

## Management of NSAID-related gastrointestinal mucosal injury

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**Abstract**—The three therapeutic goals in patients with NSAID-induced gastroduodenopathy are treatment of dyspeptic symptoms, management of NSAID-related ulcers and their complications, and prophylaxis against recurrent gastrointestinal toxicity. Both H<sub>2</sub>-receptor antagonists and proton pump inhibitors (PPIs) appear to be helpful in relieving the symptoms associated with NSAID use, while treatment of NSAID-induced gastroduodenal ulcers, whether the NSAID is continued or not, is best achieved by the use of PPIs. However, because symptoms do not often predict the presence of gastroduodenal ulcers, the goal of prevention has become paramount in the treatment of patients with an increased likelihood of gastrointestinal toxicity. The best prophylaxis against NSAID-related toxicity is the use of an alternative agent such as salsalate or paracetamol (acetaminophen). However, if an NSAID is to be used, prophylaxis is best accomplished with a PPI or misoprostol, a prostaglandin E<sub>1</sub> analogue. The use of misoprostol is limited by its frequent dosing, at least 200 µg three times a day, and its own gastrointestinal side effects. Future therapy will include NSAIDs that maintain their anti-inflammatory effects, while possessing superior safety profiles, and include preferential and highly selective COX-2 inhibitors and nitric oxide releasing compounds.

**Key words:** Gastrointestinal; NSAIDs; COX-2; gastrointestinal toxicity; ulcers; gastrointestinal hemorrhage; proton pump inhibitors; prostaglandins.

### I. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) have become one of the most commonly used medications. Over 70 million NSAID prescriptions and 30 billion over-the-counter preparations are sold annually in the United States (Wolfe *et al.*, 1999). The majority of NSAID users tolerate these medications without untoward effects, but adverse gastrointestinal effects are seen with relative frequency. In 1984, the Center for Disease Control reported that 100,000 to 200,000 hospitalizations

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and 10,000 to 20,000 deaths occur annually in the United States due to the gastrointestinal side effect of these medications. Side effects range from dyspepsia to complicated gastroduodenal ulcers associated with hemorrhage or perforation. NSAIDs thus constitute a class of drugs that can be best characterized as a 'double-edged sword', medication that is very effective, yet carries a substantial risk potential.

## 2. PATHOGENESIS OF GASTROINTESTINAL DAMAGE

Topical and systemic effects contribute to the mucosal damage associated with NSAID use, and although generally considered a primary cause of gastroduodenal ulcers, NSAIDs are capable of inducing widespread injury throughout the gastrointestinal tract and liver. Lanas *et al.*, 1992 recently reported that approximately 35% of NSAID-induced gastrointestinal bleeding occurred below the ligament of Treitz, with a spectrum of small intestinal and colonic injury ranging from a protein- and blood-losing enteropathy and colitis resembling inflammatory bowel disease to colonic perforation and bleeding.

In the esophagus, injury induced by NSAIDs has been reported and is thought to result from local acidic injury to the esophageal mucosa, a condition termed pill esophagitis (Minoch *et al.*, 1991). In the stomach and duodenum, topical injury results from both direct and indirect mechanisms. In the presence of highly acidic gastric contents, nonionized lipophilic NSAIDs are easily absorbed and migrate through gastric mucus to the surface epithelium, where NSAIDs are dissociated into the ionized form, resulting in  $H^+$  ion trapping (Somasundaram *et al.*, 1995). In addition, NSAIDs reduce the hydrophobicity of gastric mucosa and render the surface epithelium susceptible to injury by gastric acid (Lichtenberger, 1995). Indirectly, mucosal erosion may result from duodenogastric reflux of bile containing active NSAID metabolites (Wolfe *et al.*, 1999).

Although topical effects of NSAIDs are a significant cause of mucosal damage, the fact that NSAID-induced gastroduodenal injury occurs with equal frequency using enteric-coated preparations and following either rectal or parenteral administration suggests that the systemic effects of these compounds may play an even greater role. This contention is further supported by the observation that prodrugs such as sulindac, a compound whose effect is mediated by an active metabolite, have been associated with gastroduodenal ulceration.

