The vascular effects of COX-2 selective inhibitors

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Summary

Drugs, such as celecoxib and rofecoxib, which selectively inhibit the COX-2 enzyme, are as efficacious as other non-steroidal anti-inflammatory drugs, but reduce the risk of serious gastrointestinal bleeding and ulceration. However, the improved tolerance of the COX-2 selective inhibitors may come at the cost of an increased risk of thrombosis in patients with ischaemic heart disease if they are not also taking aspirin. Like the older non-steroidal anti-inflammatory drugs, the COX-2 selective inhibitors can also increase blood pressure, induce or worsen cardiac failure and impair kidney function to the point of renal failure. In a recent unpublished trial, on the use of rofecoxib to prevent colon cancer, the risk of myocardial infarction and stroke after 18 months of treatment was high enough to prompt the removal of rofecoxib from the market. If another COX-2 selective drug is prescribed for patients at risk of thrombosis it should be used at the lowest effective dose and for short periods wherever possible. Prophylaxis with low-dose aspirin or other anti-thrombotic treatment should be continued.

Key words: celecoxib, lumiracoxib, rofecoxib, thrombosis.

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Introduction

The COX-2 selective inhibitors, such as rofecoxib and celecoxib, were introduced to decrease the gastrointestinal morbidity and mortality associated with older non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit both the COX-1 and the COX-2 enzymes. However, confusion still surrounds the role of COX-2 selective inhibitors because of an increased risk of myocardial infarction and other thrombotic events.

This risk first emerged in the VIGOR study which involved over 8000 patients. Although the absolute risk was low, there was a significantly higher rate of myocardial infarction with rofecoxib (18 cases) than naproxen (3 cases). However, the dose of rofecoxib (50 mg/day) was twice the dose recommended to treat rheumatoid arthritis while naproxen was given at the appropriate anti-inflammatory dose (1000 mg/day). Further, this trial was conducted in patients with rheumatoid arthritis, an inflammatory disorder that is associated independently with increased risk of thrombosis, particularly myocardial infarction. In retrospect, about half the patients who had infarctions during the trial should have been taking low-dose aspirin as prophylaxis. However, the trial did not allow patients to take aspirin.[1]

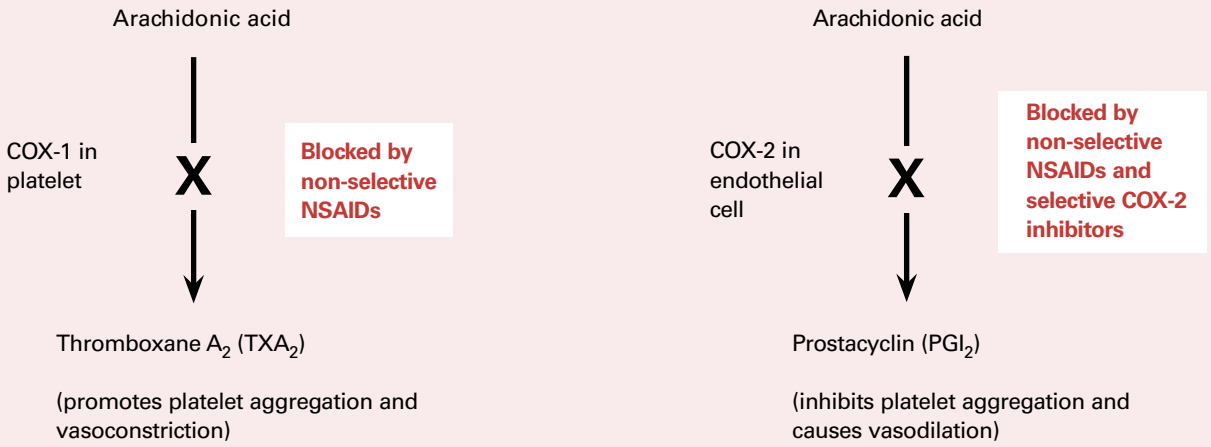
There have been a large number of claims and counter-claims about the risk of myocardial infarction with the COX-2 selective inhibitors, particularly rofecoxib. These were based on retrospective analyses, other controlled studies in osteoarthritis and rheumatoid arthritis, epidemiological studies, meta-analyses of published and unpublished studies and a recent large controlled trial of lumiracoxib in over 18 000 patients.[2,3] Most importantly, a recent unpublished trial on the use of rofecoxib to prevent colon cancer (the APPROVe study) found that treatment with rofecoxib was associated with a risk of myocardial infarction and stroke which became apparent after 18 months' treatment. The manufacturer has removed rofecoxib from the market because of this risk. Does the same risk apply to celecoxib, the other widely used COX-2 selective inhibitor presently available in Australia? Was this a class effect of COX-2 selective inhibitors and did increasing selectivity for COX-2 inhibition increase the risk? Did the underlying disease influence the findings? More importantly, should prescribers avoid COX-2 selective inhibitors in patients with vascular disease or a known risk of myocardial infarction?[4]

Mechanisms of action

The analgesic and anti-inflammatory actions of NSAIDs including COX-2 selective inhibitors are due to their effective inhibition of prostaglandin synthesis catalysed by the COX-2 isoenzyme (Fig. 1). This isoenzyme is massively up-regulated in inflammatory states such as rheumatoid arthritis, so inhibiting it reduces inflammation.

