Cyclooxygenase-2: From Arthritis Treatment to New Indications for the Prevention and Treatment of Cancer

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Arthritic conditions most likely have existed as long as human beings have walked the earth, but the first recorded history of treating inflammatory rheumatic diseases was discovered on ancient stone tablets from the Sumerian period. The tablets describe the use of willow leaves to treat these painful conditions. The Egyptians also understood the analgesic properties of the willow leaves and the decoction of myrtle for the relief of joint and uterine pains (Jack, 1997; Pepper, 2000). The history of humankind’s endeavors to treat painful joint and musculoskeletal conditions has progressed from the 18th through the 21st centuries with the development of acetylsalicylic acid (i.e., aspirin), corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs), ultimately leading to the discovery of a new class of agents known as the cyclooxygenase-(COX-) 2 inhibitors.

The Inflammatory Process

Understanding the mechanism of action of NSAIDs and COX-2 inhibitors begins with knowledge of the inflammatory process. Inflammation is the body’s response to tissue injury and is a complex process initiated by a variety of foreign insults. This process causes vasodilation and increased vascular permeability, permitting fluid, protein, and cells to migrate to the affected site to facilitate tissue repair and healing (Carpenter, 2001; Fung & Kirschenbaum, 1999).

Inflammatory mediators are released from infiltrating cells during an inflammatory response. These mediators, the prostanooids, are preformed and exist in cytoplasmic granules; some are formed from the metabolism of membrane phospholipids, such as prostaglandins (PGs) and leukotrienes (Carpenter, 2001). PGs are short-lived local hormones that mediate inflammation and have a key role in tissue homeostasis and function. PGE2, a potent vasodilator, is primarily responsible for erythema, edema, and pain caused by inflammation (Carpenter). Leukotrienes also are powerful mediators and cause bronchoconstriction, leukocyte adhesion to vessel walls, vasodilation, and edema (Simon, 1999).

Arachidonic acid (AA) is stored in the cellular membrane of all cells and is central to the generation of PGs and leukotrienes. AA is released from cellular membranes by phospholipase enzymes and, once released, is oxidized directly or converted by two distinct pathways—the COX pathway and the lipoxygenase pathway—to form PGs or leukotrienes (Halverson, 1999).

The discovery of the isoenzymes cyclooxygenase-(COX-) 1 and COX-2 led to the development of newer nonsteroidal anti-inflammatory drugs (NSAIDs) designed to block COX-2, such as rofecoxib, celecoxib, and valdecoxib. Because of the specificity of COX-2 expression, COX-2 inhibitors have the potential to reduce the risk of gastrointestinal bleeding experienced with the use of classic NSAIDs. With their crucial role in the control of inflammation, the COX-2 agents originally were marketed for the treatment of rheumatoid and osteoarthritis. However, promising new indications for COX-2 agents in the prevention and treatment of cancer are under investigation. The role of aberrant COX-2 expression in the development of cancer has been studied most widely in patients with colon cancer and adenomas. Recent studies suggest that COX-2-derived prostaglandins may play an important role in tumor viability, growth, and control of metastasis. Possible new indications for the use of COX-2 inhibitors to prevent and treat cancers may be monumental. However, therapy with these agents is not without risk. Oncology nurses must be aware of the potential problems inherent in the use of COX-2 as well as COX-2 agents for chemoprevention in certain cancers.

Key Words: chemoprevention; cyclooxygenase inhibitors; anti-inflammatory agents, non-steroidal

Submitted April 2002. Accepted for publication June 18, 2002. (Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Clinical Journal of Oncology Nursing or the Oncology Nursing Society.)

Digital Object Identifier: 10.1188/03.CJON.21-29
Cyclooxygenase Inhibition

In the early 1970s, Sir John Vane proposed that the beneficial and harmful effects of NSAIDs resulted from the blockade of COX (Emery, 2001). In the 1980s and 1990s, two separate COX isoforms, COX-1 and COX-2, were found to initiate the metabolism of AA to PG (Emery; Lipsky, 2001). COX-1 is expressed constitutively (i.e., a constituent of normal cells) in most tissues and governs the production of AA metabolites, which are necessary for the maintenance of the protective and homeostatic functions listed in Table 1. COX-1 regulates these homeostatic functions by maintaining prostanooids PGI₂ and thromboxane A₂ synthesis in the stomach, kidneys, endothelial cells, platelets, and the brain. For example, COX-1 catalyzes the synthesis of PGE₂ and PGI₁ in the stomach to maintain the integrity of the gastroduodenal mucosa. Additionally, COX-1 preserves normal renal function in compromised kidneys, especially during circulatory collapse (Kulkarni, Jain, & Singh, 2000).

