%) of 671 patients receiving 400 mg celecoxib twice daily (HR 3.4; 95% CI 1.4 to 7.8) developed cardiovascular adverse events (death, MI, stroke or heart failure). The review also stated that the observed increase in cardiovascular risk was based on only a small number of events in a trial that was not designed nor powered to evaluate this risk.

A third study on the safety of valdecoxib and its intravenous pro-drug parecoxib in the treatment of postoperative pain after coronary artery bypass graft (CABG) surgery²³ demonstrated a cluster of cardiovascular events. In this study, 1671 patients were randomized to receive intravenous parecoxib for at least three days, followed by oral valdecoxib, intravenous placebo followed by oral valdecoxib, or placebo through to day 10 post-operatively. The primary end point was the frequency of adverse events, including cardiovascular, occurring within 30 days of follow up. Both groups receiving active drugs had more patients with at least one adverse event (7.4% in each group vs 4.0% in the placebo group; risk ratio [RR] 1.9; 95% CI 1.1 to 3.2; $P=0.02$). Cardiovascular events occurred in 2.0% of patients given parecoxib/valdecoxib, compared with 0.5% of placebo patients (RR 3.7; 95% CI 1.0 to 13.5; $P=0.03$).

Not all of the trials conducted around this time showed increased cardiovascular adverse effects with COX-inhibitors. For instance, a separate long term (three years) study for the Prevention of Spontaneous Adenomatous Polyps (PreSAP) enrolled patients taking 400 mg celecoxib daily; this group had no increased cardiovascular risk compared to patients in the placebo group (12 [1.9%] patients in the placebo group vs 20 [2.1%] patients in the celecoxib group; hazard ratio [HR] 1.1; 95% CI 0.6 to 2.3). These findings were based on the same statistical analyses as the one applied to assess the cardiovascular risk in the APC trial. In the Alzheimer's Disease Anti-Inflammatory

Prevention Trial (ADAPT), 2000 patients at high risk of Alzheimer's disease were enrolled. The study compared celecoxib, naproxen and placebo for the prevention of Alzheimer's disease. An analysis of 750 patients who were on 400 mg celecoxib daily did not reveal an increased risk of cardiovascular adverse events. Surprisingly the authors did detect an increase in cardiovascular risk associated with naproxen use (naproxen 220 mg twice daily). This finding has since been questioned, as reviews of all observational studies, post-marketing surveillance data and all published clinical trials of naproxen did not show any evidence of an increased risk of MI or cerebrovascular events.

In view of all this new data, the FDA issued a public health advisory (PHA)²⁴ in December 2004, concerning the use of non steroidal anti-inflammatory drugs (NSAIDs), including the COX-2 selective agents. This required re-evaluation of all current studies involving Celecoxib (Celebrex®) and valdecoxib (Bextra®) by their respective review boards. In a statement on 14 February 2005, the Australian Therapeutic Goods Administration (TGA) also introduced new measures, after evaluating this information. The Australian Drug Evaluation Committee (ADEC) of TGA recommended a black box warning in the product information of all COX-2 inhibitors, highlighting the increased risk of cardiovascular adverse events from this group of drugs. They also recommended patients on more than 200 mg celecoxib or more than 15 mg meloxicam have their treatment regime reviewed.

Other proposals contained with the FDA paper include:

- Cancellation of registration of the drug parecoxib (Dynastat®);
- Withdrawing the indication "management of arthritis" for the drug valdecoxib, which is yet to be marketed in Australia;
- Limiting the approved uses of two other COX-2 inhibitors (etoricoxib and lumiracoxib) which have yet to be marketed in Australia.

Summary

In summary, the question remains how these changes impact on current anaesthetic practice. NSAIDs have a prominent role in the concept of multimodal analgesia. COX-2 inhibitors with their lack of anti-platelet activity at therapeutic dosages, provide additional options in the management of post-operative pain, especially in situations where conventional NSAIDs are contraindicated. The extent of risk for the remaining two COX-2 inhibitors (celecoxib and parecoxib) remaining available in Australia is clearly unknown and requires further investigation. The duration of treatment and populations at risk also remain unclear.

