MATTERS ARISING

LETTER

Cardiovascular safety of rofecoxib (Vioxx): lessons learned and unanswered questions

A recent editorial on the safety and recent withdrawal of rofecoxib has stimulated a number of letters
(Med J Aust 2004; 181: 524-525)

Withdraw all COX-2-selective drugs

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To the Editor: Langton et al claim that "the celecoxib studies have not demonstrated an increased risk of thrombosis".[1] However, the European Agency for the Evaluation of Medicinal Products concluded that "there is a trend towards a higher MI [myocardial infarction] risk associated with the use of celecoxib compared with naproxen and diclofenac", and decided that a warning statement was required for all cycloxygenase 2 (COX-2)-selective drugs.[2] It is surprising that celecoxib may be worse than diclofenac, because diclofenac is similarly COX-2-selective as celecoxib.[3,4]

A retrospective analysis of the full CLASS study data for people not taking aspirin found the rates of serious thromboembolic cardiovascular events were celecoxib 1.4% and diclofenac 1.6%, as against 0.7% for ibuprofen.[5] These differences were not individually statistically significant, but CLASS was underpowered for cardiovascular events. However, pooling the results for the two similarly COX-2-selective drugs versus ibuprofen reveals a significant difference (relative risk [RR], 2.1; 95% CI, 1.1–3.9). In the full CLASS data, celecoxib did not have a lower rate of complicated ulcers (RR, 0.83; 95% CI, 0.46–1.5) and there was a trend towards more serious adverse events of all types (RR, 1.17; 95% CI, 0.99–1.39) than in the combined ibuprofen and diclofenac groups.[3,6]

We conclude that the case against all COX-2-selective drugs has not been proven beyond doubt because they have not been studied adequately. However, on the balance of probabilities, they are all likely to have a similar propensity to rofecoxib to increase thrombotic cardiovascular events to some extent. This prothrombotic effect may be reduced by combining them with aspirin, but then the main gastrointestinal benefit is likely to be lost,[3,4] so use of such combinations is not justified.

Overall, celecoxib is no more effective, more expensive, no safer (and possibly less safe) than non-selective drugs. Meloxicam has not been shown to be any better. COX-2-selective drugs should not be used unless a subpopulation can be identified for whom these drugs have an advantage over the non-selective drugs. In theory, COX-2-selective drugs may be useful for a tiny group of people who are at greater risk of serious harm from gastrointestinal injury than from vascular events. However, there is no proven way to identify such people and there are no relevant trials to guide us. For example, no trials have been done in patients with a history of peptic ulcer.

All COX-2-selective drugs should be removed from the market until they have been properly evaluated.

1 Langton PE, Hankey GJ, Eikelboom JW. Cardiovascular safety of rofecoxib (Vioxx): lessons learned and unanswered questions [editorial]. *Med J Aust* 2004; 181: 524-525. Previously published online, 26 October 2004.
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COX-2 selectivity varies across class

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To the Editor: Langton et al document the history of rofecoxib approval in 1999 and withdrawal in 2004.[1] They also provide an outline of the possible mechanisms for increased cardiovascular risk, which we detailed in the Journal in August 2001.[2] Their editorial raises the issue of whether the increased cardiovascular risk is a class effect of all selective cyclooxygenase 2 (COX-2) inhibitors and notes that no increased risk has been identified to date with celecoxib use. While this is correct, the editorial omits to state that, although several drugs are categorised as "COX-2 inhibitors", the selectivity for COX-2 over COX-1 inhibition varies greatly between different drugs (see Box).[3]

Selectivity for COX-2 for different "COX-2 inhibitors"[3]

Drug	COX-1 / COX-2 (IC_{50} ratio)
Aspirin	<0.5
Ibuprofen	0.5
Meloxicam	18
Diclofenac	29
Celecoxib	30
Rofecoxib	267