Fig. 1

Mechanisms of action of non-steroidal anti-inflammatory drugs



Aspirin and the non-selective NSAIDs inhibit COX-1 and COX-2 isoenzymes (Fig. 1). The COX-1 isoenzyme is involved in the synthesis of prostaglandins. These prostaglandins protect the gastric mucosa from ulceration and participate in platelet aggregation via the prostaglandin derivative, thromboxane A_2. Inhibition of COX-1 has been strongly implicated in the gastric ulceration and bleeding induced by the non-selective NSAIDs.

In platelets, inhibition of COX-1 leads to inhibition of thromboxane A_2 synthesis. This very effectively inhibits platelet aggregation. Low-dose aspirin irreversibly inhibits platelet aggregation via this mechanism and is therefore widely employed as prophylaxis against thrombotic cardiovascular disease. At therapeutic doses, COX-2 selective inhibitors have little effect on the COX-1 enzyme, so they do not inhibit platelet aggregation.

Thrombosis

As COX-2 selective inhibitors do not inhibit thromboxane A_2 synthesis they could be predicted to increase the risk of thrombosis. Thromboxane A_2 is not only a stimulus for platelet aggregation but also a powerful vasoconstrictor (Fig. 1). Its effects are opposed by prostacyclin, a vasodilator prostaglandin and inhibitor of platelet aggregation. Prostacyclin is produced largely by COX-2, especially in vascular tissues and probably more so in diseased vessels. COX-2 inhibition without COX-1 inhibition will therefore preserve the synthesis of the vasoconstrictive thromboxane A_2 and inhibit production of the vasodilator prostacyclin, tipping the balance toward vasoconstriction and thrombosis. Adding to this COX-2 induced imbalance, recent evidence shows that prostacyclin feeds back negatively on the synthesis of thromboxane A_2, so when prostacyclin synthesis is reduced by COX-2 selective inhibitors it leads to greater production of the prothrombotic thromboxane A_2.

Advantages of COX-2 inhibitors

COX-2 selective inhibitors were developed to reduce the risk of gastrointestinal ulceration caused by non-selective NSAIDs. By selectively inhibiting COX-2 they reduced the risk of upper gastrointestinal bleeding associated with other NSAIDs. In studies of rofecoxib and lumiracoxib, the absolute risk of serious upper gastrointestinal ulceration and bleeding is reduced by 50–60% or more compared to other NSAIDS.[1,2]

In the VIGOR study it was concluded that only 41 patients would need to be treated with rofecoxib rather than naproxen to avert one upper gastrointestinal event in a one-year period.[1] This figure was calculated from all patients in the trial and the number should be even smaller in patients who are at risk of upper gastrointestinal adverse reactions. This risk increases in patients with a history of peptic ulcer or bleeding, those taking anticoagulants and possibly patients taking oral glucocorticosteroids. If these patients require treatment with anti-inflammatory drugs, they should probably be prescribed COX-2 selective inhibitors rather than non-selective NSAIDs.[5]

The bleeding tendency associated with NSAIDs and aspirin is not seen with COX-2 selective inhibitors. They or paracetamol should be used in patients taking anticoagulants or if post-surgical bleeding is likely and a mild analgesic is indicated.

COX-2 selective drugs have no efficacy advantage

As non-selective NSAIDs inhibit both COX-1 and COX-2 there was no reason to expect that COX-2 selective inhibitors would have greater efficacy because they only inhibited the isoenzyme responsible for inflammation. Unfortunately, consumers and some prescribers were under the false impression that these medicines would be more effective as well as safer. This is part

of the reason for the gross overuse of celecoxib and rofecoxib outside the criteria of the Australian Pharmaceutical Benefits Scheme.[6] There is no evidence of increased efficacy of COX-2 selective inhibitors compared to conventional NSAIDs.

Adverse effects on renal function

Conventional NSAIDs are known to impair renal function, sometimes to the point of renal failure. This effect is observed particularly when the drugs are used perioperatively in older and sicker patients and in patients with already impaired renal function. In these situations maintenance of renal perfusion and function relies on renal prostaglandin synthesis. The possibility that COX-2 selective inhibitors might not manifest this adverse reaction has unfortunately not turned out to be the case. The risks for renal impairment are similar to those of other NSAIDs and increase with the dose of COX-2 selective inhibitor. We now know that maintenance of renal function is dependent on prostaglandins generated via the COX-2 isoenzyme.

