COX-2 inhibitors and the cardiovascular system: is there a class effect?

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Abstract

Selective inhibition of COX-2 preferentially inhibits the production of prostaglandins responsible for vasodilation and inhibition of platelet aggregation. This potentially creates a pro-thrombotic state. This review examines the evidence that selective COX-2 inhibitors have adverse effects on the heart and circulation. The risk of myocardial infarction and other vascular ischaemic events, the effects on blood pressure and decompensation of treated heart failure are discussed. Conclusions are drawn about the relative risk with the different members of the drug class, and recommendations for clinical practice presented.

Key words: non-steroidal anti-inflammatory drugs (NSAIDs), prostaglandins, COX-2 selective inhibitors (coxibs), myocardial infarction, cardiovascular events, blood pressure.

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Introduction

Conventional non-steroidal anti-inflammatory drugs (NSAIDs) produce many of their therapeutic effects by inhibiting the cyclo-oxygenase enzyme (COX) and blocking the conversion of arachidonic acid to pro-inflammatory prostaglandins and thromboxane A_2. However, many of the unwanted effects of these drugs are also caused by COX inhibition, such as gastro-intestinal toxicity and salt and water retention by the kidney. The discovery that there are several different COX isoenzymes provoked a search for selective drugs that would have less gastric toxicity than conventional NSAIDs. The COX-1 isoenzyme was believed to play a major role in gastro-protection, and this led to the development of COX-2 selective inhibitors (coxibs). The physiological principles underlying these assumptions have been previously reviewed in this journal by Schachter.[1]

Controversy over the cardiovascular effects of the coxibs has increased since the publication of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study in 2001,[2] which suggested that taking rofecoxib increased the risk of myocardial infarction (MI). This was followed by numerous other reports that led to the withdrawal of rofecoxib from the market in 2004. Rofecoxib is one of the most selective COX-2 inhibitors but the cardiovascular safety of the other coxibs has also been questioned. This review examines the evidence for a class effect of COX-2 inhibitors on the cardiovascular system.

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COX-2 inhibitors and vascular physiology

Two prostaglandins (PGs) have major physiological roles in the vasculature: thromboxane A_2 (TXA_2) and prostacyclin (PGI_2). TXA_2 promotes platelet activation, vasoconstriction and smooth muscle proliferation. It is mainly produced in platelets and its formation is increased when platelets are activated. Prostacyclin is a vasodilator and a potent inhibitor of platelet aggregation. It is produced by macrovascular endothelial cells. Selective blockade of the production of prostacyclin by coxibs may lead to a pro-thrombotic state.

While one recent study has raised the question of the cardiovascular safety of naproxen, most data suggest that conventional NSAIDs either have no impact on the risk of thromboembolic vascular events, or may even be cardioprotective although to a lesser extent than aspirin.

COX-2 inhibitors and cardiovascular thrombotic events

The potential for an increase in cardiovascular events, such as MI, stroke and sudden cardiovascular death, has been a major area of concern for patients taking long-term treatment with COX-2 inhibitors.

The potential problem was initially raised by the VIGOR study.[2] Although designed to investigate comparative gastric toxicity, treatment with rofecoxib was associated with an increased risk of confirmed MI when compared to treatment with naproxen. The authors argued that the choice of naproxen as a comparator was the reason for the difference, since three of four previous case-control studies had shown that naproxen has a cardiovascular protective effect similar to aspirin. This protective effect has not been found with other NSAIDs. However, any antithrombotic effect of naproxen in the VIGOR trial would have greatly exceeded that expected from aspirin (average risk reduction for MI with aspirin 30%; apparent risk reduction with naproxen 80% [confidence intervals 42–93%]).[3]

By contrast, in the Celecoxib Long-Term Arthritis Safety Study (CLASS),[4] the incidence of serious cardiovascular events was similar for those patients taking celecoxib and those taking

diclofenac or ibuprofen, except that there were significantly more strokes among the patients taking ibuprofen than those receiving celecoxib. However, a subsequent analysis shows that the annual incidence of MI during treatment with rofecoxib and celecoxib in VIGOR and CLASS was similar at 0.74% for rofecoxib and 0.80% for celecoxib. These rates are significantly higher than in the placebo-treated populations of the primary prevention trials of aspirin therapy (0.52%).[5] While such information is suggestive of a problem, the patient populations may not be truly comparable.

Konstam *et al*.[6] performed a meta-analysis of 23 placebo- and NSAID-controlled studies with rofecoxib, including 26,000 patients. They concluded that treatment with rofecoxib was associated with an increased risk of a thrombotic cardiovascular event when compared with naproxen, but not when compared with other classical NSAIDs (ibuprofen, diclofenac and nabumetone). However, many of these studies were of short duration (1–3 months), and subsequent longer-term observational studies began to reveal a different pattern of risk.

