Current Practice

COX-2 INHIBITORS: What's the message for practicing physician?

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ABSTRACT:
The development of Cox-2 inhibitors as potentially gastro-safe NSAIDs is based on the notion that Cox-1 predominates in the stomach, yielding protective prostaglandins, while Cox-2 is induced in inflammation giving rise to pain, swelling and stiffness. The conventional NSAIDs are the most widely prescribed drugs. Despite excellent efficacy in rheumatic disorders their toxicity can lead to significant morbidity and mortality. With the introduction of Cox-2 specific inhibitors, there is a widespread belief that at last safe anti-inflammatory drugs are at hand and are being used extensively.This article reviews the available data regarding their safety on gastrointestinal and cardiorenal systems. It will help the physicians to make a decision while prescribing these drugs to their patients especially who have risk factors.

KEY WORDS: Cox-2 inhibitors, gastrointestinal, cardiorenal, safety, NSAIDs, risks.

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Over 100 years ago Felix Hoffman successfully synthesized acetylsalicylic acid as the first non-steroidal anti-inflammatory drug (NSAID)[1,2]. This was named aspirin by the then Bayer's chief pharmacist Hermann Dreser[3]. Since then aspirin is extensively used in the treatment of fever, pain, rheumatic diseases and cardiovascular prophylaxis. In 1938 Douthwaite and Lintott provided endoscopic evidence that aspirin could cause gastric mucosal damage[4].

From early 1970's onwards numerous new NSAID were developed that were initially believed to have no gastrointestinal and other toxicities, but few, if any, are entirely harmless. These agents constitute one of the most widely used classes of drugs and are effective in terms of relieving pain and improving functions. In view of this, the major clinical issues are those of safety and tolerability. The most common side effect is dyspepsia occurring in up to a third of patients treated[5,6]. In addition, serious upper gastrointestinal complications like ulceration, hemorrhage and perforation may occur from NSAID use in a small but important percentage of patients, resulting in substantial morbidity and mortality. The mortality rate among patients who are hospitalized for NSAID induced upper gastrointestinal bleeding is 5-10%[7]. Other side effects include renal failure, worsening of hypertension, bronchospasm, edema etc.

Observations have shown that NSAID act on cyclo-oxygenase to inhibit prostaglandin synthesis. Prostaglandins produced during acute and chronic inflammatory processes appear to mediate many of the symptoms of inflamma-

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tion such as pain and edema[8,9].

Prostaglandins are derived from arachidonic acid, which originates from cell membrane phospholipids through the action of phospholipase A2. This metabolism of arachidonic acid to prostaglandins and leukotrienes is catalyzed by the cyclooxygenase pathway and 5-lipoxygenase pathway respectively[1,10]. Two related but unique isoforms of cyclooxygenase, designated cox-1 and cox-2 have been demonstrated[11,12]. Despite their structural similarities, they are encoded by distinct genes and differ with regard to their distribution and expression in tissues[13,14]. Cox-1 is primarily expressed constitutively whereas Cox-2 is thought to be the inducible form that is nearly undetected in most (but not all) tissues under normal physiological conditions. Cox-1 appears to function as a "house keeping" enzyme in most tissues, including the gastric mucosa, kidneys and the platelets, whereas the expression of Cox-2 can be induced by inflammatory stimuli[15].

It has been suggested that the anti- inflammatory properties of NSAIDs are mediated through the inhibition of Cox-2, whereas adverse effects, such as gastroduodenal ulceration, occur as a result of effect on the constitutively expressed Cox-1[12,15]. This concept has led to the development of specific Cox-2 inhibitors in order to avoid the adverse effects of the traditional NSAID. This concept has limitations. Many gastrointestinal cells can produce inflammatory responses by expressing Cox-2. In particular, the acute gastritis caused by Helicobacter pylori is associated with Cox-2 expression[16], which raises the possibility that Cox-2 inhibitors would inhibit the synthesis of protective prostaglandins in these circumstances. Moreover, most NSAID use is for conditions not regarded as inflammatory, despite this, Cox-2 inhibitors are analgesic in such conditions[17].

GASTROINTESTINAL SAFETY

The two major studies widely quoted for the safety of Cox-2 inhibitors are Celecoxcib Long-term Arthritis Safety Study (CLASS)[18] and Vioxx Gastrointestinal Outcomes Research (VIGOR)[19]. Both were similar in design and outcomes. In CLASS, Celecoxcib was used in comparison with ibuprofen and diclofenac. Aspirin use for cardiovascular prophylaxis was permitted. In VIGOR, Reocoxcib was used in comparison with naproxen however concurrent aspirin use was not permitted. Both trials found that arthritis patient's not taking low-dose aspirin that were randomized to receive Cox-2 inhibitors had significantly fewer symptomatic and complicated ulcers than patients randomized to nonselective NSAIDs. A significant risk reduction was not demonstrated, however, in patients in the CLASS trial who were taking low-dose aspirin, itself an independent risk factor for the endpoint. These data validate the Cox-2 hypothesis and support recommendations that a Cox-2 selective inhibitor should be used in treatment of patients at increased risk for symptomatic and complicated ulcers. Further studies are needed to determine whether Cox-2 selective inhibitors are safer than nonselective NSAIDs when used in patients receiving low-dose aspirin.
Paul Emery et al in his study concluded that celecoxcib showed sustained anti-inflammatory and analgesic activity similar to diclofenac, with a lower frequency of upper gastrointestinal ulceration or gastrointestinal adverse events, and tolerability was better[20].

