ABSTRACT

In the United States, an estimated 40 million people, many of whom are elderly, rely on nonsteroidal anti-inflammatory medications (NSAIDs) for the treatment of chronic conditions such as rheumatoid arthritis and osteoarthritis. While these medications are effective inhibitors of the mediators of the inflammatory processes responsible for the painful signs and symptoms of arthritis, these beneficial effects come at a price. Frequent use of NSAIDs may cause a variety of gastrointestinal side effects in patients, ranging from dyspepsia, nausea, and abdominal pain to the more serious complications of gastric or duodenal ulcer and gastrointestinal bleeding. While use of the newer selective cyclooxegenase-2 (COX-2) inhibitors can temper these effects, these are also not a panacea. Since COX-2 inhibitors by themselves are not cardioprotective, users of these medications who are at risk for cardiovascular disease still require daily low-dose aspirin therapy. Nonselective NSAIDs and aspirin all affect the gastrointestinal tract and platelets to some degree, placing the patient at risk for bleeding.

It is best to discontinue these medications in the presence of serious adverse effects. However, when use of NSAIDs cannot be avoided, cotherapy with the prostaglandin analogue, misoprostol, or a proton pump inhibitor (PPI) may be appropriate. Studies now reveal PPIs to be the most effective medications in inhibiting acid secretion, healing ulcers, and preventing ulcer recurrences without the frequent untoward side effects caused by misoprostol.

Serious morbidity, mortality, and significant healthcare costs are all associated with NSAID use. Many elderly patients must continue to take these medications for treatment of arthritis and prevention of coronary events. For such individuals, PPIs now offer a practical and effective option to reduce the risk of adverse events. (Adv Stud Med. 2003;3(3A):S128-S134)

Effective management of gastrointestinal side effects within the context of polypharmacy is of vital importance to clinicians today, particularly since more geriatric patients are taking multiple medications to both treat and prevent various chronic illnesses. Of particular concern is the use of aspirin and other nonsteroidal anti-inflammatory medications (NSAIDs) due to their propensity to cause dyspepsia, ulcer disease, and even gastrointestinal (GI) bleeding.

NSAID USE AND ULCERS: A PROBLEM OF GREAT MAGNITUDE

According to the National Arthritis Data Workgroup, an estimated 40 million adults in the United States have some form of arthritis, with 21 million of these individuals reporting symptoms of
osteoarthritis (OA). Osteoarthritis is the leading cause of both work-related disability and disability in elderly patients. It has been reported that 70% of individuals older than 65 years take NSAIDs at least weekly, and 34% take at least 1 tablet per day, according to Talley and colleagues, who studied the effects of aspirin and nonaspirin NSAIDs.

Talley found that patients taking NSAIDs had an almost 2-fold greater associated risk of experiencing upper GI tract symptoms as compared with elderly community-dwelling individuals not taking the medications. Specifically, 15% to 20% of patients taking NSAIDs on a regular basis experience dyspepsia and another 15% to 30% develop ulcers (15% to 20% gastric; 5% to 8% duodenal). GI bleeding occurs in 1.5% of NSAID users overall. In fact, approximately 1 in 10 individuals started on an NSAID will have to stop their medication due to an untoward GI side effect. Unfortunately, most patients who develop an adverse event are asymptomatic and, thus, may unknowingly be at even greater risk of experiencing an extremely serious event since symptoms cannot reliably predict risk for complications. It has been suggested that more than 100 000 hospitalizations each year are attributed to NSAID use, with an estimated 10 000 to 16 000 deaths resulting annually from NSAID-related GI side effects. According to the National Center for Health Statistics database, there were nearly as many deaths related to NSAID use as from human immunodeficiency virus HIV, and more deaths from NSAID use than from several common forms of cancer or certain chronic illnesses, such as asthma (Figure 1). Silverstein et al found that those at greatest risk for developing an untoward side effect from NSAID use, specifically an NSAID-associated ulcer, were individuals with a history of either a complicated or uncomplicated ulcer. Those also at risk included patients older than 70 years and individuals receiving multiple and/or high doses of NSAIDs, anticoagulants, or steroids. This issue potentially impacts a large number of Americans both medically and financially, as between 111 and 112 million prescriptions are written annually for NSAIDs at a cost of $4.8 billion.

