Life after Vioxx: the clinical implications

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The withdrawal of Vioxx, as a result of concerns regarding cardiovascular risk, has left unanswered questions about the safety of COX-2 inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) in general. However, to what extent should the concerns about Vioxx be extended to other anti-inflammatory drugs?

The sudden withdrawal of Vioxx by Merck has prompted a rapid reassessment of the safety of COX-2 inhibitors and NSAIDs. Selective COX-2 inhibitors were heralded as a 'safer aspirin' with the anti-inflammatory benefits of COX-2 inhibition and gastroprotective benefits of COX-1. Intensive marketing brought COX-2 inhibitors to millions of people, and a worldwide return of an estimated $20 billion (Dieppe et al, 2004). Now their therapeutic role has been brought into question.

COX1 and COX-2 inhibition

Arachidonic acid, the main precursor for prostaglandins and thromboxane can be metabolized by a large number of routes, including cyclooxygenase and lipoxygenase enzymes (*Figure 1*).

Prostacyclin is the main product of cyclooxygenase in endothelium and inhibits platelet aggregation, promotes vasodilation, and prevents proliferation of vascular smooth muscle cells in-vitro. These are regarded as beneficial effects with respect to cardiovascular risk, especially in patients with atheromatous change. It was assumed that prostacyclin was derived largely from COX-1 since this is expressed constitutively in endothelial cells. However, COX-2 is also expressed in microvascular endothelial cells and in association with inflammation and atheroma.

Inhibitor studies (Fitzgerald and Patrono, 2001) suggest that COX-2, not COX-1, is the main source of the whole body prostacyclin. Thromboxane, which is derived from the COX-1 isoform in platelets, is a potent platelet activator and causes vasoconstriction.

Aspirin is unique in binding to cyclooxygenase enzymes by irreversible ethylation, leading to prolonged and selective inhibition of platelet thromboxane. Non-selective NSAIDs, such as ibuprofen, inhibit both thromboxane and prostacyclin. Selective COX-2 inhibitors do not normally affect gastric prostaglandin synthesis, thereby preserving the protective mechanisms. In the vasculature, however, selective COX-2 inhibitors only inhibit prostacyclin so that, in theory, the potential harmful effects of thromboxane remain unopposed (*Table 1*).

Beyond this simplistic view, it is important to realize that only profound inhibition of thromboxane significantly affects platelet function. The net effect of most non-selective NSAIDs and selective COX-2 inhibitors could be the same. Indeed, non-selective NSAIDs, by inhibiting both COX-1 and COX-2 dependent vascular prostacyclin, might have a more profound effect on a vascular prostacyclin than selective COX-2 inhibitors. An exception might be naproxen, which has a particularly prolonged and profound effect on platelet cyclooxygenase activity, which is similar (with twice daily dosing) in extent and duration to that achieved with aspirin.

Early data on the cardiovascular effects of COX-2 inhibitors appeared reassuring. In phase 3 studies, cardiovascular mortality in patients on rofecoxib was similar to that seen on placebo and substantially less than seen in NSAIDs (Daniels and Rahway, 1999). However, subsequent studies have cast doubt on this.

Figure 1. Metabolism routes of arachidonic acid. (CYP = Cytochrome P450, DiHETE = Dihydroxy-eicosatetraenoic acids, EET = epoxyeicosatrienoic acids, HETE = Hydroxyeicosatetraenoic acids, PGD = Prostaglandin D, PGE = Prostaglandin E, PGF = Prostaglandin F, PGI2 = Prostacyclin, TXA2 = Thromboxane)

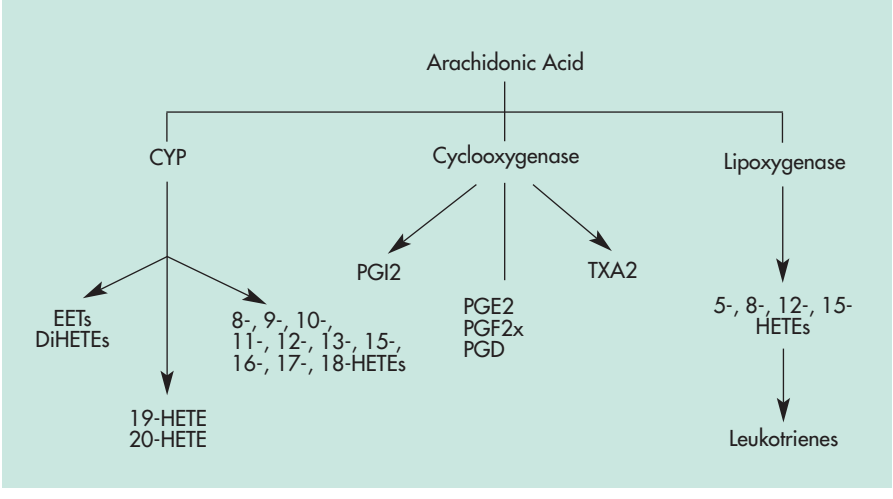

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Table 1.
Relative effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors on thromboxane, prostacyclin and the microvasculature

	Thromboxane Pro-aggregatory vasoconstriction	Prostacyclin Anti-aggregatory vasodilation
COX-2 inhibitors	–	↓↓
Ibuprofen	↓	↓↓
Aspirin	↓↓	–
Naproxen	↓↓	↓↓

Non-selective NSAIDs by definition affect both prostacyclin and thromboxane. Naproxen has been shown to inhibit thromboxane profoundly.