In contrast, COX-2 is usually absent or present in low concentrations in normal cells but induced in response to inflammatory mediators, such as growth factors, bacterial endotoxins, and tumor promoters (Lipsky, 2001; Pepper, 2000). COX-2 expression can increase from 10- to 80-fold at the site of inflammation within one to three hours and can be detected in high concentration in macrophages, monocytes, synovial cells, leukocytes, and fibroblasts (Fung & Kirschbaum, 1999). The key to NSAIDs and COX-2 agents is their ability to exert their anti-inflammatory effect by inhibition of COX; this mechanism is the cause of their toxicity, as well as their therapeutic effect.

Selective Cyclooxygenase-2 Inhibitors

Theoretically, agents that inhibit COX-2 selectively would retain the potent anti-inflammatory and analgesic effects of classic NSAIDs without affecting COX-1 and its important physiologic functions and avoid NSAID-associated toxicities (Fung & Kirschbaum, 1999; Goldenberg, 1999). The COX inhibitors may be classified into four groups based on their selectivity for COX-1 and COX-2 (see Table 2). The first of these COX-2 inhibitors, celecoxib (Celebrex®, Pfizer Inc., New York, NY), was introduced in 1999 and became the most successful drug launched in history (Rubins & Rubins, 2002). Shortly after, the second COX-2 selective inhibitor, rofecoxib (Vioxx®, Merck & Co., Inc., West Point, PA) was released. By October 2000, celecoxib and rofecoxib sales exceeded $3 million in the United States, and the prescription volume surpassed 100 million in 2001 (Mukherjee, Nissen, & Topol, 2001). In November 2001, a third COX-2 inhibitor, valdecoxib (Bextra®, Pharmacia, Kalamazoo, MI) was approved by the U.S. Food and Drug Administration (FDA) (Goldman & Schutzer, 2002).

As many as six additional COX-2 selective inhibitors are in the research and development phase (IMS Health, 2002). Positioned to lead the next generation of COX-2 selective inhibitors are etoricoxib and parecoxib, which are being studied in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, and chronic low back pain (Brater, Harris, Redfern, & Gertz, 2001; Harper et al., 2001). Parecoxib is the first injectable form of a COX-2 inhibitor and currently is in phase III clinical trials. Initial results using parecoxib following hip replacement surgery found that patients required 39% less morphine for postoperative pain control (Doctor’s Guide, 2002). Presently, selective COX-2 inhibitors have FDA approval for the treatment of rheumatoid and osteoarthritis, acute pain, and primary dysmenorrhea. Only celecoxib has FDA approval for the reduction in the number of adenomatous polyps in patients with familial adenomatous polyposis (Gupta & Crofford, 2001) (see Table 3).

Cyclooxygenase-2 Agents and Patients With Cancer

Colorectal cancer has become the most commonly occurring gastrointestinal (GI) malignancy in the western world (Bus, Verspaget, Lamers, & Griffioen, 2000). Adenocarcinomas usually follow a progression from normal epithelium through an inflammatory, metaplastic, or other stage, ultimately leading in dysplasia and invasive cancer; this pattern is typical of colorectal cancer (Lynch, 2001). Cancer chemoprevention attempts to inhibit or reverse the tumorigenic process through pharmacologic interventions given before...
cancer occurs (Hawk, Lubet, & Limburg, 1999).

Epidemiology studies have shown a 40%–50% reduction in the incidence of colorectal cancer in patients who were taking NSAIDs (Dannenberg & Zakim, 1999; Dempke, Rie, Grothey, & Schmoll, 2001; Howe, Subbar- maiah, Brown, & Dannenberg, 2001). For more than 20 years, researchers have known that high concentrations of PGs exist in hu-
man and animal tumor tissues (Taketo, 1998a). The COX-2 protein is upregulated during colorectal carcinogenesis, and inhibition of this enzyme results in a therapeutic effect (Bus et al., 2000). COX-2 inhibitor agents are believed to have anti-inflammatory effects because of their ability to inhibit COX activity. Although some researchers have hypothesized that the antitumor effect results from a change in the metabolism of AA, the specific mechanism of action that causes its anticancer effect is unknown (Dempke et al.). Other researchers studying effects on animals believed that overexpression of COX-2 results in resistance to apoptosis (i.e., programmed cell death) and various changes that could lead to interference of cell growth and normal cell death (Oviedo & Wolfe, 2001). Dannenberg and Zakim theorized that overexpression of COX-2 promotes the production of angiogenic factors. Invasive tumors rely on their ability to digest biological membranes and reduce intercellular adhesion; COX-2 inhibitors also may have a role in reversing this process (Giercksky, 2001).

