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REVIEW

NONSTEROIDAL ANTIINFLAMMATORY DRUGS AND THE GASTROINTESTINAL TRACT

The Double-Edged Sword

DAVID R. LICHTENSTEIN, SAPNA SYNGAL, and M. MICHAEL WOLFE

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are used commonly in Western societies for a variety of rheumatic disorders. Over 35 million NSAID prescriptions and billions of over-the-counter aspirin, ibuprofen, and naproxen preparations are sold annually in the United States (1), and more than 1% of the American population uses these drugs on a daily basis (2). For the majority of individuals, they are well tolerated; nevertheless, in a significant minority, gastrointestinal (GI) side effects may result in serious complications necessitating their discontinuation (2). Physicians responsible for appropriately prescribing these medications must balance their antiinflammatory and analgesic benefit against their potential for inducing serious GI toxicity. Adverse effects from these medications as a group are reported to the Food and Drug Administration more frequently than from any other medication class (3).

Although adverse events affect only a small proportion of those taking NSAIDs, their widespread use translates into a substantial number of affected persons. Furthermore, complications associated with these side effects contribute considerably to increased morbidity and mortality, and treatment of these common but debilitating diseases entails significant costs. Consecutive rheumatoid arthritis (RA) patients (n = 1,949) enrolled in the Arthritis, Rheumatism, and Aging Medical Information System were studied prospectively for an average duration of >3 years. The data gathered from these studies showed that GI-related hospitalizations were 6 times more frequent in patients with RA who were taking NSAIDs than in those who were not and that deaths from GI causes occurred approximately twice as frequently in RA patients as in the general population (4). NSAIDs thus constitute a class of drugs that can best be characterized as a "double-edged sword"—medication that is remarkably effective, yet carries a significant risk potential.

David R. Lichtenstein, MD, Sapna Syngal, MD, M. Michael Wolfe, MD: Harvard Medical School and the Brigham and Women's Hospital, Boston, Massachusetts.

Address reprint requests to M. Michael Wolfe, MD, Brigham and Women's Hospital, Gastroenterology Division, 75 Francis Street, Boston, MA 02115.

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Pathogenesis of NSAID-induced GI mucosal damage

A thorough understanding of normal mechanisms involved in mucosal defense is requisite for understanding the pathophysiology of NSAID-induced GI injury. In general, gastroduodenal ulcers develop when aggressive factors, such as gastric acid and pepsin, overwhelm the normal defensive properties inherent to the mucosa. More than 90% of such ulcers are associated with chronic infection with the bacterium *Helicobacter pylori* or the use of NSAIDs, both of which impair mucosal defense and allow acid and other potentially noxious agents to cause damage. Therefore, gastric acid is still believed to play a central role in the pathogenesis of ulceration. Over the years, however, concepts regarding NSAID-induced mucosal damage have evolved from simply one of topical injury to theories coordinating multiple mechanisms that include both local and systemic effects. No single property can account for the ability of the mucosa to withstand injury from NSAIDs and other noxious agents. NSAIDs affect several factors believed to represent integral components of mucosal defense, including prostaglandin inhibition, alterations in

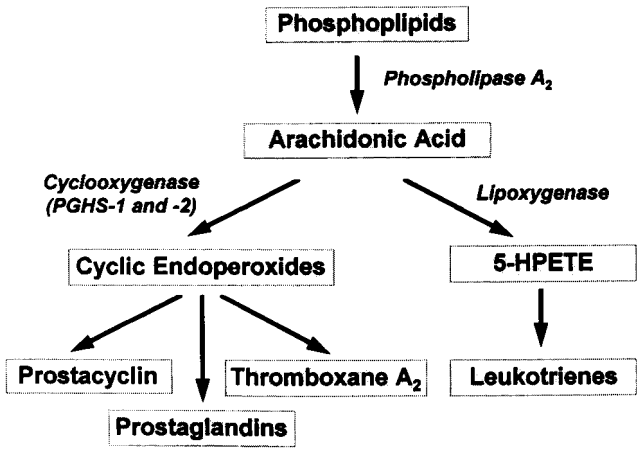

Figure 1. Pathways depicting the synthesis of prostaglandins and leukotrienes, derived from membrane phospholipids. PGHS-1 and 2 = prostaglandin H synthase–1 and –2.

mucosal blood flow, active ion transport, permeability to H^+ ions, and the ability to buffer acid.

The role of prostaglandins

Prostaglandins belong to a class of polyunsaturated 20-carbon fatty acids derived from arachidonic acid (Figure 1), a phospholipid component present in all cell membranes. Arachidonic acid is released from the cell membrane into the cytoplasm by phospholipase A_2 and is converted to prostaglandins or leukotrienes by the enzymes cyclooxygenase and 5-lipoxygenase, respectively. Synthesis of specific prostaglandins is tissue specific, and the most prevalent in the gastroduodenal mucosa are prostaglandin E_2 (PGE_2), PGI_2, and $PGF_{2\alpha}$ (5). Prostaglandins inhibit gastric acid secretion endogenously, and when administered exogenously, by reducing the generation of intracellular cAMP. They are also a critical component of gastroduodenal mucosal defense, protecting the mucosa from damage from a wide variety of noxious agents (6). The finding that prostaglandins defend against mucosal injury at concentrations below those required to inhibit acid secretion had previously been termed "cytoprotection" (7). Originally identified based on gross morphologic observations, mucosal damage due to NSAIDs has now been detected by histologic examination (8), and it has thus been suggested that the term "mucosal protection" is preferable (9). Prostaglandins have been shown to enhance mucosal protection by stimulating all the inherent local components of defense listed above.

Mechanisms of NSAID toxicity in the GI tract

Schoen and Vender introduced the dual injury hypothesis, in which NSAID-induced damage is believed to occur as a result of a dual insult to the gastroduodenal mucosa (Figure 2). The initial injury is believed to occur by NSAID-mediated direct damage, followed by a systemic effect in which prostaglandin synthesis is inhibited (10). Topical injury may also occur as a result of the biliary excretion of active hepatic metabolites and subsequent duodenogastric reflux. The effects are additive; either topical or systemic mechanisms alone are sufficient to produce gastroduodenal mucosal damage. Much of our understanding of the mechanisms involved in NSAID-induced mucosal damage is derived from early studies using salicylates, such as aspirin, which produce a pH-dependent local damaging effect. At an intragastric pH of <3.5, a level of acidity commonly found in the stomach, aspirin predominates in its nonionized lipophilic form. These conditions favor transport across plasma membranes into mucosal epithelial cells and "ion trapping": the dissociated ions are trapped inside the cell. Within a few minutes of aspirin ingestion, denudation of the surface epithelium occurs, resulting in increased mucosal permeability (10). Na^+ and K^+ enter the luminal fluid, and H^+ ions "back-diffuse" into the gastric lumen. Back-diffusion of H^+ ions, in turn, leads to further mucosal damage.

