COX-2 inhibitors and cardiovascular risk

MIKE SCHACHTER

Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) have potentially dangerous side effects, which has led to intense interest in the development of the cyclo-oxygenase (COX) inhibitors. This article reviews the science, safety and clinical evidence to date with these drugs.

They appear to have fewer gastrointestinal and equivalent renal risks to NSAIDs. Reviewing the clinical evidence, particularly the complex cardiovascular effects of the COX inhibitors, the article discusses the clinical relevance of their thrombogenic and anti-atherosclerotic potential. Since many of the studies are retrospective analyses, randomised clinical trials are needed to ascertain whether these cardiovascular effects constitute a problem or an unexpected benefit, and whether there are differences between the different COX-2 inhibitors.

Key words: Non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2 inhibitors, renal toxicity, thrombosis, cardiovascular risk.

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Why COX-2 inhibitors?

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the world's most widely used and misused therapeutic agents. Many are available not only on prescription but also over the counter, often not even restricted to pharmacies. Despite the undoubted anti-inflammatory and analgesic efficacy of the NSAIDs, these are potentially dangerous compounds. The main types of adverse effects are:[1]

- Gastrointestinal: the most common and usually the most dangerous, ranging from mild dyspepsia to peptic ulceration with haemorrhage or perforation. This is believed to be due to mucosal damage related to inhibition of the synthesis of cytoprotective and vasodilator prostaglandins

Department of Clinical Pharmacology, Imperial College of Science, Technology and Medicine, St Mary's Hospital, Praed Street, London, W2 1NY.
Mike Schachter, Senior Lecturer and Honorary Consultant Physician
Correspondence to: Dr M Schachter
(email: m.schachter@ic.ac.uk)

Mike Schachter

- Renal: also wide ranging and most frequent in the elderly with already impaired renal function. Many of the adverse effects are related to intrarenal vasoconstriction, again due to failure of prostaglandin synthesis, at its most extreme leading to papillary necrosis. Interstitial nephritis occurs rarely, which may also be partly ischaemic in aetiology. There are also believed to be direct effects on the renal tubules, leading to retention of sodium, water and potassium, resulting, in some patients, in oedema or hyperkalaemia or both
- Cardiovascular: largely secondary to the renal effects on sodium and water handling, leading to exacerbation or emergence of raised blood pressure or heart failure.

In addition to these 'type A' adverse effects, which are directly linked to the drug's pharmacology, other rare idiosyncratic problems also occur, such as bronchospasm and a variety of rashes, some with serious systemic complications.

There has therefore been every incentive to develop drugs which combined the efficacy of the NSAIDs with much greater safety. Cyclo-oxygenase (COX) was discovered over 30 years ago and recognised as the key enzyme in the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (see figure 1).[2] It was recognised as the target for the original NSAID, aspirin which has emerged as the least typical of the NSAIDs. The opportunity for a more selective therapeutic approach came in the late 1980s when it was found that there were at least two cyclo-oxygenases, COX-1 and COX-2.[3] COX-3 has recently been

Figure 1. Scheme of comparative effects of standard NSAIDs and coxibs on endothelial cells and platelets. The association of TxA_2 (thromboxane A_2) with COX-1 and of prostacyclin (PGI_2) with COX-2 is not exclusive

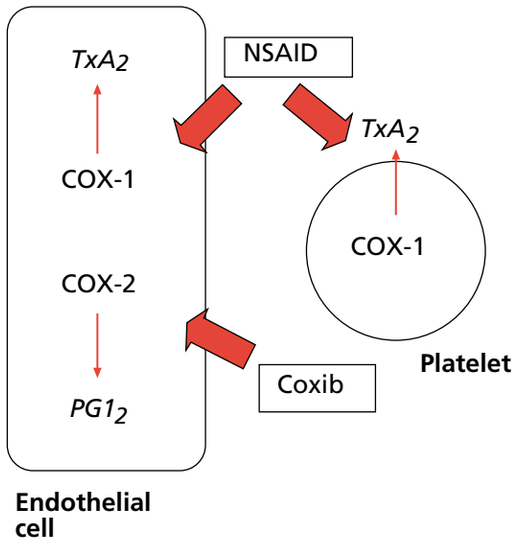

Table 1. COX-1 and COX-2 selectivity of non-steroidal anti-inflammatory drugs (NSAIDs)

