THE CLEVELAND CLINIC FOUNDATION

CLEVELAND CLINIC JOURNAL OF MEDICINE

COXIBS: EVOLUTION OF A REVOLUTIONARY CLASS

EVOLVING CONCEPTS AND ISSUES SURROUNDING COX-2 INHIBITORS

SUPPLEMENT 1 TO VOLUME 69, 2002

SPECIAL ISSUE

Journal Supplements

With this supplement devoted to COX-2–inhibiting drugs, the *Cleveland Clinic Journal of Medicine* is undertaking a new venture, which will result in a series of single-topic, sponsored collections of papers of interest to practicing physicians. The *Journal* has indeed published supplements from time to time, but this venture represents a focused effort to actively develop *Journal* supplements that will be of interest to our readers. The guest editor for each supplement, in this case Dr. Marc Hochberg of the University of Maryland, will be a respected leader in the field under discussion. The guest editor will have full editorial control, including peer review, of the content. Our role at the *Journal* will be to select the topics forming the basis of the supplements and to make sure that authors fully disclose their relationships with sponsors.

Development of the *Journal*'s supplements program will provide an additional useful service for our readers, i.e., more in-depth discussion of topics relevant to clinicians by experts in the field. We believe that the coxib supplement gets us off to a great start with this program, and we hope you agree with us. More to come…

JOHN D. CLOUGH, MD
Editor-in-Chief

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Preface

This supplement was developed from a roundtable entitled **"Coxibs: Evolution of a Revolutionary Class,"** held on August 4 and 5, 2001, in New York, New York. Subtitled *"Evolving Concepts and Issues Surrounding COX-2 Inhibitors,"* this event involved 10 experts representing perspectives from various specialty areas concerned with COX-2–selective inhibitors, including gastroenterology, rheumatology, nephrology, cardiology, pharmacology, anesthesiology, and primary care. Participants were asked to present information to their colleagues that would form the basis for the supplement articles. The interactive discussions initiated by the presentations helped shape the articles. Guest editor Marc C. Hochberg, MD, MPH, moderated the roundtable discussions and provided input during the article development process. The overall goal of the supplement is to provide a comprehensive analysis of the current role of coxibs in various chronic and acute treatment settings, and to characterize some of the underutilized and potential use areas of these agents. Furthermore, points of particular interest to the primary care physician are highlighted throughout each article.

The following objectives will be addressed in the supplement:

- The evolution of the NSAID class and the role of COX-2–selective inhibitors
- The clinical profiles of particular COX-2–selective inhibitors and their appropriate applications
- The class side effect profile of the NSAIDs and points of differentiation for the COX-2–selective inhibitors
- The use of particular NSAIDs in various patient types
- The current and potential uses of coxibs in the perioperative setting
- New research into potential use areas for coxibs.

Foreword

MARC C. HOCHBERG, MD, MPH, EDITOR

The discovery of cyclooxygenase-2 (COX-2) has led to the development of an important new subclass of nonsteroidal anti-inflammatory drugs (NSAIDs) with similar efficacy to nonselective NSAIDs, but with an improved toxicity profile. Like many nonselective NSAIDs, coxibs are currently used to treat osteoarthritis (OA), rheumatoid arthritis (RA), menstrual pain, and acute pain. OA and RA are among the most prevalent chronic illnesses and the leading causes of disability in the United States. These ailments result in a significantly reduced quality of life and confer a substantial economic burden. Coxibs have proven to be useful in a variety of therapeutic areas and ongoing research may identify additional applications. The first article in the supplement, by Clifton O. Bingham III, MD, traces the development of the COX-2–selective inhibitors and provides the foundation for the subsequent articles in the supplement.

Elucidation of the structures of COX isoenzymes has been key in the development of coxibs. The second supplement article, by Bruce N. Cronstein, MD, summarizes some of the key aspects of COX

biochemistry, structure, and function and the evolution of understanding the mechanism of action of COX-2–selective inhibitors.

In numerous clinical trials, coxibs have been shown to be at least as effective as nonselective NSAIDs in relieving pain and inflammation associated with OA and RA, and, notably, with a significantly lower risk of NSAID-related adverse gastrointestinal (GI) events. Thomas J. Schnitzer, MD, PhD, and I review existing efficacy data regarding coxibs in OA and RA, and discuss appropriate use of coxibs in these clinical settings.

GI complications associated with NSAID use often emerge without the appearance of prior symptoms. David A. Peura, MD, reviews risk factors associated with GI complications and discusses risk-reduction strategies, including appropriate use of coxibs in particular patient populations. Additionally, James M. Scheiman, MD, reviews four major GI outcomes studies comparing coxibs to nonselective NSAIDs, including an in-depth review of the GI outcomes from Vioxx Gastrointestinal Outcomes Research (VIGOR) trial and Celecoxib Long-term Arthritis Safety Study (CLASS).

While a significant difference in GI complications between nonselective NSAIDs and coxibs has been well established, other safety comparisons are less well characterized. Marvin A. Konstam, MD, and Matthew R. Weir, MD, provide perspective on issues surrounding the comparative cardiovascular safety profiles of the nonselective NSAIDs, aspirin, and coxibs. In a subsequent article, Dr. Weir reviews the renal effects of nonselective NSAIDs and coxibs. In both articles, appropriate use of these agents and proper precautions are described.

Pharmacoeconomic considerations for the use of coxibs among patients with varying degrees of risk for GI injury are discussed by A. Mark Fendrick, MD. This article examines some of the key factors in determining the cost-effectiveness of coxib therapy. Clinical and economic data are presented on issues from basic costs to clinical effects and economic consequences of available treatment options.

The final two supplement articles discuss the use of coxibs in the acute and perioperative pain settings, as well as important future use areas. There is concern about preoperative use of nonselective NSAIDs, mainly because of the potential for excessive bleeding. The use of opioids has long been a concern in the perioperative setting, because of the potential for tolerance and other problematic postoperative complications such as constipation. Warren A. Katz, MD, reviews the use of coxibs in the acute and perioperative settings. In the final article, Mark J. Lema, MD, PhD, reviews some emerging clinical areas for coxibs and discusses research into novel therapeutic applications. The rationale and data on the use of coxibs in treating the progression of both Alzheimer's disease and colorectal cancer are discussed. Dr. Lema also discusses the role of coxibs in the management of cancer pain.

It is clear that the benefits of COX-2–selective inhibitors have continued to expand into a variety of therapeutic categories since their initial development for pain associated with arthritis. Accompanying this expansion has been an increased understanding of the mechanisms underlying inflammation and pain and the more complex roles coxibs may play. It is our hope that this supplement will serve to provide those clinicians who serve a broad spectrum of patients and specialty areas with the most recent data and, indeed, the most current discussion on evolving concepts and issues surrounding these truly revolutionary agents.

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

CLIFTON O. BINGHAM III, MD

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.

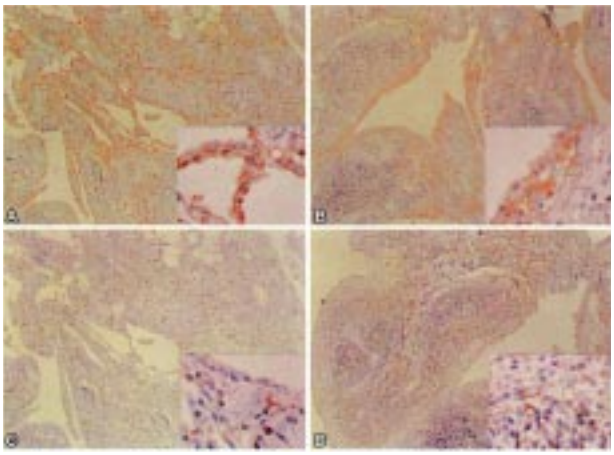

FIGURE 1. Immunohistologic staining of COX-1 (A, B) and COX-2 (C, D). Samples are the same synovial tissues from OA (A, C) and RA (B, D). Positive immunoreactivity of COX-1 is seen in the synovial lining cells in OA (A) and RA (B), and COX-2 expression is seen to be intense in inflammatory cells from 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

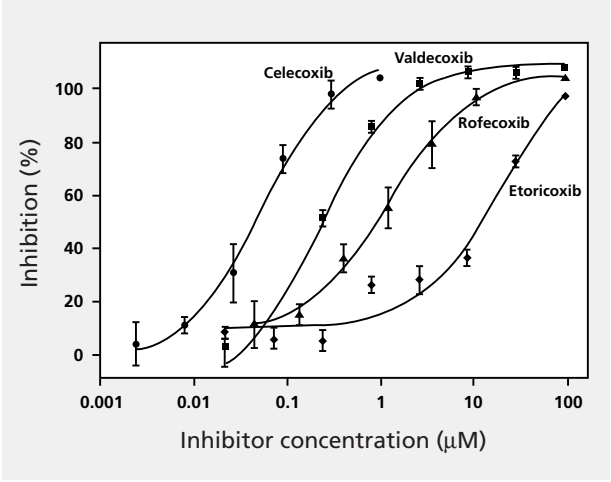

FIGURE 2. Inhibition of COX-1 by COX-2–selective agents as determined with a sensitive microsomal assay. (Adapted from Riendeau et al with permission.)[5]

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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Cyclooxygenase-2–selective inhibitors: Translating pharmacology into clinical utility

BRUCE N. CRONSTEIN, MD

ABSTRACT

Anti-inflammatory agents have been used for centuries, but only in the last few decades has medical science gained insight into the complex biologic roles of the primary mediators of inflammation, the eicosanoids and their derivatives. Detailed understanding of the prostaglandins and leukotrienes provides a framework for the treatment of pain, inflammation, and fever with aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), but these agents have exacted a substantial side effect burden. The discovery of cyclooxygenase-2 (COX-2) has guided development of rationally designed therapeutic agents that have the benefits of older NSAIDs with reduced gastrointestinal toxicity. Elucidation of the structure of COX isoenzymes has been key in the development of coxibs, the COX-2–selective subset of NSAIDs. Methods to determine the degree of COX-2 selectivity have been refined and are indispensable for comparing the relative selectivity of these agents.

This review summarizes some of the key aspects of COX biochemistry, structure, and function and the evolution of understanding the mechanism of action of COX-2–selective inhibitors. The clinical relevance of COX-1 compared with COX-2 inhibition is discussed to provide a framework upon which clinicians can better appreciate current and future therapeutic applications of coxibs.

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Plant-derived salicylates have been used traditionally by many cultures for the treatment of pain and fever. In a 1763 publication, Edmund Stone described the use of salicin-containing willow bark to treat fever in a series of patients in England.[1] The synthesis of acetylsalicylic acid in the 1890s ushered in the era of pain management with aspirin,[2] which became the most frequently used drug in the world. Many nonsteroidal anti-inflammatory drugs (NSAIDs) have been developed since aspirin was discovered: over 50 NSAIDs and over 200 aspirin-containing compounds are currently available in the United States. More than 13 million people use an NSAID daily.[3]

Despite widespread clinical use of NSAIDs for nearly a century, their mechanism of action was not understood until 1971, when it was proposed that these agents inhibit prostaglandin synthesis.[4] Cyclooxygenases are critical enzymes in the biosynthetic pathways of many bioactive compounds originating from arachidonic acid, including prostaglandins, thromboxanes, and prostacyclins. Together with the lipoxygenases, cyclooxygenase (COX) enzymes play a key role in inflammation,

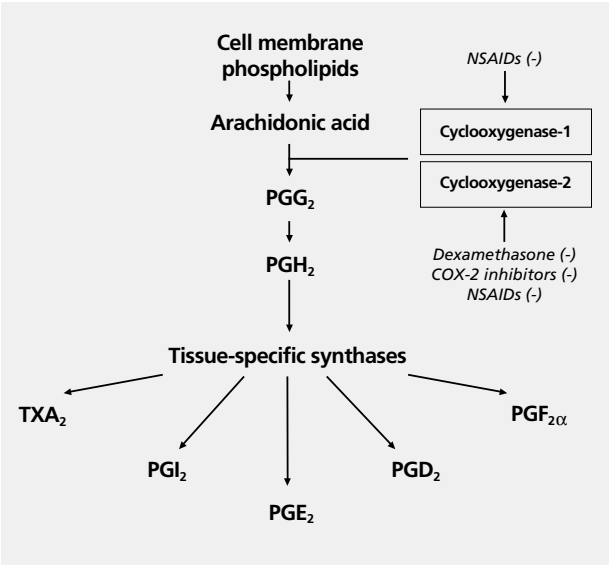

FIGURE 1. Schematic summary of the biosynthetic pathway for eicosanoids derived from arachidonic acid.[9,10]

pain, and other biologic processes. Specifically targeting these enzymes has been a major goal of drug design for the past 2 decades.

The discovery of two separate COX isoforms, COX-1 and COX-2, led to the hypothesis that the therapeutic, and conversely, adverse effects of NSAIDs lay in the specific distribution and function of each isoenzyme.[4] Inhibition of COX-1, the enzyme involved in the synthesis of prostaglandins responsible for integrity of the gastrointestinal (GI) mucosa, would lead to GI damage, while COX-2–selective inhibition should specifically alleviate pain and inflammation. This general dichotomy of action has been shown for COX-2–selective inhibitors, or coxibs, in large clinical trials for the treatment of pain and inflammation.[5,6] This review summarizes the role of COX-1 and COX-2 in prostaglandin-mediated biologic activities and the human pharmacology of selective COX-2 inhibitors, putting into clinical context the basis for the different/unique therapeutic assets of these agents.

■ EICOSANOIDS AND PROSTAGLANDINS

Milestones in eicosanoid research

In the 1930s, researchers in the United States and Sweden independently reported that compounds found in human semen had smooth muscle contraction and vasopressor properties. From their origin, von Eular called these compounds *prostaglandins*.[7] The biochemistry of prostaglandins remained elusive for 3 decades, primarily due to their paucity and instability. Elucidation of related biosynthetic pathways by Hamberg and Samuelsson in 1967 led to recognition of an abundance of biologically active compounds.[8] In 1971, Vane showed that aspirin could inhibit the synthesis of prostaglandins.[4] Aspirin is now known to target COX, a prostaglandin synthase responsible for the bicyclic endoperoxidation of fatty acids to prostaglandins. An additional pathway in eicosanoid metabolism was found to be mediated by lipoxygenases, resulting in the elucidation of the leukotriene-related pathways in the 1980s and the lipoxins in the 1990s.[9] Together, the prostaglandins, leukotrienes, lipoxins, and related compounds are known to occupy a crucial role in many biologic processes, giving the eicosanoids prominence in modern pharmacology and medicine.

Prostaglandins in physiology and pathophysiology

Eicosanoids are produced from arachidonic acid (a 20-carbon polyunsaturated fatty acid) after its liberation from the cell membrane by phospholipase in response to diverse stimuli.[10] Arachidonic acid is metabolized to eicosanoids by 2 groups of enzymes: the cyclooxygenases, which produce prostaglandins and thromboxane; and the lipoxygenases, which catalyze leukotriene and lipoxin synthesis. Eicosanoids play a key role in inflammation (**Figure 1**).[10]

The COX enzyme ultimately catalyzes the formation of prostaglandin (PG) H_2 from arachidonic acid. Within the tissues, PGH_2 is converted to a series of prostaglandins with a wide spectrum of biologic activities.[11] NSAIDs can inhibit the COX isoenzymes. Three lipoxygenases catalyze the metabolism of arachidonic acid to the leukotrienes through a series of reactions.[10] The lipoxygenases are not inhibited by NSAIDs.

Prostaglandin receptors

Prostaglandins possess diverse biologic activities and are therefore significant in the pathophysiology of a wide array of diseases. The tissue-specific and nonoverlapping properties of prostaglandins reflect the compartmentalized nature of receptors through which they act.[12] Many prostaglandin receptors are G-protein coupled receptors, designated EP, FP, IP,

TP, and DP; their cognate ligands are PGE_2, $PGF_{2\alpha}$, PGI_2, TXA_2, and PGD_2, respectively.

In light of the many activities of PGE_2, it is not surprising that 4 distinct receptor subtypes ($EP_{1\text{-}4}$) have been found to transmit signals from this molecule.[12] All 8 prostaglandin receptors have been cloned and their physiologic roles explored in receptor knock-out mice. Although there is obvious therapeutic potential in the ability to block specific activities of prostaglandins, the physiologic role of the receptors is only partially characterized, and subtype-selective antagonists remain elusive.

■ CYCLOOXYGENASES

Discovery

In 1988, the synthesis of a COX-like enzyme was shown to occur in response to interleukin (IL)-1 and bacterial lipopolysaccharide.[13,14] An induced form of COX was described that was immunologically distinct from a constitutive enzyme.[15] It was mitogenesis research, however, that led to the discovery of the COX-2 gene. In a study of gene activation in response to *src*, an mRNA expressed in Rous sarcoma virus–transformed cells was found that was homologous to COX.[16] COX-2 has been cloned from a variety of species, including humans.[17]

Similarities, differences, and interactions of COX enzymes

The ability of COX isoenzymes to orchestrate complex prostaglandin-mediated physiologic functions reflects an elaborate interplay between the 2 forms of the enzyme. Contributing to this balance are differences in their structure, level of expression, interaction with other enzymes, and feedback regulation.

In all species examined, COX-1 and COX-2 proteins have approximately 60% amino acid sequence identity.[18] The 3-dimensional structure of the COX enzymes are strikingly similar to each other.[19,20] COX isoenzymes are similar in active site structure. Both isozymes have an active site consisting of a hydrophobic channel, and amino acids in this region are nearly identical. Three amino acid differences, however, result in a larger and more accessible channel, in COX-2 (**Figure 2**).[21] Inside the hydrophobic channel of COX-2, substitution of a valine for isoleucine at residue 523 of COX-2 creates a "side pocket" that selectively allows certain

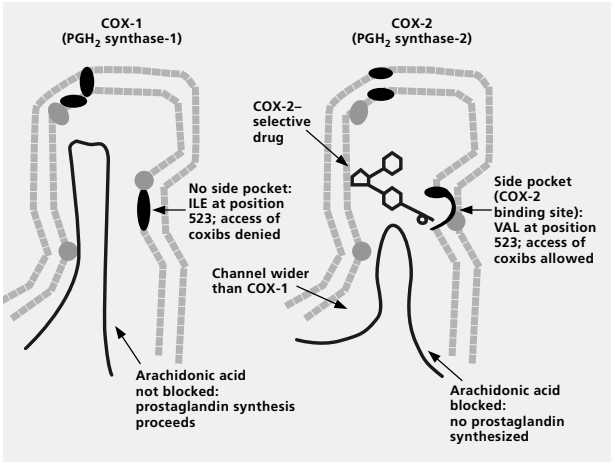

FIGURE 2. Structure of the COX-1 and COX-2 enzymes.[21] Schematic showing active site similarities and differences. ILE = isoleucine; VAL = valine.

agents to bind and inhibit this enzyme.[22]

Although the overall structure and essential catalytic activity of the 2 COX isoenzymes are similar, there are vivid distinctions in their regulation and expression. The 2 enzymes are encoded on different chromosomes, and differ in translational and post-translational regulation. In general, COX-1 is constitutive, and its expression is regulated by hormonal signals involved in maintaining physiologic homeostasis.

Consistent with the properties of "housekeeping" genes, COX-1 lacks a TATA box.[18] COX-1 is developmentally controlled, and little is known about how COX-1 expression is regulated. COX-1 is expressed in all tissues, albeit at different levels and not necessarily in all cells of a given tissue. Importantly, COX-1 but not COX-2 is constitutively expressed in the stomach, where it is involved in mucosal defense and repair.

Though COX-2 can also be constitutive in some tissues, COX-2 expression and activity is largely responsive to adverse stimuli, such as inflammation and physiologic imbalances. The COX-2 promoter has several putative regulatory regions that bind transcription factors. Although dozens of COX-2 stimulatory factors have been identified, those commonly seen in inflammation, and upregulated in the proinflammatory milieu, are key in regulation of COX-2 signaling pathways. These include transcription factors that respond to bacterial endotoxin, IL-1, and TNF-α such as NFκB, C/EBP, and protein kinases (ERK1/2 and MAPK).[23] The presence

of a cyclic adenosine monophosphate (cAMP) response element (CRE) in the COX-2 promoter may allow for COX-2 expression to be directly regulated by feedback from prostaglandins through their influence on cellular cAMP levels.[24] The presence of cytokines stabilizes COX-2 transcripts. Control of COX-2 transcription and translation is thought to be the primary mechanism by which steroids such as cortisol and dexamethasone modulate this enzyme. Post-transcriptional factors also play a role in the expression of COX-2, an immediate early gene, whose expression is controlled by mRNA splicing and translational efficiency.[18,24]

Some prostaglandin-mediated physiologic activities are carried out by only one COX isoenzyme while other activities involve both isoenzymes. For example, COX-1 is essential for thromboxane-mediated aggregation of human platelets and parturition, whereas COX-2 is essential to ovulation and nidation.[25] Other processes, such as inflammation and carcinogenesis, are mediated by both COX-1 and COX-2. In inflammation, COX-2 plays dual roles, both initiating and resolving inflammation.

Some of the segregated activities of COX-1 and COX-2 in cells simultaneously expressing both isoenzymes can be explained by the local concentration of arachidonic acid substrate. The level of enzyme expression itself also plays a role. The activity of each isoenzyme may be regulated in other ways. For example, COX-1 is subject to negative allosteric inhibition such that at lower concentrations of arachidonic acid, COX-2 may be exclusively active, despite the presence of COX-1.[23]

COX isoforms differ in their ability to interact with the terminal enzymes of prostaglandin synthesis.[23] For example, in the presence of COX-1, COX-2 appears to selectively target specific prostaglandin synthases, resulting in a shift from the production of several prostaglandins to a preferential production of PGE_2 and prostacyclin.[26]

The initial notion that COX-1 and COX-2 have unique and mutually exclusive functions has evolved to a concept incorporating multiple and complicated physiologic pathways and function. The view of COX-2 as *the inducible COX enzyme* is an oversimplification. While it is upregulated in response to certain stimuli, COX-2 is expressed constitutively in some tissues. In most tissues where COX-2 is constitutively expressed—notably the brain and kidney—the enzyme is involved in biologic response to physiologic stress. In the kidney, the macula densa is an important component of the renin-angiotensin system that orchestrates sodium balance and fluid volume by monitoring salt concentration.[27] COX-2 is constitutively expressed in the macula densa, and levels there are increased during salt deprivation, suggesting that prostaglandins produced by COX-2 are important in sodium reabsorption in response to volume contraction.[28] In the brain, prostaglandins are involved in nervous system functions such as sleep-waking cycles, fever induction, and pain transmission. While COX-2 is constitutively expressed in the brain, it is also upregulated in parallel with fever and in response to seizures.[29]

■ CYCLOOXYGENASE INHIBITORS

Pharmacologic inhibition of COX enzymes

Insight into cyclooxygenase structure and function has helped clarify the mechanisms through which NSAIDs produce their therapeutic benefits and toxicity. The different ways in which nonselective NSAIDs and coxibs, the selective COX-2 inhibitors, interact with each isoenzyme can explain many of the observed clinical effects, both good and bad, of these agents. Furthermore, this understanding has also provided the basis for a rational approach to designing safer drugs.

The "classical" nonselective NSAIDs bind to both COX-1 and COX-2, interacting with the hydrophobic channel of the COX isoenzymes. Aspirin, unlike other NSAIDs, irreversibly acetylates a serine residue in both COX-1 and COX-2 to prevent binding of arachidonic acid. Other nonselective NSAIDs compete directly for arachidonic acid, inhibiting cyclooxygenase activity in a rapid but reversible manner.[23] Although nonselective NSAIDs bind both COX-1 and COX-2, each isoform is inhibited to different degrees. Coxibs, the COX-2–selective inhibitors, preferentially bind to and inhibit COX-2. Coxibs are selective agents because they bind COX-1 poorly and in a rapidly reversible manner, whereas they bind COX-2 more tightly. This occurs in 2 stages; binding of coxibs to COX-2 during the second stage is tight, with dissociation occurring only slowly (minutes to hours). Preferential inhibition of COX-2 is thought to be due to the additional space in the COX-2 hydrophobic channel, as well as to the presence of a side pocket in the channel. This side pocket can discriminate the coxibs from nonselective agents based

on the different overall structures of these agents, in particular, by the presence in coxibs of specific side chains (**Figure 2**).[21]

COX-2 selectivity

Coxibs spare the beneficial activity of COX-1, that is, its role in the synthesis of prostaglandins important to the GI mucosa. This led to the idea that COX-1–sparing drugs are likely to be less ulcerogenic. Assays were developed in order to delineate the degree of selectivity a given NSAID may have for COX-1 or COX-2. This determination has become especially important for the newer coxibs.

There are in vitro as well as ex vivo methods to determine the 50% inhibitory concentration (IC_{50}) of various NSAIDs and coxibs for each enzyme (**Figure 3**).[30] The results of in vitro assays, which rely on recombinant enzymes, are useful for drug screening but are difficult to interpret and are sometimes contradictory. This may be due to factors like enzyme and substrate used, incubation periods, and other experimental variables. Whole-blood assays (ex vivo), which use whole blood from healthy adults, are the most widely accepted for the determination of COX selectivity.

Activity of COX-1 is determined by measuring thromboxane B_2 synthesis by platelets in whole blood. For COX-2, activity is measured as the synthesis of PGE_2 in whole blood. The use of ex vivo assays is most successful when tests are highly standardized and results are based on large numbers of subjects, as variation between individuals may be as high as 20%.[31] In addition, membrane effects and biotransformation may influence results. Another limitation of this approach is that selectivity in blood may not reflect selectivity at the mucosa. For example, whole-blood assays showed that diclofenac, the most effective COX-2 inhibitor among traditional NSAIDs, remained a potent inhibitor of prostaglandin production in gastric mucosal biopsies.[32] Use of biopsies, however, is not necessarily representative of the in vivo events, and COX enzymes may be differentially expressed in patients with ulcers compared with healthy donors used in these experiments. Although ex vivo assays identify inhibition of COX enzymes at therapeutic plasma levels, COX selectivity at the concentrations seen in the tissues remains unknown.

The IC_{50} values obtained using in vitro or ex vivo assays are expressed as a ratio of COX-1 to

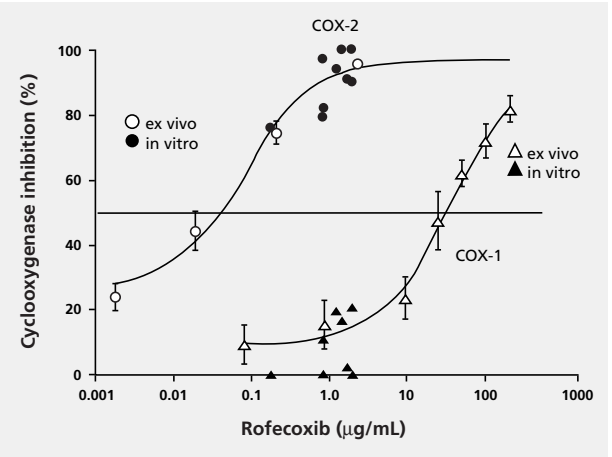

FIGURE 3. In vitro and ex vivo inhibition of cyclooxygenases by the COX-2–selective agent rofecoxib. Rofecoxib concentration-effect curves for COX-1 and COX-2 determined in vitro (filled circles and triangles), and ex vivo inhibition of COX-1 and COX-2 in patients with rheumatoid arthritis who received 50 mg rofecoxib once daily for seven days (open triangles and circles). (Adapted with permission from FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001; 345:433–442. Copyright © 2001 Massachusetts Medical Society. All rights reserved.)

COX-2 inhibition. As a more selective drug requires a lower concentration (IC_{50}) to be effective, the ratio for a COX-2–selective agent will be higher than 1. These pharmacologic methods have potential drawbacks that necessitate careful interpretation of the data.

Several important considerations should not be overlooked in the discussion of the pharmacology of COX inhibitors. First, the relation between the relative inhibition of COX-1 and COX-2 and alteration of prostaglandin-mediated biologic functions is not linear.[33] As pharmacologic targets, the dose-effect thresholds of efficacy and safety for COX-1 and COX-2 inhibition are probably undefinable. Even if it were possible to accurately predict the relative selectivity of COX inhibitors in vivo, it is still not known to what extent, and for how long, COX-1 can be inhibited without an increased risk of GI toxicity. Conversely, the degree of COX-2 inhibition needed to produce anti-inflammatory responses in vivo also is unknown.[31] There are currently insufficient data to accurately correlate biochemical and pharmacologic measures of COX selectivity with clinical efficacy and safety, and the question of how to determine the clinically measurable benefit of selective COX-2 inhibition remains.[3]

What is clinically relevant COX selectivity?

Clinical endpoints, ascertained through trials, are necessary to determine whether COX-2–specific inhibition translates to efficacy and greater GI safety. Various clinical endpoints have been employed for this purpose. GI symptoms, such as dyspepsia, are poorly correlated to gastric lesion formation, and the role of COX-1 in these events is unclear.[33] Endoscopic data are more favorable, and a baseline and post-treatment comparison should provide strong evidence for ulcerogenesis in a clinical setting.[31] Endoscopic studies remain a surrogate for outcomes studies, which should be sought after as the definitive arbiters of GI safety as well as analgesic/inflammatory efficacy.

COX-2–selective inhibitors

In light of the collective evidence for COX selectivity, only a few drugs have a COX-1/COX-2 ratio suggesting that limited inhibition of COX-1 would occur at therapeutic levels. Three drugs that have existed for some time—meloxicam, nimesulide, and diclofenac—all have a COX-1/COX-2 ratio in the range of 10 to 30.[33,34] These drugs, while preferentially inhibiting COX-2, have considerable COX-1 inhibitory activity. Meloxicam, nimesulide, and diclofenac show significant inhibition of COX-1 at therapeutic levels.[35–37] Furthermore, large clinical trials have not been able to show a substantial GI benefit with these agents.[30]

Two drugs approved by the US Food and Drug Administration, rofecoxib and celecoxib, have been shown to have the greatest selectivity for COX-2. In vitro and ex vivo studies show that these coxibs have COX-1/COX-2 ratios that are 10- to 100-fold greater than existing nonselective NSAIDs.[21,33,38] Furthermore, ex vivo assays following single doses in normal hosts showed negligible (~10%) inhibition of TXB_2 release by platelet COX-1. Unlike rofecoxib, however, celecoxib inhibited release of TXB_2 in a dose-dependent manner and had an interindividual variation in response that ranged from 10% to more than 80% inhibition.[39] Both rofecoxib and celecoxib have been examined in clinical trials large enough to have sufficient statistical power for detection of clinical specificity.[5,6] The results fulfilled expectations that COX-2–specific inhibitors could achieve efficacy equal to nonselective NSAIDs with less GI toxicity (see article by Scheiman, this supplement). Additional COX-1–sparing drugs (etoricoxib, valdecoxib, and COX-189; see article on the development of coxibs in this supplement) are in preclinical and clinical development. The outcomes of clinical trials evaluating coxibs are discussed in detail in a recent review.[40]

■ CONCLUSIONS

The magnitude of NSAID use, the high incidence of gastropathy in NSAID users, and the significant morbidity and mortality of NSAID-associated GI outcomes underscore the need for less toxic NSAIDs. In a single decade since the discovery of COX-2, a deeper appreciation of the complexity of prostaglandin metabolism has emerged, leading to new therapeutic avenues capable of overcoming the limitations of classical NSAID toxicity. Despite the challenges of defining COX selectivity, the paradigm that COX-1–sparing drugs are safer has successfully guided the development of promising new anti-inflammatory agents. Patient variability, pharmacodynamics, and preexisting risk factors influence COX-2–specificity, which is why it has been imperative to show COX specificity in large clinical trials with adequate numbers of patients and events. Clinical trials convincingly show that agents specifically inhibiting COX-2 are equivalent in efficacy to nonselective NSAIDs and have a lower incidence of GI toxicity. Although clinical specificity of COX-2 inhibitors has been shown, there is still much not known about COX-1 and COX-2 across the spectrum of health and disease. Intimate knowledge of the pharmacology of COX-2 inhibitors in health and disease will likely open the door to new clinical applications for these drugs.

