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Ibuprofen and COX-2 selective NSAIDs: what the evidence tells us

It was hoped that the introduction of the coxib class of COX-2 selective NSAIDs (rofecoxib, celecoxib, etoricoxib, valdecoxib) had at last overcome the problem of poor gastrointestinal tolerability with many NSAIDs. These new agents, by selectively inhibiting inducible COX-2 not constitutive COX-1, should have offered a safer treatment for arthritis. Instead, they became yet another example of misguided optimism, as long-established and evidence-based treatments were discarded in favour of relatively untested new drugs.

What were the concerns about non-COX selective NSAIDs?

There was no evidence of differences in efficacy among older NSAIDs so attention naturally focused on their relative safety. Before the advent of the coxibs, the major concern about non-aspirin NSAIDs was dose-related gastrointestinal (GI) toxicity. It was estimated that 10 - 20 percent of patients had dyspepsia while taking an NSAID and 5 - 15 percent discontinued treatment within 6 months primarily due to adverse GI effects¹. In 1994 the Committee on Safety of Medicines ranked the most widely prescribed non-aspirin NSAIDs in order of the risk of upper GI toxicity: ibuprofen was associated with least risk; diclofenac, naproxen, ketoprofen and indomethacin with intermediate risk; and piroxicam with highest risk². Compared with ibuprofen, these agents were associated with a 1.6 - 4.2-fold increased risk of gastrointestinal bleeding and peptic ulcer perforation³.

Non-aspirin NSAIDs were also associated with other serious adverse effects such as renal, hepatic, allergic and haematological reactions but these events were less common than GI toxicity and the differences between NSAIDs were less marked².

What did COX-2 selective NSAIDs offer?

COX-2 selective NSAIDs reduced the risk of GI toxicity compared with non-selective NSAIDs. Two large trials appeared to support this. The CLASS study compared celecoxib, diclofenac and ibuprofen in 8059 patients with rheumatoid arthritis or osteoarthritis⁴. It found that celecoxib was associated with a significantly lower incidence of upper GI bleeding, perforation or ulceration and symptomatic ulcers (1.40 vs 2.91 percent with the other NSAIDs combined) after 6 months; there were no differences in the risk of cardiovascular events. The VIGOR study compared rofecoxib and naproxen in 8076 patients with rheumatoid arthritis⁷. After 9 months, rofecoxib was associated with less than half the risk of upper GI bleeding, perforation or ulceration and symptomatic ulcers (2.1 vs. 4.5 percent).

Recently published data have revealed the enthusiasm with which the coxibs were prescribed in the first years following their introduction. Analysis of US national statistics showed that COX-2 selective NSAIDs accounted for 35 percent of prescriptions for NSAIDs arising from GP and hospital consultations in 1999; this figure rose to 55 percent in 2000 and 61 percent in 2001/02⁸. However, much of this use was inappropriate because 63 percent of this growth occurred in patients who could have taken an older NSAID. In the England, the coxibs accounted for 0.9 percent of all NSAID prescribing by GPs in 1999⁹ and for 22 percent in 2003¹⁰.

Was the promise fulfilled?

These findings appeared to confirm that COX-2 selective NSAIDs had solved the thorniest problem of using NSAIDs but this optimism was misplaced. The major

studies were of short duration (when people with arthritis take an NSAID for years) and the long-term safety of the new drugs remained unknown. Serious gastrointestinal events still occurred during treatment with a COX-2 selective agent and risk factors for these events (age, history of ulcer disease, concurrent use of aspirin, antiplatelet agents warfarin and corticosteroids) were the same as for other NSAIDs¹¹. Finally, serious misgivings about the quality of evidence began to emerge.

CLASS was strongly criticised⁵ and data from the US Food and Drug Administration (FDA) suggested that, after 12 - 16 months, there was no difference between celecoxib and the other NSAIDs in the rate of ulcer complications⁶. In VIGOR, rofecoxib was associated with a 4-fold higher incidence of myocardial infarction than naproxen (0.4 vs. 0.1 percent). The FDA concluded: '*... the potential advantage of decreasing the risk of complicated PUB's [peptic ulcer bleeds] was paralleled by the increased risk of developing cardiovascular thrombotic events*' and that '*Despite a substantial risk reduction compared to naproxen in the VIGOR study, the risk of serious GI complications with rofecoxib is still a concern*'¹¹. The incidence of all serious adverse events was in fact slightly higher with rofecoxib than naproxen (9.3 vs. 7.8 percent) and there were 22 deaths among patients taking rofecoxib but 15 among those taking naproxen¹¹.

The fall of the coxibs

Rofecoxib was withdrawn in September 2004 when, in the APPROVe trial, it was associated with a 2-fold increased risk of myocardial infarction and stroke (6 events per 400 pt.yrs vs. 3 per 400 pt.yrs with placebo)¹². This was subsequently confirmed by a meta-analysis of clinical trials¹³. Next, another unpublished placebo-controlled trial linked celecoxib with an increased risk of cardiovascular events (2.3-fold increased risk at 400 mg/day and 3.4-fold increased risk at 800 mg/day)¹⁴. The European Medicines Evaluation Agency (EMA), Europe's drug regulatory body,

then advised that valdecoxib and parecoxib (licensed only for the treatment of pain in the UK) were contraindicated in patients undergoing coronary artery bypass surgery because of an increased risk of serious cardiovascular thromboembolic events^{15,16}. Following a review of the safety of the coxibs by the EMEA, the UK Medicines and Healthcare Products Agency issued advice that the coxibs should not be prescribed for patients with ischaemic heart disease or cerebrovascular disease (formerly they could be prescribed with caution for patients with ischaemic heart disease), or in patients with moderate to severe heart failure; an alternative treatment (an NSAID with gastroprotection if indicated) should be considered for all patients¹⁷.