Several lines of investigation have lent support to the belief that local effects are not the only factors involved in NSAID-induced mucosal damage. For example, enteric-coated tablets produce less acute gastroduodenal mucosal injury than do regular formulations, but are nevertheless ulcerogenic (11). Gastroduodenal ulcers also occur following parenteral (12) and rectal (13) administration of NSAIDs, without

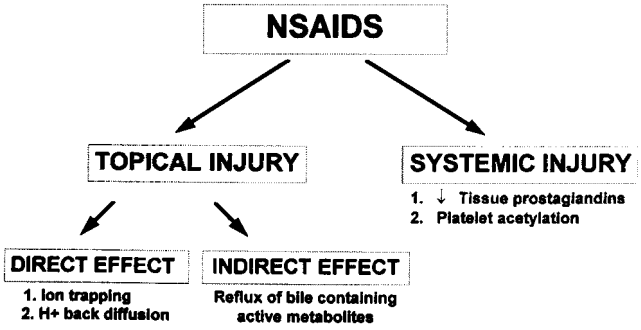

Figure 2. Mechanisms by which nonsteroidal antiinflammatory drugs (NSAIDs) induce gastroduodenal mucosal injury. (Adapted from the dual injury hypothesis of Schoen and Vender [10].)

causing changes in gastric transmucosal potential difference. Prodrugs have been developed that exert their antiinflammatory effects only after absorption and biologic transformation to their active moiety. Such drugs, although leading to little superficial damage, are still associated with gastroduodenal ulceration (14,15).

The systemic manifestations of NSAIDs have been shown to involve decreased mucosal synthesis of various prostaglandins through the inhibition of the enzyme cyclooxygenase. The mechanisms by which reduced mucosal prostaglandin synthesis leads to mucosal injury have not been fully elucidated, although, as stated previously, prostaglandins can affect virtually any component of mucosal defense. Recent studies (16,17) have demonstrated the presence of 2 related but unique cyclooxygenase isoenzymes in mammalian cells (Figure 1). The 2 enzymes, referred to as prostaglandin endoperoxide (prostaglandin H) synthase–1 and –2 (PGHS-1 and PGHS-2), are ~60% homologous. They possess nearly the same affinity for and capacity to convert arachidonic acid to prostaglandin H_2, the first committed step in prostaglandin synthesis. PGHS-1 is expressed constitutively, while PGHS-2 is nearly undetectable in most tissues under normal physiologic conditions. In response to inflammation, however, its expression increases dramatically, while expression is nearly abolished by glucocorticoids. Meade et al (18) have reported that nabumetone, a nonacidic prodrug, selectively inhibits PGHS-2, without any effect on PGHS-1 expression, in COS cells transfected with complementary DNAs for the respective isoenzymes. Although this interesting in vitro observation must be confirmed in human studies before its clinical relevance can be suggested, it represents an attractive hypothesis that may lead to the development of new NSAIDs that target only those prostaglandins involved in inflammation, without any effect on the regulation of normal cellular processes.

The x-ray crystal structure of PGHS-1 has recently been shown to consist of 3 distinct folding unit domains. The first domain, whose role is as yet undefined, has a structure very similar to that of epidermal growth factor. The second domain consists of multiple α-helices that likely function to allow insertion of the enzyme into the membrane lipid bilayer, and the third is the catalytic domain containing the cyclooxygenase and peroxidase active sites. Although the significance of these structural characteristics is presently unknown, a thorough understanding of the structure of PGHS isoenzymes may permit elucidation of the mechanisms involved in NSAID inhibition (19).

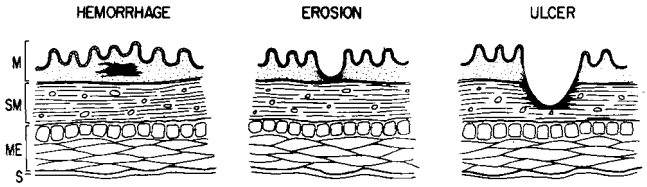

Figure 3. Schematic diagram of gastroduodenal injury caused by nonsteroidal antiinflammatory drugs. Mucosal hemorrhage is limited to the mucosa (M), while erosions and ulcers extend to the submucosa (SM) and muscularis externa (ME), respectively. Although not depicted, deep ulcers may on occasion extend to the level of the serosa (S). In general, the risk of hemorrhage is increased by the depth of the injury.

Types of NSAID injury

The spectrum of injury from NSAIDS includes a combination of punctate subepithelial hemorrhages, erosions, and ulcerations (Figure 3). The true distinction between erosions and ulcerations is dependent upon a pathologic definition of lesion penetration, i.e., to the level of the submucosa for ulcers and superficial involvement confined to the mucosa for erosions. From an endoscopic standpoint, the distinction is quite subjective and is based on a combination of lesion size, shape, and depth. Erosions are more likely to be small, linear, and superficial, whereas ulcers tend to be larger and deeper. In most endoscopic studies, a size cutoff (3–5 mm) is arbitrarily utilized to define the two lesions, and is based on little or no scientific evidence. Using depth as a criterion is more problematic since this parameter is more difficult to quantify, and deep ulcers may lack visible depth due to the presence of an exudate within the ulcer base. Several scoring scales have been devised to grade the severity of mucosal injury as a continuum, by assigning a numeric score to each of the categories of submucosal hemorrhages, erosions, and ulcers. These scales are generally not useful, and it is preferable to focus attention on each of these categories individually. It is rational to consider a patient with a deep, large ulcer to be at higher risk than one with a small superficial erosion or submucosal hemorrhage, since only the former lesion is typically associated with significant hemorrhage or perforation.

