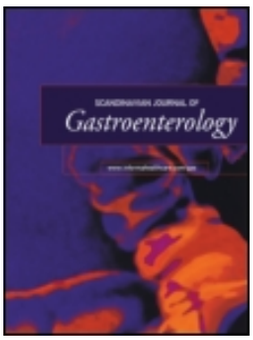

Scandinavian Journal of Gastroenterology

ISSN: 0036-5521 (Print) 1502-7708 (Online) Journal homepage: https://www.tandfonline.com/loi/igas20

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To cite this article: S. Sandmark, R. Carlsson, O. Fausa & L. Lundell (1988) Omeprazole or Ranitidine in the Treatment of Reflux Esophagitis: Results of a Double-Blind, Randomized, Scandinavian Multicenter Study, Scandinavian Journal of Gastroenterology, 23:5, 625-632, DOI: 10.3109/00365528809093923

To link to this article: https://doi.org/10.3109/00365528809093923

Omeprazole or Ranitidine in the Treatment of Reflux Esophagitis

Results of a Double-Blind, Randomized, Scandinavian Multicenter Study*

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Sandmark S, Carlsson R, Fausa O, Lundell L. Omeprazole or ranitidine in the treatment of reflux esophagitis. Results of a double-blind, randomized, Scandinavian multicenter study. Scand J Gastroenterol 1988, 23, 625–632

One hundred and fifty-two patients with endoscopically verified erosive and/or ulcerative esophagitis entered a double-blind, randomized study comparing 20 mg omeprazole given once daily and ranitidine 150 mg twice daily. The efficacy and safety of 4 to 8 weeks' treatment were studied. Macroscopic healing of esophagitis was defined as complete epithelialization of all esophageal erosive and/or ulcerative lesions. One hundred and forty-four patients completed the first 4 weeks of treatment in accordance with the protocol. The healing rate was 67% in the omeprazole group and 31% in the ranitidine group ($p < 0.0001$). The corresponding figures after 8 weeks' treatment were 85% and 50%, respectively ($p < 0.0001$). The higher healing rate for omeprazole was also accompanied by a significantly faster and more substantial improvement in reflux symptoms. In the patient's own overall evaluation of symptoms, these had resolved in 51% of the omeprazole-treated patients already at the end of the 1st week of treatment, compared with 27% of those given ranitidine ($p = 0.009$). Both omeprazole and ranitidine were well tolerated, and there were no adverse events or clinically significant changes in the laboratory values attributable to the trial medication.

Key words: Omeprazole; ranitidine; reflux esophagitis

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The broad spectrum of therapeutic approaches towards gastroesophageal reflux disease is based on a multifactorial model of the pathogenesis (1, 2). Reflux of hydrochloric acid has been considered to have a central pathogenetic role in this disorder, and drugs that reduce gastric acid secretion, predominantly histamine H_2-receptor antagonists, have been widely used and estab-

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lished as a first line of therapy (3). Despite the significant achievement in the treatment of reflux esophagitis by the introduction of these drugs, a large number of patients still cannot be adequately managed with this therapy.

Omeprazole is a gastric acid secretion inhibitor that specifically blocks the enzyme H^+, K^+-ATPase in the parietal cell (4) and inhibits basal and stimulated acid secretion in man, with a long duration of action (5). Studies of the 24-h intragastric acidity during treatment with different doses of omeprazole (10–30 mg/day) have shown that the intragastric acidity is reduced by 90% with as little as 20 mg/day (6). Recently, 60 mg of omeprazole given once daily was shown to be superior to ranitidine in relieving symptoms and promoting healing of esophageal mucosal lesions in patients with reflux esophagitis (7). Preliminary results from a placebo-controlled study have indicated the potential of lower doses of omeprazole in the treatment of this disease (8), in analogy with the efficacy of a low dose of omeprazole in the treatment of peptic ulcer disease (9). In the present study we have compared 20 mg/day of omeprazole with ranitidine in the treatment of patients with erosive and/or ulcerative esophagitis.