GASTROINTESTINAL OUTCOME STUDIES

Rofecoxib and the Vioxx Gastrointestinal Outcomes Research (VIGOR) Study

In the VIGOR study (Bombardier et al, 2000), 50 mg/day rofecoxib (a supratherapeutic dose) was found to cause fewer perforations, ulcers and bleeds (PUBS) than 1000 mg/day naproxen, but was associated with an increase in myocardial infarction (0.4% *vs* 1.0%, relative risk 0.2; 95% CI 0.1–0.7) (Bombardier et al, 2000). Aspirin use and patients with indications for aspirin was prohibited by trial design. A *post hoc* analysis suggested that the increase in myocardial infarction risk was particularly evident in those who had cardiovascular risk factors, for whom aspirin was indicated, and who entered into the study wrongly.

From this analysis, six possible explanations for the cardiovascular findings of the VIGOR study emerge:

- The increased risk with rofecoxib is a consequence of unopposed prostacyclin inhibition, not seen in previous studies because lower doses were used.
- The difference between rofecoxib and naproxen is a result of an anti-platelet effect of naproxen, an effect that would not be seen in previous studies that compared rofecoxib with non-naproxen NSAIDs. The magnitude of the effect, however, argued against this being the whole explanation since it was bigger than that seen in trials of aspirin.
- The differences in the VIGOR study result from a combination of a harmful effect of rofecoxib and the beneficial effect of naproxen.
- The results have occurred by chance, but the extent of the difference made this unlikely.
- Effects may have been a consequence of sustained hypertension.
- The magnitude of rofecoxib's effect on cardiovascular events is not explained solely by the mechanisms of prostacyclin and thromboxane homeostasis or hypertension (Baigent and Patrono, 2003) and other mechanisms need to be considered.

The results of VIGOR prompted investigation into whether non-selective NSAIDs, selective COX-2 inhibitors and naproxen affected the risk of thrombotic complications of cardiovascular disease. Some studies found a reduction in risk with naproxen (Rahme et al, 2002; Watson et al, 2002) especially at high dose, while others did not (Ray et al, 2002; Solomon et al, 2002). Other observational studies have shown no difference in myocardial infarction between rofecoxib, celecoxib and NSAIDs (Mamdani et al, 2003), although the mean follow-up of less than 1 year may be insufficient to detect an effect, given the 18 months before an effect was seen in the adenomatous polyp prevention of Vioxx (APPROVe) study.

EPIDEMIOLOGICAL STUDIES

Celecoxib and Celecoxib Long-term Arthritis Safety Study (CLASS)

In the CLASS study (Silverstein et al, 2000), the primary endpoint was again a comparison between celecoxib and non-selective NSAIDs (ibuprofen and diclofenac) on upper gastrointestinal events. Aspirin use for cardiovascular prophylaxis was permitted. The interim results revealed no increased cardiovascular risk with celecoxib (relative risk 1.1, 95% CI 0.7–1.6; *P* not significant.

Lumiracoxib and the TARGET study

In the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) (Farkouh et al, 2004; Schnitzer et al, 2004) the final analysis reveals a non-significant trend of increased cardiovascular events for lumiracoxib compared with naproxen or ibuprofen (0.26 *vs* 0.18 per 100 patient years; hazard ratio 1.47).

Lumiracoxib was compared with naproxen and ibuprofen on a 2:1:1 basis, with the latter two used to throw light on the extent to which any differences between the coxib and an NSAID was specific to naproxen. Patients taking lumiracoxib had numerically fewer cardiovascular events and myocardial infarctions than patients on ibuprofen, but more than those on naproxen, although differences were not significant.

APPROVe

The true test of a drug effect is comparison with placebo, but this is difficult in a population of arthritis sufferers for any meaningful length of time. Studies into a possible protective role of COX-2 inhibitors in colonic polyps provided an ideal opportunity to test cardiovascular safety *vs* placebo.

The (APPROVe) study investigated polyp prevention with rofecoxib in patients undergoing regular colonoscopy. This study was stopped 2 months before completion when it became apparent that there was a 3.9 times risk of serious thromboembolic events (myocardial infarction, stroke) in patients on 25 mg/day rofecoxib compared with placebo. The absolute difference in cardiovascular events was 25 in the placebo group compared with 45 in the rofecoxib arm (no subjects died). The absolute risk difference was about 0.75% per annum over the study.

In contrast to VIGOR, there was no increase in thromoembolic events until 18 months. This has led some to suggest that the cardiovascular effects of rofecoxib require sustained treatment (perhaps through inducing hypertension) until they are evident, but this conclusion seems premature (Ray et al, 2002).

The use of COX-2 inhibitors in colon prevention and Alzheimer's disease studies are now on hold (Couzin, 2004).