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COX-2–selective inhibitors in the treatment of arthritis

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ABSTRACT

Therapy with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) has long been the cornerstone of pharmacologic management of patients with osteoarthritis (OA) and rheumatoid arthritis (RA). Many patients with OA or RA, however, are at increased risk of developing clinically significant adverse events associated with NSAID therapy, particularly upper gastrointestinal (GI) complications including symptomatic and complicated ulcers. The introduction of cyclooxygenase (COX)-2–selective inhibitors (coxibs) represents a major advance in the pharmacologic approach to the signs and symptoms of arthritis. In addition to the first two members of this class, celecoxib and rofecoxib, other coxibs have been introduced or are in development (valdecoxib, etoricoxib). In numerous clinical trials, coxibs have been shown to be as effective as nonselective NSAIDs in relieving pain and inflammation associated with OA and RA, and notably, with a significantly lower risk of NSAID-type adverse events. The use of coxibs to treat OA and RA is recommended as first-line therapy when symptoms of pain and inflammation are present in patients vulnerable to potential NSAID-associated GI toxicity.

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Affecting nearly 43 million Americans, arthritis is one of the most prevalent diseases and major causes of disability in the United States.[1] By the year 2020, it is estimated that more than 18% of adults in America will have some form of arthritis.[2]

Rheumatoid arthritis (RA) is a systemic disease marked by inflammatory changes in synovial membranes and articular structures that lead to widespread degeneration of collagen fibers and destruction of bony structures. Osteoarthritis (OA) is believed to be caused by a combination of abnormal biomechanical stresses on the joint and abnormal biochemical and metabolic changes in the chondrocyte and articular cartilage. Unlike RA, when OA inflammation is present, it is usually mild and localized to the affected joint. Nevertheless, proinflammatory cytokines play a pivotal role in the development of OA disease.[3]

The disease process in OA affects the entire joint

and can result in inflammatory changes in the synovium similar to those of RA. These manifest as joint stiffness, loss of physical mobility, and occasionally as joint swelling or redness.[3] Synovial inflammation may be present in early stages of OA, but it is more often seen in advanced stages. OA joint pain, however, does not correlate with histologic evidence of joint inflammation.[4]

Most patients with arthritis are treated by primary care physicians. Therapy for OA is largely palliative, aimed at increasing physical function by relieving joint pain and reducing inflammation.[5] Control of systemic inflammation and prevention or slowing of disease progression are additional treatment goals in patients with RA. While no pharmacologic agents have been shown to prevent or delay the progression of structural damage in OA, disease-modifying antirheumatic drugs (DMARDs) appear to have the capacity to alter the clinical course of RA.[6,7]

Because of their analgesic and anti-inflammatory effects, nonsteroidal anti-inflammatory drugs (NSAIDs) are the class of medication most commonly used to treat joint pain and stiffness in patients with OA and RA.[4,8–10] Nonselective NSAIDs inhibit the isozymes of cyclooxygenase (COX), COX-1 and COX-2. (See articles by Bingham and Cronstein in this supplement.) Preclinical studies strongly suggest that inhibition of COX-2 is primarily responsible for many of the therapeutic benefits of NSAIDs, while inhibition of COX-1 can lead to toxic effects.[8,11,12] For this reason, the American College of Rheumatology (ACR) recently recommended replacing nonselective NSAID therapy with therapy with a coxib agent, a COX-2–selective inhibitor, when treating a patient with OA at increased risk of developing an NSAID-related toxicity.[5] Patients with OA or RA at increased risk of developing NSAID-related gastrointestinal (GI) toxicities include those who are older (65 years of age and above), have a history of a prior symptomatic or complicated ulcer, require chronic high-dose NSAID therapy, or take concomitant corticosteroid or anticoagulant therapy.[4,5,13–15]

The introduction of coxibs represents one of the most rapid development programs of a pharmacologic agent in rheumatology. The first two coxibs, celecoxib and rofecoxib, were approved for use in the United States only a few years after COX-2, the inducible form of COX, was first identified[16] and its pathogenic role in pain and inflammation proposed.[17] An aggressive program of clinical trials rapidly followed and provided the evidence-based proof of coxib efficacy in managing the signs and symptoms of OA and RA required by the regulatory approval process.

The efficacy of coxibs in the treatment of osteoarthritis

Celecoxib, rofecoxib, and valdecoxib are approved for the treatment of OA in the United States.

The efficacy of celecoxib 100 mg twice daily, 200 mg once daily, and 200 mg twice daily in OA is comparable to that of diclofenac 50 mg three times daily and naproxen 500 mg twice daily and significantly superior to placebo.

The efficacy of rofecoxib 12.5 mg once daily and 25 mg once daily in OA is comparable to ibuprofen 800 mg three times daily, nabumetone 1,500 mg once daily, and diclofenac 50 mg three times daily and significantly superior to placebo.

In direct comparisons in OA patients, rofecoxib 25 mg when given once daily in the morning was significantly more effective than celecoxib 200 mg once daily or acetaminophen 1,000 mg four times daily.

The efficacy of valdecoxib 5 mg once daily, 10 mg twice daily, or 10 mg once daily in OA is comparable to naproxen 500 mg twice daily and superior to placebo.

Etoricoxib 60 mg once daily and 90 mg once daily are significantly more effective than placebo and comparable to naproxen 500 mg twice daily in the treatment of OA.

COX-189, an experimental coxib, 50 mg, 100 mg, 200 mg twice daily or 400 mg once daily, provides relief of OA symptoms comparable to diclofenac SR 75 mg twice daily and is significantly superior to placebo.

■ OUTCOME MEASURES IN ARTHRITIS CLINICAL TRIALS

Clinical trials of pharmacologic agents in OA or RA employ several measures of efficacy recommended by Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT), a group endorsed by the International League of Associations of Rheumatology (ILAR) and the World Health Organization (WHO). These outcome measures are designed to detect minimal clinically significant changes in the severity of joint pain or physical disability associated with OA or RA.[18,19]

Many of these instruments, such as the Patient

Assessment of Pain, require evaluation by the patient. The sensitivity and reliability of these self-report measures have been validated by comparative and radiographic studies.[20–23] One commonly utilized self-rating scale is the visual analog scale (VAS), a continuous numerical scale that ranges from 0 mm, indicative of the best outcome (eg, no pain), to 100 mm for the worst outcome (eg, extreme pain). Another scale often employed in quantifying patient or physician global assessment of disease activity is the Likert scale, a 5-point scale in which 0 designates the best outcome and 4 designates the worst outcome. Minimal clinical significance is generally considered a Likert scale change of at least 0.4 units.[24]

Either the VAS or Likert scale can be used to quantify a patient's status following therapeutic intervention. Many recent OA clinical trials employ the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[18,25] The WOMAC OA Index is composed of 24 items in three subscales that evaluate pain (five questions), physical function (17 questions), and stiffness (two questions).[23,26] Minimal clinically significant change is considered a decrease of 9.7, 9.3, and 10 mm, respectively, in the WOMAC pain, physical function, and stiffness subscales (VAS).[24] The Lequesne Algofunctional Index, graded on a composite scale ranging from 0 to 24, with lower scores indicating better condition, is an outcome instrument commonly employed in clinical trials of hip or knee OA conducted in Europe.[26,27]

The common outcome measure used in RA trials is the ACR 20.[28] The ACR developed a binary outcome measure of response based on the seven items in the ILAR/WHO core set. These include the number of painful/tender and swollen joints determined by physical examination, the duration of morning stiffness, patient and physician global assessment of disease activity, severity of pain, a measure of physical disability (eg, Health Assessment Questionnaire [HAQ]), and a measure of an acute-phase reactant (eg, the erythrocyte sedimentation rate or C-reactive protein). To achieve an ACR 20 response, the patient must have at least a 20% improvement in the number of painful/tender and swollen joints as well as an improvement of 20% or more in three of the remaining five outcome measures. While originally developed for use in randomized placebo-controlled trials of DMARDs, the ACR 20 is now widely used in trials of NSAIDs, including COX-2–selective inhibitors.

With few exceptions, all clinical trials of coxib efficacy in OA or RA to date were designed to establish efficacy in patients who had been previously treated with an NSAID and who had experienced a "flare" in symptoms after discontinuing NSAID therapy shortly before study enrollment. (For further discussion of the "withdrawal flare" trial design, see Scott-Lennox et al, 2001[29]). When an NSAID was the active comparator, the higher anti-inflammatory dose of NSAID was generally employed. Most of these coxib trials were short-term, conducted for 6 or 12 weeks. The exceptions were two long-term studies, of 52 weeks' duration, in OA patients comparing rofecoxib with diclofenac,[11,30] and one 24-week study comparing celecoxib with diclofenac SR in patients with RA.[31] Two studies of the new coxib, etoricoxib, include a 46-week study versus diclofenac in OA patients[32] and a 52-week study comparing etoricoxib with naproxen in OA patients.[33] (See **Tables 1 and 2** for trial summaries.)

■ CLINICAL TRIALS OF COXIBS IN OA

Celecoxib

The first published trial of a coxib was a 2-week, placebo-controlled, dose-ranging study of celecoxib 40 mg, 100 mg, or 200 mg twice daily in 293 patients with OA of the knee. Although all three doses demonstrated clinical improvement, only the two higher doses maintained mean improvements significantly greater than with placebo ($P \leq .048$).[8]

Another study, conducted in 1,003 patients with OA of the knee, was reported the following year. In this 12-week trial, clinical improvements with celecoxib 100 mg or 200 mg twice daily were greater than with celecoxib 50 mg twice daily and comparable to naproxen 500 mg twice daily. Mean measures of efficacy with celecoxib 100 mg or 200 mg twice daily or naproxen 500 mg twice daily were significantly superior to outcomes with placebo ($P \leq .05$).[34]

Another placebo- and active-comparator controlled study of celecoxib in OA involved 600 patients with OA of the knee who were treated for 6 weeks with celecoxib 100 mg twice daily, diclofenac 50 mg three times daily, or placebo. Mean improvements with celecoxib or diclofenac were comparable and significantly superior to outcomes with placebo ($P < .001$).[35]

A 6-week, placebo-controlled study compared treatment with celecoxib 100 mg twice daily to

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TABLE 1
CLINICAL STUDIES OF COXIB EFFICACY IN OSTEOARTHRITIS

Author	N	Study drug	Comparator	Duration	Clinical response
Simon et al[8]	293	**Celecoxib** 40 mg BID (n = 73) 100 mg BID (n = 76) 200 mg BID (n = 73)	**Placebo** (n = 71)	2 weeks	All 3 celecoxib regimens superior to placebo in mean improvements of disease status ($P \leq .048$)
Bensen et al[34]	1,003	**Celecoxib** 50 mg BID (n = 203) 100 mg BID (n = 197) 200 mg BID (n = 202)	**Naproxen** 500 mg BID (n = 198) **Placebo** (n = 203)	12 weeks	Celecoxib 100 mg and 200 mg BID comparable to naproxen, superior to placebo in mean improvements in WOMAC index, global assessments ($P \leq .05$)
McKenna et al[35]	600	**Celecoxib** 100 mg BID (n = 201)	**Diclofenac** 50 mg TID (n = 199) **Placebo** (n = 200)	6 weeks	Celecoxib comparable to diclofenac, superior to placebo in mean decrease in VAS pain, percent with 2-grade improvements in disease status ($P < .001$)
Singh et al[36]	13,194	**Celecoxib** 100 mg BID 200 mg BID	**Naproxen** 500 mg BID **Diclofenac** 50 mg BID	12 weeks	Celecoxib comparable to diclofenac in mean decrease in VAS pain
Williams et al[26]	718	**Celecoxib** 100 mg BID (n = 243)	**Celecoxib** 200 mg QD (n = 231) **Placebo** (n = 244)	6 weeks	Celecoxib QD, BID regimens comparable, superior to placebo in mean improvements in VAS pain, WOMAC index, global assessments ($P < .05$)
Ehrich et al[39]	672	**Rofecoxib** 5 mg QD (n = 149) 12.5 mg QD (n = 144) 25 mg QD (n = 137) 50 mg QD (n = 97)	**Placebo** (n = 145)	6 weeks	Rofecoxib 12.5-mg, 25-mg, 50-mg regimens produced dose-dependent efficacy superior to placebo in mean improvements in VAS pain, WOMAC index, global assessments ($P < .001$)
Ehrich et al[37]	219	**Rofecoxib** 25 mg QD (n = 73) 125 mg QD (n = 74)	**Placebo** (n = 72)	6 weeks	Both rofecoxib regimens comparable, superior to placebo in mean improvements in VAS pain, WOMAC index, global assessments ($P < .001$)
Day et al[40]	809	**Rofecoxib** 12.5 mg QD (n = 244) 25 mg QD (n = 242)	**Ibuprofen** 800 mg TID (n = 249) **Placebo** (n = 74)	6 weeks	Rofecoxib comparable to ibuprofen, superior to placebo in mean improvements in VAS pain, WOMAC index,global assessments ($P \leq .009$)
Geba et al[41]	1,042	**Rofecoxib** 12.5 mg QD (n = 424)	**Nabumetone** 1,000 mg QD (n = 410) **Placebo** (n = 208)	6 weeks	Rofecoxib superior to nabumetone ($P < .05$) and placebo ($P < .001$) in mean improvements in global assessment
Truitt et al[13]	341	**Rofecoxib** 12.5 mg QD (n = 118) 25 mg QD (n = 56)	**Nabumetone** 1,500 mg QD (n = 115) **Placebo** (n = 52)	6 weeks	In patients ≥80 years, rofecoxib comparable to nabumetone, superior to placebo in mean improvements in VAS pain, WOMAC index, global assessments ($P < .05$)
Saag et al[30]	736	**Rofecoxib** 12.5 mg QD (n = 219) 25 mg QD (n = 227)	**Ibuprofen** 800 mg TID (n = 221) **Placebo** (n = 69)	6 weeks	Rofecoxib comparable to ibuprofen, superior to placebo in mean improvements in WOMAC index, global assessments ($P < .001$)

(continued)

TABLE 1 *(continued)*

Author	N	Study drug	Comparator	Duration	Clinical response
Saag et al[30]	693	**Rofecoxib** 12.5 mg QD (n = 231) 25 mg QD (n = 232)	**Diclofenac** 50 mg TID (n = 230)	52 weeks	Rofecoxib 25 mg comparable to diclofenac, superior to placebo in mean improvements in WOMAC index, global assessments ($P < .001$)
Cannon et al[11]	784	**Rofecoxib** 12.5 mg QD (n = 259) 25 mg QD (n = 257)	**Diclofenac** 50 mg TID (n = 268)	26 weeks	Rofecoxib comparable to diclofenac, superior to placebo in mean improvements in VAS pain, WOMAC index (taken to week 26), global assessments
Geba et al[42]	382	**Rofecoxib** 12.5 mg QD (n = 96) 25 mg QD (n = 95)	**Celecoxib** 200 mg QD (n = 97) **Acetaminophen** 1,000 mg QID (n = 94)	6 weeks	Rofecoxib 25 mg statistically superior to celecoxib, acetaminophen in mean improvements in VAS pain, WOMAC index, global assessments, onset of relief
Schnitzer et al[43]	1,082	**Rofecoxib** 25 mg QD (n = 471)	**Celecoxib** 200 mg QD (n = 460) **Placebo** (n = 151)	6 weeks	Rofecoxib statistically superior to celecoxib, placebo in mean improvements in VAS pain, WOMAC index, global assessments, onset of relief
Eskiyurt[46]	138	**Rofecoxib** 12.5 mg QD	**Rofecoxib** 25 mg QD	6 weeks	In Turkish population, rofecoxib regimens comparable in mean improvements in WOMAC, Lequesne Algofunctional indices
Fiechtner et al[47]	642	**Valdecoxib** 0.5 mg BID 1.25 mg BID 2.5 mg BID 5 mg BID 10 mg QD 10 mg BID	**Naproxen** 500 mg BID **Placebo**	6 weeks	Valdecoxib produced dose-dependent efficacy comparable to naproxen at 5 mg BID, 10 mg QD, and 10 mg BID; superior to placebo at all dosages except .5 mg BID in mean improvements in VAS pain, WOMAC index, global assessments ($P \leq .004$)
Curtis et al[32]	617	**Etoricoxib** 5 mg QD (n = 117) 10 mg QD (n = 114) 30 mg QD (n = 102) 60 mg QD (n = 112) 90 mg QD (n = 112)	**Placebo** (n = 60)	6 weeks (Part I)	Etoricoxib produced dose-dependent efficacy superior to placebo in mean improvements in VAS pain, global assessments ($P < .05$)
Curtis et al[32]	617	**Etoricoxib** 30 mg QD 60 mg QD 90 mg QD	**Diclofenac** 50 mg TID	46 weeks (Part II)	Etoricoxib 60-mg, 90-mg regimens superior to 30-mg regimen in mean improvements in VAS pain, global assessments
Fisher et al[33]	496	**Etoricoxib** 60 mg QD (n = 222)	**Naproxen** 500 mg BID (n = 218) **Placebo** (n = 56)	12 weeks (Part I)	Etoricoxib 60 mg comparable to naproxen, superior to placebo in mean improvements in VAS pain, WOMAC index, global assessments
Fisher et al[33]	496	**Etoricoxib** 60 mg QD (n = 248)	**Naproxen** 500 mg BID (n = 248)	40 weeks (Part II)	Etoricoxib 60 mg comparable to naproxen in mean improvements in VAS pain, WOMAC index, global assessments
Schnitzer et al[48]	583	**COX-189** 50 mg BID 100 mg BID 200 mg BID 400 mg QD	**Diclofenac SR** 75 mg BID **Placebo**	4 weeks	All regimens of COX-189 comparable to diclofenac, superior to placebo in mean improvements in VAS pain, WOMAC index, HAQ index, global assessments

TABLE 2
CLINICAL STUDIES OF COXIB EFFICACY IN RHEUMATOID ARTHRITIS

Author	N	Study drug	Comparator	Duration	Clinical response
Simon et al[8]	330	**Celecoxib** 40 mg BID (n = 81) 200 mg BID (n = 82) 400 mg BID (n = 82)	**Placebo** (n = 85)	4 weeks	Celecoxib 200-mg, 400-mg regimens superior to placebo in mean improvements in global assessment ($P < .001$); number tender, swollen joints ($P \leq .005$); percent improved by ACR 20 criteria ($P \leq .025$)
Simon et al[12]	1,149	**Celecoxib** 100 mg BID (n = 240) 200 mg BID (n = 235) 400 mg BID (n = 218)	**Naproxen** 500 mg BID (n = 225) **Placebo** (n = 231)	12 weeks	Celecoxib 200 mg, 400 mg regimens comparable to naproxen, superior to placebo in mean improvements in global assessments; HAQ index; number tender, swollen joints; percent improved by ACR 20 criteria ($P < .05$)
Emery et al[31]	655	**Celecoxib** 200 mg BID (n = 326)	**Diclofenac SR** 75 mg BID (n = 329)	24 weeks	Celecoxib comparable to diclofenac in mean improvements in VAS pain; global assessments; HAQ index; number tender, swollen joints; percent improved by ACR 20 criteria
Bensen et al[51]	1,089	**Valdecoxib** 10 mg QD 20 mg QD 40 mg QD	**Naproxen** 500 mg BID **Placebo**	12 weeks	Valdecoxib, all doses, comparable to naproxen, superior to placebo in ACR 20 response
Schnitzer et al[15]	658	**Rofecoxib** 5 mg QD (n = 158) 25 mg QD (n = 171) 50 mg QD (n = 161)	**Placebo** (n = 168)	8 weeks	Rofecoxib 25-mg, 50-mg regimens superior to placebo in mean improvements in VAS pain; global assessments; HAQ index; number tender, swollen joints; percent improved by ACR 20 criteria ($P < .001$)
Truitt et al[49]	1,058	**Rofecoxib** 25 mg QD (n = 315) 50 mg QD (n = 297)	**Naproxen** 500 mg BID (n = 147) **Placebo** (n = 299)	12 weeks	Rofecoxib comparable to naproxen, superior to placebo in mean improvements in VAS pain; HAQ index; number tender, swollen joints; percent improved by ACR 20 criteria ($P < .05$)
Truitt et al[50]	909	**Rofecoxib** 12.5 mg QD (n = 148) 25 mg QD (n = 311)	**Naproxen** 500 mg BID (n = 149) **Placebo** (n = 301)	12 weeks	Rofecoxib 25 mg comparable to naproxen, superior to placebo in improvements in VAS pain; global assessments; number tender, swollen joints; percent improved by ACR 20 criteria; rofecoxib 12.5 mg superior to placebo in VAS pain, global assessments, and percent improved by ACR 20 criteria
Curtis et al[52]	581	**Etoricoxib** 10 mg QD (n = 78) 60 mg QD (n = 126) 90 mg QD (n = 134) 120 mg QD (n = 120)	**Placebo** (n = 123)	8 weeks	Etoricoxib 90-mg and 120-mg regimens superior to placebo in mean improvements in VAS pain, global assessments, HAQ index ($P < .05$)
Melian et al[53]	816	**Etoricoxib** 90 mg QD (n = 323)	**Naproxen** 500 mg BID (n = 170) **Placebo** (n = 323)	12 weeks	Etoricoxib superior to naproxen, placebo in mean improvements in HAQ index; number tender, swollen joints; percent improved by ACR 20 criteria ($P < .05$)

Continued from page SI-22

The efficacy of coxibs in the treatment of rheumatoid arthritis

Celecoxib and valdecoxib are the only coxibs currently approved for the treatment of RA in the United States.

Celecoxib 200 mg twice daily or 400 mg twice daily is as effective as naproxen 500 mg twice daily in the treatment of RA.

Celecoxib 200 mg twice daily is as effective as diclofenac SR 75 mg twice daily in the treatment of RA.

Rofecoxib 25 mg once daily or 50 mg once daily is as effective as naproxen 500 mg twice daily in the treatment of RA.

Valdecoxib 10 mg once daily is as effective as naproxen 500 mg twice daily in the treatment of RA.

Etoricoxib 90 mg and 120 mg once daily is significantly more effective than placebo in the treatment of RA.

Etoricoxib 90 mg once daily is as or more effective than naproxen 500 mg twice daily in the treatment of RA.

celecoxib 200 mg once daily in 718 patients with OA of the knee. Both regimens achieved comparable outcomes ($P < .05$).[26] In a recent 12-week study designed to examine safety, 13,194 patients with OA of the knee, hip, or hand were treated with celecoxib 100 mg or 200 mg twice daily, naproxen 500 mg twice daily, or diclofenac SR 50 mg twice daily. Mean improvements with either regimen of celecoxib were comparable to those achieved with diclofenac or naproxen.[36]

Rofecoxib

Ten studies of the efficacy of rofecoxib in the treatment of OA have been reported to date.

Two phase II studies tested a range of rofecoxib dosages during a 6-week period.[37–39] In the first, the efficacy of rofecoxib 5 mg, 12.5 mg, 25 mg, or 50 mg once daily was compared with a placebo in 672 patients with OA of the hip or knee.[39] Mean improvements with rofecoxib at all doses were superior to those with placebo. The outcomes with rofecoxib 12.5 mg, 25 mg, and 50 mg once daily were superior to those seen with rofecoxib 5 mg once daily. The second study was conducted in 219 patients with OA of the knee treated with rofecoxib 25 mg or 125 mg once daily, or placebo. Both rofecoxib regimens demonstrated comparable efficacy, each resulting in significantly better responses than seen with placebo ($P < .001$).[37]

Six phase III studies compared the efficacy of rofecoxib with a nonselective NSAID and/or placebo. Two 6-week trials enrolled patients with OA of the hip or knee who were treated with rofecoxib 12.5 mg or 25 mg once daily, ibuprofen 800 mg three times daily, or placebo. Mean improvements seen with rofecoxib were comparable to those with ibuprofen and significantly superior to those with placebo ($P \leq .009$ and $P < .001$, respectively).[29,40]

Another 6-week trial compared the efficacy of rofecoxib 12.5 mg once daily with nabumetone 1,000 mg once daily or placebo in 1,042 patients with OA. In this study, the efficacy of rofecoxib was significantly superior to nabumetone ($P < .05$), and both treatments had greater efficacy than placebo ($P < .001$).[41] In an elderly population of 341 patients at least 80 years of age with OA of the hip or knee who were treated for 6 weeks with rofecoxib 12.5 mg or 25 mg once daily, nabumetone 1,500 mg once daily, or placebo, the mean improvements with rofecoxib were comparable to those with nabumetone and significantly superior to placebo ($P < .05$).[13]

Two 1-year trials evaluated the efficacy of rofecoxib 12.5 mg or 25 mg once daily and diclofenac 50 mg three times daily in patients with OA of the knee or hip. The efficacy of both rofecoxib regimens was comparable to that with diclofenac.[11,30]

Comparative trials of rofecoxib and celecoxib

Several phase IV studies comparing the efficacy of rofecoxib with that of celecoxib have been done. In one study, patients with OA of the knee were treated for 6 weeks with rofecoxib 12.5 mg or 25 mg once daily, celecoxib 200 mg once daily, or acetaminophen 1,000 mg four times daily; no rescue analgesics were allowed, and all medications given once daily were dosed in the morning. By all outcome measures, rofecoxib 25 mg once daily was significantly superior to acetaminophen. In addition, rofecoxib 25 mg once daily was significantly more efficacious than celecoxib 200 mg once daily as assessed by patient global assessment of response to therapy and by mean improvement on the WOMAC pain and stiffness scales.[42]

A second, larger study involving 1,082 patients with OA evaluated rofecoxib 25 mg once daily, celecoxib 200 mg once daily, or placebo after 6 weeks of treatment; again, all medications were dosed in the morning. All outcome measures were significantly superior with rofecoxib than with celecoxib or placebo.[43]

Such findings have clinical significance, bolstering their statistical significance. Another study, however, found the efficacy of celecoxib 200 mg once daily and rofecoxib 25 mg once daily in treating OA of the knee to be comparable (both were superior to placebo).[44] However, in this study, all medications were dosed once in the evening. These results are consistent with the half-life of each of the two agents.

The findings that the recommended dose of rofecoxib for the treatment of OA was significantly more effective than the recommended dose of celecoxib for the treatment of OA may be related to the fact that rofecoxib has a longer half-life compared with that of celecoxib.[45] It is likely that this results in clinically significant sustained relief of pain and stiffness throughout the day with rofecoxib when both drugs are dosed once daily in the morning.