Piroxicam, Diclofenac, Aspirin, Indomethacin, Naproxen, Ibuprofen	**Relatively COX-1 selective/ non-selective***
Etodolac, Meloxicam	**Relatively COX-2 selective**
Celecoxib, Rofecoxib, Etoricoxib	**COX-2 selective**

Key: * the rank order of drugs in this group varies widely between publications

Table 2. Possible renal roles of COX-2 and renal effects of coxibs

- COX-2 expression in medulla increased by high-salt diet and dehydration
- Similar response in cortex, also in response to angiotensin converting enzyme inhibitors and angiotensin II receptor blockers
- Feedback inhibition of COX-2 expression by angiotensin II
- Reduction in glomerular filtration with coxibs most marked in predictably high-risk patients (elderly, pre-existing renal impairment)
- Renal failure described with both rofecoxib and celecoxib
- In some circumstances (possibly diabetes and renovascular hypertension) COX-2 inhibition may be renoprotective

Overall, from safety perspective conventional NSAIDs ≡ coxibs

characterised and this will be discussed later. COX-1 and COX-2 have considerable similarities in structure and enzymatic activity but are encoded by different genes on different chromosomes.

COX-1 versus COX-2

The interesting and important difference between the two COX isoforms is in the way that they are regulated. The presumption initially was that one could make a simple distinction: COX-1 was a constitutive enzyme involved in 'housekeeping' processes, such as the protection of mucosa in the gastrointestinal tract and vasodilatation in the kidney. By contrast, COX-2 was regarded as an inducible enzyme, upregulated as a crucial part of the inflammatory response. It was established that the standard NSAIDs, such as indomethacin, diclofenac and ibuprofen, discriminated much less in their inhibition of the two enzymes, or if anything preferentially favoured COX-1 inhibition. The methodology of determining selectivity ratios is not straightforward and there is certainly scope for some differences in interpretation. However, the classification and sequence shown in table 1 is widely accepted.[4] Celecoxib, rofecoxib and eterocoxib (the coxibs), all currently available, were all designed as COX-2 selective agents and others are in development.

It is not within the scope of this review to consider the efficacy of these drugs in any detail but it should be noted that they are not necessarily interchangeable, for instance in their suitability for treating acute pain. A much more controversial area has been the question of the gastrointestinal safety of these drugs, the prime motivation for their development. Much of the discussion has focused on the design, interpretation and reporting of pivotal clinical trials, notably the Vioxx Gastrointestinal Outcomes Research (VIGOR) study for rofecoxib and the Celecoxib Long-term Arteries Safety Study (CLASS) for celecoxib.[5-7] The tentative conclusion at present, is that the coxibs are associated with fewer serious upper gastrointestinal adverse effects than the established NSAIDs, although dyspeptic symptoms may be quite similar. But these issues are almost as complex as the main theme of this review!

COX-2 and renal and cardiovascular physiology

As already mentioned, the original COX-1/COX-2 model was based on the assumption that the kidney would not, under normal conditions, contain COX-2 but only the constitutive COX-1 enzyme. But it is now clear that COX-2 is present constitutively in the kidney and other tissues, though at lower levels than COX-1.[8] Its location within the kidney is in the juxtaglomerular appa-

ratus and even more in intraglomerular podocytes, which influence intrarenal haemodynamics. The current understanding of the renal role of COX-2 and the coxibs is summarised in table 2.[9,10] The main message, at present is that the renal risks associated with the COX-2 inhibitors appear very similar to those seen with standard NSAIDs.

The cardiovascular role of COX-2 has proved to be rather more complex than anticipated. While both COX-1 and COX-2 are present in the endothelium, only COX-1 occurs in the platelet.[11,12] It follows that COX-2 inhibitors will be lacking antiplatelet activity and this is certainly a key point in the later discussion of cardiovascular risk. The unstimulated endothelium, expresses almost exclusively COX-1, as one might expect; under conditions of stress, however, such as ischaemia and inflammation, the expression of COX-2 is induced. COX-1 generates mostly thromboxane A_2 (TxA_2) but COX-2 activation leads largely to production of prostacyclin and PGE_2 (figure 1).[12] This has been seen as a protective response of the endothelium but in terms of the actions of the coxibs can be regarded as potentially pro-thrombotic.

