Specific COX-2 Therapy Is the Future

Lee S. Simon, MD

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs throughout the world, with an estimated 17 million persons in the United States using them on a daily basis [1,2]. These drugs have been proven to be effective in the treatment of acute and chronic painful and inflammatory musculoskeletal conditions. However, due to widespread use of NSAIDs, the incidence of NSAID-induced adverse effects has become a problem. The most common toxic effects induced by NSAIDs are gastric and/or duodenal ulcers; ulcer complications, potentially including bleeding, perforation, or obstruction of the gastrointestinal tract; and alterations in kidney function [3–6]. These serious complications of ulcer disease can lead to death.

For many years clinicians have been tantalized by announcements of "new and safer" NSAIDs. Unfortunately, the hoped-for increased safety was typically associated with some sacrifice in efficacy, and when more of the safe drug was used by the individual patient to attain an improved clinical effect, the incidence of NSAID-induced gastrointestinal damage increased (although less than observed with the older NSAIDs). Many of the important toxic effects of NSAIDs are primarily due to their primary mechanism of action: the inhibition of prostaglandin synthesis through the inhibition of the rate-limiting synthetic enzyme cyclooxygenase (COX). With the discovery of the COX isoforms, the reasons for the problems with traditional NSAIDs became more clear, and we now have available drugs that provide efficacy through the inhibition of COX-2 only. In this editorial, I will review the evidence that shows that COX-2–specific inhibitors provide efficacy equal to that of traditional NSAIDs without conveying the same risk to the gastrointestinal tract or platelet.

The NSAIDs currently available effectively reduce pain and inflammation due to many different conditions and diseases, including the chronic arthritis seen in rheumatoid arthritis and osteoarthritis. This effect is by inhibition of the activity of COX, the enzyme that catalyzes the synthesis of cyclic endoperoxides from arachidonic acid to form proinflammatory and other forms of prostaglandins [5,6]. Prostaglandins, when synthesized at sites of inflammation, are clearly important in increasing local inflammation and enhancing pain sensation. Yet, in the gastric mucosa, prosta-glandins promote the generation of a protective barrier of mucous and bicarbonate, decrease the synthesis of gastric acid, stimulate glutathione production (which acts to scavenge superoxides), and promote adequate blood flow to meet the needs of the cells of the gastric mucosa [7–10]. All of these positive effects serve to protect the cells that comprise the gastric lining from the extreme conditions found within the gastric lumen. These include not only the normally highly acidic contents of the gastric lumen but also potential ingested toxins such as alcohol or NSAIDs. In the kidney, prostaglandins act to modulate intrarenal plasma flow and water and electrolyte balance [5,6]. Thus, there are both good and bad effects with the inhibition of prostaglandin synthesis.

Recently, 2 isoenzymes of COX were identified: COX-1 and COX-2 [9–17]. Although they are products of 2 different genes, there is 60% homology between the enzymes. There is 95% homology in the active site of the 2 peptides, which differ only in 1 of 25 amino acids within the binding site for arachidonate or NSAID. COX-1 acts predominantly as a constitutive enzyme in the gastric mucosa, producing prostaglandins that generate the protective barrier in the gastric lumen and probably those prostaglandins active in the renal parenchyma, particularly in the glomerulus. It is the only available isoform in platelets. Thromboxane is the important prostaglandin in promoting platelet aggregation; inhibition of its synthesis by decreasing COX-1 activity leads to a decreased ability to clot, a prolonged bleeding time, and an increased propensity to bleed. Inhibition of COX-1 activity is considered a major cause of the gastrointestinal toxic effects of NSAIDs, although COX-2 activity is upregulated when there is injury [13,18], perhaps associated with the attempt to repair.

