Specific cyclooxygenase-2 (COX-2) inhibitors

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are currently among the most widely prescribed drugs worldwide. Their therapeutic benefits and their side effects in the gastrointestinal tract and kidney, as well as in hemostasis, are of great importance in modern medicine. Within the past decade, new insights into how NSAIDs produce both their therapeutic benefits and their serious side effects have been discovered. It is now known that there are two forms of the cyclooxygenase (COX) enzyme that metabolize arachidonic acid into prostaglandins. Drugs that specifically inhibit the COX-2 enzyme were formulated and put into clinical trials during the past 5 years. These drugs are now available to treat patients in the United States. Specific COX-2 inhibitors offer the benefit of being able to treat the pain and inflammation of arthritis with potentially little risk of serious gastrointestinal injury.

(Key words: Nonsteroidal anti-inflammatory drugs [NSAIDs], osteoarthritis, rheumatoid arthritis)

It has been about 100 years since aspirin was discovered as an effective treatment for the pain and inflammation associated with arthritis. Only in 1971, however, did Vane and others¹ discover the principal mechanism of action of aspirin and related nonsteroidal anti-inflamma-

tory drugs (NSAIDs). Vane showed that NSAIDs are anti-inflammatory because they inhibit the cyclooxygenase (COX) enzyme. NSAIDs are currently among the most widely prescribed drugs worldwide. Their therapeutic benefits and their side effects in the gastrointestinal (GI) tract and kidney, as well as in hemostasis, are of great importance in modern medicine.

On any given day it is estimated that 70 million people throughout the world take prescribed NSAIDs, and when over-the-counter drugs are included, the total number of individuals being treated is more than 300 million. The impact of NSAIDs on health and society is tremendous. The side effects of NSAIDs are also of growing concern because of the number of people taking these drugs for prolonged periods. The most common and serious side effect of NSAIDs is GI toxicity, characterized by gastric erosions and ulcerations. In persons who use NSAIDs on a long-term basis, GI hemorrhage and perforation can develop, which may result in death.

COX and prostaglandin production

Prostaglandins appear transiently in the body but are important both in normal physiology and in some pathologic conditions. Prostaglandins maintain normal gastric mucosa and influence kidney function. Thromboxane A₂, which is formed from prostaglandins, helps to promote platelet aggregation. Prostaglandin E₂ (PGE₂) is detected in inflammatory conditions and is a crucial mediator for the pain and swelling associated with acute and chronic inflammation. Phospholipase A₂ initiates prostaglandin production by releasing arachidonic acid, which is a substrate for COX. Ultimately, this action results in an increased synthesis of prostaglandin and thromboxane (Figure 1). NSAIDs act primarily by inhibiting COX, thereby blocking the formation of prostaglandins in both normal and inflamed tissues.

Until recently, all prostaglandin synthesis was thought to result from only one form of the COX enzyme. The discovery of two isoforms of COX has provided insight into how NSAIDs produce therapeutic benefits on one hand but can cause serious side effects on the other. During the middle 1980s, it was noted that the amount of COX enzyme was substantially increased in inflamed tissues. Fu and associates² reported in 1990 that bacterial endotoxin induced human blood monocytes to substantially increase the activity of COX without affecting the activities of phospholipase. In addition, steroids were shown to completely block the expression of COX in an in vitro model.³ Of interest is that the steroids had no effect on baseline prostaglandin production but did eliminate the enhanced prostaglandin production and COX expression that were stimulated by endotoxins.

These studies, as well as others, seemed to indicate that the COX enzyme was "inducible" and could be upregulated by inflammatory stimulants such as cytokines. This finding led to the hypothesis that a second form of the COX enzyme had been present and was inducible. This hypothesis was confirmed in 1991, when the COX-2 gene was iden-

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tified.⁴ COX-1 is located on human chromosome 9, whereas COX-2 is found on human chromosome 1.

Comparison of COX-1 and COX-2

We now know that COX-1 is constitutive and may be responsible for “housekeeping” functions throughout the body. COX-2 is inducible in many body compartments, particularly at sites of inflammation. COX-2 represents a therapeutic target for anti-inflammatory actions, although the enzyme may be found routinely in organs such as the brain and kidneys. Because different genes encode the two different COX enzyme isoforms, the hypothesis has been formulated that the anti-inflammatory effects of NSAIDs are related to their capacity to inhibit COX-2, but their antithrombotic and ulcerogenic effects are due to their capacity to inhibit COX-1.⁵ If one could design a specific COX-2 inhibitor, it would have all the traditional benefits of NSAIDs, with few other side effects (*Figure 2*). These theories have led to the discovery and development of specific COX-2 inhibitors, celecoxib (Celebrex) and rofecoxib (Vioxx), which were approved by the Food and Drug Administration for clinical use in the United States beginning in 1999.^{6,7}

COX-activated inflammation stimulates an increase in the expression of COX-2. Tissue destruction may also increase COX-2. Bacteria products such as endotoxin increase COX-2 expression as part of an overall stimulation of the immune inflammatory processes caused by infectious agents.⁷ Lymphocytes and macrophages, which migrate to inflamed tissues, may produce cytokines such as interleukin-1 and tumor necrosis factor- α , which may also increase COX-2. Corticosteroids and other cytokines that decrease inflammation have been shown to suppress the expression of COX-2.