Acute NSAID effects

"Short-term" endoscopic studies of NSAID administration to normal volunteers have demon-

strated dose-dependent gastroduodenal mucosal injury (3), with virtually all NSAIDs showing the potential to produce a superficial injury termed "NSAID gastropathy." This term is ill defined and may refer to a spectrum of lesions that includes subepithelial hemorrhages, erosions, and ulcers. Short-term administration of NSAIDs can cause ultrastructural gastric surface epithelial damage within minutes and gross endoscopic gastroduodenal subepithelial hemorrhages and erosions within several hours of ingestion (20). As mentioned above, the incidence and severity of acute mucosal injury are dose dependent; virtually 100% of subjects develop lesions after a single 650–1,300 mg dose of aspirin. However, in response to long-term aspirin administration, mucosal adaptation occurs in most individuals, resulting in diminished damage despite continued use (21,22). No area of the stomach is resistant to NSAID-induced mucosal injury; however, the most frequent and severely affected site is the gastric antrum (20).

The clinical importance of "acute" NSAID-induced gastroduodenal injury is not clear since few data are available to stratify risk based on the endoscopic appearance and nature of acute NSAID-induced mucosal damage. Although the incidence and severity of acute injury vary among different NSAID formulations (3,23), a poor correlation exists between the acute injury observed during short-term NSAID administration and the subsequent development of mucosal ulceration or serious complications during prolonged use (24). In most, but not all, studies, superficial gastric damage is not a necessary prerequisite for, nor is its absence a guarantee against, the development of NSAID-induced ulceration. This point is best demonstrated by the prodrug sulindac, which causes only minimal gastroduodenal damage when administered on a short-term basis (14), yet in a recent retrospective cohort study exhibited the highest relative risk for overt upper GI bleeding when compared with many other NSAIDs (15).

Misoprostol (25,26), a prostaglandin analog, and the H_2-receptor antagonists cimetidine (25,27) and ranitidine (21) have been shown to protect the duodenal mucosa from injury during short-term (up to 2-week) administration of aspirin and other NSAIDs. Although the H_2-receptor antagonists and sucralfate may also prevent the development of gastric subepithelial hemorrhages (21,27), only misoprostol has been shown to unequivocally protect the gastric mucosa when damage is defined as erosive injury rather than mucosal hemorrhage (25,26). As determined by studies using ^{51}Cr-labeled red blood cells, prostaglandins (28), sucralfate (22), and H_2-receptor antagonists (29) have all been shown to reduce fecal blood loss in normal subjects and arthritis patients taking salicylates or other NSAIDs, reflecting a reduction in mucosal injury.

Long-term NSAID effects

Unlike short-term NSAID use, long-term therapy with these agents can lead to gastroduodenal ulceration (4,30–32) and associated serious complications—hemorrhage, perforation, and death (33–35). A life-threatening, previously asymptomatic complication may be the presenting manifestation of NSAID injury in as many as 58% of subjects (32), and as many as 35% of individuals with upper GI hemorrhage report a recent exposure to NSAIDs. Duodenal mucosal injury occurs less commonly and is generally less severe than the corresponding gastric damage. However, ulcer complications associated with NSAIDs occur with approximately equal frequency in these two sites (13,31), suggesting that duodenal ulcers are more virulent or, alternatively, that their complications reflect an exacerbation of an underlying ulcer diathesis.

A number of prospective cross-sectional endoscopic studies have consistently demonstrated mucosal damage in 50–75% of arthritis patients treated with long-term NSAID therapy. These studies have shown a combined prevalence of gastric and duodenal ulcers of 10–20% (33,36), a value 5–15-fold greater than would be expected in an age-matched healthy population. Retrospective case–control (30,31) and cohort (15,37,38) research designs have been used to demonstrate the association of long-term NSAID use with the risk of development of peptic ulcer complications. The odds ratio for development of ulcers and complications among NSAID users varies greatly in these studies, ranging from 1 to 30. These disparate findings can largely be attributed to differences in study design; drug type, dosage, and duration; and study population.

As stated above, although the relative risk per patient prescription for complication from an NSAID-associated ulcer is quite small, this small risk translates into a large number of actual complications when one considers the millions of individuals taking prescribed or over-the-counter NSAIDs. Estimates of the incidence of serious adverse GI events approximate 1–2 per 1,000 users per year, with rates ranging from 0.4/1,000 in the young to 4/1,000 in the elderly

(13,32,39). A similar risk of major upper GI hemorrhage, of ~1 episode in 10,000 months of aspirin use, was calculated from a prospective study of non-ulcer patients taking 1 gm of aspirin daily for the prevention of myocardial infarction (40).

Risk factors for NSAID gastroduodenopathy complications

No subgroup of patients is completely free from the risk of NSAID-associated ulcers or complications. Although NSAID use may result in an increased incidence of abdominal discomfort (36), the presence of dyspepsia is an unreliable marker for the presence of gastroduodenal mucosal injury. Approximately 30–40% of patients receiving long-term NSAID treatment experience symptoms of dyspepsia. Symptoms correlate poorly with the endoscopic appearance and severity of mucosal injury: up to 40% of individuals with endoscopic evidence of erosive gastritis are asymptomatic (36,40), and conversely, as many as 50% of patients with dyspepsia have normal-appearing mucosa (36). Of the 4,524 patients in the Aspirin Myocardial Infarction Study, only 5% of those with dyspepsia were found to have ulcers (41). A second study, by Armstrong and Blower (42), found no antecedent symptoms in 58% of NSAID-treated patients hospitalized for GI hemorrhage, compared with 25% of non–NSAID-related hemorrhages. Considering the extent to which symptoms are unreliable predictors of ulcers and gastroduodenal complications in patients receiving NSAIDs, it would be useful if other risk factors could be utilized to identify subgroups of NSAID users who are at particularly high risk for developing complications.

Testing for fecal occult blood has been proposed as a predictor of NSAID-induced mucosal ulcer; however, its presence has not proven to be a reliable predictor either of mucosal injury or of which patients are most likely to develop ulcer complications. Furthermore, the presence of occult GI bleeding cannot be assumed to be due to NSAID-associated mucosal lesions, since a similar incidence of colorectal tumors is found in patients with occult GI bleeding independent of NSAID use (43,44).

Several factors appear to increase the risk of ulcers and complications in persons taking NSAIDs (Table 1). These include a prior history of peptic ulcer disease; type, dose, and duration of NSAID; patient age; concomitant corticosteroid use; and a previous NSAID-associated complication. In a recent meta-analysis involving 16 studies (9 case–control and 7 cohort), the risk for development of a serious GI complication during NSAID use was 3 times higher than in nonusers (45). Significant risk factors included age >60 years, previous history of GI complications, and concomitant corticosteroid use, with relative risk ratios for these factors of 5.5, 4.8, and 1.8, respectively.

