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Practice

Practice pointer

Understanding the NSAID related risk of vascular events

Harald E Vonkeman, Jacobus R B J Brouwers, Mart A F J van de Laar

Concern is growing about an increased risk of thrombotic events (including myocardial infarction and stroke) during the use of non-steroidal anti-inflammatory drugs (NSAIDs), in particular the so called selective cyclo-oxygenase-2 (COX 2) inhibitors. Although clinical trials give conflicting results with respect to the incidence of vascular events, increasing evidence shows that a class effect might exist for selective COX 2 inhibitors. Even before the massive introduction of selective COX 2 inhibitors, observational studies showed that the use of NSAIDs causes congestive heart failure in elderly patients.^{1,2} Conversely, the discontinuation of NSAIDs has also been associated with increased risk of myocardial infarction, especially in the first several weeks after stopping chronic NSAID treatment.³

Many different mechanisms could explain the different effects of classic NSAIDs and selective COX 2 inhibitors in relation to thrombotic vascular events. In this review we link biochemical facts concerning NSAIDs and COX inhibitors with data from clinical trials.

Key enzymes: COX 1 and COX 2

The key step in the synthesis of prostaglandins, the transformation of arachidonic acid to prostaglandin H₂, is catalysed by two different isoenzymes—cyclo-oxygenase-1 and cyclo-oxygenase-2.⁴ COX 1 is expressed constitutively at variable concentrations and regulates normal physiology, such as the maintenance of gastric mucosal integrity, kidney function, and platelet aggregation. Conversely, COX 2 is usually undetectable in most tissues and is selectively expressed after exposition to inflammatory mediators or trauma (fig 1).

The hypothesis formed is that the adverse gastrointestinal effects of NSAIDs are attributable to the inhibition of COX 1 and that selective inhibition of COX 2 would yield effective but gastrointestinally safer drugs. A number of pharmaceutical companies developed and tested this hypothesis and several selective COX 2 inhibitors were subsequently marketed.

The COX 2 hypothesis does, however, have an unexpected and dark side. Within the endovascular lumen, COX 1 and COX 2 have an important role in the interaction between platelets and endothelial cells and in thrombogenesis.⁵ Activated platelets produce COX 1 dependent thromboxane A₂. Thromboxane A₂



Merck withdrew Vioxx in 2004

acts as a platelet agonist and vasoconstrictor, and its effect can be considered as prothrombotic. Nearby endothelial and smooth muscle cells produce COX 2 dependent prostaglandin I₂ (prostacyclin), especially after cell damage has occurred, as occurs in the formation of atherosclerotic plaques.⁶ Prostacyclin is a natural platelet inhibitor and has vasodilatory effects. Prostacyclin thus modulates the interaction between platelets and the endovascular wall, inhibiting thrombogenesis and atherosclerosis.⁷ Selective COX 2 inhibitors may, by their irreversible covalent binding, strongly impair the synthesis of the antithrombotic prostacyclin while lacking any antiplatelet effects, thus tipping the scales of homeostasis in favour of thrombogenesis and vasoconstriction. As shown previously by our group and others, platelet function is inhibited by non-selective NSAIDs but not by selective COX 2 inhibitors.^{8,9} These in vitro findings suggest that selective COX 2 inhibitors may increase the risk of vascular events, including myocardial infarction and stroke, especially in patients with pre-existing endothelial damage or a history of thromboembolic events—that is, elderly patients.

Using human whole blood assays, NSAIDs can be assessed and ranked for their in vitro level of COX 2 selectivity.¹⁰ Some classic NSAIDs more or less equivalently inhibit COX 1 and COX 2; others show some COX 2 selectivity. Selective COX 2 inhibitors on the other hand, have shown a 200-300-fold selectivity for

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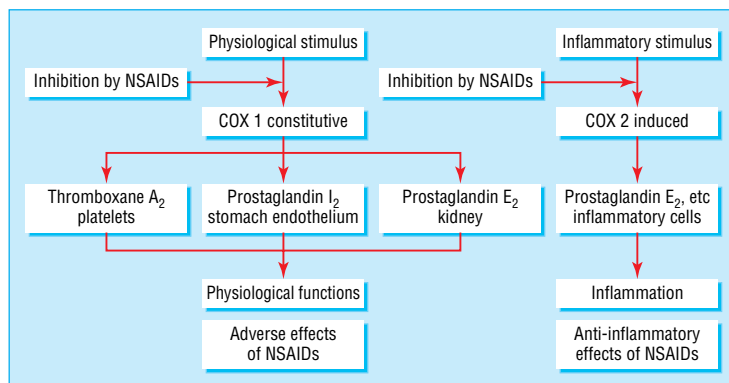