COX-2 is present in most tissues constitutively in small amounts, particularly in the brain, ovulating ovum, vas deferens, bone near the periosteum, macula densa, and tubules of the kidney. It is highly inducible at sites of inflammation. Cytokines and growth factors have been demonstrated to increase COX-2 mRNA and thus more COX-2 protein,

Lee S. Simon, MD, Associate Professor of Medicine, Harvard Medical School, Assistant Chief of Medicine, Beth Israel Deaconess Medical Center, Boston, MA.

resulting in the generation of proinflammatory prostaglandins [19]. All of the currently available NSAIDs inhibit to a variable degree the synthesis of both COX-1 and COX-2 activity and are effective therapies as analgesic and anti-inflammatory drugs because they inhibit COX-2; however, at the same time they potentiate increased risk for toxicity due to their similar inhibition of COX-1.

Data show that there are degrees of COX-1 and COX-2 inhibition. Some investigators have tried to associate the potential for gastrointestinal toxic effects with the extent of COX-1 and COX-2 inhibition by any one of the various NSAIDs [20]. Unfortunately, all of the presently available NSAIDs affect these 2 enzymes to various degrees but probably not selectively enough to be clinically important. Thus, when an effective therapeutic blood level is achieved, both COX-1 and COX-2 are inhibited. For example, etodolac has been demonstrated to have small differential effects on each of the 2 enzymes that are dose-dependent. Glaser et al [13] demonstrated in experiments using human cells that low doses of etodolac, which yield low serum levels of the available NSAID, have little effect on COX-1 while inhibiting the activity of COX-2 by about 50%. Unfortunately, with such selective COX-2 drugs, when an anti-inflammatory dose of etodolac is prescribed and a serum level of 10 to 15 μm is achieved, then about 30% to 40% of COX-1 activity also will be inhibited. Similarly, meloxicam at 7.5 mg/day has only a 10% to 15% effect on COX-1, whereas 15 mg inhibits somewhere between 30% to 40% of the enzyme activity. This selectivity of COX-2 inhibition is observed when drugs are less than 100-fold selective based on in vivo experiments [21].

In contrast, drugs that are highly selective or specific, inhibiting only COX-2 at therapeutic doses without any effects on COX-1, are now available. These drugs are at least 200- to 300-fold more selective for COX-2 than COX-1. In in vivo and ex vivo experiments, they have been demonstrated to only affect COX-2 levels and to have no effect on COX-1 activity at effective serum drug levels. Celecoxib has been shown to decrease pain and inflammation in patients with osteoarthritis and rheumatoid arthritis with equal efficacy to ibuprofen 2400 mg/day, naproxen 1000 mg/day, or diclofenac 150 mg/day [22,23]. Rofecoxib has demonstrated efficacy comparable to ibuprofen 2400 mg/day or diclofenac 150 mg/day in osteoarthritis patients. These doses of celecoxib and rofecoxib translate to serum levels that range between 0.4 to 1 μm of drug. At this blood level, neither drug has been shown to specifically affect COX-1 while adequately inhibiting COX-2. At the same time, it has been shown that at efficacious therapeutic doses in vivo both rofecoxib and celecoxib have no discernible effect on the gastroduodenal mucosa by endoscopic examination or on platelet aggregation or bleeding time [18,22–27]. The platelet only has COX-1 activity leading to increased platelet aggregation; this observation further demonstrates that specific COX-2 inhibitors such as celecoxib and rofecoxib at therapeutic doses have no effect in vivo on COX-1 activity [22,27].