PATIENTS AND METHODS

Study design and patient selection

The study was performed as a randomized, double-blind, multicenter trial with two parallel groups, using a double-dummy technique. Only patients with esophagitis grade 2–4 (Table I) verified by endoscopy within 1 week before start of treatment were eligible to enter the study. The main exclusion criteria were age below 18 and above 80 years, pregnancy, lactation, concomitant peptic ulcer in the stomach or duodenum, previous esophageal or gastric surgery, severe concomitant cardiac, hepatic, or renal disease, malignancy, and clinically significant abnormal laboratory findings at the pre-entry assessment. Patients were randomly allocated to treatment with 20 mg omeprazole once daily or 150 mg ranitidine twice daily, in accordance with a computer-generated, blocked-randomization list, stratified for centers. Patients were initially treated for 4 weeks and then for another 4 weeks if the esophagitis was unhealed at endoscopic examination on day 29. The trial medication was dispensed in blister packs coded with the randomization number for each patient. The patients were instructed to take one capsule and one tablet in the morning and another tablet in the evening. All patients were supplied with antacid tablets containing aluminum–magnesium hydroxide with an acid-binding capacity of 12.5 mmol H^+/tablet. No other medication recommended in the treatment of esophagitis was allowed after commencement of trial medication. The study was approved by the regional ethics committees and registered with the National Swedish Board of Health and the National Centre for Medical Products Control (Norway). Each patient was given written information about the study, and verbal informed consent to participate was obtained before inclusion.

Table I. Endoscopic classification

Grade 0 = Normal esophageal mucosa; no abnormalities noted.
Grade 1 = Erythema or diffusely red mucosa; edema causing accentuated folds.
Grade 2 = Isolated round or linear erosions extending from the gastroesophageal junction upwards in relation to the folds.
Grade 3 = Confluent erosions extending around the entire circumference or superficial ulceration but without stenosis.
Grade 4 = Complicated: erosions as described above plus deep ulceration, stricture, or columnar epithelium-line esophagus.

Clinical assessments

A general medical history was obtained before entry. Details on alcohol and tobacco consumption were also recorded. The esophagus, stomach, and duodenum were examined endoscopically in each patient within 1 week before commencement of treatment. Endoscopy was repeated on day 29 (±5 days), and if the esophagitis was unhealed at that time, endoscopy was repeated on day 57 (±5 days). The macroscopic appearance of the esophageal mucosa was graded as shown in Table I. Endoscopy was performed by the same investigator on all occasions whenever possible. Before entry and at the scheduled visits

all patients were questioned concerning the presence and severity of heartburn, regurgitation, dysphagia, and odynophagia. The severity of reflux symptoms was scored from 0 to 3 (0 = no symptom, 3 = severe symptom). Other symptoms, such as vomiting, hematemesis, and melena, were reported only as present or absent. On day 29 and day 57, if applicable, the patients were asked to give an overall assessment of their reflux symptoms compared with those on the day of entry by rating them as completely gone, improved, unchanged, or worse. In addition, each patient was asked to record the severity and frequency of their reflux symptoms before inclusion and at the end of each week during the initial 4 weeks of treatment. A physical examination was performed before entry and repeated on day 29 or day 57, when the trial medication was withdrawn. Before inclusion and at 4-week intervals during the study, blood and urine samples were taken for hematologic and biochemical analyses. The patients were asked to return the remaining trial medication at each visit, and the number of returned tablets and capsules was recorded, as was the number of antacid tablets.

Endoscopic healing was defined as macroscopically complete epithelialization of all esophageal erosive and/or ulcerative lesions. Patients with Barrett's esophagus were regarded as healed when the macroscopic mucosal erosions and/or ulceration in the stratified squamous epithelium were healed. Esophageal biopsy specimens were only taken to exclude malignancy.

