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The Role of Gastroprotection in Patients on NSAID Therapy

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Learning Objectives

After completing this continuing education article, the health care provider should be able to:

1. *Identify the prevalence of gastropathy in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs).*
2. *Assess the impact that this treatment complication can have on health care costs, medical outcomes, and patient quality of life.*
3. *List asymptomatic gastric complications that can result from NSAID use.*
4. *Discuss the mechanisms by which NSAIDs can cause gastric injury.*
5. *Identify patients at risk for gastric injury associated with NSAID use.*
6. *Describe the range of treatment options for patients at risk for gastric injury, including substituting a non-NSAID analgesic or a cyclooxygenase-2 inhibitor, reducing the NSAID dose, or adding a gastroprotective agent.*
7. *Employ guidelines to assist in the treatment selection for patients at risk for NSAID-associated gastropathy.*
8. *Counsel patients regarding monitoring parameters for the recurrence of gastric injury.*

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain one of the most commonly prescribed medication classes for the treatment of pain and inflammatory conditions. Numerous agents are available in the United States, both with over-the-counter (OTC) availability and by prescription (Table 1). Data suggest that >111 million prescriptions were written in the United States in 2000 for these medications.[1] This volume occurs at a cost of almost $5 billion per year, with another $3 billion per year being spent on nonprescription NSAIDs.[1] As patients age, the use of NSAIDs can increase dramatically. It has been suggested that 34% of patients aged ≥65 years use these agents on a daily basis, with 70% using them at least once per week.[1,2]

NSAID therapy is indicated for the treatment of pain, inflammation, and fever, with aspirin also used extensively for both primary and secondary reduction of cardiovascular (CV) and cerebrovascular events.[1] While demonstrating significant efficacy in the ability to treat and prevent these disease states, NSAID therapy also is associated with substantial morbidity and mortality related to gastrointestinal (GI) toxicity and subsequent gastropathies.[1]

Epidemiology and Prevalence

NSAID therapy has been associated with numerous adverse events. The GI complaints and complications ascribed to these medications are the most common, however.[3-6] These adverse events have been characterized in the literature as falling into 3 groups: (1) mild symptoms, such as dyspepsia, heartburn, nausea, vomiting, and abdominal pain; (2) lesions as identified by radiology or endoscopy, such as ulcers or erosions within the gastric mucosa; and (3) critical GI complications, such as ulcer perforation or profound GI bleeding requiring admission to a hospital.[3] Common dys-

Table 1

Commonly Available NSAIDs in the United States

Classification of NSAIDs	Examples
Salicylates	
Acetylated	Aspirin†
Nonacetylated	Salsalate, trisalicylate
Nonsalicylates	
Nonselective COX-1/COX-2s or traditional NSAIDs	Ibuprofen†, indomethacin, naproxen†, sulindac, ketoprofen, ketorolac, fenoprofen, diclofenac, piroxicam, diflunisal, oxaprozin, tolmetin
Semiselective NSAIDs*	Meloxicam, etodolac, nabumetone
COX-2 selective inhibitor	Celecoxib

*Greater COX-2 inhibition than COX-1; †Available over the counter.
NSAIDs = nonsteroidal anti-inflammatory drugs; COX = cyclooxygenase.

pepsia has been suggested to occur in up to 60% of patients taking NSAIDs.[5,6]

In patients with rheumatoid arthritis (RA), dyspeptic symptoms have been estimated to be associated with up to a 15% discontinuation rate.[7] Evidence to date, however, has not shown a significant correlation between dyspepsia and endoscopically identifiable mucosal injury.[8] In fact, it has been shown that the majority of patients treated for significant NSAID-induced gastropathy are asymptomatic prior to presentation.[3,9,10] Singh and colleagues estimated that 81% of such patients were asymptomatic.[3] Additional evidence related to this finding includes the possibility that NSAIDs actually may mask the pain associated with the ulcer and may exacerbate an already developing "silent" ulcer.[10] Endoscopically determined ulcers, which usually are defined as mucosal breaks ≥3 mm in diameter, occur in approximately 15% to 30% of patients who regularly take NSAID pharmacotherapy.[1] Interestingly, some patients may develop these gastric lesions within 7 days with consistent NSAID use. These findings are not necessarily clinically significant because the majority of these patients do not go on to have any significant adverse GI outcomes.[1] Research from clinical trials has suggested that clinically important upper GI events occur in approximately 3% to 4.5% of patients with life-threatening events, such as bleeding, perforation, and gastric outlet obstruction, occurring in 1.5% of patients taking NSAIDs.[1] When considering these more significant NSAID-associated GI complications, it has been shown that these agents are responsible for 107 000 hospitalizations and 16 500 deaths per year in the United States alone.[3]

Pathogenesis

Numerous theories have been identified that describe the relationship between NSAIDs and GI injury.[5,6] The 2 most commonly described mechanisms are (1) the direct, or topical, irritant potential these agents have on the gastric epithelium and (2) the inhibition of the synthesis of protective GI prostaglandins.[5,6] The latter mechanism appears to be the more important with regard to the development of serious complications.[11]

