Coxibs controversy

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Introduction

The sudden worldwide withdrawal of Vioxx (rofecoxib) on 30 September last year was an unprecedented move by a pharmaceutical company. A clinical trial comparing rofecoxib to placebo was halted prematurely as evidence of an increased risk of cardiovascular toxicity emerged. Faced with the certain prospect of litigation, Merck, Sharp and Dohme (MSD) made a commercial decision that led to the loss of an important medication that many patients have found irreplaceable.

Further, the move heightened concern about other members of the same group. The Coxibs (Cyclo-oxygenase-2 inhibitors) had been developed as alternatives to non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs), in response to the observed increase in gastrointestinal toxicity of the latter. The decision to withdraw Vioxx from the market came as a consequence of an interim report by the data monitoring committee of a trial comparing rofecoxib 25mg to placebo in the prophylaxis of spontaneous adenomatous polyposis. The early response by regulatory authorities (including New Zealand's Medical Adverse Reactions Committee) forecasting a complete removal of Coxibs from the market was less than helpful, and the publicity that arose as a consequence placed the Coxibs as a group in dark shadow. It was assumed that nsNSAIDs were innocent of any association with increased cardiovascular risk, but it soon became apparent that Coxibs were being asked questions about cardiovascular safety that nsNSAIDs never had to answer. When observational studies did address these questions across both groups, some interesting answers emerged. These answers are the subject of this discussion.

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Why Coxibs?

Aspirin (or acetylsalicylic acid) was developed in the late 1800s and marketed in tablet form in 1899. It is the prototypical nsNSAID. The term 'non-steroidal anti-inflammatory drug' results from comparative studies in the 1950s between aspirin and cortisone, at a time when cortisone was thought (erroneously as it turns out) to have solely anti-inflammatory properties. The side effects of cortisone prompted a search for medications that would have the same anti-inflammatory effect, but were not based on steroids. Indomethacin was the first such nsNSAID, becoming available in 1963 followed in 1969 by ibuprofen. These agents, and the numerous others that followed them, have been in use for many years without any question being raised over their cardiovascular toxicity.

Concern has been raised however as to their gastrointestinal toxicity. Numerous epidemiological studies have confirmed an association between the use of nsNSAID and gastrointestinal complications including indigestion or, more seriously, gastrointestinal bleeding, perforation or obstruction. Three major trials[1,2,3] have documented clinically significant reductions in both relative and absolute risk of these events when using Coxibs in contrast to nsNSAID. The same epidemiological data that suggested the increase in gastrointestinal toxicity also raised some interesting observations including a reduction in bowel cancer for patients taking aspirin or nsNSAID on a regular basis, and a reduction in other tumours as well. There also seemed to be a reduced incidence of Alzheimer's disease, but there was no significant suggestion of increased cardiovascular risk.

In the early 1990s the recognition of two isoforms of the important cyclo-oxygenase enzyme raised the possibility that the Holy Grail of inhibiting inflammatory prostaglandins whilst maintaining normal levels of homeostatic prostaglandins could be achieved if the cyclo-oxygenase-2 ('inducible') enzyme could be inhibited without blocking cyclo-oxygenase-1 ('constitutive'). The first

two trials to report success in terms of efficacy and reduction of GI side effects were reported in 2000.[1,2] It was within the body of the first paper (the VIGOR Trial) that some asymmetry of cardiovascular morbidity was noted. In this trial of over 8000 patients, comparing rofecoxib with naproxen, a rate of myocardial infarction of 0.4% was noted in the rofecoxib group compared with 0.1% in the Naproxen group. Initially, this disparity was ascribed to one of three reasons. Firstly, some patients that entered the trial were at increased cardiovascular risk and should have been on low dose aspirin. This group was disproportionately represented in the rofecoxib arm of the trial. Secondly, a proposition was put that naproxen may of itself have a cardioprotective role; and finally, because of the low numbers involved, it was considered reasonable that this might merely have been a consequence of chance. No such asymmetry of cardiovascular morbidity was noted in either the CLASS[2] or the TARGET[3] trials. The TARGET trial in particular was reassuring in that this was a trial of 18 000 patients over a 12-month period in which cardiovascular events were identified as a specific end point. The study drug was lumaricoxib, and the comparators were again naproxen and ibuprofen.