NSAIDs have caused regression of preexis-
ting adenomas in patients with familial adenomatous polyposis (Oviedo & Wolfe, 2001). Sulindac (Clinoril®, Merck & Co., Inc.), an NSAID, first was noted to induce regression of colorectal adenomas in patients with familial adenomatous polyposis in 1983 (Lynch, 2001; Taketo, 1998b). In fact, Steinbach et al. (2000) reported a 28% reduction in the mean number of colorectal polyps and a 30.7% reduction in polyp diameter in patients with familial adenomatous polyposis treated with celecoxib. Patients (N = 77) were randomized to placebo or treatment with celecoxib 100 or 400 mg twice daily for a period of six months. The significant regression of polyps was seen only in the patient cohort receiving 400 mg twice daily (twice the antiarthritic dose) (Steinbach et al.).

Although aberrant COX-2 expression first was described in patients with colorectal carcino-
mas and adenomas, a relationship has been found in those with lung and breast can-
cers as well (Sjodahl, 2001; Yao, Rioux, Castonguay, & You, 2000). Researchers have been studying chemoprevention in breast cancer, which led to the approval of tamoxifen for risk reduction in women at high risk of breast cancer (Brown & Lippman, 2000). COX-2 overexpression has been discovered in murine mammary gland tissue and is sufficient to cause tumor formation (Howe et al., 2001). Elevated COX-2 expression is seen more commonly in patients with breast cancer who have poor prognostic characteristics (Ristimaki et al., 2002). Half et al. (2002) also recently reported overexpression of COX-2 in invasive human breast cancers, suggesting that inhibitor agents are potentially useful in this patient population (Ristimaki et al.).

Retrospective studies examining the con-
nection between breast cancer incidence and NSAID use have been conflicting; several studies reported no significant relationship between aspirin use and the risk of developing breast cancer (Paganini-Hill, Chao, Ross, & Henderson, 1989). However, other reports have revealed a positive association between NSAID use and a decreased breast cancer risk. Friedman and Ury (1980) compared 4,867 women taking indomethacin to age-matched controls and found that women on indomethacin had a reduced risk of breast cancer. Twelve of the women in the indomethacin group developed breast cancer rather than the statistically expected 26.4 (p < 0.01). Although the researchers recommended more detailed studies to determine whether a direct causal relationship existed, the results were intriguing (Friedman & Ury).

In 1996, another group of researchers compared NSAID use in 511 women with

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**Table 1. Comparison of Cyclooxygenase-1 and Cyclooxygenase-2 Inhibitors**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Function</th>
<th>Location</th>
<th>Regulation</th>
<th>Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX-1</td>
<td>Maintains homeostasis,</td>
<td>Normal tissues: stomach, kidneys,</td>
<td>Constitutive (present in all tissues)</td>
<td>Aspirin and NSAIDs</td>
</tr>
<tr>
<td></td>
<td>&quot;housekeeping&quot; role</td>
<td>platelets, and the brain inflammatory sites: macrophages, synoviocytes, and fibroblasts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX-2</td>
<td>Inflammatory response</td>
<td></td>
<td>Inducible (rapidly induced at sites of inflammation): cytokines, growth factors, endotoxins, and tumor promoters</td>
<td>Aspirin, NSAIDs, and COX-2 inhibitors</td>
</tr>
</tbody>
</table>

**Note.** Based on information from Fung & Kirschenbaum, 1999; Pepper, 2000.

COX — cyclooxygenase; NSAID — nonsteroidal anti-inflammatory drug

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**Table 2. Classification of Cyclooxygenase-2 Inhibitors**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective COX-1 inhibitors</td>
<td>Low-dose aspirin</td>
</tr>
<tr>
<td>Nonselective COX inhibitors</td>
<td>Most available NSAIDs, including naproxen, ibuprofen, and diclofenac</td>
</tr>
<tr>
<td></td>
<td>Magnesium salicylate (various)</td>
</tr>
<tr>
<td></td>
<td>Meloxicam (Mobic®, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT)</td>
</tr>
<tr>
<td>Highly selective COX-2 inhibitors</td>
<td>Celecoxib (Celebrex®, Pfizer Inc., New York, NY)</td>
</tr>
<tr>
<td></td>
<td>Rofecoxib (Vioxx®, Merck &amp; Co., Inc., West Point, PA)</td>
</tr>
<tr>
<td></td>
<td>Valdecoxib (Bextra®, Pharmacal, Kalamazoo, MI)</td>
</tr>
<tr>
<td></td>
<td>Parecoxib (pending FDA approval)</td>
</tr>
<tr>
<td></td>
<td>Etoricoxib (pending FDA approval)</td>
</tr>
</tbody>
</table>

**Note.** Based on information from Fung & Kirschenbaum, 1999; Kulkarni et al., 2000.

COX — cyclooxygenase; FDA — U.S. Food and Drug Administration; NSAID — nonsteroidal anti-inflammatory drug
newly diagnosed breast cancer to 1,534 control subjects. The relative risk of breast cancer was reduced to 66% in those women using NSAIDs at least three times a week over a period of one year (Harris, Namboodiri, & Farrar, 1996).

