Development and clinical application of COX-2–selective inhibitors for the treatment of osteoarthritis and rheumatoid arthritis

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ABSTRACT

Osteoarthritis (OA) and rheumatoid arthritis (RA) are among the most prevalent chronic illnesses and leading causes of disability in the United States. The clinical symptoms of OA and RA, pain and inflammation, are biologic processes mediated in part by prostanoids—prostaglandins, prostacyclin, and thromboxanes. The intermediate enzymes responsible for prostaglandin biosynthesis, cyclooxygenase (COX)-1 and COX-2, have been the target of arthritis therapy using nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). An understanding of the biochemistry and molecular pharmacology of COX enzymes has allowed for the development of agents that specifically inhibit COX-2. COX-2–selective inhibitors have efficacy in OA and RA that is similar to that of NSAIDs but with a lower potential for upper gastrointestinal injury, a serious side effect of nonselective NSAIDs. COX-2–selective inhibitors have been increasingly used in the treatment of OA and RA as well as other inflammatory arthropathies including ankylosing spondylitis and gout. Clinical trials with two currently available drugs, rofecoxib and celecoxib, have demonstrated efficacy comparable to nonselective NSAIDs but with a lower risk of gastrointestinal side effects. In general, these drugs are well tolerated in patients with aspirin-sensitive asthma. Rofecoxib is well tolerated in patients with sulfonamide sensitivities; further studies are needed to fully characterize the utility of celecoxib in these patients. Clinical experience shows that because of their improved GI safety, rofecoxib and celecoxib, and newer COX-2–selective inhibitors (valdecoxib, etoricoxib, parecoxib), represent a significant advance in the treatment of arthritis and other related inflammatory conditions.

Osteoarthritis (OA) and rheumatoid arthritis (RA) are among the most prevalent chronic illnesses and the leading causes of disability in the United States. These debilitating diseases result in a diminished quality of life and carry substantial economic costs.[1]

The clinical hallmarks of OA and RA are pain and inflammation, and prostanoids are important mediators of these processes. It is now known that nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins from arachidonic acid through their actions on critical interme-

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diate biosynthetic enzymes, cyclooxygenase (COX) or prostaglandin-endoperoxide synthase, which has 2 isoforms.[2] Briefly, COX-1 is a homeostatic, largely constitutively expressed enzyme found in most tissues. The prostaglandin-mediated mucosal defense mechanisms of the gastrointestinal (GI) tract are linked to COX-1 expression. In contrast, COX-2 is largely inducible at inflammatory sites, and this isoform is thought to generate prostaglandins responsible for pain and inflammation.[3] This view of COX isoenzyme–segregated activity has led to the hypothesis that damage to the GI system by NSAIDs is a result of COX-1 inhibition, while the analgesic and anti-inflammatory effects of NSAIDs are mediated by inhibition of COX-2. Accordingly, the ability to inhibit COX-2 while sparing COX-1 should provide therapeutic benefits in the management of pain and inflammation, without deleterious effects on the integrity of GI mucosa.[3]

Insight into the structure, biochemistry, and molecular pharmacology of the COX isoenzymes has provided the opportunity to design new NSAIDs, coxibs, that selectively inhibit COX-2[4] (see Cronstein, this supplement). Two of these drugs, rofecoxib and celecoxib, have been shown to have no clinically relevant inhibition of COX-1 activity.[5] These agents have efficacy similar to that of nonselective NSAIDs but with a low potential for mucosal injury and GI complications.[6,7] In addition, one new COX-2, valdecoxib, has recently received FDA approval for OA, RA, and menstrual pain; several COX-2 inhibitors are in clinical development. The development and clinical application of COX-2–specific inhibitors are reviewed here.