Coxibs and the prophylaxis of spontaneous adenomatous polyposis

The epidemiological observation of reduced bowel cancer in patients treated with long-term aspirin or non-steroidal anti-inflammatory drugs had led to some physiological investigations suggesting that this was a function of the suppression of cyclo-oxygenase-2 activity in bowel mucosa. Three trials investigating the use of rofecoxib and celecoxib in the reduction of bowel adenomas were drawing to an end in 2004. Each had enrolled more than 2000 patients and divided them into an active and placebo arm. The data monitoring committee of the APPROVe Trial drew the attention of the sponsoring company (MSD) to a statistically significant increase in cardiac events occurring in the rofecoxib arm when compared with placebo.[4] A hazard ratio of 2.8, achieving statistical significance was sufficient to prompt MSD to withdraw Vioxx from the market. Soon thereafter the APC Trial showed a similar increase in hazard ratio with the use of celecoxib.[5] Although interim data from two other trials (one in colorectal adenoma prevention, the other in Alzheimer's disease) failed to show any increase in risk of celecoxib, the wide publicity that accompanied the publication of the above trials and the decision by MSD to withdraw Vioxx led to the assumption that this was a class effect of the Coxibs in general.

However, and importantly, Coxibs have not been the only agents trialled in the prevention of bowel adenomas. In a trial involving a somewhat smaller number of patients, aspirin in two doses (81mg and 325mg daily) had been compared to placebo in a trial published in 2003.[6] Although the numbers were insufficient to achieve statistical significance, the adverse events profile in this trial documented a crude rate of untoward cardiovascular events of 2.9 in the aspirin group compared with 1.1 in the placebo group. Thus, both aspirin and Coxibs increase the risk of cardiovascular events in patients at risk of colorectal adenomas. This observation raises some important questions that have yet to be answered, but it also clearly identifies that Coxibs are no different from aspirin, and logically nsNSAIDs in compounding cardiovascular risk in this patient group.[7]

Observational studies

In August of 2004, at the Annual Meeting of the International Society for Pharmaceutical Engineering held in Bordeaux, France, Dr David Graham from the FDA Office of Drug Safety presented data from an observational study drawn from the Kaiser Permanente data base. This study was subsequently published in modified form in *The Lancet*.[8] It is a retrospective cohort study comparing patients with remote (>6 months prior) use of either Coxibs or nsNSAIDs with present use. The study was prompted by the assertion that naproxen had a cardio-protective effect and covered more than two million patient years of exposure. What the study did show was that in comparison to remote use, recent use of either Coxibs or nsNSAIDs was associated with a statistically increased hazard ratio of 1.11. Sub group analysis also showed that naproxen was associated with such an increased risk with a hazard ratio of 1.14, but most emphasis was placed on the hazard ratio of 3.00 that was found with rofecoxib >25mg a day. However, this hazard ratio was based on an absolute number of events of 10 in the actively treated group, and eight in controls. Projecting this hazard ratio onto the prescription numbers over the same period for Vioxx in the United States, Dr Graham made the widely publicised statement that at least 88 000 Americans had suffered a serious cardiovascular event as a consequence of taking Vioxx, of whom at least a third would have died. The fact that current users taking 25mg a day or less of rofecoxib did not show a statistically significantly greater hazard ratio than controls was ignored.

Two subsequent cohort studies comparing remote with recent use of both Coxibs and non-steroidal anti-inflammatory drugs have been subsequently published or presented.[8,9] In both of these studies, the observation was made that recent use of Coxibs or nsNSAIDs were all associated with a relative risk or hazard ratio of up to 1.7 when compared to remote use. In both of these latter studies, long established nsNSAIDs such as ibuprofen and indomethacin share the same hazard ratio as the newer Coxibs.

Summary

The commercial decision to withdraw Vioxx from the worldwide market has been validated in recent weeks as trial judges in the United States have awarded damages to the relatives of patients who have suffered myocardial infarctions whilst on this drug. However, it is apparent from the above that the assumption that Coxibs differ from either aspirin or nsNSAIDs is poorly based, and the real question as to why the prescription of either Coxibs or nsNSAIDs seems to be related to a small but statistically significant increase in hazard ratio has yet to be answered. The numbers needed to harm are indeed very small; the Hippesley-Cox Study[8] suggests figures in the hundreds. It is more likely that the inflammatory process associated with the pain of active arthritis is culpable as the initiating factor in cardiovascular events than the coincident prescription of medicines designed to relieve pain, improve function and restore quality of life.

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