A Prescription Event Monitoring study in the UK reported that the risk of cardiovascular events was greater in people taking celecoxib or rofecoxib when compared to the less selective COX-2 inhibitor meloxicam.[7,8] The rates for cardiac events had wide confidence intervals (CIs), but showed an increase in age- and gender-adjusted relative risk of 1.72 for celecoxib (CI 0.87–3.40) and of 1.33 for rofecoxib (CI 0.71–2.67). However, the relative risks for cerebrovascular thrombotic events were 1.66 for celecoxib (CI 1.10–2.52), and 1.68 for rofecoxib (CI 1.15–2.46). Data from the New England Healthcare claims database provided a comparison of thrombo-embolic events in hypertensive patients taking NSAIDs, celecoxib or rofecoxib. The relative risk compared to non-NSAID users was 1.11 for NSAIDs (p=0.4), 1.35 for celecoxib (p=0.06) and 2.45 for rofecoxib (p=<0.0001).[9]

Ray and co-workers[10] examined the Tennessee Medicaid programme database for dose-related cardiovascular effects of rofecoxib. They concluded that users of doses of rofecoxib greater than 25 mg daily were 1.7 times more likely than non-users to have a serious coronary heart disease event, although there was no evidence of increased risk among users of 25 mg daily or less, or among users of other NSAIDs. By contrast, a case–control study by Solomon *et al*.[11] showed that all doses of rofecoxib were associated with an increased relative risk of MI compared with the use of celecoxib (relative risk 1.24) or no NSAID usage (relative risk 1.14). The risk was elevated in the first 90 days of use of rofecoxib, but not thereafter, while the use of celecoxib was not associated with any excess risk.

Rofecoxib withdrawal

The final nail in the coffin for rofecoxib came from three year follow-up data from the Adenomatous Polyp Prevention on Vioxx (APPROVe) study. This study was designed to evaluate the efficacy of rofecoxib, 25 mg daily, in preventing recurrence of colorectal polyps in 2,600 patients with a history of colorectal adenomas. There was an increased relative risk for confirmed MI during treatment with rofecoxib compared to placebo. The risk was only increased after 18 months of treatment with rofecoxib, and persisted at three years. The cumulative incidence of cardiovascular events was 7.5 per 1,000 patients receiving placebo compared with 15 per 1,000 patients receiving rofecoxib.[12] This led the data safety monitoring board for this study recommending that the study be stopped in September 2004. Three days later rofecoxib was withdrawn from the market.

Celecoxib

This left the question of the cardiovascular safety of the remaining coxibs. This had not been fully resolved for celecoxib, with some signals that there might be a problem, although not as great as for rofecoxib. The issue was brought to prominence with the announcement of the premature cessation of the Adenoma Prevention with Celecoxib (APC) trial in December 2004.[13] This study was designed to investigate the ability of celecoxib 200 mg or 400 mg twice daily to prevent the development of colorectal cancer after the removal of an adenomatous polyp. Compared to placebo, both doses of celecoxib were associated with an excess of cardiovascular events, with evidence of a dose-related increase in risk. The absolute excess risk for the lower dose of celecoxib was 13 per 1,000 patients (relative risk 2.5), and for the higher dose was 21 per 1,000 patients (relative risk 3.4).

Pfizer, the company that market celecoxib, have responded by stating that the Prevention of Spontaneous Adenomatous Polyps (PreSAP) study, a separate long-term study using celecoxib at a dose of 200 mg twice daily, does not show any increase in cardiovascular risk for celecoxib when compared to placebo. However, an independent analysis of a study carried out by the National Cancer Institute also suggests an increased risk with high-dose celecoxib. In this unpublished analysis, the absolute risk of cardiovascular events was small at 0.9% with placebo, but 2.2% with celecoxib 400 mg daily and 3% with celecoxib 800 mg daily.

A pooled analysis of the cardiovascular safety of several COX-2 inhibitors in a high-risk Medicaid population did not provide any evidence of an increased risk.[14] However, this observational study could mask an increased risk with individual drugs.

Other coxibs

Data for other coxibs are less robust, in part due to shorter follow-up periods as well as smaller numbers of patients. Etoricoxib has been studied in about 12,000 patients in comparison with placebo and classical NSAIDs but with only 6,500 patient-years of observation. There was a relative risk of a cardiovascular event of 1.1 (CI 0.32–3.81) compared to placebo, of 0.83 (CI 0.26–2.64) compared to non-naproxen NSAIDs, and 1.7 (CI 0.91–3.18) compared to naproxen.[15] The wide confidence intervals of these estimates indicate the lack of the power of the studies to determine the true risk.