Very recent studies have examined the roles of COX-1 and COX-2 inhibitors in the pressor response to angiotensin II.[13] In COX-2 knockout mice and those treated with selective COX-2 inhibitors, angiotensin II produced a significantly augmented pressor response and failed to induce prostacyclin and PGE_2 synthesis in the renal medulla. In COX-1 knockouts and COX-1 inhibitor-treated animals there was, surprisingly, no pressor response to angiotensin II. Selective COX-1 inhibitors, which are of course not intended for clinical development, may in fact lower blood pressure in animal models.

It has also been proposed that COX-2 activation may be atherogenic in the longer term.[14] The enzyme is upregulated in the activated monocyte/macrophage and can lead to the generation of TXA_2, thromboxane and PGI_2, as elsewhere, though the balance of production is not known at present. In low density lipoprotein (LDL)-deficient mice, coxibs attenuate atherosclerosis, and animals that lack COX-2, as well as LDL receptors, also have diminished atherogenesis. In both of these circumstances one must, of course, be cautious in extrapolating data from animal to human physiology but the clinical implications are potentially important. The difficult and controversial question arises: what exactly are the clinical consequences of COX-2 inhibition?

Coxibs and cardiovascular risk

Considering that these are relatively new drugs the literature and debate already generated is quite enormous (recent editorials include references [15-17]). New contributions appear almost weekly and it is clear that there are strongly held views on this topic. Essentially we are asking two related but separable questions:

1. Do the coxibs share the cardiovascular adverse effects of the conventional NSAIDs, notably as regards worsening of heart failure and hypertension?
2. Do they actually have enhanced risk, mainly because of prothrombotic effects? If so, is this because they simply lack the antithrombotic potential of the older drugs, or do they themselves positively promote thrombosis?

'Conventional' adverse effects

The published evidence suggests that the coxibs do have a small but detectable effect on blood pressure in treated hypertensive patients.[18-19] The data are limited but indicate that celecoxib may produce a smaller effect than the older NSAIDs and that the effect of rofecoxib may be somewhat greater, comparing doses of celecoxib 200 mg daily and rofecoxib 25 mg daily. The nature of the antihypertensive therapy seems to be relevant, since only patients taking beta blockers or angiotensin-converting enzyme (ACE) inhibitors were affected, not those on diuretics or calcium channel blockers: in other words, only those taking drugs that suppressed the renin-angiotensin system. With respect to oedema, about 8% of patients taking rofecoxib developed this problem, nearly double the rate for celecoxib. There is even less information on the development of clinically apparent heart failure, but a case report describes four elderly patients in whom heart failure reappeared after starting coxib therapy, in three cases with rofecoxib.[20] Furthermore, the number of patients in the VIGOR trial developing hypertension was greater in those taking rofecoxib as compared to naproxen. This is in keeping with our knowledge of the renal implications of coxib therapy.

Thrombosis-related risks

It is here that we are on much less secure ground. To summarise our current information:

- In the VIGOR study, the excess risk for thrombotic vascular events was 2.37 when compared to the standard NSAID, naproxen. The risk was much greater (nearly five-fold) in the relatively small subgroup of patients in whom aspirin would have been indicated because of high pre-existing cardiovascular risk.[21]
- In the celecoxib-based CLASS study, there was no excess of such events, this time in comparison with ibuprofen.
- In both studies these were retrospective analyses, since no increase in cardiovascular complications was anticipated when they were designed.
- If only confirmed myocardial infarcts are considered, separately from other cardiovascular events, there is an increased incidence in both the VIGOR and the CLASS trials: an annual rate of 0.74% and 0.8% as compared to a predicted rate of 0.52% (although this was calculated using a meta-analysis including other studies).[22]
- A review of 23 osteoarthritis trials involving rofecoxib, with a total of 28,000 patients, indicated that there was an increased risk with the drug compared to naproxen (odd ratio 1.69) but not in comparison with other NSAIDs or with placebo.[23]
- A retrospective study in over 170,000 NSAID users, of whom some 24,000 were taking rofecoxib, showed a 1.7-fold excess of coronary disease in patients taking high-dose rofecoxib, (i.e. over 25 mg per day). Patients taking lower doses showed no additional risk.[24]
- Another retrospective analysis, involving over 5,400 participants in eight osteoarthritis trials, found no difference between the incidence of cardiovascular events in patients on