Table 1. Risk factors for nonsteroidal antiinflammatory drug (NSAID) ulcer complications

Definite
Age >65
Prior ulcer disease or complication
High-dose, multiple NSAIDs
Concomitant corticosteroid therapy
Duration of therapy (<3 months)
Possible
Condition necessitating NSAID treatment (e.g., rheumatoid arthritis)
Female sex
Smoking
Alcohol
Helicobacter pylori

It has been theorized that NSAIDs may mask the warning symptoms of ulceration due to their analgesic action (41). However, a recent study demonstrated a similar prevalence of symptoms in patients with ulcer complications independent of NSAID use, after controlling for the age-related decline in epigastric pain (13). This study suggests that age, and not NSAID use, may represent the primary determinant of painless ulcer complications. Sex does not appear to be an independent risk factor since an increased susceptibility to NSAID complications among women has been an inconsistent finding in the literature (13), and no sex-related effect was found in the above-mentioned meta-analysis (45). Previous findings of an elevated risk among women may thus merely reflect an increased consumption of NSAIDs by this group.

A strong interaction between NSAIDs and corticosteroids has been noted, with an increased risk of ulcers in corticosteroid users confined only to those who concomitantly take NSAIDs (46). The relative risk of complications with combined use is up to 10.6-fold greater than observed for NSAID use alone (46). However, these studies have not been controlled for the severity of underlying illness, and those taking the combined medication may be expected to be at increased risk for ulcer hospitalization due to a greater prevalence of comorbid illness. The presence of a rheumatic disorder has also been said to confer an increased risk of gastroduodenal ulcer in NSAID users

(47). However, this association may possibly be explained by the consumption of higher doses for longer durations by these individuals.

The type, dose, and duration of NSAID therapy appear to independently determine the risk for development of gastroduodenal ulcers and their complications. The ulcer risk is present throughout the duration of therapy, but appears to be greatest during the first month (13,30,42,45). In one series, 25% of serious ulcer complications developed during the first month of NSAID therapy, and some within the first week of treatment (42). A study by Griffin et al (30) identified a relative risk of 7.2 for those patients with a total duration of use of <30 days, compared with a relative risk of 3.9 for those with >90 days of use. Gabriel et al (45) identified a risk that varied with duration of NSAID use, from an 8.0-fold increased risk for ≤1 month of exposure, to 3.3-fold for 1–3 months of exposure, to 1.9-fold for ≥3 months of exposure. These data suggest that the increased risk during the early course of NSAID therapy may signify the development of mucosal adaptation, allowing the gastroduodenal mucosa to withstand injury during long-term use. Unfortunately, the mechanisms responsible for mucosal adaptation and the reasons for its failure in those who develop ulcers remain unknown.

As with acute mucosal injury, a direct relationship has been found between NSAID dose and the risk of GI complications (13,30). Griffin et al (30) found a relative risk that increased from 2.8 during therapy with standard doses to a relative risk of 8.0 for the highest-dose category. Some investigators have found an additive risk when NSAIDs are used in combination with aspirin or a second non-aspirin NSAID (13), while others have not confirmed such an association (34). Although information is limited, the risk associated with the use of a combination of a non-aspirin NSAID and low-dose aspirin (<150 mg daily) does not appear to be greater than that with the use of an NSAID alone (13).

All NSAIDs possess the potential to initiate serious adverse GI events; however, the relative risk may vary among different formulations. These differences may occur as a result of variations in relative potency for inhibiting prostaglandin synthesis, duration of action, systemic absorption, drug solubility in gastric juices, and pH-dependent partition in the gastroduodenal mucosa. Griffin et al (30) reported relative risks for ulcer formation with several NSAIDs from a low of 2.3 for ibuprofen to a high of 8.7 for meclofenemate. Likewise, a meta-analysis (45) and a case–control study by Henry et al (13) found the greatest risk of complications with piroxicam, with progressively lower risk ratios for indomethacin, aspirin, naproxen, and ibuprofen.

A number of modifications in the formulation of NSAIDs have been introduced in an attempt to reduce the toxicity of the various preparations. Conventional over-the-counter buffered aspirin products appear to offer little protection against the risk of mucosal injury due to their insufficient buffering capacity. Use of enteric-coated preparations of aspirin (48) results in delayed, but not decreased, salicylate absorption, and leads to a similar degree of gastric mucosal prostaglandin inhibition. Although superficial mucosal injury may be reduced because of decreased topical exposure of the mucosa, the risk of ulcer development may not be affected. Salsalate, a nonacetylated salicylate that is insoluble at the usual acidic gastric pH, does not appreciably inhibit gastric mucosal prostaglandin synthesis (49) and as a result, topical gastroduodenal mucosal injury observed with this agent is generally less than that seen with enteric-coated aspirin, despite equivalent serum salicylate concentrations. Although unproven, a reduction in the ulcerogenic potential with this preparation during long-term use may be possible (50). Avoidance of topical mucosal injury by the parenteral administration of an NSAID such as ketorolac (12) or the rectal administration of NSAIDs (13) has also failed to reduce the development of ulcer complications.

The development of prodrugs to avoid topical proximal GI tract toxicity has met with variable success. For example, sulindac appears to confer little protective advantage over other NSAIDs (15). Following absorption, this prodrug undergoes hepatic metabolism to its active moiety, sulindac sulfide, which undergoes biliary excretion and inhibits cyclooxygenase. A newer prodrug, nabumetone, has been reported to be less toxic due to several factors, including selective inhibition of peripheral prostaglandin synthesis (34). In addition, this prodrug is a weak cyclooxygenase inhibitor with a nonacidic structure that avoids mucosal trapping and topical mucosal injury. It is converted in the liver to its active metabolite, 6-methoxy-2-napthylacetic acid, which does not significantly inhibit gastric prostaglandin synthesis and is not excreted into the biliary tree. Finally, as discussed above, selective inhibition of the cyclooxygenase isoenzyme PGHS-2, without an effect on PGHS-1, may theoretically improve the safety profile of nabumetone (18). Another new NSAID, etodolac, in con-

trast to nabumetone, is ingested in a metabolically active form, but similarly does not inhibit gastric prostaglandin synthesis (34).