The mucosal production of prostaglandins (PGs) appears to play an integral role in the stimulation of several mucosal components necessary for maintaining normal mucosal integrity and possibly reducing gastric acid secretion (Table 1) (Wolfe *et al.*, 1999). PGs are derived from arachidonic acid by the action of cyclooxygenase (COX). Two related cyclooxygenase isoenzymes, COX-1 and COX-2, are expressed in mammalian cells. COX-1 is expressed constitutively in most tissues, including the gastric mucosa, and is thought to function as a 'housekeeping' enzyme. The expression of COX-2, especially in macrophages and synovial cells, is induced

**Table 1.**

Protective properties of the gastroduodenal mucosa

Mucus secretion
Bicarbonate secretion
Mucosal blood flow
Intercellular tight junctions
Maintenance of tissue acid-base status
Epithelial restitution

**Table 2.**

Risk factors for development of NSAID-related ulcers

Definite	Advanced age
	Prior history of ulcer
	Concomitant corticosteroid therapy
	Concomitant anticoagulation therapy
	High doses of NSAIDs
	Short duration of therapy (< two weeks)
	Serious systemic diseases
Possible	Concomitant <i>H. pylori</i> infection
	Smoking
	Alcohol

by inflammation or mitogen stimulation. Therefore, it has been hypothesized that the anti-inflammatory action of NSAIDs are secondary to their inhibitory effect on COX-2, while their adverse properties are the result of the inhibition of COX-1. Despite strong evidence that PGs play an important role in NSAID-induced gastrointestinal toxicity, recent studies performed in COX-1 ( $-/-$ ) mice did not demonstrate spontaneous ulcer formation, suggesting that other mechanisms may be involved as well (Wolfe *et al.*, 1999).

### 3. RISK FACTORS FOR NSAID-RELATED GASTRODUODENAL TOXICITY

Patients who use NSAIDs develop gastrointestinal complications at a rate three times higher than those patients who avoid these medications. Unfortunately, the presence or absence of gastrointestinal symptoms does not correlate with gastroduodenal pathology, and for this reason, it is important to identify patients at an increased risk of developing complications (Table 2).

Although corticosteroids alone do not appear to cause gastroduodenal ulcers, their combination with NSAIDs is associated with a more than ten fold increase in gastrointestinal complications. Age also seems to play a significant role in NSAID-associated complications, with data revealing a 5.6-fold increase in gastrointestinal complications in patients over the age of 70. A prior history of gastroduodenal ulcers is another important risk factor for the development of NSAID-related ulcers

(Wolfe *et al.*, 1999). Whether a history of *Helicobacter pylori*-related ulcers further increases this risk is not known. In a group of *H. pylori* infected individuals, Chan *et al.*, 1997 recently reported a significant decrease in naproxen-induced ulcers in individuals whose *H. pylori* infection was eradicated. Further investigation is needed to determine whether screening for *H. pylori* infection prior to instituting NSAID therapy is indicated.

In addition, the type, dose, and length of therapy appear to influence the rate of complications. Several studies have reported a greater risk of complications with piroxicam and a relatively lower risk with the use of ibuprofen. While the risk of complications is also proportional to the dose of the NSAID given, it appears to be inversely proportional to the duration of therapy (Wolfe *et al.*, 1999). Therefore, those patients at greatest risk for complications may be the elderly who require short or intermittent courses of NSAIDs at high doses.

#### 4. TREATMENT OF NSAID-ASSOCIATED DYSPEPSIA

Dyspepsia is a broad term used to describe an array of upper abdominal symptoms including pain, cramping, distention, nausea, anorexia and/or heartburn. At least 5–20% of patients taking NSAIDs in large epidemiological studies encountered dyspeptic symptoms (Wolfe *et al.*, 1999). Several studies have evaluated the effect of H<sub>2</sub>-receptor antagonists in treating NSAID-related gastrointestinal symptoms. Bijlsma *et al.* (1988) performed a prospective, double-blinded study evaluating the effectiveness of cimetidine in treating NSAID-related dyspeptic symptoms. They found that 72% of patients receiving cimetidine 400 mg BID reported resolution of their symptoms, while only 49% of those receiving placebo became symptom free. Taha *et al.*, 1996 examined famotidine 20 mg BID and 40 mg BID in patients with arthritis receiving NSAIDs and found that abdominal symptoms decreased by 36.6 % and 43.3%, respectively. These studies thus support the use of H<sub>2</sub>-antagonists in individuals with NSAID associated dyspepsia. As discussed below, proton pump inhibitors (PPIs) also provide excellent symptomatic relief in addition to their capacity to decrease the incidence of NSAID-induced ulcers.

