Non-steroidal anti-inflammatory drugs and cardiovascular risk – a rheumatologist's reply

To the Editor: The cyclo-oxygenase-2 (COX-2) inhibitors and other non-steroidal anti-inflammatory drugs (NSAIDs) have been the subject of scrutiny generated mainly by evidence suggesting that rofecoxib is associated with increased cardiovascular risk. Chin and Commerford[1] have summarised some of the large volume of data; however, a critical review of published work yields interesting insights.

A meta-analysis[2] of the cardiovascular risk associated with the use of rofecoxib yielded a risk ratio (RR) of 2.24 at 1 year, with a confidence interval (CI) of 1.24 - 4.02; a fairly wide range but the lower limit above 1. This can be regarded as convincing for a relative RR. In the Juni *et al*. study[2] of 14 studies involving 21 432 patients, there were 64 events; this represents 0.0029 events per patient year – not an impressive number. The RR for rofecoxib is not demonstrated in many other trials assessing cardiovascular risk with celecoxib and non-selective NSAIDs that generated risk ratios of less than 2.0 with CI intervals having lower limits of less than 1.0 in most cases.[3,4] Publication bias can account for a bias of 1.5, while heterogenicity can also influence the risk ratio. Most studies corrected for heterogenicity, but current correction techniques are not adequate.[5]

Difficulties in the interpretation of low RRs have been acknowledged,[3,4] and McGettigan and Henry[3] state: 'Typically, there is reluctance in pharmaco-epidemiological studies to accept as causal RR estimates much below 2'. A further complicatory factor may be found in the dose of NSAIDs in the randomised controlled trials, where the doses were typically at the upper end of the conventional dosages.[6,7]

A large cohort study examined 74 838 users of various selective and non-selective NSAIDS and found a modest RR of 1.14 for rofecoxib, but could not demonstrate an increased cardiovascular risk for any of the others.[8] Brophy[9] accepts that a cardiovascular risk is associated with the use of rofecoxib. He concludes that studies on celecoxib and other NSAIDs have suggested that any risk with coxibs is likely to be small and comparable to traditional NSAIDs. Combined with the conclusions that celecoxib was not associated with an elevated risk of vascular occlusion,[3] one can readily conclude that these drugs are not associated with an increased risk of cardiovascular disease. Gislason *et al*.[10] found that the numbers treated to cause an additional death was alarmingly low for the preparations examined; however, we are not informed as to the causes of death, and a causal effect is assumed. They also assumed that the patients consumed the preparations purchased. Interestingly, an odds ratio for low-dose ibuprofen and diclofenac of 0.57 and 0.86 respectively was documented. Can we assume that low doses of these preparations had a (mildly) protective effect?

The Nurses Health Study[11] found that the highest mortality occurred among the older cohort, where risk factors were greatest for musculoskeletal pathology and cardiovascular risks. The RR for NSAIDs among non-smokers was 1.11, compared with 1.82 among smokers. The latter figure could explain the modestly raised overall RR. In this study, the RR for paracetamol was 1.30, which in pharmaco-epidemiological terms carries little significance.[3] Cynically, one could comment that one can find evidence for almost any point of view except for the consistent finding that rofecoxib carries a small increase in cardiovascular risk. The argument that there are sound physiological reasons for assuming that non-steroidals could be associated with cardiovascular events is important. However, perhaps we should remember the oestrogen saga.

Another aspect is the importance of these drugs in pain relief. NSAIDs have been demonstrated to be more effective than analgesics for pain relief in osteoarthritis[12] and are critical in the treatment of inflammatory back pain.[13] I agree that over-the-counter sale of these drugs should be discouraged, but a backlash against them could result in patients being denied pain relief.

David Sackett stated: 'Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient'.[14] Chin and Commerford have done us a service by raising this issue, but I would argue that there is sufficient evidence to choose what one wants to believe. This discussion has just begun.

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