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Non-steroidal anti-inflammatory drugs—changes in prescribing may be warranted

Non-steroidal anti-inflammatory drugs (NSAIDs) are among one of the most frequently prescribed classes of drugs. Both their benefits and harms arise due to inhibition of cyclooxygenase (COX) of which there are two isoenzymes, COX 1 and 2. Both COX isoenzymes have a hydrophobic tunnel, through which the substrate accesses the active site. The tunnel is larger in the COX 2 isoenzyme with a side pocket, a property exploited in the development of specific COX 2 inhibitors [1]. The premise of the initial, COX 2 hypothesis was that the gastrointestinal side effects arose due to inhibition of COX 1 whereas their anti-inflammatory or analgesic properties were COX 2 mediated. Although now appreciated to be rather naïve, the superiority of the selective COX 2 inhibitors in preventing gastroduodenal mucosal ulceration over the non-selective NSAIDs is striking [2, 3].

There has been continuing scientific and media attention on reports that selective COX 2 inhibitors increase the risk of cardiovascular events. In an early study of major gastrointestinal events, an unexpected 5-fold increase in the risk of acute myocardial infarction (AMI) with rofecoxib was observed when compared with naproxen [4]. At the time, many suggested and aggressively pursued the hypothesis that the increased frequency of events was a spurious observation not due to any prothrombotic effects of rofecoxib, but the cardioprotective properties of naproxen. However, subsequent placebo-controlled studies of both rofecoxib, and celecoxib in chemoprevention also reported an approximate 2-fold increase in cardiovascular events with both drugs [5, 6].

More recently, attention has turned to the effects of the non-selective NSAIDs. As aspirin confers its cardiovascular benefits by inhibiting COX 1 [7], received wisdom has never considered the possibility that the non-selective NSAIDs could increase the risk of cardiovascular events. However, in February 2005, the Food and Drugs Administration (FDA) decided to advise that the risk of cardiovascular events for both selective COX 2 and non-selective NSAIDs is similar and has taken the step to categorize this as a class effect [8]. In the US, all COX 2 selective and non-selective NSAIDs now carry a black-boxed warning on the package insert advising patients of the potential increased cardiovascular risk [9]. The European Agency for the Evaluation of Medicine Products (EMEA) [10] and the Medicines and Healthcare Products Regulatory Agency (MRHA) [11] have, however, been much more reassuring with regard to non-selective NSAIDs and advised that 'the data are insufficient to warrant changes in current prescribing'.

The association between increased AMI risk and non-selective NSAIDs has been evaluated predominantly in observational studies [12–28]. These were primarily based on data from large population and hospital databases that recorded the prevalence of NSAID use combined with confirmed AMI diagnosis. While most studies also accounted for the presence of other risk factors, confounders and use of aspirin, few recorded the indication and duration of NSAID use [15, 16, 18]. Overall, a general direction of effect has been reported from the observational studies—with the exception of one study [21], which reported no effect between non-selective NSAID use and AMI, all studies showed a similar trend of increased risk of AMI compared with remote and non-use, ranging from relative risk

of 1.00 (95% CI: 0.73–1.37) [21] to 1.47 (95% CI: 1.00–2.16) [22]. Although the size of the overall relative risk appears small, however, due to the large number of patients prescribed NSAIDs, the absolute risk may be considerable. In addition, these studies have presented data that suggested a differential risk between individual NSAID such as diclofenac, naproxen and ibuprofen, but there is insufficient evidence to conclude whether this truly represents a class effect.

The main concern in the context of these studies is whether the small effect observed is a real one or due to unknown or unmeasured confounding factors, a limitation that is inherent to all observational studies. However, such studies may be the only feasible method to determine the potential harms of drugs if the effects are small.

It has been advocated that the only method to resolve the issue would be to undertake a large randomized-control trial of non-selective NSAIDs vs placebo [29]. However, it is unlikely that such trial would ever be funded, and it would be unethical to randomize patients to an intervention that may be potentially harmful.

Kearney *et al.* [30] have undertaken a meta-analysis of data of vascular events from randomized-controlled trials of selective COX 2 inhibitors. They found that in all studies selective COX 2 inhibitors increased the risk of vascular events, mainly AMI by 42% (rate ratio 1.42; 95% CI: 1.13–1.78). Trials that compared a COX 2 inhibitor with a traditional NSAID ($n=91$ trials) showed no significant difference in the risk of vascular events (rate ratio 1.16; 95% CI: 0.97–1.38). There were no significant differences whether all non-selective NSAIDs were considered together, in combination, or alone when compared with COX 2 inhibitors. However, a comparison of non-selective NSAIDs with placebo showed differences between NSAIDs—naproxen was associated with the lowest risk (0.92; 95% CI: 0.67–1.21), but there were insufficient data to show a cardioprotective effect; whereas the rate ratios for ibuprofen and diclofenac were 1.51 (95% CI: 0.96–2.37) and 1.63 (95% CI: 1.12–2.37), respectively. This study thus confirms the findings of the epidemiological studies, but the number of cardiovascular events were small, a limitation acknowledged by the investigators. Furthermore, none of the comparative studies of COX 2 inhibitors with non-selective studies were conducted in patients with high cardiovascular risk or specifically powered to evaluate cardiovascular events.

The MEDAL programme and PRECISION studies are pharmaceutical industry sponsored trials designed to address these concerns. The MEDAL programme consists of three studies (EDGE, EDGE II and MEDAL), and is a non-inferiority comparison of cardiovascular events between etoricoxib and diclofenac [31]. The EDGE studies were originally designed to compare the gastrointestinal tolerability of etoricoxib compared with diclofenac in osteoarthritis and rheumatoid arthritis, whereas the MEDAL study is specifically designed to compare cardiovascular events in 17 804 osteoarthritis and 5700 rheumatoid arthritis patients treated with either etoricoxib or diclofenac. All three studies will continue until the total number of confirmed thrombotic reaches 635 with at least 430 in the MEDAL study. The PRECISION study is a multi-centre comparative study

of celecoxib, diclofenac or ibuprofen coordinated by the Cleveland Clinic which is to report in 4 yrs time [32].

Common to both non-selective NSAIDs and COX 2 inhibitors is the adverse event of hypertension [33, 34]. Most NSAIDs raise blood pressure by approximately 3–5 mmHg [34]. Even such a modest rise will result in a significantly increased frequency of cardiovascular events; a 3 mmHg rise in systolic blood pressure increases the frequency of congestive cardiac failure by 10–20%, increases the risk of stroke up to 20% and angina by 12% [35]. It has also been predicted that a 3 mmHg in blood pressure in rheumatoid arthritis patients in the US will result in an additional 21 390 ischaemic heart disease and stroke events [36]; when extrapolated to the UK rheumatoid arthritis population, this is equivalent to 2058 potentially avoidable fatal events.

The current evidence strongly suggests that the risk for cardiovascular events to be similar for both non-selective NSAIDs and COX 2 inhibitors. The potential size of the problem is substantial. Physicians should reconsider their prescription of non-selective NSAIDs in line with those advocated by the FDA. Any other advice on current prescribing is unwarranted.

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