Topical Irritation of the GI Mucosa

Topical damage to the mucosal epithelium occurs through the acidic nature of NSAIDs and their ability to reduce the hydrophobicity of the gastric mucosa on the epithelial lining, thus allowing for potential injury by gastric acid and pepsin.[12] Damage also may occur as a result of "ion trapping," which takes place when an acidic NSAID, such as aspirin, remains un-ionized within the acidic environment of the stomach. These conditions allow acidic NSAIDs to remain lipid-soluble, facilitating diffusion across the cell membrane. This mechanism leads to accumulation within the mucosal epithelial cell. The NSAID ionizes in the physiologically neutral pH and becomes trapped, because it can no longer back-diffuse across the cell membrane. This mechanism results in accumulation of hydrogen ions and subsequent damage through cell lysis.[6]

Despite the drug's potential to cause topically mediated damage to the gastric epithelium, these mechanisms appear to play only a minor role in subsequent ulceration.[5,6] This hypothesis is supported by studies that involve aspirin, which suggest that reducing the dose, buffering the medication, or modifying the release of the formulation—such as with enteric coating of the tablet—has no substantial benefit in reducing the frequency of gastric or duodenal ulcerations.[13-15] These findings suggest that systemic effects of NSAIDs play the largest role in the development of GI ulceration.

Systemic Effects on the GI Mucosa

The inhibition of mucosal prostaglandin synthesis is considered the primary mechanism for the development of NSAID-related gastropathy (Figure).[5,6] These prostaglandins are derived from arachidonic acid by the enzyme cyclooxygenase (COX).[16] Two individual isoforms have been described: COX-1 and COX-2.[6,16] The COX-1 enzyme is constitutive and produces prostaglandins associated with GI cytoprotection. Regulation of GI mucosa integrity occurs through production of epithelial mucus, secretion of bicarbonate, improved mucosal blood flow, and regulation of

epithelial cell turnover.[5,17] The inhibition of these prostaglandins by traditional NSAIDs increases the susceptibility of the GI tract to risk for damage from gastric acid, pepsin, and bile.[5] COX-1 also is associated with prostaglandin production related to the regulation of platelet function (primarily aggregation) and renal function.[5,6]

The COX-2 enzyme generally is considered to be inducible. It produces prostaglandin secondary to proinflammatory mediators, such as cytokines, as a response to pain, fever, and inflammation.[16,17] Nonselective or traditional NSAIDs inhibit both COX-1 and COX-2, with varying ratios.[5,16,18,19] This understanding led to the development of the COX-2–selective NSAIDs. The belief is that the more selective the NSAID is toward the inhibition of COX-2, the less is the chance of compromising the gastric integrity while producing similar efficacy in pain and inflammation compared with a nonselective NSAID.[5]

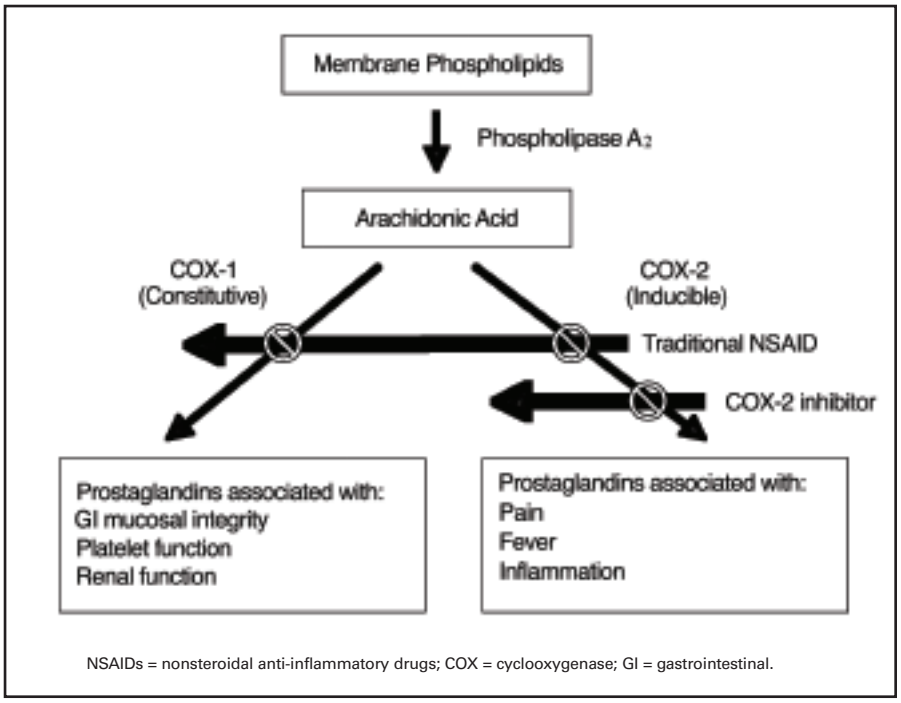
Risk Factors for NSAID-induced Gastropathy

