Cox 2 Inhibitors and the Risk of Cardiovascular Thrombotic Events

Abstract:

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In 1971, Vane 1 showed that the analgesic action of traditional NSAIDs relies on inhibition of the cyclo-oxygenase (COX) enzyme, which in turn results in the production of pro-inflammatory and pro-thrombotic eicosanoids. Two decades later COX was shown to exist as two distinct isoforms: COX-1, which supports the beneficial homeostatic functions whereas the inducible COX-2 becomes up-regulated by inflammatory mediators. COX-2 is involved in the pathophysiology of inflammatory diseases such as rheumatoid and osteoarthritis. Despite the benefits of NSAIDs for acute and chronic pain one of the most clinically significant and well characterized adverse effect is GI mucosa. The search for NSAIDs with a reduced capacity to produce the selective cyclo-oxygenase-2 (COX-2) inhibitor has resulted in the development of COX-2 selective inhibitors (Coxiels). Ibuprofen (COX-1 sparing) inhibitors are associated with reduced GI mucosal damage as demonstrated in several trials. In light of the overwhelming and substantial amount of evidence regarding the safety of COX-2 agents this article will summarize the available evidence regarding cardiovascular (CV) safety data and contemporary recommendations for prescribing of COX-2 selective NSAIDs.

The Controversy

The first suggestion that COX-2 selective NSAIDs might increase cardiovascular risk arose from the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial 10. This randomized controlled trial (RCT) included 8076 patients with RA who were randomized to two groups (rofecoxib 50 mg daily or naproxen 500 mg twice a day) to examine if rofecoxib provided more effective pain relief for patients with RA. The relative risk of developing cardiovascular events in the rofecoxib group compared with the naproxen group was 2.38. An increased risk of cardiovascular events associated with rofecoxib was also shown by Adenomatous Polyposis Prevention on Vioxx (APPROVe) study in which the risk of cardiovascular events was 1.92 times higher in patients taking rofecoxib after 18 months of treatment. These data led to the withdrawal of rofecoxib from the world market in September 2004 and since then controversies have reemerged on cardiovascular safety not only of rofecoxib but the COX-2 class of drugs in general. Questions began to be asked about the validity and probity of study data not only pertaining to CV safety but also to benefit as a direct result the structure and survival of clinical trials has changed and their interpretation has been questioned. But with time the dust has settled and further major study data are now available for us to make evidence based judgements upon these controversies.

The Evidence

The data sets available on CV risk include randomized-controlled trials such as the VIGOR, CLASS, TARGET, ADAPT and MEDAL studies and experimental use of COX-2s in placebo-controlled trials such as APPROVe, APC and PreSAP and finally population-based observational studies. Contradicting the VIGOR and APPROVe data are the Arthritis Study (CLASS) 15, the Prevention of Spontaneous Adenomatous Polyposis (PreSAP) study and the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) did not show an increased risk for CV events in patients taking cetoibex. The reasons for the difference in the results from VIGOR and CLASS are not entirely clear but a number of factors argue strongly that the 706 people randomized to rofecoxib who did not have cardiovascular events in the above data the potential difference in COX-2 specificity both stimuli induce similar selective suppression of systemic prostacyclin without a concomitant inhibition of platelet aggregation. The total number of major cardiovascular events in VIGOR was small and in addition, there were several important differences in study design that may account for the disparate findings including selection of comparator NSAIDs, patient populations and concomitant cardiovascular events. The NSAID comparator was naproxen in VIGOR and diclofenac and ibuprofen in CLASS and neither study included a placebo arm. Although all traditional NSAIDs inhibit COX-1 different NSAIDs have different selectivity and thus varying potential for cardioprotection. Evidence suggests that the antiprotein effects of naproxen are significant and comparable to those of aspirin while they are smaller or non-existent for ibuprofen and diclofenac. Indeed unlike other NSAID's ibuprofen blocks the binding of aspirin to platelets negating its inhibition of cardiovascular events. This inhibition of platelet activation by ibuprofen may be particularly relevant in the absence of low-dose aspirin and in patients at higher risk for adverse cardiovascular events.