Valdecoxib

Valdecoxib was recently approved in the United States for the treatment of OA at a dosage of 10 mg once daily, making it the third coxib available for that indication. The efficacy of valdecoxib in OA was shown in a 6-week, dose-ranging trial conducted in 642 patients with OA of the knee. Patients were treated with valdecoxib 10 mg either twice daily or once daily, 0.5 mg, 1.25 mg, 2.5 mg, or 5 mg twice daily; or naproxen 500 mg twice daily; or placebo. Maximum efficacy with valdecoxib was achieved with the 5 mg once daily, 10 mg twice daily, and 10 mg once daily regimens. These were comparable to naproxen and superior to placebo in all outcome measures.[47]

Etoricoxib

Currently under investigation, etoricoxib is a second-generation coxib that has demonstrated efficacy for the treatment of OA. A 6-week, dose-ranging study was conducted in 617 patients with OA of the knee. Treatment with etoricoxib 5 mg, 10 mg, 30 mg, 60 mg, and 90 mg once daily produced dose-dependent efficacy that was superior to placebo and maximal at a dosage of 60 mg once daily ($P < .05$). Patients receiving either placebo or etoricoxib 5 mg or 10 mg once daily were then reallocated to treatment with etoricoxib 30 mg, 60 mg, or 90 mg once daily or diclofenac 50 mg three times daily for an additional 46 weeks. Etoricoxib 60 mg once daily or 90 mg once daily was more effective than 30 mg once daily in all outcome measures and comparable to diclofenac.[32]

A second study of etoricoxib efficacy was conducted in 496 patients with OA of the knee or hip. In the initial phase of the trial, patients were treated with etoricoxib 60 mg once daily, naproxen 500 mg twice daily, or placebo for 12 weeks. Placebo-treated patients were then reallocated to treatment with either etoricoxib 60 mg once daily or naproxen 500 mg twice daily for an additional 40 weeks. By all outcome measures, the efficacy of etoricoxib at week 12 was significantly superior to the outcomes with placebo, and at week 12 and week 52 was comparable to that of naproxen.[33]

COX-189

A multinational, dose-ranging trial evaluated the efficacy of an experimental coxib, COX-189, in 583 patients with OA of the hip or knee. Patients were treated for 4 weeks with COX-189 400 mg once daily; COX-189 50 mg, 100 mg, 200 mg twice daily; diclofenac SR 75 mg twice daily; or placebo. The minimum effective COX-189 dosage was 50 mg twice daily. By both primary and secondary outcome measures, all regimens of COX-189 provided comparable efficacy to diclofenac and significantly better improvement than placebo ($P < .05$).[48]

■ CLINICAL TRIALS OF COXIBS IN RA

Celecoxib

Celecoxib is approved for the treatment of RA in the United States. Efficacy of celecoxib was established in a dose-ranging study and two phase III trials. In a 4-week dose-ranging study, 330 patients with RA were treated with celecoxib 40 mg, 200 mg, or 400 mg twice daily, or placebo. Mean improvements with celecoxib 200 mg or 400 mg twice daily were significantly superior to placebo.[8]

A 12-week phase III trial compared the efficacy of celecoxib 100 mg, 200 mg, or 400 mg twice daily with naproxen 500 mg twice daily or placebo in 1,149 patients with RA. Treatment with celecoxib 200 mg or 400 mg twice daily produced mean improvements comparable to those with naproxen and significantly superior to outcomes with placebo ($P < .05$).[12]

In a second phase III study, 655 patients with RA were treated for 24 weeks with celecoxib 200 mg twice daily or diclofenac SR 75 mg twice daily. Mean improvements with celecoxib were comparable to outcomes with diclofenac.[31]

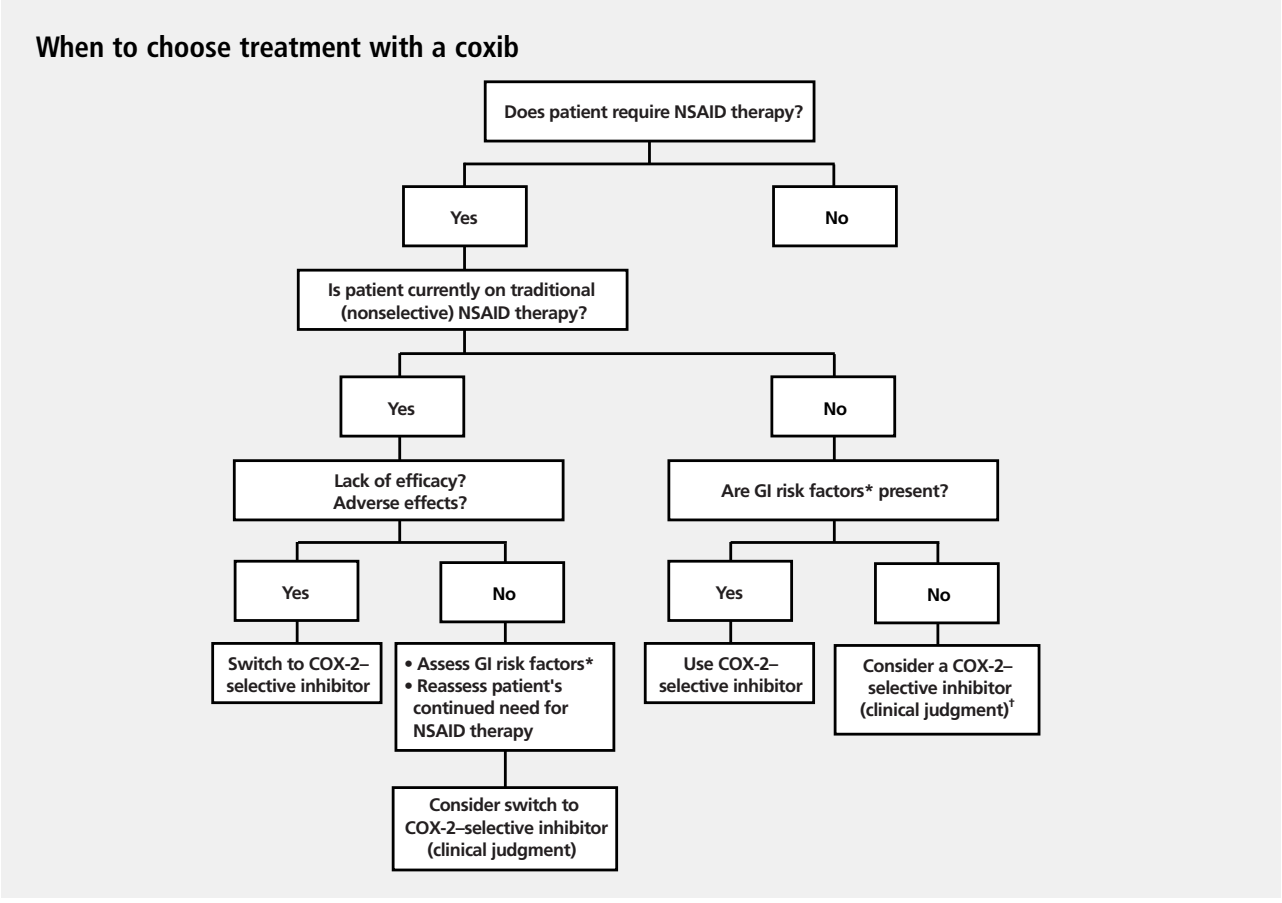

FIGURE 1. The recommendation to "Switch to COX-2–selective inhibitor" for lack of efficacy and adverse effects of nonselective NSAIDs is based in part on numerous studies that have shown treatment with coxibs to be associated with lower rates of discontinuations, less need for GI (protective) cotherapy, less need for GI procedures, and lower risk of developing perforations, ulcers, and bleeds (PUBs). *Risk factors for serious upper GI complications from traditional NSAIDs include age above 65 years, the need for chronic high-dose NSAID therapy, history of peptic ulcer disease, and concomitant treatment with an anticoagulant or glucocorticoid agent. † Includes discussion of risks and benefits with the patient. (Reprinted from the *American Journal of Medicine*, vol. 110(3A), P.E. Lipsky, "Recommendations for the clinical use of cyclooxygenase-2–specific inhibitors," pp 3S-5S, copyright 2001, with permission from Excerpta Medica Inc.[14])

Rofecoxib

The efficacy of rofecoxib in the treatment of RA has been studied, and a claim for use in RA is pending. In an 8-week dose-ranging trial, 658 patients with RA were treated with rofecoxib 5 mg, 25 mg, or 50 mg once daily, or placebo. Mean improvements with rofecoxib 25 mg or 50 mg once daily were significantly superior to the responses to placebo ($P < .001$).[15]

Two phase III studies were conducted in approximately 2,000 patients with RA. In one study, participants were treated with rofecoxib 25 mg or 50 mg once daily, naproxen 500 mg twice daily, or placebo for 12 weeks.[49] In the other study, patients were treated with rofecoxib 12.5 mg or 25 mg once daily, naproxen 500 mg twice daily, or placebo for 12 weeks.[50] In all outcome measures, rofecoxib at doses of 25 and 50 mg once daily was comparable to naproxen and significantly superior to placebo ($P < .05$).

Valdecoxib

The recent approval of valdecoxib also includes its use for the treatment of RA at a dosage of 10 mg once daily. At this dosage, a 12-week study found the efficacy of this agent superior to placebo and similar to that of naproxen (500 mg BID) but with improved GI tolerability compared with naproxen.[51]

Etoricoxib

Etoricoxib is under investigation also for the treatment of RA. An 8-week dose-ranging study was conducted in 581 patients with RA. Patients were treated with etoricoxib 10 mg, 60 mg, 90 mg, or 120 mg once daily, or placebo. Etoricoxib 90 mg and 120 mg once daily were significantly superior to placebo in all outcome measures ($P < .05$).[52] Maximal improvement was noted with etoricoxib 90 mg once daily.

A 12-week study compared the efficacy of etoricoxib 90 mg once daily with naproxen 500 mg twice daily or placebo in patients with RA. Mean improvements in all primary and key secondary measures were significantly better with etoricoxib compared with naproxen or placebo ($P < .05$).[53]

■ CLINICAL GUIDELINES FOR THE USE OF COXIBS

Celecoxib and rofecoxib, the first-generation coxibs, both demonstrate efficacy in OA and RA and have been included in the updated ACR recommendations for OA management.[54] Newer entrants to the coxib class, valdecoxib, etoricoxib, and others, will provide further treatment options whose value will be assessed after additional data are available. Simple analgesics, such as acetaminophen, are still recommended as first-choice agents for pharmacologic management of patients with OA.[5] An algorithm for the use of coxibs in patients with OA and RA is shown in **Figure 1**. The guidelines recommend coxibs as an alternative to nonselective NSAIDs in patients at risk of developing GI toxicity associated with NSAID therapy.[5]

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Gastrointestinal safety and tolerability of nonselective nonsteroidal anti-inflammatory agents and cyclooxygenase-2–selective inhibitors

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all drugs and are the most common medications used by persons aged 65 years or more. NSAIDs have a number of side effects, of which the most prevalent and serious is gastrointestinal (GI) toxicity. GI side effects of NSAIDs range from dyspepsia and gastroduodenal ulcers to serious, potentially fatal GI complications including bleeding and perforation. Serious GI complications often lack warning signs; knowledge of risk factors for NSAID-related gastropathy can identify patients at high risk, allowing for initiation of the appropriate therapeutic intervention. Risk factors include advanced age, NSAID dose, prior GI complications, infection with *Helicobacter pylori*, and use of corticosteroids and anticoagulants. There are few well-established strategies to prevent GI complications in NSAID users. Risk assessment and cotherapy with acid suppressors (H_2-receptor antagonists and proton pump inhibitors) or prostaglandin replacement (misoprostol) and *H pylori* eradication are beneficial. Cyclooxygenase-1 (COX-1) is a key enzyme in gastroprotective mucosal defenses, and the best way to prevent GI toxicity is to avoid drugs that inhibit COX-1. Clinical studies of the COX-2–selective inhibitors rofecoxib and celecoxib have demonstrated efficacy equivalent to nonselective NSAIDs with lower rates of GI side effects (for example, incidence of endoscopic ulcers equivalent to placebo). Selective COX-2 inhibitors (coxibs) provide effective treatment of pain and inflammation while reducing risk of gastropathy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all drugs. It is estimated that 1% to 2% of the world population takes at least 1 aspirin tablet daily, and in the United States alone 20 to 30 billion tablets are purchased each year.[1,2] NSAIDs are among the medications most commonly used by persons aged 65 years or more.[3] Though effectively addressing pain and inflammation, nonselective NSAIDs are associated with several untoward side effects including gastric intolerance, gastric ulceration, inhibition of platelet function, and alterations in renal function.[4]

The most prevalent and significant adverse outcomes of NSAID use are gastrointestinal (GI) ulcer-

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Safety of nonselective NSAIDs and coxibs

Gastrointestinal (GI) side effects of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) due to cyclooxygenase-1 (COX-1) inhibition are responsible for significant morbidity and mortality

Epidemiologic and clinical studies have identified important risk factors for NSAID-related gastropathy; namely, advancing age, high NSAID dose, prior GI complications, *Helicobacter pylori* infection, and use of anticoagulants or corticosteroids

The incidence of GI complications can be reduced by risk assessment and risk-reduction strategies

Small trials and observational studies show that *H pylori* eradication and cotherapy with prostaglandin replacement and acid suppression reduce risk of serious GI complications

The selective COX-2 inhibitors rofecoxib and celecoxib (coxibs) have efficacy equivalent to nonselective NSAIDs with no new unexpected side effects

ation and serious GI complications such as perforation and bleeding.[2,5] Estimates show that in the United States approximately 107,000 patients are hospitalized each year for NSAID-related GI complications and 16,500 NSAID-related deaths occur in arthritis patients alone.[6] In a prospective study of more than 11,000 patients with osteoarthritis (OA) or rheumatoid arthritis (RA), risk of hospitalization due to serious NSAID-related GI complications was 2.5 to 5.5 times greater than that of the general population.[6] The mortality rate among patients hospitalized for serious NSAID-related bleeding complications is 10% to 15%.[5] There are often no warning signs for serious GI complications, and prospective studies show that more than 80% of patients with these complications had no previous GI illness.

Upper GI symptoms, ulcers, and ulcer complications due to NSAID use are a significant cause of morbidity and mortality. Approximately 25% of NSAID users will have endoscopic lesions of at least 3 mm in the gastric mucosa, and 1% to 4% of patients using NSAIDs will have symptomatic ulcers or ulcer complications.[6] The mortality rate attributed to NSAID-related GI toxicity is 0.2% per year with an annual relative risk of 4.21 compared with NSAID nonusers.[2]

NSAID-related morbidity and mortality come at a high price to society in both human and economic terms. It is estimated that each NSAID-related hospitalization costs an average of $15,000 to $20,000, with annual direct medical costs of these complications exceeding $2 billion in the United States alone.[2] Among those aged 65 years or more, costs have been estimated to be $500 million per year.[3]

■ GASTROINTESTINAL RISK AND NSAIDs

NSAID-associated gastropathy

NSAIDs have the common property of treating fever, pain, and inflammation by inhibiting synthesis of prostaglandins. NSAIDs bind reversibly or irreversibly (in the case of aspirin) to cyclooxygenase (COX) enzymes (**Figure 1**). COX-1–derived prostaglandins are responsible for mucosal defense and cytoprotection in the GI tract, while COX-2–derived prostaglandins mediate inflammation, pain, and fever. Most NSAIDs are nonselective, blocking both COX-1 and COX-2 isoenzymes. Deleterious effects of nonselective NSAIDs on gastroprotection result from their inhibition of COX-1.[2] With the development of COX-2–selective inhibitors, it has been possible to achieve the level of clinical efficacy of nonselective NSAIDs without the GI-toxic effects associated with COX-1 inhibition.

There are three levels of gastric mucosal defense relevant to gastric toxicity of NSAIDs caused by COX-1 inhibition (**Figure 2**). The first line of gastric defense is the mucous gel, which protects against the acidic contents of the gastric lumen. Surface epithelial cells, which can withstand pH as low as 2.5, provide the second line of gastric defense. Finally, the postepithelial barrier prevents deep mucosal damage because of the buffering effect of bicarbonate release by parietal cells; mucosal blood flow also removes damaging H^+.[1] Prostaglandin inhibition resulting from the blocking of COX-1 affects all three defense mechanisms by causing decreases in epithelial mucus production, bicarbonate secretion, mucosal blood flow, and epithelial proliferation.[2] Diminished mucosal protection makes the GI tract vulnerable to the endogenous insults of gastric acid, bile, and enzymes, and may enhance damage by exogenous factors, such as alcohol and other injurious agents.

The clinical scope of NSAID-related Gl injury ranges from self-limited dyspepsia to ulcers, gastroduodenal hemorrhage, perforation, and death. Erosions are superficial, limited to the mucosal layer, whereas ulcers penetrate to the level of the submucosa. GI injury is usually assessed by endoscopic examination and is based on subjective mea-

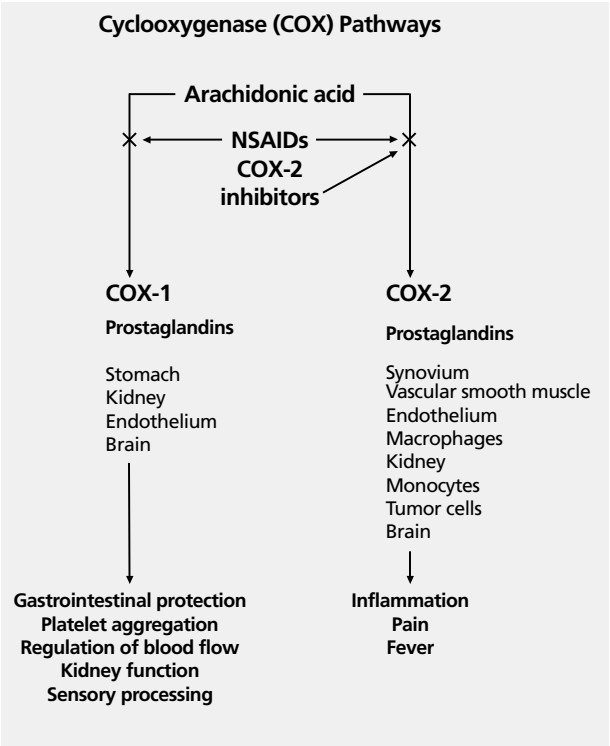

FIGURE 1. Mechanisms of NSAID-induced injury and potential sites for pharmacologic strategies for prevention of GI toxicity.[2]

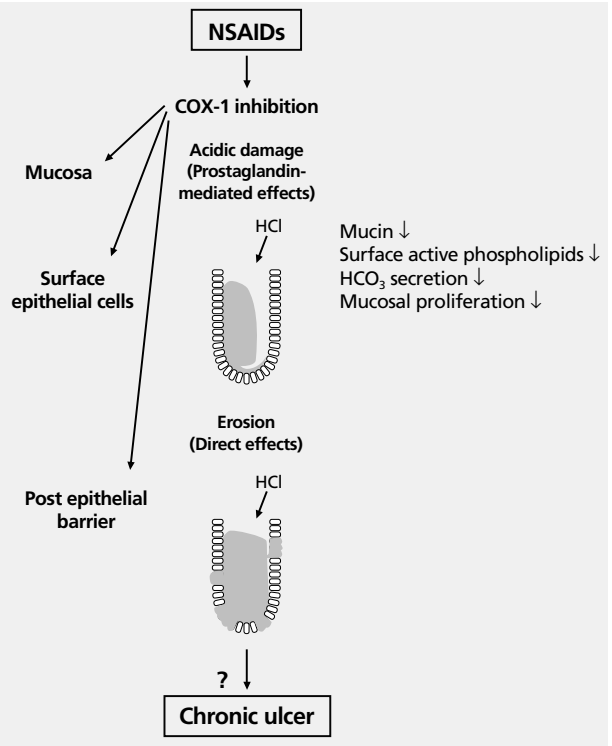

FIGURE 2. COX-1 inhibition and GI toxicity. (Adapted from Scheiman[1] with permission.)

sures such as the size and depth of the lesion. A size of 3.0 mm and some observable depth are usually employed in clinical trials to differentiate between erosions and ulcers. Histologic examination has been used to confirm endoscopic findings. Biopsy can reveal gastric mucosal injury and inflammation associated with *Helicobacter pylori* infection or focal injury and acute inflammation associated with NSAID damage.[7] Damage to the gastric epithelium is seen within minutes of NSAID ingestion, and erosions can be detected endoscopically within hours.[8] The relation of endoscopic lesions to resulting GI hemorrhage and perforations, however, is unclear. For this reason, the best measures of the clinical effect of NSAIDs on gastric mucosa are long-term endoscopic and clinical trial data.[9]

Risk assessment

Knowledge of risk factors for NSAID-associated gastropathy offers a means to identify patients at high risk. Bleeding and perforation often occur without warning and are associated with a high mortality rate. In the absence of cautionary signs of serious complications, it is important to define risk factors that can initiate appropriate therapeutic intervention. A number of epidemiologic and clinical studies have examined risk factors using case-control, retrospective studies, prospective cohort analyses, and meta-analysis methodologies. These studies have consistently identified a number of risk factors for serious GI complications, including advanced age,[10–14] higher NSAID dose,[15–17] prior serious GI complications or hospitalization,[11–13,18,19] anticoagulant use,[10,19,20] corticosteroid use,[11,12,19,21] and current or previous NSAID use.[10,11,13,15,19–21] Results of epidemiologic studies examining risk associated with gender or alcohol and tobacco use have been less consistent.[6] While most studies have compared relative risks in various subgroups (eg, aged <60 years vs aged ≥60 years, etc), the magnitude of absolute risk of NSAID use is clinically relevant.[17]

The greatest risk of developing a serious GI complication occurs in the first 30 days of use. In a meta-analysis of 16 studies, it was found that with less than 1 month of NSAID exposure the odds ratio (OR) for a serious GI event was 8.00 (95% confidence interval [CI], 6.37–10.06). For longer than 1

month but less than 3 months' exposure, the OR decreased to 3.31 (95% CI, 2.27–4.82), and to 1.92 (95% CI, 1.19–3.13) for NSAID exposure longer than 3 months.[12] While risk is highest early in exposure, prospective studies have shown that risk is a persistent feature of NSAID use. The Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) study followed 1,600 patients from the onset of NSAID use and found that risk remained constant over a 10-year follow-up, suggesting that there is not a mucosal adaptation to NSAIDs.[6]

Age is one of the strongest predictors of NSAID-related GI complications, and most studies defined older age as greater than 60 years. ARAMIS, which has followed clinical outcomes prospectively in over 11,000 patients, showed that risk of hospitalization for NSAID-related GI complications increases by approximately 4% per year of age.[6]

All nonselective NSAIDs are associated with a similar spectrum of GI complications, and the relative risk of NSAID use compared with nonuse is fairly uniform across case-control and prospective studies for the various drugs examined. In ARAMIS, toxicities of 12 different NSAIDs were examined, and the majority of agents had a similar degree of toxicity.[6] In this study, ibuprofen was least toxic, whereas ketoprofen and indomethacin were most toxic. It is important to note that the toxicity of aspirin even at low doses is clinically relevant. Aspirin use resulted in significant increased absolute risk of GI bleeding at doses as low as 75 mg/d[22,23] and without evidence of the dose response seen with other nonselective NSAIDs. In a meta-analysis of 24 randomized trials involving nearly 66,000 participants, the incidence of GI hemorrhage was similar in patients taking low or high doses of aspirin (2.47% vs 2.30% for >163 mg/day and <163 mg/day, respectively).[24] In the United Kingdom Transient Ischemic Attacks trial, however, the prospective examination of 2,435 patients receiving placebo, aspirin 300 mg/day, or aspirin 600 mg twice daily demonstrated a greater risk of GI ulcer bleeding with the higher aspirin dose.[25] Furthermore, there is no evidence that the use of buffering or enteric coating of aspirin decreases this risk.[23,24,26]

Risk reduction

There are currently few well-established strategies for the prevention of ulcers and GI bleeding in patients taking NSAIDs. The best way to prevent the adverse effects of NSAIDs is to avoid the use of nonselective drugs that block COX-1. In addition, alternative analgesics such as acetaminophen (paracetamol) carry a very low risk of causing ulcers.[27] Patients taking nonselective NSAIDs who are at high risk for GI complications should be considered for cotherapy with a mucosal protective agent.

The ability of various cotherapeutic agents to reduce the incidence of nonselective NSAID-induced GI ulcers has been examined. In endoscopic studies, the H_2-receptor antagonists cimetidine and ranitidine and the surface active agent sucralfate showed no benefit in preventing NSAID-related gastric ulcers compared with placebo.[28–30] H_2-receptor antagonists may have some protective effect on the duodenum, and famotidine in large doses (40 mg twice daily) reduced the cumulative incidence of gastric ulcers.[31,32]

Proton pump inhibitors (PPIs) are potentially more effective acid suppressors than high-dose H_2-receptor antagonists. For patients with difficult-to-treat acid-related disorders, PPIs may be the drugs of choice, especially with the advent of newer-generation agents of this class.[33] Lansoprazole is useful for managing acid-related disorders and is currently the only PPI approved by the US Food and Drug Administration (FDA) for the prevention and treatment of NSAID-induced injury.[34–36]

Two large trials have examined another PPI, omeprazole, for secondary prevention of chronic ulcers: the Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) trial, and the Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT).[37,38] In both studies, omeprazole was shown to be superior to placebo for ulcer healing and in the prevention of relapse. More patients receiving omeprazole were in remission at 6 months compared with those receiving misoprostol and ranitidine; these comparator drugs were used at suboptimal doses, however.[39]

Misoprostol is a prostaglandin analog that is also approved by the FDA for the prevention of NSAID-induced ulcers. Misoprostol acts as both an antisecretory agent and as a replacement for mucosal prostaglandin deficiency due to the inhibition of COX-1 by NSAIDs.[39] The Misoprostol Ulcer Complications Outcomes Study Assessment (MUCOSA) examined over 8,800 patients with RA in a randomized, double-blind trial of 200 μg

misoprostol four times daily compared with placebo. GI complications were assessed clinically, not endoscopically. Overall, the incidence of serious upper GI complications was approximately 40% lower in patients receiving misoprostol but there was no significant reduction in GI bleeding.[14] In an earlier trial of 638 patients, the same misoprostol regimen resulted in a significant decrease in the incidence of the endoscopic endpoints of duodenal and gastric ulcers.[40] In both studies, misoprostol reduced but did not entirely eliminate ulcers or complications, and the mortality rates were similar in the misoprostol and placebo groups. Misoprostol is relatively poorly tolerated, causing diarrhea and abdominal pain. In MUCOSA, significantly more participants in the misoprostol group than the placebo group withdrew from the study as a result of adverse GI events, and nearly 30% of those in the active arm of the study group could not take the full dose of misoprostol also because of side effects.[14] Health economic studies show that misoprostol is cost-effective only for high-risk patients.[41,42]

A recent meta-analysis of controlled clinical trials evaluating the ability of H_2-receptor antagonists, PPIs, and misoprostol to prevent NSAID-related GI damage found that strategies utilizing these agents were effective for short-term prevention of NSAID-related damage.[43] PPIs and misoprostol were more effective than H_2-receptor antagonists in preventing such NSAID-induced injury. Notably, this benefit was more pronounced in healthy subjects than in patients with arthritis, highlighting the need for agents that may minimize NSAID-related injury in this patient population.

The relation of *H pylori* to NSAID-associated ulcer and ulcer complications remains controversial. NSAIDs and *H pylori* contribute to ulcer formation by different mechanisms, but it is not possible to distinguish whether an ulcer is caused by NSAIDs, *H pylori*, or both.[44] In patients using NSAIDs, it remains unclear whether *H pylori* infection is an independent risk factor, or whether *H pylori* infection and NSAID use interact in an additive manner. A history of ulcers is known to greatly increase GI risk associated with NSAID use. Several studies suggest that the presence of *H pylori* infection may be associated with an increased incidence of duodenal ulcers in NSAID users.[31,32,45–48] A meta-analysis evaluating the impact of *H pylori* and NSAID use on the risk of peptic ulcer disease suggested that NSAIDs and *H pylori* have additive/interactive effects.[49] While the incidence of peptic ulcers was higher with NSAID use alone (25% vs 5.5%, NSAID-takers and non-NSAID takers, respectively; OR = 5.7 among *H pylori*-negative subjects), the presence of *H pylori* was associated with even higher incidences in both groups. In *H pylori*-positive subjects, the incidence of peptic ulcer was 49.2% among NSAID takers compared with 26% in non-NSAID-takers. Notably, presence of both *H pylori* and NSAID use was associated with an OR = 16.5 compared with absence of *H pylori* and non-NSAID use.[49]

The eradication of *H pylori* is possible, and treatment of infection in NSAID users could decrease risk of ulcers. One study compared the benefit of *H pylori* eradication in secondary prevention with the benefit of PPI cotherapy by examining the prevention of recurrence of upper GI bleeding in patients with *H pylori* infection who were taking NSAIDs.[50] Patients taking 80 mg of aspirin daily or 500 mg of naproxen twice daily were randomized to receive either 20 mg of omeprazole daily or *H pylori* treatment consisting of bismuth subcitrate, tetracycline, and metronidazole. In patients taking aspirin, the eradication of *H pylori* led to a decrease in recurrent GI bleeding that was equivalent to treatment with omeprazole. For patients taking naproxen, omeprazole cotherapy was superior to *H pylori* eradication for secondary prevention of upper GI bleeding.[50]

■ SAFETY AND TOLERABILITY OF COX-2–SELECTIVE INHIBITORS

Clinical results

Given the risk of GI complications associated with NSAID use and the limitations of cotherapies such as misoprostol and acid-suppression therapy for primary and secondary prevention, the use of COX-1–sparing drugs has a critical role in treatment of pain and inflammation. Prospective studies have shown that selective COX-2 inhibitors are associated with lower risk of GI adverse events than NSAIDs that inhibit both COX-1 and COX-2. These studies demonstrate the ability of COX-2–selective agents to provide efficacy equivalent to nonselective NSAIDs while reducing the three main categories of GI events, namely, adverse GI symptoms (nausea, vomiting, abdominal pain); mucosal lesions (as shown by endoscopy or x-ray); and serious GI complications (bleeding, perforation, and obstruction).[6]

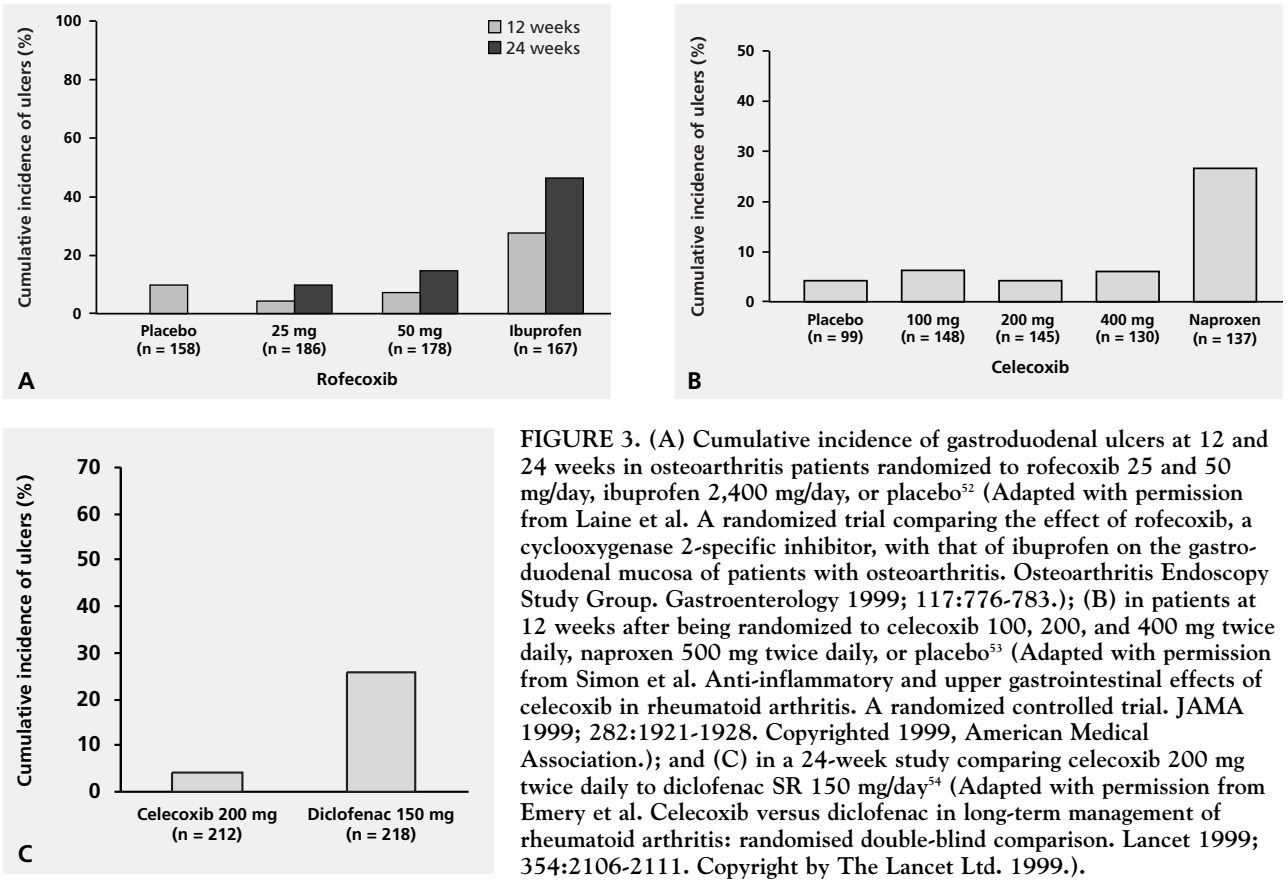

FIGURE 3. (A) Cumulative incidence of gastroduodenal ulcers at 12 and 24 weeks in osteoarthritis patients randomized to rofecoxib 25 and 50 mg/day, ibuprofen 2,400 mg/day, or placebo[52] (Adapted with permission from Laine et al. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Osteoarthritis Endoscopy Study Group. Gastroenterology 1999; 117:776-783.); (B) in patients at 12 weeks after being randomized to celecoxib 100, 200, and 400 mg twice daily, naproxen 500 mg twice daily, or placebo[53] (Adapted with permission from Simon et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis. A randomized controlled trial. JAMA 1999; 282:1921-1928. Copyrighted 1999, American Medical Association.); and (C) in a 24-week study comparing celecoxib 200 mg twice daily to diclofenac SR 150 mg/day[54] (Adapted with permission from Emery et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. Lancet 1999; 354:2106-2111. Copyright by The Lancet Ltd. 1999.).

