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Review Article

Efficacy and Safety of COX-2 Inhibitors in the Clinical Management of Arthritis: Mini Review

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In the clinical management of arthritis, the choice of nonsteroidal anti inflammatory drug (NSAID) remains confusing and controversial. A common practice on the choice of NSAID in clinical management of arthritis is the risk benefit ratio. The main objective of this review is to addresses the main arguments for the pharmacological and clinical use of COX-2 inhibitors in relation to nonselective NSAIDs for the clinical management of arthritis. This review concluded that, both NSAIDs and COX-2 inhibitors are equally effective and are associated with increased risk of GI, renal, and CV, adverse effects. Complete understanding of the patient's comorbid conditions and concomitant medications, coupled with precise monitoring during the treatment, may help to decrease the threat of adverse effects induced by nonselective NSAIDs and selective COX-2 inhibitors.

1. Introduction

Arthritis is a complex disorder that comprises more than hundred distinct conditions involving damage to the joints of the body. Many mediators are known to be involved in the pathophysiology and progression of arthritis. These include cartilage-degrading enzymes, cytokines, leukotrienes (LTs), and prostaglandins (PGs). LTs and PGs are produced by the activity of three enzymes—5-lipoxygenase, cyclooxygenase (COX)-1 and COX-2—as part of the arachidonic acid (AA) pathway. PGs have various physiological and pathophysiological effects. PGs produced by COX-1 isoenzyme exert house-keeping functions, including gastric mucosal defense and renal homeostasis, whereas COX-2 synthesizes detrimental PGs which are responsible for inflammation and pain. The activity of COX-2 leads to production of a narrower spectrum of PGs, specifically PGE_2 and PGI_2. The vasodilatory properties of these two molecules increase mucus production and reduce acid and pepsin levels in the stomach, thereby protecting the integrity of the gastrointestinal (GI) mucosa [1–4].

The ultimate goal for arthritis treatment is the modification of disease progression, in combination with anti-inflammatory and analgesic efficacy [5–7]. Traditional non-selective, nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used to relieve the pain and inflammation due to osteoarthritis and rheumatoid arthritis. These drugs possess potent anti-inflammatory, analgesic, and antipyretic activity and are among the most widely used drugs worldwide and represent a mainstay in the treatment of acute and chronic pain [8]. However, numerous reported adverse drug reactions, case-control, and postmarketing surveillance studies have revealed that their use is frequently associated with a relatively high incidence of adverse reactions in the GI tract [9–11]. GI toxicity is clinically important because it has been shown to increase morbidity and mortality rates in patients, particularly in the elderly, with chronic therapy [12–18].

Traditional NSAIDs act by inhibiting both COX-1 and COX-2, thereby blocking the synthesis of PGs. The GI adverse events of NSAIDs are majorly due to the decrease in synthesis of the gastroprotective prostaglandins PGE_2 and

PGI_2, which are mainly produced by COX-1 [1–4, 10]. To significantly reduce the GI toxicity of NSAIDs, associated with acute and chronic use and to obtain similar or better efficacy, pharmaceutical companies conducted intensive international research which led to the development of COX-2 inhibitors [19, 20]. Due to the great expectation, these drugs were rapidly introduced in the market and gained a remarkable commercial and therapeutic success [19–23].

2. Safety of Traditional NSAIDs versus COX-2 Inhibitors

A number of clinical trials have been conducted over the past 15 years that generally support the favorable GI side effect profile of COX-2 selective inhibitors. Traditional nonselective NSAIDs vary in their propensity to cause serious GI adverse effects. Ibuprofen is associated with the lowest risk; diclofenac, naproxen, indometacin, and ketoprofen have intermediate risks [24]. It was reported that the point prevalence of ulcers in patients on long-term NSAID treatment is about 20%, and the annual incidence of serious complications from these ulcers is 1–4% [25].

A recently published systematic review investigated the relationship between NSAID use and lower GI outcomes. This study reported an increase in lower GI injury and clinical events with traditional NSAIDs, which was consistent across the heterogeneous collection of trials [26]. Many other systematic reviews and meta-analysis have demonstrated comparatively better GI safety for celecoxib, nimesulide, and etodolac in comparison with the traditional NSAIDs [27–31].