Postmarketing surveillance data (35,51) and short-term endoscopic studies (52,53) indicate a lower incidence of gastroduodenal erosive injury with both of these agents. In a 12-week endoscopic study involving 37 arthritis patients, significantly less gastroduodenal ulceration was observed with nabumetone 1,000 mg daily when compared with naproxen 500 mg daily. Among naproxen-treated patients, 5 developed an ulcer and 5 developed erosions, in contrast to the group treated with nabumetone, in which only 1 patient developed an ulcer and 1 an erosion (52). Roth et al (54) recently reported no significant difference in the incidence of gastroduodenal ulcers in patients treated for 3 months with either nabumetone alone or a combination of ibuprofen and misoprostol (1.7% and 0% cumulative incidence, respectively). In the same prospective study, 15.1% of patients treated with ibuprofen alone were found to have endoscopically verified ulcers >5 mm in size. In a postmarketing survey study of 1,912 nabumetone-treated arthritis patients in the United States, ulcers were identified in only 13 (0.7%), and no complications were reported (35). In the United Kingdom, an evaluation of 10,800 arthritis patients treated with nabumetone revealed only 11 serious complications (0.1%), 7 of which were GI hemorrhage (55). A review of treatment with etodolac in 3,702 patients participating in double-blind studies and 8,334 patients in open-label clinical trials showed a 0.3% incidence of gastroduodenal ulcer formation, with no reports of bleeding or perforation (51).

These preliminary results are encouraging, particularly when compared with ulcer rates of 15–20% and complication rates of 0.5% observed in studies of older NSAIDs. As discussed below, whether a decrease in the incidence of gastroduodenal ulceration is associated with a concomitant decrease in the rate of complications, principally GI hemorrhage, is unknown and must await the performance of large-scale, randomized, prospective comparative trials.

Other potential, but unproven, risk factors for NSAID-induced ulcers include smoking, alcohol, anticoagulation treatment, and *H pylori* infection. Smoking is an established risk factor in peptic ulcer formation, but whether smoking increases the risk in NSAID users is unknown. Preliminary reports cite an increased risk for development of bleeding ulcers in patients who are taking oral anticoagulants and NSAIDs concurrently, suggesting the need for caution when prescribing NSAIDs in patients receiving long-term anticoagulation therapy (56). The relationship between *H pylori* infection and NSAID use, and whether the two act synergistically in the pathogenesis of gastroduodenal ulceration, is unknown. Both independently impair mucosal defense and are permissive factors in the formation of ulcers. "Pure" NSAID-related ulcers can, nevertheless, be distinguished from *H pylori*–related ulcers by histologic examination of the mucosa. *H pylori* induces an acute and chronic inflammatory infiltrate in the gastric mucosa termed "chronic active gastritis," whereas pure NSAID ulcers occur in the background of normal mucosa (56). Owing to age-related increases in both *H pylori* infection and osteoarthritis, a large number of patients with gastric colonization by this organism will be taking NSAIDs. However, 3 large studies of patients taking therapeutic doses of NSAIDs have failed to demonstrate an increase in mucosal injury or dyspepsia in *H pylori*–infected subjects (57–59). Therefore, screening for *H pylori* prior to institution of NSAID therapy does not appear to be warranted at the present time.

Prophylaxis against NSAID gastroduodenopathy

Due to the significant rate of complications and the inability of dyspepsia symptoms to reliably predict the presence of mucosal ulcerations, recent efforts have been directed at the prevention of NSAID-induced mucosal injury. One obvious way to eliminate this risk is to avoid the use of NSAIDs whenever possible. In many patients, when analgesia rather than an antiinflammatory effect is the goal of therapy, the NSAID dosage may be reduced or acetaminophen may be substituted (60).

As stated previously, prostaglandins, principally of the E type, diminish acute gastric mucosal damage induced by irritants such as acid, ethanol, bile salts, and boiling water. At low doses, prostaglandins exert their beneficial effects exclusively by enhancing endogenous mucosal defense mechanisms, while at higher doses, they also inhibit acid secretion by preventing the generation of intracellular cAMP. Numerous studies have shown that misoprostol, a synthetic PGE_1 analog, is effective in preventing NSAID-induced gastroduodenal ulcers, but only when administered in doses sufficient to inhibit acid secretion. Therefore, despite their reputation as mucosal protective agents, the clinical efficacy of prostaglandins cannot be separated from their antisecretory properties.

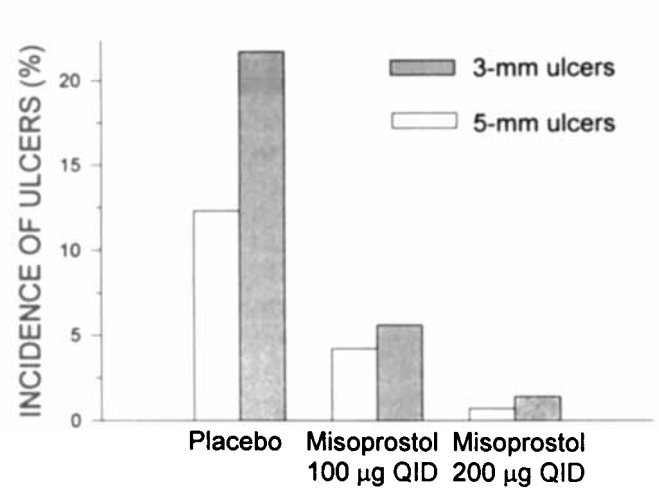

Figure 4. Cumulative (12-week) incidence of gastric ulcer following nonsteroidal antiinflammatory drug therapy with and without concomitant misoprostol prophylaxis (ref. 33).