Gastrointestinal symptoms ranging from heartburn, nausea, and abdominal pain, so-called nuisance symptoms, to more serious GI complications occur in more than one third of patients taking NSAIDs.[6,18] These symptoms have no demonstrated correlation with endoscopic or clinically relevant events but are important to the quality of life of patients who use NSAIDs. To evaluate such quality-of-life effects, a meta-analysis of the GI adverse events among 5,435 patients enrolled in eight randomized, double-blind trials of rofecoxib was undertaken. In this analysis, the 6-month cumulative incidence of dyspeptic side effects in patients receiving 12.5, 25, or 50 mg of rofecoxib daily was significantly lower than in those receiving nonselective NSAIDs (ibuprofen, diclofenac, or nabumetone).[51] While the cumulative incidence of symptoms in the two groups converged at 12 months, the rate of discontinuation due to adverse GI events in those patients taking NSAIDs continued to be about 30% higher than that of patients taking rofecoxib. The VIOXX Gastrointestinal Outcomes Research (VIGOR) trial examined safety and efficacy of rofecoxib in 8,076 patients.[47] This study showed that incidences of the leading five GI nuisance symptoms were similar for both rofecoxib and naproxen (dyspepsia, abdominal pain, epigastric discomfort, and heartburn). Again in the rofecoxib group, significantly fewer patients discontinued treatment as a result of any one of these symptoms than did patients in the naproxen group (3.5% vs 4.9%). The Celecoxib Long-term Arthritis Safety Study (CLASS), another large GI-outcomes study carried out in patients with OA or RA, demonstrated similar results with celecoxib.[18] The most commonly reported GI symptoms in this study were dyspepsia, abdominal pain, diarrhea, nausea, and constipation. With the exception of diarrhea, the incidence of these events was significantly lower with celecoxib than with the comparator nonselective NSAIDs. For individual NSAIDs, rates of dyspepsia, abdominal pain, and nausea in patients receiving celecoxib were similar to those for ibuprofen and significantly less than those for diclofenac. The CLASS publication[18] reported limited data, out to 6 months. The full 9-month (median follow-up) data

were reported in February 2001 and are available at http://www.fda.gov/ohrms/dockets/ac/01/briefing/367761_01_searle.pdf (FDA website address).

Prospective studies have shown that COX-2–selective inhibitors are associated with less frequent incidence of endoscopic ulcers than are nonselective NSAIDs. Rofecoxib was compared with ibuprofen and placebo in a randomized clinical trial in 742 patients with OA.[52] At 12 and 24 weeks, the cumulative incidence of gastroduodenal ulcers of at least 3 mm with rofecoxib (25 or 50 mg once daily) was significantly lower than with ibuprofen (800 mg 3 times daily) and statistically equivalent to placebo (**Figure 3A**). A similar 12-week trial compared the cumulative incidence of gastroduodenal ulcers of at least 3 mm with celecoxib (100, 200, or 400 mg), naproxen (500 mg twice daily), or placebo in 1,149 patients with RA.[53] The incidence of ulcers with all doses of celecoxib was similar to placebo and significantly lower than with naproxen (**Figure 3B**). Another 24-week randomized trial compared celecoxib (200 mg twice daily) with diclofenac SR (150 mg daily) in 655 patients with RA. This trial showed significantly lower incidence of gastroduodenal ulcers in patients receiving celecoxib compared with diclofenac (**Figure 3C**).[54] Long-term outcomes studies of rofecoxib and celecoxib confirm the clinical tolerability and safety of these agents.[18,47] (See article by Scheiman in this supplement.)

SAFETY OF AGENTS IN DEVELOPMENT

Newer COX-2–selective agents also have demonstrated improved GI safety. One such agent, etoricoxib, is being evaluated for the treatment of OA, RA, and chronic lower back pain. An analysis of eight randomized, double-blind, phase II–III efficacy trials (N = 2,651) of this COX-2–selective inhibitor showed significantly fewer (43% less) treatment discontinuations due to NSAID-type symptoms or GI symptoms in general compared with nonselective NSAIDs.[55] A similar analysis of all phase II–III trials (n = 3,123) found that etoricoxib significantly reduced the incidence of investigator-reported and confirmed upper-GI perforations, ulcers, and bleeds by approximately 50% compared with treatment with nonselective NSAIDs (diclofenac, ibuprofen, naproxen).[56] Further trials will help to fully characterize the potential benefits and GI safety and tolerability of etoricoxib.

CLINICAL STRATEGIES TO REDUCE NSAID-RELATED GASTROPATHY

There are several strategies that healthcare providers can employ to decrease the risk of NSAID-related GI complications:

- Risk assessment with special management of those at increased risk should guide clinical strategies
- Risk factors should be modified when possible; eradication of *H pylori* may decrease long-term risk of gastroduodenal ulcers
- As recommended by the practice guidelines of the American College of Rheumatology, a non-NSAID such as acetaminophen (paracetamol) with low GI toxicity should be used as the first line of analgesic therapy
- When a nonselective NSAID is used, the lowest effective dosage is recommended. Although large long-term trials are lacking, there is evidence that some NSAIDs such as nabumetone, etodolac, and meloxicam may be among the more tolerable nonselective NSAIDs
- Cotherapy with an acid-suppressing agent such as a PPI or possibly misoprostol should be considered. This may reduce risk for patients with a history of ulcer bleeding, including those free of *H pylori* infection
- COX-2–selective inhibitors can be used to significantly decrease risk of GI toxicity.

CONCLUSIONS

NSAIDs are responsible for significant morbidity and mortality with high associated direct and indirect costs. Although serious GI complications in NSAID users often have no specific warning signs, patients at high risk for NSAID-related gastropathy have recognizable risk factors. Selective COX-2 inhibitors have efficacy equivalent to that of nonselective NSAIDs with no new unexpected side effects. Rates of dyspepsia reported in patients receiving COX-2 inhibitors in clinical trials were similar to those for nonselective NSAIDs; however, discontinuation rates for dyspeptic symptoms were lower with COX-2 inhibitors than with comparator NSAIDs. Endoscopic damage in patients taking COX-2–selective inhibitors was equivalent to placebo even when coxibs were administered at high dosages. The development and application of COX-2–selective agents is a significant advance, as

these agents have overcome one of the major obstacles of NSAID therapy—the risk of ulcers and their potentially fatal complications. In reducing the risk of NSAID-related gastropathy, these drugs also provide an avenue for cost reduction by controlling the economic burden of these complications. In conclusion, coxibs, the selective COX-2 inhibitors, offer a well-tolerated and cost-effective addition to the armamentarium available for the treatment of patients with arthritis.

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Outcomes studies of the gastrointestinal safety of cyclooxygenase-2 inhibitors

JAMES M. SCHEIMAN, MD

ABSTRACT

Short-term endoscopic studies of the highly selective cyclooxygenase-2 (COX-2) inhibitors (coxibs) rofecoxib and celecoxib have shown that these agents are well tolerated and have efficacy equivalent to nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) with fewer adverse effects on the upper gastrointestinal (GI) tract. These studies are limited, however, as the detection of endoscopic lesions is not well correlated with symptomatic ulcers and ulcer complications. Outcomes studies of the GI safety are, therefore, essential to understanding how coxibs are likely to perform in a clinical practice setting. Four large outcomes studies (Vioxx Gastrointestinal Outcomes Research, VIGOR; Assessment of Difference Between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness trial, ADVANTAGE; Celecoxib Long-term Arthritis Safety Study, CLASS; and the Successive Celecoxib Efficacy and Safety Studies, SUCCESS) examined the GI safety of rofecoxib and celecoxib in over 39,000 patients with osteoarthritis or rheumatoid arthritis. Results of these studies showed that patients taking a supratherapeutic dose of rofecoxib or celecoxib had significantly lower rates of GI-related adverse events than those taking a nonselective NSAID (naproxen, ibuprofen, or diclofenac). Reduced risk of upper GI events was seen in patients with multiple risk factors and in patients using low-dose aspirin and corticosteroids concomitantly with a coxib. Results of large outcomes studies provide support for the COX-2 hypothesis and demonstrate the long-term safety and tolerability of coxibs.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy in patients with osteoarthritis (OA) who do not respond to nonpharmacologic modalities. NSAID use is widespread, with more than 30 billion over-the-counter tablets sold and 70 million prescriptions filled annually in the United States.[1]

Most NSAIDs inhibit both forms of cyclooxygenase (COX), the enzyme that catalyzes prostaglandin synthesis. COX-1, which is constitutively expressed, generates prostaglandins critical to gastrointestinal (GI) mucosal defenses.[2] COX-2 is induced at sites of inflammation and generates prostaglandins that mediate inflammation and pain.[3] As a result of COX-1 inhibition, nonselective NSAIDs have detrimental effects on the GI mucosa. GI-related serious adverse effects affect as many as 30% of those using NSAIDs, resulting in 103,000 hospitalizations annually.[1] The negative outcomes of NSAID use have provided the impetus to develop drugs that specifically inhibit COX-2 and therefore control pain and inflammation without damage to the GI mucosa.[4]

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TABLE 1
Comparison of characteristics of the VIGOR and CLASS trials[11–13]

Characteristic	VIGOR (n = 8,076)	CLASS (n = 7,968)
Patients		
Disease, %		
Rheumatoid arthritis	100	27.4
Osteoarthritis	0	72.6
Concomitant medications, %		
Aspirin use (< 325 mg)	0	20.7
Glucocorticoids	56.0	30.1
Anticoagulants	0	1.1
Helicobacter pylori infection, %	43.0	38.4
Previous GI perforation, ulcer, or bleeding, %	7.8	9.9
End points		
Primary	Symptomatic ulcers	Ulcer complications
Secondary	Ulcer complications	Symptomatic ulcers
Treatment		
Drug	Rofecoxib 50 mg/day	Celecoxib 800 mg/day
Comparator(s)	Naproxen 1,000 mg/day	Ibuprofen 2,400 mg/day Diclofenac 150 mg/day
Duration	9 months (median)	6 months
Analysis	5,396 patient-years Intent to treat	2,825 patient-years 6 months reported

The US Food and Drug Administration (FDA) has approved two drugs that specifically inhibit the COX-2 enzyme (coxibs), rofecoxib and celecoxib. These drugs were shown in 12- and 24-week clinical studies to have efficacy similar to that of nonselective NSAIDs for the treatment of OA and rheumatoid arthritis (RA) with lower risk of GI complications.[5–7] As serious GI adverse events (perforation, obstruction, and bleeding) have an annual incidence of only 0.2% to 0.3%, large numbers of patients are necessary to accumulate sufficient events for safety studies.[8] To overcome this, endoscopic evidence of lesions has been used as a surrogate measure of serious upper GI events. Endoscopic results, however, do not necessarily correlate with GI complications.[9] Of patients with a break in the gastric mucosa of equal to or greater than 3 mm in size, approximately 25% have an ulcer, and 1% to 4% will have a clinically significant GI complication. In addition, reduced incidence of endoscopic lesions, such as that resulting from use of misoprostol or proton pump inhibitors, does not reflect an equivalent reduction in risk of serious GI complications.[10] Long-term studies in large numbers of patients are therefore necessary for assessment of GI safety. To be relevant, these studies should report incident events of clinical significance (eg, hospitalizations or serious GI events), and patients should be those with risk factors generalizable to real-world clinical settings. The results of four outcomes studies characterizing the long-term GI safety of coxibs are reviewed here.

OUTCOMES STUDIES OF COXIBS

Several large, long-term studies have examined the GI safety outcomes of coxibs. Rofecoxib studies include the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial and the Assessment of Difference Between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness (ADVANTAGE) trial. Trials of celecoxib include the Celecoxib Long-term Arthritis Safety Study (CLASS) and the Successive Celecoxib Efficacy and Safety Studies (SUCCESS). A summary of VIGOR and CLASS trials is shown in **Table 1**.[11–13]

VIGOR

The VIGOR trial compared twice the recommended dose of rofecoxib (50 mg daily) with the most common dose of naproxen (1000 mg daily) in 8,076 patients with RA (**Table 1**).[11] VIGOR was a 13-month, placebo-controlled, double-blind trial con-

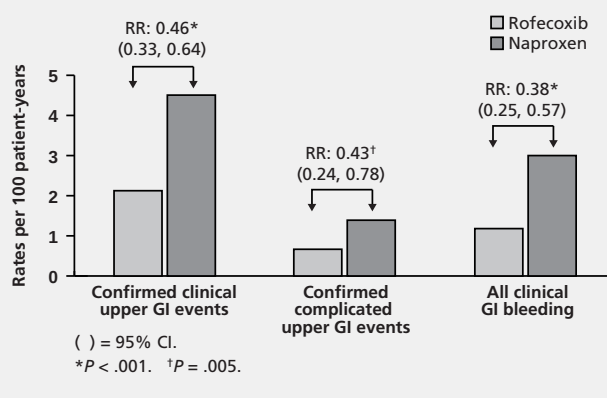

FIGURE 1. Summary of clinical end points for the VIGOR trial.[13]

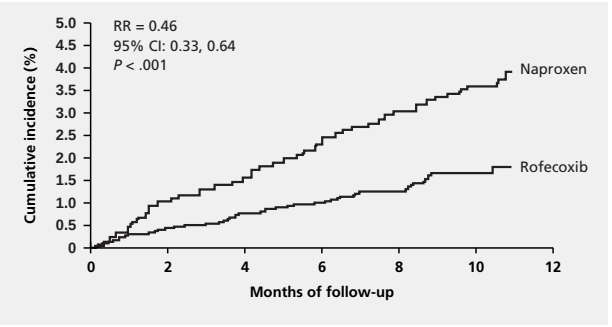

FIGURE 2. Time to confirmed clinical primary end point in VIGOR.[13]

ducted prospectively in 301 centers in 22 countries. Median treatment was 9 months. Patients over 50 years of age and using NSAIDs for at least 1 year were included. Those with a positive fecal blood test, and those using aspirin, anticoagulants, antiplatelet agents, or prescribed antiulcer medications, were excluded from VIGOR.

The primary end point of VIGOR was symptomatic ulcers, including clinical upper GI events of perforation, obstruction, and bleeding. The secondary end point was complicated upper GI events (perforation; obstruction; and major bleeding resulting in ≥2-g drop in hemoglobin, transfusion, or hypotension).[11] The RA patient population of VIGOR was selected because RA patients use NSAIDs chronically and have a substantially higher risk of NSAID-related GI events than do patients with OA.

Rofecoxib significantly decreased the incidence of all GI end points studied in VIGOR (**Figure 1**).[13] The comparative event rates for all upper GI end points for rofecoxib compared with naproxen were 2.1 and 4.5 per 100 patient-years, respectively, resulting in a relative risk (RR) of 0.46 (95% confidence interval [CI], 0.33–0.64; $P < .001$). For complicated upper GI events, the rates were 0.6 and 1.4 per 100 patient-years for rofecoxib and naproxen, respectively (RR = 0.43; 95% CI, 0.24–0.78; $P = .005$). All GI bleeding rates for rofecoxib and naproxen were 1.1 and 3.0 per 100 patient-years, respectively (RR = 0.38; 95% CI, 0.25–0.57; $P = .001$).[11]

The time to GI end point events is shown in **Figure 2**.[13] Patients randomized to rofecoxib had half the risk of perforation, obstruction, and major bleeding as those receiving naproxen (RR = 0.5; 95% CI, 0.33–0.64; $P < .001$). The lower incidence of GI events in the rofecoxib group was apparent after the first month, and new events occurred at a significantly lower rate than in the naproxen group for the remainder of the study.[11]

The rates of discontinuation due to lack of efficacy for rofecoxib and naproxen were comparable (6.3% and 6.5%, respectively).[11] The rate of discontinuation for any GI events (including clinical end points) was significantly lower in the rofecoxib group compared with the naproxen group (7.8% and 10.6%, respectively; $P < .05$).[11] There was significantly less use of prescribed H_2-receptor antagonists, proton pump inhibitors, or prostaglandin analogs in the rofecoxib group compared with the naproxen group (11.2% vs 14.5%, RR = 0.77; 95% CI, 0.68–0.87).[14]

Analysis of risk factors among VIGOR participants showed that those factors independently associated with increased risk of GI events included advanced age, prior history of clinical GI events or GI symptoms, arthritic disease severity, and prior H_2-receptor antagonist use. Corticosteroids are among the major risk factors for ulcers and ulcer complications.[1] The prevalence of steroid use in VIGOR was 56%, suggesting that patients had a high baseline risk. The subgroup of patients in VIGOR using steroids at study entry had a significantly increased risk of GI clinical events (RR = 1.59; 95% CI, 1.15–2.18, $P = .005$).[15]

In patients receiving rofecoxib, RR of clinical GI events among the group with risk factors (≥65 years of age, history of ulcer or GI event, *Helicobacter pylori*-positive, or steroid user) was reduced by 51%, similar to the 54% reduction in risk for the entire rofecoxib group. The RR reduction in the low-risk group (that is, none of the four risk factors) receiving rofecoxib was 88% (**Figure 3**).[13,15] The probability of GI complications in patients taking NSAIDs depends on preexisting risk factors, and these data show that rofecoxib can reduce risk incrementally in patients both with

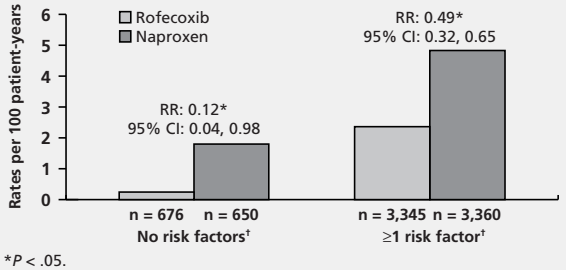

FIGURE 3. Relative risk (RR) of confirmed upper GI events by risk category in VIGOR.[13]

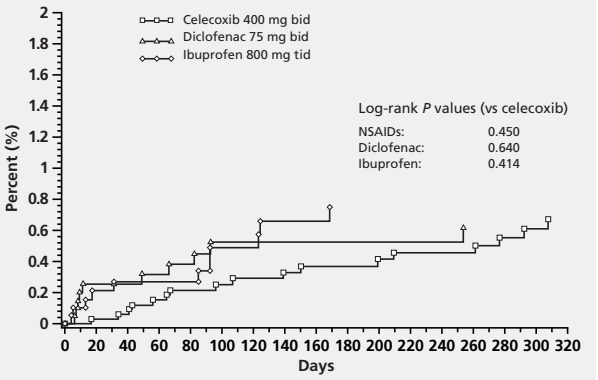

FIGURE 4. Time to upper gastrointestinal outcomes in the CLASS trial. Results are for entire study using intent-to-treat analysis.[18]

and without multiple risk factors.

VIGOR also compared the efficacy of rofecoxib 50 mg daily to naproxen 500 mg twice daily for a median of 9 months. Global Assessment Disease Activity scores were assessed by patients and physicians as well as by using the Modified Health Assessment Score. The results showed that rofecoxib was indistinguishable from naproxen on all efficacy measures.[11]

ADVANTAGE

ADVANTAGE was a 12-week, double-blind, randomized, prospective trial in 5,597 patients with OA in the United States and Sweden who were randomized to receive rofecoxib (25 mg daily) or naproxen (500 mg twice daily). Patients using low-dose aspirin (<81 mg/day) were included in the trial. The primary end point of ADVANTAGE was GI tolerability as defined by the incidence of discontinuations due to GI adverse events. The secondary end point was use of concomitant medication to treat GI symptoms.[16] Most patients (71%) were women, and the mean age of study participants was 63 years old. Twelve percent of patients used low-dose aspirin during the trial, and baseline characteristics of the treatment groups were similar.

At study end, a significantly lower rate of GI adverse event-related discontinuations occurred with rofecoxib (5.9% vs 8.1% for rofecoxib vs naproxen; $P = .005$). Significantly fewer patients receiving rofecoxib (9.1%) required concomitant GI medications compared with patients receiving naproxen (11.2%; $P = .014$). Concomitant use of low-dose aspirin did not significantly affect relative rates of discontinuation due to adverse events, serious adverse events, or drug-related adverse events.[16] While ADVANTAGE was limited to 12 weeks, the results are important because they show that concomitant use of low-dose aspirin with rofecoxib does not significantly increase risk of adverse events.

CLASS

The CLASS trial (**Table 1**) was carried out in 7,968 patients from 386 centers in the United States and Canada and compared celecoxib (400 mg twice daily; two and four times the maximum dosage for RA and OA, respectively) with two nonselective NSAIDs: diclofenac (75 mg twice daily) or ibuprofen (800 mg thrice daily).[12] While ibuprofen is nonselective, diclofenac has a COX-1/COX-2 IC_{50} (concentration that inhibits 50%) ratio similar to that of celecoxib (29 vs 30 for diclofenac and celecoxib, respectively).[17] CLASS enrolled patients from September 1998 to March 2000; 57% of enrolled patients received treatment for 6 months. Only data from the first 6 months of the trial have been published.[12] However, 9-month (median) data were presented in February 2001 to the FDA and are available on the FDA website.[18] Efficacy was not reported for CLASS.

The primary end point in CLASS was the incidence of ulcer complications (ulcer perforation, gastric outlet obstruction, or upper GI bleeding). The secondary end point was complicated and symptomatic ulcer events. Patients taking low-dose aspirin (≤325 mg/day) were allowed to enroll.

In CLASS, the annualized incidence rates for upper GI ulcer complications were 0.76% and 1.45% for celecoxib and NSAIDs, respectively ($P = .09$).[12] While the difference in rates favored celecoxib, it did not reach statistical significance. Comparison of the time

GI outcomes with coxibs

Long-term outcomes studies provide the best evidence for gastrointestinal (GI) safety of coxibs in patients with arthritis and preexisting risk factors.

Prospective studies in over 39,000 arthritis patients compared the long-term GI safety of coxibs and nonsteroidal anti-inflammatory drugs (NSAIDs).

Outcomes studies show rofecoxib and celecoxib have favorable GI safety profiles at supratherapeutic doses and significantly decrease GI adverse events compared with NSAIDs.

The magnitude of the safety advantage of coxibs in the setting of concomitant aspirin use remains unresolved.

Coxibs decrease risk of upper GI ulcers and ulcer complications in patients with and without ulcer risk factors.

to primary end point for the entire study is shown in **Figure 4**.[18] The cumulative rate of complicated ulcer favored celecoxib within the first month of the study, and this trend continued at 6 months ($P = .09$). There were no further GI events in the ibuprofen group after day 170, and the last event in the diclofenac group occurred at day 250. At study end, the trend favoring celecoxib was no longer apparent ($P = .45$).[18]

A caveat of unbiased time-to-event analysis is that the basis of withdrawal from the study (censoring) must be independent of the outcome event being measured. Treatment-emergent symptoms (dyspepsia, abdominal pain, diarrhea, nausea, and vomiting) were found to be a significant risk factor for the primary and secondary end points of CLASS, particularly in patients receiving diclofenac. The RR of ulcer complications in patients with moderate-to-severe GI symptoms vs patients without moderate-to-severe GI symptoms was 3.9 overall and 13.8 for diclofenac.[18] The RR of symptomatic ulcer plus ulcer complications in patients with moderate-to-severe GI symptoms vs patients without moderate-to-severe GI symptoms was 6.3 overall and 11.5 for diclofenac. More patients in the diclofenac group withdrew owing to GI symptoms than did patients in the other treatment groups (9.5% for diclofenac vs 7.5% for celecoxib and ibuprofen; $P < .05$). As early withdrawal of patients in the diclofenac group could have biased results, celecoxib and diclofenac could not be meaningfully compared in an intent-to-treat analysis in CLASS.[18]

For the secondary end point of CLASS, patients in the celecoxib group had significantly lower rates of symptomatic and complicated ulcers than those in the NSAID group; annualized incidence rates were 2.08% and 3.54% for celecoxib and NSAIDs, respectively ($P = .02$).[12]

There are several possible explanations for why the primary end point of the CLASS trial was not met. The design of the CLASS study may have provided inadequate statistical power to demonstrate a decrease in primary end point events with celecoxib. CLASS was designed with power to detect a 75% reduction in risk, while the results were closer to a 50% reduction.

The inability to demonstrate a statistically significant difference in end point rates of the treatment groups may also reflect the higher-than-expected event rate in the celecoxib group. The annualized event rate in CLASS patients receiving celecoxib (0.76%) was almost four times that predicted from previous trials (0.2%).[12] This likely reflects the 21% of participants using aspirin during the trial, about twice the number in other trials of celecoxib.[6] Among aspirin users, the annualized incidence of complicated ulcers was similar in the celecoxib and NSAID groups (2.01% vs 2.12%; $P = .92$) as were the rates of symptomatic and/or complicated ulcers (4.7% vs 6.0%; $P = .49$). Overall, the RR of ulcer complication for participants taking celecoxib and aspirin concomitantly, compared with those taking celecoxib without aspirin, was 4.5 ($P = .01$).[12] The increased risk of adding aspirin to celecoxib in CLASS participants was comparable to the risk incurred by a moderate dose of an NSAID alone and about half the risk of taking aspirin concomitantly with a nonselective NSAID.[19] When CLASS participants not using aspirin were examined in a posthoc analysis, the rate of annualized incidence of complicated ulcers was significantly lower in those taking celecoxib than in those taking NSAIDs (0.44% vs 1.27%; $P = .04$; **Figure 5**),[12] and event rates were similar to those of other celecoxib trials.[12] These results suggest that aspirin use may offset the GI benefits of celecoxib use.

For reasons that are unclear, the rate of withdrawals in CLASS (40.4% and 44.8% in the celecoxib and NSAID groups, respectively) was considerably higher than that in other coxib trials. The withdrawal rate for adverse events was significantly higher in patients receiving NSAIDs compared with those receiving celecoxib (20.6% vs 18.4%, respectively; $P < .01$).[12]

■ SUCCESS

SUCCESS was a 12-week, double-blind, randomized trial in 13,274 patients that compared the incidence of upper GI hospitalizations in patients with

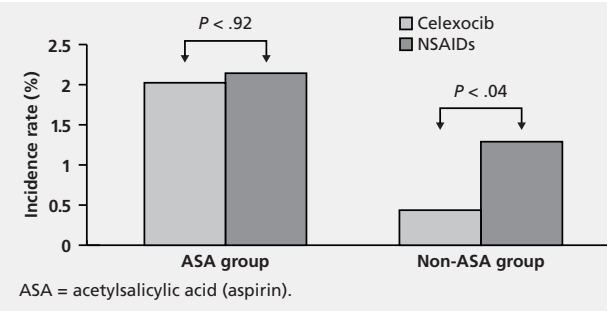

FIGURE 5. Annualized incidence of primary end point for CLASS trial (complicated ulcers) among users and nonusers of low-dose aspirin (ASA).[12]
(Adapted with permission from Silverstein et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study—a randomized controlled trial. JAMA 2000; 284:1247-1255.)

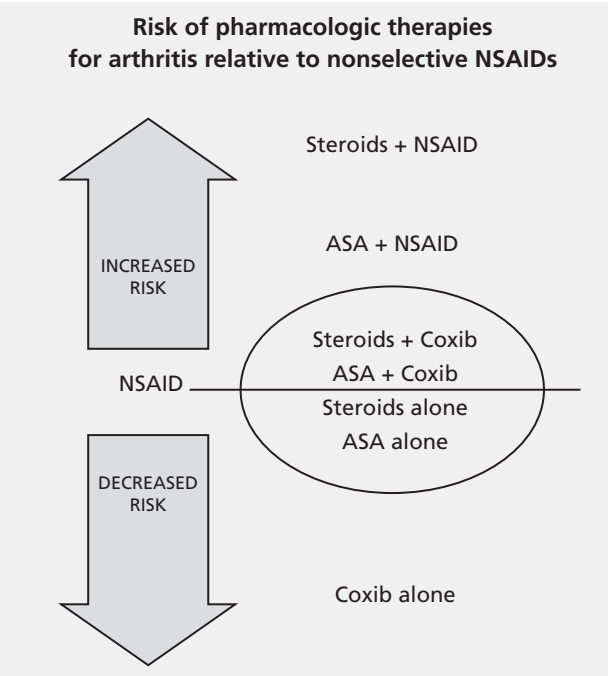

FIGURE 6. Risk of upper GI adverse events associated with pharmacologic therapies in patients with arthritis. Risks are relative to common NSAIDs as approximated from prospective studies. Risks vary with dose and individual agents.[11,12,19]

OA taking celecoxib (200 or 400 mg daily), diclofenac (100 mg daily), or naproxen (1,000 mg daily).[20] In an effort to closely parallel a general practice, patients and clinicians reported clinically significant GI events, which were then adjudicated as ulcer complications and symptomatic ulcers (as defined in CLASS). The rate of hospitalization was significantly lower in the celecoxib group (1.17 vs 2.34 per 100 patient-years for celecoxib vs NSAIDs), resulting in an RR of 0.5 (95% CI, 0.28–0.90; $P < .02$).[20] For the primary end point of ulcers plus ulcer complications, the rates per 100 patient-years as determined by a blinded panel were 0.32 and 1.27 for celecoxib vs NSAIDs, respectively (RR = 0.25; 95% CI, 0.09–0.67; $P < .006$).

In SUCCESS, there were significantly fewer nuisance symptoms in the celecoxib group compared with the NSAID group. Symptoms of dyspepsia, abdominal pain, or nausea were reported by 4.8%, 4.8%, and 2.4%, respectively, in the celecoxib group, and by 5.9%, 6.2%, and 3.4%, respectively, in the NSAID group ($P < .05$, celecoxib vs NSAIDs for all categories). In addition, fewer patients taking celecoxib (5.2%) than taking NSAIDs (6.8%) withdrew due to GI-related adverse events ($P < .05$).[21]

SUCCESS also measured efficacy in patients with OA. Results of the trial showed that both dosages (200 and 400 mg daily) of celecoxib were as efficacious as NSAIDs.[22]

■ COMMENTS

The results of long-term trials of coxibs provide evidence supporting the hypothesis that COX-2–specific inhibition results in relief from arthritis symptoms without accompanying deleterious effects on mucosal defenses. Perhaps more importantly, these studies offer insight into how coxibs might be expected to perform in a real-world clinical setting. The clinical end points of these trials—ulcers and ulcer complications—are more valid than surrogate endoscopic measures commonly used in short-term trials. Furthermore, by striving for a naturalistic setting, the study design and entry criteria of these trials produced findings that can be generalized to most patients encountered in clinical practice. The results of coxib outcomes studies also revealed the ability of coxibs to reduce GI risk even when patients face a combination of other risk factors such as advanced age, steroid use, or *H pylori* infection.