Are all COX-2 inhibitors the same?

There may be clinically significant pharmacological differences between COX-2 inhibitors. First, rofecoxib has a long plasma half life (up to 17 hours) compared with celecoxib (11 hours), or lumiracoxib (4 hours), hence once daily *vs* twice daily dosing. This may allow longer unopposed thromboxane effects.

Second, there are important differences in COX-2 selectivity; rofecoxib does seem to have a higher selectivity ratio than celecoxib (Warner et al, 1999), although relative comparisons are difficult (Hawkey, 1999).

Third, COX-2 inhibitors are difficult to formulate for easy absorption, and marketed doses of rofecoxib appear to be effectively higher than those of celecoxib. It is possible that a lower dose and limited absorption protects celecoxib from achieving harmful concentrations as readily as rofecoxib.

Finally, the structure of lumiracoxib differs substantially from all other coxibs; the relative importance of these differences is not known.

Cardiovascular benefits of COX-2 Inhibitors?

Some data suggest that celecoxib may have favourable effects on the endothelium in animals and humans (Chenevard et al, 2003; Hermann et al, 2003; Widlansky, 2003). Celecoxib improves endothelium-dependent vasodilation as measured by brachial artery flow studies, implying possible benefit in patients taking aspirin, but this may come at the cost of promoting thrombosis (Widlansky, 2003).

Non-selective NSAIDs

One worrying aspect of the response to the APPROVe study has been the failure to consider whether non-selective NSAIDs are associated with the same cardiovascular risk as selective COX-2 inhibitors. Patients taking COX-2 inhibitors have generally been switched back to non-selective NSAIDs with or without proton pump inhibitor protection, a reaction that may be both complacent and illogical. Overall, trends across NSAID studies suggest these drugs may also be associated with an increase risk of myocardial infarction, but the position is sufficiently unclear that direct investigation in this area is urgently needed.

Further, NSAIDs impair renal perfusion and, through COX-2 inhibition, cause sodium retention, predisposing to hypertension and oedema. Evidence suggests that an untreated 5 mmHg rise in blood pressure carries an annual cardiovascular event risk of 4/100019. There is no evidence that COX-2 inhibitors cause more hypertension than NSAIDs and, the size of this effect in terms of cardiovascular risk is too small to explain the apparent risk of rofecoxib.

Even if platelet and endothelial interactions are shown to be more favourably affected with non-selective NSAIDs than with COX-2 inhibitors, the most important prescribing point is that both non-selective NSAIDs and selective COX-2 inhibitors cause significant hypertension and the best thing a prescriber can do to maximize safety in patients taking these drugs is to measure the blood pressure and treat it.

NSAIDs abrogate benefits of aspirin and vice versa

The most valuable and proven drug for prevention of thrombosis is aspirin, however, there are mechanistic and clinical data to suggest this may be lost with concurrent use of non-selective NSAIDs, but not selective COX-2 inhibitors (Catella-Lawson et al, 2001). Pre-dosing with ibuprofen but not diclofenac or rofecoxib competitively blocks the effects of aspirin on thromboxane levels and therefore platelet aggregation. It is possible that switching to NSAIDs, other than naproxen, in patients on aspirin with cardiovascular risk factors would be more harmful than combining a COX-2 inhibitor with aspirin.

To further complicate the picture for patients with arthritis and cardiovascular risk factors, the CLASS study suggests that the combination of low dose aspirin with celecoxib abolishes its superior gastrointestinal safety profile compared with non-selective NSAIDs.

Medical politics

Commentators have been quick to condemn (Horton, 2004). While some have directed their fire at Merck for failures of pharmacovigilance, others have pointed the finger of blame at the food and drug administration and the process of drug approval (Horton, 2004).

There has been a call for drug companies to release findings of adverse events immediately on completion of clinical trials (Dieppe et al, 2004), without any proof that Merck has concealed unfavourable data. The current level of noise comes with the benefit of hindsight. What is required is robust research on the safety of all NSAIDs with robust cardiovascular outcomes. The fact that this research has been largely driven by drug companies goes to the heart of issues regarding research funding. Drug companies may not limit the results as much as restrict the initial question.

CONCLUSIONS

The fallout from the withdrawal of vioxx has been dramatic, but there is insufficient evidence to conclude that COX-2 inhibitors are more harmful than non-selective NSAIDs, let alone discriminate between individual COX-2s. When the dust has settled, prescription of these effective drugs should continue as outlined, with a careful and calm appraisal of the risk-benefit ratio. **HM**

Conflict of interest: none

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KEY POINTS

- Use non-steroidal anti-inflammatory drugs (NSAIDs) only when necessary at the lowest possible dose and preferably on an as required basis.
- Check the blood pressure and treat it in all patients taking non-selective NSAIDs or selective COX-2 inhibitors.
- Remember that it is possible that non-selective NSAIDs also increase the risk of myocardial infarction.
- Bear in mind that NSAID prescription may well abrogate the cardiovascular benefit of aspirin although this is far from clear.
- Do not base prescribing on one article or one editorial in a journal.

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