When considering that NSAID-induced complications do not occur in the majority of patients, coupled with the fact that most patients who develop complications are asymptomatic, it is increasingly important that health care providers are aware of the risk factors associated with the development of disease.[1,7,9] Numerous risk factors for the development of NSAID-induced gastropathy have been identified (Table 2).[1,3,5] All traditional NSAIDs have been associated with an increased risk of GI complications due to the inhibition of COX-1 and COX-2, which ultimately prevents the production of protective prostaglandins. Some NSAIDs, however, have been described as having a greater risk.[1,17] Piroxicam, ketorolac, and naproxen have been associated with a significantly higher risk, whereas nonacetylated salicylates, such as salsalate, have demonstrated a reduced risk, as have the semi-COX-2–selective traditional NSAIDs, such as etodolac, nabumetone, and meloxicam.[1,4,17] Selective COX-2 inhibitors, such as celecoxib, have been suggested as having the lowest overall risk of ulcer formation.[4,17]

Increasing the dose of traditional NSAIDs also has been associated with increasing the overall risk ratio.[1,17,20-22] Increasing the dose of ibuprofen from low dose (1200 mg/day) to high dose (2400 mg/day) increases the relative risk (RR) from 1.6 (95% confidence interval [CI], 0.8-3.2) to 4.2 (95% CI, 1.8-9.8), respectively.[20]

When considering individual risk factors, patients with a history of previous gastric or duodenal ulceration or associated GI complications are considered at highest risk, with a 14-fold increased risk for NSAID-induced GI ulceration over patients without this history.[21,23] The use of NSAIDs in combination with anticoagulants, such as warfarin, has been associated with a substantially higher risk as well.[24] Shorr and colleagues evaluated the risk for hospitalization due to bleed-

Figure. Pharmacology of Traditional NSAIDs and Selective COX-2 Inhibitors on Prostaglandin Synthesis[6]



NSAIDs = nonsteroidal anti-inflammatory drugs; COX = cyclooxygenase; GI = gastrointestinal.

Table 2

NSAID-induced Ulceration and Upper GI Complication Risk Factors[1,3,5]

Known Risk Factors

History of previous GI ulceration or associated GI complication

Concomitant anticoagulation or coagulopathy (including antiplatelet therapy)

Advancing age (especially ≥60 years)

Multiple NSAID use, including use of concomitant aspirin

Corticosteroid use

High-dose NSAID therapy

Presence of comorbidities, such as CVD and RA

Monotherapy with aspirin, including cardioprotective doses

Potential Risk Factors

Duration of NSAID use

Presence of dyspepsia

Helicobacter pylori infection

NSAID = nonsteroidal anti-inflammatory drug; GI = gastrointestinal; CVD = cardiovascular disease; RA = rheumatoid arthritis.

ing ulcers in patients receiving concomitant NSAID therapy and oral anticoagulants.[24] This analysis found approximately a 13-fold greater risk of hemorrhagic peptic ulcer disease (PUD) in patients receiving both medications compared with nonusers of either medication, and a 3-fold risk increase over patients on NSAID therapy alone.[24] Recent evidence also has shown that antiplatelet agents, such as clopidogrel, used concomitantly with NSAIDs increase the risk of serious GI events, especially in patients with a previous history of PUD.[25]

Advancing age has been determined to be an independent risk factor for the development of NSAID-associated disease. The age at which the risk begins to increase significantly, however, has not been determined.[1,17,21,26] One of the most frequently cited meta-analyses determined that patients ≥60 years of age have an approximately 5.5-fold greater risk than younger patients of developing a GI complication while being treated with NSAID therapy.[26]

The use of multiple NSAIDs in combination, especially with aspirin, also has demonstrated an increased risk of GI bleeding. Sørensen and colleagues evaluated this risk in a cohort study performed in Denmark.[27] This study involved >27 000 patients. It identified that concomitant use of traditional NSAIDs and cardioprotective doses of aspirin produced a 2-fold greater risk of hospitalization due to GI bleeding over the use of low-dose aspirin alone (standardized incidence ratio, 5.6 [95% CI, 4.4-7.0] vs 2.6 [95% CI, 2.2-2.9], respectively).[27] Aspirin alone, even at low doses as demonstrated in this latter study, is still associated with an increased risk, and this risk has been demonstrated in other studies as well.[15,27,28]

Incremental risk associated with the dose of aspirin has been identified, although it was not statistically significant.[15,27,28] In the meta-analysis performed by Derry and colleagues, patients taking any dose of aspirin had an overall 1.7-fold greater risk of GI hemorrhage than patients receiving placebo. Patients on low-dose aspirin (<163 mg/day), however, still had a 1.6-fold greater risk compared with those on placebo.[15]

Another case-control study found a trend in the risk of upper GI bleeding with escalating doses of aspirin.[28] Doses of 75, 105, and 300 mg of aspirin were associated with an increased risk of 2.5, 3.2, and 3.9 times, respectively, when compared with the risk in matched hospital and community control patients.[28] The results with escalating doses of aspirin were not statistically significant but demonstrate a trend toward increased risk.[28]