Patients with RA commonly use low-dose aspirin for cardiovascular prophylaxis. While the risk of aspirin use to the upper GI tract is recognized, the increased risk incurred by those taking low-dose aspirin and a coxib has been controversial. In the ADVANTAGE trial, concomitant use of aspirin with rofecoxib resulted in no significant effect on GI adverse events, discontinuations, or symptomatic ulcers. In CLASS, low-dose aspirin was an independent risk factor for ulcers in patients taking celecoxib,

and aspirin offset the GI benefit of celecoxib. In contrast to CLASS, SUCCESS showed that—relative to concomitant nonselective NSAIDs and aspirin—the risk of GI adverse events is substantially reduced with concomitant celecoxib and aspirin, albeit to a lesser degree than celecoxib without aspirin (**Figure 6**).[11,12,19] With the exception of CLASS, favorable outcomes of these trials suggest that in patients using coxibs for relief of arthritis symptoms, the cardiovascular benefits of low-dose aspirin may weigh against the incremental risk of GI events. For patients at high risk for ulcer complications, cotherapy may be required when a coxib is prescribed with aspirin.

Other controversy has centered on possible inhibitory effects of coxibs on the protective effects of aspirin. A detailed analysis revealed that coxibs do not inhibit platelet aggregation and do not contraindicate low-dose aspirin therapy for appropriate patients.[23] In particular, rofecoxib (and other nonselective NSAIDs except ibuprofen) does not inhibit the beneficial effects of aspirin.[24]

In conclusion, four coxib outcomes studies (VIGOR, ADVANTAGE, CLASS, and SUCCESS) were conducted in over 39,000 patients with OA and RA. These studies showed that the COX-2–specific inhibitors, rofecoxib and celecoxib, resulted in significantly fewer clinically important upper GI adverse events than did nonselective NSAIDs, while having similar efficacy. Treatment of large numbers of patients has helped to define the role of selective COX-2 inhibitors in symptom management in arthritis while providing convincing evidence that coxibs can reduce the risk of symptomatic ulcers and ulcer complications.

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Current perspective on the cardiovascular effects of coxibs

MARVIN A. KONSTAM, MD, AND MATTHEW R. WEIR, MD

ABSTRACT

Aspirin and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for their anti-inflammatory and analgesic effects. In addition, aspirin is documented to reduce cardiovascular events in selected populations, presumably because of inhibition of platelet aggregation. Yet these drugs are not without toxicity, particularly adverse effects on the gastric mucosa. The gastrointestinal toxicity of nonselective NSAIDs and aspirin derives from the inhibition of the cyclooxygenase (COX) enzyme, COX-1, which synthesizes gastroprotective prostaglandins, while the anti-inflammatory and pain-relieving effects are largely derived from inhibition of COX-2–derived prostaglandins. Available data indicate that the harmful gastric effects of nonselective NSAIDs are reduced by substitution of agents that only inhibit the COX-2 protein. The COX-2–selective inhibitors, however, have also been shown to inhibit the production of vascular prostacyclin, which has vasodilatory effects and inhibits platelet aggregation; unlike nonselective NSAIDs, they do not inhibit the production of thromboxane, an eicosanoid that promotes platelet aggregation. Whether these effects could potentially contribute to a prothrombotic environment is the subject of current, intensive debate. In the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, there was a higher incidence of cardiovascular thrombotic events in the rofecoxib- vs the naproxen-treated group: 1.67 vs 0.70 per 100 patient years. However, in a pooled analysis of rofecoxib studies, the risk of sustaining a thrombotic cardiovascular event was similar when comparing patients receiving rofecoxib with those receiving placebo, or when comparing patients receiving rofecoxib with those receiving non-naproxen nonselective NSAIDs. These findings are likely to result, at least in part, from the antiplatelet action of naproxen, which has been shown to be potent and sustained during a typical dosing regimen (500 mg twice daily in VIGOR). In contrast, the other NSAID comparators effect weaker and/or nonsustained antiplatelet action. In the Celecoxib Long-term Arthritis Safety Study (CLASS) trial, there was no difference between celecoxib and the nonselective NSAIDs explored (which did not include naproxen) in cardiovascular event rates. Unlike those in VIGOR, patients in the CLASS trial were allowed to take low-dose aspirin. Thus, despite concerns raised by results of VIGOR, other existing data, including those pooled from existing placebo-controlled trials, do not support a clinically relevant prothrombotic effect of the COX-2 inhibitors. Additional placebo-controlled data, from patients at both high and low risk for cardiovascular events, are warranted to clarify the cardiovascular effects of this class of agents.

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Aspirin and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for their anti-inflammatory and analgesic effects. In addition, aspirin, an effective antiplatelet agent, is documented to reduce cardiovascular risk in select populations.[1,2] Yet these drugs are not without toxicity, particularly adverse effects on the gastric mucosa. The gastrointestinal side effects of aspirin and NSAIDs derive from the inhibition of cyclooxygenase (COX)-1–derived prostaglandin synthesis. COX-1 is an isoform constitutively expressed in many tissues.[3] It facilitates the production from arachidonic acid of homeostatic prostaglandins, which preserve gastrointestinal mucosal integrity and renal blood flow. This same isoform is also expressed in platelets, producing thromboxane A_2, which promotes platelet activation and aggregation. Nonselective NSAIDs also inhibit COX-2, an enzyme induced at sites of inflammation that facilitates the production of prostanoids, which mediate pain and inflammation.[3,4]

Identification of the COX-2 enzyme allowed the development of COX-2–selective inhibitors. It was believed that the harmful gastric effects of nonselective NSAIDs—those NSAIDs that inhibit both COX-1 and COX-2—would be alleviated by agents that selectively inhibited the COX-2 protein. The COX-2–selective inhibitors, however, have also been shown to inhibit the production of vascular prostacyclin, which has important vasodilatory properties and inhibits platelet aggregation. In the absence of significant inhibition of COX-1, these agents do not inhibit platelet thromboxane production.[5,6]

It has been theorized that by inhibiting production of prostacyclin but not thromboxane, COX-2 selective inhibitors could be prothrombotic. This article will summarize current findings regarding cardiovascular thrombotic events in patients taking nonselective NSAIDs and selective COX-2 inhibitors. We will review the data from major clinical trials and attempt to put the results of the VIGOR trial and other analyses into a useful perspective.

BACKGROUND

Cyclooxygenase is a family of enzymes that catalyze the metabolism of arachidonic acid to various eicosanoids or prostanoids including various prostaglandins, prostacyclins, and thromboxane.[4] To date, two distinct COX isoforms have been identified. COX-1 is expressed constitutively in many tissues, including platelets and the gastrointestinal mucosa. COX-2 is largely inducible and expressed at sites of inflammation, but is also a constitutive enzyme in some tissues[3,7] and is responsible for endothelial production of prostacyclin.

Aspirin serves as a useful model to illustrate the vascular protective effects of potent and sustained inhibition of platelet aggregation. As demonstrated convincingly in the Second International Study of Infarct Survival (ISIS 2), administration of aspirin, which irreversibly inhibits platelet aggregation, reduces the incidence of major cardiovascular thromboembolic events in patients with suspected myocardial infarctions (MIs).[1]

Although definitive studies are lacking, it is possible that some of the nonselective NSAIDs may also provide a variable degree of cardioprotection through their ability to inhibit platelet thromboxane. In contrast to aspirin, however, the antiplatelet action of these agents is reversible, with the duration of effect linked to the pharmacokinetics of each agent.[8] Naproxen is one agent that, when given in a typical dosage of 500 mg twice daily, produces greater than 90% inhibition of platelet thromboxane production throughout the dosing interval.[6] **Figure 1** shows the effects of typical doses of the nonselective NSAIDs—diclofenac, ibuprofen, and naproxen—and the COX-2–selective inhibitor rofecoxib on platelet aggregation. Using typical dosing, diclofenac produces minimal antiplatelet effect, and ibuprofen produces a significant effect but one which is not sustained. Only naproxen (dosed in a conventional, twice-daily manner) produces an antiplatelet effect comparable to that achieved with aspirin and sustained through its dosing interval. COX-2–selective inhibitors do not inhibit platelet function.[5,6]

Results of a recently published study investigating potential interactions between aspirin and commonly prescribed arthritis therapies found that, when administered with aspirin, ibuprofen (but not rofecoxib, acetaminophen, or diclofenac) antagonizes the irreversible platelet inhibition induced by aspirin.[9] This ex-vivo analysis tested platelet function in isolation. Further clinical evaluation is required to determine whether some NSAIDs limit the cardioprotective effects of aspirin.[10]

Figure 2 schematically illustrates the effects of aspirin, NSAIDs, and COX-2–selective inhibitors

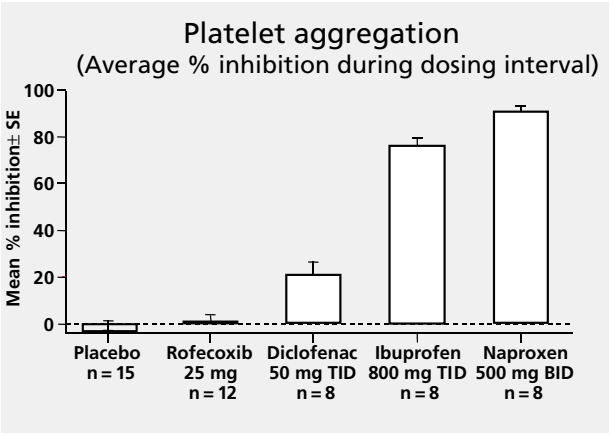

FIGURE 1. Platelet aggregation observed over 8 hours postdose on day 6 versus baseline.[6]

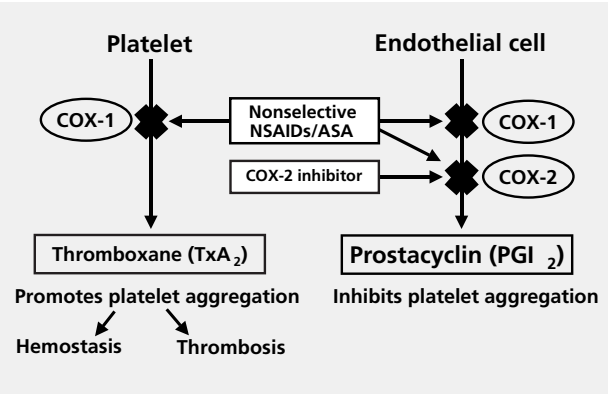

FIGURE 2. How aspirin, nonselective NSAIDs, and COX-2–selective inhibitors affect thromboxane and prostacyclin.

on thromboxane and prostacyclin. Like the nonselective NSAIDs, COX-2–selective inhibitors can inhibit production of systemic prostacyclin, a prostanoid that induces both vasodilation and inhibition of platelet aggregation. The ability of COX-2–selective inhibitors to inhibit endothelial cell prostacyclin without inhibiting platelet aggregation could theoretically create an imbalance resulting in a tendency toward increased thrombosis.[5] Because of this possibility, careful review of available data regarding the cardiovascular effects of COX-2–selective inhibitors is warranted.

EVIDENCE FROM MAJOR COX-2–SELECTIVE INHIBITOR CLINICAL TRIALS

The VIGOR trial. The Vioxx Gastrointestinal Outcomes Research (VIGOR) study was carried out to test the hypothesis that administration of the COX-2–selective inhibitor, rofecoxib, is associated with a reduced incidence of major gastrointestinal adverse events relative to that seen with the nonselective NSAID, naproxen.[11]

Eight thousand seventy-six patients (mean age, 58 years) with rheumatoid arthritis were randomly assigned to receive either rofecoxib 50 mg once daily (a dosage which is 2 to 4 times higher than that indicated for chronic use) or naproxen 500 mg twice daily. Patients taking low-dose aspirin or other antiplatelet agents were excluded. Over a median follow-up of 9 months, compared with naproxen-treated patients, patients receiving rofecoxib had a statistically significantly lower rate of confirmed gastrointestinal events, defined as gastroduodenal perforation or obstruction, upper GI bleeding, and symptomatic gastroduodenal ulcers: 2.1 per 100 patient years with rofecoxib vs 4.5 per 100 patient years with naproxen ($P < .001$).[11]

Data on cardiovascular events were collected as adverse events during the VIGOR trial. Investigator-reported events were confirmed by an independent adjudication committee. The rate of confirmed cardiovascular thrombotic events was 0.70 and 1.67 per 100 patient years in the naproxen group and in the rofecoxib group, respectively.[12] In each group, 0.2% of patients experienced ischemic cerebrovascular events. The rate of death from cardiovascular causes was also 0.2% in each group. The incidence of MIs in the rofecoxib-treated group vs the naproxen group was 0.4% vs 0.1%, respectively.[11]

A post-hoc analysis found that 4% of the participants in the VIGOR trial met US Food and Drug Administration criteria for use of aspirin as a secondary cardiovascular prophylaxis. These aspirin-eligible patients accounted for 38% of the patients who had MIs. Although the event rate was lower in the remaining population, this population likewise displayed an imbalance, favoring naproxen, in the number of thrombotic events within the two groups. The rate of MIs in those patients who did not meet FDA criteria for low-dose aspirin was 0.2% and 0.1% in the rofecoxib and naproxen groups, respectively.[11]

Cardiovascular findings in VIGOR suggest three possible explanations: a prothrombotic effect of rofecoxib, an antithrombotic effect of naproxen, or the play of chance.[13] The potential for a cardiopro-

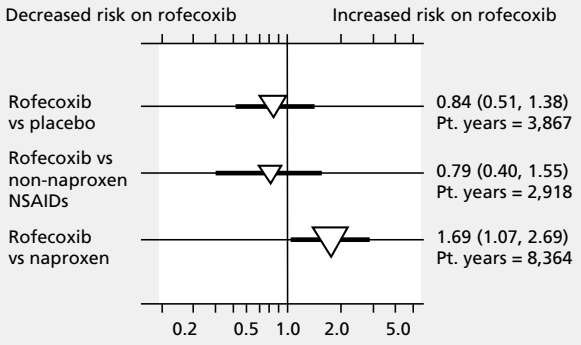

FIGURE 3. Relative risk of the APTC endpoint for rofecoxib relative to placebo, non-naproxen NSAIDs, and naproxen in the rofecoxib pooled analysis. Triangles represent relative risk, and triangle size represents patient-years of exposure. Bars indicate 95% CI. (Reprinted with permission from Konstam MA, Weir MR, Reicin A, et al. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. Circulation 2001; 104:2280–2288.)[12]

NSAIDs, coxibs, and cardiovascular risk

Aspirin reduces the incidence of major cardiovascular thromboembolic events in selected populations in the 81 to 162 mg/day dose range.

Possible explanations for the VIGOR trial results include the possibility that naproxen offered some cardioprotection; however, current data do not support naproxen for this use until properly evaluated in prospective trials.

Prophylactic use of aspirin against cardiovascular events was not permitted in the VIGOR trial, a possible confounding factor.

Clinicians should be aware that blood pressure may become elevated in some patients receiving an NSAID or COX-2–selective inhibitor. This BP-raising effect must be weighed against the therapeutic impact.

Clinicians should consider each individual patient's gastrointestinal and cardiovascular risk profile when selecting among nonselective NSAIDs and coxibs.

tective effect of naproxen is supported by the potent and sustained antiplatelet actions of this agent, cited above.[6] Alternatively, rofecoxib may have had a prothrombotic effect. To further explore the possibility of a prothrombotic effect of rofecoxib, we conducted a pooled analysis of cardiovascular events across the randomized controlled trials of rofecoxib.[12]

Rofecoxib pooled analysis. To further characterize the potential impact of rofecoxib on the incidence of thrombotic cardiovascular adverse events, we conducted a pooled analysis of data derived from the existing and ongoing randomized-controlled clinical trials involving rofecoxib.[12] We included the entire patient data set of randomized controlled trials of rofecoxib, except those of less than 4 weeks' duration and those in which the rofecoxib dosage was below 12.5 mg/day.[12] Patients were included in the analysis only if they received at least one dose of study drug.

Individual patient data were combined to explore the relative risk of cardiovascular thrombotic events among patients taking rofecoxib, placebo, naproxen, and other nonselective NSAIDs (diclofenac, ibuprofen, and nabumetone).[12] The endpoint investigated was that employed by the Antiplatelet Trialists Collaborative (APTC): cardiovascular, hemorrhagic, and unknown death, nonfatal MI, and nonfatal cerebrovascular accident. The pooled analysis included over 28,000 patients from 23 studies, representing more than 14,000 patient-years at risk (**Figure 3**). When comparing rofecoxib with placebo, there was no evidence of an increased incidence of APTC events (relative risk, rofecoxib vs placebo, 0.84). Similarly, there was no evidence of an increased incidence of APTC events for rofecoxib when compared with the non-naproxen NSAIDs (relative risk, 0.79) The analysis confirmed a significant disparity in events, favoring naproxen over rofecoxib (relative risk, 1.69), an effect which was primarily driven by the findings of VIGOR. These findings lend further credence to an antithrombotic effect of naproxen as the principal explanation for the cardiovascular findings seen in VIGOR.[12]

The CLASS study. The Celecoxib Long-term Arthritis Safety Study (CLASS) was a double-blind, randomized, controlled trial investigating the relative effects of celecoxib and nonselective NSAIDs on gastrointestinal events.[14] It enrolled 8,059 patients (mean age, 60.6 years) with osteoarthritis or rheumatoid arthritis who were randomized to receive celecoxib 400 mg twice daily or either ibuprofen 800 mg 3 times daily or diclofenac 75 mg twice daily. In contrast to VIGOR, use of aspirin as prophylaxis against cardiovascular events was permitted.

A total of 4,573 patients (57% of all patients randomized) received treatment for 6 months. The primary endpoint of the study was the number of com-

plicated ulcers. There was no statistically significant difference in treatment arms with regard to the primary endpoint. There was a lower incidence of symptomatic ulcers and ulcer complications with celecoxib, which was given at two to four times higher than clinically indicated dosages, compared with NSAIDs given at standard dosages.

No difference was observed between celecoxib and the nonselective NSAIDs with regard to incidence of cardiovascular events. MIs occurred in 0.3% of all patients taking either celecoxib or a nonselective NSAID. MIs occurred in less than 0.1% and 0.1% of patients not receiving aspirin within the celecoxib group and the nonselective NSAID group, respectively.[14]

There are several major differences between the VIGOR and CLASS trials, aside from the COX-2 inhibitor investigated. VIGOR exclusively enrolled patients with rheumatoid arthritis, whereas CLASS enlisted patients with either osteoarthritis or rheumatoid arthritis. This difference may be important, since rheumatoid arthritis is associated with an increased incidence of cardiovascular events, when correction is made for other population differences.[15-17] As noted, the two trials employed different comparator NSAIDs, a factor that is likely to be of critical importance given the difference in platelet inhibitory effects of these various agents. Finally, approximately 20% of patients in CLASS were taking aspirin for cardiovascular prophylaxis whereas VIGOR did not allow aspirin use. Nevertheless, analysis of cardiovascular endpoints from CLASS does not support the hypothesis of a prothrombotic action of selective COX-2 inhibitor agents.

Alternative analysis of rofecoxib/celecoxib cardiovascular data. Recently, Mukherjee and colleagues reviewed four published randomized controlled trials with COX-2–selective inhibitors, VIGOR, CLASS, and two smaller rofecoxib trials, each involving approximately 1,000 patients, to investigate a potential influence of COX-2–selective inhibitors on the rates of cardiovascular thrombotic events.[18] The authors observed that the annualized rates of MI for rofecoxib within VIGOR (0.74%) and for celecoxib within CLASS (0.80%) were higher than those observed within the pooled placebo group from a meta-analysis of four primary prevention trials (0.52%).[19] Conclusions must be drawn cautiously from these findings because of significant limitations to the analysis. These include 1) comparison of event rates across different trials is generally hazardous; 2) the populations within the primary prevention studies are likely to be substantially different from those within VIGOR and CLASS, which enrolled older patients with a variety of comorbidities (including rheumatoid arthritis, which is known to confer an increased risk of MI); and 3) in fact, the MI rates observed within VIGOR and CLASS fell within the range of those observed within the composite primary prevention trials utilized in this meta-analysis.

■ DISCUSSION AND CONCLUSIONS

The effect of COX-2–selective inhibitors on the incidence of cardiovascular events remains unresolved. Of the available clinical trial data, only those from the VIGOR trial provide reason for concern, based on an increased incidence of thrombotic events in patients randomized to rofecoxib compared with those randomized to naproxen. However, there is reason to anticipate a significant cardiovascular protective effect of naproxen, based on the potent and sustained antiplatelet effect achieved with this agent. Importantly, our pooled analysis of data from the randomized-controlled trials of rofecoxib provides no evidence for an increased incidence of cardiovascular events for rofecoxib relative to either placebo or non-naproxen NSAIDs. Likewise, data from CLASS provide no evidence for an excess of cardiovascular events for celecoxib relative to either diclofenac or ibuprofen, agents that do not produce sustained antiplatelet effect. This information, in aggregate, makes it likely that the results of VIGOR derive, at least in part, from a cardioprotective effect of naproxen. At present, low-dose aspirin should be prescribed in patients with an increased risk of cardiovascular events, since this agent has been shown to reduce the incidence of cardiovascular events in appropriate patient populations.

Additional prospective, placebo-controlled data are needed to fully clarify the cardiovascular effects of COX-2 inhibitors. Such data will be forthcoming from ongoing trials in disorders such as Alzheimer's disease and intestinal polyp disease. Randomized, controlled trials in patients with a high risk for cardiovascular events are also warranted.

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Renal effects of nonselective NSAIDs and coxibs

MATTHEW R. WEIR, MD

ABSTRACT

Despite the ubiquitous use of both over-the-counter and prescription nonsteroidal anti-inflammatory drugs (NSAIDs), clinical syndromes—NSAID-related hypertension, salt and water retention, edema, and hyperkalemia—are highly infrequent. Nevertheless, they remain a concern, and patient populations at risk for renal adverse effects from NSAIDs can be prospectively identified. Patients at risk include those with age-related declines in glomerular filtration rate; those with hypovolemia, particularly patients taking loop diuretics; and those with congestive heart failure, cirrhosis, or nephrosis. The following patient populations are at higher risk for increases in blood pressure with concomitant use of an NSAID and an antihypertensive: those with congestive heart failure, liver disease, or kidney disease, and those taking angiotensin-converting enzyme inhibitors or diuretics. Nonselective NSAIDs and COX (cyclooxygenase)-2–selective inhibitors (coxibs) appear to have similar effects on renal function if dosed equivalently, and standard precautions to avoid renal toxicity with use of nonselective NSAIDs apply to coxibs.

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Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used. These agents share anti-inflammatory, analgesic, and antiplatelet properties and also have many side effects in common. The most frequent is ulcerogenesis; by inhibiting cyclooxygenase (COX)-1, the nonselective NSAIDs can alter protective mechanisms in the gastric mucosa and increase acid secretion.[1] By selectively inhibiting only the COX-2 isoform, the COX-2–selective inhibitors (coxibs) are less likely to cause ulcerogenesis and have shown improved gastrointestinal safety and tolerability.[2–7] Nevertheless, there are renal syndromes and toxicities common to both the nonselective NSAIDs and the coxibs.

This article will summarize current knowledge regarding nonsteroidal renal syndromes associated with nonselective NSAIDs and COX-2–selective inhibitors. It will identify patients at risk for developing renal toxicity with the use of these drugs, and provide strategies to primary care physicians to minimize these risks.

PHYSIOLOGIC AND PATHOPHYSIOLOGIC ROLES OF PROSTAGLANDINS IN THE KIDNEY

COX-1–related prostaglandins are largely constitutive and responsible for maintaining the integrity of the gastrointestinal mucosa, platelet adhesion, and acid secretion. Though constitutive in some physio-

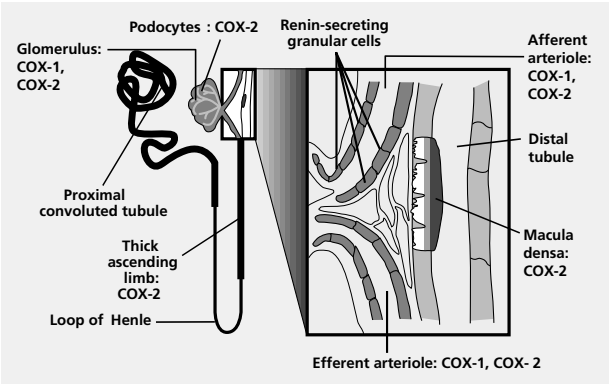

FIGURE 1. The role of prostaglandins in the kidney.[8,9]

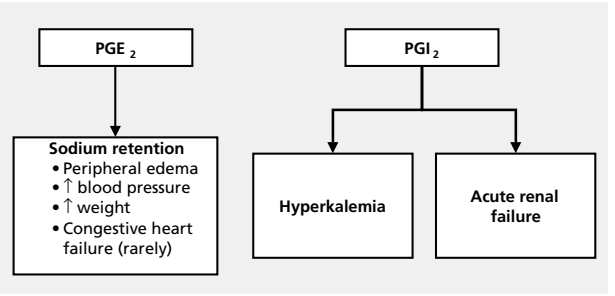

FIGURE 2. Renal syndromes caused by NSAID effects on prostaglandins.[10]

logical systems, COX-2–related prostaglandins are largely inducible and mediate pain and inflammation. NSAIDs alter renal function through their effects on renal prostaglandins.

In general, COX-1 functions in the control of renal hemodynamics and the glomerular filtration rate (GFR); COX-2 functions affect salt and water excretion, although there is some overlap. This separation of COX-mediated functions in the kidney is based in part on the physiologic/anatomic distribution of COX-1 compared to COX-2 (**Figure 1**); blockade of either or both of these enzymes can have, therefore, different effects on renal function.[8,9] However, renal syndromes associated with the use of nonselective NSAIDs and COX-2–selective inhibitors can be either prostaglandin-dependent (ie, functional) or prostaglandin-independent (ie, anatomic).

As shown in **Figure 2**,[10] the renal syndromes caused by nonselective NSAIDs and coxibs can be grouped according to their effects on prostaglandin (PG)E_2 and PGI_2. So whereas PGI_2, or prostacyclin, mostly affects renal homeostatic mechanisms, PGE_2 and PGD_2 dilate the renal vascular bed, lower renal vascular resistance, and increase renal perfusion.[1] In a person with normal renal hemodynamic parameters, prostaglandins do not play a dominant physiologic role in maintaining renal blood flow; PGE_2 and PGI_2 also normally play minor roles in maintaining the GFR.[1] However, in a person with compromised renal hemodynamics (for example, decreased circulating volume), the kidney synthesizes vasodilating prostaglandins to offset vasoconstricting autocoids and to maintain renal perfusion.[11] These prostaglandins become critically involved in maintaining the GFR. When production of PGI_2 is blocked, hyperkalemia and acute renal failure can result. The effects of blocking production of PGE_2 may include peripheral edema, increased blood pressure, weight gain, and, though rare, congestive heart failure.[10]

■ CLINICAL CONSIDERATIONS

Overall, the different nonselective NSAIDs produce similar renal effects. And, despite the ubiquitous use of both over-the-counter and prescription NSAIDs, the most frequent clinical syndromes related to their use—hypertension, salt and water retention, edema, and hyperkalemia—are relatively infrequent. Nevertheless, they remain a concern. But patient groups who are at risk for renal adverse effects from NSAIDs can be prospectively identified. Especially at risk are those with extreme liver dysfunction, or nephrotic patients with high-level proteinuria, or those with very low renal function.[10] Furthermore, the increased risk for ARF and subsequent hospitalization due to NSAID use has been known for some time. Because of the role of COX-2 in regulating salt and water excretion, the COX-2–selective inhibitors, rofecoxib, celecoxib, and, most recently, valdecoxib, would be expected to have similar effects. Therefore, the standard renal precautions that apply to use of nonselective NSAIDs also apply to use of coxibs.

When effective arterial blood volume is diminished, greater susceptibility to renal prostaglandin inhibition and changes in renal function can occur. In patients with preexisting decreased renal blood flow, the inhibition of vasodilating prostaglandins contributes to a further decrease in glomerular blood flow and overall renal perfusion.

COX-2–derived PGE_2 is found primarily on the thick ascending limb of the loop of Henle; it pro-

motes diuresis and natriuresis by inhibiting reabsorption of sodium and water. NSAID-induced decreases in PGE_2 can increase sodium and water reabsorption and can produce some weight gain and occasionally edema. As noted, in persons with decreased circulating volume, vasodilating prostaglandins are produced by the kidneys to offset other vasoconstricting autocoids. In clinical settings in which renal blood flow depends on prostaglandin synthesis, NSAIDs can significantly decrease renal blood flow, with resultant acute renal failure.[12,13] Patients at risk include those with age-related declines in GFR; those with hypovolemia, particularly patients taking loop diuretics; and those with congestive heart failure, cirrhosis, or nephrosis. Similarly to use of a nonselective NSAID, use of a COX-2–selective inhibitor should be carefully assessed in patients with any of these risk factors.

Some drug therapies, eg, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, also cause functional, but reversible, renal insufficiency that may worsen with NSAIDs. NSAIDs can lessen response to diuretics, especially the loop-acting diuretics (eg, furosemide), by as much as 20%. This effect may be more pronounced in patients likely to retain sodium, such as in those with congestive heart failure or cirrhosis.[10]

Concomitant use of NSAIDs and antihypertensives

Another concern is the 20 million people in the United States who currently take both an antihypertensive drug and an NSAID. Nonselective NSAIDs can induce dose-related fluid retention and raise blood pressure (BP) in some patients. Age-related declines in renal blood flow are more prominent in hypertensive persons and, as noted, NSAIDs can reduce renal blood flow and also cause a dose-dependent form of BP salt sensitivity. This can be clinically significant in susceptible persons.

