Should Selective COX-2 Inhibitors be Used More?

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The discovery of inducible cyclooxygenase-2 enzyme led to the development of a new generation of nonsteroidal antiinflammatory drugs, most commonly known as coxibs. Within a short span of time, coxibs became the most widely prescribed drugs (with annual sale of more than $5 billion in the US) due to their gastroprotective effect. But immediate and voluntarily withdrawal of rofecoxib due to excessive cardiac morbidity reported with its chronic use has raised questions about their superior overall safety profile. This review summarizes the evidence regarding the use of coxibs and associated cardiovascular risk; mechanisms underlying the coxibs-mediated cardiovascular risk and other thrombotic events, evidence for a differential effect on cardiotoxicity among coxibs, and recent trends in the antiinflammatory therapy.

Cyclooxygenase (COX) catalyses the conversion of arachidonic acid (AA) to prostaglandins (PGs), prostacyclins, and thromboxanes. It is well reported that the traditional nonselective nonaspirin nonsteroidal antiinflammatory drugs (NSAIDs) provide their effects through the inhibition of these COX enzymes[1]. Subsequent studies in the same direction demonstrated that COX enzymes have two isoforms, viz., COX-1 and COX-2. The COX-1 is constitutive in nature and expressed in tissues, such as gastrointestinal (GI) mucosa to produce mucoprotective prostaglandins. The COX-1 enzyme plays housekeeping roles in stomach protection, platelet activation, and kidney function; while COX-2, an inducible enzyme expressed in response to tissue inflammation, is responsible for the associated pathology of diseases[2,3]. The recognition of two isoforms of COX enzymes led to the concept that COX-1 enzyme is responsible for production of 'good' PGs for physiological functions, including stomach protection, platelets and kidney functions; while COX-2 enzyme is responsible for production of 'bad' PGs for pathological functions, including arthritis, hyperalgesia, neurodegenerative disorders and colorectal cancer. In addition, this hypothesis also suggested that inhibition of COX-1-mediated production of 'good' PGs by traditional nonaspirin NSAIDs is mainly responsible for their unwanted side effects such as GI bleeding[4]. Therefore, selective inhibitors of COX-2 enzyme would have the improved/or similar antiinflammatory properties without GI toxicity by unaffecting the COX-1 enzyme[5]. Large body of evidences validated this hypothesis and confirmed that selective COX-2 inhibitor shows the stomach-protective effects with beneficial properties of nonselective nonaspirin NSAIDs[6-8]. This has led to the widespread use of these drugs, which have become the most widely prescribed drugs with yearly sales of more than $5 billion.

Selective COX-2 inhibitors (also known as coxibs) are widely used for the treatment and management of various arthrides and pain syndromes. DuP697 and NS-398 were the first compounds designed for inhibition of COX-2 enzyme. They had shown about 80- and 1000-fold selectivity for COX-2 enzyme in *in vitro* assays using human recombinant COX-1 and COX-2 enzymes[9,10]. Subsequently, celecoxib and rofecoxib were synthesized by using DuP697 as a starting compound[11-13]. Out of these first generation COX-2 inhibitors, celecoxib marketed as celebrex (Pfizer Inc., New York) was approved for osteoarthritis, rheumatoid arthritis and familial adenomatous polyps (FAP); while rofecoxib, marketed as Vioxx (Merck & Co., Inc., New Jersey), was approved for osteoarthritis, rheumatoid arthritis and management of acute pain of primary dysmenorrhea. Recently, the number of selective coxibs, including valdecoxib, parecoxib, etoricoxib, and lumiracoxib were approved for clinical use that constitutes as second generation coxibs.

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They are associated with more COX-2 enzyme selectivity than that of first generation coxibs.

