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Billions of doses of aspirin[5] and other nonsteroidal anti-inflammatory drugs (NSAIDs) are consumed each year in the United States; even 10 years ago, 100 million prescriptions for nonaspirin NSAIDs were written in the United States.[35] Because 40% to 60% of patients regularly taking NSAIDs have gastric erosions and approximately 10% to 30% have gastric ulcers,[20, 23, 43, 63] NSAIDs are probably the most common cause of gross gastric injury in the United States today.

## ENDOSCOPIC FINDINGS OF NSAID GASTROPATHY

The endoscopically visible lesions induced by NSAID use may be labeled *NSAID gastropathy* and include subepithelial hemorrhages, erosions, and ulcers. Subepithelial hemorrhages have the appearance of petechiae or bright red areas of mucosa without any visible break ("blood under clear plastic wrap"). Although many have used the term *submucosal hemorrhage* to describe this finding, *subepithelial* is a much better term because it leaves open the possibility that the hemorrhage is located either in the mucosa or the submucosa. Furthermore, as discussed later, histologic examination of these lesions reveals blood in the mucosa, just beneath the epithelium.[32]

Erosions are visible breaks in the mucosa that are flat or minimally depressed, often surrounded by a halo of erythema. The base is generally

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were damaged on light and electron microscopic examination of blind gastric biopsies.

On endoscopic examination, multiple subepithelial hemorrhages develop within 15 to 30 minutes after a one-time ingestion of aspirin.[15, 19, 50] These lesions appear to progress to their maximal extent by 1 to 2 hours after ingestion, and they may begin to decrease at 24 hours. Erosions, on the other hand, seem to be unusual after a single dose of an NSAID. Hemorrhagic lesions may occur in the body or the antrum of the stomach.

Continued aspirin ingestion for 1 day (650 mg four times a day) leads to development of gastric erosions at 24 hours. Unlike subepithelial hemorrhages, erosions occur primarily in the antrum[19, 43, 50] and seem to occur in the areas that show the most severe mucosal hemorrhage after one dose of aspirin.[19]

After 1 week of regular NSAID ingestion, ulcers may be identified in a significant minority of subjects. Lanza[37] examined his data from a variety of studies of over 900 volunteers and reported an 8% incidence of ulcers developing after 7 days of NSAID use (aspirin 9%, nonaspirin NSAIDs 7%).[37] Evaluation of placebo groups in large trials of medical prophylaxis for NSAID-induced ulcers provides the best information for estimating the proportion of patients who develop new ulcers during 1 to 3 months of NSAID ingestion. The incidence of new ulcer formation is quite variable, however, from study to study. For example, two similarly designed studies evaluating the efficacy of misoprostol in arthritis patients taking NSAIDs reported an intent-to-treat 3-month incidence of gastric ulcers in 30 of 138 (22%) patients assigned to placebo in the first study[18] and in 25 of 323 (8%) patients in the placebo group in the second study.[20]

Graham et al[19] have suggested that gastric adaptation occurs with prolonged use of NSAIDs. Thus, ulcers and erosions might be seen more commonly at endoscopy soon after initiation of NSAID use and might decrease in frequency with prolonged use. As mentioned, virtually all subjects given aspirin develop erosions within 1 to 2 days and yet only half of patients regularly using aspirin or other NSAIDs have erosions found on endoscopy.

## CLINICAL SIGNIFICANCE OF NSAID GASTROPATHY

Hemorrhagic and erosive gastropathy is of minor clinical significance. Gastritis is frequently implicated as a cause of upper gastrointestinal

Southern California Medical Center revealed that hemorrhagic or erosive gastropathy was considered the cause of bleeding in 3% of cases, and virtually never led to life-threatening hemorrhage or large transfusion requirements.[27]

Subepithelial hemorrhages and erosions are strictly mucosal lesions, whereas all blood vessels of significant size are in the submucosa or deeper. Thus, unlike ulcers, which can induce severe bleeding when they erode into arteries below the mucosa, subepithelial hemorrhages and erosions generally do not cause major bleeding. When severe bleeding occurs in association with NSAID use, it indicates that an ulcer, rather than an erosion, is present as the source of the hemorrhage.

Dyspepsia is common in patients taking NSAIDs. Larkai et al[42] studied 245 rheumatic patients taking NSAIDs and found that 16% had daily dyspepsia, 29% had symptoms in the preceding week, and 37% had dyspeptic symptoms in the preceding 2 months. No studies, however, have documented that NSAID gastropathy correlates with abdominal symptoms. The lack of association between gross NSAID-induced lesions identified at endoscopy and NSAID-associated symptoms is well demonstrated in studies of the prevention of NSAID-induced gastric ulcers. Graham et al[18] showed that although misoprostol was significantly better than placebo in preventing gastric ulcers (discussed later), the frequency of abdominal symptoms, such as dyspepsia, abdominal pain, and nausea was similar in the misoprostol and placebo groups.

A number of epidemiologic studies (case control and cohort) have demonstrated an increased risk of complicated ulcers (e.g., bleeding, perforation, hospitalization, death) and overall gastrointestinal complications in patients taking NSAIDs.[64] A 1991 meta-analysis[13] reported that the odds ratio of risk for adverse gastrointestinal events related to NSAID use was 2.7 (95% CI, 2.5 to 3). Age over 60 years, prior gastrointestinal event, use of steroids, and less than 1 month of NSAID use all significantly increased the risk of adverse events. Griffin et al[21] found the relative risk for development of a gastric ulcer leading to hospitalization with NSAID use in Tennessee was 5.5 (95% CI, 4.4 to 6.9) (duodenal ulcer relative risk was 4.3 [95% CI, 3.5 to 5.2]). The risk of hospitalization for peptic ulcer rose with increasing dose and with shorter (≤30 days) duration. In the United Kingdom, Langman et al[36] reported a relative risk of 4.5 (95% CI, 3.6 to 5.6) for peptic ulcer bleeding with NSAID use; the risks of bleeding from gastric ulcers and duodenal ulcers were similar.