#### 5. TREATMENT OF NSAID-ASSOCIATED ULCERS

Since abdominal symptoms do not reliably predict the presence of NSAID-related gastroduodenal ulcers, patients with acute ulcers should have their NSAID therapy discontinued whenever possible or should have their current NSAID substituted with a nontoxic analgesic such as acetaminophen or salsalate, a non-acetylated salicylate that does not inhibit prostaglandin synthesis. If NSAID therapy is discontinued, treatment directed at healing the ulcer can be instituted with one of several agents discussed below, and at rates that compare favorably to those patients with 'idiopathic' peptic ulcers (Lancaster-Smith *et al.*, 1990).

### 5.1. Sucralfate

Sucralfate, a basic aluminum salt of sucrose octasulfate, is effective in the treatment and prophylaxis of duodenal ulcers and appears to be as effective as H<sub>2</sub>-antagonists in the healing of gastric ulcers. In patients who remain on NSAIDs, sucralfate has been found to heal duodenal ulcers as effectively as H<sub>2</sub>-antagonists; however, its benefit in healing gastric ulcers in this setting has not been proven (Wolfe *et al.*, 1999).

### 5.2. H<sub>2</sub>-receptor antagonists

Several open, uncontrolled, non-randomized studies (Croker *et al.*, 1980) and prospective, randomized studies (Davies *et al.*, 1986) have demonstrated that treatment with conventional doses of H<sub>2</sub>-receptor antagonists for 6 to 12 weeks results in healing of approximately 75% (50–88%) of gastric ulcers and 87% (67–100%) of duodenal ulcers despite the continued use of NSAIDs. When NSAIDs are continued, healing appears to be delayed and is largely dependent on the initial ulcer size with ulcers greater than 5 mm in diameter healing at a substantially lower rate than those less than 5 mm.

### 5.3. Prostaglandins

The role of PGs in the treatment of NSAID-associated ulcers is not well known. In 1998, Hawkey *et al.*, 1998 published a double-blind study of 935 patients comparing the efficacy of misoprostol to omeprazole in the healing of NSAID-associated gastroduodenal ulcers or erosions (greater than 10 erosions). The number of patients successfully treated after eight weeks was somewhat superior in those receiving omeprazole compared to those administered 200 µg QID of misoprostol. Healing of gastric ulcers occurred in 89%, 89%, and 77%, in those treated with 20 mg of omeprazole, 40 mg of omeprazole, and misoprostol, respectively, while healing of duodenal ulcers was 80%, 87%, and 73%, respectively, in these groups. Of note, omeprazole was better tolerated than misoprostol.

### 5.4. Proton pump inhibitors

Recent data suggests that PPIs possess an improved capacity to heal NSAID-related gastroduodenal ulcers independent of whether the NSAID is continued or not. A recent study comparing omeprazole to ranitidine in 541 patients with gastroduodenal ulcers demonstrated healing rates of 80% and 79% in patients treated with omeprazole 20 mg and 40 mg, respectively, while the healing rate with ranitidine was 63% (Yeomans *et al.*, 1998). Agrawal *et al.*, 1998 compared the efficacy of lansoprazole and ranitidine in the healing of gastric ulcers greater than 0.5 cm in diameter in patients continuing NSAID therapy. After 8 weeks, ulcers were healed in 73% and 75% of those patients treated with lansoprazole 15 mg and 30 mg, respectively, while the healing rate in the individuals receiving ranitidine was 57%.

## 6. PROPHYLAXIS AGAINST NSAID-INDUCED GASTRODUODENAL ULCERS

Because of the potential risks associated with NSAID use, efforts have recently focused on the prevention of mucosal injury. As mentioned earlier, prophylaxis is best accomplished by the avoidance of these medications in patients at increased risk from their toxicity. Alternative strategies to be considered include the co-administration of an agent with protective properties or the development of new anti-inflammatory agents with improved safety profiles.

### 6.1. Sucralfate

The exact mechanism by which sucralfate protects gastroduodenal mucosa is not known. Sucralfate has been shown by Caldwell *et al.*, 1987 to reduce gastroduodenal mucosal injury associated with NSAIDs. However, Agrawal *et al.*, 1991 reported no significant beneficial effect of sucralfate in the prevention of gastric ulcers in osteoarthritis patients receiving NSAIDs.

