

Coxibs: The new super aspirins or unsafe pain killers?

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ABSTRACT

The new generation of analgesics and antiinflammatory drugs, namely, the selective inhibitors of cyclooxygenase-2 (COX-2) enzymes, popularly known as Coxibs, have become a very popular class of drugs because of their gastro-sparing property. Coxibs were the widely prescribed drugs (nearly 8 million people round the globe take these drugs) until the recent setback with rofecoxib, which was withdrawn from the market by the innovator due to increased risk of heart attacks and strokes observed with its long-term use. The withdrawal of this popular NSAID has not only caused a great setback in the global market of coxibs but has also questioned the ethics involved in the toxicity testing and sharing of information with the end users of this new class of drugs. This article briefly reviews the developments in coxib theory, the clinical efficacy and safety of these agents in the light of the latest cardiovascular concerns.

KEY WORDS: Adverse effects, COX-2 inhibitors, NSAIDs, rofecoxib

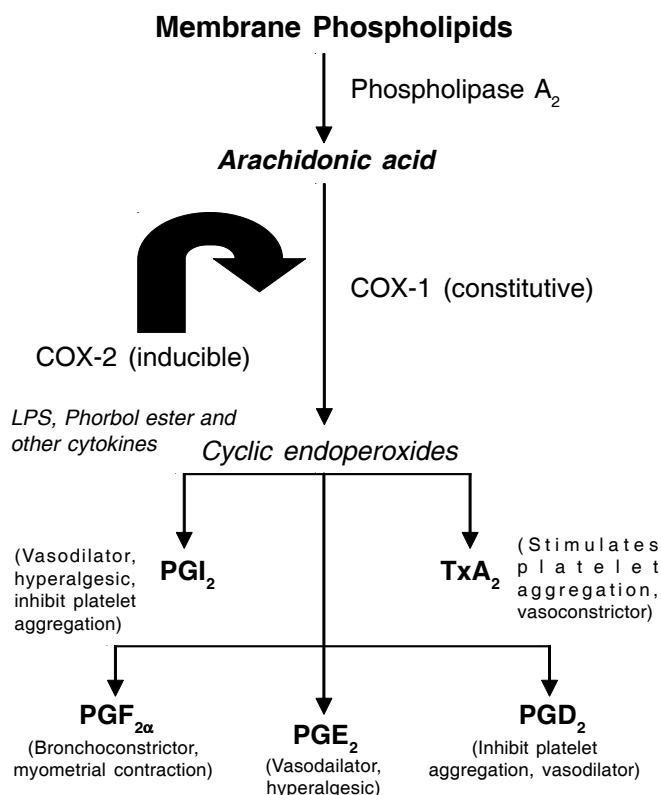
Introduction

Cyclooxygenase enzymes (COXs) catalyze the metabolism of arachidonic acid into prostaglandins. This is a rate-limiting step in the formation of prostaglandins (PGs). Sir John Vane (1971) for the first time reported that aspirin and other aspirin like drugs show their biological effects by inhibiting the COX enzymes thereby the prostaglandin synthesis.^[1] Subsequently, wide exploration of arachidonic acid – prostaglandin pathways led to the discovery of two isoforms of the COX enzyme, namely, COX-1 and COX-2. This was a landmark discovery in the pharmacotherapy of pain and inflammation as it helped to delineate the side effects of NSAIDs from their therapeutic usefulness.^[2] Also, this led to the designation of COX enzymes as constitutive (housekeeping, COX-1) and inducible (inflammation, COX-2) isoenzymes.^[3] Further, a new generation of COX-2 inhibitors were developed for selective action. The gastro-sparing agents known as “coxibs” became widely prescribed drugs (nearly 80 million people around the globe take these drugs) for pain and skeletal-muscular inflammatory disorders. Rofecoxib and celecoxib were the first coxibs approved by the USFDA as a new generation of NSAIDs with reduced gastrointestinal side effects of NSAIDs. These agents acted by sparing the COX-1 enzyme in the gastric epithelium. The second generation COX-2 inhibitors, valdecoxib, etoricoxib and lumiracoxib, supposed to be highly selective inhibitors of the enzyme followed soon. A number of clinical trials have demonstrated the supremacy of coxibs over the classical NSAIDs in gastrointestinal tolerability.^[4,5] The COX-2 inhibitors became blockbusters and were soon nicknamed “The new super