Fig 1 Differential prostanoid synthesis, showing differential prostanoid synthesis by different cells in different tissues. NSAIDs' anti-inflammatory effects are due to cyclo-oxygenase-2 (COX 2) inhibition, and adverse effects occur because of COX 1 and also COX 2 inhibition

COX 2 (fig 2). As their effect is temporary and reversible, only continuous high dosage of classic NSAIDs will considerably inhibit COX 1 and COX 2. For selective COX 2 inhibitors, conversely, because of irreversible covalent binding, considerable inhibition of COX 2 (but not COX 1) might also be expected during intermittent use and at lower dosage. In inflammatory states like in synovitis this irreversible COX 2 binding would be advantageous because of massive overexpression of COX 2. However, in the interaction between platelets and the endothelial wall, no continuous overabundant expression of COX 2 is to be expected. One could surmise that under normal circumstances, the use of classic NSAIDs would not greatly influence the production of platelet COX 1 dependent thromboxane A_2 or the concentrations of endothelial COX 2 dependent prostacyclin, thus retaining the endothelial prothrombotic and anti-thrombotic balance. However, cell damage, atherosclerotic plaques, and laminar shear forces selectively upregulate the expression of COX 2 by endothelial cells in an attempt to maintain homeostasis.¹¹ In clinical syndromes of platelet activation, therefore, COX inhibition by any NSAID, but especially by selective COX 2 inhibitors, could be expected to upset the thrombotic equilibrium, increasing the risk of cardiovascular events.

Clinical data on cardiovascular events

On 7 April 2005, Pfizer agreed to suspend the marketing and sale of valdecoxib (Bextra) in the United States and European Union pending further discussions with the US Food and Drug Administration on the drug's overall risk versus benefit profile.¹² Previously, on 30 September 2004, Merck Sharp & Dohme removed its selective COX 2 inhibitor rofecoxib (Vioxx) from the market. The reason for this was a raised risk of cardiovascular events, especially myocardial infarctions. The Vioxx gastrointestinal outcome research study (VIGOR) had previously shown that rofecoxib, compared with naproxen, has noticeably less serious gastrointestinal side effects. The same study, however, also showed that rofecoxib, compared with naproxen, carried an increased risk for thrombotic cardiovascular events. In the group taking 50 mg of rofecoxib, 45 events occurred compared with 19 in the group taking 1000 mg of naproxen ($P < 0.002$).¹³ Overall, there were

more serious side effects with rofecoxib than with naproxen and the way in which the VIGOR data were presented has elicited an "expression of concern" as not all observed myocardial infarctions were reported, apparently purposely, resulting in an understatement of the difference in risk.¹⁴⁻¹⁶

Although many subsequent retrospective case-control studies seemed to confirm this raised risk, it was the prospectively randomised adenomatous polyp prevention on Vioxx study (APPROVE) which definitively showed an increased risk for cardiovascular events, such as myocardial infarctions and stroke. In the APPROVE study, 46 of 1287 (3.6%) participants taking 25 mg of rofecoxib compared with 26 of 1299 (2.0%) taking placebo, had a confirmed thrombotic event after 18 months (relative risk 1.92, 95% confidence interval 1.19 to 3.11).¹⁷ Although the risk was relatively low, at 1.50 per 100 patient years, this was reason for the voluntary worldwide withdrawal of rofecoxib.

These series of events have led to greater scrutiny of the remaining selective COX 2 inhibitors and also of the NSAID group as a whole. Soon after the withdrawal of rofecoxib yet another selective COX 2 inhibitor—namely, celecoxib (Celebrex), came under fire. In the adenoma prevention with celecoxib study (APC), 2035 participants were randomised to either a daily dose of 400 mg or 800 mg of celecoxib or placebo. The study was designed to assess whether (high dose) celecoxib can prevent colon polyps. It was to finish in spring 2005 but was terminated early by the National Institutes of Health. In the APC study, participants who took 400 mg of celecoxib seemed to have 2.3 (0.9 to 5.5) times as much risk of having a major cardiovascular event, compared with participants who took placebo. In those taking a daily dose of 800 mg of celecoxib the risk was increased by 3.4 (1.4 to 7.8)-fold. After an average of 33 months, there were seven cardiovascular events in 679 subjects in the placebo