A relatively high percentage of patients (21%) in the CLASS trial were receiving therapy with cardioprotective doses of aspirin use of aspirin was one of the exclusion criteria. A retrospective analysis of the VIGOR study examined the rates of cardiovascular events among patients with risk factors associated with recommendations for prophylactic use of low-dose aspirin (history of stroke, MI, unstable angina, angina pectoris, or surgical or percutaneous coronary revascularization). A total of 321 patients were identified in this group representing 4% of the total study population. Almost half of the total MIs (47%) occurred in this group of patients. On completion of the study in 2006 the data demonstrated no significant difference in rates of acute MI, sudden cardiac death, stroke, or other forms of thrombosis between the treatment groups. The MEDAL study did provide the answer to one of the most controversial issues regarding COX-2 inhibitors. The COX-2 selective inhibitor celecoxib was associated with increased cardiovascular morbidity and mortality among patients with RA compared with the general population or with OA patients.

Cunnington et al 11 looked retrospectively at 16.580 subjects chronically exposed to celecoxib, 9800 to rofecoxib, 2907 to naproxen and 51.593 who were non-exposed chronically exposed controls. With a median follow up of 506 days there were 2116 ischaemic heart disease events. The strongest predictors of MI were factors of ischaemic stroke (HR 2.34, 2.12-2.59) and age 65+ years (HR 2.28, 2.07-2.52). Celecoxib and naproxen were not associated with increased risks. Whereas the post hoc subgroup analyses of the (APC) trial showed an increase in cardiovascular events in patients taking celecoxib there was no difference in the risk of a composite cardiovascular event when patients were stratified by age, sex, baseline cardiovascular risk factors, diabetes, aspirin use or lipid lowering agent use. The MEDAL study was designed to compare the thrombotic CV events between etoricoxib versus diclofenac. A total of 17,804 patients with OA and 5700 patients with RA were enrolled and randomized to receive etoricoxib (90 or 90 mg once daily in OA, 90 mg once daily in RA) or diclofenac 75 mg twice daily. Upon completion of the study in 2006 the data demonstrated no significant difference in rates of acute MI, sudden cardiac death, stroke, or other forms of thrombosis between the treatment groups. The MEDAL study did provide the answer to one of the most controversial issues regarding COX-2 inhibitors. The COX-2 selective inhibitor celecoxib was associated with increased cardiovascular morbidity and mortality among patients with RA compared with the general population or with OA patients.

In patients at extremely high risk for CV events, specifically those treated almost immediately after coronary artery bypass graft surgery, studies (CABG1 & CABG2) with paracoxib, an IV form of valdecoxib, revealed that a high dose was associated with an increased risk for myocardial infarction, stroke, and sudden death. One study published in Circulation (May 2009) found that in patients recently hospitalized for serious coronary heart disease taking naproxen had better cardiovascular safety than diclofenac or ibuprofen or high doses of celecoxib and rofecoxib suggesting once again that as with the NS- NSAIDs, there are differences in the pharmacologic actions of the selective COX-2 inhibitors and comparing efficacy to traditional NSAIDs is not a valid approach.

Most recently (June 2010) Foblot et al 18 published a review of data from a nationwide Danish health register from 1997 to 2004 for the risk of cardiovascular events and found that naproxen was not associated with increased CV risk (odds ratio for cardiovascular death 0.84) and ibuprofen and interestingly diclofenac were (OR 1.62 and 1.91 respectively) with a dose dependent increase in risk. Ibuprofen was found to be a risk factor for death and incidence of stroke (OR 1.29). Weighing the above evidence it appears that as with the NS- NSAIDs, there are differences in the pharmacologic actions of the selective COX-2 inhibitors and that the CV effects in response to these agents. In terms of efficacy COX-2 selective inhibitors are comparable to NS-NSAIDs in several chronic and acute situations but have lower GI toxicity. All NSAIDs, both NS-NSAIDs and COX-2 agents, should be used with caution in patients with cardiovascular risk factors in the lowest effective dosing and for the shortest period of time. Naproxen appears safer from a CV perspective than other NSAIDs, both traditional and COX-2 selective inhibitors have shown increased cardiovascular morbidity and mortality among patients with RA compared with the general population or with OA patients.

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References

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