SELECTIVE COX-2 INHIBITORS AND CARDIOVASCULAR RISK: EVIDENCE EXPLAINED

The accumulation of clinical data - from large number of trials demonstrated that coxibs protect the stomach from ulceration and irritation with more selectivity as compared to classical NSAIDs, which was the main reason for the overuse of coxibs in the management of various pain syndromes[14,15]. Within a short span of time, large body of evidences reported that COX-2 enzyme has wide distribution throughout the body, and their actions are not just limited to the site of inflammation. The outcomes of selective COX-2 inhibition by coxibs have also proved that COX enzymes have effects well beyond the earlier expectations. Recently, the immediate and voluntary withdrawal of blockbuster drug Vioxx (rofecoxib) by Merck in September of 2004 due to increased risk of cardiovascular events with its treatment have raised questions about their improved overall safety compared to classical NSAIDs. Recently, Pfizer Inc. also reported the adverse cardiac effects of Bextra (valdecoxib) after cardiac surgery[16]. The present review tried to provide the clinical evidences regarding the association between COX-2 inhibitors and increased risk of cardiovascular events (Table 1).

ROFECOXIB TRIALS

APPROVe (adenomatous polyps prevention on Vioxx) trial:

The recent withdrawal of Vioxx (rofecoxib) was based on the results emerging from the APPROVe trial. As COX-2 enzyme is also expressed at the site of neoplasms, its inhibition might have preventive effect on cancer development, and this hypothesis was specifically tested in this trial. Total 2586 patients with history of colorectal adenomas were randomized to receive either rofecoxib (25 mg/d) or placebo and were followed up to 158 w. Originally, this study was designed for 3 y to evaluate the efficacy of rofecoxib against risk of adenomatous polyps in patients of colorectal adenomas, but it was prematurely stopped on September 30, 2004, by external safety monitoring board. At the time of termination, the study results demonstrated that 3.6% patients of rofecoxib arm and 2% patients of placebo arm had experienced various thrombotic events, including cardiac, cerebrovascular, and peripheral vascular events. It is therefore reported that rofecoxib treatment was associated with the increased risk of cardiovascular events[17].

VIGOR (Vioxx gastrointestinal outcomes research) trial:

This study demonstrated that rofecoxib as compared to naproxen had less upper GI toxicity with increased incidence of thrombotic events in rheumatoid arthritis

TABLE 1: SOME MAJOR STUDIES INVESTIGATING THE ASSOCIATION BETWEEN SELECTIVE COX-2 INHIBITORS AND CARDIOVASCULAR RISK

Studies	Disease treated	Mean follow-up	Cardiovascular outcome
Celecoxib trials CLASS	Celecoxib 400 mg, diclofenac 75 mg BID and diclofenac 75 mg TID in arthritis	6 mo	No difference CV outcomes at 6 mo FDA review of 1 y data showed non-significant trend toward increased CV events in celecoxib group
APC study	Celecoxib 200 mg, 400 mg BID and placebo in adenomatous polyps	2.8-3.1 y	Showed dose related increase in CV events
ADAPT	Celecoxib 200 mg, naproxen 220 mg BID and placebo in Alzheimer's disease	Up to 3 y	No difference in CV event celecoxib vs. placebo Increased CV events in naproxen group compared with placebo
Rofecoxib trials VIGOR trial	Rofecoxib 50 mg daily and naproxen 500 mg BID in rheumatoid arthritis	9 mo	Similar mortality in groups.Risk of MI significantly great in rofecoxib group (0.4% vs. 0.1%)
APPROVe trial	Rofecoxib 25 mg daily and Placebo in adenomatous polyp	2.4 y	Rofecoxib associated with increase risk of thrombotic cardiovascular, cerebrovascular, & peripheral vascular events, Study terminated prematurely and drug subsequently withdrawn from market by manufacturer
Valdecoxib and parecoxib trials McSPI CABG trial	Parecoxib IV x 3 d then valdecoxib x 14 d and placebo for post CABG pain relief	17 d	Trend toward increased MI, cerebrovascular events and renal dysfunction in COX-2 group
Nussmeier's CABG trial	Parecoxib IV x 3 d, then valdecoxib orally for 7 d, Placebo IV for 3 d, then valdecoxib orally for 7 d, IV placebo x 3 d, then oral placebo x 7 d for post CABG pain relief	10 d	Combined COX-2 group had relative risk of CV events of 2.9 compared with placebo

patients. In this trial, patients of rheumatoid arthritis were randomized to rofecoxib (50 mg, twice daily) and naproxen (500 mg, twice daily) treatment. Nine-month follow-up revealed that rofecoxib treatment was associated with less GI complications, but risk of myocardial infarction was about four fold higher in rofecoxib-treated patients as compared to naproxen-treated patients[6].

