Pain Killers – Bane or Boon? (NSAIDs or COXIBs)

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Relief of pain and inflammation is one of the major advances of pharmacology and the last five decades saw predominantly gastrointestinal side effects due to NSAIDs. Therefore pharmacology modified NSAIDs to make them super selective and discovered newer indications. In the zest and zeal of this selective Cox-2 inhibitors-COXIBs were developed. However, Cox-2 inhibitors increase risk of coronary heart disease & myocardial infarction and even metabolic syndrome & diabetes. They can lead to metabolic abnormalities like hyperkalaemia also. Since last year COXIBs came under pharmacovigilance but now new data is emerging which puts the whole category of NSAIDs under scrutiny. At high doses, both NSAIDs and COX-2 inhibitors (COXIBs) modestly increase the risk of heart attacks in patients with arthritis, suggesting that they should be used on the basis of their relative gastrointestinal and cardiovascular safety profiles rather than the selectivity of their class.

Selective and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of a first MI, results of an observational study suggest.1 Diclofenac and ibuprofen now both pose about as much risk as the COX-2 inhibitor rofecoxib.1 Rofecoxib (Vioxx) was withdrawn from the pharmaceutical market at the end of September 2004 after use of the drug was linked to adverse cardiac effects. Since then, however, questions remain, such as whether all NSAIDs share these harmful effects.

Drs. Julia Hippisley-Cox and Carol Coupland, from the University of Nottingham, UK, conducted a population-based nested case-control study using the QRESEARCH database of information from UK general practices recently reported in British Medical Journal.2 In their study included 9,218 cases of a first MI in people between the ages of 25 and 100 during study period from 2000 to 2004, and 86,349 controls matched by age, calendar time, gender and practice.2 The authors identified all prescriptions for NSAIDs for each case and control in the 3 years before their index date (specifically celecoxib, rofecoxib, ibuprofen, diclofenac, naproxen, other selective NSAIDs and other nonselective NSAIDs). Their multivariate analyses adjusted for comorbidities, medications, and other confounders. The adjusted odds ratio (OR) for rofecoxib use within the 3 months before an MI was 1.32; for ibuprofen it was 1.24 and for diclofenac it was 1.55 (p < 0.01). The authors observed a tendency to increased risks with use of other selective NSAIDs (OR = 1.27), naproxen (OR = 1.27) and other nonselective NSAIDs (OR = 1.21), though these did not reach the 0.01 significance level.2 Hippisley-Cox and Coupland estimate the number-needed-to-harm for patients age 65 years and over were 521 for diclofenac, 1,005 for ibuprofen and 695 for rofecoxib.2 They feel that given the high prevalence of the use of these drugs in elderly people and the increased risk of myocardial infarction with age, even the relatively large number of patients needed to harm could have considerable implications for public health. They conclude that enough concerns exist to warrant a reconsideration of the cardiovascular safety of all NSAIDs.2 In an accompanying editorial, Juni et al urge that these data be “interpreted with caution,” given that they are observational and other trials have yielded discrepant results.3 What is called for now, they contend, are complete meta-analyses, which should “help decision-making about issues such as the need for additional trials ... to establish the best and safest treatment for patients with musculoskeletal pain.”3

Singh et al from Stanford University School of Medicine, California, looked at the risk of acute myocardial infarction in 650,590 patients over 18 years old diagnosed with arthritis and treated with NSAIDs or selective COX-2 inhibitors between January 1999 and June 2004. His group found that many, but not all, of the NSAIDs increased the probability of heart attacks: indomethacin by 71%, sulindac by 41%, and ibuprofen by 11%. Among the COXIBs, rofecoxib increased the risk by 32% and celecoxib by 9%. As a class, non-coxib NSAIDs increased the risk of acute myocardial infarction by 12%, while rofecoxib was the only COX-2 inhibitor having a significantly increased risk of heart attacks compared to non-COXIBs (OR 1.18). The risk of heart attack appeared to be dose-dependent. For instance, rofecoxib increased the risk from 16% at daily doses of 12.5 mg to 240% at daily doses over 50 mg. “Doctors need to consider individual patient risks and concerns related to the cardiovascular system, and other areas where NSAIDs are known to have an impact, especially.
the stomach, liver and kidneys, and they need to be vigilant about which patients they prescribe each type of drug to,” Dr. Singh told participants at a recent annual European Congress of Rheumatology, where the findings were presented. These findings demonstrated we should now consider that cardiovascular risk is an inherent risk of most anti-inflammatory drugs, independently of being an NSAID or a selective COX-2 inhibitor.¹

On December 17, 2004, Pfizer and the US National Cancer Institute announced that they have stopped administering Celecoxib (celebrex), a cyclooxygenase-2 (COX-2) inhibitor, in an ongoing clinical trial investigating its use to prevent colon polyps because of an increased risk of cardiovascular events. In Canada, celecoxib has been approved in the treatment of rheumatoid arthritis, osteoarthritis and familial adenomatous polyposis.⁴ The risk of myocardial infarction and cerebrovascular accident has been found to be increased in patients taking 400–800 mg/day of celecoxib, but not in patients taking lower doses. The future use and availability of the drug is uncertain.⁵ Detailed study results have not been released. Given that two of the COX-2 inhibitors have shown adverse cardiovascular events, will others eventually reveal the same problems? Some physicians have recommended against prescribing another COX-2 inhibitor, valdecoxib (Bextra), until “there are better safety data.”⁶ It is known that valdecoxib can cause serious skin side effects, and it increases the risk of heart attack 3-fold in patients after coronary-artery bypass grafting.⁶

COX-2 inhibitors, which were originally studied on a theoretical basis for possible beneficial effects in cancer prevention, prompted other research directed at their antiinflammatory effects in joints without causing the gastrointestinal bleeding associated with nonselective NSAIDs.⁷ The indication for COX-2 inhibitors is very narrow: short-term pain control in elderly patients at high risk of gastrointestinal bleeding in whom NSAIDs might be relatively contraindicated. However, they soon became widely and indiscriminately used in place of NSAIDs even though preliminary trial evidence with rofecoxib showed excess, although not statistically significant, cardiovascular and neurovascular events compared with nonselective NSAIDs. In this issue Das UN has elegantly discussed how COX-2 inhibitors increase cardiovascular and stroke risk by interfering with the formation of eNO, PGI₂, LXs, and resolvins and implies that combining Essential Fatty Acids with COX-2 inhibitors could prevent these complications.⁸ He offers an attractive solution of Essential Fatty Acid co-prescription with pain killer to maintain optimal cardiovascular health. This will need validation through clinical trials.

REFERENCES