Experimental studies provide a much more reliable estimate of the risk of NSAID-associated gastrointestinal complications. Very few large-

tially increasing the risk of complications. Four clinical characteristics were identified as independent predictors of NSAID-associated gastrointestinal complications: (1) age greater than or equal to 75 years (odds ratio: 2.5 [95% CI, 1.5 to 4.1]); (2) history of peptic ulcer (2.3 [95% CI, 1.3 to 4.1]); (3) history of gastrointestinal bleeding (2.6 [95% CI, 1.3 to 5]); and (4) history of heart disease (1.8 [95% CI, 1.1 to 3.2]).

With the increasing use of aspirin for vascular prophylaxis, the risk of complications in this group of patients also must be assessed. Although many large-scale studies of aspirin prophylaxis are available, careful attention to gastrointestinal events is not usually a primary aim of the study. Kurata and Abbey,[26] in a study of 4524 subjects receiving 0.5 g of aspirin twice a day or placebo for at least 3 years, reported a relative risk for gastric ulcer hospitalization of 9.1 (95% CI, 1.2 to 71) higher for the aspirin group than the placebo group (risk for duodenal ulcer hospitalization was 10.7 [95% CI, 2.5 to 45.5]). Shorrock et al,[60] in a study of 2435 patients for transient ischemic attack prophylaxis, found that 300 mg of aspirin every day was associated with a 7.7-fold increased risk of upper gastrointestinal bleeding (from all causes) as compared with a placebo (95% CI, 1.7 to 33.8) and 600 mg of aspirin twice a day was associated with an odds ratio of 14.4 (95% CI, 3.4 to 60).

**Table 1.** RISK OF SERIOUS NSAID-ASSOCIATED GASTROINTESTINAL COMPLICATIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS: A 6-MONTH DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF MISOPROSTOL

| Gastrointestinal Event | Misoprostol (N = 4404) | Placebo (N = 4439) | Odds Ratio (95% CI) |
|---|---|---|---|
| Perforated ulcer | 1 (0.02%) | 7 (0.16%) | 0.14 (0.02–1.15) |
| Bleeding ulcer or erosion | 15 (0.34%) | 23 (0.52%) | 0.66 (0.33–1.31) |
| Perforated ulcer, gastric outlet obstruction, or bleeding ulcer or erosion | 16 (0.36%) | 33 (0.74%) | 0.49 (0.27–0.89) |
| Clinical evidence of upper gastrointestinal bleeding | 32 (0.73%) | 42 (0.95%) | 0.77 (0.47–1.24) |
| Perforation, gastric outlet obstruction, or clinical evidence of upper gastrointestinal bleeding | 33 (0.75%) | 52 (1.17%) | 0.64 (0.40–1.01) |

*From* Silverstein FE, Graham DY, Senior JR, et al: Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 123:241, 1995; with permission. The American College of Physicians is not responsible for the accuracy of the translation.

a nearly significant relative risk of gastrointestinal bleeding of 2.8 (95% CI, 0.9 to 8.7) in a Swedish trial of prophylaxis for cerebrovascular events.[58]

Doses as low as 30 mg of aspirin have been shown to be effective for vascular prophylaxis.[10] A Dutch study comparing 30 mg with 283 mg of aspirin in 3131 patients followed for a mean of 2.6 years revealed a nonsignificant relative risk of major gastrointestinal bleeding for 30 mg compared with 283 mg of 0.7 (95% CI, 0.4 to 1.3).[10] Although any risk of gastrointestinal complications should be lower at these doses, Cryer et al[8] have recently shown that doses as low as 10 mg of aspirin a day still significantly decrease gastric prostaglandin production to levels that are similar to the inhibition seen with 81 mg and 325 mg of aspirin. These data suggest that any dose of aspirin has the potential to induce gastric lesions and gastrointestinal complications.

## PATHOGENESIS OF NSAID GASTROPATHY

NSAIDs cause gastric damage by both topical and systemic effects, although inhibition of prostaglandin synthesis (a systemic effect) is thought to be the major mechanism of action.[4, 64] Most NSAIDs are weakly acidic (pka ranging from 3 to 5), and in gastric juice they are relatively nonionized and lipophilic. The NSAIDs move rapidly across gastric mucosal cell membranes into the neutral environment within the cell, where the neutral pH leads to conversion of the nonionized NSAID to the ionized form of the NSAID and a hydrogen ion. The NSAID thus accumulates within the cell at a higher concentration than outside the cell leading to direct local damage.

Although this topical damage may explain the endoscopically visualized lesions seen soon after the initiation of NSAIDs, this topical effect does not appear to be of primary importance in the development of gastric injury and complications. Parenteral NSAIDs, given via intravenous, intramuscular, or rectal routes, are well documented to cause ulcers.[6, 39, 64] Furthermore, prodrugs, such as sulindac, which require absorption and metabolism before they exert their pharmacologic effect, induce relatively little initial endoscopic damage[37] but are still associated with a significant risk of bleeding ulcers.[21]

Several lines of reasoning indicate that inhibition of prostaglandin synthase H (cyclooxygenase) and thus prostaglandin synthesis is a major mechanism of NSAID-induced gastric damage. NSAIDs do inhibit prostaglandin synthesis and induce gastric injury, although correlation of gastric mucosal prostaglandin production and gastric injury is relatively weak

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