■ ARTHROPATHIES AND INFLAMMATION

Osteoarthritis

Osteoarthritis is the most common of articular disorders. Though the etiology of OA remains unknown, it is increasingly appreciated that inflammation is a component of this disease.[8] Fundamentally, OA is a process of cartilage degradation accompanied by incomplete repair. This cascade of events is usually initiated by biomechanical insult or intrinsic factors such as genetic, metabolic, endocrine, or neuropathic disorders.[9]

Prostaglandins are central to the pathophysiology of arthritides. In healthy joint cartilage, prostaglandins likely contribute to homeostasis.[10] In the arthritic joint, the overproduction of prostaglandins may lead to inflammatory and degradative processes.[10] As OA progresses, chronic inflammation ensues, characterized by the disproportionate activities of growth factors and cytokines.[9] Synovial fibroblasts, macrophages, and chondrocytes become activated, and multiple proinflammatory mediators are released into the synovial fluid. With further disease progression, chondrocytes fail and proteolytic enzymes overwhelm matrix defenses. Cartilage degradation occurs as proteoglycans are lost, and cartilage becomes less elastic. Cartilage fibrillation and subchondral sclerosis is seen; osteophytes and subchondral bony cysts develop.[11]

A major role of prostaglandin E_2 (PGE_2) in the pathogenesis of OA is supported by in vitro data, which show that chondrocytes isolated from patients with OA produce 50-fold more PGE_2 than chondrocytes from patients without OA.[12] PGE_2 appears to have an autocrine effect on chondrocytes, increasing proteoglycan production. High concentrations of prostaglandins can inhibit collagen synthesis, and the inhibitory effects of interleukin 1 (IL-1) on collagen transcription may be mediated in part by prostaglandins.[13] Prostaglandins also have significant effects on osteoclasts and osteoblasts, participating in the regulation of bone generation and resorption. Degradation of the joint may also result from prostaglandin-stimulated release of matrix metalloproteinases (MMPs).[14]

Rheumatoid arthritis

Initiation of RA begins with an immune event in the form of antigen presentation to T cells, leading to activation, with T_H1 responses predominating.[15] The activation of macrophages by T_H1 cytokines and their release of proinflammatory cytokines, including tumor necrosis factor-α (TNFα) and IL-1, lead to further activation of cells in the synovium including synovial fibroblasts and endothelial cells. Cytokines released by the accumulated cells regulate growth, differentiation, and activation of other cells in the environment, including chondrocytes and osteoclasts. The result is mediator generation—MMPs including collagenase, prostaglandins, and nitric oxide—with eventual destruction of bone and cartilage.[16]

Prostaglandins are involved in a number of biologic activities relevant to the pathogenesis of RA. Prostaglandins are found in elevated levels in rheumatoid synovial fluid, and the bone-resorbing

activity produced by rheumatoid synovial tissues was shown to be mediated in part by PGE_2.[17] Fibroblasts from patients with either OA or RA release greater amounts of PGE_2 compared with normal fibroblasts.[18] Increased proliferative responses to PGE_2 may occur similarly for both OA and RA, mediated by the proinflammatory cytokine, IL-1.[18]

It is likely that many of the PGE_2 effects on bone and cartilage potentially involved in OA are also important in RA.[13,19] In addition, prostaglandins probably contribute to such symptoms as swelling, redness, fever, and pain. By interacting with bradykinin and IL-1β, PGE_1 and PGE_2 may enhance vasopermeability and are thought to be hyperalgesic.[12]

SIGNIFICANCE OF COX-1 INHIBITION BY NSAIDS

For decades, NSAIDs have been the cornerstone of pharmacologic management of arthritic and rheumatologic illnesses. NSAIDs are generally well tolerated, but they have tissue-specific toxicity. GI intolerance and GI bleeding were recognized early during NSAID use and have been persistent features of NSAID therapy for nearly a century. Prospective studies have shown significant risk of serious gastrointestinal complications and mortality associated with NSAID use,[20–26] which results in about 16,500 mortalities annually in the United States.[27] Although individual nonselective NSAIDs vary in their relative inhibition of COX-1 and COX-2, their toxicity is rather uniform.