Corticosteroids alone have shown conflicting results regarding their potential to cause gastric ulceration and are not considered an independent risk factor by themselves. The combined use of corticosteroids and traditional NSAIDs, however, has demonstrated a nearly 2-fold increase in gastropathy as compared with the use of NSAIDs alone.[1,17,26,29]

Comorbid diseases, such as RA and cardiovascular disease (CVD), also may have an influence on the risk of NSAID-induced GI disease.[30-32] These 2 chronic disease states have demonstrated small-to-moderate incremental increased risk rates in multivariate analyses from 2 clinical trials with regard to CVD and in 1 meta-analysis for RA.[1,30-32] Prolonged duration of NSAID use, dyspepsia, and *Helicobacter pylori* infection remain controversial but are still potential risk factors for the development of NSAID-associated disease.[1,17,32]

Options for Patients at Risk for NSAID-associated GI Complications

Numerous pharmacotherapy options exist for reducing the risk of NSAID-associated GI complications. The use of non-NSAID analgesics and the absolute avoidance of NSAIDs whenever possible are the only options to remove risk of these complications,[1] but these options are likely to be inappropriate for most patients with inflammatory disease processes. As discussed previously, using the lowest effective dose of an NSAID that will alleviate the patient's symptoms will reduce the overall risk of GI complications.[1] For a significant proportion of higher-risk patients, the use of concomitant therapy with protective agents or the use of selective COX-2 inhibitors remains a viable option.

Misoprostol

As previously mentioned, the inhibition of gastroprotective prostaglandins by NSAIDs plays a very important role in the development of gastropathies.[5,6] Thus, physiologic replacement with exogenous prostaglandin analogs is an acceptable option for the prevention of NSAID-induced gastric toxicity. Misoprostol, a synthetic prostaglandin E_1 analog, is currently the only Food and Drug Administration (FDA)-approved oral prostaglandin analog for the prevention of NSAID-induced gastric ulcers in patients at high risk for developing complications. Misoprostol has demonstrated efficacy in numerous studies versus placebo in both the primary and secondary prevention of NSAID-induced gastric ulceration.[32-37] The benefits of misoprostol appear to be dose-related, with 800 μg daily having the greatest benefit.[33,34]

The benefit of misoprostol was first discovered in a double-blind, placebo-controlled trial in patients with osteoarthritis and abdominal symptoms who were on NSAID therapy. The trial determined that gastric ulceration occurred in 1.4% of patients receiving 200 μg of misoprostol 4 times daily, in 5.6% of patients receiving 100 μg of misoprostol 4 times daily, and in 21.7% of the placebo group. Interestingly, this trial demonstrated no benefit in terms of the reduction of NSAID-associated dyspepsia.[33]

A follow-up to this study demonstrated similar efficacy in the prevention of duodenal and gastric ulcers in patients with either osteoarthritis or RA who were receiving either misoprostol 200 μg

4 times daily or placebo.[35] Both of these trials used endoscopically identified ulcers of ≥3 mm in diameter as clinical end points. As previously mentioned, however, this finding may not predict serious GI outcomes or complications. The Misoprostol Ulcer Complications Outcomes Safety Assessment (MUCOSA) study was performed to evaluate this issue.[32] This large study, which involved 8843 older patients with RA who were on long-term NSAID therapy, showed a 40% reduction in the development of gastric perforation, upper GI bleeding, or gastric outlet obstruction when patients were given misoprostol 200 μg 4 times daily versus placebo over a 6-month period.[32]

Misoprostol has been compared directly with proton pump inhibitors (PPIs) for secondary prevention.[36,37] The maintenance phase of the Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) study evaluated the use of misoprostol 200 μg twice daily versus omeprazole 20 mg daily in patients with previously healed ulcers who still required NSAID pharmacotherapy.[36] Omeprazole was found to be equally as effective as misoprostol in the secondary prevention of gastric ulcers (13% and 10%, respectively, experienced relapse), but it was statistically superior for the secondary prevention of duodenal ulcers (3% and 10%, respectively) in patients 6 months after ulcer healing.[36] An important point with regard to this trial was that the dose of misoprostol was half (400 μg/day) of the most effective dose (800 μg/day) determined in previous clinical trials.

Lansoprazole, at doses of 15 mg and 30 mg once daily, has been directly compared with misoprostol 200 μg 4 times daily in patients with a history of ulcers.[37] Similar rates of patients remaining ulcer-free at 12 weeks with lansoprazole 15 mg and 30 mg (79% and 83%, respectively) and misoprostol 200 μg (88%) were determined from this trial.[37]

Despite the proven efficacy of misoprostol in reducing the risk of NSAID-induced gastropathy, its use is limited because of its adverse-effect profile. Diarrhea and abdominal cramping have been reported to occur in up to 50% of patients receiving 800 μg/day in clinical trials.[32-34,36,37] Reducing the daily dose of misoprostol to 400 to 600 μg has shown a lower incidence of these adverse effects. Efficacy in the prevention of NSAID-induced gastropathy was compromised, however.[33] Misoprostol also has abortifacient activity secondary to its ability to increase the contractility of uterine smooth muscle, and thus it is contraindicated in pregnant patients.[5]