Pathophysiology of Ulcers
Within the Context of NSAID Use

NSAIDs exert their anti-inflammatory effect via the inhibition of prostaglandin synthesis. Specifically, they affect the cyclooxygenase (COX) enzyme that catalyzes the conversion of arachidonic acid to prostaglandins and the thromboxane precursor cyclic endoperoxide. There are 2 isoforms of the COX enzyme: COX-1, which makes prostaglandins that protect the stomach lining and regulate blood platelets, and COX-2, which formulates the prostaglandins that cause pain, fever, and inflammation (Figures 2 and 3). Prostaglandins E and F are the main mediators of local and systemic inflammation. Prostaglandin E2 suppresses gastric acid secretion, helps maintain the mucosal barrier, and regulates microcirculation. Traditional NSAIDs (nonselective types) impair these prostaglandin-dependent mucosal-protective mechanisms and are believed to cause damage to the gastric mucosa that is exacerbated by the presence of acid. Acidity also promotes the absorption of NSAIDs in their nonionized form into the gastric epithelial cells where they are trapped and disrupt cell metabolic functions. As these cells are damaged, the presence of additional acid can further injure the tissue, forming deeper lesions including actual ulcers.

It is best to avoid NSAID use whenever possible, especially in high-risk individuals. When NSAIDs cannot be avoided or discontinued, histamine type-2...

Figure 1. Mortality from NSAID-Induced Complications vs Other Diseases in US
receptor antagonists (H2RAs) (eg, ranitidine), prostaglandin analogues (eg, misoprostol), and proton pump inhibitors (PPIs) (eg, lansoprazole) have been used in an attempt to prevent the adverse effects of dyspepsia, ulcer formation, and bleeding. Generally, PPIs are more effective than H2RAs and better tolerated than prostaglandin analogues.

**Management of NSAID-Related Ulcers**

Individuals who have previously been treated for a bleeding ulcer have a 1 in 5 chance of recurrence within a year, and such individuals who also need to take an NSAID have a 13.5-fold increased risk. Therefore, effective therapy is vital, first to heal and then to prevent a second event.

**Healing of Active Ulcer Disease**

Agrawal and colleagues conducted a prospective, double-blind, multicenter, parallel-group study of 350 patients with a gastric ulcer measuring ≥5 mm confirmed by endoscopy who continued to require stable doses of NSAIDs. The patients were randomized to 1 of 3 treatment groups, including the H2RA, ranitidine (150 mg bid), and 2 different doses of the PPI, lansoprazole (15 mg qd or 30 mg qd). While both therapies were effective for some patients, lansoprazole was significantly more successful in healing the ulcers in 8 weeks (53% of patients taking H2RAs; 69% of patients taking lansoprazole 15 mg qd; and 73% of patients taking lansoprazole 30 mg qd; P <0.05). Investigators found that 8-week therapy with a PPI would permit continued healing of most gastric ulcers, even in the continued presence of NSAIDs. While almost three quarters of the ulcers in this study healed by week 8 with lansoprazole, one quarter of the ulcers remained active. Therefore, it may be prudent to extend treatment, for example, to 12 weeks to maximize the chance of complete ulcer healing. In another double-blind study of patients experiencing either gastric or duodenal ulcers, Yeomans and associates randomly assigned 541 patients who required continuous treatment with NSAIDs to another PPI, omeprazole, 20 mg qd or 40 mg qd, or ranitidine 150 mg bid. They were treated over a period of 4 to 8 weeks based on the success of therapy. Success was measured according to endoscopic assessments of the stomach and duodenum looking for the resolution of ulcers and the reduction in the numbers of erosions present. Again, PPIs seemed to heal more ulcers in shorter periods of time than H2RAs. Specifically, 81% of patients receiving omeprazole 20 mg qd versus 64% of patients receiving ranitidine 150 mg bid were healed of gastric ulcers after 8 weeks of treatment (P <0.01).

**Figure 2. Normal Distribution of COX Isoenzymes**

**Figure 3. How Do the Mechanisms of NSAID and Coxibs Compare?**

COX = cyclooxygenase.


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week healing rates with the PPI were actually superior to the 8-week healing rates with the H2RA. Overall, results with duodenal ulcers were even more encouraging. By week 8, 81% of ulcers in those taking the H2RA and 92% in those taking the PPI were healed ($P = .03$). Again, the PPI was superior to the H2RA.

