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FOR DEBATE...

Older people should NOT be prescribed 'coxibs' in place of conventional NSAIDs

An historical perspective

Following the demonstration of the value of anti-inflammatory therapy in diseases like rheumatoid arthritis [1], most major pharmaceutical companies began to develop an NSAID of their own. Between the 1970s and 1990s many different products that inhibit the enzyme cyclooxygenase (COX), crucial to the formation of prostaglandins, were licensed; in the UK we can now prescribe some 30 different 'conventional' NSAIDs. These agents are clearly valuable in inflammatory diseases. However, as their numbers have grown so has their market, and they are now used extensively in painful, non-inflammatory conditions, such as osteoarthritis, headaches and dysmenorrhoea. As their usage increased, so did concerns about their safety. Early work was concerned with cardiovascular, renal and gastrointestinal safety [2], as the prostaglandin system was known to affect each of these systems, but more recently the major emphasis has been on the gastrointestinal [GI] tract alone. It became clear that 'conventional NSAIDs' confer a large increase in the risk of serious GI events, particularly in older people [3].

Then in the early 1990s it was found that there were two isoforms of COX that showed distinct patterns of expression, COX-1 and COX-2 [4]. COX-1 was found to be expressed constitutively in most tissues, including gastroduodenal mucosa, kidneys and platelets. In contrast, COX-2 expression was induced by inflammation, especially in macrophages and synovial cells [5]. It was suggested that the anti-inflammatory properties of NSAIDs were related to a COX-2 inhibition, whereas their adverse effects occurred because of a COX-1 inhibition. A drug that selectively inhibited COX-2, rather than COX-1, might therefore not result in GI side-effects. Understandably, this led to a second massive era of pharmaceutical development, which has resulted in the current introduction of a group of new, COX-2 selective NSAIDs – the 'coxibs'. The most important of such agents to be licensed – celecoxib and rofecoxib – were launched with massive advertising campaigns and what we believe to have been inappropriately aggressive marketing. They quickly cut into the huge NSAID market, as well as further expanding it. The marketing strategy was based on the contention that these agents had as much efficacy as a conventional NSAID, but had as little GI toxicity as a placebo. The claims were supported by the publication of the results of large trials in reputable journals [6, 7].

In our view, the pharmaceutical industry, presumably driven by the massive market for NSAIDs (they are now worth over US$30 billion/annum), have made several important mistakes during the development of the coxibs, these include:

i. Aggressively marketing all NSAIDs for non-inflammatory conditions in the absence of convincing data that they are any better than simple analgesics for such disorders [8].
ii. Concentrating on GI toxicity, whilst ignoring potential problems with the cardiovascular, renal and other systems affected by prostaglandins.
iii. Excluding older people and those at high risk of side-effects from the majority of trials, i.e. the practice of protectionism rather than inclusivity.
iv. In at least one case, and possibly more, publishing data from trials that include analyses that are different from those specified in the protocol, and widely disseminating the resulting, misleading information [9].

Two pivotal trials – CLASS and VIGOR

In September 2000, an article on the Celecoxib Long-term Arthritis Safety Study (CLASS) was published [6]. It was funded by celecoxib's manufacturer Pharmacia and was described as a double-blind randomised controlled three-arm trial, comparing celecoxib (400 mg twice daily) with two traditional NSAIDs, ibuprofen (800 mg three times daily) and diclofenac (75 mg twice daily) in 8,059 patients with osteoarthritis or rheumatoid arthritis [6]. The main outcome measures were reported to be clinically relevant upper GI ulcer complications (bleeding, perforation, or obstruction) and symptomatic ulcers during the first 6 months of treatment. Comparing celecoxib with the pooled NSAIDs, the annualised rates of ulcer complications alone and combined with symptomatic ulcers were 0.76% *versus* 1.45% ($P = 0.09$), and 2.08% *versus* 3.54% ($P = 0.02$) per annum, respectively, and it was concluded that 'celecoxib […] was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, as well as other clinically important toxic effects, compared with NSAIDs […]' [6].