GI mucosal injury is believed to result from local and systemic events. Inhibition of COX-1–mediated prostaglandin leads to decreased mucus and bicarbonate, lowered mucosal blood flow, and inhibition of epithelial proliferation.[27] Additional side effects of blocking COX-1 include inhibition of platelet aggregation and increased bleeding, which contribute to GI consequences. NSAIDs also have renal effects and can result in fluid retention[28] (see Weir, this supplement).

ROLE OF COX-2 IN ARTHROPATHY

COX-2 and inflammatory arthritis

The molecular biology of COX-2 regulation is consistent with observations that COX-2 expression increases in response to inflammatory stimuli, duress, and tissue repair.[3] Prostaglandins are clearly influential in the pathogenesis of arthritic disorders. Therefore, the relative expression of COX enzymes in arthritic tissues may offer clues to the potential therapeutic benefit of COX-2 inhibition.

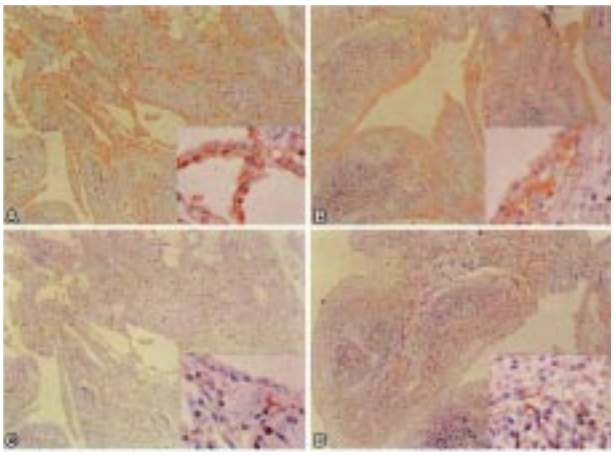

FIGURE 1. Immunohistologic staining of COX-1 (A, B) and COX-2 (C, D). Samples are the same synovial tissues from OA (A, C) and RA (B, D). Positive immunoreactivity of COX-1 is seen in the synovial lining cells in OA (A) and RA (B), and COX-2 expression is seen to be intense in inflammatory cells from OA (C) and RA (D) (high power field, ×400). (From Lee et al with permission.)[36]

In synovial tissues, the regulation of COX-2 transcription is under the influence of a number of cytokines abundant during arthritic inflammation, including IL-1β and TNFα.[29] IL-1β enhanced de novo COX-2 transcripts but not COX-1 transcripts in synovial explants from patients with RA.[30] In addition, COX-2 mRNA is upregulated in the cellular response to fluid shear stress in the joint.[31] The effect of COX-2–selective inhibitors has been examined in rheumatoid synoviocytes and found to prevent PGE_2 production in response to IL-1 and TNFα.[32,33] In animal models of inflammatory arthritis, COX-2 synovial expression increased markedly, paralleling amplified PGE_2 levels. Furthermore, pharmacologic inhibition of COX-2 abrogated inflammation in these models.[34,35] In humans, COX-1 levels are similar in normal synovium and that from patients with OA or RA. In synovia of OA and RA patients, however, significant upregulation of COX-2 transcription and expression occurs (**Figure 1**).[12,36–38]

COX-2 and nitric oxide

The nitric oxide (NO) and COX pathways share a number of potentially significant similarities.