In different studies of selective and nonselective NSAIDs, a 3- to 5-mm Hg increase in BP is seen across populations. In a meta-analysis by Pope and colleagues of 54 clinical trials involving 123 NSAID treatment arms and 1,324 participants, the effects of NSAIDs on BP, after adjusting for dietary salt intake, were noted only in hypertensive subjects. Indomethacin and naproxen raised mean arterial pressure by 3.59 and 3.74 mm Hg, respectively, while placebo, ibuprofen, and aspirin each lowered

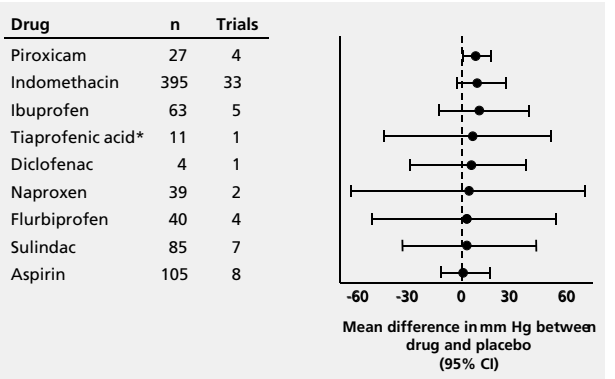

FIGURE 3. Hypertension with traditional NSAIDs. Adapted with permission from Johnson et al. Ann Intern Med 1994; 121:289–300.[15] *Not available in the United States.

mean arterial pressure. The investigators concluded that, in short-term use, NSAIDs vary considerably in their effects on BP.[14]

In their meta-analysis of pooled data from 50 trials and 771 patients, Johnson and colleagues showed that NSAIDs increased supine mean arterial BP by 5 mm Hg (**Figure 3**). Mean weight gain was 0.3 kg; mean decrease in urinary sodium was 0.1 mmol/day, and urinary PGE_2 decreased by 162.7 ng/day.[15]

The effect of coxibs on BP is less well studied. A 6-week analysis by Geba and colleagues compared rofecoxib (25 mg QD), celecoxib (200 mg QD), and placebo in 1,082 patients with osteoarthritis of the knee or hip after withdrawal of previous osteoarthritis therapy. More than 40% of patients had a history of hypertension. Predefined changes in systolic blood pressure (>140 mm Hg and increase of >20 mm Hg) occurred in 9.6%, 9.4%, and 3.3% of patients taking rofecoxib, celecoxib, and placebo, respectively. This difference was significant in coxibs vs placebo (P = .015), but not between rofecoxib and celecoxib. Mean changes in systolic blood pressure were 1.9 mm Hg, 0.2 mm Hg, and –4.3 mm Hg for rofecoxib, celecoxib, and placebo, respectively.[16]

In the VIGOR trial, rofecoxib increased mean systolic and diastolic BP by 4.6 and 1.7 mm Hg vs increases of 1.0 and 0.1 mm Hg, respectively, with naproxen.[17] In the same trial, the incidence of renal-related adverse events was low and similar in the two treatment groups: 1.2% in the rofecoxib group and 0.9% in the naproxen group.[6] (The cardiovascular effects noted in the VIGOR trial are detailed elsewhere in this issue.)

Renal effects of NSAIDs and coxibs

The standard renal precautions that apply to use of nonselective NSAIDs also apply to coxibs. They should be used carefully in patients with hypertension, particularly those taking ACE inhibitors and/or potassium-sparing diuretics; patients taking salt substitutes; in patients with diabetes, particularly those with type IV renal tubular acidosis and possibly renal insufficiency; and in patients who are volume-depleted or who have cirrhosis or congestive heart failure.

If dosed in therapeutically equivalent ways, nonselective NSAIDs and coxibs show no evidence of major differences in renal effect.

Clinicians should be aware of the 3- to 5-mm Hg increase in BP seen across populations in different studies of COX-2–selective and nonselective NSAIDs. This BP-raising effect must be weighed against the therapeutic impact.

When a patient's BP increases, the following strategies are recommended: use a lower dose of nonselective NSAID or coxib; try to restrict dietary salt; inquire about patients' home remedies and over-the-counter drug use, including NSAIDs; review all medications being taken, including over-the-counter NSAIDs; and adjust the antihypertensive as appropriate.

NSAID-related renal syndromes include hypertension, salt and water retention, edema, and hyperkalemia. Despite the ubiquitous use of NSAIDs, these clinical syndromes occur infrequently. Nevertheless, they remain a concern, given the large number of patients at risk.

The clinical significance of an increase of as much as 5 mm Hg in mean arterial BP is unclear. Increases of this size in systolic and diastolic BPs have been shown to increase the risk for stroke and heart failure.[18] For the vast majority of patients, the BP increase seen with concurrent use of an NSAID and an antihypertensive is probably clinically insignificant and can be treated with a reduction in dietary salt or an adjustment of medication.

Still, there are patient populations that are at higher risk for an increase in BP with concomitant use of an NSAID and an antihypertensive—those with congestive heart failure, liver disease, or kidney disease, and those taking ACE inhibitors or diuretics. In such patients, more careful management is mandated. It may be necessary to use additional diuretics to maintain a patient with congestive heart failure in an edema-free state. Frequent monitoring of BP, weight, and serum creatinine and potassium levels is appropriate.[1]

The following strategies are recommended to clinicians when treating hypertension in a patient taking an NSAID: lower the dose of the nonselective NSAID or coxib as much as possible, without compromising efficacy; lower salt intake; retitrate the antihypertensive; and inquire about the patient's use of over-the-counter NSAIDs. Another strategy is to use aspirin or the atypical opioid-like agent, tramadol. Use of a non-NSAID or aspirin is preferable to use of those NSAIDs that have been described as "renal-sparing" (nabumetone), since the renal-sparing effects have never been convincingly demonstrated.[10]

■ RENAL EFFECTS OF COX-2–SELECTIVE INHIBITORS

Before discussing the renal-effects profile of COX-2–selective inhibitors, NSAID-related renal syndromes will be briefly summarized. Several distinct syndromes of disturbed renal function—including fluid and electrolyte disorders, acute renal dysfunction, nephrotic syndrome/interstitial nephritis, and renal papillary necrosis—are associated with the use of nonselective NSAIDs. In addition, by blunting the homeostatic renal effects of prostaglandins, NSAIDs can hinder BP control, particularly with concomitant use of ACE inhibitors, diuretics, and beta-blockers. The risk of congestive heart failure is also significantly increased when NSAIDs are given to patients receiving diuretic therapy who have cardiovascular risk factors.[19]

Rossat and colleagues studied the renal effects of celecoxib vs naproxen in 40 healthy young men (age range 18 to 35 years) who were randomized to one of four treatment groups: celecoxib 200 or 400 mg twice daily, naproxen 500 mg twice daily, or placebo for 7 days. Subjects were salt-depleted by a low-sodium diet that began 5 days before drug administration and continued through the 7-day study. (Prostanoid-dependent renal function may become more pronounced in the setting of sodium depletion.) On days 1 and 7, GFR, renal blood flow, urine output, and urinary sodium were measured before and for 3 hours after drug administration.[20]

Selective inhibition of COX-2 with celecoxib resulted in as much sodium and potassium retention as that seen with naproxen. At 400 mg twice daily, celecoxib transiently lowered the GFR and effective renal plasma flow; these effects were not seen with naproxen. Rossat and colleagues concluded that selective inhibition of COX-2 with celecoxib caus-

es as much sodium and potassium retention as with a nonselective coxib in salt-restricted persons. Unlike the nonselective NSAID, high-dose celecoxib transiently but significantly lowered GFR and effective renal plasma flow.[20]

The effect of celecoxib on GFR in the elderly has also been studied. Whelton and colleagues administered celecoxib and naproxen to 29 healthy elderly subjects (age range, 65 to 80 years) using a single-blind, randomized, crossover format. Participants received celecoxib 200 mg twice daily for 5 days followed by 400 mg twice daily for 5 days, or the alternate schedule of naproxen 500 mg twice daily for 10 days. After a 7-day washout, subjects were crossed over to the other regimen. GFR was measured with radiolabeled sodium 2 days before drug administration and then 3 to 5 hours after drug administration on days 1 and 6 of treatment. Sodium intake was not controlled.[21]

Naproxen lowered the GFR with the first dose; the difference between naproxen and celecoxib in lowering GFR was statistically significant on day 6 (change from baseline on day 6, naproxen vs celecoxib, –7.5 ± 2.4 vs –1.1 ± 1.9 mL/min/1.73 m^2, respectively, $P = .004$). Small, transient decreases in sodium excretion, which returned to baseline by study end, were seen with both drugs.[21] None of these changes are likely to be clinically significant.

Catella-Lawson and colleagues administered rofecoxib under double-blind conditions to 36 healthy older adults who were sodium restricted.[22] Participants received rofecoxib 50 mg once daily, or indomethacin 50 mg three times daily, or placebo for 2 weeks. As seen in **Figure 4**, in the first 72 hours of treatment, both rofecoxib and indomethacin decreased urinary sodium excretion significantly. The change seen in the rofecoxib arm, however, was transient; only indomethacin lowered the GFR significantly vs rofecoxib and placebo. Neither agent produced any significant change in BP or weight.

Swan and colleagues also gave rofecoxib to 60 elderly subjects (age range, 65 to 80 years) on a low-salt diet using a randomized, multidose, parallel-group design. On day 6, peak effect on GFR was measured after the first dose. Both rofecoxib and indomethacin significantly lowered the GFR compared to placebo. On day 6, however, neither urinary sodium nor potassium was significantly lowered. The investigators note that the study subjects were generally healthy. Predisposed persons who have lower effective circulating fluid volume (eg, those with congestive heart failure, with cirrhosis, or taking diuretics) may have clinically significant renal insufficiency with use of coxibs, similar to NSAID-induced alterations. Renal precautions that are observed for nonselective NSAIDs should also be observed for COX-2–selective inhibitors.[23]

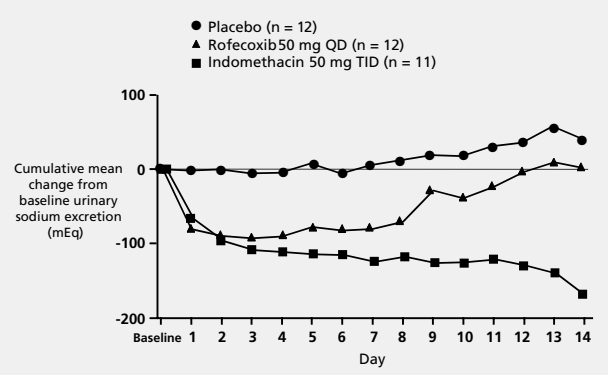

FIGURE 4. Renal effects of rofecoxib: mean change from baseline in urinary sodium excretion. Adapted with permission from Catella-Lawson et al. J Pharmacol Exp Ther 1999; 289:735–741.

In a direct comparison study, Schwartz and colleagues administered rofecoxib (25 mg QD), celecoxib (200 mg BID), naproxen (500 mg BID), or placebo to 67 healthy elderly subjects for 2 weeks (age range, 60 to 80 years), and measured urinary sodium excretion. There were no significant differences among the three active treatments in daily average sodium excretion over the first 3 days or over 2 weeks of treatment. Peripheral edema did not occur. One subject each given rofecoxib and celecoxib experienced an increase in systolic BP. The investigators concluded that rofecoxib and celecoxib have similar effects on urinary sodium excretion, and that these effects are similar to those of nonselective NSAIDs.[24]

These clinical trials comparing changes in renal function between nonselective NSAIDs and coxibs indicate only subtle changes in renal hemodynamics and BP. Thus, the renal effects of celecoxib and rofecoxib appear to be similar to nonselective NSAIDs and class specific. However, how to use these drugs in patients at higher risk for nonsteroidal renal syndromes has not been fully elucidated, as these studies have not been conducted in patients with renal disease.

CONCLUSIONS

Nonselective NSAIDs and COX-2–selective inhibitors are widely used drugs that appear to be similar in terms of their effects on renal function if they are dosed in therapeutic equivalents. Although the prevalence of renal toxicity in patients treated with NSAIDs is relatively low, the extensive use of both prescription and over-the-counter agents places many persons at risk. The mechanisms whereby these agents affect the kidney are understood, which allows at-risk patients—eg, the elderly and the hypovolemic, or patients with diabetes, hypertension, or congestive heart failure—to be identified prospectively. Standard precautions to avoid renal toxicity with use of nonselective NSAIDs also apply to COX-2–selective inhibitors.

An increase in BP is often seen with concomitant use of an NSAID and an antihypertensive. Although this increase is probably clinically insignificant, the following strategies are recommended if BP increases in a patient taking a nonselective NSAID or a COX-2–selective inhibitor with an antihypertensive: lower the dose of the nonselective NSAID or coxib; lower salt intake; retitrate the antihypertensive; and inquire about the patient's use of over-the-counter NSAIDs. Another strategy is to use a non-NSAID, eg, tramadol or aspirin.

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Developing an economic rationale for the use of selective COX-2 inhibitors for patients at risk for NSAID gastropathy

A. MARK FENDRICK, MD

ABSTRACT

Arthritis causes considerable patient morbidity and substantial health care resource utilization. One important contributing component to the overall cost burden of this condition is the variety of expenditures attributable to the adverse effects of arthritis therapy. Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are a mainstay of medical treatment for patients with arthritis because of their well-established anti-inflammatory and analgesic effects. Generally well tolerated, traditional NSAIDs nevertheless cause adverse gastrointestinal (GI) effects in a proportion of patients. Because nonselective NSAIDs are so widely used, these GI adverse events cause significant morbidity and mortality, accounting for substantial additional health care expenditures. Data from controlled investigations document the enhanced GI safety of cyclooxygenase (COX)-2–selective inhibitors, or coxibs, when compared with nonselective NSAIDs. As a result of this improved safety profile, patients treated with coxibs use significantly fewer GI-related health care resources (eg, medications, procedures) than patients treated with nonselective NSAIDs. Thus, available clinical and economic data suggest that the use of coxibs has the potential to result in important clinical GI benefits at an acceptable incremental cost for all chronic NSAID users. For individuals who are at an increased risk of developing GI complications attributable to NSAIDs, coxibs are clearly a cost-effective treatment option.

More than 20 million adults in the United States have arthritis, a general diagnosis used to describe joint inflammation or pain. The two most common forms of arthritis are osteoarthritis and rheumatoid arthritis. Although rarely fatal, arthritis causes considerable disability and morbidity.[1] Yelin and Callahan used the 1990-1992 National Health Interview Survey and a literature review to estimate that health care utilization due to all musculoskeletal conditions totaled $149.4 billion.[2] Nearly half (48%) of these expenditures were due to direct medical care costs (315 million physician visits and over 8 million hospitalizations), and the remaining amount resulted from lost wages. An updated economic burden of musculoskeletal conditions was derived using the 1996

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Medical Expenditure Panel Survey, a national sample of 21,571 people, 4,161 (19%) of whom reported at least one musculoskeletal condition.[3] An analysis of health care utilization by this cohort of patients, representing nearly 54 million Americans with at least one musculoskeletal condition, revealed that persons with musculoskeletal conditions were more likely to use *every* type of health care service than either persons without chronic conditions or those with other chronic conditions. Persons with musculoskeletal conditions had total medical care expenditures that were more than 50% higher than those of persons without musculoskeletal conditions—$3,578 versus $2,313. This figure extrapolates to a national total of $193 billion annually. The three largest components of care were: hospitalizations (37%), physician visits (23%), and prescription drugs (16%).[3]

FOCUS ON PRESCRIPTION DRUGS

Prescription drugs account for approximately one-sixth of arthritis expenditures and 8% to 10% of spending for health care in the United States. Despite this relatively small share of the health care dollar, pharmaceutical expenditures have come under considerable scrutiny largely due to a double-digit rate in cost growth in recent years. This growth rate in the pharmaceutical sector has far surpassed other medical care cost components such as hospitalizations and physician salaries. Published studies suggest that increasing rates of utilization of old and new drugs, *not* rising drug prices, is the main driving force behind increases in drug spending.[4] It follows that health care payers, in an attempt to address the rapid escalation in pharmaceutical costs, will intensely examine the "value" of new drugs to determine if the additional dollars spent are justified in terms of incremental health benefits.

The availability of the cyclooxygenase-2 (COX-2)–selective inhibitors (coxibs) has markedly changed the management of arthritis. Health care payers have closely followed the widespread adoption of coxibs and resultant increases in pharmaceutical expenditures for this disease and related conditions. Determining which nonsteroidal anti-inflammatory drug (NSAID) users should have access to these more expensive agents should depend on the clinical and economic effects of these agents. In order to constrain health care expenditures, clinical practice guidelines and drug formularies often recommend using less expensive (often generically available compounds) NSAIDs first while restricting coxibs for treatment failures. Since chronic NSAID users may fail initial therapy, experience dyspepsia, or suffer a complication necessitating a change in therapy, the clinical and cost consequences of NSAID therapy depend on subsequent diagnostic and treatment decisions that occur over the entire natural history of disease. Thus, the most cost-effective NSAID regimen does not depend entirely on the differences in complication rates and/or treatment costs at time of use, but also on the likelihood of switching medications, the variation in patients' symptomatic response, and the resultant ulcer- and non-ulcer–related health care expenditures.

NSAID THERAPY AND ASSOCIATED GASTROPATHY

Nonselective NSAIDs are a mainstay of medical treatment for arthritis, owing to their well-established anti-inflammatory and analgesic effects. These NSAIDs account for more than 70 million annual prescriptions, and more than 30 billion over-the-counter tablets are sold every year in the United States.[5] NSAIDs are associated with adverse gastrointestinal (GI) effects ranging from mild dyspepsia to serious, potentially fatal complications such as bleeding peptic ulcer.[6] Although the probability is low that any chronic NSAID user will experience a drug-related complication, the fact that millions of Americans use these agents on a regular basis makes nonselective NSAID-related gastropathy an important problem from both clinical and economic perspectives.[7]

The Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS), a prospective observational database of 36,000 rheumatoid arthritis patients, reported that 1.3 serious GI complications occurred for every 100 patient-years of NSAID use.[7] Based on these data, an estimated 100,000 hospitalizations and 10,000 to 20,000 deaths each year in the United States can be attributed to complications related to prescription NSAIDs.[5,8] The risk of a hospitalization caused by a GI adverse event is even more pronounced among elderly NSAID users; these agents should be used with caution in this patient subpopulation.[9]

The high costs that result from NSAID-related GI toxicity have been noted for many years. Studies using claims databases have reported that nearly one-third of aggregate medical expenditures for arthritis patients can be attributed to GI adverse effects.[10]

TABLE 1
Strategies to prevent NSAID-related gastropathy

Stop the NSAID
Decrease the NSAID dosage
Use a safer NSAID with similar efficacy
Coprescribe a gastroprotective agent Misoprostol Histamine$_2$-receptor antagonist Proton pump inhibitor
Use a non-NSAID analgesic

Pharmacoeconomics of coxib therapy

Generic NSAIDs are a cost-effective way to treat arthritis pain. However, the cost of treating NSAID-related gastropathy adds to cost of using NSAIDs.

Use of GI co-therapies and endoscopy rates decrease with use of COX-2 inhibitors.

COX-2–selective inhibitors are cost-effective in patients at increased risk for developing GI-related side effects.

Any patient with a history of prior GI bleeding or any patient with rheumatoid arthritis who is steroid dependent should be prescribed a COX-2–selective inhibitor first line instead of a traditional NSAID.

There is an incremental cost to using a COX-2–selective inhibitor versus a generic NSAID. This cost differential is nominal in high-risk patients but becomes more pronounced in low-risk patients.

Among elderly members of one health maintenance organization, Johnson and colleagues estimated that for every dollar spent on NSAID therapy, $0.35 was spent to treat NSAID-related gastropathy.[11]

The scope of this problem has led the Food and Drug Administration (FDA) to include a formal warning in the package labeling regarding the risk of adverse GI events for patients using traditional NSAIDs.[12] Despite attempts to educate patients, most regular NSAID users have a lack of awareness of the potential side effects of NSAIDs.[13] Controversy remains among clinicians on how best to weigh the potential clinical benefits of nonselective NSAIDs against the possibility of adverse events associated with their use. Identification of risk factors for the development of NSAID-related complications may aid clinicians in identifying patients at highest risk.[14]

There is no consensus on how best to minimize NSAID-related adverse events, but it is clear that assessments of available treatment options must account for both clinical effects and economic consequences. Strategies to prevent NSAID-related gastropathy include discontinuing the NSAID or decreasing its dosage, or using a non-NSAID analgesic, gastroprotective agent (GPA), or a safer NSAID with similar efficacy (**Table 1**).

GPAs are often used to prevent the GI adverse effects of nonselective NSAID therapy. GPAs, however, are not completely effective in prophylaxis and treatment of NSAID-related GI events, may have their own side effects, and contribute substantially to the costs of treatment. Coprescribing rates of GPAs in the setting of nonselective NSAID use range from 17% to 34%.[1] These agents include misoprostol, histamine$_2$-receptor antagonists, and proton pump inhibitors.

Misoprostol is approved by the FDA for use to prevent NSAID-related adverse events. Published economic analyses suggest that this agent is cost-effective for patients at increased risk for NSAID gastropathy.[15] However, misoprostol is associated with its own adverse effects.[16] As a result, acid inhibitory drugs are more frequently utilized to reduce NSAID-associated symptoms and adverse effects. While histamine$_2$-receptor antagonists may reduce NSAID-associated dyspepsia,[17] these agents are not effective in preventing NSAID-associated ulcers and their related complications at traditional dosages.[18] Since potent acid suppression with high-dose histamine$_2$ antagonists[19] or proton pump inhibitors[20–22] has been demonstrated to heal and even prevent the recurrence of endoscopic ulcers in randomized controlled trials, these agents have become common management options.

CLINICAL AND ECONOMIC RATIONALE FOR COX-2–SELECTIVE INHIBITORS

An attractive alternative to GPAs to reduce NSAID toxicity is the use of a COX-2–selective inhibitor, an equally effective anti-inflammatory agent with reduced propensity for GI injury. The differences in the relative safety of currently available NSAIDs may be explained by their pharmacologic properties, as discussed elsewhere in this supplement in greater detail. The elucidation of the roles of the cyclooxygenase isoenzymes (COX-1 and -2) has led to an improved understanding of the pathophysiolo-

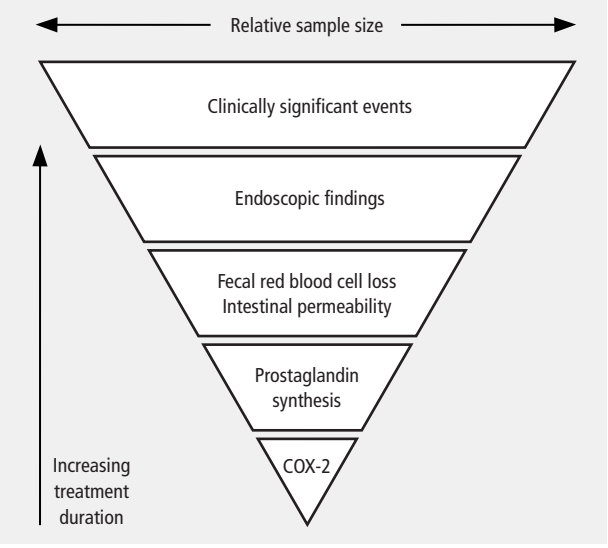

Figure 1. Proving the "coxib hypothesis."

gy of NSAID gastropathy.[23] (See articles by Bingham and by Cronstein, this supplement). The relative inhibition of COX-1 activity (central to the maintenance of GI mucosal integrity) to COX-2 activity (reduces inflammation) may provide an explanation for the basis and observed rates of different NSAIDs to produce varying rates of GI injury.[8] The capacity of NSAIDs to inhibit platelet function (by inhibition of COX-1) may also influence whether an NSAID-associated lesion remains silent or develops clinically apparent bleeding.

The scientific evidence that coxibs provide superior GI safety when compared with nonselective NSAIDs has emerged from the laboratory and from clinical studies. The steps necessary to prove the "coxib hypothesis," from test tube to human subjects, are shown in **Figure 1**. Laboratory-based investigations demonstrating differences in COX-1 and COX-2 selectivity among available NSAIDs and their impact on prostaglandin synthesis in tissue culture are discussed elsewhere in this supplement. Translating such findings from the laboratory bench to bedside is often complicated, but a notable example of this was a single study that demonstrated significantly less fecal red-blood-cell loss by healthy subjects taking rofecoxib when compared with healthy individuals given similar doses of ibuprofen.[24] The controlled clinical studies in arthritis patients, which found that patients taking coxibs experienced significantly fewer endoscopic lesions and clinically meaningful GI events, are described in detail in the supplement article by James Scheiman, MD.[25]

NSAID CHOICE AND HEALTH CARE RESOURCE USE

To accurately assess the clinical and economic trade-offs between a lower rate of drug-related complications and resultant higher pharmaceutical expenditures, both the incremental costs and benefits should be carefully measured and compared with available alternatives. On the cost side, it is critical to look beyond direct cost comparisons of drugs under investigation. All the health care resources incurred over the entire episode of care must be accounted for, especially since a proportion of individuals prescribed one agent may eventually be prescribed the other. The clinical indications for, and side effects of, chronic anti-inflammatory therapy often necessitate changing NSAIDs or adding cotherapy for prophylaxis or symptom control.

Analysis of data from the prospective outcome trials described by Dr Scheiman in this supplement provides a perspective on resource utilization that can be used to make an economic argument for the use of COX-2–selective inhibitors in certain populations. Using data from the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial,[26] Bombardier and colleagues compared rates of use of GPAs (histamine$_2$-receptor antagonists, proton pump inhibitors, sucralfate, and prostaglandins) and GI diagnostic procedures and hospitalizations for upper GI perforation, ulcer, or bleeding in patients treated with either rofecoxib or naproxen. The rofecoxib-treated patients were significantly less likely to require new use of GPAs (11.2% versus 14.5%, $P < .001$) and were hospitalized significantly less often for perforation, ulcer, or bleeding (.4% versus .9%, $P = .01$; **Table 2**).[27]

Similar decreases in resource use were found in an analysis of the subset of participants reporting GI adverse events (**Table 2**). New use of GPAs was significantly less in the rofecoxib group (25.5% versus 32.2%, $P < .001$). Rofecoxib-treated patients also had fewer GI procedures (12.4% versus 15.8%, $P = .01$) and fewer hospitalizations for GI perforation, ulcer, or bleeding (1.2% versus 2.3%, $P = .02$).[27]

An analysis of resource utilization using pooled data from rofecoxib trials in patients with osteoarthritis was recently reported. Under base-case circumstances, cost savings attributable to fewer GI adverse events with rofecoxib (versus nonselective

TABLE 2
Rates of GI events, new use of GPAs, and GI procedures in rofecoxib versus naproxen[27]

	Rofecoxib	Naproxen	*P* value
VIGOR (n = 8,076)			
Hospitalizations for PUBs	.4%	.9%	= .01
New GPAs	11.2%	14.5%	< .001
GI procedures	5.6%	6.9%	= .02
VIGOR subset (n = 2,937)			
Hospitalizations for PUBs	1.2%	2.3%	= .02
New GPAs	25.5%	32.2%	< .001
GI procedures	12.4%	15.8%	= .01

PUBs = perforation, ulcer, or bleeding; GI = gastrointestinal; GPAs = gastroprotective agents.

NSAIDs) was $0.81 per day. These expected savings offset 85% of the increased purchase price of rofecoxib when compared with nonselective NSAIDs.[28]

In an attempt to quantify the trade-off between higher coxib acquisition costs and savings due to reduced GI-related adverse events, Fendrick and colleagues constructed a symptom-driven simulation to capture clinical outcomes and health care costs associated with chronic NSAID use.[29] Specifically, the cost-effectiveness of a practice to restrict the use of a safer, more expensive coxib was compared with a strategy that allowed its unrestricted use. The analysis revealed that decisions regarding access to safer, more expensive NSAIDs (coxibs) depend on the cost differential between agents, relative safety among available agents, and patients' ulcer risk.

The model estimated that for chronic NSAID users at average ulcer risk, the unrestricted use of coxibs has the potential to decrease ulcer-related adverse events at an incremental cost that approximates published values for misoprostol.[15] Sensitivity analysis revealed that under no circumstances would the unrestricted use of the safer agent generate cost savings in average-risk patients. However, the simulation estimated that the incremental cost to prevent an NSAID-related ulcer falls dramatically as the patients' risk of NSAID-related adverse event increased.[29] For patients at above-average ulcer risk (eg, those with risk factors such as prior GI hemorrhage, concomitant steroid or anticoagulant therapy), there is considerable merit in the clinical and economic argument for routine use of coxibs in this population.[30]

CONCLUSIONS

Nonselective NSAIDs are a mainstay of medical treatment for arthritis because of their well-established anti-inflammatory and analgesic effects. They are generally well tolerated, but their use can be associated with adverse GI effects ranging from uncomplicated dyspepsia to life-threatening hemorrhage. A wealth of controlled clinical trial data conclude that the risk of an NSAID-related GI adverse event depends on an individual patient's risk factors and the specific NSAID used. While effective in reducing NSAID-related dyspepsia at low dosages and protective against GI ulcers at higher levels of acid suppression, the use of GI-protective agents as prophylaxis or to treat a GI adverse event can contribute substantially to the cost of treating patients with arthritis.

COX-2–selective inhibitors are alternative treatments for pain and inflammation in patients with arthritis. There is substantial evidence of enhanced GI safety with COX-2–selective inhibitors when compared with traditional NSAIDs. The coxib class constitutes an important advance over nonselective NSAIDs due to its equivalent efficacy compared with nonselective NSAIDs and its reduced risk of GI complications. However, as shown in economic models, since incremental expenditures are necessary to achieve these reductions in GI adverse events, decision-makers must consider whether these additional costs are worthwhile, given other demands for scarce health care resources.

Stratifying patients according to their risk for developing GI-related complications is a useful strategy in demonstrating the value of the coxib class.

Using the best data available, it appears that for patients at average risk for developing GI-related complications, the unrestricted use of COX-2–selective inhibitors could decrease ulcer-related adverse events but at an incremental cost. For high-risk patients, unrestricted access to COX-2–selective inhibitors could be both clinically and economically advantageous because of the high likelihood of adverse events and the safety benefits of coxibs. Therefore, even in an era of cost constraint, COX-2–selective inhibitors should be offered as first-line agents to these high-risk patients.

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Cyclooxygenase-2–selective inhibitors in the management of acute and perioperative pain

WARREN A. KATZ, MD

ABSTRACT

Postsurgical pain is often undertreated. Opioids are frequently used in perioperative analgesia, but concern about side effects can result in administration of an inadequate dose for pain relief. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used increasingly for postoperative analgesia. The use of balanced analgesia—a combination of opioids, NSAIDs, and local anesthesia utilizing agents from other classes (eg, ketamine, clonidine)—improves the efficacy of pain relief and decreases risk of side effects. While lacking some of the troublesome side effects of opioids, nonselective NSAIDs may cause bleeding as a result of their inhibitory effects on COX-1. For this reason, COX-2–selective inhibitors (coxibs) are attractive opioid-sparing analgesic options in the perioperative setting. Factors in addition to side effects such as time to onset of action, duration of action, maximum pain relief, use of rescue medication, and other factors relevant to a given pain model are important in determining overall analgesic efficacy. Clinical studies show that COX-2–selective inhibitors are effective for the treatment of preoperative and postoperative pain and reduce postsurgical requirements for opioids. This evidence supports a role for COX-2–derived prostaglandins as key mediators of nociceptive pain and peripheral sensitization (hyperalgesia). Pain management in the perioperative setting and the role of COX-2–selective inhibitors in acute and postoperative pain are reviewed here.