Interestingly, COX-2 is overexpressed in HER2-neu–positive breast cancers; these agents may be useful in the treatment of patients who are HER2 positive (Howe et al., 2001). Levels of HER2-neu expression also reportedly have increased in patients with late-stage colorectal cancer; therefore, targeting both COX-2 and HER2-neu may lead to improved response in these patients (Mann et al., 2001). Additional evidence has shown that COX-2–derived PG also may augment aromatase activity; as a result, combining COX-2 inhibitor agents with an aromatase inhibitor may be beneficial for patients with breast cancer (Howe et al.). These conclusions are intriguing and point to the need for further research and study in this area, not only with breast and colon cancers, but other cancers as well.

Currently, a large number of ongoing clinical trials are examining the role of COX-2 inhibitors and patients with cancer. Treatment trials for patients with breast and prostate cancers are active, as well as further study of prophylaxis for and treatment of colorectal cancer (Giercksky, 2001; Moyad, 2001b). Additionally, researchers are evaluating the role of COX-2 agents, NSAIDs, and aspirin in bladder cancer prevention (Castelao, Yuan, Gago-Dominguez, Yu, & Ross, 2000; Moyad, 2001a). Experimental evidence indicates that COX-2 is overexpressed in patients with Barrett’s esophagus (i.e., abnormal precancerous cellular changes that may develop in people with gastroesophageal reflux disease or esophagitis), esophageal adenocarcinoma, squamous cell carcinoma, and gastric cancer (Krishnan & Brenner, 2001). A recent animal study concluded that COX-2 inhibitors can inhibit inflammation, COX-2 activity, and development of adenocarcinoma induced by reflux (Buttar et al., 2002). COX-2 inhibitors, therefore, may have a role in chemoprevention in many epithelial malignancies (Krishnan & Brenner).

Patients with premalignant lesions with possible inflammatory pathogenesis are targeted as potential responders (Giercksky, 2001). Because COX-2 agents may work in tandem with conventional chemotherapy agents (e.g., paclitaxel), oncology nurses will continue to be involved in future research of these possible combination therapies. Considerations for utilizing COX-2 agents include their major side effects, including GI and renal toxicity (Bus et al., 2000).

Future directions for COX-2 inhibitors include the use of celecoxib for the prevention of skin cancer. Nonmelanoma skin cancers in the United States are increasing, and the use of potentially nontoxic agents for chemoprevention are of great interest (New York-Presbyterian, 2002). A recent study in hairless mice assessed the preventive effect of celecoxib in ultraviolet-induced skin cancer. Seventy-five mice were randomized into the control group or the low-dose (i.e., 200 mg of celecoxib twice daily at a human dose equivalent) or high-dose (i.e., 400 mg twice daily at a human dose equivalent) group. The mice received 1 J/kg daily total irradiation to induce skin cancer. Results indicated that both low doses and high doses of celecoxib significantly lengthened the tumor latency period (p < 0.03 and p < 0.003). The researchers concluded that celecoxib is an effective and safe chemopreventive agent in ultraviolet-induced carcinogenesis (Orense et al., 2002). Human trials currently are under way in a planned phase II/III study of celecoxib for the prevention of actinic keratoses, a precancerous condition, and in the prevention of basal cell carcinomas (National Cancer Institute, 2001; New York-Presbyterian).

### Treatment Considerations

#### Gastrointestinal Effects

The most prevalent adverse effect of NSAIDs is GI toxicity. These toxicities may consist of minor GI symptoms, such as acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea, and vomiting, to more life-threatening events, such as GI bleeding or perforations of gastroduodenal ulcers (Buttgereit, Burmester, & Simon, 2001; Singh & Triadafilopoulos, 1999). Patients who chronically use NSAIDs have a three to four times greater risk of developing an upper GI erosion or ulcer than nonusers (Buttgereit et al.). Annually in the United States, 100,000 patients are hospitalized and 16,500 die from NSAID-induced GI bleeds (Bombardier et al., 2000). This number of GI-related deaths from the use of NSAIDs is greater than the combined deaths attributed to asthma, cervical cancer, and Hodgkin’s disease and is comparable to the number of deaths caused by AIDS (Straus & Ofman, 2001). Unfortunately, the presence of occult blood in stool, dyspepsia, or endoscopic findings cannot predict who will develop these more serious complications (Pepper, 2000).

To help minimize NSAID-induced GI events, clinicians have attempted to suppress acid secretion with H-2 antagonists or proton pump inhibitors. Another treatment strategy combines misoprostol (Cytotec®), Searle & Company, Chicago, IL), a PG analog, with NSAIDs. Using gastroprotective agents can significantly reduce, but not eliminate, the risk of NSAID-induced ulcers (Buttgereit et al., 2001).