CELECOXIB TRIALS

CLASS (celecoxib long-term arthritis safety study) trial:
This study compared the clinical efficacy of celecoxib with ibuprofen, diclofenac, and naproxen for the incidence of upper GI events. The patients of rheumatoid arthritis or osteoarthritis were randomized to receive celecoxib (400 mg twice daily), diclofenac (75 mg once daily), ibuprofen (800 mg three times daily), and naproxen (500 mg twice daily) for 26 to 52 w. The study results reported that celecoxib treatment was not associated with improved efficacy in treating arthritis and reducing the incidence of upper GI events than alternative treatments. FDA review of 1 y data showed non-significant trend toward increased CV events in celecoxib group[7,18].

APC (adenomatous prevention with celecoxib) study:
Specifically, this study was designed to access the clinical efficacy of celecoxib in reducing the occurrence of adenomatous polyps following removal of benign polyps. Outcomes from this study demonstrated that celecoxib treatment results in dose-related increase in incidence of cardiovascular events with no increase in all-cause mortality. Due to such worrisome outcomes, safety-monitoring board prematurely halted the study[19].

ADAPT (Alzheimer's disease antiinflammatory prevention trial):
The purpose of this randomized double-blind placebo-control trial was to test the ability of the nonsteroidal antiinflammatory medications naproxen and celecoxib to delay or prevent the onset of Alzheimer's disease and age-related cognitive decline. A total 2625 participants who had serious age-related memory loss, senility, dementia or Alzheimer's disease were randomized in a ratio of 1:1:1.5 to receive celecoxib (200 mg twice daily) or naproxen (220 mg twice daily) and/or placebo. Although preliminary data from ADAPT did not link celecoxib to a statistically significant increase in heart problems, it suggested a possible link between long-term use of naproxen and increased risk of heart attack and stroke[20].

VALDECOXIB AND PARECOXIB TRIALS

Mc SPI CABG trial, a first clinical study, designed to access the clinical efficacy and overall safety of coxibs following coronary artery bypass grafting (CABG).

At the time of data analysis, the present study reported that parecoxib/valdecoxib (i.v. parecoxib for initial 3 d followed by 14 d of oral valdecoxib) receiving patients were at high risk of cerebrovascular complications, myocardial infarction, and renal dysfunction as compared to the placebo group. The risk of above-mentioned serious adverse events was twofold more in coxibs-receiving patients in comparison with placebo[21]. Recently, Nussmeier *et al.* have reported similar findings that valdecoxib treatment in patients who underwent CABG was associated with more risk of cardiovascular events[22].

The unanticipated outcomes of several clinical studies raised a number of issues regarding the clinical efficacy and overall safety of selective coxibs. The important issue that has to be resolved is that the coxib-mediated cardiotoxicity is limited to individual drug or a class effect. To what extent, pharmacokinetic and pharmacodynamic properties of individual COX-2 inhibitor affect its efficacy and safety profile. Some studies provided the possible explanation for a differential effect on cardiotoxicity among COX-2 inhibitors. In a case control study, Kimmel and colleagues[23] found no evidence for a class effect of COX-2 inhibitors for cardiovascular toxicity but reported that the use of rofecoxib was associated with increased risk of myocardial infarction when compared with celecoxib use. In addition, findings of VIGOR trial[6] revealed an increased risk of MI in rofecoxib (50 mg) treated patients, whereas similar large trials with celecoxib[7] or lumiracoxib[8] demonstrated nonsignificant differences in cardiovascular events when compared with nonselective nonaspirin NSAIDs. Several large observational studies provided evidences for increased incidence of coronary heart disease with high-dose rofecoxib but not with celecoxib[23,24]. Recently, Solomon and colleagues[19,25] reported that rofecoxib treatment with any dosage was associated with increased risk for acute MI but not with celecoxib. Overall results of these studies led to speculate that not all COX-2 inhibitors are

associated with increased cardiovascular risk as rofecoxib, but some more studies are warranted to exclude the possibility of a COX-2 inhibitor class effect[26].