Recommendations for prescribing

Prescribers should first consider 'non-drug options' in the management of common musculoskeletal problems such as soft tissue conditions, osteoarthritis, mechanical spinal pain problems, and inflammatory arthritis such as rheumatoid arthritis and gout. These options, including weight loss, physical therapy, and leg alignment correction via orthotics, are effective and evidence-based, but are unfortunately overlooked by prescribers. The next consideration should be whether paracetamol or an NSAID is a reasonable first pharmacotherapeutic option. Paracetamol is still recommended as first line for the bulk of musculoskeletal conditions because it is effective and relatively safe. NSAIDs including COX-2 selective inhibitors are not disease-modifying drugs, but are more appropriate if the condition is primarily inflammatory.

The more inflammatory the condition, the more reasonable prescribing an NSAID becomes. Whatever the condition being treated, the lower the dose and the shorter the exposure to these drugs, the lower the risk is for upper gastrointestinal bleeding and ulceration. Optimally, the patient can match the intake of drug with their own need for analgesia, thereby reducing unnecessary exposure. Should the patient have an increased risk of upper gastrointestinal ulceration and bleeding then prescribing expensive COX-2 selective drugs can be justified as they become cost-effective in this situation. However, this needs to be tempered with concern for adverse effects – those known to be associated with all NSAIDs and those that might be peculiar to COX-2 selective inhibitors.

If NSAIDs, including COX-2 selective inhibitors, are prescribed for patients with renal impairment, cardiac failure or hypertension, each patient should be monitored closely.[7,8] This should include eliciting symptoms and signs of heart failure, measuring weight and blood pressure and monitoring plasma creatinine and electrolytes soon after starting the drug (for example 2–4 weeks) and at regular reasonable intervals depending on the individual case.

Concomitant medicines including anticoagulants, prednisone, diuretics, beta blockers, ACE inhibitors and other antihypertensive drugs can have serious interactions with NSAIDs, including COX-2 selective inhibitors. Appropriate monitoring is needed if a decision is made to prescribe interacting drugs.[5]

Patients at risk of thrombosis

Individuals with a history of myocardial infarct, angina, coronary artery stents or known risk factors such as hypertension, hyperlipidaemia, smoking, diabetes or obesity are at risk of arterial thrombosis. Uncontrolled inflammation itself, as found in conditions such as rheumatoid arthritis, is an important independent risk factor for accelerated cardiovascular disease. If the patient is also elderly then the risk is further increased.

These patients are often prescribed low-dose aspirin or other platelet inhibitory therapy. The CLASS study suggested that the gastrointestinal safety advantage of celecoxib over a conventional NSAID is lost when low-dose aspirin is taken concomitantly.[9] This was again noted in the large study of lumiracoxib.[2] Other data have suggested that the gastrointestinal safety of a COX-2 selective inhibitor together with low-dose aspirin is greater than a combination of a non-selective NSAID with aspirin[10], but this view is much less likely to be correct in the light of the lumiracoxib data.[2] However, low-dose aspirin should not be stopped if COX-2 selective inhibitors or other NSAIDs (despite their platelet inhibitory actions) are prescribed.

Unknowns

It may be that the greatest risk of inducing a myocardial infarction is in a patient with undiagnosed coronary vascular disease. Before COX-2 selective inhibitors became available, this patient may have been prescribed another NSAID. This would have had an aspirin-like antiplatelet effect and, if anything, might have been expected to reduce the risk of infarction. If the patient is instead commenced on a COX-2 selective inhibitor the balance swings towards a prothrombotic state that theoretically might result in an infarction. This theoretical point is supported by the results of the VIGOR study and the termination of the APPROVe study because of an excess risk of myocardial infarction and stroke in patients taking rofecoxib for 18 months.

The APPROVe study was a three-year randomised controlled trial to see if rofecoxib 25 mg/day could suppress the recurrence of colonic polyps. Among the 2600 patients enrolled, 45 taking rofecoxib and 25 taking placebo suffered confirmed, serious adverse thrombotic events. This difference was only apparent

after 18 months. The relative risk is about 2.0, but the extent to which this risk of myocardial infarction or stroke has been proven is currently unclear because of the absence of detailed published information.

In vitro studies indicate that celecoxib is somewhat less COX-2 selective than rofecoxib and may therefore be safer in patients at risk of thrombosis. There has not been as strong a signal for thrombotic risk with celecoxib[11,12], but further studies are clearly required as placebo-controlled trials of the size and duration of APPROVe are not yet available.

Until more data are available, the COX-2 selective inhibitors should only be used in low doses and for short periods. Low-dose aspirin or other anti-thrombotic treatment should be continued in patients at risk of thrombosis.

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Further reading

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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.

Self-test questions

The following statements are either true or false (answers on page 165)

1. Patients taking low-dose aspirin, for the prevention of heart disease, should stop their aspirin if they are prescribed a COX-2 selective inhibitor.
2. The efficacy of COX-2 selective inhibitors is significantly greater than the efficacy of other non-steroidal anti-inflammatory drugs.