aspirins” because they appeared to deliver a double whammy, knocking out both inflammation and pain without gut-wrenching side effects. Due to gastro-sparing properties, these drugs have been aggressively marketed throughout the world. Celecoxib is approved for rheumatoid arthritis, osteoarthritis and the reduction of the number and size of precancerous polyps in patients with Familial adenomatous polyposis (FAP). Rofecoxib is approved for osteoarthritis and acute pain of primary dysmenorrhea. In recent years as we understood more about their clinical utility, their COX-2 selectivity has been a cause for concern for their cardiovascular safety.^[6,7] Since they do not inhibit the COX-1 enzyme, which plays a key role in thrombosis and vasoconstriction they do not possess the antithrombotic property of aspirin.^[8] The recent withdrawal of rofecoxib by the innovator has questioned the safety vs. clinical efficacy of this class of NSAIDs. This article briefly reviews the developments in COX-theory and the clinical efficacy and safety of coxibs to highlight their cardiovascular concerns.

COX enzymes

COX, the enzyme that catalyzes the synthesis of cyclic endoperoxides from arachidonic acid (Figure1) was isolated in 1976 and cloned in 1988.^[9] Prostaglandins intercede several key pathophysiological functions from host inflammatory response to regulation of blood flow. In 1990, the COX enzyme was demonstrated to exist in two distinct isoforms COX-1 and COX-2. COX-1 has been found to be constitutively expressed in most tissues of the human body, and synthesizes the PGs which preserves the integrity of the stomach lining and maintains normal renal functions. In addition COX-1 is also

Figure 1. Prostaglandin synthesis pathway.

present in platelets and is responsible for thromboxane A_2 production. By contrast, COX-2 is undetectable or very low in most mammalian tissues (low levels of basal constitutive expression in brain, kidneys and female reproductive system) but its expression can be induced by pro-inflammatory stimuli and mitogens at the sites of inflammation/tissue injury.^[10]

According to the COX concept, COX-1 generates 'good' PGs for 'housekeeping' functions such as gastric mucosal integrity, platelet homeostasis and regulation of renal blood flow, while COX-2 forms the 'bad' PGs involved in inflammatory reactions (i.e. arthritis, pain, hyperalgesia), neurodegenerative disorders and colorectal cancer. This hypothesis suggested that the antiinflammatory actions of NSAIDs are due to the inhibition of COX-2 enzyme, whereas the unwanted side effects such as gastrotoxicity, a major clinical limitation of NSAIDs, are due to the inhibition of the constitutive COX-1 isoenzyme. A new isoform of the COX family, namely COX-3, has been discovered very recently.^[11] However, the initial findings suggested that the inhibition of COX-3 could represent a primary central mechanism by which paracetamol and other NSAIDs decrease fever. The relevance of COX-3 in humans is still debatable.

Development of selective COX-2 inhibitors

Despite wide clinical use of classical NSAIDs as analgesics, antipyretics, and antiinflammatory agents, their gastrointestinal toxicity (upper GI adverse events such as perforation, ulceration and bleeding in up to 4% of patients per year, and up to 20% of those taking long-term NSAIDs) is a major clinical limitation. This adverse effect is associated with their ability to inhibit COX-1 in the gastrointestinal tract.^[4,12]

The discovery of the COX-2 isoenzyme led to the understanding that COX-1 is predominantly present in the gastric epithelium and accountable for the maintenance of gastro-mucosal integrity, while COX-2 is induced under inflammatory conditions and is responsible for the associated pathology of the diseases. Therefore, it was conceptualized that the inhibition of COX-2 would be sufficient to achieve the therapeutic benefits of the classical NSAIDs with considerably lower gastric toxicity. Subsequently, the selective COX-2 inhibitors emerged as potentially gastro-friendly NSAIDs. The COX theory was not only widely accepted and also validated by the clinical utility of COX-2 inhibitors.