Studies indicate that COX-1 is found in virtually all tissues under baseline conditions. COX-1 is present in gastric mucosa, platelets, blood vessels, endothelial cells, and renal collecting ducts. COX-2 expression is more limited, but the enzyme certainly is present in the brain

Figure 1. Mechanism of prostaglandin production.

and certain regions of the kidney. COX-2 is present in the amygdala-hippocampus complex,⁸ the portion of the brain that is important for memory. Renal cortical cells that express COX-2 include the macula densa and the adjacent portions of renal tubules, structures important for regulation of salt and water balance.⁹

COX-1 and COX-2 are remarkably similar except for about 25% of their structures. Both COX-1 and COX-2 are membrane proteins that reside within an inner leaflet of the lipid bilayer of intracellular phospholipid membranes. They have several enzymatic functions; one is a COX activity that converts arachidonic acid to prostaglandin G₂ (PGG₂), and another is a peroxidase activity that converts PGG₂ to prostaglandin H₂ (PGH₂). After the structures of the enzymes were clarified, it became possible to design compounds that would specifically inhibit COX-2. Inhibition of both COX isoforms by NSAIDs is due to the fact that these drugs occupy a COX-active site in a way that prevents access of arachidonic acid.⁵ A compound that would specifically inhibit COX-2 would block inflammation, pain, and fever but would be associated with a remarkable reduction in the side effects related to the inhibition of COX-1.

Specific COX-2 inhibitors versus traditional NSAIDs

The tests that are used to assess a drug's COX selectivity are controversial. Dif-

ferent in vitro assays have been used to evaluate COX-1 and COX-2 activity. As yet, however, there is no standardization in the types of assays to be used. Because several different in vitro assay systems are being used, different drugs may vary in terms of their COX-2 specificity from laboratory to laboratory. None of the traditional NSAIDs that were available in the United States before 1999 were highly specific in their ability to block COX-2.

In the upper GI tract, prostaglandins are responsible for protecting against mucosal injury. Virtually all the COX activity in the upper GI tract has been found to be COX-1 activity, and this fact would explain the GI toxicity associated with the use of traditional NSAIDs. Studies have demonstrated gastric mucosal damage in up to 40% of arthritis patients treated with long-term NSAID therapy.¹⁰ Gastric erosions are present in 10% to 30% of all patients taking NSAIDs. The incidence of serious complications increases with age, particularly after the age of 65 years. Other risk factors for GI toxicity include previous peptic ulcers, concomitant use of glucocorticoids, and the presence of other comorbid conditions such as cardiovascular disease. COX-1 is expressed in the gastric mucosa,¹¹ so one would predict that inhibitors specific to COX-2 would have much less GI toxicity with no decrease in efficacy. NSAIDs, in contrast, disrupt the GI mucosal barrier by lowering the rate of mucous secretion, altering the release of surface-active phospholipids, and depressing bicarbonate secretion. NSAIDs also decrease epithelial blood flow in the GI tract.

Platelets, which are essential for blood clotting, contain COX-1 but not COX-2. Thromboxane A₂, which is a product of COX-1 activity, is a central component in clotting. Platelets cannot regenerate enzymes, so once platelet COX-1 has been irreversibly inhibited by aspirin, a platelet cannot synthesize thromboxane A₂ for the rest of its life in the circulation. Decreasing thromboxane A₂ production in platelets by low doses of aspirin is standard medical care now used to lower the risk of heart attacks and strokes.

Specific COX-2 inhibitors do not affect platelet aggregation and therefore do not affect bleeding time.¹² Theoretically, specific COX-2 inhibitors would be safe to use in persons with active bleeding or coagulation disorders, or in patients taking warfarin.

Aspirin and other nonspecific COX inhibitors impair kidney function in persons exhibiting sodium depletion, hypertension, or heart failure. Both forms of COX are expressed in the kidney, but in different places. COX-1 is present in the collecting ducts and vasculature, and to a lesser degree in interstitial cells of the renal papillae. COX-2 is present in glomerular podocytes and interlobular arteries, arterioles, and veins. The renal effects of specific COX-2 inhibitors may be less significant than the renal effects seen with dual inhibitors because of the widespread expression of COX-1 in renal tissue.