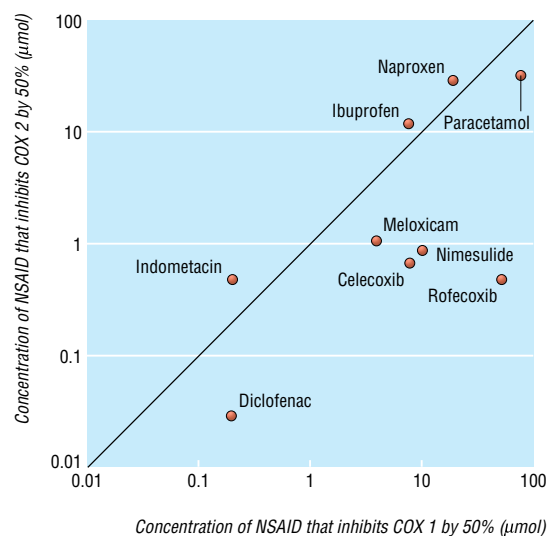


Fig 2 Inhibition of cyclo-oxygenase-1 (COX 1) and COX 2, showing the concentration of non-steroidal anti-inflammatory drugs needed to inhibit the activity of COX 1 and COX 2 by 50% in assays of whole blood. Diagonal line shows equivalence (adapted from Fitzgerald and Patrono¹⁰)

group, 16 in 685 in the 400 mg group, and 23 in 671 in the 800 mg group.¹⁸ However, in two other long term follow-up celecoxib studies, the celecoxib long term arthritis safety study (CLASS) and the prevention of spontaneous adenomatous polyps study (PreSAP) preliminary reports do not suggest an increased cardiovascular risk.¹⁹

A meta-analysis on two trials in high risk patients, who had recently undergone coronary artery bypass graft surgery, showed a significantly greater cardiovascular risk for the selective COX 2 inhibitor valdecoxib (Bextra) (relative risk 3.08; 1.20 to 7.87).²⁰ Likewise, in a study after coronary artery bypass graft surgery in which patients received intravenous parecoxib (Dynastat), a pro-drug which is converted into valdecoxib, followed by oral valdecoxib, patients receiving valdecoxib showed an increased risk of myocardial infarction compared with patients receiving placebo.²¹ For the selective COX 2 inhibitor lumiracoxib (Prexige), no significant increase in cardiovascular events was found compared with non-selective NSAIDs. In the therapeutic arthritis research and gastrointestinal events trial (TARGET), 18 325 patients with osteoarthritis were randomly treated with lumiracoxib, naproxen, or ibuprofen for one year.²² Event rates were similar, and the adjusted hazard ratio did not increase significantly (hazard ratio 1.14, 0.78 to 1.66). But absence of evidence is not evidence of absence, as in this trial patients with a high risk for cardiovascular events were excluded and the number of events was quite low.

Recently, Merck Sharp and Dohme discussed cardiovascular safety for the selective COX 2 inhibitor etoricoxib (Arcoxia) in their new drug application briefing. An increase of cardiovascular events was seen for etoricoxib, compared with placebo or non-selective NSAIDs. Furthermore, the marginal gastrointestinal advantage of etoricoxib compared with naproxen was entirely lost in users of low dose aspirin.²³ However, the original publications should be awaited before these results can be taken into consideration.

To confuse matters, preliminary results from the three year ongoing placebo controlled Alzheimer's disease anti-inflammatory prevention trial (ADAPT) also suggested an increased cardiovascular risk for the classic non-selective NSAID naproxen.²⁴ In the ADAPT trial, 2500 elderly patients had been taking 400 mg of naproxen, 400 mg of celecoxib, or placebo from 2001 onwards to test the hypothesis that NSAIDs might protect against the onset of Alzheimer's disease in those at risk. The National Institutes of Health recently terminated this study early, after finding that those taking naproxen had a 50% increase in cardiovascular events compared with placebo.

