

REVIEW ARTICLE

The Fall of Titans: The Need to Reassess COX-2 Inhibitors

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INTRODUCTION

Two of the most popular arthritis medications came under great skepticism from the medical and scientific community in 2004. Long term clinical trials for both rofecoxib and celecoxib, also known as Vioxx and Celebrex, respectively, were stopped short by the Food and Drug Administration (FDA) due to increased cardiovascular risks to its subjects. The news came after five years of their use by the general public.

In 1999, an estimated 4 million Canadians and their doctors eagerly awaited the public launch of a revolutionary class of drugs: cyclooxygenase-2 (COX-2) inhibitors (1). These drugs were part of a new class of non-steroidal anti-inflammatory drugs (NSAIDs) that offered a welcomed alternative to the traditional non-selective NSAIDs that were already on the market. The main effects of COX-2 inhibitors were to reduce inflammation and to provide pain relief for osteoarthritis and rheumatoid arthritis patients without the unpopular gastrointestinal (GI) complications of acetylsalicylic acid (ASA) and other traditional NSAIDs. Pharmaceutical companies aggressively marketed these "miracle" drugs to doctors and patients --and it worked.

In the first three months of Pfizer Inc.'s public release of celecoxib, Canadian pharmacies filled more than 428,400 prescriptions worth \$20,736,000 in sales (2). Celecoxib became the fastest selling consumer product, breaking the record of the widely-used sildenafil, better known as Viagra, which also happened to be a Pfizer product, of \$13,306,000 in 1998 (2). Only six months later, Merck & Co. Inc. grabbed their part of the pie with their launch of their COX-2 selective inhibitor, rofecoxib. Rofecoxib was no ordinary copycat. It

quickly became more popular than celecoxib and in 2003, rofecoxib was the 10th most prescribed medication in Canada (3). It became exceedingly common for an arthritis patient to walk out of a clinic with a COX-2 inhibitor prescription.

The popularity of these drugs was not at all surprising. Arthritic pain was and continues to be an important issue to many Canadians. Health Canada reported that nearly 4 million Canadians suffered from a form of arthritis, representing 16% of the population in 2000 (1). Arthritis was the second and third most common chronic condition reported by women and men, respectively. Although arthritis is commonly thought of as a disease of the elderly, nearly 60% of people that reported having arthritis were under the age of 65 (1). By 2026, Health Canada estimates the prevalence of arthritis to be 20.6%, or 6,360,000 million Canadians.

COX AND COX INHIBITORS

ASA and other NSAIDs are used primarily for their anti-inflammatory and analgesic effects through the inhibition of arachidonic acid hydrolysis by cyclooxygenase (COX). This leads to decreased production of prostaglandins and thromboxanes, collectively known as prostanoids, which are the end-products of the COX pathway. These various end-products perform a myriad of physiological functions ranging from constricting or dilating blood vessels, stimulating or inhibiting platelet aggregation, to causing pain sensation.

There are currently two defined COX genes: COX-1 and -2. COX-1 and COX-2 are believed to subserve different physiological functions due to their different expression patterns. COX-1 is considered a "house-keeping" gene that is constitutively expressed in most tissues. However, this may be an oversimplification because COX-1 expression can be regulated in T-cell

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development and altered in disease states such as atherosclerosis. COX-1 has important homeostatic functions, which include maintaining gastric mucosal integrity and mediating normal platelet function. In contrast, COX-2 expression is low and highly restricted under basal conditions. However, during inflammatory responses, COX-2 expression is dramatically upregulated. Its parallel expression with inflammation increases with inflammatory mediators such as interleukin-1 (IL-1) and tumour necrosis factor- α (TNF- α), and decreases with glucocorticoids.

Although structurally similar to COX-1, COX-2 has small yet important differences. COX-2 has a valine substitution for isoleucine at position 523 (4). The smaller valine amino acid leaves a gap in the wall of the enzyme, giving rise to a "side pocket", which is the binding site of many selective inhibitors, including rofecoxib and celecoxib (4,5). When isoleucine was substituted with valine in the COX-1 enzyme, it was also inhibited by COX-2 selective inhibitors (6).

ASA and other traditional NSAIDs effectively decrease inflammation and reduce pain by non-selectively inactivating both COX enzymes. ASA irreversibly acetylates a specific serine residue on COX, thereby inhibiting its function. On the other hand, the traditional NSAIDs include both reversible and irreversible competitive inhibitors for the binding site of arachidonic acid. Interestingly, splice variants of both these enzymes exist. A splice variant of COX-1, sometimes referred to as COX-3, is thought to be the active target of another analgesic, acetaminophen (7). Although patients receive the anti-inflammatory and analgesic effects with the inhibition of COX-2 using traditional therapies, some patients endure the undesirable side effects from the inhibition of COX-1, namely GI irritation, erosion, ulcer and even haemorrhaging (8). Intuitively, COX-2 inhibitors would achieve the desired effects of traditional medications without their side effects. This indeed was the outcome of many of the first trials published.