SELECTIVE COX-2 INHIBITORS AND CARDIOVASCULAR RISK: MECHANISMS EXPLAINED

Various mechanisms are proposed for explaining the coxibs-mediated cardiotoxicity[27]. As already mentioned, COX enzymes are more widely distributed in a variety of tissues throughout the body. These enzymes have shown a wide array of effects not restricted to inflammatory sites only. The clinical outcomes from large number of trials revealed that COX enzymes have effects beyond the expectations. The prostcyclins produced through COX-2 enzyme are involved in vasodilation, preventing thrombosis and smooth muscle proliferation. All the above mechanisms are considered to be beneficial in preventing heart attacks and other cardiovascular diseases. On the other hand, COX-1 enzyme produces thromboxanes in platelets, which has effects opposite to those of prostacyclin, including promotion of vasoconstriction, platelet aggregation, and smooth-muscle cell proliferation. Thus, impaired production of vascular COX-2-derived beneficial prostacyclin with simultaneous presence of unopposed COX-1-mediated thromboxane production and vasoconstriction progressively increases the risk of thrombotic events[6,28-31].

Earlier, it was believed that COX-2 enzyme induced only at inflammatory site, but it is now known that like COX-1, COX-2 can also be constitutively expressed in a variety of non-inflammatory tissues, including kidney, brain, neoplasms, bone, and cartilage[28,32-36]. In the kidney, COX-2-mediated PGs are responsible for regulation of vascular tone, homeostasis of salt and water. Therefore, selective inhibition of either or both of the COX enzyme isoforms by NSAIDs or selective COX-2 inhibitors may result into renovascular adverse events[36,37]. In support of this fact, VIGOR trial also reported the increased incidence of hypertension and/or fluid retention with rofecoxib (50 mg) treatment and subsequent increase in risk of myocardial infarction[6]. Moreover, some studies demonstrated that selective COX-2 inhibitors, like conventional NSAIDs, cause comparable rates of oedema and hypertension and may impair compensated renal function in the setting of CHF or volume depletion[28,36-39].

FUTURE PERSPECTIVES: SELECTIVE COX-2 INHIBITORS AND THEIR ALTERNATIVES

Although, coxibs are widely prescribed drugs due to their stomach-friendly nature, recent controversies regarding their cardiovascular safety have raised questions about their chronic use in the management of various arthrides and pain syndromes. With the acceptance of stomach-sparing effect of coxibs, there is urgent need of improvement in coxibs therapy for their overall efficacy and safety. In this regard, efficacy and safety of coxibs can be achieved by designing them with pharmacokinetic properties that favour short half-lives with more targeted at inflammatory site[40]. It can also be achieved by combining them with co-therapies, including combination of conventional nonselective NSAIDs plus gastroprotective agents *vs.* coxibs, combination of low dose aspirins plus coxibs *vs.* conventional NSAIDs plus aspirin in patients with CV risk factors, and nitric oxide linked NSAIDS (NO-NSAIDs) such as nitro-naproxen and nitro-aspirin[41-44]. Due to the antiulcerogenic effect of nitric oxide on the gastric mucosa and gastric microcirculation, NO-NSAIDs have stomach-protective effects[45-46]. NO-mediated increase in production of 'good' PGs by the gastric mucosa also contributes to gastroprotective effects of NO-NSAIDs. Such combinations of coxibs with co-therapies may be helpful to overcome or reduce the potential toxicities of the individual drug.

Thus, it is fair to accept the coxibs when patient is at high risk of GI bleeding and not tolerating or responding to the conventional NSAIDs. But simultaneously, the risk for various thrombotic events should be taken into account. Although findings of the various experimental and clinical studies will decide the future antiinflammatory treatment, the healthcare provider and patients are the persons who should be seriously concerned about using these drugs.

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