Cyclooxygenase-2 inhibitors: introduction to a new class of drugs

CHERYLE GURK-TURNER, RPH

From the Department of Pharmacy Services, Baylor University Medical Center, Dallas, Texas.

Corresponding author: Cheryle Gurk-Turner, RPh, Department of Pharmacy Services, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246.

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) has progressively increased, due in part to their availability without a prescription. Gastrointestinal-related side effects of the NSAIDs have been implicated in approximately 7600 deaths and 76,000 hospitalizations annually in the USA alone (1). Such statistics have led to the pursuit of new agents to treat pain syndromes. Initially, agents that protected the gastric mucosa were employed. For example, misoprostol, a synthetic prostaglandin analog, was used, but side effects were seen when therapeutically effective dosages were given, so its clinical application was limited. Histamine antagonists also have been tested with varying degrees of success. An acceptable alternative to NSAIDs may be proton-pump inhibitors, but further study is needed with this class of drugs. The most promising development has been the cyclooxygenase (COX)-2 selective agents, but definitive reports in the literature are lacking (2, 3).

The Food and Drug Administration recently approved 2 agents from this new class of drugs known as the COX-2 inhibitors. The first, celecoxib (Celebrex, Searle Pharmaceuticals, Chicago, Ill), was approved for use in treating the symptoms of osteoarthritis and rheumatoid arthritis in adults. Rofecoxib (Vioxx, Merck & Co, West Point, Pa) was approved in May 1999 and is indicated for the treatment of osteoarthritis, rheumatoid arthritis, and primary dysmenorrhea. Prostaglandin synthesis and its biochemical properties will be reviewed to clarify the mechanism of action of this new class of drugs. Data collected during clinical trials of the 2 agents will also be presented to establish a better understanding of the future role of this class of drugs.

COX ACTIVITIES

After its release from membrane phospholipids, arachidonic acid is metabolized via 2 main pathways. One pathway, which is controlled by the enzyme lipoxygenase, produces lipoxin A1B, the leukotrienes, and hydroperoxyeicosatetraenoic acid. The other pathway is controlled by the enzyme prostaglandin endoperoxide synthetase, or fatty acid COX, and produces thromboxane A2 and the various prostaglandins (prostaglandin E2 [PGE], prostaglandin I [prostacyclin, PG1], prostaglandin D2, prostaglandin F2 [PGF]). The COX enzyme is thought to exist as 2 similar isoforms (COX-1, COX-2), each with distinct sites of action and roles in human physiology.
COX-1 is present in blood vessels, the stomach, the intestines, the kidneys, and platelets, where it exerts its effects. The resulting prostaglandins are primarily potent vasodilators in most vascular beds. In the gastrointestinal tract, the predominant effect of PGE and PGF is contraction of the muscles of the stomach and the colon. Gastric acid secretion is inhibited by PGE and PG1, while blood flow to the gastric mucosa is regulated by PG1 alone. In the kidney, renal blood flow and urine formation are positively regulated by prostaglandins. PG1 inhibits while thromboxane A2 induces platelet aggregation, offering the balance necessary for homeostasis. As a result, the COX-1 enzyme activity produces compounds responsible for a variety of protective functions within the human body.

In contrast, some researchers believe that COX-2 production is stimulated only in response to inflammation and is undetectable in most tissues under normal conditions. Cytokines, growth factors, and other serum factors can induce COX-2 formation in macrophages when needed to correct imbalances caused by pain and swelling, such as that seen with arthritic pain (4).

COXACTIVITY AND NSAID TOXICITIES

NSAIDs are thought to be nonselective inhibitors of both isoforms of the COX enzyme. It is further postulated that the negative effects patients experience while on NSAID therapy (ulceration, renal toxicity) are explained in part by inhibition of COX-1, while the benefits are due to COX-2 properties. Gastrointestinal ulceration cannot be explained by the inhibition of COX-1 alone, and another component of this effect is thought to be related to direct gastric epithelial contact with the offending agent (4, 5).

Interestingly, research is being conducted on the function of COX-2 in the human kidney. Komhoff et al designed a study to identify the sites of COX-1 and COX-2 activity in adult and fetal human kidney cells (6). They found that COX-2 might contribute to the regulation of glomerular hemodynamics through production of thromboxane A2, a finding which sheds doubt on an agent with COX-2 selectivity being truly renal sparing. Indeed, flosulide, an agent with high selectivity for COX-2, has been withdrawn from clinical development due to renal toxicities seen during preliminary studies.

