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Effect of Ranitidine Gastroduodenal Mucosal Damage Induced by Nonsteroidal Antiinflammatory Drugs

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The effect of ranitidine in preventing mucosal damage caused by nonsteroidal antiinflammatory drugs (NSAIDs) was evaluated for eight weeks in a prospective study of 144 patients requiring NSAIDs. Patients with normal endoscopic findings were randomly assigned to receive either ranitidine 150 mg twice daily or placebo for eight weeks, along with either ibuprofen, indomethacin, naproxen, sulindac, or piroxicam. Duodenal damage was significantly less in the ranitidine group compared with the placebo group by weeks 4 and 8 ($P \leq 0.01$). Duodenal ulcers did not develop in any patients on ranitidine (0/57) compared with 4/49 patients (8%) on placebo ($P = 0.02$). No significant difference was found between treatment groups with respect to gastric damage; 6/60 (10%) in the ranitidine group compared with 6/50 (12%) in the placebo group developed gastric ulcers. These findings suggest that acid suppression is of greater importance for mucosal protection in the duodenum than in the stomach, where other defense mechanisms may be operative. While ranitidine is an effective prophylaxis for NSAID-induced damage in the duodenum, further studies are needed to define specific risk groups and to assess the potential usefulness of more complete acid suppression in preventing gastric mucosal damage.

KEY WORDS: ranitidine; NSAIDs; gastroduodenal damage.

Nonsteroidal antiinflammatory drugs (NSAIDs) remain the standard treatment for pain and inflammation associated with various forms of arthritis and other musculoskeletal discomfort. There is ample evidence, however, that NSAIDs are associated with gastroduodenal damage (1–3), including bleeding, ulceration, and perforation (4–7). Even short-term use of these agents may lead to severe mucosal injury (1–3).

Experimental countermeasures to NSAID-induced damage, such as prophylaxis with sucralfate (8, 9), prostaglandins (10, 11) and H_2 antagonists (12–15), have produced variable results, the clinical significance of which cannot be easily extrapolated to the general population. Differences in sample size, length of study, and patient type have also made comparisons between studies difficult.

We report the results of the first large-scale, placebo-controlled study in the United States to evaluate whether prophylactic administration of the H_2 antagonist ranitidine can protect endoscopically

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normal patients against gastric and duodenal damage caused by NSAID therapy.

MATERIALS AND METHODS

Patient Population. One hundred forty-four patients requiring NSAID therapy primarily for arthritis were enrolled in this multicenter, randomized, double-blind, placebo-controlled trial. The choice of NSAID was specified for each patient by the referring physician or randomly assigned if the physician had no preference. The NSAID dosages were established by study protocol as follows: ibuprofen ≥1600 mg/day, naproxen ≥750 mg/day, sulindac ≥300 mg/day, indomethacin ≥100 mg/day, and piroxicam ≥20 mg/day. The protocol was approved by the Institutional Review Board at each of the 10 centers, and written informed consent was obtained from each participant.

Candidates were excluded from the study for any of the following reasons: a baseline stomach or duodenum endoscopy score of greater than 0 (Table 1); previous gastric surgery; Zollinger-Ellison syndrome or other pathological secretory condition; renal impairment (serum creatinine ≥2 mg/dl); elevated SGPT level (3× normal); hypersensitivity to H_2 antagonists; use of NSAIDs within 48 hr prior to the study; consumption of anticholinergics, tricyclic antidepressants, potassium supplements, reserpine, H_2 antagonists, sucralfate, or steroids during the week prior to the study; use of greater than 10 mg prednisone or equivalent per day; any unstable medical problem, mental impairment, or alcoholism; pregnancy or lactation.

Study Design. Baseline information was obtained at the initial visit through a complete physical examination and medical history. Laboratory tests (complete blood count and blood chemistry analysis), symptom assessment (frequency and severity of abdominal pain, heartburn, constipation, nausea, and dyspepsia) and an endoscopic examination were also performed.

