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Editorial

RATIONAL USE OF PAIN KILLERS – DO WE NEED SELECTIVE COX-II INHIBITORS?

The coxibs are a subclass of NSAIDS which selectively inhibit COX-2 enzyme involved in inflammation.

Conventional NSAIDS inhibit both COX-1 and COX-2 ISO-enzymes. Their use is often associated with gastro-intestinal toxicity. COX-2 inhibitors were expected to confer gastro-intestinal protection and solve the problem of NSAIDS therapy adverse effect.

In May 1999, the USA Federal Drug Agency (FDA) granted Merk Pharmaceutical a licence to market rofecoxib (Vioxx) a selective COX-2 inhibitor. Soon there were reports of increased cardio-vascular events in the form of heart attacks and strokes amongst the rofecoxib users but neither the company nor the FDA took any action. However, the UK Commission Safety Medicines (CSM) issued a warning about these risks but the company kept on aggressively promoting rofecoxib. Over the next five years rofecoxib's annual sale topped to two and half billions dollars.

Obviously there is an imperfect system of drugs post-marketing surveillance. Many new drugs have played havoc with patients lives before they were belatedly withdrawn from the market. Thalidomide tragedy is very well known event, but obviously the powerful industry gets over these human murders. The new drugs receive aggressive promotional publicity while the old ones are subjected to adverse publicity amid propaganda of their harmful side-effects. The worst sufferers are the people of the developing countries where the regulatory authorities are very prompt in registering drugs for reasons of vested interests and their lack of professional acumen.

Pakistan drug situation is grim. The market is flooded with irrational drugs while many of the much needed essential drugs are either not available or scarcely available.

It was not until the early results of the published "APPROVE TRIAL" emerged that rofecoxib was deemed unsafe. The study designed to show the efficacy of rofecoxib in preventing the recurrence of colorectal polyps in patients with a history of colorectal adenomas found a 3.9 fold increased incidence of thrombo-embolic adverse events in the rofecoxib group compared with placebo [1].

Although the effects of coxibs on prostaglandin synthesis are beneficial in treating inflammation, there are some other effects which may explain the increased cardiovascular risk observed with rofecoxib. Coxibs inhibit endothelial COX-2 derived PGI2 synthesis. PGI2 prevents platelet aggregation and causes vaso-dilatation. These effects contrast with platelet aggregation, vasoconstriction and vascular proliferation. Thus selective blockade of COX-2 tips the balance in favour of TXA2 and potentially predisposes to hypertension, myocardial infarction and stroke.

On 30th September 2004 the company withdrew rofecoxib because of increased cardio-vascular events and fatalities after five years of its use.

A lot of patients who suffered serious complications and relatives of fatal cases have filed legal suits against the company, claiming compensations which run into billions of US dollars. Recently a widow who lost her husband, was ordered a compensation of two hundred and fifty million US dollars.

In Pakistan where drugs are available without prescriptions and are misused on

enormous scale without any accountability and therapeutic audit, it is likely that many people have suffered from the adverse effects of Coxib-2 drugs and are still undergoing complications.

Although rofecoxib has been removed from the market by the company, still there are other COX-2 inhibitors on the market. The question arises whether the deleterious cardiovascular outcomes associated with rofecoxib could be extrapolated to other Coxibs. Meta-analysis of data relating to another coxib, valedocoxib revealed a three – fold increase in myocardial infarction and stroke [2].

Furthermore, a trial comparing placebo against celecoxib was prematurely terminated due to excess of cardiovascular events in the Coxib group [3]. There are differences in the affinities of different coxibs for the two COX iso-enzymes. Rofecoxib inhibits COX-2, 80 times more than COX-1 whereas celecoxib inhibits COX-2 only nine times more than COX-1. The ratio of COX-2 : COX-1 inhibition for the non-selective NSAIDs ibuprofen and naproxen is 0.4 to 0.3 respectively and for diclofenac is about 50% of each, indomethacin is 80% COX-1 and 20% COX-2 selective and most prone to gastro-intestinal side-effects whereas the ratio of etodolac and meloxicam is 30%. There are also recent reports of increased incidence of cardiovascular events with prolonged use of naproxen as compared with placebo though to a small extent. This shows that there can be complications involving gastrointestinal (GI) tract possibly also cardiovascular system with other NSAIDs as well. But there is no proof of it as yet. Of course aspirin does not cause cardiovascular problems. Only rofecoxib has been shown to reduce gastro-intestinal complications compared with naproxen and not other coxibs. From the class trial, comparing celecoxib with ibuprofen or diclofenac, it is shown that celecoxib does not differ from traditional NSAIDs in its effect on the predefined gastro-intestinal end points [4]. Moreover there is no evidence of superiority of coxibs over traditional NSAIDs in relief of arthritic pain.

Coxibs are expensive, and have serious cardiovascular risks with high risk-benefit ratio. Therefore, it is prudent to avoid their use more so in individuals predisposed to coronary and cerebro-vascular risk.

In conclusion, there is no rationale in retaining in the formulary COX-2 inhibitors. For ordinary pain, paracetamol serves the purpose best, for severe pains opioids may be used judiciously and for inflammatory conditions, ibuprofen has the lowest risk followed by diclofenac. To protect G.I tract in susceptible individuals, these latter drugs can be combined with proton-pump inhibitors. H2 antagonists do not provide good protection against duodenal ulcer while misoprostol reduces the risk of perforation and gastric out let obstruction but not GI bleeding. Aspirin is a cost-effective NSAID and its risk index is not high, it can also be used as an anti-inflammatory drug. NSAIDs are very commonly misused for the relief of ordinary pains. Considering the risks and cost involved, there is no rationale for using NSAIDs for ordinary pains. The same applies to mefanamic acid which can cause haemolysis and agranulocytosis.

The combinations of paracetamol with prohoxyphene and codeine are used quite frequently as pain killers. UK's CSM commission after doing a comprehensive study has concluded that these combinations have no advantage over paracetamol used alone in efficacy but cause toxicity, therefore the commission has decided to remove these combinations from the market [5]. There are also irrational combinations of paracetamol and muscle relaxants in inadequate doses which do not increase efficacy but add to the cost and toxicity. We should also stop the use of these combinations and these should be de-registered by the regulatory authorities. There is a clear lesson that one should be very

cautious in using drugs which have not stood the test of time. As a general rule one NSAID be prescribed using the lowest recommended dose and for the shortest possible period, avoid concomitant asprin use, avoid use in renal impairment and use cautiously in patients on oral cortico-steroid therapy.

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