It is potentially significant that celecoxib is only modestly COX-2 selective compared with rofecoxib. Because COX-2-selective inhibition can lead to selective inhibition of vascular prostacyclin synthesis with little or no effect on vascular or platelet thromboxane synthesis,[1] a highly selective COX-2 inhibitor such as rofecoxib is expected to disrupt the balance between antithrombotic prostacyclin and prothrombotic thromboxane. The relatively modest COX-2 selectivity of celecoxib may be one explanation for the lack of adverse cardiovascular effects demonstrated to date. It would also explain its lack of upper gastrointestinal tract protection relative to diclofenac, as both drugs have similar COX-2 selectivity.[4]

The newer coxibs, like rofecoxib, are significantly more COX-2-selective than celecoxib and, if this selectivity is the basis for the adverse cardiovascular events, then caution is needed with these newer agents. Although the editorial states that trials have not shown increased risk with the newer coxibs, this is not correct. On 15 October 2004, Pfizer announced that valdecoxib, when used for pain management in coro-

nary artery bypass surgery, caused an increased number of adverse cardiovascular events.[5]

As the editorial states, the VIGOR study with rofecoxib in treating rheumatoid arthritis revealed a greatly increased incidence of adverse cardiovascular events compared with naproxen, and yet rofecoxib sales continued for another four years at a high level.[1] Perhaps the most important question for prescribers arising from the experience with rofecoxib is not whether clinical trial results are conclusive, but how should prescribers respond to apparent conflicts in the medical literature. In such a situation, resort to ethical and legal obligations for disclosure of information will be the prudent approach, as we have detailed.[6]

For prescribers considering the loss of rofecoxib, some perspective is provided by the following. The number needed to treat (NNT) to cause an increase in one fatal or non-fatal cardiac event in the VIGOR study was 225 (average trial duration was 9 months). In trials with statins in which coronary heart disease was absent at enrolment, the NNT per year to prevent one fatal or non-fatal coronary event was 217 to 256.[7]

1 Langton PE, Hankey GJ, Eikelboom JW. Cardiovascular safety of rofecoxib (Vioxx): lessons learned and unanswered questions [editorial]. *Med J Aust* 2004; 181: 524-525. Previously published online, 26 October 2004.
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Possible genetic predisposition to cardiac effects

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To the Editor: In their editorial on the rofecoxib controversy, Langton et al point out that large-scale but inconclusive studies failed to recognise an increased risk of heart attack and stroke in patients treated with this cyclooxygenase 2 (COX-2) inhibitor.[1] Might something still be learned from these studies? Both COX-2 and 5-lipoxygenase (5-LOX) use the same substrate (arachidonic acid) to produce prostaglandins and leukotrienes, respectively. Overactive 5-LOX increases the risk of heart attack and stroke,[2,3] and may be involved in the comorbidity of these disorders with anxiety and depression.[4] In contrast, COX-2 appears to be cardioprotective.[5]

Genetic diversity is responsible for overactive 5-LOX in some individuals and increases their risk for cardiovascular pathology.[2,3] It is likely that patients with these alleles might be more susceptible to cardiovascular pathology in the absence of COX-2 activity — that is, be at increased risk of rofecoxib-provoked myocardial infarction and stroke.

If possible, retrospective studies should be attempted to determine the genotype of subjects treated with rofecoxib for 5-LOX[2] and 5-LOX-activating protein[3] polymorphisms and to relate these findings to rates of myocardial infarction and stroke.

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Paracetamol should be first-line therapy in osteoarthritis

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To the Editor: We consider that it is important to comment on the views expressed by Langton et al on the limited value of paracetamol in the treatment of musculoskeletal pain.[1]

Langton et al recognise that paracetamol is widely recommended as first-line therapy to reduce chronic pain, but they largely dismiss its usefulness, noting that:

> . . . when used alone paracetamol appears to be less effective than NSAIDs and there are no studies of the safety of the long-term intake of paracetamol.[1]

However, paracetamol is widely recommended as the first-line drug treatment in the management of osteoarthritis. This is based on its efficacy and safety as compared with nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase 2 (COX-2) inhibitors. This position is supported by published guidelines, including those of the American College of Rheumatology[2] and the European League of Associations of Rheumatology (EULAR).[3] In these guidelines, NSAIDs are recommended for use in moderate to severe osteoarthritis pain (American College of Rheumatology guidelines) or where the pain is unresponsive to paracetamol (EULAR guidelines). Our own Australian Therapeutic Guideline series and National Prescribing Service publications similarly recommend paracetamol as first-line treatment in osteoarthritis[4] (see National Prescribing Service, Fact Sheet 8, October 2004 <www.nps.org.au>).