Patients were randomly assigned to receive either ranitidine tablets (150 mg) or placebo tablets twice daily for eight weeks. Antacid (Maalox No. 1) was allowed for relief of dyspeptic symptoms. Clinical evaluations were scheduled after weeks 1, 4, and 8, and laboratory tests, endoscopic examinations, and symptom assessments were repeated at these visits. Counts of returned investigational medications and antacid tablets were recorded at each follow-up visit, as were reports of adverse events. Patients were withdrawn from the study if they developed a gastric and/or duodenal ulcer or clinically significant gastroduodenal bleeding.

Statistical Analyses. Efficacy analyses were based on endoscopic evaluations of stomach and duodenal injury using maximum mucosal damage scores (the highest grade of lesion observed). A Cochran-Mantel-Haenszel test controlling for investigators was used to compare the two treatments.

Background characteristics were compared by using a two-sample t test, a Cochran-Mantel-Haenszel test, or Fisher's exact test. For symptom assessment, a Cochran-Mantel-Haenszel test was used to compare the ordered categories of incidence of peptic distress, gastrointestinal pain, and NSAID symptoms, and Fisher's exact test was used to compare the presence/absence of heartburn, abdominal pain, constipation, nausea, and dyspepsia. The Wilcoxon rank-sum test was used in the antacid use comparisons.

All statistical tests were two-sided and P values of ≤0.05 were considered statistically significant.

TABLE 1. GRADING SYSTEM FOR GASTRIC AND DUODENAL MUCOSA AS DETERMINED BY ENDOSCOPIC EXAMINATION†

Description	*Grade*
Gastric mucosa	
0–2 superficial erosions or petechial hemorrhages confined to one anatomic area	0
3–5 erosions or mucosal hemorrhages confined to one area	1
>5 erosions or mucosal hemorrhages in one anatomic area;† or 6–10 for the entire stomach	2
>10 erosions or mucosal hemorrhages	3
Gastric ulcer;† or multiple erosions and hemorrhages too numerous to count	4
Duodenal mucosa	
0–1 erosions	0
2–5 erosions	1
6–10 erosions	2
>10 erosions	3
Duodenal ulcer†	4

*Adapted from Lanza et al (1).
†Anatomic areas of the stomach: prepyloric antrum, body, proximal antrum, and fundus.
‡Ulcer defined as a lesion >0.5 cm in diameter causing a definite depression in the mucosal surface.

RESULTS

Seventy-two of the 144 patients enrolled in the study were randomly assigned to each treatment group. The two study groups were found to be comparable at baseline with respect to background characteristics (Table 2). Eighteen patients in the placebo group and 11 in the ranitidine group were excluded from efficacy analyses for either protocol violations or for failure to complete study visits.

All patients included in the efficacy analyses had mucosal damage scores of 0 at baseline. By weeks 4 and 8, there was a significant difference in the distribution of the maximum duodenum grades between the ranitidine and placebo groups ($P \leq 0.01$). Eighty-two percent (47/57) of the patients on ranitidine therapy had no mucosal damage in the duodenum by the end of the study compared with 65% (32/49) of the patients receiving placebo (Figure 1). None of the patients in the ranitidine group had a damage score greater than 2 by the end of the study. Retrospective analyses additionally showed that

TABLE 2. BACKGROUND CHARACTERISTICS

Characteristics	*Ranitidine (N = 72)*	*Placebo (N = 72)*
Sex		
Male	29 (40%)	22 (31%)
Female	43 (60%)	50 (69%)
Age (years, mean ± SEM)		
Male	50.1 ± 3.1	45.9 ± 3.2
Female	47.0 ± 2.5	43.1 ± 2.0
Ethnic origin		
White	62 (86%)	58 (81%)
Black	7 (10%)	9 (13%)
Other	3 (4%)	5 (7%)
Cigarette smoking		
Smokers	19 (26%)	23 (32%)
Nonsmokers	53 (74%)	49 (68%)
Alcohol consumption		
Drinkers	24 (33%)	19 (26%)
Nondrinkers	48 (67%)	53 (74%)
NSAIDs		
Naproxen	27 (38%)	25 (35%)
Sulindac	19 (26%)	17 (24%)
Ibuprofen	12 (17%)	17 (24%)
Piroxicam	7 (10%)	5 (7%)
Indomethacin	5 (7%)	8 (11%)
Other	2 (2%)	0 (0%)

neither smoking nor alcohol consumption interfered with ranitidine's effectiveness in preventing duodenal damage.