Statistical methods

The number of patients planned for the study ($n = 150$) gives a test power of 80% to detect a true difference between the treatment groups of 25 percentage points at the 5% significance level (two-tailed test) in macroscopic healing of esophagitis. Two approaches were used in analyzing the healing data: 'intention to treat', including all patients entering the study except patients withdrawn because of esophageal malignancy or clinically abnormal findings in the pre-entry laboratory screen, and 'per protocol', including all patients who completed the study with no major violation of the protocol. Patients withdrawn from the study because of worsening of symptoms or lack of treatment effect were included as treatment failures and regarded as non-healed in the statistical analyses. In the intention-to-treat analyses, patients in whom an endoscopy was not repeated were considered non-healed in the statistical analysis. All decisions to exclude patients from the statistical analyses were taken before breaking the treatment code. The chi-square test was used to compare the outcome of treatment in all patients. A multivariate analysis of the healing data was performed with a logit model, using treatment, pre-entry grade of esophagitis, sex, age, smoking, and alcohol consumption as possible prognostic factors. Reflux symptoms were analyzed in accordance with the per protocol approach with a Wilcoxon rank test with pre-entry grade of esophagitis as strata. The chi-square test was used to analyze the difference between the treatment groups, comparing the proportion of patients with or without symptoms according to the weekly recordings made by the patients. The overall evaluation of symptoms was analyzed with a ridit analysis, with ranitidine-treated patients as the reference group. Within each treatment group, mean changes in laboratory variables were analyzed with confidence intervals. Differences between the groups were compared with the two-sample t test or the chi-square test.

The time period in symptomatic remission after endoscopic healing of the two treatment groups was compared by the actuarial life-table method (the SPSSX program SURVIVAL). Patients not healed during 4 to 8 weeks' treatment were given time in remission equal to 0.

RESULTS

Patients

One hundred and fifty-two patients entered the study between 25 February and 26 November 1986. Fifty-three men and 22 women were allocated to treatment with omeprazole and 53 men and 24 women to ranitidine. Patient demographics and severity of esophagitis at the pre-entry assessment were similar in the two groups

Table II. Demographic data

Characteristics	Omeprazole, $n = 73$	Ranitidine, $n = 77$
Age (years)		
Mean ± SD	57.1 ± 16.3	58.7 ± 13.3
Range	19–80	19–80
Sex (n), male/female	51:22	53:24
Weight (kg), mean ± SD		
Men	82.2 ± 12.9	78.5 ± 12.7
Women	70.0 ± 11.8	69.3 ± 10.2
Height (cm), mean ± SD		
Men	176.2 ± 7.2	175.6 ± 6.4
Women	161.3 ± 5.8	162.7 ± 4.3
Smokers (n)	19	16
Alcohol consumers (n)	31	26
Esophagitis pre-entry		
Grade 2	42	52
Grade 3	21	12
Grade 4	10	13
Duration of GER disease (months)		
–24.0	27	18
24.1–60.0	19	30
60.1–	26	29
Duration of current episode (months)		
–6.0	43	44
6.1–12.0		16
12.1–	11	15
Previous complication of GER disease		
Hemorrhage (n)	3	2
Stricture (n)	5	3

* Two patients excluded because of base-line characteristics.

(Table II). Eleven patients were withdrawn from the study. Two patients in the omeprazole group were withdrawn after a few days of treatment when the result of the pre-entry assessments became available, one because of esophageal malignancy and the other because of an increased alanine aminotransferase level. Treatment was discontinued in four patients (two in each group) because of the occurrence of adverse events. One patient in each group was lost to follow-up, and three patients (one omeprazole, two ranitidine) withdrew from the study due to worsening of symptoms. Two patients given omeprazole and one given ranitidine took less than 75% of the trial medication and were subsequently exluded from the per-protocol analysis.

Forty-two patients in the omeprazole group and 48 in the ranitidine group had been treated for esophagitis within the month before entering the study. Twenty-six patients receiving omeprazole and 33 of those who were randomized to ranitidine were treated for concomitant diseases before inclusion and through the study period.

Healing of esophagitis

The healing rates of patients receiving omeprazole were markedly superior to those given

Table III. Macroscopic healing of esophagitis: ratio of number of patients healed to total number (per-protocol analysis)

Treatment group	4 weeks	8 weeks
Omeprazole	46:69 (67%)	56:66 (85%)
Ranitidine	23:75 (31%)	33:66 (50%)
Pre-entry grade of esophagitis		
2 Omeprazole	30:41 (73%)	36:40 (90%)
2 Ranitidine	22:50 (44%)	30:47 (64%)
3 Omeprazole	8:18 (44%)	10:16 (63%)
3 Ranitidine	1:13 (8%)	3:10 (30%)