The COX-2 inhibitors are safer than traditional NSAIDs in terms of their effects on the gastrointestinal tract as determined by endoscopic evaluation, yet their efficacy is equal to that of traditional NSAIDs. These drugs are clearly specific inhibitors of COX-2 activity, as shown by in vitro effects against recombinant enzyme, cell membrane, and whole cell systems as well as in vivo experiments that demonstrate no effect on the platelet or endoscopically in the upper gastrointestinal tract at efficacious therapeutic doses. These drugs fulfill the need for therapeutics that have analgesic and anti-inflammatory activity equal to traditional NSAIDs without the risk for significant upper gastrointestinal mucosal damage. A meta-analysis of the randomized controlled trials [27] has demonstrated that rofecoxib not only decreases endoscopic damage but decreases potential complications of ulcers, such as bleeding. These data are limited in that they included studies of various lengths. Therefore, we continue to await results from pending trials that will demonstrate whether these drugs will be associated with fewer endoscopically identified upper gastrointestinal ulcers and will induce fewer complications of bleeding, perforation, and obstruction. Furthermore, once we know whether these drugs are not associated with gastrointestinal complications and do not inhibit the healing of a damaged gastrointestinal mucosa any differently than do NSAIDs, perhaps effective pharmacoeconomic evaluations can be pursued.

Unfortunately, at this juncture we do not have the same extensive database regarding COX-2–specific inhibitors and their effects on the cardiovascular and renal systems. We have learned that patients treated with celecoxib at any dose in the randomized clinical trials had no increased incidence of peripheral edema or hypertension greater than what would be expected with a traditional NSAID [23]. Similarly, rofecoxib at doses recommended to treat osteoarthritis had no increased incidence of hypertension or peripheral edema [18,24,26]. It is clear that patients at risk for an NSAID-induced kidney problem are at similar risk of developing the same problem with a COX-2–specific inhibitor. Thus, patients who are significantly salt-depleted (or significantly dehydrated) or who have clinically significant congestive heart failure, cirrhosis with or without ascites, or clinically significant chronic renal failure are at risk of developing either an NSAID-induced or COX-2 inhibitor–induced kidney toxic event. Until these high-risk patients are further studied, judicious use of these agents needs to be considered.

We also have little information about the use of the COX-2–specific inhibitors and the risk of thrombosis due to no effect of these drugs on platelets. As the randomized clinical trials were not designed to address this question, we await postmarketing

surveillance to help resolve this problem. Furthermore, we have no information demonstrating that traditional NSAIDs are safer or more useful than the COX-2–specific inhibitors in this regard. Only aspirin has been studied prospectively, and low-dose aspirin should be given concomitantly with either NSAIDs or specific COX-2 inhibitors in patients at risk for thrombosis. Given the additive ulcergenic potential associated with the use of multiple NSAIDs, it is advisable to use specific COX-2 inhibitors with aspirin when considering combination cardioprotective/anti-inflammatory therapies.

Clinical Implications

Given the accumulated efficacy and safety data, patients who are at high risk for developing NSAID-induced gastrointestinal mucosal damage and/or complications should clearly be treated with a COX-2–specific inhibitor unless there is a compelling past history of intolerance. These high-risk patients include those who have a past history of peptic ulcer disease, previous NSAID-induced injury, gastrointestinal bleeding of any cause, patients older than 65 years, patients who are planning to use high-dose NSAIDs or multiple NSAIDs, patients with severe comorbid illnesses such as clinically significant cardiovascular disease, patients who are planning to use concomitant glucocorticoids with their NSAID, older or frail patients planning to use concomitant warfarin, and patients who are determined to be sicker than others after analysis of a health assessment questionnaire [3,4,8–10]. COX-2 inhibitors cost approximately the same as co-therapy with misoprostol and traditional NSAIDs; as this form of therapy has been shown to be cost-effective in high-risk patients, use of COX-2 inhibitors should be considered equally logical. Given the cost of COX-2–specific inhibitors and measured in the context of the cumulative gastrointestinal risk associated with long-term NSAID use, these drugs should be considered only in those patients who are required to chronically use analgesic or anti-inflammatory agents. Until the aforementioned prospective bleeding and complication trials are completed and the data support the observations of the endoscopy trials, it is more difficult to advocate that all patients who require NSAID-type therapy be treated with COX-2–specific drugs. However, it is prudent to remember that in choice of therapy, the first rule is to do no harm.

Author address: 110 Francis St. 5A, Boston, MA 02215

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