Histamine$_2$-receptor Antagonists

The histamine$_2$ (H_2)-receptor antagonists have demonstrated effectiveness in reducing the incidence of NSAID-induced gastric and duodenal ulceration.[38-40] Standard doses used in placebo-controlled, double-blind trials, however, reduced the incidence of duodenal ulcers only.[39,40] Ehsanullah and colleagues evaluated the use of ranitidine 150 mg twice daily versus placebo in patients with RA or osteoarthritis who were on long-term NSAID pharmacotherapy. The incidence of duodenal ulceration was significantly reduced in the ranitidine group (1.5%) compared with the placebo group (8%) at 8 weeks. Yet, no significant reduction in gastric ulceration was identified (6% in both groups).[39]

A similar study by Robinson and colleagues resulted in similar outcomes. In this prospective study, arthritic patients requiring daily NSAID therapy also were randomized to ranitidine 150 mg twice daily or placebo for 8 weeks. Duodenal ulcers developed in 8% of the patients randomized to placebo, while none (0%) appeared in patients on ranitidine—a statistically significant finding. There was no difference in gastric ulceration between patients given ranitidine and those given placebo (10% and 12%, respectively).[38]

Based on the results of these trials, Taha and colleagues performed a 24-week dose analysis with famotidine 20 mg and 40 mg twice daily versus placebo for the prevention of NSAID-induced gastric and duodenal ulcers. Only famotidine 40 mg twice daily was able to reduce the incidence of gastric ulcers when compared with placebo (8% and 20%, respectively). Both doses of famotidine were able to significantly reduce the incidence of duodenal ulcers.[40]

These study findings suggest that the prevention of NSAID-induced gastric ulceration requires a greater level of acid suppression with higher doses of H_2-receptor antagonists compared with duodenal ulceration. These agents also have been compared directly with PPIs; however, those trials assessed only the standard prescription doses of the H_2-receptor antagonists. Those studies will be discussed in the next section.

PPIs

The use of PPIs for the prevention of NSAID-induced gastric and duodenal ulcers has been studied in numerous randomized, double-blind, multicenter, active, and placebo-controlled trials.[36,41-43] The largest limitation of these trials was that the primary end points included endoscopically determined gastric or duodenal ulceration or symptom reduction rather than prevention of clinically significant GI complications.[36,41] The efficacy of omeprazole 20 mg once daily versus ranitidine 150 mg twice daily for 6 months as secondary maintenance therapy in patients still requiring NSAID therapy was evaluated in the Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT) study.[41] In this study, the recurrence of ulcers was prevented in 72% of the patients receiving omeprazole versus 59% of the patients receiving ranitidine.

Subgroup analysis of *H pylori*–positive patients in this study found that the omeprazole-treated patients had a higher likelihood of remaining ulcer-free versus those treated with ranitidine. It

should be noted, however, that in this study the patients randomized to ranitidine were given only the standard dosage (150 mg twice daily). This dose had not been demonstrated to be effective in the prevention of gastric ulcers as described in the previously reviewed studies on H_2-receptor antagonists.[41] High-dose H_2-receptor antagonist therapy has not been compared head to head against the use of PPIs to date.

Two recent placebo-controlled trials have been published evaluating the benefit of PPIs in the prevention of GI complications in high-risk patients (defined as those with a previous history of GI bleeding who require continued aspirin or NSAID therapy).[42,43] Chan and colleagues evaluated the use of omeprazole in patients with healed ulcers and concomitant *H pylori* infections. Patients taking aspirin prior to randomization were placed on aspirin 80 mg per day, and those on NSAID therapy were placed on naproxen 500 mg twice daily. These patients were then randomized to either omeprazole 20 mg daily for 6 months or *H pylori* eradication therapy consisting of bismuth, tetracycline, and metronidazole for 7 days. After 6 months, the patients receiving low-dose aspirin therapy were no more likely to develop recurrent upper GI bleeding with omeprazole (0.9%) than with *H pylori* eradication therapy (1.9%). In the naproxen group, however, omeprazole significantly reduced this risk (occurring in 4.4% of patients) versus eradication therapy (18.8%).[42]

Lai and colleagues evaluated the issue of whether *H pylori* eradication alone or in combination with lansoprazole would prevent recurrence of ulcer complications in patients with *H pylori*–infected gastric or duodenal ulceration who required continuation of cardioprotective doses (100 mg) of aspirin. After healing of ulcers and eradication of *H pylori* infection in all patients, they were randomized to lansoprazole 30 mg daily or placebo for 12 months. Aspirin 100 mg daily was reinitiated in all patients.[43] At 12 months, ulcerative complications occurred in 14.8% of the patients receiving placebo and in 1.6% of the patients receiving lansoprazole. These findings suggest that *H pylori* eradication alone may not be appropriate for the prevention of recurrent ulcer complications in patients who still require low-dose aspirin.[43] (Comparisons of concomitant PPI therapy with traditional NSAIDs and misoprostol were reviewed earlier in this article.[36,37])