The first COX-2 inhibitors DuP697 and NS-398 were already in the developmental stages when COX-2 was discovered. These compounds were previously reported for their gastrointestinal sparing properties in various animal models and when tested in *in vitro* assays using human recombinant COX-1 and COX-2, they were shown to be 80- and 1000 fold selective for the inhibition of COX-2 isoenzyme.^[13,14] Paradoxically, both these compounds were later discontinued, but the structure of DuP697 served as a starting point for the synthesis of the first generation COX-2 inhibitors namely, celecoxib and rofecoxib.^[15-17] These long awaited specific inhibitors of COX-2 were approved by the USFDA in 1999 for clinical use. Celecoxib was primarily approved for osteoarthritis, rheumatoid arthritis and reduction of the number and size of precancerous polyps in FAP. Rofecoxib was approved for osteoarthritis, rheumatoid arthritis and acute pain of primary dysmenorrhea. Since then, both the drugs have become the most commonly prescribed medications in the United States and in many other countries. Recently, the number of COX-2 selective agents termed "Second generation Coxibs" have been approved for clinical use. These include valdecoxib, parecoxib, etoricoxib and lumiracoxib. They are more selective COX-2 inhibitors than the first generation coxibs (Table 1).

COX-2 inhibitors and cardiovascular safety: Early death of rofecoxib?

A number of clinical trials and extensive clinical use of selective COX-2 inhibitors for arthritis and pain management demonstrated their efficacy as superior to placebo and equivalent to classical NSAID. The reduced GI ulceration and GI complications with coxibs as compared to non-selective NSAIDs remained the primary justification of their extensive use in clinics.^[4,5,18] With more and more information available,

Table 1

Classification of NSAIDs on the basis of COX selectivity

Non -selective NSAIDs	Aspirin, naproxen, indomethacin, diclofenac, flurbiprofen, ibuprofen, ketorolac
Preferential COX-2 selective NSAIDs	Nimesulide, etodolac, meloxicam
First generation Coxibs	Celecoxib, rofecoxib
Second generation Coxibs	Valdecoxib, parecoxib*, etoricoxib, lumiracoxib

* Parecoxib is an injectable pro-drug of valdecoxib.

it has now been realized that COX-2 enzyme is more widely distributed in the body than what was first suspected and not restricted to the inflammatory sites alone.

The VIGOR (Vioxx Gastrointestinal Outcomes Research) trial demonstrated that patients taking rofecoxib had lesser GI complications and also reported increased incidence of acute myocardial infarctions (AMIs) than the naproxen-receiving group.^[4] Further, Phase III trial of coxibs also indicated elevated risks of AMIs.^[19,20] CLASS trial (celecoxib long term arthritis safety study) which compared celecoxib with ibuprofen and diclofenac, reported no increase in the risk of AMIs with celecoxib.^[21] Moreover, it was featured that elevated risk of AMIs were associated only with rofecoxib when it was used at doses > 25 mg as compared with celecoxib or no NSAID use.^[22,23] Recently, Solomon *et al* have reported similar findings that rofecoxib (>25 mg) was associated with increased risk of AMIs when compared with celecoxib use and no NSAID use.^[24] This study was conducted as a matched case control study in 54,475 patients in the age group of 65 years or older. Population-based retrospective cohort study reported that NSAID-naïve individuals aged 66 years or older, patients on rofecoxib and on non-selective NSAIDs had an increased risk of admission for congestive heart failure (adjusted rate ratio 1.8, 95% CI 1.5-2.2, and 1.4, 1.0-1.9, respectively), but not those on celecoxib (1.0, 0.8-1.3).^[25]

On September 30, 2004 Merck & Co., the innovators of rofecoxib announced the voluntary withdrawal of the drug from the market, worldwide, because of the concern that it produced an increased risk of heart attacks and strokes.^[26,27] This decision of Merck to withdraw Vioxx from the market was based on the new data from the APPROVe (Adenomatous Poly prevention on Vioxx) trial. Merck had launched Vioxx in United States in 1999 and subsequently in more than 80 countries the world over. Rofecoxib is approved in the US for osteoarthritis and acute pain of primary dysmenorrhea. Recent data posted by the US Food and Drug Administration (FDA) on its website suggests that Vioxx may have contributed to almost 28,000 heart attacks in the US between 1999 and 2003 (Table 2).^[28]

APPROVe study, which is being stopped, was originally designed to evaluate the efficacy of rofecoxib 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. This study revealed that there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in patients taking Vioxx (by factor 3.9) compared to those taking placebo. However, results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events with rofecoxib. In withdrawing the drug, the company had claimed that it was concerned about the potential cardiovascular toxicity of the drug against its commercial interests in the sale of the drug and added that what was more serious was the damage that the drug had already done due to its extensive use and how to prevent such things to happen in the future. It is argued that the clinical trial reports of pharmaceutical companies should be made available to the public and communications between regulatory authorities and the industry be strictly scrutinized in a transparent way to avoid such catastrophes to occur in the future.

