Inflammopharmacology, Vol. 7, No. 3, pp. 277–286 (1999)

Management of NSAID-related gastrointestinal mucosal injury

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Received 10 August 1999; accepted 18 August 1999

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_2-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 E1 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.

1. 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 *H. pylori* 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_2-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_2-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_2-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_2-antagonists; however, its benefit in healing gastric ulcers in this setting has not been proven (Wolfe *et al.*, 1999).

5.2. H_2-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_2-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 [illegible] 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%.

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