COX-2 Inhibitors

The substantial GI risk associated with the use of traditional nonselective NSAID therapy, coupled with the understanding that COX-2 is associated with the development of prostaglandins that produce pain and inflammation, led researchers to develop new agents with greater COX-2 selectivity.[16] A selective COX-2 inhibitor would have a similar ability to reduce pain and inflammation as a traditional NSAID but would not have any adverse effects on GI mucosa that can be linked to the inhibition of COX-1 activity.[16] These agents also must not inhibit platelet function.[16]

Two large multicenter, double-blind, outcome-based studies demonstrated the efficacy of selective COX-2 inhibitors in the prevention of endoscopically defined NSAID-associated gastropathy.[44,45] The Celecoxib Long-term Arthritis Safety Study (CLASS) evaluated the use of celecoxib 400 mg twice daily versus either ibuprofen 800 mg 3 times a day or diclofenac 75 mg twice daily for at least a 6-month period. The results of this trial demonstrated a lower incidence of upper GI ulcer complications in those patients assigned to celecoxib than in those assigned to traditional NSAIDs (0.76% vs 1.45%, respectively), as well as a significant reduction in the combined incidence of upper GI ulcer complications and symptomatic ulcers (2.08% vs 3.54%). An important issue to note regarding the CLASS trial is that patients were allowed to continue low-dose cardioprotective aspirin (<325 mg/day) during the study. In fact, 21% of the patients in this trial continued to use low-dose aspirin, and, when this subpopulation was evaluated, the gastroprotective benefits of celecoxib over traditional NSAIDs disappeared.[44] The rationale for this finding is that the addition of aspirin, a nonselective NSAID, to a selective COX-2 inhibitor renders the combination nonselective because both COX-1 and COX-2 are inhibited. This issue potentially may have skewed the results of the study. The FDA subsequently evaluated the long-term data from the CLASS trial and determined that the rate of ulcer complications with celecoxib was no better than the rate with ibuprofen or diclofenac and suggested a loss of long-term benefit.[4]

The second trial was the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, which compared rofecoxib 50 mg daily with naproxen 500 mg twice daily.[45] Rofecoxib produced a significant reduction in clinical upper GI events versus naproxen (2.1 and 4.5 events per 100 patient years, respectively), as well as significantly reducing complicated upper GI events, such as perforation or obstruction (0.6% and 1.4%), at 9 months.[45] A major difference between the CLASS and VIGOR studies was that the VIGOR study excluded all patients taking aspirin.[44,45]

The gastroprotective benefits of rofecoxib in the VIGOR study unfortunately have been tempered by the identification of potential CV risks. Patients randomized to rofecoxib demonstrated a higher myocardial infarction (MI) rate (0.4%) than those randomized to naproxen (0.1%).[24] This finding resulted in the hypothesis that selective inhibition of COX-2 will inhibit the synthesis of prostacyclin without altering the synthesis of thromboxane A_2, thus potentially creating a prothrombotic environment within the vasculature.[46]

Table 3

Pharmacotherapy Strategies for NSAID Therapy Based on GI and CV Risk[6]

	Patients with No or Minimal GI Risk	Patients with High GI Risk
Patients with no CV risk and not on aspirin	Nonselective NSAID	Selective COX-2 inhibitor *or* nonselective NSAID and PPI *or* determine whether potential exists for use of a non-NSAID analgesic
Patients requiring aspirin for CV risk	Nonselective NSAID and PPI if sufficient risk of NSAID-associated gastropathy *or* determine whether potential exists for use of a non-NSAID analgesic	Nonselective NSAID and PPI *or* determine whether potential exists for use of a non-NSAID analgesic

NSAID = nonsteroidal anti-inflammatory drug; GI = gastrointestinal; CV = cardiovascular; COX = cyclooxygenase; PPI = proton pump inhibitor.

The data from the VIGOR study were then followed in 3 individual studies, each with a different COX-2 inhibitor, that added to the evidence that COX-2 inhibitors are potentially associated with a great risk for cardiac toxicity.[47-49] The Adenoma Prevention with Celecoxib (APC) study was performed with 2035 patients to evaluate the use of 2 different doses of celecoxib (200 mg and 400 mg twice daily) in the prevention of adenomatous polyps in the colon and rectum.[47] The study demonstrated, however, that patients on celecoxib (both groups combined) had a nearly 3-fold increased risk of adverse CV events, such as MI, stroke, and heart failure (hazard ratio, 2.8; 95% CI, 1.3-6.3).[47]

The Adenomatous Polyp Prevention On Vioxx (APPROVe) trial evaluated the use of rofecoxib 25 mg daily versus placebo in patients with a medical history of colorectal adenomas. The study was discontinued early and showed an approximate 2-fold higher incidence of thrombotic events (RR, 1.92; 95% CI, 1.19-3.11) in patients treated with rofecoxib.[48] In both of these trials, CV events appeared at approximately 18 months, suggesting an increased risk with prolonged duration of therapy.[47,48]