### 6.2. $H_2$ -receptor antagonists

In two placebo-controlled, prospective studies investigating the protective effects of ranitidine in arthritis patients treated with NSAIDs, an eight-week course of ranitidine 150 mg BID was demonstrated to be effective in preventing duodenal ulcers with rates of 0% and 1.5% in the treated patients, compared to 8% in the placebo-treated patients (Robinson *et al.*, 1989; Ehsanullah *et al.*, 1988). In contrast, ranitidine was ineffective in preventing gastric ulcers in both studies. Furthermore, Taha *et al.*, 1996 recently reported a beneficial effect of *high* dose famotidine (40 mg BID) in preventing both gastric and duodenal ulcers in arthritis patients receiving NSAIDs for 24 weeks. Although  $H_2$ -receptor antagonists appear to be effective in reducing NSAID-related ulcers and dyspeptic symptoms, Singh *et al.*, 1996 recently found that asymptomatic rheumatoid arthritis patients receiving  $H_2$ -receptor antagonists had a significantly higher risk for developing GI complications than those not taking these drugs. Thus, the *routine* use of  $H_2$ -receptor antagonists in the prevention of NSAID-associated ulcers cannot be recommended.

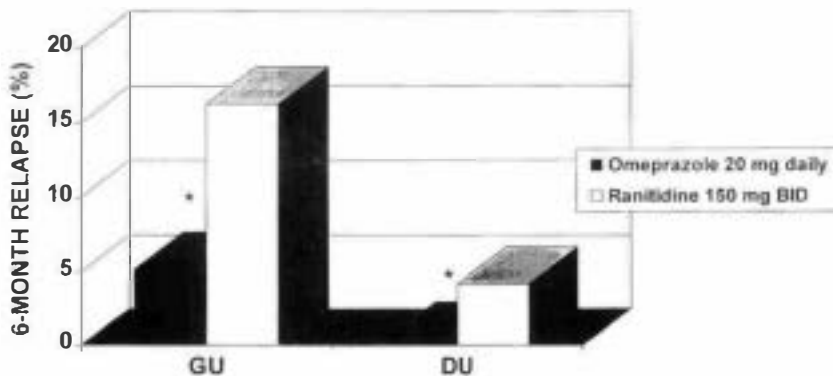
### 6.3. Misoprostol

Graham *et al.*, 1988 examined the prevalence of gastric ulcers in patients with osteoarthritis who had abdominal pain and were receiving NSAIDs. Patients were prescribed misoprostol 100  $\mu$ g QID, misoprostol 200  $\mu$ g QID, or placebo. Ulcers were detected in 1.4%, 5.6%, and 21.7%, respectively. In a subsequent study of 638 patients with chronic arthritis, Graham *et al.* (1993) further demonstrated that misoprostol significantly reduced the incidence of duodenal ulcers from 4.6% in those taking placebo to 0.6% in those taking misoprostol. Despite these encouraging results, dyspeptic symptoms did not improve in these studies, and diarrhea developed in 39% of patients taking 200  $\mu$ g of misoprostol. In a study

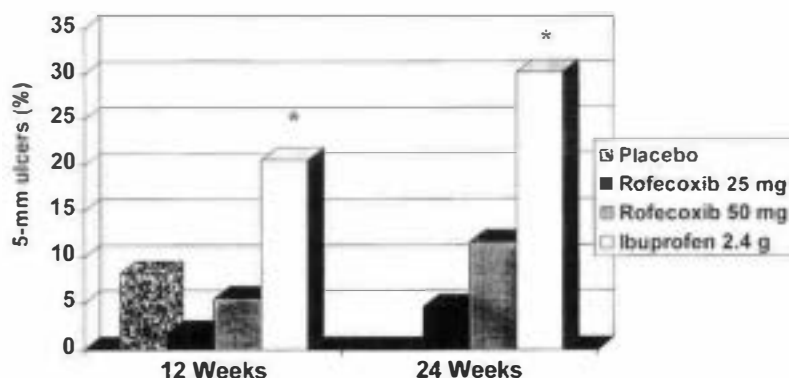
by Raskin *et al.* (1995) evaluating the prophylactic effect of misoprostol at doses of 200  $\mu$ g BID, TID and QID, the authors found that lower doses of misoprostol were better tolerated, but that a significant protective effect was only seen with the TID and QID regimens. Although the results of the above studies suggest that misoprostol is indeed effective in preventing NSAID-induced gastroduodenal ulcers, it is associated with significant side effects which include not only diarrhea and abdominal pain, but also increased uterine contractility that can lead to spontaneous abortion. Misoprostol is thus contraindicated in women of childbearing age who are sexually active.