Eleven months later, an article in the *Washington Post* [10] indicated that complete information on the trial available on the US Food and Drug Administration (FDA) Web site (http://www.fda.gov) contradicted these conclusions. The original article by Silverstein and colleagues describing CLASS [6] referred to the combined analysis of the results of the first 6 months of two separate trials of longer duration. Table 1 shows that CLASS as it was published differed from the original protocol in many important aspects, including design, outcomes, duration of follow-up and analysis. Two

Table 1. Differences between the published results and the protocol of the 'CLASS' study

	Published	According to protocol
Design	One randomised double-blind three arm trial	Two randomised double-blind two arm trials
Main outcome measures	Upper gastrointestinal ulcer complications (one single definition) alone and combined with symptomatic ulcers	Upper gastrointestinal ulcer complications (two different definitions)
Duration of follow-up	Up to 6 months	Up to 12 and 15 months
Statistical analysis	One-step procedure for both outcomes: celecoxib versus NSAIDs	Two-step procedure for both definitions. First, comparing celecoxib with NSAIDs. Secondly, if this comparison statistically significant, then: celecoxib versus ibuprofen – celecoxib versus diclofenac

primary treatment comparisons were specified originally in the protocol: celecoxib *versus* ibuprofen and celecoxib *versus* diclofenac. The FDA was concerned that selective COX-2 inhibitors could interfere with the benefits of COX-2 in ulcer healing [11]. This could lead to a long-term increase of ulcer related complications that occur without warning symptoms [12]. Therefore the pre-specified primary outcome was ulcer complications, not symptomatic ulcers, in both trials, while the maximum duration of follow-up was 15 and 12 months, respectively. When analysed according to the procedures pre-specified in the protocol, no significant differences remained between the comparison groups. Almost all of the ulcer complications that had occurred during the second half of the trials were in users of celecoxib at a generally steady rate through the end, and similar numbers of ulcer complications were observed after 12 months in the three comparison groups: relative risk [RR] for celexoxib *versus* diclofenac 1.10, 95% confidence interval [CI] = 0.47–2.58; RR for celecoxib *versus* ibuprofen 0.54, 95% CI = 0.20–1.47 (top of Figure 1). When the alternate definition was used to address more serious bleeding, a non-significant trend was found even in favour of the diclofenac group (RR for celexoxib versus diclofenac 2.00, 95% CI = 0.68–5.84) [13]. Indicating that there is no evidence to support the notion that celecoxib is superior to diclofenac, and insufficient evidence favouring celecoxib over ibuprofen, these results clearly contradicted the conclusions drawn in the published article. They were available when the manuscript was submitted [14], but neither were referred to in the published article, nor reported to the journals' editors.

Two months after the publication of CLASS [6], the Vioxx Gastrointestinal Outcomes Research (VIGOR) was reported. In contrast to CLASS, VIGOR was meticulously reported by Bombardier and colleagues [7]. It was a double-blind randomised controlled two-arm trial in 8,076 patients suffering from rheumatoid arthritis, comparing rofecoxib (50 mg once daily) with naproxen (500 mg twice daily). Confirmed upper gastrointestinal events (gastroduodenal perforation or obstruction, upper gastrointestinal bleeding, and symptomatic gastroduodenal ulcers) were stipulated *a priori* to be the main outcome measure. VIGOR found an unequivocal gastrointestinal benefit of rofecoxib as compared with naproxen [7]. Treatment with rofecoxib was associated with a significantly lower incidence of upper gastrointestinal

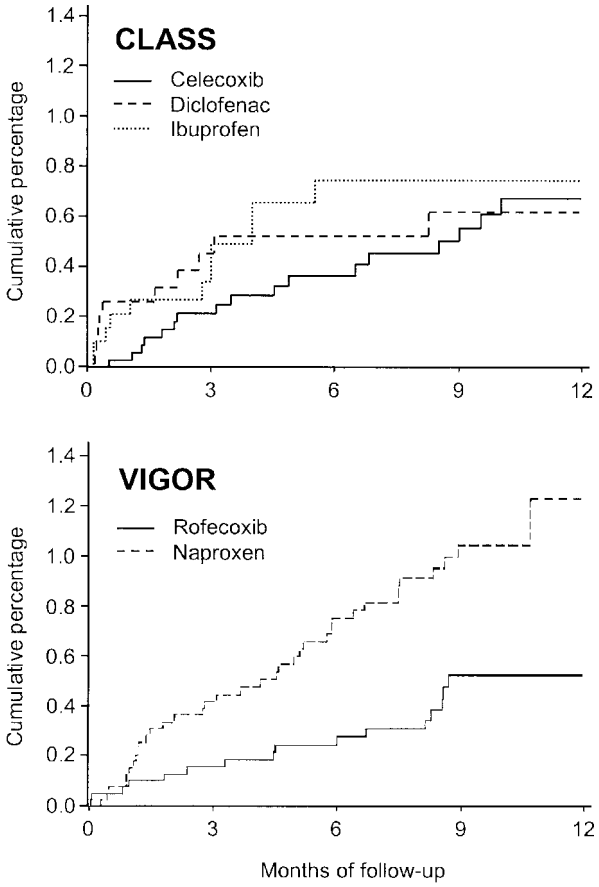

Figure 1. Kaplan-Meier estimates for ulcer complications in the VIGOR and CLASS trials [6, 7]. Results are truncated after 12 months, no ulcer complications occurred after this period. Adapted from Lu 2001 and Li 2001 [25, 26].