The third study, a 3-arm evaluation of intravenous parecoxib followed by oral valdecoxib, valdecoxib along with placebo, or placebo alone used to treat postoperative pain in patients undergoing cardiac surgery, suggested an increased risk of CV events with the COX-2 inhibitors. Thus, these agents are not best suited for use in this setting.[49]

Studies also have demonstrated potential dose relationships with adverse CV events. A retrospective cohort study using the Tennessee Medicaid database was designed to assess event rates with traditional NSAIDs and selective COX-2 inhibitors. This study found that rofecoxib in doses of ≤25 mg per day did not show a significant increase in CV events (adjusted RR, 1.02; 95% CI, 0.76-1.37). Doses >25 mg/day, however, were significantly associated with an increased risk (adjusted RR, 1.93; 95% CI, 1.09-3.43).[50]

More recently, a case-control study using the California Kaiser Permanente database found a similar significant dose relationship with rofecoxib and risk for MI.[51] Once again, patients taking ≤25 mg per day showed no increased risk (adjusted odds ratio [AOR], 1.47; CI, 0.99-2.17), and patients taking >25 mg/day showed an increased risk (AOR, 3.58; CI, 1.27-10.11).[51]

Interestingly, neither of these 2 cohort studies demonstrated an increased risk with celecoxib.[50,51] An unexpected result of the latter study is that naproxen demonstrated a significant increased risk of MI (AOR, 1.36; CI, 1.06-1.75).[51] Previous meta-analyses regarding naproxen and causation of MI, however, failed to find a significant association.[52] The overall findings of these studies led to the voluntary withdrawal of rofecoxib in September 2004 and the removal of valdecoxib in April 2005 from the US market.

PPI Plus a Nonselective NSAID Versus Selective COX-2 Inhibitors

Two studies have evaluated the secondary prevention of NSAID-associated GI bleeding with selective COX-2 inhibitors versus traditional NSAIDs in combination with PPIs.[53,54] Both of these trials ensured that patients were ulcer- and *H pylori* infection–free prior to randomization.[53,54]

Chan and colleagues evaluated the outcomes of 287 patients with arthritic disease who were randomized to celecoxib 200 mg twice daily plus placebo once daily or diclofenac 75 mg twice daily plus omeprazole 20 mg once daily for 6 months.[53] Comparable outcomes were found between the treatment groups with respect to recurrent bleeding (4.9% with celecoxib and 6.4% with diclofenac and omeprazole).[53]

Lai and colleagues randomized 224 patients with previous NSAID-associated ulcer disease to treatment for 24 weeks with either celecoxib 200 mg daily or naproxen 750 mg daily concomitantly with lansoprazole 30 mg daily.[54] Treatment with the selective COX-2 inhibitor was just as efficacious in preventing recurrences of GI ulcer complications as a traditional NSAID in combi-

nation with a PPI (3.7% in the celecoxib group and 6.3% in the naproxen with lansoprazole group).[54]

Managing Patients on Long-term NSAID Therapy

Health care providers must now consider all the evidence, including potential CV risk, when making pharmacotherapy decisions for the prevention of NSAID-induced gastropathy. Strategies and guidelines have been developed to assist the practitioner in the selection of appropriate pharmacotherapy for patients who require long-term anti-inflammatory pharmacotherapy.[55-61] The majority of the recommendations are based on the evaluation of patient risk for associated gastropathy.

Given the current need to assess for CV risk as well as potential for gastric toxicity, however, the recommendations have evolved. After the withdrawal of rofecoxib and valdecoxib from the US market, and because of concern regarding the previously discussed CV issues with the remaining COX-2 inhibitors, new guidelines have been developed for use when considering long-term therapy with NSAIDs (Table 3).[59,61] Prior to the initiation of NSAID therapy in any patient, the option of a non-NSAID should be considered if at all possible to remove the risk of NSAID-induced gastropathy.[1,61]

As seen in Table 3, the patient who does not have any significant risk factors for the development of NSAID-associated complications and does not require cardioprotective aspirin for coronary heart disease (CHD) would be best managed with a traditional NSAID alone. If dyspepsia should develop in this patient, an antacid or antisecretory therapy (H_2-receptor antagonist or PPI) could be initiated.[60,61]

The patient who has a significant risk (eg, history of gastric ulceration, anticoagulation, etc) of developing NSAID-associated GI complications but does not take prophylactic aspirin would be best suited for treatment with either a traditional NSAID in combination with a PPI or monotherapy with a selective COX-2 inhibitor. These 2 options have been considered equivalent with respect to recurrence of bleeding in high-risk individuals, as previously discussed, but an important point to remember is that gastropathy can still occur in approximately 6% of these patients. If the patient is already on PPI therapy for another reason (eg, gastroesophageal reflux disease), the addition of a traditional NSAID to this regimen would be appropriate.[60,61]