Lumiracoxib has been the subject of the largest randomised study programme to study cardiovascular risk. The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) enrolled 18,000 patients, but follow-up was confined to one year and their risk for cardiovascular disease was low. The results indi-

cated that treatment with lumiracoxib conferred a non-significantly greater risk of confirmed or probable MI when compared to naproxen, but a non-significantly lower risk when compared to ibuprofen.[16] Once again the confidence intervals for these estimates were wide and do not confirm or refute a real risk.

Two studies have investigated the use of valdecoxib in a high-risk patient group following coronary artery bypass surgery.[17,18] Valdecoxib has a similar degree of COX-2 selectivity as rofecoxib, and the results were disturbing with a three-fold increase in adverse cardiovascular outcomes with valdecoxib compared to placebo. These studies used a higher dose of valdecoxib than that usually recommended for the treatment of arthritis. Valdecoxib has recently been withdrawn from the UK market, but mainly due to concerns about serious skin reactions.

COX-2 inhibitors and fluid retention

Both COX-1 and COX-2 are expressed in the kidney and contribute to regulation of renal function. COX-1 is constitutively expressed in the vascular endothelium and has a role in haemodynamic regulation, through generation of prostacyclin (PGI_2). COX-2 is constitutively expressed in the vasculature, glomerulus, tubular segments and interstitium of adult mammalian kidney. In addition, COX-2 expression, but not COX-1, is induced by high renin states, low salt diet and water deprivation. COX-2 catalyses the production of both prostacyclin and prostaglandin E_2 (PGE_2). In the kidney, PGE_2 decreases sodium reabsorption. Prostacyclin increases potassium excretion, preserves renal blood flow and glomerular filtration rate, and in conditions of decreased actual or effective circulating volume.

Salt and water retention can occur when renal prostaglandins are inhibited – these will be particularly troublesome in patients with heart failure. Several studies have suggested that the incidence of oedema is higher with rofecoxib than with celecoxib.[19-21] The clinical relevance of this observation was explored in a population-based observational study of 145 000 patients. This showed that treatment for heart failure was more likely to be started in all users of NSAIDs or COX-2 inhibitors than in non-NSAID users.[22] However, the risk of hospitalisation for heart failure was higher in those taking NSAIDs or rofecoxib than in non-NSAID users, but not in those who took celecoxib.

COX-2 inhibitors and hypertension

Classical NSAIDs produce a mean increase in blood pressure of 5 mmHg,[23] and an observational study found that NSAIDs users had an increased risk of starting antihypertensive medication.[24] The increase in blood pressure associated with classical NSAIDs is probably caused by an inhibition of prostaglandin-dependent counter-regulatory mechanisms in the renal vasculature, which seems to occur early during the use of these agents. Since COX-2 inhibitors also affect renal prostaglandin synthesis, they also have the potential to increase blood pressure.

The first question is whether patients who take these drugs are more likely to develop hypertension. This has been addressed in observational and case-control studies.[25-27] These suggest that new onset hypertension was between 1.4 and 2.08 times more common in patients who took rofecoxib when compared to those taking other NSAIDs, celecoxib or with non-NSAID users.

The second issue is whether patients with pre-existing hypertension are more likely to experience loss of blood pressure control if they take a COX-2 inhibitor. Two trials have compared celecoxib and rofecoxib in older hypertensive patients with osteoarthritis. In both trials, there was a mean increase in systolic blood pressure of 2.6–3.0 mmHg during treatment with rofecoxib and a slight drop of systolic blood pressure in those who took celecoxib.[19,20] However, these studies used doses of the drugs that did not have clinically comparable effects; the dose of celecoxib (200 mg daily) was at the lower end of the dose range for arthritis, while that of rofecoxib (25 mg daily) was at the upper end of the dosage range.

Other studies have found that celecoxib 400 mg daily does not increase the morning or the 24-hour average blood pressure in patients whose hypertension was controlled with an angiotensin-converting enzyme (ACE) inhibitor.[28-30] But when compared to diclofenac, celecoxib increased blood pressure to a similar extent at peak plasma drug concentration. The lack of an overall effect on blood pressure control may, therefore, be a reflection of the short plasma half-life of celecoxib. Rofecoxib did not affect day-time blood pressure on ambulatory blood pressure monitoring.[31] By contrast, the effect on night-time blood pressure was substantial, with a mean increase of 15.7/8.5 mmHg. In the same study, the increase in nocturnal blood pressure with nabumetone was only 5.0/4.9 mmHg. The increase in 24-hour blood pressure load produced by rofecoxib, as a consequence of loss of the circadian blood pressure variation, may have contributed to the excess cardiovascular events associated with this drug.