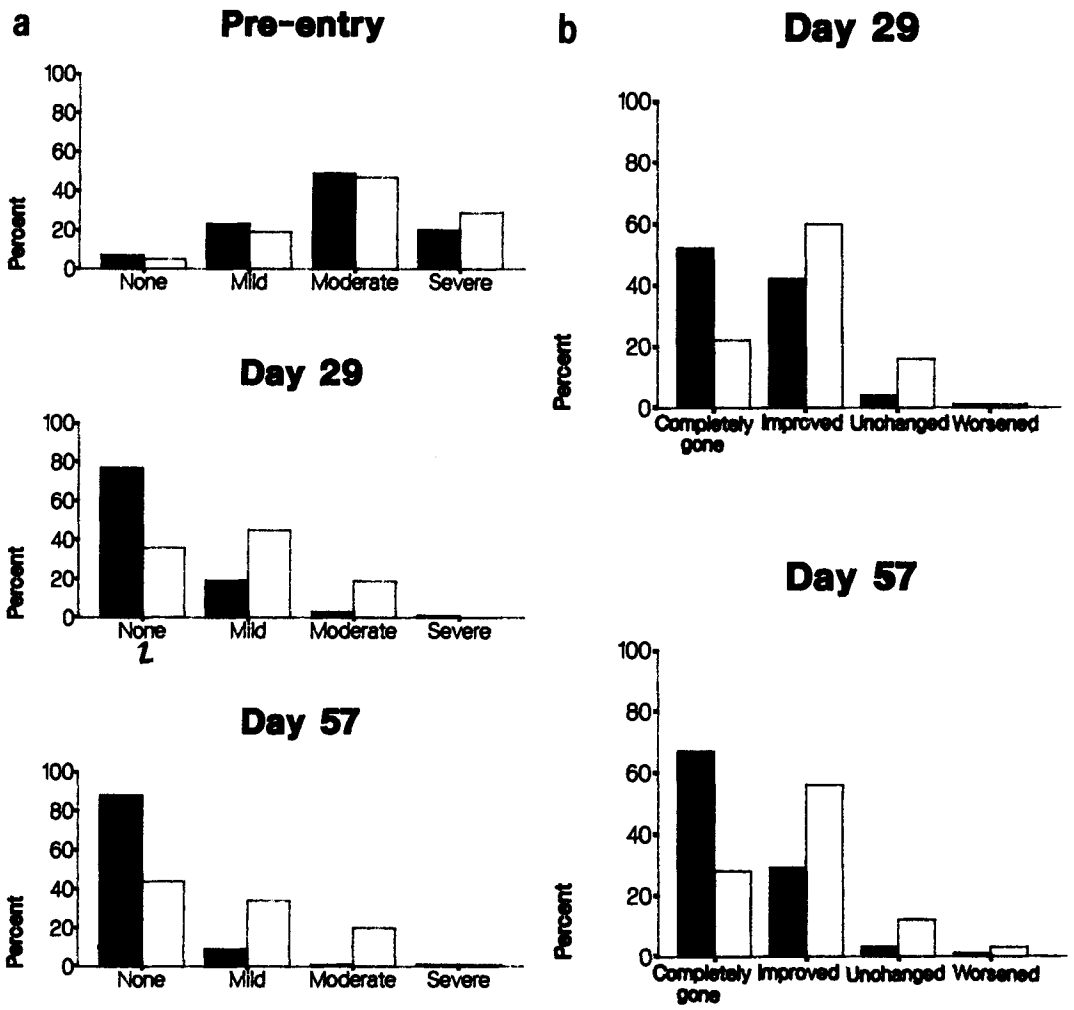

Fig. 1. Severity of reflux symptoms at the pre-entry visit and on completion of treatment (a) and the patients' own overall evaluation of symptoms (b), per-protocol analysis. Omeprazole (filled bars); ranitidine (open bars).

ranitidine with both approaches of statistical analysis. After 4 weeks (Table III) esophagitis had completely resolved in 67% of patients given omeprazole, as compared with 31% in those receiving ranitidine ($p < 0.0001$). The corresponding figures after 8 weeks of treatment were 85% and 50%, respectively ($p < 0.0001$). In the subgroup of patients with complicated esophagitis (that is, concomitant Barrett's esophagus and/or stricture), all 10 omeprazole-treated patients healed, compared with none of the 9 patients receiving ranitidine. By excluding patients classified as grade 4 from the further statistical analyses, it became possible to compare the healing rates in patients without complicated disease. Omeprazole was still superior to ranitidine after both 4 and 8 weeks' treatment ($p = 0.001$ and 0.002, respectively (Table III)).