Three multicenter, prospective, randomized, single- or double-blind trials have addressed the question of whether administration of misoprostol prevents gastroduodenal ulceration in patients taking NSAIDs (33,61,62). The first of these studies was reported in 1988 and included patients with osteoarthritis who had associated abdominal pain while taking ibuprofen, piroxicam, or naproxen (33). Patients with gastric ulcers, defined as mucosal breaks of >0.3 cm in diameter, at the initial endoscopic evaluation were excluded from randomization, as were those patients with a history of recurrent peptic ulcer. Of the 420 patients enrolled, 139 were randomly assigned to receive high-dose misoprostol (200 μg 4 times daily), 143 to receive low-dose misoprostol (100 μg 4 times daily), and 138 patients to receive placebo during continued NSAID use. All enrolled patients underwent repeat endoscopy 1, 2, and 3 months after the initiation of therapy. The cumulative 3-month prevalence of gastric ulcers was 1.4% for high-dose misoprostol, 5.6% for low-dose misoprostol, and 21.7% for placebo (Figure 4). These numbers are somewhat inflated since ~40% of the "ulcers" were lesions 2–4 mm in diameter, and were thus more likely to be erosions. Nevertheless, if only lesions >0.5 cm in diameter are considered, the results of the study remain significant, with a cumulative 3-month gastric ulcer prevalence of 0.7%, 4.2%, and 12.3%, in the 3 treatment groups, respectively (Figure 4). Although ulcer depth (in all likelihood an important variable) was not assessed, this study led to the approval of misoprostol at a dosage of 200 μg 4 times daily for the prevention of NSAID-induced gastric ulcers.

A second trial of similar design, by the same investigators (61), found sucralfate to be ineffective in preventing gastric ulcer formation in symptomatic patients with rheumatic disorders who were taking naproxen, ibuprofen, or piroxicam. Gastric ulcers occurred during 3 months of prophylactic therapy in 21 of 131 patients (16%) taking sucralfate 1 gm 4 times daily, compared with only 2 of 122 (1.6%) of those taking misoprostol 200 μg 4 times daily. When ulcer diameter was restricted to those >0.5 cm, the ulcer rates were 9.2% and 0.8%, respectively.

With regard to duodenal ulcer prevention, the first misoprostol study noted the development of duodenal ulcers in only 12 patients (2.9%) (4 in the misoprostol 200 μg 4 times/day group, 3 in the misoprostol 100 μg 4 times/day group, and 5 in the placebo group), numbers insufficient for meaningful conclusions. The second study was not designed to assess duodenal ulcer prophylaxis. However, a retrospective review of the 253 evaluable patients in this latter study revealed the development of only 3 duodenal ulcers, 2 in the misoprostol-treated group and 1 in the sucralfate group. These promising results led Graham et al to study the ability of misoprostol to prevent NSAID-induced duodenal ulcers in a third study (62). A group of 638 patients with chronic arthritis, but no ulcers on screening endoscopy, were randomized to receive misoprostol 200 μg 4 times daily or placebo while continuing NSAID treatment with ibuprofen, piroxicam, naproxen, sulindac, tolmetin, indomethacin, or diclofenac. Unlike the previous 2 studies, the presence of symptoms was not required for patient entry. This study confirmed the efficacy of 3 months of misoprostol cotherapy in preventing gastric ulcers. Moreover, misoprostol significantly reduced the incidence of duodenal ulcers from 4.6% in those taking placebo to 0.6% in those taking misoprostol. In all studies, misoprostol therapy did not interfere with the antiinflammatory effects of the NSAID, and dosage adjustments were not required for patients with renal insufficiency.

Despite the efficacy of misoprostol in preventing gastroduodenal ulcers, a beneficial effect on dyspepsia symptoms attributable to NSAIDs has not been proven. During the initial study by Graham et al (33), 70% of misoprostol-treated patients were pain free after 3 months of treatment. However, 57% of placebo-treated patients were similarly pain free, a difference that was not statistically significant. Furthermore, diarrhea developed in a dose-dependent manner in

13% of placebo-treated patients, 25% of patients taking 100 μg of misoprostol 4 times/day, and 39% of those taking 200 μg of misoprostol 4 times/day. These results indicate that misoprostol is ineffective in preventing symptoms caused by NSAIDs and confirm the previously stated lack of correlation between symptoms and mucosal damage. Misoprostol thus cannot be recommended as prophylaxis for symptoms produced by NSAIDs. Another significant side effect of misoprostol is increased uterine contractility, which can lead to spontaneous abortion. Misoprostol is therefore contraindicated in women of childbearing age who are sexually active.

Two placebo-controlled, prospective studies investigated the protective effect of concomitant pure antisecretory therapy with an H_2-receptor antagonist in arthritis patients receiving NSAID therapy (63,64). An 8-week course of treatment with ranitidine 150 mg twice daily proved to be effective in preventing duodenal ulcer formation, with rates of 0% and 1.5% in the 2 studies, compared with 8% in placebo-treated patients in both studies. In contrast, ranitidine was ineffective in preventing gastric ulcers in both studies. Unfortunately, no long-term studies have directly compared the ability of misoprostol and H_2-receptor antagonists to prevent gastroduodenal ulcer formation.

Despite advances in the understanding, treatment, and prevention of NSAID-induced gastroduodenal injury, a number of questions remain unanswered. Does misoprostol prevent ulcers during aspirin use? None of the 3 published misoprostol trials included patients who were taking salicylates. Does misoprostol reduce NSAID-induced ulcer complications during prolonged NSAID use? Is misoprostol equally effective in high-risk patients with a prior history of recurrent ulcer disease? Unfortunately, this group of patients was excluded from prior investigations. Does the eradication of *H pylori* infection affect prophylactic measures? Finally, is prophylaxis really cost effective? Further prospective, randomized studies are necessary to address these questions, as well as to define the optimal length of therapy and the groups of individuals most likely to benefit from prophylaxis. The average cost for a 1-month course of misoprostol ranges from $50 to $75. Reports on the cost-effectiveness of misoprostol are based on the assumptions that hospitalization and complications are prevented by therapy and that the results of the studies can be applied to unselected groups of patients (65).

No clear guidelines are universally accepted for prophylactic treatment with misoprostol; however, it appears rational to treat patients who are at the highest risk for developing gastroduodenal ulceration (Table 1). This group includes those with a history of peptic ulcer disease, patients receiving high-dose NSAID therapy, those receiving concomitant corticosteroid or anticoagulation treatment, and patients with other significant comorbid medical illnesses in whom the development of an ulcer complication would be poorly tolerated. In addition, the elderly should be considered potential candidates for prophylactic therapy due to the logarithmic increase in mortality from GI hemorrhage in these individuals. Although the ultimate value of ulcer prophylaxis remains unclear, preliminary data from the MUCOSA trial (Misoprostol Ulcer Complication Outcomes Safety Assessment) suggest a true reduction in complications. In that double-blind, randomized, controlled trial, complications of upper GI bleeding, perforation, and gastric outlet obstruction developed in 25 of 4,406 misoprostol (200 μg 4 times daily)–treated and 42 of 4,443 placebo-treated patients during a 6-month observation period, a 40% reduction in overall complications (66). These encouraging preliminary results thus indicate that a decrease in the incidence of ulcers may be extrapolated to imply a decrease in the rate of complications.

