

## **Cox-2 Inhibitors - Recent Controversies**

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed group of drugs worldwide. These drugs are prescribed for patients suffering from OA, RA, soft tissue injuries, traumatic arthritis and other inflammatory disorders, dysmenorrhea, post traumatic pain etc. Furthermore, NSAIDs are also marketed as over the counter (OTC) drugs which increase the number of uses, selective Cox-2 inhibitors (Celecoxib, Rofecoxib, Valdecoxib) were developed with the aim of producing lesser gastrointestinal adverse effects. Initial clinical studies showed that Cox-2 inhibitor rofecoxib resulted in significantly fewer clinically important upper gastrointestinal (GI) events than naproxen.

Similarly celecoxib in clinical study when used for six months in a dosage 2 to 4 times the maximum therapeutic dosage was associated with a lower incidence of combined clinical upper GI adverse effects than ibuprofen and diclofenac.

But there was abrupt withdrawal of rofecoxib on September 30, 2004 alongwith safety concern related to use of Cox-2 inhibitors. The withdrawal of rofecoxib (Vioxx) was because of an interim analysis of a prospective randomized, placebo controlled double blind Trial (APPROVE). In summary, the three years data from this trial showed that after 18 months of drug therapy, patients receiving rofecoxib had almost twice the risk of Cardiovascular events compared to those taking placebo. The rate of myocardial infarction and stroke was 3.5%

in the rofecoxib group versus 1.9% in the placebo group.

Also clinical concern emerged with the report of VIGOR trial in November 2000. This study compared the occurrence of clinically important upper gastrointestinal events with rofecoxib 50 mg/day or naproxen 1000 mg/day in 8076 patients with RA. These patients were given drug therapy for a mean period of nine months. The results of VIGOR trial indicated the gastrointestinal safety of rofecoxib, also it showed relative risk of developing either a serious thrombotic cardiovascular adverse event or a MI with rofecoxib compared with napeoxen.

Furthermore in addition to safety concern about Cardiovascular safety of Valdecoxib, there are adverse effect reports of serious skin reactions (Toxic epidermal necrolysis) sometimes with fatal outcome. Both rofecoxib and Valdecoxib have been banned in India.

To conclude, the Coxib saga is an important reminder to clinicians that adverse effect profile of a new drug cannot be completely known when it is introduced in practice. Therefore, a new drug should be given with caution to lesser number of patients in early years after its release.

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## Cox-2 inhibitors - Controversy over Controversy

As if the above was not enough. I felt, I must add to the confusion in an effort to achieve clarity on the subject. As a clinician getting feedback from the patients on whom we can sufficiently rely on, specially those who have used these drugs for a long period of time prescribed or not prescribed, the choice of the analgesic and anti-inflammatory drug if left with the patient, the patients would prefer to take the drug which is effective in giving them relief for a sufficient period, does not require frequent dosage, is gastro-friendly and apparently does not harm them. To most patients, Cox-2 inhibitor drugs were a boon. Considering the prescription of NSAIDs, Analgesics and Cox-2 inhibitors, the quantum amounted to over 10,000 prescriptions in one year in my out-patients, of which about two thirds were of Cox-2 inhibitors until the time preceding the ban on Rofecoxib about an year ago and on Valdecoxib about six months ago in India. Specifically getting the history of uncontrolled hypertension was amongst the contra-indications of using the Cox-2 inhibitors though with Valdecoxib as per the drug safety profile the risk predicted was relatively lesser than Rofecoxib, hence Valdecoxib was prescribed more freely than Rofecoxib. The efficacy of Rofecoxib as well as Valdecoxib in the control of pain reported by the patients was very good. Even patients having acute inflammation because of arthritic conditions or trauma reported appreciable relief of pain lasting more than 24 hours with a single dose of Rofecoxib 25 mg or Valdecoxib 20 mg. With controlled hypertension the drug was used with caution and the patient was asked to have frequent recording of the blood pressure. A few (less than 10) reported a little upward variation of the blood pressure where they were asked to stop the drug. To say that these occurred specifically with Cox-2 inhibitors would be wrong to say, the challenge to the blood pressure, kidneys or a mere edema in the legs or generalized including the face was a feature more or less equally observed amongst various NSAIDs and Cox-2 inhibitors, though not that a frequent occurrence altogether, under 20 patients in a year with no major catastrophe. As per the gastric safety of the Cox-2 inhibitors was concerned about six patients on Valdecoxib reported frank gastric upset relieved after stoppage of the drug. Three patients on Valdecoxib reported maculo-papular rashes, relieved after stopping the drug and treated with Cetrizine. The behaviour of the patients who were on Rofecoxib and Valdecoxib after non-availability of these drugs in the market has been typical. Those on Rofecoxib easily accepted Valdecoxib after the ban on the former, but those on Valdecoxib were not satisfied to take any other drug even though some other medication was prescribed. The patients reportedly coaxed the chemists and druggists

to obtain drugs lying with them or even consumed expired medicines saying that those gave good relief with lesser side effects, even though told about the ban and potential dangers of consuming the banned medicines.

The questions that are raised are many. First of all, the above comments are based solely on the personal experience without any statistical analysis and are only rough estimates. These would not stand before any scientific scrutiny in the present format. These have been taken preliminarily from part of the project being run in our department to find out the adverse effects of NSAIDs being used in the PMR setting. A more organized analysis from a larger patient database will be available in future. A recent report on the selective cox-2 inhibitors [Coporali R. Montecucco C., Cardiovascular effects of coxibs, *Lupus*. 2005; 14 (9): 785-8] quotes "based on the recent withdrawal of rofecoxib that some concerns arose even for a possible cardiotoxicity of non-selective non-steroidal anti-inflammatory drugs." It further adds "from the data available so far, it seems that coxibs still remain a rational choice for patients with low cardiovascular risk and high gastrointestinal risk. Long term studies with a cardiovascular endpoint involving both selective and non-selective anti-inflammatory drugs are warranted." In the US the drugs were not banned but only withdrawn by the manufacturer from the market with a warning. In India, they were not banned initially but with a lot of pressure from whatever sources, they were banned rather than just a similar warning issued. Maybe we can compare that the literacy rate of India with that of the US and say that people in India may not be that well informed about the side-effect profile hence would not care to take a drug with caution. With no offence meant to anyone, but the question is wherefrom those well informed people came to create a lot of hue and cry about Rofecoxib and Valdecoxib. Where were they when Analgin was marketed in India for ages when it was actually banned in the developed world. What about Piroxicam that was introduced in the market after earning such a bad name in the USA. No one has pushed the government to ban those drugs which carry equally heavy warning about their cardio-vascular and renal safety. Why are we selective to pin-point the selective cyclooxygenase-2 inhibitors. I do not think I can answer the question but only conclude with a controversial remark, as far as India is concerned that their ban was unwarranted. Perhaps we could have left it as our American friends did. Do we always follow the western world? Perhaps no, not in this case, or should we, at least in this case.

– Dr U Singh  
Editor