Classical NSAIDs produce GI mucosal injury by both local irritation and systemic effects. The use of NSAIDs nonselectively inhibits the two isomers of COX: COX-1 and COX-2. This indiscriminate inhibition of COX-1 and COX-2 impairs mucosal protective mechanisms, which are PG dependent (Buttgereit et al., 2001). PGs have cytoprotective properties, which protect the gastric mucosal integrity by stimulating mucus and bicarbonate secretion, maintaining mucosal blood flow, stabilizing mast cell membranes, and promoting epithelial cell proliferation. The inhibition of COX-1 alters these mechanisms, increasing the risk for a GI adverse

### Table 3. Indications and Dosages of Selective Cyclooxygenase-2 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib (Celebrex®, Pfizer Inc., New York, NY)</td>
<td>Osteoarthritis</td>
<td>100 mg twice a day</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
<td>200 mg once a day</td>
</tr>
<tr>
<td></td>
<td>Familial adenomatous polyposis</td>
<td>100 mg twice a day</td>
</tr>
<tr>
<td></td>
<td>Acute pain</td>
<td>200 mg twice a day</td>
</tr>
<tr>
<td></td>
<td>Dysmenorrhea</td>
<td>400 mg initially, then 200 mg twice a day</td>
</tr>
<tr>
<td>Rofecoxib (Vioxx®, Merck &amp; Co., Inc., West Point, PA)</td>
<td>Osteoarthritis</td>
<td>12.5–25 mg once a day</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
<td>25 mg once a day</td>
</tr>
<tr>
<td></td>
<td>Acute pain</td>
<td>50 mg once a day</td>
</tr>
<tr>
<td></td>
<td>Dysmenorrhea</td>
<td>50 mg once a day</td>
</tr>
<tr>
<td>Valdecoxib (Bextra®, Pharmacia, Kalamazoo, MI)</td>
<td>Osteoarthritis/rheumatoid arthritis</td>
<td>10 mg once a day</td>
</tr>
<tr>
<td></td>
<td>Dysmenorrhea</td>
<td>20 mg once a day</td>
</tr>
</tbody>
</table>

*Note.* Based on information from Physician’s Desk Reference, 2002.
event (Golden & Abramson, 1999). Unrelated to the inhibition of COX is the local effect of NSAIDs on the gastric mucosa caused by direct toxic action involving mitochondrial injury (Buttgereit et al.).

Therefore, with the advent of selective COX-2 inhibitors, which offer a GI safety profile superior to conventional NSAIDs, clinicians now have an alternative to treat inflammatory conditions with fewer GI toxicities. Two large outcome studies, the Celecoxib Long-Term Arthritis Safety Study (CLASS) and Vioxx GI Outcomes Research (VIGOR) trial, were conducted to test the hypothesis that patients receiving a COX-2 inhibitor would have fewer upper GI events than patients taking classic NSAIDs (Bombardier et al., 2000; Silverstein et al., 2000). CLASS concluded that celecoxib in dosages two to four times the maximum therapeutic dosage was associated with significantly fewer incidences of combined upper GI events than NSAIDs (Silverstein et al.). Shortly after the findings of CLASS were reported, Bombardier et al. found that the results of the VIGOR study demonstrated significantly fewer clinically important upper GI events in patients receiving a COX-2 inhibitor than patients receiving naproxen.

Renal Effects

Selective COX-2 inhibitors have decreased the risk of GI problems, generating optimism that renal function also would be spared. Approximately 5% of individuals exposed to NSAIDs can develop one or more forms of renal complications (Whelton, 2001). Human nephrectomy and autopsy specimens have revealed COX-2 throughout the kidneys, suggesting that COX-2 has a role in salt and water balance (Perazella, 2001). Whether COX-2 inhibitors offer any improvement in renal safety over nonselective inhibitors still is under clinical investigation.

The importance of renal PG regulation lies in preserving the kidneys’ homeostasis during physiologic states that cause intravascular volume depletion or reduced renal blood flow. These conditions include vomiting, dehydration, diarrhea, diuretic therapy, congestive heart failure, cirrhosis, and nephrotic syndrome, which cause the upregulation of renal COX activity and PG biosynthesis. Renal PG production also is increased in chronic renal insufficiency and affects salt and water homeostasis (Brater et al., 2001; Perazella, 2001). Individuals most at risk for an NSAID-related renal event are those with conditions that make renal function dependent on PG synthesis to ensure sufficient blood flow and maintain the glomerular filtration rate and salt and water homeostasis. The use of NSAIDs in this patient population can cause renal ischemia and acute deterioration of renal function (Whelton, 2001).