The multivariate analysis of the healing data showed that only two factors were of prognostic importance: pre-entry grade of esophagitis ($p = 0.004$) and treatment ($p = 0.0009$).

Reflux symptoms

Patients allocated to treatment with omeprazole experienced a more rapid and profound

relief of symptoms than those given ranitidine (Fig. 1a). At the end of the 1st week of treatment, symptoms had already resolved in 51% of patients receiving omeprazole, as compared with 27% in the ranitidine group ($p = 0.009$). This difference was maintained throughout the study period, and at the end of week 4 the corresponding figures were 73% and 46%, respectively ($p = 0.002$). Omeprazole was also found to be superior to ranitidine with regard to the overall assessment of symptoms in the two study groups (Fig. 1b). The consumption of antacid tablets was lower in the omeprazole group (median, 13 tablets) as compared with 38.5 in patients given ranitidine ($p = 0.002$).

Safety assessments

Four patients were withdrawn because of the occurrence of adverse events. In the ranitidine group, one patient returned on day 6 with a large-bowel obstruction, and a carcinoma was diagnosed and surgically treated. Another patient was hospitalized on day 35 because of hemiparesis. In the omeprazole group one patient returned on day 5 with hematemesis. The bleeding stopped spontaneously, but the trial medication was discontinued. The second patient reported itching before inclusion and increasing complaints after starting treatment. The symptoms were considered related to a psychiatric disability, and the patient was withdrawn and referred to a mental hospital. Minor adverse events were reported in a similar frequency in the two groups except for aggravated reflux symptoms, which were reported by 18 patients during treatment with ranitidine, as compared with 5 patients in the omeprazole group ($p = 0.006$). Minor deviations from the reference values in the laboratory screening were noted in both groups, but there were no clinically and/or statistically significant changes either within each treatment group or between the two groups.

Recurrence of esophagitis

Patients healed after 4 or 8 weeks of treatment were included in a follow-up study including an

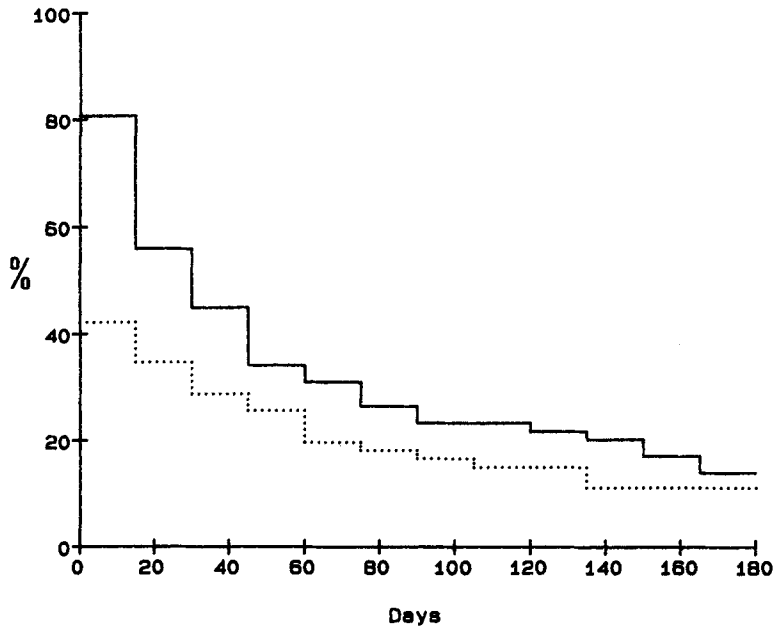

Fig. 2. Proportion of patients in symptomatic remission after endoscopic healing in accordance with life-table analysis. The analysis was performed at intervals of 15 days. Omeprazole (——); ranitidine (·····).