**Prevention of Recurrence**

Because older patients frequently require long-term NSAID treatment for chronic conditions such as arthritis, and possibly also aspirin therapy for cardiovascular risks, it is not sufficient for an antiulcer medication to merely repair erosive gastritis or heal peptic ulcers. It is also vital to attempt to prevent a recurrence of pathology. Data from Yeomans et al again showed that prophylactic therapy with omeprazole was more effective than that with ranitidine in preventing recurrence of NSAID-associated ulcers. In patients receiving maintenance therapy with omeprazole or ranitidine while continuing NSAIDs, at the end of 6 months, 72% of patients receiving a PPI were ulcer-free compared with 59% receiving an H2RA. Of the patients taking omeprazole, 5.2% experienced a recurrence in gastric ulcers and 0.5% developed another duodenal ulcer ($P < .05$). By contrast, recurrence of gastric and duodenal ulcers in patients taking ranitidine was 16.3% and 5.7%, respectively.

Until recently, the only agent approved for prevention of NSAID-induced gastric ulcer was misoprostol, a prostaglandin analogue. Unfortunately, while effective, misoprostol is not as well tolerated as H2RAs or PPIs and is known to cause diarrhea, among other adverse effects. In one study by Graham et al, misoprostol was "on paper" the most effective agent, preventing 93% of patients from developing ulcers while taking NSAIDs over 12 weeks. The PPI, lansoprazole, was nearly as effective (80% to 82%, depending on dosage), but better tolerated. Both of these agents were significantly more effective than placebo in reducing the risk of gastric ulcer recurrence in the 357 Helicobacter pylori-negative long-term NSAID users studied. Again, study patients taking 200 mcg qid of misoprostol reported more than twice the number of adverse effects than those taking lansoprazole and more than 3 times the adverse effects than those taking placebo. Not surprisingly, this led to noncompliance and early withdrawal from the study of patients assigned to take misoprostol, essentially making the efficacy of misoprostol equivalent to that of lansoprazole 15 or 30 mg qd.

**A Comparison of Adverse Events—Nonselective NSAIDs Versus COX-2 Selective Inhibitors**

One might speculate as to whether simply ensuring that a patient who needs an NSAID for a prolonged period of time takes a selective COX-2 inhibitor would prevent adverse GI effects, particularly ulcers and complications. A trial by Bombardier et al, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, compared upper GI toxicity of rofecoxib 50 mg qd (twice the recommended dose) and naproxen 500 mg bid in 8076 middle-aged to elderly patients with rheumatoid arthritis. Whereas both drugs had similar efficacy against arthritis symptoms, the risk of a serious upper GI event, such as gastroduodenal perforation or obstruction, upper GI bleeding, or symptomatic gastroduodenal ulcers, was cut approximately in half through the use of a selective versus a nonselective NSAID. Similarly, Silverstein et al, the Celecoxib Long-term Arthritis Safety Study (CLASS), examined 8059 patients with either rheumatoid arthritis or in a double-blind, randomized, controlled trial comparing celecoxib 400 mg bid with ibuprofen 800 mg tid or diclofenac 75 mg bid. Unlike the VIGOR trial, these investigators also permitted enrolled subjects to use aspirin for cardiovascular prophylaxis. Even with selective COX-2 inhibitor dosages in excess of those recommended, patients experienced less GI side effects, complications, and toxicity when receiving celecoxib compared with therapeutic dosages of nonselective agents.

The relative GI safety of the COX-2 selective NSAIDs may be explained by the fact that they do not affect the enzyme, COX-1, which protects the GI mucosa but selectively inhibits COX-2. In theory, a selective COX-2 inhibitor would prevent inflammation while preserving the beneficial effects of prostaglandins in the kidneys, platelets, and digestive system. However, it has been found that in doing so, a selective COX-2 inhibitor might affect the cardiovascular system. Specifically, McAdam and colleagues compared the effects of ibuprofen, a nonselective COX inhibitor, with that of celecoxib, a selective COX-2 inhibitor, in terms of their effects on platelet production of thromboxane and production of prostacyclin. Celecoxib had no effect on platelets, unlike ibuprofen, which inhibited platelet thromboxane. Both drugs, however, inhibited prostacyclin. The role of thromboxane in the body is to promote platelet aggregation, hemostasis, and thrombosis, whereas...
prostacyclin in the vascular endothelium has a counter-regulatory effect, inhibiting platelet aggregation. When nonselective agents are used, balance is maintained between promotion and inhibition of platelet effects (Figure 4).\textsuperscript{17} Theoretically, however, by not blocking COX-1 effects, platelet aggregation continues unopposed, and, thus, concerns about genesis of thrombotic events have been raised. These observations are used to explain data from the VIGOR study, which found that the incidence of myocardial infarction (MI) was lower among patients in the naproxen group versus those in the rofecoxib group.\textsuperscript{15}