ROFECOXIB

In the Merck-sponsored randomized, double-blinded, stratified Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, 8076 patients suffering from rheumatoid arthritis participated in determining the incidence of GI complications between rofecoxib and naproxen, a non-selective NSAID (9). The incidence of upper GI events such as perforations, obstructions, bleeding and/or ulcers, were significantly decreased in patients receiving rofecoxib treatment as compared to those using naproxen. This brought about wide acceptance of rofecoxib by many physicians and the general public. Luckily, some skeptics remained.

As clinicians and scientists sifted through the data from the VIGOR trial, questions were raised and skepticism grew. It was realized that only particular data were published for public reading, while other data were left out. Cardiovascular event data were later submitted to and reviewed by the FDA. The FDA Data and Safety Monitoring Board (DSMB) recommended a blinded adjudication of cardiovascular events of rofecoxib versus naproxen. A total of 98 cases (65/4047 from the rofecoxib group, 33/4029 from the naproxen group) were adjudicated for adverse events. There were 46 cases (in 45 people) in the rofecoxib group compared to 20 in the naproxen group to have confirmed serious adverse thrombotic cardiovascular events, such as myocardial infarctions (MI), unstable angina, cardiac thrombi, resuscitated cardiac arrests, sudden or unexplained deaths, ischemic strokes, and transient ischemic attacks. The cumulative incidence of developing thrombotic events was significantly higher with a relative risk (RR) of 2.38 (95% CI, 1.39-4.00), $P < .001$ in the rofecoxib group (10,11).

In addition, a subgroup analysis was performed on patients with a past medical history of stroke, transient ischemic attack, MI, unstable angina, angina pectoris, coronary artery bypass grafting, or percutaneous coronary interventions, who were classified as aspirin-indicated, versus those whom aspirin was not indicated. The RR of developing thrombotic events between the rofecoxib group and the naproxen group was 4.89 (95% CI, 1.41-16.88, $P = .01$) and 1.89 (95% CI, 1.03-3.45, $P = .04$) in aspirin-indicated patients and aspirin not indicated patients, respectively. Rofecoxib clearly increased the risk of suffering cardiovascular events, especially in patients with a previous history of significant cardiovascular disease (10,11).

Although the sponsors of the VIGOR trial attempted to explain the increased cardiovascular risk of rofecoxib compared to naproxen was primarily due to naproxen's anti-platelet cardioprotective effect (11), the DSMB nevertheless suggested the Vioxx label include a warning to consumers of the increased cardiovascular risks. Unfortunately for Merck, this would not be the end of its problems.

On September 30th, 2004, Merck voluntarily announced a worldwide withdrawal of rofecoxib after preliminary results from a clinical trial showed a significant overall increase in incidence by a factor of 3.9 of serious thromboembolic events such as MIs and strokes in patients receiving 25mg/day of rofecoxib compared to placebo (12). The planned 3-year clinical trial called APPROVe (Adenomatous Polyp Prevention of Vioxx) was forced to stop short by two months by the DSMB. The randomized, double-blinded study, which enrolled about 2600 patients at 100 sites, was evaluating

the efficacy of rofecoxib in preventing the recurrence of colorectal polyps in patients with a past medical history of colorectal adenomas. After 18 months of treatment, patients receiving rofecoxib were 1.8 times more likely (attributable risk=1.5%) to suffer from MIs or strokes compared to those receiving placebo (13).

CELECOXIB

Since rofecoxib's withdrawal from the market, Pfizer's celecoxib, the next most commonly prescribed COX-2 inhibitor, received major attention as to its safety. Canada's Adverse Drug Reaction Information System (CADRIS) database maintained by Health Canada showed nearly the same number of suspected adverse reaction reports for both celecoxib and rofecoxib (14). Although these are unproven reports from patients, consumers, doctors, pharmacists, and/or other health professionals, Health Canada uses this database as an early detection system for possible safety concerns with medications.