Traditional NSAIDs are associated with several renal syndromes, such as acute renal failure, edema, sodium retention, and hyperkalemia. Edema and sodium retention are the most common adverse renal effects and, on rare occasions, can progress to congestive heart failure (Pepper, 2000; Perazella, 2001). NSAID-induced renal sodium retention appears to be responsible for both the onset of new hypertension and exacerbation of previously controlled hypertension (Perazella). NSAID therapy may cause an elevation in mean arterial pressure from 5 to 10 mm Hg. Researchers have estimated that a sustained increase as small as 5–6 mm Hg in diastolic blood pressure results in a 67% increase in the risk of cardiovascular accident and a 15% increase in the risk of coronary artery disease (Brater et al., 2001; Whelton, 2001). Hyperkalemia develops from NSAID-induced reduction in the synthesis of renin and aldosterone, preventing the excretion of renal potassium (Brater et al.; Perazella).

Whether COX-2 inhibitors adversely affect kidney function and lower the incidence of renal effects is unclear (Pepper, 2000; Perazella, 2001). To date, a few clinical studies have shown only a modest difference in sodium retention, glomerular filtration, urinary sodium, and potassium excretion glomerular filtration between those receiving COX-2 inhibitors and traditional NSAIDs (Whelton, 2001). A quantitative difference appears to exist between celecoxib and rofecoxib, with the latter having a greater incidence of peripheral edema at the doses approved for clinical use (Whelton, 2000). To assume that COX-2 inhibitors are not free of adverse renal effects and share similar risks, possibly to a lesser extent, as nonselective NSAIDs is reasonable (Brater et al., 2001; Perazella). To what degree COX-2 inhibitors affect renal outcomes has yet to be determined.

Controversies Involving Cyclooxygenase-2 Inhibitor Agents

Cardiovascular

Researchers recently reported a possible risk of cardiovascular events with the use of COX-2 inhibitor agents. Two large randomized studies of patients receiving either rofecoxib (Vioxx) or celecoxib (Celebrex) documented efficacy of these agents in treating arthritis. However, recent review of the data has raised some concerns regarding cardiovascular risk.

The VIGOR trial, which enrolled a total of 8,076 patients with rheumatoid arthritis comparing rofecoxib with naproxen, found a significantly increased risk of cardiovascular events with the use of rofecoxib (Mukherjee et al., 2001). Altogether, 111 patients experienced serious cardiovascular events, compared with 50 patients in the naproxen group. The type of cardiovascular events reported ranged from myocardial infarction, unstable angina, and resuscitated cardiac arrest to ischemic stroke and transient ischemic attacks. Interestingly, CLASS, which enrolled 7,968 patients and studied celecoxib compared to ibuprofen and diclofenac, did not reveal significant differences in cardiovascular events in those patients receiving celecoxib (Mukherjee et al.; Silverstein et al., 2000).

Interpretation of the trial data on cardiovascular effects has generated significant controversy. Cardiovascular events were not originally intended as end points in the design of the VIGOR trial. Although the patients with rheumatoid arthritis studied in the trial were at increased risk for cardiovascular events because of their diagnosis of arthritis, the research question still exists because of the differences in cardiovascular events between rofecoxib and naproxen. All participating patients in the trial had a rheumatoid arthritis diagnosis, including those in the naproxen group (Perry, 2001; Sabo, 2001).

CLASS allowed patients to use low-dose aspirin, and the VIGOR trial did not. Although a clearly reduced risk of serious GI events for patients receiving COX-2 compared to NSAID therapy existed in both trials, patients receiving low-dose aspirin in CLASS lost this protective GI effect. The use of aspirin may have accounted for the lack of significant increase in cardiovascular event rates with celecoxib in the trial. However, when researchers compared large scale analysis of other heart disease prevention trials to the VIGOR trial and CLASS, both agents increased cardiovascular event risk (Sabo, 2001). Some researchers feared that the COX-2 agents actually may lead to increased prothrombotic activity (Mukherjee et al., 2001).

FitzGerald, Cheng, and Austin (2001) reviewed the incidence of cardiovascular events from both the VIGOR trial and CLASS as well. Their study of the data revealed that the incidence of cardiovascular events was indeed higher in patients receiving rofecoxib versus those receiving naproxen and that the incidence did not vary between the groups in CLASS. Although cardiovascular results were detected in the review, FitzGerald et al. could not definitively conclude whether the differences resulted from chance or the trial design. They concluded that individuals who need low-dose aspirin for cardioprotection may have less...
chance for a GI event if they combine aspirin with rofecoxib rather than traditional NSAIDs; however, this belief is not yet supported by direct evidence (Fitzgerald et al.).

White et al. (2002) compared the thromboembolic events in the patients participating in CLASS treated with celecoxib versus ibuprofen or diclofenac. These researchers reviewed the data to determine the incidence of serious cardiovascular thromboembolic events and conducted separate analyses for all patients and for those not taking aspirin. White et al. found that the incidence of serious cardiovascular thromboembolic events was similar between celecoxib and the NSAIDs studied and concluded that no increased risk of serious events is associated with celecoxib. New studies are needed to fully evaluate these concerns because no consensus exists regarding the cardiovascular risk associated with the COX-2 inhibitor agents (Mukherjee et al., 2001).