Understanding pain is central to the goals of medicine as pain may be both a cardinal manifestation of disease and a cause of suffering. Strategies of pain management have evolved to include an appreciation that pain is composed of physiologic as well as psychologic dimensions. Current concepts in pain management recognize the sensory perception of pain (nociception) as the progenitor of the psychic experience of pain, which can lead to suffering.[1] In chronic pain, there may be no discernible pathologic basis for pain, making syndromes like low-back pain and fibromyalgia difficult to understand and treat.[2,3] The importance of pain management to the care of patients is underscored by the fact that pain is now likened to a "fifth vital sign."

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standard for management of pain stresses the adverse physiolog-

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ic and psychologic burden of unrelieved pain.[4] The main tenets of the JCAHO standard are: continuous pain assessment—specially tailored assessments for special populations (ie, the elderly, people with AIDS or cancer, children); education about pain and pain management for patients and providers; and thorough ongoing documentation of reported pain as well as pharmacologic and nonpharmacologic interventions.[4]

Clinicians frequently cite several barriers to providing ample pain treatment. Among these are the safety and efficacy of analgesics. For opioid analgesics, several concerns exist, some more supported by clinical evidence than others, including serious side effects, the development of tolerance, and regulatory considerations. Such concerns may lead to the curtailed use of opioids in chronic pain.[5] However, concern for dependence may be exaggerated.[6] Increased education is needed in order that clinicians avail themselves of advances in diagnosis and pharmacologic management of pain.[5]

UNMET NEED IN PAIN MANAGEMENT

The clinical significance of pain may be said to lie fundamentally in its undertreatment.[5,7–9] As much as 10% to 20% of the adult population of the United States suffers from chronic pain, which is often inadequately treated and debilitating.[3] In the large Outpatient Pain Needs Assessment Survey (1990–1991), 42% of respondents reported they experienced cancer pain that was undertreated with inadequate analgesia.[7] Elderly persons are more likely to suffer from pain—especially chronic pain—and are more likely to be undertreated.[10] An extensive study of nursing home residents' nonmalignant pain, and impact of pain on their functional status and psychologic well-being, found, briefly, that of the 26.3% who experienced daily pain, 25% received *no* form of analgesia.[11]

It is estimated that over 31 million people in the United States each year undergo painful surgical and nonsurgical operative procedures, half of which may be inadequately treated for pain.[9,12] Undertreatment of pain has broad clinical implications and has been correlated with poor surgical outcomes such as delayed return to respiratory, bowel, and gastric function after surgery, immune suppression, and development of chronic pain.

A study of acute pain management in the postoperative setting showed that 77% of adults experienced inadequately treated pain after surgery: 71% still experienced pain even after being administered medication, and most of these (80%) described the pain as moderate to extreme.[13]

The Agency for Healthcare Policy and Research (AHCPR) and, more recently, the American Society of Anesthesiologists, published guidelines for the management of acute pain in the perioperative setting.[14,15] The major goals of these guidelines are to facilitate the efficacious and safe use of perioperative analgesia while reducing the severity of postoperative pain. The guidelines stress the importance of being proactive in planning analgesia and having patients and families involved in pain management. Education of patients and healthcare providers is needed to encourage optimal and safe use of analgesics. While authoritative guidelines are available, considerable effort is needed in their implementation. A study in 1995 found that only 46% of the hospitals surveyed had acute pain management programs or written guidelines, though an additional 22% planned to implement a pain management program in the near future.[13]

PATHOPHYSIOLOGY OF PAIN

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[5] *Nociceptive pain* is transiently invoked when pain-sensitive neurons (nociceptors) are activated by noxious stimuli (eg, physical, chemical, thermal). This pain is a protective response to adverse stimuli and subsides with removal of the stimulus. Nociceptive pain may initiate a phase of persistent acute pain triggered by tissue damage; the cellular and neuronal release of inflammatory mediators, such as prostaglandins, is involved.[16] Uncontrolled pain here increases patients' sensitivity.[8] Prolonged tissue damage and inflammation sensitizes nociceptors, resulting in a decreased pain threshold and protracted response (frequency of neuronal firing), or, *hyperalgesia*. Like nociceptive pain, hyperalgesia is linked to an adverse stimulus and diminishes with healing and decreased inflammation. Prolonged acute pain and hyperalgesia, however, can evolve into *chronic pain*.[16]

In contrast to acute pain, chronic pain is not a protective response and is no longer linked to a stimulus.[3] Progressive and prolonged stimulation of pain causes increased excitation of neurons in the

dorsal horn of the spinal cord.[5] This phenomenon is sometimes referred to as "wind-up pain." Once established, this abnormal condition continues independently of the initial cause (stimulus) and, for that reason, is considered pathologic pain.[17] Acute pain and hyperalgesia, which take place in the peripheral nervous system can, therefore, be distinguished from chronic pain, which takes place in the central nervous system. Mechanisms maintaining chronic pain are poorly understood.

The role of COX-2 in pain

Management of resolvable pain (eg, postsurgical pain) has benefited from advancements in understanding of the biochemical and molecular basis of pain. In injured tissue, acute pain is evoked locally, being mediated by released cellular components of the inflammatory process. Prominent among these are products of the cyclooxygenase (COX)-2 enzyme, in particular prostaglandin E_2 (PGE_2) and prostacyclin.[3] PGE_2 signals pain input by binding to receptors that regulate the calcium and sodium channels of nociceptive neurons.[18] PGE_2 can activate neurons or increase their sensitivity to pain. Following tissue injury, nociceptive fibers themselves are neuroeffective, as stimulated fibers release polypeptide mediators such as substance P, which enhances prostaglandin production.[6]

Inflammation in the periphery also generates pain hypersensitivity in adjacent tissues (*secondary hyperalgesia*) caused by spinal sensitization and a syndrome of muscle and joint pain, fever, lethargy, and anorexia.[19,20] Therefore, the effects of acute pain are inexorably linked to secondary events resulting from the widespread induction of COX-2 expression and subsequent production of prostaglandins in the spinal cord and brain. Inhibiting central COX-2 activity greatly reduces inflammatory pain hypersensitivity. The role of COX-2 in peripheral and central pain is the rationale for the use of COX-2-selective inhibitors to treat pain and its accompanying syndromes.[21]

TABLE 1
DRUGS USED IN RELIEF OF PAIN

- **Opioid analgesics**
  - Codeine
  - Oxycodone
  - Morphine
  - Hydromorphone
  - Levorphanol
  - Methadone
  - Meperidine
  - Butorphanol
  - Fentanyl
  - Tramadol
- **Nonopioid analgesics**
  - Nonselective NSAIDs
    - Aspirin
    - Ibuprofen
    - Naproxen
    - Fenoprofen
    - Indomethacin
    - Ketorolac (parenteral)
  - COX-2–selective inhibitors
    - Rofecoxib
    - Celecoxib
    - Valdecoxib
  - Others
    - Acetaminophen
    - Clonidine
    - Ketamine
- **Antidepressants**
  - Doxepin
  - Amitriptyline
  - Imipramine
  - Nortriptyline
  - Desipramine
  - Venlafaxine
- **Anticonvulsants**
  - Phenytoin
  - Carbamazepine
  - Gabapentin
- **Topical agents**
  - Capsaicin
  - Bupivacaine

■ OPTIONS FOR PAIN TREATMENT

Opioid analgesics

Pain medications may be broadly divided into two major categories: opioids and nonopioids (**Table 1**). Despite significant side effects, opioid analgesics remain the most potent and widely used pain-relieving drugs.[6]

These agents bind to opioid receptors where, acting as agonists, they inhibit pain-transmitting neurons and stimulate pain-inhibitory neurons. The μ- and Δ-opioid types of receptors are most commonly associated with pain relief.[16] Opioids are typically thought of as acting centrally, but peripheral opioid receptors are present in humans. The identification of such receptors may help explain the analgesic effect of some opioids. Intra-articular morphine, for example, has a significant analgesic effect mediated through peripheral receptors.[22]

Opioid analgesics differ in their potency, speed of

onset, duration of action, and route of administration. The most common side effects are sedation, respiratory depression, vomiting, enuresis, pruritus, and constipation. Although tolerance and dependence may each occur with opioid use, the risk of addiction with appropriate medical management is minimal.[6] Concerns about the development of dependence on the part of patients, physicians, and pharmacists lead to underuse or suboptimal dosing of opioids in pain management.[2]

Tramadol is a centrally acting weak μ-opioid receptor agonist that also possesses nonopioid mechanisms of action. Tramadol modulates monoaminergic pathways, increasing synaptic levels of norepinephrine and serotonin in central neurons.[23] The side effects of tramadol are less severe than those of other opioids and the risk of dependence is low.[2] There are no organ-damaging risks.

Nonopioid analgesics

Aspirin and acetaminophen are two of the most widely used analgesics and are effective for mild-to-moderate headache and pain of musculoskeletal origin. Acetaminophen apparently inhibits central prostaglandin synthesis and fever but has no anti-inflammatory effects. Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are nonopioid analgesics that act peripherally at the site of tissue damage by blocking prostaglandin synthesis. Drugs in this class have varying degrees of anti-inflammatory, antipyretic, and analgesic properties as well as different side effects, time to onset of action, and duration of action. Aspirin, like other nonselective NSAIDs, inhibits both COX-1 and COX-2; therefore, gastrointestinal (GI) toxicity and bleeding are undesirable side effects of these analgesics. GI toxicity associated with NSAID use is substantial. Each year there are more than 100,000 NSAID-related hospitalizations, with mortality of rates of 5% to 10%.[24]

Ketorolac, a nonselective NSAID, is approved for the short-term management of moderately severe postoperative acute pain. Ketorolac has the distinction of being the only non-narcotic analgesic available in a parenteral formulation that can be administered for the relief of acute pain. Because ketorolac is nonselective, it may be contraindicated in patients with GI disorders, hypertension, renal disease, and in patients on anticoagulation therapy. Caution must be used when administering ketorolac to volume-depleted patients. All of the above conditions may complicate the perioperative state.[25]

Coxibs in acute and perioperative pain management

Postsurgical pain is frequently undertreated.

COX-2–selective inhibitors are effective opiate-sparing analgesic agents in the perioperative setting and are a sound addition to balanced analgesia.

Unlike opioids and nonselective NSAIDs, COX-2–selective inhibitors do not have serious side effects (eg, bleeding) that can negatively affect surgical outcomes.

Inhibition of COX-2–mediated prostaglandin synthesis reduces nociceptive pain and prevents inflammatory pain that leads to hyperalgesia.

Analgesics provide more effective pain relief when used preemptively, owing to the prevention of peripheral sensitization.

Rofecoxib has a clinically proven longer duration of action than celecoxib and nonselective NSAIDs, making it more appropriate for preemptive analgesia.

COX-2–selective inhibitors

COX-2–selective inhibitors have rapidly become an important resource for pain treatment. Rofecoxib and celecoxib are COX-2–selective inhibitors (coxibs) with anti-inflammatory, antipyretic, and analgesic properties similar to other NSAIDs and are indicated for the treatment of acute pain. Clinical data have shown that COX-2–selective inhibitors have efficacy equivalent to NSAIDs but have significantly lower risk of side effects such as GI ulceration, inhibition of platelet aggregation, or increased bleeding time.[26–28] Therefore, COX-2–selective inhibitors have potential for use in the perioperative setting.

Antidepressants and anticonvulsants

Tricyclic antidepressants may offer relief for chronic pain. Analgesic activity of tricyclic agents is initiated sooner and at a lower dose than their antidepressant activity. In addition to their effect on neurotransmitters (eg, serotonin and norepinephrine), antidepressants may potentiate opioid analgesia.[6] Tricyclic antidepressants have significant side effects. Unfortunately, newer serotonin-selective reuptake inhibitors, such as fluoxetine, lack efficacy in pain relief. Some atypical antidepressants that are more tolerable than tricyclics, such as venlafaxine and mirtazapine, are efficacious in the management of chronic pain. Anticonvulsants, such as carbamazepine, phenytoin, and the newer agent gabapentin, help relieve neuropathic pain.[6]

Topical agents

Bupivacaine and capsaicin are used topically to treat pain associated with neuralgia, neuropathy, and arthritis. Capsaicin is thought to inhibit the synthesis, transport, and release of substance P.[2] Lidocaine (5%) patches may relieve postherpetic neuralgia.[29]

Other analgesic agents

Ketamine inhibits the actions of excitatory amino acids, which are thought to be critical mediators of nociception and hyperalgesia. Clonidine, a central α-receptor agonist, modulates monoamine release and has been effectively used in multimodal regimens.

EVOLVING CONCEPTS IN PERIOPERATIVE ANALGESIA

Preemptive analgesia

The types of acute and chronic pain (discussed earlier), and analgesic strategies to resolve them, are diagrammed in **Figure 1**. An evolving concept in perioperative pain management is the use of preemptive analgesia (**Figure 1**).[9,30] The pain and inflammation that result from surgery normally cause increased prostaglandin production and sensitization. If analgesia is administered before painful stimuli and tissue damage, hypersensitivity can be circumvented and hyperalgesia and central sensitization prevented.[9,30] Accordingly, the use of long-acting analgesic agents before surgery can avert the establishment of a sensitized state in the peripheral nervous system, greatly diminishing the degree and persistence of postoperative pain.

Balanced analgesia

Balanced analgesia uses a combination of topical anesthetics, opioids, and NSAIDs to improve analgesic efficacy and safety.[31,32] In perioperative settings, this strategy should be used whenever possible as it has the advantage of decreasing the doses and thereby the adverse effects of each drug. While opioid-sparing, balanced analgesia provides enhanced pain relief compared with opioids or local anesthetics alone.[23]

COX-2–selective inhibitors have been shown to be efficacious in the prevention of hyperalgesia when used postoperatively as part of a balanced approach to analgesia. Their tolerability and the nonadditive nature of the dose-related adverse effects of opioids make the COX-2–selective inhibitors a particularly useful resource in combination with opioids.[6]

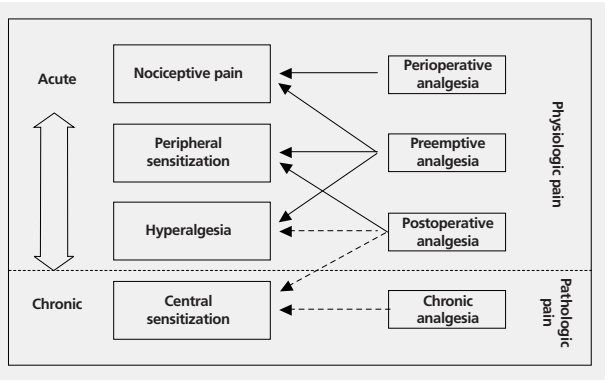

FIGURE 1. Analgesic strategies for pain management. The temporal progression of pain and approaches (and their argets) to the initiation and maintenance of analgesia. Arrows show effector pathways (dotted lines indicate lower efficacy). Adapted with permission from Kissin I. Preemptive analgesia. Anesthesiology 2000; 93:1138–1143.[30]

Though there are many analgesic choices for treating pain in general, there are fewer choices and more limitations when using analgesics in the perioperative setting. A multitude of factors come into play when a patient needs pain relief for a surgical procedure and concerns about hepatic, cardiac, and renal function are paramount. Also, patients often cannot take drugs orally and may benefit from preoperative longer-acting analgesic agents and analgesic adjuvants. Additionally, in the case of invasive surgery, platelet aggregation should not be compromised, unless risk of thrombosis signals a specific need for antithrombotic agents. Bleeding is a concern with the use of nonselective NSAIDs, and so, they are usually discontinued prior to surgery. Ketorolac presents particular concerns due to its renal effects: it may cause volume depletion and precipitate renal failure and is, therefore, contraindicated for preoperative analgesia. Despite the benefit of nonselective NSAIDs as part of a balanced analgesic regimen, their potential adverse effects may ultimately compromise pain relief. This obstacle to nonselective NSAID use may be effectively overcome with the use of COX-2–selective inhibitors.[33]

COX-2–SELECTIVE INHIBITORS IN PREEMPTIVE ANALGESIA

In the perioperative setting, preemptive analgesia can be achieved with NSAIDs, COX-2–selective inhibitors, acetaminophen, and longer-acting

TABLE 2
SUMMARY OF ACUTE PAIN STUDIES OF COX-2–SELECTIVE INHIBITORS

Model	N	Design	Drugs	Results
Primary dysmenorrhea[34]	127	R, DB PC, AC, crossover	Rofecoxib 25 or 50 mg initially plus rofecoxib 25 mg as needed Naproxen 550 mg BID	Rofecoxib 25 and 50 mg superior to placebo* Rofecoxib onset, peak, and overall analgesia comparable to naproxen Rofecoxib duration longer than naproxen*
Postoperative dental pain[35]	151	R, DB, PC, AC	Rofecoxib 50 mg Ibuprofen 400 mg	Rofecoxib superior to placebo† Rofecoxib onset, peak and overall analgesia not different from ibuprofen Rofecoxib duration longer than ibuprofen†
Postoperative dental pain[36]	272	R, DB, PC, AC	Rofecoxib 50 mg Celecoxib 200 mg Ibuprofen 400 mg	Rofecoxib and celecoxib superior to placebo‡ Rofecoxib superior to celecoxib for onset, peak, and overall duration of analgesia§ Rofecoxib and celecoxib similar to ibuprofen
Postoperative dental pain[37]	393	R, DB, PC, AC	Rofecoxib 50 mg Codeine 60 mg plus acetaminophen 600 mg	Rofecoxib superior to codeine/acetaminophen for peak, overall, and duration of analgesia‡ Rofecoxib comparable to codeine/acetaminophen for onset Codeine/acetaminophen group had significantly more adverse effects than rofecoxib group‡
Postoperative dental pain[38]	304	R, DB, PC AC	Parecoxib 20 mg IM or IV Parecoxib 40 mg IM or IV Ketorolac 60 mg IV	Parecoxib (all doses and routes) superior to placebo¶ Parecoxib routes and dosages comparable to ketorolac except parecoxib 40 mg had longer duration†

R = randomized; DB = double blind; PC = placebo controlled; PG = parallel group; AC = active comparator; IM = intramuscular; IV = intravenous; BID = twice daily.
*$P \leq .006$.
†$P < .05$.
‡$P < .001$.
§$P < .001$; $P < .003$; $P < .001$, respectively.
¶$P \leq .05$.

opioids such as codeine and propoxyphene. COX-2–selective inhibitors, or coxibs, offer advantages over nonselective NSAIDs due to their lack of COX-1 inhibition. They do not affect platelet function nor do they increase the risk of bleeding, and they are associated with less GI toxicity than nonselective NSAIDs. COX-2–selective inhibitors lack the serious side effects of opioids and complement other analgesic agents. These factors, combined with their duration of action, have prompted studies of their use in preemptive analgesia.

Acute pain

Adequate relief of acute pain may be dependent on several factors such as time to onset of analgesia, maximum analgesic effect, and duration of analgesic effect. Several key studies of coxibs in acute pain are summarized in **Table 2**. Relevant conclusions are briefly detailed here.

Primary dysmenorrhea is caused by prostaglandin-induced uterine hyperactivity and is usually treated with nonselective NSAIDs. The pain associated with dysmenorrhea is similar to perioperative pain, particularly that of abdominal surgery, and lasts about 72 hours. As it is associated with both acute and recurring pain, dysmenorrhea requires analgesic relief on a cyclical basis. Concerns about GI toxicity from the effects of long-term nonselective NSAID use are justified.

Rofecoxib is indicated for the treatment of dysmenorrhea and, at doses of 25 mg or 50 mg, provided analgesic relief comparable to naproxen (550 mg BID) in 127 women with a history of primary dysmenorrhea.[34] The main endpoints used in the study were total pain, difference in pain intensity over an 8-hour period, patient global evaluation, and time to remedication.

Patients frequently receive nonselective NSAIDs

for acute pain associated with dental surgery. A study of rofecoxib 50 mg (n = 50) and ibuprofen 400 mg (n = 51) for pain after oral surgery, compared with placebo (n = 50), assessed efficacy by evaluating pain intensity and pain relief at 12 intervals during a 24-hour period.[35] Additional primary assessments included the TOPAR8, which represents the time-weighted pain-relief score up to 8 hours.[35] Rofecoxib and ibuprofen both resulted in significantly better TOPAR8 scores than placebo (P < .05), but patients randomized to rofecoxib had longer lasting pain relief compared with the ibuprofen group (P = .039). Fewer patients (28%) receiving rofecoxib took rescue medication within the 24-hour period compared with those receiving ibuprofen (82.4%). Notably, tolerability was greatest for rofecoxib.[35]

Another study of pain due to molar excision evaluated rofecoxib (50 mg) and celecoxib (200 mg), each compared with ibuprofen, through the 24-hour period following surgery.[36] Rofecoxib had analgesic effects on all measures that were superior to celecoxib, including overall analgesic effect (TOPAR8), time to onset of pain relief, peak pain relief, and duration of effect. Notably, and as shown in other studies, rofecoxib had analgesic efficacy comparable to ibuprofen but with longer duration (P < .05) (**Figure 2**).[36]

A similar double-blind, randomized study of postoperative dental pain compared the efficacy of rofecoxib 50 mg with codeine 60 mg plus acetaminophen 600 mg in 393 patients.[37] The overall analgesic effect of rofecoxib was greater than that of codeine/acetaminophen for TOPAR8 (P < .001), as was the patient global assessment of response to therapy (PGART) at 6 hours (P < .001). The onset of analgesic effect was similar for rofecoxib and codeine/acetaminophen, but the peak analgesic effect was significantly greater in the rofecoxib group (P < .001). As seen in other studies, duration of analgesic effect was greater with rofecoxib. More patients in the codeine/acetaminophen group experienced adverse events overall (P < .05) and nausea in particular (P < .001) compared with rofecoxib.[37]

In a study of intramuscularly or intravenously administered NSAID for postoperative dental pain, the experimental parenteral coxib, parecoxib, was compared with the nonselective NSAID ketorolac.[38] Although generally comparable on all experimental measures (time-specific pain intensity, pain relief, time to onset of analgesia, and time to use of rescue medication), parecoxib effected a longer duration of analgesia than did ketorolac ($P \leq .05$).[38]

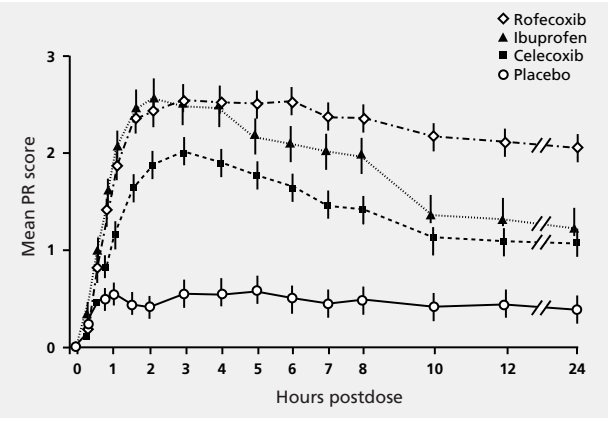

Figure 2. Mean (± SE) pain relief (PR) in patients experiencing moderate to severe postoperative dental pain over the 24 hours after dosing with rofecoxib 50 mg, ibuprofen 400 mg, celecoxib 200 mg, or placebo. Patients who used rescue medication are included (last observation carried forward). Reprinted with permission of the publisher. From Malmstrom K et al. Comparison of rofecoxib and celecoxib, two cyclooxygenase-2 inhibitors, in postoperative dental pain: a randomized, placebo- and active-comparator-controlled clinical trial. Clin Ther 1999; 21:1653–1663. Copyright 1999 by Exerpta Medica Inc.[36]

Studies show that, for commonly employed regimens, rofecoxib is superior to placebo and comparable to commonly used nonselective NSAIDs, and codeine plus acetaminophen, by many of the criteria for determining overall analgesic efficacy. Similar results may hold for parecoxib compared with ketorolac. Time to onset, peak effect, and duration of analgesia are important factors.

Celecoxib has been recently approved for acute pain: 400 mg followed by 200 mg every 12 hours as needed.[39] Another oral coxib, valdecoxib, was recently approved for osteoarthritis, rheumatoid arthritis, and menstrual pain.[40]

Preemptive and postsurgical analgesia

As discussed earlier, the use of long-lasting analgesics *before* surgery may help to avoid the establishment of a sensitized state and result in diminished postoperative pain. **Table 3** summarizes data on coxibs in preemptive and postsurgical analgesia. Some relevant details are presented here.

In the ambulatory setting, preoperative rofecoxib (50 mg, n = 19), acetaminophen (2,000 mg, n = 16), or a combination of rofecoxib 50 mg plus acetaminophen 2,000 mg (n = 14), compared with a con-

TABLE 3
SUMMARY OF COX-2–SELECTIVE INHIBITORS USED IN PREEMPTIVE AND POSTSURGICAL STUDIES

Model	N	Design	Drugs	Results
PREEMPTIVE ANALGESIA				
Ear, nose, and throat surgery[41]	68	R, DB PC, AC	Vitamin C (control) Acetaminophen 2,000 mg Rofecoxib 50 mg Rofecoxib 50 mg plus acetaminophen 2,000 mg	Rofecoxib superior to control* Rofecoxib superior to acetaminophen* Rofecoxib decreased postsurgical opioid use* Rofecoxib alone or with acetaminophen comparable
Knee arthroplasty[42]	21	R, DB PC	Rofecoxib 25 mg 3 days prior to surgery	Rofecoxib superior to placebo†
Spinal fusion[43]	60	R, DB, PC	Rofecoxib 50 mg Celecoxib 200 mg	Rofecoxib and celecoxib superior to placebo‡ Rofecoxib and celecoxib groups used less postsurgical opioids§ Rofecoxib superior to celecoxib for duration of analgesia*
Lower abdominal surgery[44]	25	R, DB PC	Rofecoxib 25 or 50 mg	Rofecoxib 50 mg superior to placebo* Rofecoxib group used less postsurgical opioids than placebo*
POSTSURGICAL ANALGESIA				
Orthopedic surgery[45]	218	R, DB PC, AC	Rofecoxib 50 mg (day 1), then 25 or 50 mg/day (days 2–5) Naproxen 550 mg	Rofecoxib 50 mg superior to placebo* Rofecoxib similar to naproxen Rofecoxib decreased postsurgical opioid use¶
Orthopedic surgery[46]	418	R, DB PC, AC	Celecoxib 200 mg TID Hydrocodone 10 mg plus acetaminophen 1,000 mg	Single-dose assessment (8 hours): Hydrocodone/acetaminophen superior to placebo at 1.5 hours Celecoxib superior to placebo at 8 hours‡ Multiple-dose assessment (5 days): Celecoxib 200 mg TID superior to hydrocodone/acetaminophen*

R = randomized; DB = double blind; PC = placebo controlled; PG = parallel group; AC = active comparator; TID = three times daily.
*$P < .05$.
†$P < .001$.
‡$P < .0001$.
§$P < .0001$ and $P < .03$, respectively.
¶$P = .005$.

trol group given vitamin C (500 mg, n = 19), were evaluated in patients undergoing ear, nose, and throat surgery.[41] Patients took medication 30 minutes before surgery and the morning after surgery. For overall analgesic efficacy, preoperative rofecoxib was significantly more effective than either placebo or acetaminophen ($P < .05$); rofecoxib also decreased the need for rescue opioid (fentanyl). Notably, the addition of acetaminophen to rofecoxib did not significantly improve analgesic efficacy.[41]

In patients undergoing total knee arthroplasty, the safety and efficacy of the preoperative and postoperative administration of rofecoxib was evaluated.[42] All patients were required to discontinue NSAID use 10 days prior to surgery and for 7 days received no medication. Three days before surgery patients were randomized to either placebo (n = 11) or rofecoxib 25 mg (n = 10). Pain measurements at rest and while moving were made during the 7-day drug-free period and the 3 days leading up to surgery, and other hematologic variables were measured, including intraoperative blood loss and postoperative measures of hemoglobin, hematocrit, platelet count, prothrombin time, and international normalized ratio. Rofecoxib resulted in significantly improved pain scores on all measurements. There were no differences in intraoperative bleeding or the variables used to assess hemodynamic factors.[42]

Reuben and Connelly also investigated the preemptive use of rofecoxib 50 mg (n = 20) and celecoxib 200 mg (n = 20) compared with placebo (n = 20) in patients undergoing spinal fusion surgery.[43] At the end of the study, patients in the placebo group had significantly higher cumulative dosages of morphine than did patients in either the celecoxib group ($P < .03$) or the rofecoxib group ($P < .0001$) (**Figure 3**).[43] The morphine dosage was significantly lower for patients in the rofecoxib group at each measurement interval compared with placebo; patients in the celecoxib group consumed as much or more morphine in the last four of the six intervals as did patients in the placebo group. No significant increase in intraoperative bleeding in patients receiving either coxib was observed.[43]

Preliminary results from a study evaluating the effect of preoperative rofecoxib (25 mg and 50 mg) on postsurgical patient-controlled analgesia (PCA) morphine usage and measurements of effort-dependent pain found that patients randomized to rofecoxib 50 mg had significantly better visual analog scale (VAS) pain scores and consumed significantly less morphine than their counterparts in the other two study groups following elective abdominal surgery.[44] The rofecoxib 50 mg group also had superior pulmonary function relative to the other two groups.

Studies of coxibs for preemptive analgesia show that a single dose of rofecoxib or celecoxib before surgery diminished both postoperative pain and postsurgical morphine use. Rofecoxib was more effective than celecoxib for preemptive analgesia. Both drugs were similarly analgesic over the initial postoperative period, but one preoperative dose of rofecoxib provided enduring relief.

For postsurgical pain, rofecoxib 50 mg (given as 50 mg on day 1, then 25 or 50 mg on days 2 to 5) was superior to placebo ($P < .05$) and similar to naproxen for all single-dose measures of pain relief following orthopedic surgery (**Table 3**).[45] Furthermore, the rofecoxib 50-mg group used less narcotic analgesia ($P = .005$) and reported less pain on global evaluations ($P = .041$) than did the placebo group.