Treatment of NSAID-associated ulcers

No firm guidelines have been established for assessing and managing NSAID-treated patients, since no strategy can reliably predict which individuals will develop gastroduodenal ulcers or complications. Investigation of all symptomatic patients receiving NSAID therapy cannot be routinely recommended since symptoms correlate poorly with the presence or absence of mucosal injury. A reasonable initial approach in "low-risk" symptomatic patients includes changing treatment to an alternative agent, reducing the dosage of current NSAID therapy, or administering empiric therapy with an H_2-receptor antagonist that has been shown to reduce dyspepsia symptoms from NSAIDs (39). It is reasonable to limit diagnostic evaluation to low-risk individuals who have persistent symptoms or to individuals with suspected ulcers who are considered to be at high risk for developing complications (Table 1). Esophagogastroduodenoscopy (EGD) is the diagnostic study recommended by most physicians. It is more expensive, but considerably more sensitive, than alternative radiographic contrast procedures (67).

Despite an abundance of literature on the treat-

ment of peptic ulcer disease, few studies have specifically addressed the short- and long-term management of NSAID-associated ulcers. A number of open, nonrandomized, uncontrolled studies (68,69), and prospective, randomized studies (70–72) suggest that treatment with conventional doses of H_2-receptor antagonists administered for 6–12 weeks, either alone or with unrestricted use of antacids, results in gastric ulcer and duodenal ulcer healing rates ranging from 50% to 88% (average 74%) and 67% to 100% (average 87%), respectively, despite continued NSAID therapy. Under circumstances in which NSAIDs are continued, healing appears to be delayed and is largely dependent upon initial ulcer diameter.

A study by Lancaster-Smith et al (73) of 190 patients with confirmed ulcers who began treatment with ranitidine 150 mg twice daily and then were randomized to continue or discontinue NSAID treatment demonstrated 8-week gastric ulcer healing rates of 63% in those taking NSAIDs compared with 95% in those who had stopped NSAID treatment. For duodenal ulcers, the corresponding healing rates at 8 weeks were 84% in the group continuing NSAIDs and 100% in those who discontinued them. Extension of ranitidine therapy for an additional 4 weeks improved healing rates among patients who continued NSAID use to 79% in those with gastric ulcers and 92% in those with duodenal ulcers. Thus, the efficacy of H_2-receptor antagonists when NSAIDs are discontinued compares favorably with rates obtained with H_2-receptor antagonists in those with "idiopathic" peptic ulcers (presumably associated with *H pylori*).

A second study by O'Laughlin et al (72) provides insight into the importance of initial gastric ulcer diameter with regard to healing rates during H_2-receptor antagonist treatment. An 8-week course of cimetidine in conventional doses combined with unrestricted antacid use led to healing of 90% of small (<5 mm in diameter) gastric ulcers despite the continued use of NSAIDs, whereas only 25% of large ulcers (>5 mm in diameter) healed during the same time period (72). Extension of therapy for an additional 6–26 months resulted in healing of 6 of the 7 large ulcers (86%). Therefore, although the healing of large gastric ulcers may be delayed with continued NSAID use, substantial healing rates are achievable if antisecretory treatment is continued for extended periods.

Does more profound acid suppression confer an advantage over conventional ulcer therapy in promoting healing? A multicenter trial comparing the proton pump inhibitor omeprazole (20 mg or 40 mg daily) with ranitidine (150 mg twice daily) in patients with gastric ulcers included a subgroup who continued to receive NSAIDs during anti-ulcer therapy (74). In the latter 68 patients, gastric ulcer healing rates at 4 weeks were 81% in the group receiving 40 mg of omeprazole daily, 61% in the group receiving 20 mg of omeprazole daily, and 32% in the group receiving ranitidine. The corresponding figures at 8 weeks were 95%, 82%, and 53%, respectively, indicating substantially improved healing rates with both dosage levels of omeprazole. Furthermore, patients treated with omeprazole had healing rates similar to those in ranitidine-treated patients who had discontinued using their NSAID treatment, suggesting that it may not be necessary to discontinue NSAID therapy in omeprazole-treated patients.

Misoprostol has been studied less extensively for the treatment of NSAID ulcers. A randomized, placebo-controlled study (75) in RA patients receiving high-dose aspirin assessed the effects of misoprostol on gastroduodenal lesions that ranged from subepithelial hemorrhage to ulcers. After 8 weeks of treatment, misoprostol at 200 μg 4 times daily was superior to placebo in healing gastric mucosal injury (70% versus 25%) and duodenal mucosal injury (86% versus 53%). Patients with gastric or duodenal ulcers on admission had superior ulcer healing rates with misoprostol (67% versus 26% with placebo). These results are difficult to interpret accurately since ulcer healing was defined as improvement from a well-defined ulcer to an erosion, rather than the usual requirement of complete ulcer healing. The use of misoprostol thus cannot presently be recommended over conventional antisecretory therapy for treating NSAID-associated gastroduodenal ulcers. The drug has no proven superiority over H_2-antagonists or omeprazole and has greater associated toxicity. There are also few data to suggest any benefit of sucralfate in the therapy of NSAID-associated mucosal injury.

The natural history of NSAID-associated ulcers after complete healing has not been elucidated. Are patients who discontinue NSAID therapy at risk for developing recurrent ulcers? Although patients are often assumed to be at high risk when NSAIDs are continued, 4 open-label, uncontrolled studies found that therapy with full-dose H_2-receptor antagonists, in conjunction with continued use of NSAIDs, led to "symptomatic" recurrences in only 7 of 169 patients (4.1%) over 6–12 months (39,68,72,76). In those with NSAID-associated duodenal ulcers who discontinued NSAID therapy, 98% remained free from symptomatic ulcer recurrence during 5 years of maintenance ranit-

idine treatment (77). The apparent efficacy of maintenance therapy must be viewed with caution, however, since serial EGD was not performed in many of these studies. More importantly, EGD was performed only in those individuals with recurrent symptoms, and, as stated previously, a majority of patients with NSAID-related ulcers are asymptomatic.