events (RR 0.46, 95% CI = 0.33–0.64). The bottom of Figure 1 indicates that ulcer complications were reduced as well (RR 0.43, 95% CI = 0.24–0.78) [15].

COX-2 results in the production of prostacyclin, a vasodilator and inhibitor of platelet aggregation. A selective inhibition of COX-2 might therefore, by suppressing prostacyclin production, inhibit the physiologic inhibition of platelet aggregation, while COX-1 that mediates production

of thromboxane A2, a prostaglandin that promotes vasoconstriction as well as platelet activation and aggregation, remains unaffected. This combination of prostacyclin inhibition and unopposed thromboxane production could lead to an increase in thrombotic cardiovascular events [16]. Based on the observed excess in cardiovascular adverse effects in one of the comparison groups in an interim analysis, VIGOR's safety monitoring board recommended blinded evaluation of cardiovascular events [17]. Forty-five patients in the rofecoxib group and 20 patients in the naproxen group were adjudicated to have serious thrombotic cardiovascular adverse events (see Figure 2) [18], including myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischaemic stroke, and transient ischaemic attacks (RR 2.37, 95% CI = 1.39–4.06) [15]. The increased risk of myocardial infarction was particularly worrying (RR 5.00, 95% CI = 1.72–14.29) and could not be explained by naproxen's cardioprotective potential [19].

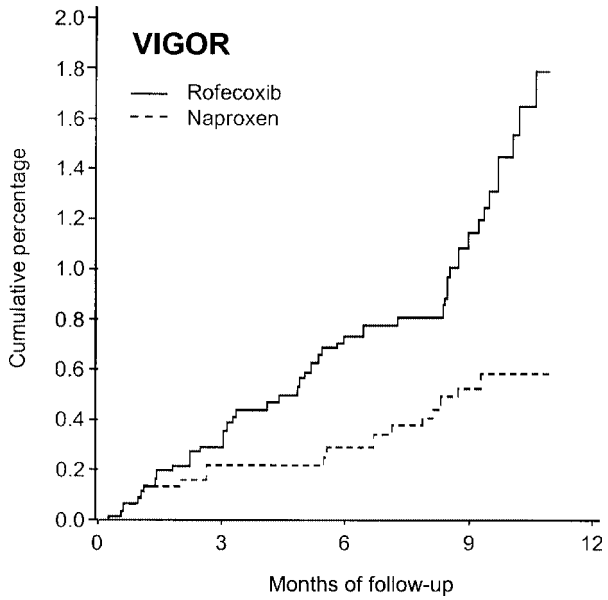

Figure 2. Kaplan-Meier estimates for serious thrombotic cardiovascular adverse events. Adapted from Li 2001 [26].

Celecoxib's manufacturer, Pharmacia, undertook great efforts to demonstrate that celecoxib was not associated with an increased risk for thromboembolic events [20]. In fact, when using the same definitions for serious thrombotic cardiovascular adverse events as in VIGOR, we found no significantly increased risk associated with celecoxib use in CLASS: RR *versus* diclofenac 0.84, 95% CI = 0.48–1.51; RR *versus* ibuprofen 1.08, 95% CI = 0.60–2.04. While confidence intervals for these estimates are wide and results of the second comparison may be partly explained by the detrimental cardiovascular effects of ibuprofen in aspirin users [21], they are hardly surprising, considering that celecoxib has considerable shortcomings as a COX-2 inhibitor with similar COX-2 selectivity as diclofenac. Based on results by Warner *et al.* [22] presented in Figure 3, there is no reason to presume different rates of serious cardiovascular events associated with celecoxib or diclofenac use, nor is there any reason to presume different rates of serious gastrointestinal events.

Figure 4 presents relative risks for serious adverse events overall, i.e. events leading to serious disability, admission to hospital, life threatening event or death observed in the three randomised comparisons from VIGOR and CLASS [6]. For all three comparisons, there were more serious non-gastrointestinal adverse events in groups allocated to coxibs. For rofecoxib, this resulted in a statistically significant increase in serious adverse events overall. For celecoxib, the two comparisons were underpowered; lower confidence limits, however, exclude a clinically relevant reduction in serious adverse events as compared with traditional NSAIDs.