Surprisingly, no increase was seen in those taking celecoxib.²⁴ This is however consistent with results from a large case-control study in over 8000 patients taking selective COX 2 inhibitors, that showed that patients using rofecoxib were more likely to have a myocardial infarction than those that took celecoxib (odds ratio 2.72; 1.24 to 5.95).²⁵ These findings were confirmed in another very large nested case-control study. In 2 302 029 person years of follow-up, 8143 cases of acute myocardial infarction and sudden cardiac death occurred. Rofecoxib increased the risk compared with celecoxib, and naproxen use did not offer any protection.²⁶ Also, in a case-control study with 10 280

Summary points

A significant increase in risk for cardiovascular events in non-steroidal anti-inflammatory drug (NSAID) users has been found in clinical trials and observational studies, especially in patients taking selective cyclo-oxygenase-2 (COX 2) inhibitors

Two selective COX 2 inhibitors have subsequently been taken off the market, but others are still available

Within the endovascular lumen platelet COX 1 dependent prothrombotic thromboxane-A₂ and endothelial COX 2 dependent antithrombotic prostacyclin are balanced and so prevent coagulation

Selective COX 2 inhibitors impair prostacyclin synthesis but lack antiplatelet effects, tipping the scales in favour of thrombogenesis and increasing the risk of cardiovascular events

Patients at risk of cardiovascular events should not be treated with selective COX 2 inhibitors

cases of first time admission to hospital for myocardial infarction and 102 797 population controls, risk for myocardial infarction was highest in users of rofecoxib, but was also raised in other selective and non-selective NSAID users, compared with non-users.²⁷

Conclusion

A significant increase in risk of cardiovascular events in NSAID users has been found in clinical trials and observational studies, especially in patients taking selective COX 2 inhibitors. Two selective COX 2 inhibitors have subsequently been taken off the market, but others are still available to doctors and patients. On the basis of the hypothesis outlined above, in at-risk patients one may infer a mechanism of prostanoicid dependent conservation of arterial blood flow

Additional educational resources

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Information for patients

Food and Drug Administration. www.fda.gov/cder/drug/infopage/COX2/default.htm. Website on cyclooxygenase-2 selective and non-selective non-steroidal anti-inflammatory drugs

due to COX 2 upregulation. Selective COX 2 inhibition, because of its sparing of COX 1 and irreversible binding of COX 2, can be expected to upset this homeostasis, increasing the risk for cardiovascular events. When prescribing NSAIDs, and especially selective COX 2 inhibitors, doctors should carefully weigh gastrointestinal harm with cardiovascular harm. Patients at risk for cardiovascular events should not be treated with selective COX 2 inhibitors.

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Dr No

As doctors, we are enormously privileged to hear reminiscences from our patients, which are especially appealing when they do not concern their illness. With the emerging news of a "new" James Bond to appear in the film *Casino Royale*, I was reminded of a story told to me by a patient while I was a house surgeon at Charing Cross Hospital in the early 1960s.

At that time, James Bond had appeared only as a literary character and was not yet well known, but the book *Dr No* had just been published and generated a huge following for the novels of Ian Fleming. I had just read the book, and I noticed that my patient had a copy on his bedside locker. He was anxious to show me the book, and, on opening it, I saw the flyleaf had a handwritten message: "To a true British patriot," which was signed "Ian Fleming."

Understandably I asked him to explain the origin of this reference.

The patient had been the head waiter at a well known restaurant in Piccadilly during the war years of 1939-45. One lunch time one of his diners came to him and said that at the table next to him were three men speaking German, and some of the words that he could understand related to military events. In the tension of those days he felt that someone should be alerted. My patient (who could not understand German) agreed, and so he decided to call the

police. They asked that they could be seated close to the table in question and for him to treat them as ordinary clients. They arrived soon after, and he did as requested.

Some time later they seemed to have heard enough and arrested the three men (in a gentlemanly way so as to not upset the other diners).

My patient felt gratified that he had acted correctly until a few days later, when he learnt that two of the men were German officers who had been captured and the third was Ian Fleming, who was not yet a successful writer but who was working in Naval Intelligence at the War Office. His method of obtaining information from prisoners of sufficient rank was to entertain them well with a good meal and suitable wines.

The "patriotic" act was therefore somewhat diminished, since events did not run their expected course.

Obviously Ian Fleming remembered the event well, and later he became a regular client at the restaurant. On the publication of *Dr No*, he took the opportunity of sending a copy, suitably inscribed, to my patient as a friendly reminder of that occasion.

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