A recent study in hypertensive patients with diabetes has confirmed the adverse effect of rofecoxib on blood pressure control. Celecoxib and naproxen produced small but non-significant increases in mean 24-hour blood pressure. However, rofecoxib produced a significant rise after six weeks of treatment, of 4.2 mmHg.[32]

A recent meta-analysis of the effects of COX-2 inhibitors on blood pressure pooled data on the risk of new-onset hypertension and significant rises in blood pressure in patients with hypertension. The authors concluded that COX-2 inhibitors were more likely to produce a significant rise in blood pressure than conventional NSAIDs.[33] The rise was numerically greater with rofecoxib than with celecoxib but this difference was not statistically significant.

Conclusions

It seems clear that rofecoxib stands out amongst the COX-2 inhibitors as carrying a greater risk of thrombotic cardiovascular events, oedema and loss of blood pressure control in treated hypertensive patients when compared to classical NSAIDs. The increase in cardiovascular risk is greatest after about 18 months of use, and many of the newer COX-2 inhibitors have not been studied adequately over such prolonged periods. However, the emerging data suggest that the increased cardiovascular risk is

Key messages

- Selective inhibition of COX-2 produces imbalance between the production of prostaglandins with vasodilator and platelet anti-aggregatory effects, and those that have vasoconstrictor and pro-aggregatory effects
- The use of COX-2 selective inhibitors produces a shift to vasoconstriction and a pro-thrombotic state
- Rofecoxib increases the risk of myocardial infarction at doses conventionally used for the treatment of arthritis
- Other coxibs may also carry a risk at higher doses than those recommended for the treatment of arthritis
- Rofecoxib, and to a lesser extent the other coxibs, increase blood pressure in hypertensive people and produce fluid retention that can result in decompensation of heart failure
- Coxibs should be avoided in people who have or are at high risk of cardiovascular disease, and should be used for the shortest possible period in other individuals

probably a class effect, although the absolute risk with drugs other than rofecoxib is small. There may also be a dose-related increase in risk with some drugs, particularly celecoxib and valdecoxib, with the greatest risk at doses higher than those usually used for the treatment of arthritis.

Currently, the Medicines and Healthcare Regulatory Agency (MRHA) recommend avoiding treatment with COX-2 selective inhibitors whenever possible in patients with known ischaemic heart disease or those who are at high risk of developing it. They also recommend that the smallest dose of a COX-2 inhibitor should be prescribed for the shortest possible duration if the drugs are used. The risk associated with the use of meloxicam, a drug with less COX selectivity, has received less attention. Current evidence has not demonstrated any differences from conventional NSAIDs, but definitive studies are awaited.

If the prescription of COX-2 selective inhibitors is considered for patients with ischaemic heart disease, then a full discussion of risk should take place, and all alternative treatment options should be explored. The long-term use of COX-2 inhibitors for patients at lower cardiovascular risk should also be reassessed in the light of the lack of evidence for a reduction in serious gastrointestinal toxicity for many of the drugs compared with classical NSAIDs.

Conflict of interest

DW has received honoraria for speaking at meetings organised by Merck. MB: none declared.

Editors' note

An article 'COX-2 inhibitors: managing comorbidities in primary care' by Rubin Minhas can be found on pages 392–3 of this issue.

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Book review

Intracoronary ultrasound

Author: Mintz GS
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This is a beautiful and authoritative work from an undisputed authority in the field. From the preface, Dr Mintz assures us that the book will help us understand the utility of intravascular ultrasound (IVUS) and the chapters that follow do not disappoint.

As an IVUS novice, I was disappointed to find that the excellent first chapter on the physics of IVUS imaging spells out in detail the many pitfalls of image interpretation generated by artefact that could go unrecognised. The following chapter on 'qualitative and quantitative analysis' describes, step by step, the path that the ultrasound beam follows as it traverses and is deflected by the arterial wall. This chapter too emphasised the potential for image misinterpretation and highlighted the point that IVUS is a technique that needs fully trained operators in order to benefit from its full utility.

The book proudly boasted an example of every situation and its extensive range of illustrations backed up this claim. The author says the book "is to be read not used as a reference" but this is more a book to gaze at since it is mainly made up of high quality black and white illustrations. Its readability is difficult at times since pages of illustrations need to be passed in order to finish a sentence. In addition, the figures and legends did not have titles and this could make it difficult to appreciate which phenomenon was being illustrated without concentrating on the entire legend text and complicated labelling. Some of the illustrations did not confer to me the information referred to in the legend text. I was left feeling unsure whether this was because of my IVUS inexperience or the fact that the illustrations were static representations of images designed to be viewed in real time.

These observations are not necessarily shortcomings and the book convinced me that IVUS conveys information that simply cannot be obtained from angiography alone. I was left feeling the need for further practical instruction in this valuable technique.

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