The efficacy of paracetamol in comparison with NSAIDs in patients with osteoarthritis has been demonstrated in patients treated for periods ranging from 3 weeks to 2 years, with total daily doses of paracetamol ranging from 2.6 g to 4.0 g,[5] but this has been contentious.[6,7] In a 2-year study involving 66 patients with osteoarthritis, Williams et al noted a higher withdrawal rate due to side effects in the naproxen group than in the paracetamol group, and slightly less efficacy in the paracetamol group.[5] Pincus and colleagues reported that a third of patients receiving paracetamol continued on this treatment for more than 24 months, and

that paracetamol was significantly less likely to be discontinued because of toxicity than NSAIDs.[8] Thus, although paracetamol is on average less effective in pain reduction compared with NSAIDs,[6] the difference in efficacy is small and a substantial proportion of patients can be treated satisfactorily and safely with paracetamol alone.[9]

Paracetamol remains the appropriate initial treatment for the management of osteoarthritis. Other medications, such as NSAIDs or COX-2 inhibitors, can be added if patient response is unsatisfactory and the risk–benefit ratios are acceptable. When considering alternative options to rofecoxib, prescribers should also review the non-drug options, such as weight loss, physiotherapy, orthotics, and, where possible, opt for paracetamol first.[10] Prescribers need to continue to be mindful of the potential for adverse effects with NSAIDs, particularly in high-risk patients or patients taking concomitant medications.

The serious public health problem of upper gastrointestinal tract bleeding caused by NSAIDs is a major consideration in the management of patients with osteoarthritis and becomes more of an issue in the elderly, many of whom have osteoarthritis.

Competing interests: Professor Day is a member of advisory committees on COX-2 inhibitors for Merck Sharp & Dohme (Aust) Pty Ltd (which markets rofecoxib and etoricoxib), and previously for Pfizer Pty Ltd (which markets celecoxib). He is a member of a general advisory committee of GlaxoSmithKline (which markets paracetamol). GlaxoSmithKline have supported research projects of Professor Graham on paracetamol.

1 Langton PE, Hankey GJ, Eikelboom JW. Cardiovascular safety of rofecoxib (Vioxx): lessons learned and unanswered questions [editorial]. *Med J Aust* 2004; 181: 524-525. Previously published online, 26 October 2004.
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Cardiovascular safety of rofecoxib (Vioxx): lessons learned and unanswered questions

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IN REPLY: Mansfield, Vitry and Wright take issue with our statement that the celecoxib studies have not shown an increased risk of thrombosis, but provide no data to support their claims, while Cleland and James highlight differences in COX-2 selectivity as a potential explanation for differences in the cardiovascular safety of coxibs. Recently published clinical data confirm an increased risk of cardiovascular events with rofecoxib but not celecoxib,[1] which is consistent with in-vivo studies suggesting that celecoxib but not rofecoxib improves endothelial function,[2,3] as well as a significantly lower incidence of oedema and hypertension with celecoxib compared with rofecoxib.[4] Nevertheless, we reiterate that it remains incumbent on drug manufacturers and regulatory authorities to demonstrate cardiovascular safety for all new and existing coxibs, including celecoxib.

The published coronary artery bypass graft surgery randomised trial referred to by Cleland and James did not report a significant excess of adverse cardiovascular events with valdecoxib,[5] nor did two recently published meta-analyses.[6,7] However, unpublished data from a second coronary artery bypass graft surgery trial, as well as meta-analyses presented at the American Heart Association meeting in New Orleans in November 2004, indicate that valdecoxib compared with placebo significantly increases the risk of adverse cardiovascular events.[8] This is reflected in the recently revised US prescribing information for valdecoxib.[9]

Manev and Manev propose enhanced 5-lipoxygenase activity as a mechanism for increased cardiovascular risk in patients treated with COX-2-selective inhibitors. We agree that this important hypothesis merits further study.