Some studies have found that the coxibs do not increase cardiovascular risk¹⁸ and the most recent analyses suggest that rofecoxib is associated with a higher risk than celecoxib^{19,20}. But not all safety concerns focused on cardiovascular events. The EMEA has warned that valdecoxib and parecoxib are associated with serious skin reactions¹⁶; and a Canadian analysis showed that the advantage of the lower GI risk associated with rofecoxib and celecoxib was outweighed by their increased use, so that total hospital admissions for GI haemorrhage actually increased after these agents were introduced²¹.

What is the mechanism underlying these effects?

There seems little doubt that the increased cardiovascular risk associated with the coxibs is a class effect, with varying degrees of expression in different drugs within the class. The underlying mechanism is still unclear but it seems likely that selective COX-2 inhibition destabilises the balanced cardiovascular effects of thromboxane A₂ and prostacyclin I₂²².

Prostacyclin I₂ is produced by endothelial cells by COX-2; it inhibits platelet aggregation, causes vasodilatation and (in vitro) prevents vascular cell proliferation.

Thromboxane A₂ is produced by platelets by COX1 has opposing effects, promoting platelet aggregation, vasoconstriction and vascular proliferation. COX-2 selective NSAIDs therefore inhibit production of prostacyclin I₂ without affecting thromboxane A₂ and this results in increased blood pressure and an exaggerated thrombotic response; animal studies also suggest it enhances atherogenesis.

The effect of the coxibs on blood pressure may be a major contributory factor to their cardiovascular risk. This effect has been quantified in a meta-analysis of 19 randomised trials published before May 2004 and involving 45,451 patients²³. The coxibs overall (rofecoxib, celecoxib, etoricoxib) raised blood pressure by 3.85/1.06 mmHg compared with placebo and by 2.83/1.34 mmHg compared with non-selective NSAIDs (naproxen, ibuprofen, diclofenac). The relative risk of hypertension (defined as such in the trials) associated with coxibs was 1.61 (CI_{95%} 0.91 - 2.84) vs. placebo and 1.25 (CI_{95%} 0.87 - 1.78) vs. non-selective NSAIDs. Rofecoxib was also compared with celecoxib and was associated with a greater increase in systolic blood pressure (2.83 mmHg); effects on diastolic pressure were not reported. The relative risk of hypertension (defined as a clinically important increase in blood pressure) of 1.50 (CI_{95%} 1.00 - 2.26) for systolic pressure and 1.55 (CI_{95%} 0.91 - 2.63) for diastolic pressure. Non-selective NSAIDs were not compared with placebo. The authors conclude that these effects on blood pressure may be clinically significant but they note possible confounding due to lack of consistency in blood pressure measurement and heterogeneity of the study populations.

TARGET: lumiracoxib vs. ibuprofen

The TARGET study is the most recent of the large trials of the gastrointestinal safety of the coxibs; gastrointestinal²⁴ and cardiovascular²⁵ outcomes were reported separately although it was not designed to test cardiovascular safety.

TARGET comprised two substudies in which lumiracoxib 400 mg/day (a 2 - 4-fold supratherapeutic dose) was compared with naproxen 500 mg twice daily or ibuprofen 800 mg three times daily over one year in patients with osteoarthritis. Compared with ibuprofen, lumiracoxib was associated with a significantly lower risk of definite or probable upper gastrointestinal ulcers in patients not taking low-dose aspirin (0.15% vs. 0.82%; hazard ratio 0.17, CI_{95%} 0.07 - 0.45) but not in aspirin users (0.51% vs. 0.52%; hazard ratio 0.92, CI_{95%} 0.27 - 3.20); findings were similar for naproxen.

The different risk of GI events between lumiracoxib and ibuprofen is difficult to interpret because, in the naproxen substudy, the incidence of GI events with lumiracoxib among all patients (non-aspirin and aspirin users) was much closer to that reported with ibuprofen (0.40% with lumiracoxib vs. 0.75% with ibuprofen). Among aspirin users GI events were actually more common with lumiracoxib in the naproxen substudy (0.84% vs. 0.52%); among non-aspirin users the difference between the drugs was smaller (0.25% vs. 0.82%). It is unclear why GI event rates with lumiracoxib vary so much in two studies of exactly similar design.

There were no differences in the risk of cardiovascular events but lumiracoxib was associated with a greatly increased risk of a 3-fold increase in transaminases, suggesting possible hepatotoxicity.

What lessons can we learn?

The rise and fall of the coxibs provides a salutary reminder that drug safety cannot be taken for granted. Premarketing clinical trials involve too few patients to provide a reliable estimate of the possible risk of uncommon but serious adverse events - particularly when those events are relatively frequent, as is the case with myocardial infarction²⁶. Only long-term use can provide the necessary clinical experience in large numbers of patients, including groups with comorbidities who are more vulnerable²⁷.

Now is the right time to reappraise the safety and efficacy of the long-established NSAIDs for which there is reliable evidence.

Risk factors are important determinants of the occurrence of adverse effects. A study of ibuprofen and other analgesics in 5692 patients with rheumatoid arthritis and 3124 patients with osteoarthritis (OA) concluded that intermittent use of analgesic doses carried little risk in patients without risk factors: serious problems were largely confined to those also taking other NSAIDs and corticosteroids, in whom the risk of GI events increased by a factor of 2 - 6²⁸.

Summary

The promise of the COX-selective NSAIDs led to widespread and often inappropriate prescribing, exposing patients to the risk of serious adverse effects not recognised during clinical trials. By contrast, the wealth of experience with ibuprofen has established a benefit/risk profile which clearly quantifies both the nature and frequency of adverse effects.

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