Briefly, both enzymes are induced in tandem in inflammatory settings.[39] Cartilage explants from patients with OA or RA produce NO ex vivo, as do synoviocytes and chondrocytes.[40] IL-1β can also stimulate inducible nitric oxide synthase (NOS) pathways.[40] NO can substantially induce prostaglandin production via upregulation of COX-2.[39] On the other hand, addition of an NOS inhibitor augments PGE_2 production in OA cartilage explants, suggesting that NO may inhibit PGE_2 release.[12] NO has detrimental effects on chondrocytes, and can inhibit collagen and proteoglycan synthesis. NO can activate MMPs, resulting in cartilage degradation. Finally, NO triggers chondrocyte apoptosis, a process enhanced by PGE_2, and specific inhibition of COX-2 blocks NO-mediated chondrocyte apoptosis.[41]

COX-2 is emerging as a pivotal enzyme in the inflammation and tissue damage that occurs in the arthritic joint. Intensified expression of COX-2 but not COX-1 in rheumatoid tissues suggests an "Achilles' heel" in the prostaglandin-mediated biologic events because PGE_2 and its downstream effects can be blocked with COX-2 inhibitors. It is this rationale that has provided the basis for the development and use of COX-2–selective inhibitors in clinical practice.

COX-2–selective inhibitors

Following cloning and characterization of COX-2, it was clear that structural differences could be exploited for the development of selective inhibitors[42] (see Cronstein, this supplement). The determination of selectivity, however, has only recently been formally addressed.

Conventional NSAIDs vary in their relative inhibition of COX-1 and COX-2 enzymes, and the reported ratio of COX-1 to COX-2 specificities for a specific agent can vary by up to 100-fold.[28] The International Consensus Meeting on the Mode of Action of COX-2 Inhibition (ICMMAC) brought together experts in rheumatology, gastroenterology, and pharmacology to assess the significance of differential inhibition of COX-1 and COX-2.[28] ICMMAC suggests that a drug be considered COX-2–selective if it inhibits COX-2 but not COX-1 across the entire therapeutic dose range based on whole blood assays. The panel concluded that, according to these criteria, with the exception of rofecoxib and celecoxib, all NSAIDs available in 1999 inhibit both isoenzymes and are COX-nonspecific.[28]

The clinical implications of even a small degree of COX-1 inhibition are unknown. Therefore, ICMMAC recommended that agents that preferentially inhibit COX-2 (based on a COX-1/COX-2 IC_{50} ratio) be considered nonselective if there is evidence that they may inhibit COX-1 at therapeutic concentrations. From a clinical perspective, the pivotal criteria for COX selectivity are safety and efficacy as demonstrated by large clinical trials in generalizable groups of patients.

CLINICAL APPLICATION OF COX-2–SELECTIVE INHIBITORS

Rofecoxib and celecoxib have been for some time the only available COX-2–selective inhibitors approved by the US Food and Drug Administration (recently, valdecoxib was approved for use in OA, RA, and menstrual pain). Rofecoxib and celecoxib are prescribed widely in the United States, and the use of COX-2–selective inhibitors is now included in the current American College of Rheumatology treatment guidelines for OA.[43] Both of these coxibs lack clinically relevant COX-1 inhibition at or above therapeutic levels, though rofecoxib is about 30 times more selective for COX-2 than celecoxib. Both result in improved GI safety, and each has efficacy equivalent to that of nonselective NSAIDs. An additional agent, meloxicam, has recently been approved for use in the United States and exhibits a high degree of specificity for COX-2 but also inhibits COX-1 at a low dosage of 7.5 mg/day.[44] Studies of inhibition of serum thromboxane B_2 show that celecoxib at single doses of 100 mg and 400 mg (but not 800 mg), and rofecoxib at doses of 12.5 mg and 25 mg do not inhibit COX-1 to a significant degree compared with placebo; meloxicam (15 mg) and ibuprofen (800 mg) both resulted in significant COX-1 inhibition.[44,45]

Detailed discussions of the efficacy of coxibs as analgesics (see article by Katz in this supplement), in the treatment of OA and RA (see article by Schnitzer), and of their GI safety (see articles by Peura and Scheiman) are presented in this supplement. The cardiovascular and renal side effect profiles of coxibs have received much attention, and these issues are also discussed in detail (see articles by Konstam and Weir).