The patient who requires daily aspirin for CHD prophylaxis but does not have any significant risk factors for NSAID-associated gastropathy would no longer be an appropriate candidate for a COX-2 inhibitor, even given the likelihood of loss of COX selectivity with the addition of aspirin and the risk of an ischemic CV event. An important issue at this point in this type of patient is the use of multiple NSAIDs (aspirin plus a traditional NSAID). This type of patient would be best managed with a traditional NSAID in combination with a PPI.[61] Caution should be exercised with the use of ibuprofen in these patients, because ibuprofen has been demonstrated in clinical studies to reduce the effectiveness of aspirin's antiplatelet effects when used in combination.[62] This finding has not been shown with other NSAIDs to date.[62]

Some patients may fall into the classification with the highest GI and CV risk. These patients not only are at high risk for NSAID-induced gastropathy, but they also must take cardioprotective aspirin in addition to the requirement for NSAID therapy. If an NSAID must be used in this population, a traditional NSAID would be used, although non-NSAID pharmacotherapy would still be preferred if possible. Gastroprotective therapy with a PPI, however, would be necessary to offer maximum protection against GI complications.[61]

Pharmacoeconomic Issues

The economic impact of NSAID-induced gastropathy can be substantial. As mentioned before, >100 000 patients are hospitalized yearly in the United States because of this condition, and each admission has been estimated to cost from $1800 to $28,000 per patient.[3,63-65] Total costs in the United States associated with hospitalization for NSAID-induced complications are suggested to be approximately $4 billion per year.[66] This number, however, does not take into account the costs associated with those patients not admitted to the hospital, which can include such costs as additional office visits, time off from employment, additional OTC pharmacotherapy, and reduction of quality-of-life issues.

Numerous pharmacoeconomic studies have attempted to analyze the costs associated with NSAID therapy by placing a dollar amount for the additional cost over the price of the drug that is associated with preventing or treating adverse GI events.[67-69] De Pouvourville and colleagues defined cost factors for many NSAID agents. For example, naproxen was associated with a cost factor of 1.36: for every dollar that is spent on naproxen, an additional 36 cents would be required to prevent and treat adverse GI events.[67] Given the rapidly changing environment associated with the cost of medications and care, however, any analysis of this type would be rapidly antiquated.

Recently, a nomogram was developed to assess cost-effectiveness associated with the use of different options for the prevention of NSAID-induced gastropathy. Based on the results of this nomogram, COX-2 inhibitors or a traditional NSAID with a PPI were considered the most cost-effective regimens. The incremental cost with this strategy was substantial in patients considered at low risk for adverse GI events and decreased significantly as risk increased—thus suggesting that the use of these agents

should be reserved for those patients at highest risk and that traditional nonselective NSAIDs should be used alone in patients with low risk.[64]

Additional cost-effectiveness data with relation to quality-adjusted life years (QALYs) have demonstrated similar findings. Spiegel and colleagues determined in a cost-utility analysis of published data that in patients with an average risk of GI complications, the use of a selective COX-2 inhibitor would cost an incremental $275,000 per year to gain one additional QALY. In patients with a previous history of GI bleeding, however, this cost per QALY was reduced to $56,000.[70]

Follow-up and Monitoring

Recommendations for the follow-up and prevention of recurrent NSAID-associated gastropathy have been described.[71] First and foremost, patients who develop NSAID-associated ulcers should discontinue all NSAID pharmacotherapy. Patients with noncomplicated ulcers should be monitored for continuation of epigastric pain, which should subside within a few days after the discontinuation of the offending agent and within 1 week of the initiation of appropriate antiulcer pharmacotherapy. *H pylori*–positive patients should be prescribed an appropriate triple or quadruple eradication regimen. Once ulcers have healed and *H pylori* has been eradicated in positive patients, anti-inflammatory therapy, if necessary, should be cautiously reinitiated with either a selective COX-2 inhibitor or a traditional NSAID plus a PPI.

These patients should be carefully monitored because they are at a significant risk for recurrence. Basic monitoring includes evaluation and education of patients for signs and symptoms associated with gastric bleeding, obstruction, or perforation, such as the presence of black, tarry stools. Patients who redevelop pain should have a consultation with a gastroenterologist and a potential follow-up endoscopy.[71]

Summary

NSAID-associated gastropathy remains a significant source of morbidity and mortality, especially in high-risk patients. Evidence suggests that the appropriate use of concomitant therapy with a PPI or misoprostol, or the use of a selective COX-2 inhibitor instead of monotherapy with a traditional NSAID, in high-risk patients will reduce the incidence of GI ulceration and complications and remain cost-effective.

Evidence to date, however, has suggested a potential risk of CV toxicity with the selective COX-2 inhibitors. Therefore, the use of these agents should be reserved for patients with no CV risk who are at high risk for GI toxicity from NSAIDs. A significant proportion of adverse NSAID-related events can be prevented if health care providers consider a patient's risk for GI ulceration and make appropriate pharmacotherapy decisions based on those risk factors.

For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. A. Stahl, Pharmacy Times, 103 College Road East, Princeton, NJ 08540; or send an e-mail request to: astahl@ascendmedia.com.