Use of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 (COX-2) inhibitors: Indications and complications

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications—both prescription and over the counter—in the United States. Gastrointestinal side effects from NSAIDs are responsible for significant patient morbidity and mortality as well as healthcare cost. With the development of cyclooxygenase-2 (COX-2) specific inhibitors, these serious adverse reactions have been significantly reduced without affecting therapeutic benefit; however, the need for careful monitoring of patients on therapy with traditional NSAIDs and COX-2 inhibitors continues. In this article, recent developments regarding COX-2 inhibitors and potential future uses of this class of drugs are also discussed.

(Key words: arthritis, cardiovascular risk, celecoxib, cyclooxygenase-2 inhibitors [COX-2 inhibitors], nonsteroidal anti-inflammatory drugs [NSAIDs], pain, rofecoxib, valdecoxib)

Use of traditional nonsteroidal anti-inflammatory drugs (NSAIDs) for arthritis and pain is commonplace in the United States. As many as 50 million Americans take NSAIDs on any given day, and approximately 100 million prescriptions are written yearly at a cost of nearly $3 billion dollars. This class of drugs is one of the most widely prescribed (or taken over the counter) so that concern about gastrointestinal (GI) and other side effects related to their use is well-founded. It is known that NSAIDs produce their analgesic, anti-inflammatory, and antipyretic actions via inhibition of cyclooxygenase, which, consequently, results in decreased synthesis of prostaglandins. Traditional NSAIDs also inhibit thromboxane A2, which is largely responsible for platelet function.

Although prostaglandin inhibition results in beneficial actions, harmful side effects, most notably affecting the GI and renal systems, may also be a direct result of this mechanism. It has been established that as many as 2% to 4% of patients older than 50 years who regularly take NSAIDs may have a serious GI side effect such as perforation, ulceration, or bleeding during long-term therapy. It has also been shown that use of traditional NSAIDs may lead to as many as 100,000 hospitalizations per year and may have significantly contributed to the death of as many as 15,000 patients annually as a result of those serious GI events.

The physician must be able to identify those at risk (Figure 1) for GI side effects and renal complications (Figure 2), and must be aware of the need for regular monitoring (Table) of these “at risk” patients. Therefore, the necessity for monitoring patients on NSAID therapy, either traditional or COX-2 inhibitors, is extremely important.

COX-2 specific inhibitors

In 1991, several research groups working independently discovered a second isoform of cyclooxygenase, namely, cyclooxygenase-2 (COX-2), which was found to have different functions and a distinct identity from cyclooxygenase-1 (COX-1). Whereas COX-1 was found in abundance in GI endothelium, renal mucosa, and was constituent, COX-2 was found to be undetectable in most normal tissues, inducible by cytokines and other inflammatory states, and highly responsible for inflammation and pain. Logic would then lead one to conclude that the selective or specific inhibition of COX-2 while sparing COX-1 should theoretically result in therapeutic benefits similar to those of traditional NSAIDs such as ibuprofen and indomethacin, while limiting serious side effects.

Celecoxib, a COX-2 specific inhibitor, was thus approved by the Food and Drug Administration (FDA) in 1998 for use in osteoarthritis and rheumatoid arthritis. Subsequently, it has received an indication for use in pain. Rofecoxib, another COX-2 specific inhibitor, was approved in 1999 by the FDA for treatment of osteoarthritis and acute pain. In keeping with the foregoing hypotheses, these two drugs significantly reduced serious GI side effects, though they were not found to be renal sparing as a result of the realization that COX-2 was present in renal macula densa.

In a world of “evidence-based medicine,” where is the proof of improved GI safety associated with COX-2 inhibitors such as celecoxib and rofecoxib? Even the busy practitioner must become familiar with two major trials dealing with the subject: the CLASS Trial (Celecoxib Long-term Arthritis Safety Study) and the VIGOR (Vioxx GastroIntestinal Outcome Research) trial. These two studies enrolled approximately 8000 patients each for the evaluation of GI complications. Celecoxib was compared with diclofenac sodium, while rofecoxib was compared with naproxen. In essence, both studies revealed about a 50% decrease in serious GI events, including perforation, obstruction, bleeding, and ulceration.
An article appearing in the New England Journal of Medicine in August 2001 discusses the possibility of an increased incidence of cardiovascular or cerebrovascular events in patients on COX-2 specific agents. This study reviewed results of many clinical trials and raised concern about thrombotic events. It must be noted that the NSAID market is still growing, and more definitive, prospective trials must be done before absolute conclusions can be reached concerning the effect of COX-2 inhibitors on cardiovascular events. There were two issues that may have contributed to the postulated increase in cardiovascular events in the population receiving rofecoxib in this trial. It appears that more definitive, prospective trials must be done before absolute conclusions can be reached concerning the effect of COX-2 inhibitors on cardiovascular events.