In another study of postorthopedic surgical pain, celecoxib (200 mg 3 times daily) compared with hydrocodone 10 mg plus acetaminophen 1,000 mg resulted in significantly lower maximum pain intensity, fewer doses of medication, and superior scores on the American Pain Society Patient Questionnaire (all $P \leq .013$).[46] Fewer patients taking celecoxib experienced adverse events compared with those taking hydrocodone plus acetaminophen (43% vs 89%; $P < .001$).[46]

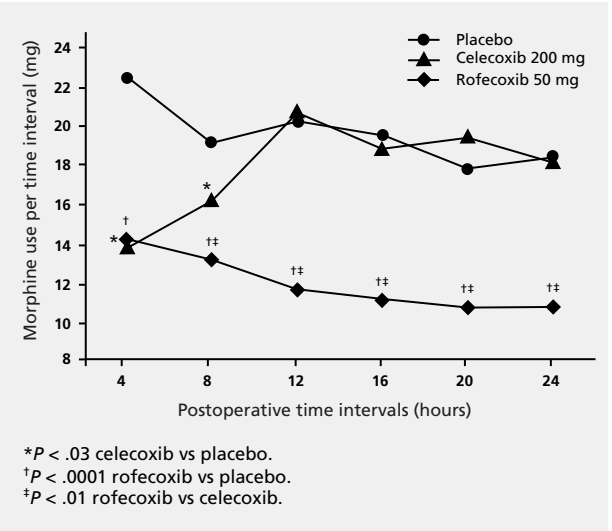

Figure 3. PCA morphine consumption at each postoperative time interval in patients undergoing spinal fusion surgery who received preemptive analgesia with a COX-2–selective inhibitor or placebo. Reprinted with permission from Reuben SS, Connelly NR. Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. Anesth Analg 2000; 91:1221–1225.[43]

Other known side effects of nonselective NSAIDs include inhibition of osteogenic activity in patients undergoing spinal fusion. Preclinical data showed that rofecoxib does not inhibit osteogenic activity. Currently, there is an ongoing double-blind controlled clinical trial to verify that rofecoxib does not interfere with spinal fusion. Additionally, a retrospective trial involving more than 300 patients who underwent spinal fusion surgery showed that rofecoxib was associated with a nonunion rate similar to that of placebo from a historical trial.[47]

■ DISCUSSION

The importance of managing patients' pain reflects the core value medicine places on the alleviation of suffering. Achieving this goal is a complex mission, and strategies must consider the biologic and psychosocial aspects of pain.

Strategies to relieve surgical pain have traditionally been dominated by postoperative opioid analgesia. The demand for opioid-sparing analgesic options, however, has been underscored by the desire for better pain management in general and concern

about opioid side effects in particular. Reliance on opioids often leads healthcare providers to balance effective pain management with prodigious efforts to avoid complications from side effects.

Developments in the pharmacology of pain have created expanding vistas, allowing discovery of interventions that are both safer and more efficacious while being appropriate to contemporary understanding of clinical pain management. Understanding of pain mechanisms has revealed the importance of proactive interventions in analgesia that aim to prevent initiation of hyperalgesia and central sensitization through preemptive analgesia. An appreciation of balanced approaches to analgesia has allowed for safer pharmacologic strategies for analgesia.

Nonselective NSAIDs are not used in the perioperative setting. The analgesic benefit of NSAIDs, however, provides a germane standard of analgesic efficacy. Coxibs, the COX-2 selective inhibitors, have emerged as a class of analgesic agents that offers pain relief similar to nonselective NSAIDs without compromising platelet aggregation or causing GI toxicity.

Clinical data evaluating the use of coxibs before or after various surgical procedures showed that there was no increased blood loss associated with rofecoxib or celecoxib use. Moreover, many surgical outcomes (eg, time to recovery) often depend on how soon a patient can regain mobility. Across studies, patients with lower opioid usage regained mobility faster than their more opioid-dependent counterparts. This feature has obvious value in both the hospital and outpatient settings.

Studies of pain are limited by the subjectivity of pain and the lack of a gold standard for pain measurement. Most studies rely on the VAS as an important endpoint for measuring pain in the perioperative setting. Nevertheless, analgesic efficacy is the outcome of many factors: time to onset of action, duration of action, side effects, maximum pain relief, usage of rescue medication, and any other specific factors relevant in a particular acute pain model. Multiple studies of pain using these criteria have shown that coxibs are an effective analgesic option in the treatment of acute and perioperative pain. Additionally, clinical data have shown that rofecoxib has a longer duration of action than celecoxib or ibuprofen when used in both the preoperative and postoperative settings. The confluence of clinical data from randomized, blinded studies suggests that COX-2–selective inhibitors contribute to an enhanced standard of care for patients.

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Emerging options with coxib therapy

MARK J. LEMA, MD, PhD

ABSTRACT

Future clinical applications of cyclooxygenase (COX)-2–selective inhibitors (coxibs) are likely to extend beyond their current use as oral analgesics in high-risk arthritis patients. The clinical utility of coxibs for the treatment of Alzheimer's disease (AD) is under investigation. Epidemiological surveys, preclinical studies, and preliminary clinical trials with nonsteroidal anti-inflammatory drugs (NSAIDs) have suggested that inflammatory mechanisms play a role in the neurodegeneration of AD. Clinical trials are currently being conducted to determine the effect of coxibs on the rate of AD progression. The use of coxibs as chemopreventive agents in colorectal cancer (CRC) is also under investigation. The chemopreventive benefits of coxibs to promote cell death (apoptosis) and inhibit angiogenesis in CRC have been shown in tumor cell lines and in animal and human models. In addition, palliative care clinicians and oncologists are increasingly including coxibs in their management of cancer pain. Coxibs are utilized for their opioid-sparing effect in the management of cancer pain, without impairing wound healing, or promoting bleeding diathesis (antiplatelet effects) or adverse gastrointestinal effects in patients receiving chemotherapy or radiation treatment.

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As the size of the aging population increases, primary care physicians, who practice at the front line of medical care, can expect to see more patients with Alzheimer's disease (AD) or colorectal cancer (CRC) in their clinical practice.[1–4] Perhaps surprisingly, cyclooxygenase (COX)-2–selective inhibitors (coxibs) may have a role in treating these diseases in addition to their established utility in the management of arthritis and other painful conditions.

AD is an age-related neurological disorder leading to progressive dementia. The number of patients in the United States with primary dementia (AD and vascular dementia) is approximately 4 million, and an estimated 100,000 new patients are expected to be diagnosed each year.[5] Slowing or preventing the neurodegenerative process in AD is one of the major challenges facing healthcare professionals today.[6]

Similarly, the risk of developing CRC grows with advancing age. The American Cancer Society estimates that in 2001 approximately 135,400 new cases of CRC will have been diagnosed and 56,700 Americans will have died from CRC.[4] While risk-minimization recommendations exist,[4,7] researchers continue to search for an effective agent that could prevent or limit the progression of CRC.

Another area of clinical concern is the control of malignant pain associated with cancer, a primary clinical objective when caring for cancer patients. The role of primary care physicians is essential in preserving patients' quality of life, as they can coordinate treatment and patient evaluation with oncologists and palliative care clinicians.[8] Strategies uti-

lizing nonsteroidal anti-inflammatory drugs (NSAIDs), alone or in association with an opioid, can effectively manage most cancer pain. However, their use is limited by side effects typically associated with NSAID therapy.

The clinical benefits of coxibs for the treatment of AD and chemoprevention of CRC are being evaluated as a result of an increased understanding of the pathophysiology of both AD and CRC. The unique pharmacology of coxibs has already demonstrated potential value in these areas, in addition to their use in the management of cancer pain. This article will review the potential COX-2–related therapeutic targets that have been revealed in these diseases and that may offer unique treatment options for sufferers and physicians alike.

■ ALZHEIMER'S DISEASE

A loss of neuronal function, most likely in glutamatergic neurons in neocortical and hypothalamic structures, is believed to be responsible for the signs and symptoms of AD.[6,9–12] The etiology of AD is not fully understood, but three interactive developments—senile plaques, neurofibrillary tangles, and inflammation—have been identified as pathogenic factors.[10,11] Notably, markers of local inflammation, such as activated microglia, reactive astrocytes, complement proteins, cytokines, and reactive mediators of oxygen and nitrogen (free radicals), all occur in close proximity to senile plaques and neurofibrillary tangles containing beta-amyloid (Aβ) and tau (τ) proteins.[9–11] Furthermore, senile plaques associated with activated complement factors, activated microglia, and reactive astrocytes—without any apparent influx of leukocytes—are strongly suggestive of a locally-induced, nonimmune-mediated inflammatory response.[9,10]

Inflammation in Alzheimer's disease

The inflammatory hypothesis of AD suggests that these inflammatory processes either directly or indirectly promote neurotoxicity and neurodegeneration.[11–15] The markers of a neuroinflammatory response detected in AD brain tissue represent a protective reaction to neuronal stress, but most likely contribute to neuronal stress as well.[9,11] One pharmacologic approach to retard AD progression, therefore, would be to suppress inflammation with anti-inflammatory treatment using nonselective NSAIDs or the COX-2–selective inhibitors.[6,9]

Epidemiological surveys have proven to be quite useful in investigating the pathogenesis of AD since circumstances associated with a decreased prevalence of disease may help to identify factors that may be providing a protective influence.[11] Several epidemiological surveys have identified chronic exposure to an anti-inflammatory agent as a protective factor for the development of AD.

Understanding the evidence

The first line of epidemiological inquiry entailed case-controlled studies of medical parameters in individuals diagnosed with AD.[16–23] In all but one of seven studies,[16] a lower prevalence of concomitant arthritis was consistently identified as a "protective" factor against AD.

Cross-sectional surveys of elderly individuals have measured the prevalence of concurrent diagnoses of AD and rheumatoid arthritis (RA), a disease typically managed by chronic anti-inflammatory treatments. Three large, population-based surveys all found a significantly lower prevalence of AD among patients with RA, providing some evidence of a positive benefit conferred by anti-inflammatory treatment.[14,24,25] Two smaller studies gave somewhat conflicting results. One study showed a significantly lower prevalence of RA among a cohort of patients with AD compared with the prevalence of RA in a cognitively intact cohort (2% vs 13%; odds ratio [OR] = 0.17; $P < .005$).[23,26] The second study reported no difference in the prevalence of RA among patients with AD than in those who were cognitively intact (6% vs 4%; OR = 1.18; 95% confidence interval [CI], 0.35–3.91).[23,27]

The impact of chronic exposure to steroid therapy on the development of AD has also been reviewed in epidemiological studies. Four case-control studies all found that exposure to steroid treatment provided a protective effect, if not as numerically large an effect as seen in studies evaluating the impact of a diagnosis of arthritis or RA.[20–23,27]

Bestowing a bit more favor on the inflammatory hypothesis of AD and the putative role for COX-2–selective inhibitors are results from studies that found a protective effect with NSAID use on the development of AD.[20–22] Notably, the overall OR for these studies was 0.50 (95% CI, 0.34–0.72; $P = .0002$), compared with that for those studies evaluating the impact of steroid therapy (0.66; 95% CI 0.43–1.00; $P = .049$). These data suggest that NSAID use (which *directly* targets COX activity as

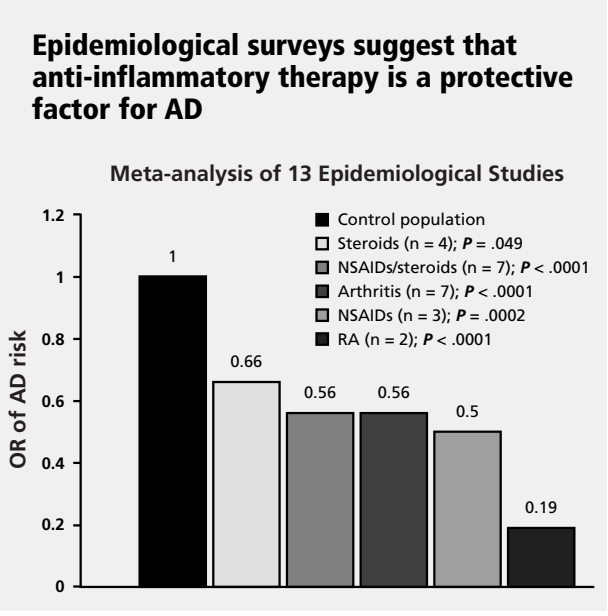

FIGURE 1. A meta-analysis of 13 epidemiological surveys suggests that prolonged exposure to an anti-inflammatory treatment confers a protective influence on the development of AD. Whether the variable was a diagnosis of arthritis or RA, or anti-inflammatory treatment with a steroid, NSAID, or both, the OR of a concomitant diagnosis of AD was well below 1.0. The greatest protection appears to occur in individuals with RA. This may be explained by the fact that the anti-inflammatory dose for NSAIDs required to control RA is higher than the dose for analgesia.[23]

contrasted to steroids, which act on the acute phase of the inflammatory response) confers a greater degree of protection against the development of AD than does steroid exposure.[20,22,23]

A comparable level of protection with NSAID use was seen in two population-based surveys. In one, the prevalence of NSAID users in the population of two AD clinical trials was 0.5% compared with a 22% prevalence of NSAID users in a control cohort from three surveys of elderly patients.[23,28] In the second population-based survey, 1.4% of 365 NSAID users were found to have AD compared with 2.5% in a cohort of 5,893 institutionalized and community-living individuals over 55 years of age.[29]

A third population-based study, the Baltimore Longitudinal Study on Aging (BLSA), followed 1,686 individuals prospectively to evaluate the effect of analgesic agents on the risk of AD.[30] With less than 2 years of nonaspirin NSAID use, the relative risk (RR) was 0.65 (95% CI, 0.33–1.29), and with 2 years or more of nonaspirin NSAID use, the RR dropped to 0.40 (95% CI, 0.19–0.84). Less benefit was seen with low-dose aspirin use: the RR was 0.74 (95% CI, 0.46–1.18). No benefit was seen with acetaminophen use, which has no anti-inflammatory properties: the RR was 1.35 (95% CI, 0.79–2.30).[30]

Another longitudinal survey was conducted at The Johns Hopkins Alzheimer's Disease Research Clinic. Among 209 patients entering the research clinic, only 15% claimed prior or current NSAID use.[31] During a 1-year period, the 32 NSAID users experienced later onset, reduced severity, and slower progression of AD symptoms when compared with age-matched and disease duration-matched patients not taking an NSAID.[23,31]

Anti-inflammatory treatment of AD

Based on these findings, several clinical trials were conducted to determine whether anti-inflammatory treatment could slow or prevent AD progression (**Figure 1**). Indomethacin, a COX-1 preferential inhibitor, was the first anti-inflammatory agent reported to have possible beneficial action in patients with probable AD (Mini-Mental Status Examination [MMSE] score of at least 16). In a small double-blind trial (n = 44), participants who received either indomethacin (100–150 mg/day) or placebo during a 6-month period experienced a 1.3% *improvement* or 8.4% *worsening* in AD symptoms, respectively; the placebo group demonstrated a typical rate of AD progression. However, five (21%) of the indomethacin-treated patients withdrew as a result of gastrointestinal (GI) adverse events, attesting to the limitations of chronic indomethacin treatment, especially in elderly patients.[32] In addition to indomethacin's adverse GI safety profile, clinicians have reported an increase in delirium or agitated behavior in their AD patients treated with indomethacin.[33–35]

Another small placebo-controlled trial evaluated diclofenac in patients with mild-to-moderate AD (MMSE score between 11 and 25). Patients treated with diclofenac 50 mg plus misoprostol 200 μg for 25 weeks were evaluated by both Alzheimer Disease Assessment Scale–cognitive (ADAS-cog) and ADAS-noncognitive scales. While not statistically significant, some observed trends suggested that the placebo group deteriorated to a greater degree than the treated group. Furthermore, the number of withdrawals due to drug-related adverse events was greater in the treatment group—50% compared

with 12% in the placebo group.[36]

In contrast to these preliminary findings with nonselective NSAIDs, no beneficial action of the steroid prednisone has been demonstrated. In one randomized, placebo-controlled multicenter trial of low-dose prednisone (10 mg/day for 1 year), 138 patients with probable AD had equivalent ADAS-cog mean scores regardless of treatment arm.[37]

Overall, these findings suggest NSAIDs but not steroids may slow AD progression, and that the antidementia activity of anti-inflammatory agents may be attributed to inhibition of prostaglandin production mediated by COX isozymes. While all NSAIDs, to one degree or another, nonselectively inhibit COX, the COX-2–selective inhibitors spare the constitutive COX-1 isozyme. By primarily targeting the inducible COX-2 isozyme, inflammation mediated by the proinflammatory prostaglandins is ameliorated.[12,38]

COX isoenzymes, coxibs, and Alzheimer's disease

The distinction between COX isozymes is not as well defined in the brain, however. Immunohistochemistry and mRNA-probe studies have found that in the normal brain, both COX-1 and COX-2 are constitutively expressed in all areas examined.[39] Some differential expression may exist, as COX-1 expression was detected in microglial cells whereas COX-2 was found in glutamatergic neurons; no COX expression was detected in astrocytes.[9,10,39,40] In AD frontal cortex, COX-2 expression is upregulated 25% over levels in normal brain, whereas COX-1 expression is decreased 10% to 15%.[39,41]

Studies have shown that COX-2 expression can be rapidly induced by nerve cell injury, tumor promoters, bacterial endotoxins, neurotoxins, cytokines, and anoxia, as well as by noninflammatory triggers such as neuronal stimulation, growth factors, and hormones.[10,39,42] Neuronal upregulation of COX-2 may be both protective as well as a pathogenic response in AD.[9,10,39]

Clinical trials of coxib therapy in AD may provide some answers. A recent 1-year trial with celecoxib (200 mg BID) was conducted in 425 patients with probable AD.[10,43] Although celecoxib was well tolerated, there was no difference between the two groups in their rates of disease progression, as measured by ADAS-cog and Clinician's Interview-Based Impression of Change (CIBIC-plus) scores.

The Alzheimer's Disease Cooperative Study (ADCS), a National Institute of Aging–sponsored consortium, is conducting a clinical trial with rofecoxib. This 1-year, three-arm study is being conducted in 330 patients with probable AD. Study treatments are rofecoxib 25 mg once daily, naproxen 200 mg twice daily, or placebo, and the primary outcome is a mean change in status measured by ADAS-cog. Results of the data analysis are expected in early 2002.

■ COLORECTAL CANCER

Evidence suggests that NSAIDs can prevent the development of CRC.[44] CRC is the second leading cause of cancer-related mortalities in the United States, approximately 57,000 in 1999.[4,45] In the United States, 93% of all CRC cases occur in patients over 50 years of age, and the 5-year survival rate for patients with CRC is approximately 60%.[46] Worldwide, CRC accounts for approximately 556,000 mortalities.

Familial adenomatous polyposis (FAP) is a condition considered to be a precursor to CRC.[47,48] It is a rare condition caused by a defect in the gene *APC* (adenomatous polyposis coli), normally a tumor suppressor, that predisposes one to develop hundreds of colonic polyps. If left untreated, polyps can lead to colon cancer.[49]

Familial adenomatous polyposis, colorectal cancer, and COX

COX-2 is believed to play a role in the development of FAP and CRC. While COX-1 is constitutively expressed in normal GI mucosa, the level of COX-2 is low or undetectable.[50–52] In animal models of FAP or CRC, however, increased expression of COX-2 has been demonstrated.

One study was conducted in multiple intestinal neoplasia (*MIN*) mice, a model for FAP in humans. In adenomas harvested from *MIN* mouse intestine, the levels of COX-2 mRNA and protein were approximately threefold higher than levels of COX-2 in normal mucosa from the same mouse. These findings implicate COX-2 expression at an early, preinvasive stage of CRC.[50] A second study with rats found increased levels of COX-2, but not COX-1, mRNA and protein in colon tumors that developed following treatment with a colorectal carcinogen.[51]

The same differential expression of the COX isozymes has been detected in human colorectal neoplasia. For example, 86% of tumor samples har-

vested from patients with CRC contained greater levels of COX-2 mRNA relative to those in the same patient's noncancerous mucosa. In 43% of the colorectal adenomas examined, an increase in COX-2 gene expression was also detected, again showing upregulation at an early stage in colorectal carcinogenesis. However, the level of COX-1 mRNA in all carcinomas examined was equivalent to the level seen in normal mucosa.[52]

COX-2, NSAIDs, apoptosis, and tumorigenesis

Apoptosis, or programmed cell death, is an active process that removes mutated or damaged cells, thus contributing to the prevention of cancer development. Disruptions in apoptosis and COX-2–mediated processes may provide some explanation for the promotion of colorectal tumor formation by COX-2 upregulation.

Briefly, upregulation of COX-2 results in decreased levels of the COX substrate, arachidonic acid (AA), and simultaneously, increased production of COX-mediated eicosanoids.[52,53] COX-2–mediated prostaglandins stimulate cell proliferation, and other COX-2–mediated factors regulate tumor angiogenesis (tumor growth beyond 2 to 3 mm in size is dependent on tumor angiogenesis).[52–54] Loss of constraint of tumor cell growth is thought to result from decreases in AA, which ultimately result in lower levels of ceramide, a potent inducer of apoptosis.[55] (AA stimulates sphingomyelinase activity to catalyze the conversion of sphingomyelin to ceramide.)

Recent in vitro studies have implicated a key role of COX-2 in mediating mitogenic growth factor signaling and in the downregulation of apoptosis in human colon cancer cell lines.[48] Notably, NSAIDs have been shown to reverse this COX-2 effect in human colon cancer cell lines, promoting apoptosis. In one study, cancer cells were treated with the nonselective NSAID sulindac or its active metabolite, sulindac sulfide. Only sulindac sulfide resulted in dose-dependent apoptosis, which was not reversed by exogenous prostaglandin E_2 (PGE_2), the major eicosanoid in colon tumors, or by other prostaglandins. Furthermore, exogenous AA, but not a control fatty acid, was a potent inducer of apoptosis, presumably due to increased levels of ceramide. In this experimental model, sulindac sulfide treatment elevated ceramide levels tenfold relative to untreated cells. A synergistic effect on apoptosis was seen when sulindac sulfide and AA were combined.[55]

Similar effects were seen with indomethacin, which also displays tumor-suppressive activity in intestinal epithelial cells. In indomethacin-treated cells, there was a three- to four-fold increase in AA and a six-fold increase in ceramide; 94% of the treated cells underwent apoptosis.[55]

An in vitro study with the coxib SC58125 found increased rates of apoptosis in a human colon-cancer cell line that maintains high constitutive COX-2 expression and prostaglandin production.[56]

Tumor-related angiogenesis mostly relies on tumor cell expression of angiogenic factors and endothelial tube formation. The role of COX inhibition on these processes was investigated in an in vitro model of tumor angiogenesis. Endothelial cells and colon carcinoma cells engineered to differentially express COX-1 and/or COX-2 were co-cultured and exposed to aspirin or to NS-398, a COX-2–selective inhibitor. Inhibition of COX-2 activity by either agent reduced tumor cell production of angiogenic factors. However, aspirin or a COX-1 antisense oligonucleotide, but not NS-398 or a COX-2 antisense oligonucleotide, inhibited endothelial tube formation. Furthermore, tumor cell expression of angiogenic factors resulted in upregulated endothelial cell expression of COX-1. These results suggest that NSAIDs may inhibit angiogenesis by two mechanisms: inhibition of COX-2 activity in colon carcinoma cells to downregulate production of angiogenic factors, and inhibition of COX-1 activity in endothelial cells to suppress endothelial tube formation.[53]

Another study examined the role of COX-1 and COX-2 in tumor growth and angiogenesis using isografts of Lewis lung carcinoma (LLC) cells in COX-deficient "knockout" mice (*COX-1*$^{-/-}$ or *COX-2*$^{-/-}$) or coxib-treated (celecoxib or SC-58125) wild-type mice. Tumor growth was diminished both in size and speed in *COX-2* null mice compared with untreated wild-type mice. However, no such difference in tumor growth was observed between *COX-1* null mice and control mice. Furthermore, prior treatment with a coxib inhibited tumor growth, but to a lesser degree than tumor growth in *COX-2* null mice. Angiogenesis was also measured using this model, and results from these experiments suggested that COX-2 activity is essential for tumor angiogenesis, implying again that COX-2 activity promotes tumor growth.[57]

The chemopreventive effect of COX inhibition has been seen in various animal models of colon

cancer. The tumor load in *MIN* mice was decreased significantly and in a dose-dependent manner by the nonselective NSAID piroxicam.[58] These results were confirmed in a study of *MIN* mice treated with sulindac.[59]

Celecoxib demonstrated a chemopreventive effect in male rats in all phases of colon carcinogenesis: initiation, promotion, and progression. The incidence of azoxymethane-induced colon tumors was inhibited in celecoxib-treated rats by 93%; the multiplicity of colon tumors was inhibited by 97%, and the overall colon tumor burden was suppressed by more than 87%.[60]

Rofecoxib resulted in a similar dose-dependent reduction in the number and size of intestinal and colon polyps in *MIN* ($Apc^{\Delta 716}$) mice. Using a rofecoxib dose comparable in plasma concentration to that achieved in humans treated with rofecoxib 25 mg once daily, there was a 55% reduction in the number of all intestinal polyps and an 80% reduction in the number of polyps more than 1 mm in size.[49]

Based on these preclinical findings, large epidemiological studies were conducted to examine the impact of NSAID use on the development of colon cancer. Almost every study found a strong correlation between continuous NSAID use and decreased incidence of CRC in humans.[47]

The mounting evidence from preclinical and epidemiological studies was the basis for clinical trials of NSAID treatment for individuals with FAP. Results from three controlled clinical trials found that treatment with sulindac resulted in substantial regression of adenomatous polyps.[61–63] However, virtually all patients experienced regrowth of adenomatous polyps after sulindac therapy was discontinued.[7,54,64]

In a recent clinical trial, celecoxib 400 mg twice daily for 6 months in 30 patients with FAP resulted in a 28% reduction in the mean number of colorectal polyps ($P = .003$) and a 30.7% reduction in polyp size ($P = .001$).[48] Based on these findings, celecoxib received US Food and Drug Administration approval for the treatment of FAP.

Implication of COX-2 in the promotion of colon cancer

There is substantial evidence that the COX-2 isozyme plays a crucial role in the promotion of FAP and CRC.

- Significant upregulation of COX-2 but not COX-1 occurs in animal models and human samples of FAP polyps and colorectal tumors.[50–52]
- COX-2–generated prostaglandins produce angiogenic factors and promote tumor angiogenesis.[53]
- PGE_2, produced by COX-2 in colon tumors, suppresses apoptosis in human CRC cell lines and colon tumors.[55]
- Both celecoxib and rofecoxib have a COX-2–specific chemopreventive effect in animal models of CRC when compared with nonselective NSAIDs.[49,60]
- Celecoxib is approved as an adjunct to standard care for the treatment of FAP, a premalignant condition that leads to colon cancer if not treated.

■ CANCER PAIN

Cancer, the second leading cause of death in the United States, is often associated with uncontrolled pain.[8] In 1986, the World Health Organization (WHO) developed a three-step therapeutic guideline, called the WHO analgesic ladder, to improve the management of increasing levels of cancer pain.[65] NSAID therapy is recommended by the WHO for use at all three steps on the analgesic ladder, either alone or in combination with an opioid and adjuvant analgesic (other drugs that enhance analgesic effects).[8,66–68]

Inflammation and cancer pain

Cancer pain is often triggered by the release of inflammatory cytokines from active tumors.[8] NSAIDs produce analgesia in part by inhibiting the release of these inflammatory mediators, thus reducing nocioceptive transmission.[8,66,69]

The most common cause of cancer pain is tumor infiltration of bone.[8,68] Bone metastases occur as a consequence of breast cancer, prostate cancer, lung cancer, or multiple myeloma.[8] One likely mechanism of pain secondary to bone metastasis is the secretion of prostaglandins by carcinomas.[8,68] For this reason, NSAIDs should be included in any regimen to control pain associated with bone metastasis.[8,68–70]

Opioid-sparing benefit of NSAIDs

Because NSAIDs do not activate opioid receptors, they can provide additive pain relief when combined with an opioid analgesic.[8,68] Thus, combining an NSAID with an opioid analgesic may provide adequate pain control with a clinically significant reduction in opioid dosage.[69] This opioid-sparing effect of NSAID therapy allows the clinician to diminish the side effects associated with opioid

therapy without sacrificing pain control.[68,70]

However, nonselective NSAIDs have clinically significant adverse effects that differ from those of opioids, which have dose-dependent side effects. It is not always possible to predict which patients are at increased risk of developing an NSAID-induced side effect.[69] Furthermore, catastrophic or irreversible idiosyncratic side effects, which are not always preceded by a minor side effect, may occur without any warning.[8,69]

Clinical factors that increase the risk of an unacceptable adverse effect with traditional NSAID therapy are often present in patients with cancer, limiting the clinical utility of these agents.[65,69] For example, the risk of developing NSAID-associated agranulocytosis is greater in cancer patients who are often pancytopenic as a consequence of their cancer treatments. Similarly, aspirin-associated platelet dysfunction via acetylation of surface proteins is more likely to be clinically significant in cancer patients who are often thrombocytopenic due to chemotherapy or radiation therapy.[66,68,69] In these patients, nonacetylated salicylates (eg, salsalate, choline magnesium trisalicylate) or even acetaminophen are routinely used as alternatives to traditional NSAIDs.[66,68] The potential for toxicity is increased when both salicylates and nonselective NSAIDs are combined with methotrexate therapy.

NSAID-associated GI side effects such as dyspepsia are also more likely to occur in cancer patients, who often experience GI toxicities following chemotherapy.[68] The possibility of developing NSAID-associated GI ulceration, perforation, or frank bleeding is more likely to develop in cancer patients who often are thrombocytopenic, or to become clinically significant in patients who are chronically anemic as a consequence of their treatment.[68,69]

Coxibs: another option for cancer pain management

Oncologists are replacing nonselective NSAIDs, nonacetylated salicylates, and acetaminophen with coxib therapy, chosen for its safety profile. Surgical oncologists are exploring the use of coxibs both preoperatively, as preemptive analgesic therapy, and during the postoperative period to reduce opioid usage and speed the recovery process.

Guidelines for the use of NSAIDs, largely empiric, are drawn from extensive clinical experience.[70] Some anecdotal reports have found that celecoxib is less effective than traditional nonselective NSAIDs in managing cancer pain. Conversely, rofecoxib (25 mg/day or 50 mg/day) seems to be more effective than nonselective NSAIDs in managing cancer pain when combined with an opioid.

■ CONCLUSION

There are several patient groups other than high-risk arthritis patients that may benefit from coxib therapy. The data from epidemiological studies suggest that chronic use of NSAIDs may have a chemopreventive effect on the development of AD, and some clinical trials have shown a slowing of AD symptoms with NSAID treatment. A recent prospective study found that nonselective NSAIDs may be protective against AD.[71] The benefits of coxib treatment of AD are under study and will become known in the coming years.

Preclinical studies suggest that COX-2 inhibition should be a therapeutic target for the chemoprevention of CRC. One coxib is indicated for the treatment of the premalignant condition FAP. Depending on the outcome of current clinical trials, coxibs may be approved soon for adjunctive treatment and/or chemoprevention of CRC.

Palliative care clinicians and oncologists are increasingly using coxibs to manage cancer pain because of their opioid-sparing effect and their lack of the adverse effects typically associated with NSAID or opioid therapy.

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