#### 6.4. Proton pump inhibitors

Yeomans *et al.*, 1998 evaluated the prophylactic effect of omeprazole compared to that of ranitidine in 432 patients who were randomly assigned maintenance therapy with either 20 mg QD of omeprazole or 150 mg BID of ranitidine. After six months, 16.3% and 4.2% of those given ranitidine developed gastric and duodenal ulcers, respectively, but only 5.2% developed a gastric ulcer and 0.5% a duodenal ulcer in the omeprazole group (Fig. 1). Another study compared the efficacy of omeprazole and misoprostol in the prevention of recurrent ulcers in 732 patients who continued to receive NSAIDs. Patients were randomly assigned either placebo, 20 mg QD of omeprazole, or 200  $\mu$ g BID of misoprostol. At six months, duodenal ulcers were detected in 12% and 10% of those treated with placebo and misoprostol, respectively, while only 3% of those treated with omeprazole developed a duodenal ulcer. Gastric ulcers recurred in 32%, 10%, and 13% of the individuals receiving placebo, misoprostol, and omeprazole, respectively. These studies suggest that omeprazole is effective in preventing both initial ulcer formation as well as ulcer recurrence in patients who continue NSAID use.



**Figure 1.** Results of a randomized, double-blind, placebo-controlled trial that compared the ability of ranitidine 150 mg BID and omeprazole 20 mg QD to prevent the development of NSAID-induced gastroduodenal ulcers. Data adapted from Yeomans *et al.* (1998). \*  $p < 0.001$ .



**Figure 2.** Incidence of gastroduodenal ulcers (> 5 mm in diameter). The placebo group was observed for 12 weeks only. Data adapted from Laine *et al.* (in press). \* $p < 0.001$  compared to both doses of rofecoxib.

### 6.5. Preferential and selective COX-2 inhibitors

Attempts have been made to reduce NSAID toxicity through novel changes in their formulation. Recent surveillance and endoscopic studies have confirmed a lower incidence of gastroduodenal mucosal injury with the use of nabumetone, etodolac, and meloxicam (Wolfe *et al.*, 1999). These drugs preferentially inhibit COX-2, with less effect on COX-1, which appears to account for their improved safety profile. New highly selective COX-2 inhibitors, celecoxib and rofecoxib, recently entered the market and been shown to reduce the incidence of NSAID-related endoscopic ulcers (Fig. 2).

## 7. FUTURE DEVELOPMENT OF SAFER NSAIDS

Several other compounds are in development with hopes of increasing NSAID safety. These include nitric oxide (NO) releasing NSAIDs and NSAIDs preassociated with zwitterionic phospholipids. Trefoil peptides and basic fibroblast growth factor (bFGF) are also being examined for their potential clinical role in protecting against NSAID-induced mucosal injury.

## 8. CONCLUSION

Because of the pervasive use of NSAIDs in our society, it is important that physicians be able to identify and manage patients affected by NSAID-related gastrointestinal toxicity. Dyspepsia is a relatively common complication associated with NSAID use which is best managed with either an  $H_2$ -receptor antagonist or a PPI. Treatment of confirmed gastroduodenal ulcers should include withholding the NSAID when possible and providing a PPI. Once ulcer healing has been achieved, if NSAID therapy is to be re-instituted, prophylaxis against gastroduodenal toxicity

**Table 3.**

Recommendations for management of NSAID-associated gastroduodenal mucosal injury

Clinical presentation	Recommendation
Dyspepsia	Empirical H <sub>2</sub> -receptor antagonists (e.g. cimetidine 400 mg BID, ranitidine/nizatidine 150 mg BID, or famotidine 20 mg BID) or proton pump inhibitor (e.g. omeprazole 20 mg QD, lansoprazole 30 mg QD, rabeprazole 20 mg QD, or pantoprazole 40 mg QD)
Active ulcer	NSAID discontinued: H <sub>2</sub> -receptor antagonist or proton pump inhibitor NSAID continued: proton pump inhibitor
Maintenance therapy	Coadministration of proton pump inhibitor Coadministration of misoprostol (at least 200 µg TID) COX-2 preferential agent (e.g. nabumetone, etodolac, or meloxicam) COX-2 selective agent (e.g. celecoxib and rofecoxib)

is best accomplished through the use of a PPI, misoprostol (at least 200 µg TID), or an NSAID that preferentially or selectively inhibits COX-2 (Table 3).

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