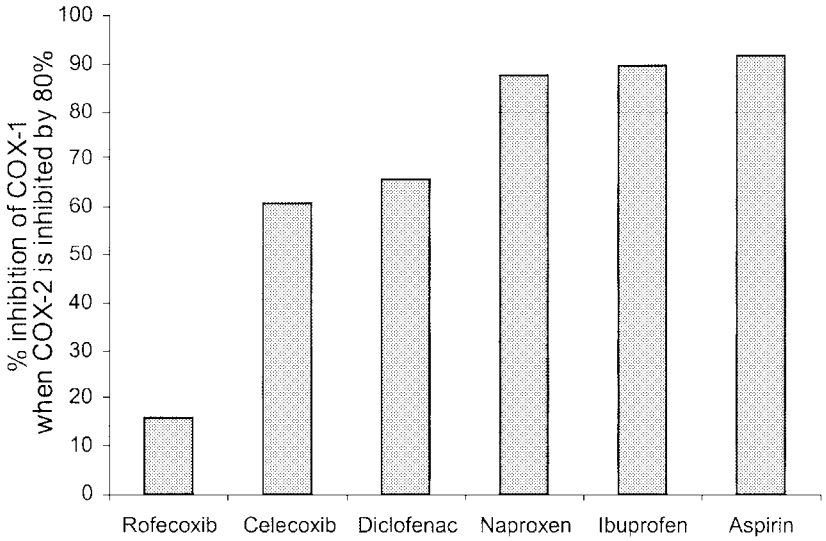

Figure 3. Analysis of the percent inhibition of COX-1 seen when COX-2 is inhibited by 80%. The dotted line indicated equiactivity, i.e. an 80% inhibition of COX-1. Adapted from Warner *et al.*, 1999 [22].

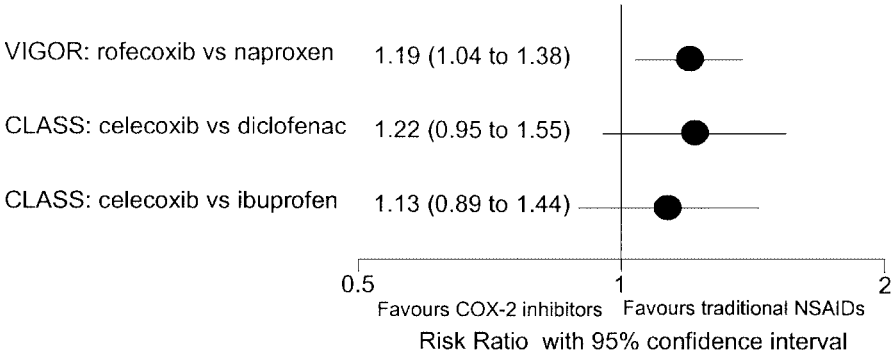

Figure 4. Relative risks and 95% CI for serious adverse events (events leading to serious disability, admission to hospital, life threatening event or death) observed in VIGOR and CLASS [6, 7]. Note that identical event rates had to be assumed in celecoxib groups of both of CLASS trials because separate trial data was unavailable.

Conclusions

When prescribing NSAIDs to older people, toxicity must be a primary concern. We believe that the heavily marketed view that coxibs are safer than conventional NSAIDs is fatally flawed: currently there is no evidence suggesting that celecoxib is safer than conventional NSAIDs for the gastrointestinal tract, while there is considerable evidence that rofecoxib has increased cardiovascular toxicity compared with traditional NSAIDs. Additional concerns include worries about renal toxicity [23, 24] and the relative paucity of older people in most of the trials. Furthermore, many older people with non-inflammatory conditions may do as well or better on simple analgesics as on NSAIDs [8].

Coxibs are relatively new. We still do not know the full extent of their potential for benefit or harm. Since the two trials described above used maximal or even supra-maximal doses of coxibs, a reduction in dosages may lead to an increased long-term safety of either agent. This hypothesis, however, remains to be confirmed in adequately powered long-term trials. For the time being, we guess that the harms of coxibs will outweigh the benefits. Time will tell, but we are not prescribing them, as we do not want our patients to be the ones to be the victims of coxibs if, as we suspect, they incur unnecessary dangers. Our evidence-based advice to others, therefore, is not to use coxibs in place of conventional NSAIDs.

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