McKenna et al in a placebo controlled, randomized, double blind comparison concluded that celecoxcib 200mg daily is as effective as diclofenac 150mg daily for relieving signs and symptoms of osteoarthritis of knee, including pain and has a rapid onset of action. However, celecoxcib appears to have a superior safety and tolerability profile[21].

Bensen et al in a multicenter, randomized, double blind, and placebo controlled trial of 1003 patients compared the efficacy and safety of celecoxib with naproxen. He concluded that celecoxib was comparable to treatment with naproxen regarding efficacy and safety[22].

Lee S. Simon et al in a randomized controlled trial compared celecoxcib with naproxen. He concluded that all dosages of celecoxcib were

efficacious in the treatment of rheumatoid arthritis and did not affect COX-1 activity in the GI tract mucosa as evidenced by less frequent incidence of endoscopic ulcers compared with naproxen[23].

Comparative studies between rofecoxib and conventional NSAIDs also have demonstrated fewer symptoms of gastroduodenal ulceration and upper GI tract perforation and bleeding with the COX-2 inhibitor[24,25].

Schnitzer in his review of large trials concludes that data are now available to support the superior gastrointestinal safety of COX-2 inhibitors, not only for endoscopic endpoints but also clinically significant outcomes. He further adds that the COX-2 inhibitors still retain some of the side effects seen with traditional NSAIDs, namely, effects on the kidney that may manifest as an increased incidence of hypertension, edema and associated clinical states. Similarly, effects on reproductive functions, endothelial function and wound healing are theoretically possible but need to be evaluated in well-controlled clinical trials[26]. Other studies have also substantiated the claim of their superiority regarding GI toxicity[27-31].

CARDIORENAL SAFETY

Besides GI intolerance, NSAIDs are also implicated in destabilizing blood pressure, causing edema, increasing the risk of congestive cardiac failure and decreasing platelet aggregation[32-35]. NSAIDs disrupt the effect of most antihypertensive medications, especially angiotensin- converting enzyme inhibitors and β-blockers[34-37]. It will be interesting to see if COX-2 inhibitors are free of these side effects.

Mengle-Gaw et al found that celecoxib 600mg twice daily (50% higher than the highest dose evaluated for efficacy in trials) had no effect on serum thromboxane or platelet function. Rofecoxib in higher doses did not affect the bleeding time[38].

Whelton et al conducted a 6 week, randomized, parallel group, double blind trial in patients with osteoarthritis who were 65 years of age and were taking anti-hypertensive drugs. Patients received once daily celecoxib or rofecoxib. Nearly twice as many rofecoxib compared with celecoxib treated patients experienced edema (9.5% vs 4.9%). Systolic blood pressure increased significantly in 17% of rofecoxib compared with 11% of clecoxib-treated patients at any study time point. Diastolic blood pressure increased in 2.3% of rofecoxib- compared with 1.5% of celecoxib-treated patients. At 6 weeks, the change from baseline in mean systolic blood pressure was +2.6 mmHg for rofecoxib compared with -0.5 mmHg for celecoxib.In conclusion patients on antihypertensive drugs receiving Cox-2 inhibitors experienced destabilization of blood pressure control and edema. Patients receiving celecoxib experienced less edema and less destabilization of blood pressure control compared with those receiving rofecoxib[37].

Conventional NSAIDs were not studied in this trial however, in CLASS study patients receiving celecoxib experienced less hypertension and edema than those receiving diclofenac and ibuprofen[18].

The effect of NSAIDs on the risk of developing congestive cardiac failure has been examined. These studies demonstrated that recent use of NSAIDs by elderly patients at least doubled the odds of hospital admission for an episode of congestive cardiac failure. This was especially true for patients with the history of heart disease. Whelton et al in their study found that only patients receiving rofecoxib developed congestive cardiac failure whereas none of the patients receiving celecoxib developed congestive cardiac failure[37].

Ray et al in a retrospective cohort study concluded that there was no evidence of raised risk of coronary heart disease among users of refocoxib at doses of 25mg or less[39].

However there is a possibility that cardiovascular adverse events may increase with highly selective COX-2 inhibitors. Hence because of potential aggravation of hypertension and fluid retention, caution should be exercised in prescribing COX-2 inhibitors to patients with congestive heart failure or hypertension[40].

WHAT'S THE MESSAGE?

Since the introduction of COX-2 inhibitors in the local market, they are being widely prescribed. The perception of their "absolute safety" is an important factor endorsed by local and other suppliers. Numerous studies have shown superior tolerability and similar efficacy of these drugs as compared to conventional NSAIDs. Although several clinical questions remain (eg. Use with low-dose aspirin, risk of thrombosis, myocardial infarction, edema and hypertension), the emergence and clinical utility of coxibs is likely to continue on the basis of their efficacy and relative GI safety advantage. In addition to the treatment of rheumatic conditions, it is possible that coxibs will also be of clinical use in protection against malignant transformation and Alzheimer disease.

Studies have also shown that COX-2 inhibitors are being prescribed for patients with multiple risk factors that may place the patient at increased risk of adverse drug reactions[41]. It is suggested that similar precautions should be taken in prescribing these agents as for conventional NSAIDs in patients who are at risk eg. advanced age, hypertension and past or active peptic ulcer disease. Careful blood pressure monitoring is essential when treating patients with coexisting hypertension and osteoarthritis. The finding that celecoxib was associated with a lower incidence of cardiorenal events compared to rofecoxib, especially with regards to hypertension, should be considered when selecting a Cox-2 inhibitor.

At present, therefore, in middle-aged and elderly populations with arthritis, especially in high-risk groups for cardiovascular events, available data suggest the cautionary use of selective COX-2 inhibitors which may adversely affect the patient's cardiovascular outcome[40].

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