The efficacy of specific COX-2 inhibitors should be equal to that of previous nonspecific NSAIDs, because the nonspecific drugs' efficacy is from inhibiting COX-2. In essence, all past and current NSAIDs are COX-2 inhibitors for treatment of arthritis and other pain conditions; they also inhibit COX-1, leading to their side effects. In fact, clinical trials of specific COX-2 inhibitors thus far have documented that their anti-inflammatory and analgesic properties are similar to currently marketed NSAIDs.^{13,14} The currently available NSAIDs have a narrow safety margin. More effective inhibition of prostaglandins could occur if one were able to raise the dose of a specific COX-2 inhibitor, as that drug would be less likely to cause side effects. Specific COX-2 inhibitors appear to be as active as NSAIDs in the treatment of osteoarthritis, rheumatoid arthritis, postsurgical dental pain. In supratherapeutic doses, however, specific COX-2 inhibitors seem to have no effect on platelet function or gastric mucosa.

The colon

Several clinical studies^{15,16} in the literature note that inhibition of COX with long-term ingestion of aspirin may be

Figure 2. Theories for the mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs).

associated with a lower incidence of colorectal malignancy. Other studies¹⁷ have shown a 50% reduction in risk for colorectal cancer in patients who continually ingest NSAIDs for more than 2 years. Because there appears to be abundant evidence that COX-2 is somehow involved in the pathogenesis of colorectal neoplasia, blocking this enzyme might have an important role in the prevention and treatment of colon cancer.

The use of nonspecific COX inhibitors such as aspirin or sulindac, while reducing colon polyps and perhaps cancer risk, causes NSAID-induced injury to the upper GI tract, thus limiting their long-term utility. Specific COX-2 inhibitors would have potential application in the prevention of colorectal adenomas and adenocarcinomas of the colon, because they could be

used on a long-term basis without injury to the upper GI tract. A recent intriguing finding is that COX-2 is overexpressed by colonic adenocarcinoma cells, raising the possibility that this enzyme may be involved in the pathogenesis of colon cancer. In mice that are genetically bred to have colon polyps, a marked reduction in polyps was seen when they were treated with a specific COX-2 inhibitor.

The brain

Recently, Sairanen and coworkers¹⁸ characterized the expression of COX-2 in human brains in response to local infarction: prostanoids produce the dilation of cerebral arteries, inflammatory cytokines may cause a rapid induction of COX-2, and COX inhibitors reduce experimental brain edema. This sequence could explain

the rapid appearance of COX products, such as prostaglandins and thromboxane, in cerebral edema. Prostanoids and free radicals aggravate tissue injury during cerebral edema, so inhibitors specific to COX-2 could reduce brain damage after either global or focal brain ischemia.

Alzheimer's disease

Alzheimer's disease is a leading cause of dementia in our aging population. It affects between 5% and 11% of people older than 65 years and as many as 45% of those older than 85 years. It has an incidence of about 4 million cases at a cost in excess of \$100 billion. Patients with Alzheimer's disease initially experience memory impairment, and the disease is often characterized by progressive cognitive decline in a period of 5 to 10 years. As previously stated, COX-2 is present in the amygdala-hippocampus complex, which is important for memory. Pathologic findings noted in patients with Alzheimer's disease include cortical atrophy, regional loss of neurons and synapses, neural fibrillary tangles, neuritic plaques, and amyloid deposits in blood vessels.

NSAIDs appear to be beneficial in Alzheimer's disease.^{19,20} The incidence of Alzheimer's disease in persons with rheumatoid arthritis is 6 to 12 times lower than expected. Patients with Alzheimer's disease who are treated with indomethacin show a reduced progression of disease. In families at high risk for Alzheimer's disease, sustained NSAID use is strongly associated with a lowered risk of the disease. A longitudinal study²⁰ indicates that prior NSAID use may reduce the risk of Alzheimer's disease by as much as 60%. Neuronal COX-2 expression is elevated in the brains of persons with Alzheimer's disease. If the hypothesis that COX-2 plays an important role in neural degeneration in Alzheimer's disease is correct, specific COX-2 inhibition could be used to slow the progression of Alzheimer's disease.

Further questions to be answered include the following:

What is the most effective dose of a specific COX-2 inhibitor in the prevention of Alzheimer's disease?

What should be the duration of therapy?

At what age should one begin therapy to maximize the benefits?^{19,20}

Comment

New, highly specific COX-2 inhibitors are now available. The advent of these drugs heralds a new era in the treatment of arthritic conditions. Further research may broaden the use of these drugs to include the prevention of colon cancer and Alzheimer's disease. In essence, then, what do we want? As physicians, we would like to have drugs that are at least as effective as current NSAIDs, we would like the specific COX-2 inhibitors to have fewer side effects than currently marketed NSAIDs. Long-term human data will ultimately determine the safety of specific COX-2 inhibition. Animal data have suggested that nephropathy, colitis, and altered CNS function may result from COX-2 inhibition.²¹ We would like specific COX-2 inhibitors to be affordable so they can benefit the maximum possible number of patients. New specific COX-2 inhibitors may soon replace traditional NSAIDs for the treatment of pain and acute inflammation in patients who are at risk for GI injury and bleeding. These drugs may gain wider use in other clinical settings as clinical experience in their use grows.

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