

Cox-2 Inhibitors : Cardiovascular Safety

Annil Mahajan, Rashmi Sharma*

Researchers have recently focused on selective COX (cyclo-oxygenase)-2 inhibitors, which are believed to reduce inflammation without influencing normal physiologic functions by inhibiting only COX-2 and have prophylactic potential against Alzheimer's disease and cancers (1). The first COX-2 selective NSAID (nonselective anti-inflammatory drug) approved by Food and Drug Administration (FDA) was celecoxib, which was followed by introduction of rofecoxib, valdecoxib, parecoxib, aceclofenac and etoricoxib (1). At first glance, these COX-2 inhibitors look like the solution to NSAIDs (nonselective COX-1 and COX-2 inhibitors) complications. COX-1, is a constitutive isoform of enzyme cyclo-oxygenase and is found in most of the normal body tissues for maintaining normal renal functions, gastric mucosal integrity and homeostasis. High concentrations of COX-1 are expressed in platelets, vascular endothelial cells, stomach and collecting tubules of kidneys (2). Whereas, COX-2 is inducible form and is involved in inflammation, mitogenesis and specialised signal transduction (1). Recent studies have shown that COX-2 also helps in the house keeping in certain organs like kidneys and brain (1). Moreover, COX-2 inhibitors may decrease vascular prostacyclin (PGI₂) production and can affect the balance between prothrombotic and antithrombotic eicosanoids. Thus they may tip the balance in favour of prothrombotic eicosanoids (thromboxane A₂) and lead to increased cardiovascular thrombotic events (1). COX-2 inhibitors have also been shown to increase blood pressure (BP) due to alterations in the renin angiotensin pathway, sodium and water retention by the kidney due to inhibition of vasodilating PG's and production of various vasoconstricting factors, including endothelin-1 and P₄₅₀-mediated metabolites of arachidonic acid (3).

In 2000, Pfizer completed a randomized trial of celecoxib in Alzheimer's patients without reporting any cardiovascular adverse events and only made them publicly available in 2005 (4). Although initial trials showed superiority of COX-2 selective drugs over nonselective drugs, but clinical experience has put their safety in question. However, in initial evaluation of the COX-2 inhibitors, use of small short term trials, expulsion of high risk patients and the methodologic inattention to cardiovascular events might be responsible for uncovering evidence of cardiovascular harm. In the VIGOR trial (5), rofecoxib 50 mg per day was compared to naproxen 500 mg BID in 8076 patients (80% female, mean age 58years) with rheumatoid arthritis over a median treatment period of 9 months. Data from the above trial demonstrated fewer serious events in naproxen group than rofecoxib group. The cumulative risk of developing serious cardiovascular thrombotic events was 1.7% in rofecoxib and 0.7% in naproxen group (5). In January, 2004 the FDA launched an awareness campaign which was established to educate consumers about the potentially lethal side effects associated with the misuse of NSAIDs. FDA has banned the use of nimesulide (hepatotoxic) in pediatric patients and rofecoxib (cardiovascular complications) in both adults and children. Following the worldwide withdrawal of rofecoxib, the European Medicines Agency (EMA) has been asked by the European Commission, as a precautionary measure, to conduct a review of COX-2 inhibitor medicines (6). The National Institutes of Health (NIH) has suspended the use of COX-2 inhibitor celecoxib for all participants in a large colorectal cancer prevention clinical trial (Adenoma Prevention with Celecoxib (APC) trial) conducted by the National Cancer Institute (NCI) (7).

From The Department of General Medicine and *Pharmacology & Therapeutics, Govt Medical College Jammu, J&K (India).
Correspondence to: Dr. Rashmi, Senior Demonstrator, P.G Department of Pharmacology & Therapeutics, Govt Medical College Jammu.

In the therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), lumiracoxib, a highly selective COX-2 inhibitor that has been approved in the U.K. showed no significant differences in ulcer complications or cardiovascular endpoint (myocardial infarction, stroke, and cardiovascular death) when compared with ibuprofen (8). However, it exhibited a trend toward more myocardial infarction than naproxen, but these differences were not statistically significant. Another study demonstrated increased risk of thromboembolic events with parecoxib and valdecoxib use after cardiac surgery, which could be attributed to pre-existing generalized atherosclerotic disease or additional risk of cardiopulmonary bypass or activation of platelets due to shear stress (9).

All these reports of cardiovascular adverse events with rofecoxib, celecoxib, valdecoxib and parecoxib created a sense of insecurity among prescribing physicians and consumers. Physicians are distressed and pharmaceutical companies are embarrassed and financially threatened. The class of drugs (COX-2 inhibitors) that has been launched approximately 6 years back with novel safety claims of superiority over non-selective NSAIDs, is now struggling for a status in rational therapeutics. The US-FDA appointed advisory committee titled "The Joint Arthritis Drug/Drug safety and Risk Management Advisory Committee (16th -18th feb.2005)" consisting of USFDA members, patient forum and manufacturers of coxib recommended (10):-

- For sale of both coxibs and NSAIDs with warning regarding cardiovascular risk.
- For "black box" warnings on cardiovascular risk for COX-2 inhibitors, i.e., report any cardiovascular event.
- Cardiovascular risk reported with valdecoxib in patients after coronary bypass surgery could not be extrapolated to the population of arthritis patients in whom COX-2 inhibitors are used for long term.

However, few weeks after the committee decision, pfizer has withdrawn valdecoxib on FDA request, as its

cardiovascular toxicity outweighs its gastroprotective benefits.

Presently the choice of COX-2 selective inhibitors for a particular patient should be based upon their relative efficacy, toxicity, concomitant drug use, concurrent disease states, hepatic and renal function and relative cost. However, Patients should be informed of the potential risks and the lowest possible dose should be used for the shortest possible time.

References

1. Mahajan A, Sharma R. COX-2 selective nonsteroidal anti-inflammatory drugs: current status. *JAPI* 2005; 53: 200-05.
2. Hinz B, Brune K. Non-steroidal anti-inflammatory drugs-old and new. In: Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC (eds). *Oxford textbook of rheumatology*, 3rd edition, Oxford University Press Inc.,New York 2004: 442-50.
3. Frishman W H. Effects of non-steroidal anti-inflammation drug therapy on blood pressure and peripheral edema. *Am J Cardiol* 2002; 89(6A) :18 D-25 D.
4. Psaty BM, Furberg CD. COX-2 inhibitors-lesson in drug safety.www.nejm.org assessed on Feb. 25, 2005.
5. Bombardier C, Laine L, Reicin A, et al, for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med*. 2000; 343:1520-28.
6. News-Medical. Net Following the withdrawal of Vioxx, the European Medicines Agency has been asked to review of COX-2 inhibitor medicines. Posted By: News-Medical in Pharmaceutical News, Published: Monday, 25-Oct-2004, last assessed on 23.12.04.
7. Celebrex suspension, Posted By: News-Medical in Pharmaceutical News. *J News-Medical. Net, Journal Watch* 3(9), 2004. Massachusetts Medical Society, Published: Sunday, 19-Dec-2004, last assessed 23.12.04.
8. Cardiovascular Effects of COX-2 Inhibitors: The Jury's Still Out. *Journal Watch (General)* September 17, 2004, Posted 10/20/2004, *Journal Watch* 3(9), 2004. Massachusetts Medical Society. Last assessed 22.12.04.
9. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors Parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005;352. www.nejm.org Last assessed feb 23,2005.
10. FDA advisory Committee.com <http://www.fdaadvisorycommittee.com> assessed on 16.03.05.