OTHER CLINICAL CONSIDERATIONS

Aspirin-sensitive respiratory reactions

Some patients with asthma experience respiratory reactions after ingesting aspirin or other NSAIDs. With the introduction of COX-2–selective inhibitors, the question was raised as to whether patients with aspirin-sensitive respiratory disease (ASRD) would tolerate these drugs. In a small double-blind, crossover study, 12 patients with ASRD received either an increasing dose of rofecoxib (1.5 to 25.0 mg over 5 days) or a placebo.[46] Patients then crossed over to the complementary arm. None of the patients receiving rofecoxib had dyspnea or decreases of >20% in forced expiratory volumes (FEV_1). In a randomized, double-blind, placebo-controlled study of 60 patients with confirmed ASRD, none of the patients receiving rofecoxib 12.5 or 25.0 mg over 48 hours had symptoms, declines in FEV_1, or changes in nasal examination findings.[47] A study of 17 patients with asthma and aspirin intolerance did not have bronchoconstriction or extrapulmonary reactions after a graded challenge with celecoxib (10, 30, 100, and 200 mg).[48] Although based on these studies selective COX-2 inhibitors appear to be tolerated by patients with ASRD, product labeling for all available agents lists this as a contraindication to therapy. It should be emphasized that these observations apply only to aspirin-sensitive respiratory reactions, not urticaria or angioedema; these processes are likely mediated through different pathobiologic mechanisms. It is also important to note that urticaria, angioedema, and anaphylaxis have been reported with the currently available COX-2–selective agents. Up to one third of patients with NSAID-induced urticaria and angioedema have had reactions when challenged with COX-2–selective agents.[49–52]

Sulfonamide hypersensitivity

The presence of a sulfonamide group in the celecoxib molecule prompted concern that patients with sensitivity to sulfonamides may be reactive to celecoxib. Patients with hypersensitivity to sulfonamides were excluded from the largest outcomes study of celecoxib safety.[7] A meta-analysis of 14 double-blind trials of celecoxib in patients with arthritis found that the overall incidence of allergic reactions with celecoxib was not statistically different from that seen with placebo or active comparators. Although patients with a history of sulfonamide hypersensitivity had a 3- to 6-fold higher incidence of dermatologic reactions, the trend was consistent in all 3 groups (placebo, NSAIDs, and celecoxib).[53] The nature and description of these dermatologic reactions is not reported, making interpretation of these results difficult. Prospective trials are needed to confirm these findings. Pending these studies, celecoxib labeling contraindicates its use in patients with known allergic reactions to sulfonamides. Rofecoxib does not possess a sulfonamide moiety, and patients with sulfonamide sensitivity were not excluded from rofecoxib clinical trials. Of note, both valdecoxib and parecoxib have sulfonamide moieties in their structures, but patients with sulfonamide sensitivity have not been excluded from clinical trials with these agents. Whether dermatologic reactions will be increased in incidence has not yet been reported.

Further discussion

A deeper understanding of the physiologic roles of COX-1 and COX-2 will clarify the clinical implications of selective COX-2 inhibition. COX-2 has a complex and uncharacterized role in normal physiology.[54] Experience with NSAIDs has verified the tolerability of COX-2 inhibition in the context of these nonselective drugs. It must be acknowledged, however, that biologic effects of prostaglandin production by unopposed COX-1 may differ from that of combined inhibition.[55] For example, COX-2–selective inhibitors decrease levels of the vasodilatory PGI_2 while COX-1–derived platelet TXA_2 production is unaffected. COX-2–selective inhibitors, therefore, may possess less antithrombotic and cardioprotective properties than nonselective NSAIDs. Animal studies suggest a role for COX-2–derived prostacyclin in coronary circulation.[56] Another area deserving further investigation is the apparent increased risk of cardiovascular events that occur in RA patients and the implications of use of coxibs in this patient population.