Thus, users of selective COX-2 inhibitors may indeed experience less GI side effects and this may be beneficial in the management of arthritis in patients at risk for ulcers. However, this benefit may be partially mitigated in patients at risk for cardiovascular disease because they may still require aspirin (ASA) therapy for its cardioprotective effect, and co-prescription of ASA will somewhat negate the beneficial GI effects of the COX-2 inhibitors. Such a mitigating of safety by aspirin is supported by data from the CLASS study that revealed that 6% of patients taking ibuprofen with concomitant aspirin and 4.70% of patients taking a COX-2 inhibitor with aspirin developed ulcers, while only 2.91% of those using ibuprofen alone and 1.40% of patients using nonaspirin and celecoxib developed ulcers.\textsuperscript{16} No NSAIDs can be considered a substitute for aspirin for cardiovascular prophylaxis in patients at risk for cardiovascular events. Since patients at cardiovascular risk will continue to take aspirin, and because NSAIDs do not afford the same level of cardioprotection, we come back to the fundamental question as to how does the clinician protect against GI toxicity?

TEMPERING THE RISKS WHILE MAINTAINING THE BENEFITS OF ASPIRIN USE FOR PRIMARY PREVENTION OF CORONARY DISEASE

EVIDENCE OF RISKS AND BENEFITS

Sanmuganathan and colleagues performed a meta-analysis of randomized trials that investigated the relative risks versus benefits of aspirin use for primary cardioprotection. Specifically, these investigators found that in the 4 randomized trials they analyzed, aspirin significantly reduced the risk of initial cardiovascular events, and particularly the risk of MI by 30%. However, according to data from these trials, neither the risk of stroke nor the risk of mortality overall was significantly reduced, and aspirin therapy significantly increased the risk for bleeding complications by 69%.\textsuperscript{18} Furthermore, a study conducted in Denmark of 27,694 users of low-dose aspirin revealed a 2.5-fold increase in the study group's risk of upper GI bleeding compared with the general population. When an NSAID was taken with the low-dose aspirin, the risk increased to 5.6 times that of the general population, and enteric coating of the aspirin did not appear to have any significance.\textsuperscript{19} Thus, aspirin therapy in a patient at high risk for both cardiac and GI complications requires careful evaluation. The solution may be the addition of a medication such as a PPI to prevent the development of ulcers and complications in patients, particularly the elderly, who require therapy both for cardioprophylaxis and arthritis.

MANAGEMENT ISSUES

In 1999, Lai and colleagues studied the effect of the addition of a PPI to aspirin therapy in 123 patients taking low-dose aspirin who had recent bleeding ulcers. After treatment for H. pylori, if it was present, aspirin 100 mg qd was restarted in these patients. Half of the patients were randomized to also receive lanso-
prazole 30 mg qd and half to receive placebo. After 12 months, 14.8% of the patients taking aspirin alone had a recurrence of ulcer complications, specifically GI bleeding, compared with 1.6% of the patients also receiving the PPI.14 The benefits of lansoprazole in low-dose aspirin users were confirmed by Graham et al. In a subset of their study patients receiving aspirin and NSAIDs, those randomized to receive lansoprazole had fewer recurrent ulcers than those receiving placebo alone (82% vs 51%). Misoprostol also reduced the risk of gastric ulcer recurrence in those receiving aspirin and NSAIDs, but it was not as well tolerated as lansoprazole, and patients had to discontinue therapy due to its adverse effects.14

Thus, in nonaspirin users at low risk of developing a GI complication, it may be safe to prescribe an NSAID alone. However, if they are also taking aspirin, their risk for GI complications is increased and the addition of a PPI should be considered. In those patients with an average to high risk of developing an ulcer and/or GI bleeding, a selective COX-2 inhibitor would be indicated, or, as an alternative, a PPI along with a nonselective NSAID. Finally, in those patients at average to high risk of a GI complication who require aspirin therapy along with their anti-inflammatory drug, it is appropriate to prescribe a PPI regardless of whether a nonselective NSAID or a selective COX-2 inhibitor is used.

**CONCLUSION**

The elderly are at high risk for developing GI complications as a result of long-term NSAID use, and this risk can sometimes be exacerbated by the need to take daily aspirin for its cardioprotective effects. Studies have shown that PPIs can safely and effectively be administered to these patients as adjunct therapies to achieve a number of goals. First, PPIs such as lansoprazole will reduce symptoms from NSAID-associated ulcers. In addition, these medications will accelerate healing of both gastric and duodenal ulcers, and finally, PPIs can prevent recurrence of ulcers in patients taking NSAIDs alone or in combination with aspirin.

**REFERENCES**