In conclusion, optimal treatment for promoting gastroduodenal ulcer healing during continued NSAID therapy has not been well defined. Whenever possible, NSAIDs should be discontinued to promote more rapid ulcer healing. Antisecretory therapy is effective in the treatment of NSAID-induced gastric and duodenal ulcer mucosal injury. Moreover, owing to their superior safety profile and patient acceptability, full-dose H_2-antagonist or omeprazole therapy would appear to be preferable to misoprostol or sucralfate in these patients. Although one small study suggests the superiority of omeprazole over H_2-antagonists in healing NSAID-associated gastric ulcers, confirmatory trials would provide helpful information for physicians caring for such patients. The optimal duration of therapy is unknown, but in general, larger ulcers and those treated while NSAIDs are continued require a longer treatment period.

Miscellaneous GI effects of NSAIDS

NSAID-induced esophageal injury has rarely been reported in the literature (78). There is a tendency for esophageal injury to occur at sites of anatomic narrowing, such as the mid-esophagus at the level of the aortic arch and left atrium. Most of these patients present with symptoms of odynophagia, dysphagia, and heartburn. Such injury is typically fully reversible with the discontinuation of the offending medication, although stricture formation, hemorrhage, fistula formation, and esophageal rupture have been described rarely. All patients should be advised to take NSAIDs while in the upright position, with sufficient quantities of liquid (at least 120 ml), and not immediately prior to bedtime, when recumbency and reduced salivation and swallowing lead to impaired esophageal clearance.

Studies by Bjarnason et al suggest that 60–70% of patients receiving long-term NSAID therapy may develop an asymptomatic enteropathy, associated with low-grade blood and protein losses (79). These losses may contribute to the development of iron deficiency anemia and hypoalbuminemia, two common problems in these patients. The amount of blood loss has generally been mild in most cases, ranging from 1 ml to 10 ml per day, a value similar to the amount of intestinal blood loss in patients with colorectal cancer. Radiologic studies (small bowel series or enterolysis) may occasionally demonstrate diaphragmatic narrowing; however, many cases have been diagnosed only at the time of exploratory laparotomy (79). The pathogenesis of NSAID enteropathy is unknown, but hypotheses for its origin include (a) damage secondary to mucosal prostaglandin depletion; (b) increased intestinal permeability, leading to an increased susceptibility to mucosal damage from biliary and pancreatic secretions and subsequent bacterial invasion; and (c) a primary vascular injury.

Less frequently, NSAIDs may cause colonic injury termed "colopathy." The spectrum of injury varies from colitis resembling inflammatory bowel disease to an increased rate of colonic perforation, bleeding, or complicated diverticular and appendiceal disease (80–83). Diaphragm-like strictures resembling those described in the small intestine have been observed in the ascending colon (79,84). The rectal administration of NSAIDs has also been associated with proctitis (85). In addition, NSAIDs may precipitate a relapse of or exacerbate preexisting ulcerative colitis or Crohn's disease (86). NSAIDs have been linked to the development of collagenous colitis, a diarrheal disorder characterized pathologically by collagen deposition beneath the surface epithelium, with associated lymphocytic inflammation in the lamina propria (87). NSAIDs may also be associated with serious complications of diverticular disease, including perforation and fistula formation (82). It has not been determined whether newer NSAIDs that diminish mucosal prostaglandin synthesis to a lesser degree will be less likely to precipitate these potentially serious complications. It is also unknown whether misoprostol or any other medication will prevent enterocolopathy in regular NSAID users (88).

In contrast to their deleterious effects, aspirin and NSAIDs also exhibit cellular antiproliferative activity on colonic mucosa, inhibit colonic mucosal cellular proliferation, and may be effective as chemoprotective agents for the development of colorectal neoplasia (89,90). These observations have been extended to include patients with adenomatous polyposis coli, in which the use of sulindac has been shown to cause partial regression and decreased recurrence of colorectal adenomas, the precursor lesion for most colorectal cancers (91). Whether this beneficial effect

translates to a reduced risk of malignancy has yet to be determined.

Most NSAIDs and aspirin may cause minor, reversible elevations in liver chemistry values, but only rarely do they cause serious liver injury, which in some cases has been fatal (92). There are differences among the various NSAIDs, with some predisposing to primarily hepatocellular, cholestatic, or mixed injury. The incidence of aspirin-related injury is dependent upon dose, serum levels, duration of intake, underlying disease, and age. Aspartate or alanine aminotransferase elevations are found in ~5%, and bilirubin values >1 mg/dl have been reported in only 3%, of cases (92). Serum liver function should be monitored when initiating NSAID therapy, and the medication should be discontinued if levels progressively increase or clinical signs or symptoms of liver disease develop.

Conclusions

Owing to the widespread use of these drugs, NSAID-induced gastrointestinal injury is a commonly encountered problem. The mechanism of gastroduodenal mucosal injury is probably multifactorial and to a great degree is due to both the topical effects of acidic compounds and the inhibition of endogenous prostaglandin synthesis. The latter effect, in turn, leads to reduced epithelial mucus and bicarbonate secretion, diminished epithelial proliferation and resistance to injury, and decreased mucosal blood flow. This impairment in mucosal resistance permits injury by endogenous factors including acid, pepsin, and bile salts, as well as ingested factors such as ethanol. The majority of mucosal injury is superficial and self-limited. However, in a significant minority of individuals, serious complications such as gastroduodenal hemorrhage or perforation, sometimes leading to death, may occur. The relative risk for serious injury is elevated approximately 3-fold among NSAID users, and may be even higher in the elderly, those with prior ulcer disease, patients who take concomitant corticosteroids, and those taking high-dose or multiple NSAIDs. Subjective symptoms and objective endoscopic evidence of injury do not reliably predict the development of complications.

Treatment of established NSAID-induced gastroduodenal ulcers is best accomplished by withholding the offending drug, although antisecretory therapy with H_2-receptor antagonists or omeprazole appears to accelerate the healing process. Misoprostol is the only unequivocally effective agent for the prevention of NSAID-induced gastroduodenal ulcers. However, the use of this drug is expensive and despite the encouraging preliminary results of the MUCOSA trial, the drug has not been proven to reduce complications, such as bleeding, perforation, or death, during long-term NSAID use. The development of NSAIDs that maintain antiinflammatory properties while sparing the gastrointestinal mucosa from injury would be the ideal strategy for addressing this commonly encountered problem.

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