Table 2

Number of excess of acute myocardial infarction (AMI) and sudden cardiac deaths (SCD) resulting from rofecoxib in the US during 1999-2003 (data from www.fda.gov)

	<i>RXs</i>	<i>Persons</i>	<i>*NNH</i>	<i>Excess AMI and SCD</i>
		<i>year</i>		
Rofecoxib ≤25 mg/day	76,406,000	5,893,650	397	14,845
Rofecoxib ≥25 mg/day	16,385,000	970,453	75	12,940
Total	92,791,000	7,005,626		27,785

* Numbers needed to harm (NNH). Compared to celecoxib, the odds ratio (OR) for serious cardiac events (AMI and SCD) with high dose of rofecoxib was 3.69 (95% CI 1.30-10.45, *P*=0.01) and with standard dose of rofecoxib 1.50 (95% CI 1.02-2.21, *P*=0.04.)

Still, it remains dubious whether the observed cardiovascular toxicity of rofecoxib is a class effect or individual drug-specific (unique chemical structure or pharmacokinetics/ tissue distribution)? One possible elucidation for the increased cardiovascular risk with rofecoxib mainly extrapolated from animal studies, is based on the biology of the COX-1 and COX-2 enzyme. COX-1 drives the synthesis of TXA₂, which mediates platelet aggregation whereas COX-2 mediates the synthesis of antiaggregatory prostaglandin (PGL₂). Since COX-2 inhibitors have no effect on platelet function but inhibit vascular PGL₂ production, they may tilt vascular prostaglandin synthesis in favor of increased eicosanoid TXA₂ which may clinically result in prothrombotic outcome.^[29,30]

Therefore, this aspect of the COX-theory should be urgently addressed in the larger interest of millions of patients who are on one or the other coxib therapy. Lumiracoxib, a newer member of coxib family being recently introduced in Europe (still under consideration with USFDA) has also failed to address this important question about cardiovascular risk raised by the VIGOR trial and by various epidemiological studies. However, the incidence of AMIs associated with lumiracoxib are not significant (0.26 Vs. 0.18 per 100 patients-year hazard ratio, 1.47) (TARGET study)^[31,32] but it poses a challenge to regulatory agencies to allow the use of coxibs in patients with increased vascular risk.^[33] Many in developed countries (Health Canada) have implemented labeling changes to reflect the findings of the VIGOR study, specifically the inclusion of information that rofecoxib should be used with caution in patients with a history of heart disease. Although it is claimed that Health Canada is actively monitoring all COX-2 selective NSAIDs for gastrointestinal and cardiovascular events, it would be an ordeal in developing countries where the regulatory requirements and monitoring practices are far from the expected norms of the developed world.

Newer perspectives: Alternatives to COX-2 inhibitors

Although the use of coxibs has enhanced our understanding of the gastrotolerability issue in the management of arthritis and inflammatory disorders, recent concern over the cardiovascular safety of coxibs in the elderly has posed serious questions regarding their continued use on a long-term basis. Recently, the hybrid compounds of NSAIDs, nitric oxide (NO)-releasing NSAIDs or NO-NSAIDs i.e. nitro-naproxen and nitro-

aspirin have been reported to spare the gastrointestinal mucosa while maintaining the antiinflammatory properties of the parent compound.^[34,35] NO-NSAIDs have shown a dramatic reduction in the GI side effects in comparison to the parent compound, due to the protective effect of NO on the gastric mucosa and gastric microcirculation.^[36] It is believed that local delivery of NO could substitute PGs in restoring the balance between the aggressive and defensive factors in the GI tract that is known to be shifted due to the inhibition of COX-1 by classical NSAIDs.

The other approach being the concomitant inhibition of 5-lipoxygenase (5-LOX) and COX enzymes (LOX-COX inhibitors) to reduce the undesirable side effects and enhance the efficacy of antiinflammatory activity. It has been reported that dual inhibition of 5-LOX and COX leads to reduced synthesis of both leukotrienes and PGs which are major culprits in the inflammatory disorders. Licofelone, a competitive inhibitor of 5-LOX and COX, is currently in clinical development for the treatment of osteoarthritis.^[37] The available clinical data indicated that licofelone may offer a safety advantage over current treatment options.^[38] But the medical community should watch the development more critically on newer coxibs as our memory with rofecoxib is still very nascent.

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