In the kidney, both COX-1 and COX-2 are constitutively expressed, and it is unclear which enzyme is predominantly responsible for NSAID-induced renal toxicity. Nephrotoxicity induced by conventional nonselective NSAIDs is most commonly associated with reduced glomerular filtration rate (GFR); COX-2 appears to be most

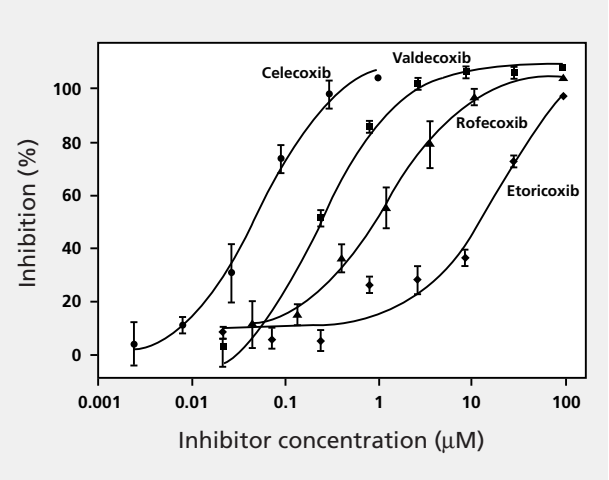

FIGURE 2. Inhibition of COX-1 by COX-2–selective agents as determined with a sensitive microsomal assay. (Adapted from Riendeau et al with permission.)[5]

important in sodium retention without a decrease in GFR.[57] Published clinical experience shows that the incidence of renal adverse events with COX-2 inhibitors is similar to that of NSAIDs.[6,7] In patients with a high risk of renal side effects, COX-2–selective inhibitors should be approached with the same caution as other NSAIDs.[58]

The advent of new COX-2–selective agents and their ensuing clinical experience may shed greater understanding on these issues, leading to optimal management of COX-2–mediated inflammatory diseases.

Etoricoxib, an investigational COX-2–selective inhibitor, demonstrates a high degree of COX-2 specificity (106-fold in ex vivo human blood assays) and has a lower potency of COX-1 inhibition than other reported agents (**Figure 2**).[5]

Parecoxib, the first COX-2–selective inhibitor formulated for parenteral use (intravenous or intramuscular), compares favorably with ketorolac. Parecoxib is not biologically active; it is a water-soluble prodrug that is rapidly hydrolyzed to valdecoxib.

CONCLUSIONS

The discovery of COX-2 and the development of COX-2–selective agents have renewed interest in the role of prostaglandins in the pathogenesis of arthritic illnesses. The complexity of COX-1 and COX-2 functions in normal physiology and pathobiology challenges our understanding of the mechanisms through which both nonselective and COX-2–selective agents act. COX-2 expression in the inflamed synovium of patients with OA and RA suggests that targeting COX-2 may be an effective therapeutic intervention. Limited insight into the normal physiologic roles of COX-2 in the joint, however, leaves unresolved the long-term consequences of unopposed COX-2 inhibition on functions such as bone remodeling and wound healing. The COX-2 agents nonetheless provide the promise of significantly decreased upper GI complications in the long-term treatment of patients with arthritis, raising the hope of alleviating a substantial human and economic cost of morbidity and mortality associated with NSAIDs. This promise extends to benefits of preemptive analgesia, and to an ever-widening arena of treatment potential including Alzheimer's disease and colon cancer. The embrace of COX-2 inhibitors should be appropriately tempered by awareness of cardiovascular and renal implications of unopposed thromboxane A_2 production and the effect of diminished prostacyclin on vascular dilation, sodium retention, and platelet aggregation. This caveat is especially important for RA patients, who appear to have a higher incidence of CV events. The needs of patients at high risk for thrombosis or NSAID-related renal toxicity, or patients with ASRD, should be considered carefully. By measures of published clinical experience, COX-2 inhibitors represent a significant advance in the therapy of rheumatic disease. With newer COX-2 agents just over the horizon, treatment options for patients may multiply, expanding the possibility of safe and efficacious therapy for many patients.

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