SELECTIVITY ISSUES

As agents with COX-2 selectivity were being designed and trials in animal models were conducted, it became apparent that quantification of selectivity would be necessary. Structural models have been developed to describe selectivity in terms of structure-activity concepts. Attempts have been made to correlate the side effect profiles of the different NSAIDs in use to the selectivity patterns displayed by the various tests currently available. Conflicting results are seen depending on the assay used and conditions at the time of testing; therefore, no concrete conclusions have been made to explain why such differences exist. Nor can it be definitively stated that an agent with COX-2 selectivity would be absolutely devoid of the untoward effects seen with the NSAID class of drugs. Despite these controversies and speculations, the COX-2 inhibitors have been launched into the marketplace. The Food and Drug Administration did mandate that labeling for both products contain a warning concerning the risks of gastrointestinal ulceration, bleeding, and perforation (7, 8).
CLINICAL TRIALS

Relatively few completed clinical trials and no comparative trials of the COX-2 agents have been published. Further, no large clinical trials of rofecoxib have been published. Most data available are in abstract form and, as such, will not be cited here.

A safety and efficacy trial conducted on SC-58635, celecoxib, was conducted by Searle Pharmaceuticals (2). This was a randomized, double-blind dosing study conducted by enrolling healthy subjects with osteoarthritis or rheumatoid arthritis. Patients with symptom flare, as defined by the inclusion criteria, were given either a 2-week course (osteoarthritis arm) or a 4-week course (rheumatoid arthritis arm) of the study drug (at doses of 40 mg twice daily, 100 mg twice daily, or 200 mg twice daily) or placebo.

The study also compared the mucosal effects of the study drug (100 mg twice daily or 200 mg twice daily) vs naproxen (500 mg twice daily) and placebo. Patients received 1 week of therapy, and all medications were given with food. Gastrointestinal endoscopy was used to enroll subjects and to assess lesion development after treatment for each group.

Platelet effects were investigated in this study as well. This was a 14-day, 2-period, open-label study design. Healthy men were enrolled and received the study drug (400 mg twice daily) for 5 consecutive days. They then received a single dose on the morning of the sixth day, when blood was drawn. After a 7-day washout period, all patients were given a single dose of aspirin (650 mg), which was expected to inhibit the COX-1–mediated platelet effects. Platelet aggregation studies were performed before and after the aspirin dose was given.

The results were difficult to analyze as only demographic data were cited. Statistical significance was reported in the osteoarthritis arm results section; however, it is unclear how this would correlate to a true clinical significance. Patient visual analog scale differences were statistically significant ($P \leq 0.048$ by analysis of covariance) but did not explain how a perceived pain of 30% vs 40% (on a 100% scale) would be different clinically.

Similar findings were reported for the rheumatoid arthritis arm, and again correlation to a clinical benefit was lacking. The American College of Rheumatology criteria were used as a data collection tool for patients receiving the higher dosage regimens, and statistical significance was seen. Validity could be questioned, however, since confidence intervals were not given with the data results. In fact, the authors of the study concluded that the results did not display a clear dose-response relation.

Results from the gastrointestinal ulceration portion of the study showed that only patients who received naproxen subsequently developed ulcers. The authors of the study state that “the results do not necessarily correlate with clinical events such as bleeding, perforation, or obstruction.” Results from the platelet aggregation studies only suggested the lack of a relation between celecoxib and COX-1 and failed to definitively prove this as well.

CONCLUSIONS

Due to the lack of published clinical trials with convincing statistical results, it would be difficult to recommend the use of this new class of drugs. It is possible that these agents will
be an alternative treatment for patients who fail conventional therapies. Given the information available thus far, it does not seem likely that the quest for agents to treat pain that are devoid of gastrointestinal or renal side effects will be resolved with this class of drugs, as initially anticipated. As with any new class of drugs, the daily cost of therapy is quite high, forcing one to ask whether the benefit is worth the added cost. Until further studies are published that can provide the data needed on side effects, toxicity, and drug interactions, as well as the true role of COX-1 and COX-2, the routine use of these drugs should be avoided.

References