Cost and Selection Criteria

The average wholesale prices of the COX-2 inhibitor agents are higher than the cost of traditional NSAIDs (see Table 4). COX-2 inhibitor agents have demonstrated equivalent efficacy compared to NSAIDs in the control of pain and disability in the treatment of rheumatoid and osteoarthritis. The justification for using these more expensive COX-2 inhibitors rests on their ability to prevent or decrease the number of serious GI complications and patient selection. Of the millions of individuals regularly using NSAIDs, 15%–30% will develop a gastric or duodenal ulcer (Bombardier et al., 2000). Therefore, an estimated 100,000 patients are hospitalized annually and about 15,000 of those hospitalized die (Rubins & Rubins, 2002). Raskin (1999) predicted that a 5%–10% mortality rate exists for patients hospitalized with NSAID-induced upper GI bleeding at a cost exceeding $3.9 billion per year.

Researchers have established that COX-2 inhibitors significantly reduce the occurrence of GI complications, thereby creating a potential for considerable overall health cost savings. To date, several studies have undertaken the task of proving the cost-effectiveness of using COX-2 inhibitors over more traditional therapies. Analysis of patients with rheumatoid arthritis receiving NSAIDs alone, NSAIDs with prophylaxis (i.e., misoprostol, omeprazole, and famotidine), and COX-2 inhibitors determined the use of COX-2 inhibitors as the most cost-effective strategy in preventing GI toxicity (Yun, Corzillius, & Kim, 2000). Kristiansen and Odense (2000) investigated replacing an NSAID with a COX-2 inhibitor in patients with rheumatoid arthritis and concluded a cost savings existed when this maneuver was restricted to patients at increased risk for GI complications.

Given that selective COX-2 inhibitors offer no greater efficacy over NSAIDs, their costs dictate that they be used when side effects which place patients at risk for a GI complication are likely to be encountered. Patients at moderate risk for adverse GI events should be considered appropriate candidates for COX-2 inhibitor therapy. The presence of certain risk factors may predispose patients taking NSAIDs to have GI ulcer complications (see Figure 2). Having two or more of the risk factors for GI bleeding warrants the use of a COX-2 inhibitor. Contraindications for the use of COX-2 inhibitors are known hypersensitivity to the COX-2 inhibitor; patients who have experienced asthma, urticaria, or an allergic-type reaction to aspirin or other NSAIDs; and a sulfonamide allergy to celecoxib (Pfizer Inc., 2001; Pharmacia Corporation, 2001). Further clinical studies are necessary to determine the safety of using COX-2 inhibitors in patient populations with renal and cardiovascular disease because COX-2 inhibitors have not been proven to reduce the risk of complications in these conditions compared to traditional NSAIDs (Lipsky et al., 2000; Whelton, 2001). In the treatment of patients with familial adenomatous polyposis, Celebrex is still the only FDA-approved agent.

Implications for Practice

Patients on long-term COX-2 therapy should be monitored for efficacy as well as side effects. No specific monitoring guidelines exist for the use of COX-2 inhibitors; however, based on traditional NSAID recommendations, nurses should monitor complete blood cell counts to assess for anemia as a sign of GI bleeding, serum creatinine and potassium for renal impairment, and liver enzyme tests for liver abnormalities (Miller, 2001). These tests usually are repeated every 6–12 months, but they are repeated more frequently in symptomatic patients (Bush, Shlitzhauer, & Imai, 1991; Pepper, 2000).

Traditional NSAIDs inhibit the activity of the COX-1 isof orm in platelets, but most do not.

Table 4. 2001 Average Wholesale Price of Selected Nonsteroidal Anti-Inflammatory Drugs and Cyclooxygenase-2 Agents

<table>
<thead>
<tr>
<th>Traditional NSAID and Dose</th>
<th>Per Tablet Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen 400 mg (generic Zenith-Goldline)</td>
<td>2.91</td>
</tr>
<tr>
<td>Diclofenac sodium 50 mg (Voltaren®, Novartis Pharmaceuticals, East Hanover, NJ)</td>
<td>2.51</td>
</tr>
<tr>
<td>Naproxen 250 mg (generic) ESI Lederle Generics</td>
<td>0.82</td>
</tr>
<tr>
<td>Choline magnesium trisalicylate 500 mg (Trilisate®, Purdue Frederick, Stamford, CT)</td>
<td>0.22</td>
</tr>
<tr>
<td>Diflunisal 250 mg (generic) Endo Generics</td>
<td>0.74</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cyclooxygenase-2 Inhibitor Agent and Dose</th>
<th>Per Tablet Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib 100 mg (Celebrex®, Pfizer Inc., New York, NY)</td>
<td>1.49</td>
</tr>
<tr>
<td>Rofecoxib 25 mg (Vioxx®, Merck &amp; Co., Inc., West Point, PA)</td>
<td>2.51</td>
</tr>
<tr>
<td>Valdecoxib 10 mg (Bextra®, Pharmacia, Kalamazoo, MI)</td>
<td>2.91</td>
</tr>
</tbody>
</table>

Note. Based on information from Cardinale, 2001.