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**COX-2 inhibitors and cardiovascular risk**

An article appearing in the New England Journal of Medicine in August 2001 discusses the possibility of an increased incidence of cardiovascular or cerebrovascular events in patients on COX-2 specific agents. This study reviewed results of many clinical trials and raised concern about thrombotic events. However, on close analysis of all data, it must be noted that the VIGOR trial in particular did not permit patients to take their daily aspirin even if at risk for cardiovascular events (~4% of patients). Approximately 0.8% of trial patients versus 0.4% of control population thus sustained a thrombotic event. The CLASS trial revealed no significant difference in cardiovascular events between the group receiving celecoxib group and the control subjects taking diclofenac. One perspective is that diclofenac (CLASS trial control drug) has a weak antiplatelet effect, whereas naproxen (VIGOR trial control drug) has a very potent antiplatelet effect. By virtue of the action of the COX-2 inhibitors, they have minimal if any effect on the platelet as they do not inhibit the production of thromboxane A₂.

Another consideration is that rofecoxib in a dosage of 50 mg (as used in the VIGOR trial) may cause edema in approximately 4% of patients (higher percentage than control subjects) and an increase in blood pressure in as many as 8% of patients compared with 1.3% of control subjects. These two issues may have contributed to the postulated increase in cardiovascular events in the population receiving rofecoxib in this trial. It appears that more definitive, prospective trials must be done before absolute conclusions can be reached concerning the effect on COX-2 inhibitors on cardiovascular events. Therefore, patients taking a COX-2 inhibitor regularly should continue their daily aspirin regimen as recommended by their personal physician.

**Updates on COX-2 inhibitors, NSAIDs and acetylsalicylic acid activity**

In 2001, Catella-Lawson and colleagues examined, by both an in vitro and ex vivo technique, the potential for NSAIDs and COX-2 inhibitors to nullify the protective effects of aspirin and reported their results in the New England Journal of Medicine. Urinary thromboxane was measured in patients given ibuprofen plus aspirin, rofecoxib plus aspirin, acetaminophen plus aspirin, and delayed-release diclofenac plus aspirin. They found that ibuprofen blocked the platelet inhibitory (eg, release of thromboxane) effect of low-dose aspirin. The same inhibitory effect was not observed with rofecoxib, diclofenac (delayed-release), or acetaminophen. An ex vivo measurement of platelet migration yielded similar results.

**Aseptic meningitis**

Recently, Bonnel et al reported five cases of aseptic meningitis.
attributed to rofecoxib use within 1 to 12 days after administration. The FDA has now concluded that aseptic meningitis should be added to the package insert for rofecoxib, yet careful review finds that this rare side effect was noted in the original rofecoxib profile. More important, it must be realized that this extremely rare complication of NSAIDs has been seen with a number of products in the past, including a drug as widely used as ibuprofen, which was released in 1974.

**Future uses of COX-2 inhibitors**

In addition to positive effects on pain and inflammation and the relative sparing of the GI system, COX-2 inhibitors may help to prevent Alzheimer’s disease. It is also well known that colonic polyps are rich in COX-2 and that administration of these specific inhibitors may inhibit polyp formation, thus leading to a potential lesser risk of bowel cancer. In fact, the FDA has also granted celecoxib an indication for the reduction of polyp formation in patients with familial adenomatous polyposis. Future ongoing trials of COX-2 inhibitors include enrolling patients on rofecoxib therapy who have undergone resection for colorectal cancer, and combining COX-2 inhibitors with cytotoxic drugs in patients with recurrent colorectal, non–small-cell lung, and cervical cancers.

**Comment**

Traditional NSAIDs and the newer COX-2 inhibitors are widely used to treat patients with pain and various forms of arthritis. The COX-2 specific inhibitors have been a welcome addition to our armamentarium in treating the arthritides and other musculoskeletal problems while reducing GI side effects. This factor does not eliminate the need for careful and regular monitoring of patients, whether they be on traditional NSAID or COX-2 inhibitor therapy, especially those at high risk as previously discussed.

There is substantial evidence supporting the lower incidence of GI events while taking COX-2 inhibitors (CLASS and VIGOR trials); potential future uses include prevention and treatment for such diverse diagnoses as colorectal cancer and Alzheimer’s disease. However, close attention should be paid to further trials concerning the possible slight increase in cardiovascular and other thrombotic events while taking antiarthritis medications that lack an antiplatelet effect. Recommended therapy is to continue prophylactic acetylsalicylic acid for those “at risk” patients who are currently taking a COX-2 inhibitor for arthritis or pain. The current and potential beneficial effects of this additional class of medications appear to be significant.

**References**