Celecoxib Long-term Arthritis Safety Study (CLASS) and Vioxx Gastrointestinal Outcomes Research Study (VIGOR)—large long-term trials—have been conducted in patients with rheumatoid arthritis and osteoarthritis, both involving more than 8,000 subjects. These studies demonstrated that both celecoxib and valdecoxob significantly reduced the risk of major GI side effects compared to traditional NSAIDs [32, 33]. Similar results were obtained in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), conducted on 18,325 patients, comparing lumiracoxib with two NSAIDs, naproxen and ibuprofen [34]. Thus findings of published data reveal that the incidence of adverse GI effects is significantly reduced among patients taking selective COX-2 inhibitors.

3. Efficacy and Safety of COX-2 Inhibitors

Even though the GI toxicity profile of selective COX-2 inhibitors is better than the traditional NSAIDs, current evidences indicate that selective COX-2 inhibitors have important adverse cardiovascular and renal effects. The cardiovascular adverse events of selective COX-2 inhibitors include increased risk for myocardial infarction, stroke, heart failure, and hypertension. The science behind the cardiovascular and renal adverse events is explained in literatures [35–38].

Rofecoxib's potential for adverse cardiovascular events was recognized during the VIGOR trial in which patients with rheumatoid arthritis were randomized to 50 mg of rofecoxib once a day or 500 mg of naproxen twice a day. This study indicated a fourfold increase in the incidence of myocardial infarction in the rofecoxib treatment group compared with the naproxen treatment group [33]. A recent study has shown that long-term etoricoxib use is associated with a risk of thrombotic cardiovascular events comparable with that of diclofenac and with a greater risk of renovascular adverse events [39]. A meta-analysis of published and unpublished tabular data from randomized trials revealed that selective COX-2 inhibitors are associated with a moderate increase in the risk of vascular events (relative risk, 1.42; 95% CI, 1.13 to 1.76), as are high-dose regimens of ibuprofen and diclofenac, but high-dose naproxen is not associated with such an excess [40]. High cardiovascular risk associated with sulphone COX-2 inhibitors such as rofecoxib and etoricoxib, as observed in recent clinical trials can be explained by the dose dependent pro-oxidant activity of these classes of drugs in human plasma samples and isolated low-density lipoprotein [41, 42].

Several randomized controlled clinical trials in patients with rheumatoid arthritis or osteoarthritis have demonstrated that COX-2 inhibitors are no more effective than traditional NSAIDs or in other words, have similar efficacy as traditional NSAIDs [27, 43–46].

4. Impact of COX-2 Inhibitors on Clinical Management of Arthritis

It is a widespread postulation that all NSAIDs, including COX-2 inhibitors, should be avoided, wherever possible, in patients with high risk of GI complications. The choice of NSAID remains confusing and controversial in the clinical management of arthritis. A common accord on the choice of drug in clinical management of arthritis is the risk benefit ratio.

Any patient requiring chronic NSAID treatment for the management of arthritis may benefit from the COX-2 therapy. Patients who are at a high risk of GI bleeding, have a history of intolerance to traditional NSAIDs, or are not responding to traditional NSAIDs may be appropriate candidates for treatment with COX-2 selective inhibitors. These include the elderly, those with documented prior ulcers, and patients on concomitant steroids. In patients who are not at a high risk of serious GI events, cost should be considered as an important factor while considering the treatment options. Physicians should exercise extra caution when prescribing COX-2 inhibitors to patients with risk factors for heart disease. Patients with established ischemic heart disease, peripheral arterial disease, or cerebrovascular disease should be switched to traditional NSAIDs and gastroprotective agents should be considered in this situation. COX-2 inhibitors may be preferable in patients taking low-dose aspirin, since they do not interfere with platelet inhibition by aspirin

5. Conclusion

Extensive evaluation of the safety and efficacy of NSAIDs and selective COX-2 inhibitors has revealed that both drugs

are equally effective and are associated with increased risk of GI, renal, and CV, adverse effects. Physicians have to revise their indications for both the traditional NSAIDs and the COX-2 inhibitors in the management of arthritis and to give considerable attention to the balance of benefits and risks. Thorough assessment of patient's comorbid conditions and concomitant medications, along with precise monitoring during therapy, may help to decrease the threat of toxicity induced by traditional NSAIDs and selective COX-2 inhibitors.

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