NSAID—nonsteroidal anti-inflammatory drug

Prior history of
- Peptic ulcer
- Gastrointestinal bleeding
- Nonsteroidal anti-inflammatory drug-related gastrointestinal symptoms (e.g., dyspepsia, acid reflux, epigastric discomfort, heartburn, nausea, vomiting)

Concurrent use of
- Corticosteroids
- Anticoagulants
- Low-dose aspirin
- Alcohol
- Comorbid diseases
- Primary coagulopathy
- Cigarette smoking
- Older age (older than 65 years)
- Physical disability
- Higher nonsteroidal anti-inflammatory drug dose

Figure 2. Risk Factors for Developing a Nonsteroidal Anti-Inflammatory Drug-Related Gastrointestinal Complication

Note. Based on information from Griffin & Scheiman, 2001; Lipsky, 2001.
not have the sustained action that provides an irreversible aspirin-like effect. Because COX-2 inhibitors do not affect platelet aggregation, all patients should be screened for risk factors of thrombosis. Low-dose aspirin may be considered for high-risk patients as these agents will not decrease thrombogenic potential (Lipsky et al., 2000).

The COX-2 inhibitor agents have been prescribed widely; in fact, combined wholesales for 2000 were approximately $5 billion (Seibold & Spector, 2001). COX-2 agents comprise about half of all new NSAID prescriptions written, which undoubtedly will increase (Seibold & Spector). Although COX-2 inhibitor agents are considered the mainstay in arthritis therapy, future roles include chemoprevention and possibly combination therapy with conventional chemotherapeutic agents. A viable role may exist for these agents in the prevention of Alzheimer’s disease as well; however, further research is needed. The exciting development of this new class of agents for oncology has great potential, and its role will continue to grow in the future as more information regarding additional tumor use becomes available.

The COX-2 inhibitors are not without significant side effects, and the possible increased cardiovascular risk is a concern that requires further study. Nurses caring for patients about to begin COX-2 therapy should take all potential problems of these medications into consideration. Assessment of GI status should include taking an accurate medical history (i.e., prior GI bleeding, dyspepsia, history of peptic ulcer disease, and aspirin or sulfa allergies). Once patients have initiated therapy, nurses should examine patients for signs and symptoms of bleeding (e.g., dark, tarry stools; abdominal pain; coffee-ground emesis). Patients should be assessed for evidence of fluid retention, such as peripheral edema and adventitious lung sounds, which may indicate renal or cardiovascular problems. Because cancer occurs more frequently in older patients, oncology nurses may see patients with comorbid rheumatologic conditions placed on COX-2 agents to minimize GI effects. Oncology nurses should be aware of the risks inherent in the use of these drugs and the use of COX-2 agents for chemoprevention of certain cancers.

**Conclusion**

The COX-2 inhibitor agents have revolutionized the treatment of patients with arthritis, allowing the administration of potent anti-inflammatory agents with reduced risk of GI effects. Although the data may not be as compelling as originally thought, reduction in GI effects for this primarily aging population of patients is a significant achievement in the armamentarium of antiinflammatory medications.

Present and future applications of these compounds in oncology are exciting and include activity in patients with familial adenomatous polyposis and possibly other solid tumors as well. Although the use of these agents in chemoprevention represents a potential breakthrough for patients with cancer, additional approaches (e.g., smoking cessation, limiting alcohol consumption, eating more fruits and vegetables) also should be stressed. Future research should address cardiovascular effects, in addition to broader applications of these medications for patients with cancer.

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**References**


Half, E., Tang, X.M., Gwyn, K., Sahin, A.,
Cyclooxygenase-2: From Arthritis Treatment to New Indications for the Prevention and Treatment of Cancer

- Cyclooxygenase-2 (COX-2) is induced in response to inflammatory mediators, such as growth factors, endotoxins, and tumor promoters.
- Selective COX-2 inhibitors have an anti-inflammatory effect and are approved for the treatment of rheumatoid and osteoarthritis, acute pain, and primary dysmenorrhea.
- Only celecoxib currently is approved for the reduction of the number of adenomatous polyps in patients with familial adenomatous polyposis.
- Contraindications for the use of COX-2 inhibitors are (a) known hypersensitivity to the COX-2 inhibitor, (b) prior history of asthma, urticaria, or allergic reaction to aspirin or other nonsteroidal anti-inflammatory agents, and (c) sulfonamide allergy to celecoxib.
- Patients taking COX-2 inhibitors should be monitored for anemia, renal impairment, and liver impairment.
- COX-2 inhibitors do not affect platelet aggregation; therefore, all patients taking these agents should be screened for risk factors for thrombosis.