The prudent method of COX-2 inhibitor use at this stage involves appropriate patient selection and using a low dose for the shortest possible duration.

References

1. Drazen J. COX-2 inhibitors: a lesson in unexpected problems. *N Eng J Med* 2005, posted online 15/02/2005.
2. Dewitt D, Smith WL. Primary structure of prostaglandin G/H synthase from sheep vesicular gland determined from the complementary DNA sequence. *Proc Natl Acad Sci USA* 1988; 85:1412-1416.
3. Seibert K, Masferrer J. Role of inducible cyclooxygenase in inflammation. *Receptor* 1994; 4:644-648.
4. Soslow R, Dannenberg A, Rush D et al. COX-2 is expressed in human pulmonary, colonic and mammary tumours. *Cancer* 2000; 89:2637-2645.
5. Chandrasekharan NV, Dai H et al. Cox-3, a cyclooxygenase-1 variant inhibited by acetoaminophen and other analgesic/antipyretic drugs: cloning, structure and expression. *Proc Natl Acad Sci USA* 2002; 99:13926-13931.

6. Wolfe M, Lichtenstein D et al. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *N Eng J Med* 1993; 340:1888-1899.
7. Zimmerman KC, Sarbia M et al. Constitutive cyclooxygenase-2 expression in healthy human and rabbit gastric mucosa. *Mol Pharmacol* 1998; 54:536-540.
8. Silverstein FE, Faich G, Goldstein JL et al. Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. *JAMA* 2000; 284:1247-1255.
9. Bombardier C, Laine L, Reicin A et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen with patients with rheumatoid arthritis. *N Eng J Med* 2000; 343:1520-1528.
10. Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. *J Rheumatol* 1997; 24:445-451.
11. Chenevard R, Hurlimann D, Bechir M, Spieker L et al. Selective COX-2 inhibition improves endothelial function in coronary artery disease. *Circulation* 2003; 107:405-409.
12. FDA Advisory Committee. Cardiovascular safety review of rofecoxib. Rockville, MD. FDA 2001.
13. Solomon DH, Glynn RJ, Levin R et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation* 2004; 109:2068-2073.
14. Kimmel SE, Berlin JA, Reilly M et al. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. *Ann Intern Med* 2005; 142:157-164.
15. Ray WA, Hall K, Griffin MR et al. Cox-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002; 360:1071-1073.
16. White WB, Borer JS et al. Cardiovascular thrombotic events in arthritis trials of the cyclooxygenase-2 inhibitor celecoxib. *Am J Cardiol* 2003; 93:411-418.
17. Konstam MA, Reicin A, Barr E et al. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. *Circulation* 2001; 104:2280-2288.
18. Mukherjee D, Nissen SE et al. Risk of cardiovascular events associated with selective cyclooxygenase-2 inhibitors. *JAMA* 2001; 286:954-959.
19. Levesque LE, Brophy JM, Zhang B. The risk of myocardial infarction with cyclooxygenase-2 inhibitors: A population study of elderly adults. *Ann Intern Med* Feb 8 2005.
20. Merck & Co. Inc. Merck announces voluntary worldwide withdrawal of Vioxx. Accessed at www.vioxx.com/rofecoxib/vioxx/consumer/index.jsp
21. U.S. Food and Drug Administration. FDA public health advisory: safety of Vioxx. Accessed at http://www.fda.gov/fdac/features/2004/604_vioxx.html
22. Solomon SD, McMurray JJV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Eng J Med* 2005; 352.
23. Ott E, Nussmeier NA, Duke PC et al. Multicenter Study of Perioperative Ischaemia (McSPI) Research Group; Ischaemic Research and Education Foundation (IREF) Investigators. Efficacy and safety of the cyclooxygenase 2 inhibitor parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2003; 125:1481-1492.
24. U.S Food and Drug Administration. FDA issues public health advisory recommending limited use of Cox-2 inhibitors. Accessed at <http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01336.html>