Key messages

- Conventional NSAIDs are associated with significant renal toxicity with indirect cardiovascular effects (worsening hypertension and heart failure)
- Selective COX-2 inhibitors (coxibs) have similar renal effects, contrary to early assumptions about the role of the enzyme
- Coxibs may have a thrombogenic effect by preferentially inhibiting endothelial prostacyclin release
- Some but not all clinical data suggest that this leads to increased cardiovascular thrombotic risk, especially for rofecoxib
- Coxibs may be preferable in patients taking low-dose aspirin, since they do not interfere with platelet inhibition by aspirin
- Caution: clinical data so far is largely based on retrospective analyses

rofecoxib and those taking a variety of non-selective NSAIDs or placebo.[25]

- In trials involving a newer coxib, etericoxib, the number of cardiovascular events were greater than expected but were actually very few, well under 1% of the total. This drug is more COX-2 selective than any of the existing agents.[26]

Conclusions and overview

It is clear that these issues are far from resolved. The thrombogenic potential of the coxibs is certainly plausible and, in the longer perspective, so is their anti-atherosclerotic activity, although we are not sure about the clinical relevance of either. Any absolute increase in risk appears to be small but it has to be emphasised that all of our clinical evidence is retrospective: we need a study, or several with different drugs, to establish whether we really have a problem, or alternatively, an unexpected benefit. Probably neither, ultimately, but we do need to know.

We also need to ascertain if the drugs do indeed differ. If there really is increased risk with rofecoxib as opposed to celecoxib. The answer might lie in the pharmacokinetics of the former with a long half-life of 17 hours and presumably prolonged and at high doses almost complete COX-2 inhibition. It is also considerably more COX-2 selective than celecoxib (some 10-fold). We may also be seeing some apparent advantage of some of the standard NSAIDs, notably naproxen, rather than harm from coxibs.[27]

Another consideration is the co-morbidity of the patients in the trials, in fact the indication for taking the drugs in the first place: it is well known that patients with rheumatoid arthritis are at increased risk of cardiovascular disease, partly because of dyslipidaemia.[28] There is at least one group of patients, however, in whom treatment with coxibs might confer indirect cardiovascular benefits. It has recently been reported that at least some of the conventional NSAIDs may attenuate the beneficial effects of low-dose aspirin, presumably by interfering with its inhibition of COX-1 in the platelet.[29] Drugs with high COX-2 selectivity do not cause this problem and may therefore be particularly suitable for those patients already taking aspirin for cardiovascular prevention.[30]

The limitations of our knowledge in this area have recently been demonstrated by two independent but almost simultaneous papers. In a prospective study of over 80,000 women between the ages of 30 and 50, the frequent use of NSAIDs was associated with almost a doubling of the risk of hypertension. This was not the case for aspirin but, rather surprisingly, was also found with regular users of paracetamol.[31] Why paracetamol? The mechanism of action of this drug has long been somewhat obscure and was thought to be linked with inhibition of brain prostaglandin synthesis. It is now known that paracetamol inhibits COX-3, a variant of COX-1 which is indeed present in the brain and heart but only sparsely elsewhere.[32] Does this have anything to do with hypertension? If so, it is not clear how, but it certainly demonstrates that we have much to learn about the functions of all the COXes in health and disease.

Note added in proof

Recent publications have failed to resolve the questions posed here, but in general do not support the likelihood of significantly increased cardiovascular risk with the COX-2 inhibitors. The quality of the evidence is still, however, inadequate to provide a definitive answer.[33,34]

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