There was no statistically significant difference between the ranitidine and placebo groups in the overall distribution of the stomach grades. However, 51% (31/61) of the patients in the ranitidine group vs 40% (20/50) of the patients in the placebo group maintained a damage score of 0 by week 8. Retrospective analyses revealed that among alcohol consumers, there was a significant difference between treatment groups by week 8 ($P = 0.01$) (Figure 2), with 45% of the ranitidine patients having no gastric damage by the end of the study compared with only 6% of the patients on placebo

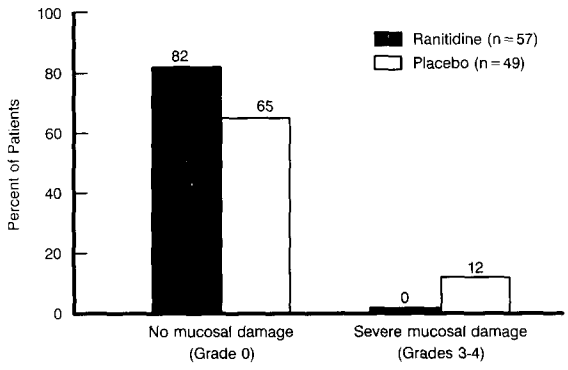

Fig 1. Distribution of duodenal damage scores by week 8.

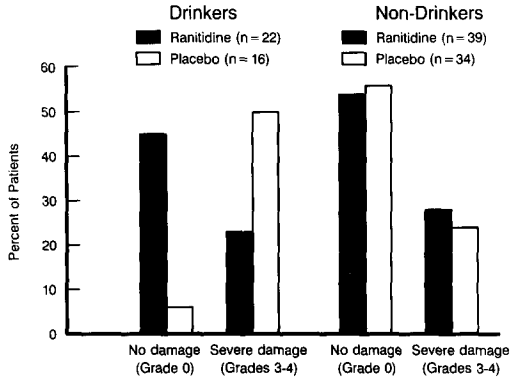

Fig 2. Distribution of gastric damage scores by week 8 among those who do and do not drink alcohol.

(Figure 2). A similar effect was not observed among nondrinkers.

The number of patients who developed ulcers during the course of the study are shown in Table 3. Four patients in the placebo group (8%) vs none in the ranitidine group developed duodenal ulcers during the study ($P = 0.02$). No difference between treatment groups was noted in the number of patients (six each) who developed gastric ulcers during the study period.

There were no statistically significant differences between treatment groups with respect to symptoms of peptic distress or incidence of gastrointestinal pain, nor was there any association between symptoms and the degree of mucosal damage documented by endoscopy. Mean daily antacid consumption was also similar between treatment groups.

Numbers of patients reporting at least one adverse event were identical in the two groups: 28% (20/72). In most cases, the adverse experience was

TABLE 3. NUMBER OF PATIENTS WITH GASTRIC AND DUODENAL ULCERS*

By week	*Ranitidine*	*Placebo*
Duodenal Ulcer		
1	0/68 (0%)	2/65 (3%)
4	0/62 (0%)†	4/57 (7%)
8	0/57 (0%)†	4/49 (8%)
Gastric ulcer		
1	1/68 (1%)	1/64 (2%)
4	3/63 (5%)	4/55 (7%)
8	6/60 (10%)	6/50 (12%)

*Patients considered treatment failures (ie, with a duodenal or gastric ulcer) were carried forward throughout the remaining scheduled follow-up endoscopies and account for differences in the denominators within treatment groups at the same week. Treatment failures at unscheduled endoscopies are also reflected.

tolerated and no causal relationship between the event and ranitidine could be attributed. Three patients in the ranitidine group and four in the placebo group, however, discontinued the study due to an adverse event, which included possible intolerance to the NSAID (2), abdominal pain (2), exacerbation of an underlying condition (2), and chills, rash, and dizziness (1).