Similar to Merck, Pfizer sponsored a large scale clinical trial to determine the efficacy of celecoxib. The Celecoxib Long Term Arthritis Safety Study (CLASS) trial consisted of two separate studies comparing the effects of celecoxib to ibuprofen (400mg bid) and diclofenac (75mg bid). In the original report, celecoxib appeared to have a decreased risk in developing GI side effects such as bleeding, perforation, and obstruction, and no increased cardiovascular risk (15). But it was soon realized that data were again withheld from the public. The study lasted 13 months but only 6 months of follow-up data were published. Analysis of the subsequent data revealed that celecoxib had no statistically significant difference in the overall incidence of the predefined GI end points (0.8% in the celecoxib group versus 1.5% in either NSAID group, $P=0.09$) (16,17). Celecoxib's lack of long-term gastroprotective effects may be explained by its low selectivity ratio (COX-2/COX-1) as compared to rofecoxib (8).

On December 17th, 2004, the National Cancer Institute announced its premature cessation of a celecoxib trial known as Adenoma Prevention with Celecoxib (APC) due to a significant increase in cardiovascular risk. The APC trial enrolled 2026 patients, who were randomized into 1 of 3 groups: placebo, celecoxib 200mg bid, or celecoxib 400mg bid. The groups were followed for an average of 33 months of a planned 60 months. There was a significant increase in the number of cardiovascular events, which included cardiovascular deaths, MIs, and strokes, in both celecoxib groups. A dose-response effect was observed between the celecoxib and placebo groups. There were 2.5-fold and 3.4-fold increases in

cardiovascular risk in those taking daily doses of celecoxib 400mg and 800mg, respectively (19,20).

PROSTANOID BALANCE

Rofecoxib, celecoxib and arguably other COX-2 inhibitors, are thought to increase the risk of adverse cardiovascular events due to the suppression of prostaglandin I_2 (PGI₂), also known as prostacyclin. PGI₂ has been shown to be the predominate COX end-product in the vascular endothelium where its functions include inhibition of platelet aggregation, inhibition of platelet and neutrophil adhesion, and dilation of bronchial and vascular smooth muscle. It was previously thought that PGI₂ was mainly derived from COX-1, but it was later shown that PGI₂ is a COX-2 product (21). The cardiovascular effects of PGI₂ contrast those of thromboxane A₂ (TXA₂), a major product of platelet COX-1. Whereas ASA and other traditional NSAIDs inhibit both COX enzymes and thus both PGI₂ and TXA₂ production, the selective COX-2 inhibitors do not appreciably inhibit TXA₂ production.

It is believed by some groups that COX-2 may be induced by haemodynamic stress on endothelial cells *in vivo* as *in vitro* studies have shown (22). If so, the suppression of PGI₂ formation by selective COX-2 inhibitors may predispose patients to thromboembolic events (12). This is especially important in patients with a history of cardiovascular disease. Depression of PGI₂ formation by COX-2 inhibitors would increase their intrinsic risks of suffering clinical cardiovascular events (23).

CONCLUSION

Individual patient accounts claim improved analgesia with COX-2 selective inhibitors over traditional NSAIDs. However, the superiority of COX-2 inhibitors over traditional NSAIDs has not been clinically tested. In considering the anecdotal efficacy, higher cost, and proven cardiovascular risks, the public use of COX-2 inhibitors is controversial, to say the least. So where does this leave arthritis patients? As the hype of these miracle drugs turn to concern, should the public turn its back to all COX-2 inhibitors? The burden of proof rests with the pharmaceutical companies to prove the safety of their drugs. Although there are other pharmacological uses and risks of these drugs that are beyond the breadth of this review, there is a clear need to exercise prudence and caution to the use of COX-2 inhibitors. More research is required to determine the safety of all COX-2 inhibitors, including Pfizer's valdecoxib (Bextra) and its prodrug, parecoxib (Dynastat). Concerns over the safety of both valdecoxib and parecoxib have already risen. Two randomized, double-blinded, placebo-controlled

clinical trials showed that both valdecoxib and parecoxib increased the risk of cardiovascular events by approximately 3-fold in patients after coronary artery bypass grafting (24,25). On April 7th, Pfizer withdrew valdecoxib from the market due to concerns over valdecoxib's associated increased risk of cardiovascular events and of serious skin reactions (26,27).

The Merck and Pfizer cases have attracted much public attention and concern. Physicians and the general public are demanding answers and some are even seeking monetary compensation through class-action lawsuits. The onus is on pharmaceutical companies to produce the required research data on their drugs. Long term, randomized, double-blinded clinical trials provide the best evidence of a drug's potential use and more importantly, of its safety. Moreover, the FDA and Health Canada have the duty and responsibility to be more stringent on their approval of drugs for public use. This is a failing on both sides. Let us hope that these important lessons are well-learned.

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