Day and Graham emphasise paracetamol as first-line drug treatment in the management of osteoarthritis, referring to recently published American, European and Australian guidelines to support their position. We do not dispute the effectiveness of paracetamol to reduce chronic pain. However, data from the 2004 systematic review quoted in our editorial[10] demonstrate that nonsteroidal anti-inflammatory drugs are better than paracetamol for pain relief and are often preferred by patients, despite a higher incidence of adverse effects. Only one of the 10 randomised controlled trials included in this systematic review followed patients beyond 3 months; this study reported the primary efficacy outcome only during the first 6 weeks and was not powered for safety.

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Acute presentation of childhood hypothyroidism

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TO THE EDITOR: We report an acute presentation of congenital hypothyroidism in a child almost 6 years old. The condition was not detected by newborn screening.

Screening of all neonates started in New South Wales in July 1977, with thyroid stimulating hormone (TSH) being measured in dried blood spots taken from a heel-prick blood sample (currently at 2–3 days of age). A whole-blood TSH level of 40 mIU/L or above triggers a request for full thyroid function testing, whereas with a level of 20–39 mIU/L a second sample is requested. We have screened over 2.3 million babies and detected 690 babies with congenital hypothyroidism. Ten babies with dyshormonogenesis or ectopic thyroid tissue had normal results and were missed by the screening test. Since screening started, "juvenile hypothyroidism" not associated with thyroid antibodies has all but disappeared.

A healthy girl aged 5 years 11 months presented with acute dysphagia and drooling. There were no previous dysphagic symptoms. Initially, epiglottitis was suspected; however, at endoscopy a lingual thyroid was visualised at the base of her tongue, and this was confirmed by a technetium scan. She had normal growth and development, with both height and weight at the 50th centiles, a pulse rate of 90 beats/min, and normal deep tendon reflexes.

The whole-blood TSH level at newborn screening on Day 3 was 40 mIU/L (reference range [RR], < 20 mIU/L). Thyroid function testing at another hospital on Day 10 showed a serum TSH level of 16.6 mIU/L and a serum free thyroxine (FT_4) level within the normal range (12 pmol/L; RR, 11–30 pmol/L). These results were interpreted as normal, whereas, in fact, the TSH level was above the reference range for 10 days of age (< 10 mIU/L), although within the reference range for 2–7 days.

On the patient's admission for treatment of acute dysphagia, the TSH level was 10.9 mIU/L and the FT_4 level was 18 pmol/L. A diagnosis was made of compensated hypothyroidism secondary to the ectopically placed lingual thyroid. Thyroxine treatment was commenced on diagnosis, and regular follow-up arranged. Three months after the start of treatment, the results of thyroid function tests (FT_4, 17 pmol/L; TSH, 2.7 mIU/L) were within the normal range.

Acute presentation of a lingual thyroid is most unusual.[1] This case emphasises that further investigations must be performed when thyroid function test results are equivocal. Unfortunately, the thyroid status was considered normal because the FT_4 value was within the normal range. All babies whose TSH results remain elevated while the FT_4 levels are normal should have a thyroid scan, as we recommend when reporting results.

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MJA The Medical Journal of Australia

The Medical Journal of Australia (MJA) is published on the 1st and 3rd Monday of each month by the Australasian Medical Publishing Company Proprietary Limited, Level 2, 26-32 Pyrmont Bridge Rd, Pyrmont, NSW 2009. ABN 20 000 005 854. Telephone: (02) 9562 6666. Fax: (02) 9562 6699. E-mail: medjaust@ampco.com.au. The Journal is printed by Offset Alpine Printing Ltd, 42 Boorea St, Lidcombe, NSW 2141.

MJA on the Internet: http://www.mja.com.au/

Published in 2 volumes per year.
Annual Subscription Rates for 2005 (**Payable in Advance**) to: **AMPCo**, Locked Bag 3030, Strawberry Hills, NSW 2012
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28,516 circulation as at 30 September, 2004

ISSN 0025-729X