DISCUSSION

The results of this eight-week prospective study show that ranitidine was effective in preventing NSAID-induced mucosal damage, including ulcers, in the duodenum but not in the stomach. These findings pose an interesting dilemma regarding the benefit of prophylaxis with an H_2 antagonist for a condition purported to affect primarily the stomach and not the duodenum (16, 17).

The ratio of gastric to duodenal ulcers in the present study, which is the largest U.S. trial to date to evaluate the effect of prophylaxis on NSAID-induced damage, was 1.5:1, indicating that the difference in incidence between NSAID-induced gastric and duodenal ulcer may not be as great as previously thought. Duodenal ulcer developed in 8% of our patients, which is a higher incidence than reported in other smaller studies (18, 19). The incidence in our study is identical, however, to that of a similarly designed European study of 297 patients (20), in which duodenal ulcers outnumbered gastric ulcers 1.3:1. It would appear from these recent data that duodenal ulcer may be underrated as a potential consequence of chronic NSAID use.

The importance of the present study centers on its implications regarding the pathogenesis of gastric vs duodenal lesions induced by NSAIDs. Although it is clear from this and other studies (13, 20) that therapeutic doses of ranitidine may help avoid NSAID-induced duodenal ulceration, gastric damage has generally not been amenable to prophylaxis with H_2 antagonists (15, 20). This supports the theory that pathogenic and defense mechanisms in the duodenum may be different from those in the stomach.

The exact mechanisms by which NSAIDs induce gastric damage are unknown; however, two mechanisms have been proposed: inhibition of prostaglandin synthesis (interfering with "cytoprotective" properties that prevent damage to the gastric mucosa) and disruption of the gastric mucosal barrier (permitting back-diffusion of hydrogen ions and consequent erosive gastritis). We believe that once the epithelium is damaged, acidity is likely to potentiate the gastric mucosal injury; control of acid secretion, therefore, should help to reduce mucosal damage. It is possible that more complete acid suppression is required in the stomach than in the duodedum for mucosal protection to occur. If so, higher dosages of ranitidine might be used in future studies to test this hypothesis.

Specific risk factors for NSAID-induced damage have been difficult to define. The present study failed to demonstrate any increased risk associated with smoking, alcohol, age, or type of NSAID. Although not examined in the present study, previous history of peptic ulcer has been identified as a significant risk factor for recurrent ulceration in patients taking NSAIDs (19–21). Patients with a previous ulcer history also appeared to obtain greater protection with ranitidine 150 mg bid than patients who had never had an ulcer (20). Clinch et al (22) described an increased risk of duodenal ulcer in elderly female patients in the United Kingdom, which is thought to have a relation to the dramatic increase in NSAID use in that population.

Our findings also confirm reports that rheumatic patients who chronically use NSAIDs often remain symptom-free, despite gastroduodenal damage, and that symptoms do not necessarily predict the presence of mucosal damage (1, 2, 7, 23). It has been suggested that NSAIDs may even mask ulcer symptoms due to their analgesic effect (24). Thus current assessments of the number of patients seriously affected by chronic NSAID use may be underestimated.

In summary, our findings demonstrate that ranitidine therapy (150 mg bid) was effective in preventing duodenal, but not gastric, injury resulting from eight weeks of NSAID treatment. We conclude that prophylactic treatment with ranitidine may be appropriate in some patients who require NSAIDs regularly; however, identification of specific patients at risk requires further definition. Future studies should also address the potential utility of more complete acid suppression in preventing gastric mucosal damage.

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