



## **Aspirin 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 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 effects<sup>1</sup>. 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 risk<sup>2</sup>. Compared with ibuprofen, these agents were associated with a 1.6 - 4.2-fold increased risk of gastrointestinal bleeding and peptic ulcer perforation<sup>3</sup>.

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 marked<sup>2</sup>.

*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 osteoarthritis<sup>4</sup>. 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) 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 arthritis<sup>7</sup>. 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 2001/02<sup>8</sup>. 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 1999<sup>9</sup> and for 22 percent in 2003<sup>10</sup>.

*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 NSAIDs<sup>11</sup>. Finally, serious misgivings about the quality of evidence began to emerge.

CLASS was strongly criticised<sup>5</sup> 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 complications<sup>6</sup>. 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*'<sup>11</sup>. 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 naproxen<sup>11</sup>.

#### *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)<sup>12</sup>. This was subsequently confirmed by a meta-analysis of clinical trials<sup>13</sup>. Next, another unpublished 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)<sup>14</sup>. 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<sup>15,16</sup>. Following a review of the safety of the coxibs by the EMA, 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 patients<sup>17</sup>.

Some studies have found that the coxibs do not increase cardiovascular risk<sup>18</sup> and the most recent analyses suggest that rofecoxib is associated with a higher risk than celecoxib<sup>19,20</sup>. But not all safety concerns focused on cardiovascular events. The EMA has warned that valdecoxib and parecoxib are associated with serious skin reactions<sup>16</sup>; 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 introduced<sup>21</sup>.

*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 A<sub>2</sub> and prostacyclin I<sub>2</sub><sup>22</sup>.

Prostacyclin  $I_2$  is produced by endothelial cells by COX-2; it inhibits platelet aggregation, causes vasodilatation and (in vitro) prevents vascular cell proliferation. Thromboxane  $A_2$  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  $I_2$  without affecting thromboxane  $A_2$  and this results in increased blood pressure and an exaggerated thrombotic response; animal studies also suggest it enhances atherogenesis.

#### *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 infarction<sup>23</sup>. Only long-term use can provide the necessary clinical experience in large numbers of patients, including groups with comorbidities who are more vulnerable<sup>24</sup>. Now is the right time to reappraise the safety and efficacy of the long-established NSAIDs for which there is reliable evidence.

#### *Re-evaluating aspirin*

Aspirin has been in widespread use as an analgesic and anti-inflammatory agent for over 100 years and it is now widely prescribed and bought over the counter (OTC) for self-treatment; in recent years, low-dose aspirin has become the drug of choice for primary and secondary prevention of cardiovascular events. Nevertheless, misconceptions persist about the GI tolerability of aspirin which are particularly inappropriate to these roles.

Risk factors are important determinants of the occurrence of adverse effects. A study of aspirin 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 - 6<sup>25</sup>.

There is also strong evidence that aspirin is well tolerated when taken at analgesic doses consistent with OTC use. For example, an observational study of OTC NSAIDs in Italy concluded that the prevalence of GI symptoms associated with aspirin, paracetamol, ibuprofen, ketoprofen, diclofenac and piroxicam was similar<sup>26</sup>. In the treatment of migraine and tension-type headache, single doses of aspirin 500 - 1000 mg are associated with transient, mild to moderate adverse effects with frequency comparable to other treatments or placebo<sup>27-30</sup>. A Cochrane review of 72 randomised trials of single-dose aspirin concluded that aspirin is an effective analgesic for pain of mild to moderate severity; drowsiness (affecting 1 in 28 users) and gastric irritation (affecting 1 in 38 users) were the main adverse effects<sup>31</sup>.

The balance of risk and benefit strongly favours the use of low-dose aspirin as primary prevention of myocardial infarction. A meta-analysis of clinical trials concluded that, for every 1000 patients with a 5 percent risk of coronary heart disease events who were treated with low-dose aspirin for 5 years, 6 - 20 myocardial infarctions would be avoided at a cost of up to 2 haemorrhagic strokes and 2 - 4 major gastrointestinal bleeding episodes<sup>32</sup>. In the UK, low-dose aspirin is recommended as primary prevention in people whose risk of developing coronary heart disease over 10-year is 15 percent or greater and as secondary prevention of thrombotic cardiovascular or cerebrovascular disease for all at-risk individuals<sup>33</sup>, in whom low-dose aspirin reduces the risk of vascular events by 32 percent<sup>34</sup>.

### *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 aspirin has established a benefit/risk profile which clearly quantifies both the nature and frequency of adverse effects.

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Created: Feb 2005