endoscopy at 12 months or earlier in case of recurrence of symptoms. The time in symptomatic remission was registered at a scheduled or unscheduled visit. The following patients were included in the analysis, with time in remission equal to 0: patients withdrawn from treatment during the treatment period because of lack of effect or worsening of symptoms and patients who after completion of treatment still had non-healed esophagitis and/or symptoms requiring medical treatment other than antacid tablets. Patients whose esophagitis healed but who were subsequently lost to follow-up study were included in the analysis at time 0 and thereafter withdrawn. Consequently, these patients affect the remission curve only at time 0. Patients lost to follow-up study or withdrawn from the study for reasons other than symptomatic relapse have in the analyses been considered to have been at risk until the time of the last visit at the outpatient clinic. Consequently, 70 patients in the omeprazole group and 73 in the ranitidine group were included in the final analyses. As can be seen in Fig. 2, only a low proportion of patients spent half a year in continuous symptomatic remission. The curve showing the proportion of patients in symptomatic remission during the follow-up period was more favorable for patients treated with omeprazole than for ranitidine ($p = 0.0003$, Lee-Desu statistics). This advantage of omeprazole seems to pertain to the differences in endoscopic healing rates during the 4- to 8-week treatment period.

DISCUSSION

Despite the multifactorial pathogenesis of gastroesophageal reflux disease, pharmacologic acid inhibition induced by histamine H_2-receptor antagonists has been the cornerstone in the medical treatment. Both cimetidine and ranitidine have been found to relieve heartburn in most short-term studies; although this treatment is superior to placebo in promoting healing of macroscopic esophagitis, this goal is achieved only in 20–50% of the patients (10–15). One reasonable explanation for the low healing rates of H_2-receptor antagonists in patients with reflux esophagitis as compared with those with duodenal ulcer disease may be the predominant influence of 24-h intragastric acidity in the pathogenesis of reflux disease. Ranitidine, 300 mg/day, or cimetidine, 1 g/day, has been found to increase the median pH of gastric juice from 1.4 to 1.7 and 2.4, respectively (16). Omeprazole is known to cause a sustained and prolonged acid inhibition, although not complete, even with the doses used by us (5). The present results clearly show that omeprazole is more effective than a histamine H_2-receptor antagonist in relieving symptoms and in endoscopic healing of the mucosal lesions in patients with reflux esophagitis. Twenty milligrams of omeprazole, given once daily, seemed to achieve the same high endoscopic healing rates after 8 weeks of treatment as has previously been shown to follow administration of 60 mg/day (7). The 95% confidence limits for the differences in healing rates observed after 4 and 8 weeks were 19% to 53% and 18% to 51%, respectively, in favor of omeprazole. These figures give an estimation of the true difference and may be interpreted as the therapeutic gain of omeprazole as compared with a histamine H_2-receptor antagonist in the short-term treatment of gastroesophageal reflux disease.

Twenty-four-hour pH-monitoring in the distal esophagus of patients before and during treatment with H_2-receptor antagonists has shown a marginal or, at best, a significant effect on acid exposure of the esophagus as a result of drug treatment (17, 18). Corresponding observations during omeprazole treatment have shown a more profound reduction in the acid exposure of the esophageal mucosa (19). At the present state of knowledge it is reasonable to assume that sustained, well-adjusted acid inhibition during 24 h constitutes the basis for the medical treatment of most patients with gastroesophageal reflux diseases, and this goal seems to be most effectively achieved by omeprazole administration. It should, however, be pointed out that 10–15% of the patients will not heal with 20 mg or higher doses of omeprazole, indicating pathophysiologic factors of importance other than reflux of acid.

It has previously been shown that the pre-entry severity of esophagitis and the smoking habits of

the patients are of prognostic importance for the healing rate during histamine H_2-receptor antagonist treatment (3). We experienced the greatest difference in healing rate between omeprazole and ranitidine in patients with grade-4 esophagitis, but we were unable to demonstrate any influence of smoking habits on the healing rate. This observation may reflect the potency of omeprazole rather than the lack of importance of smoking (20–22). It should, however, be pointed out that in the present study we classified patients with erosive and/or ulcerative esophagitis proximal to a columnar-lined epithelium as grade 4, a classification that is not generally appreciated, although application of a different endoscopic classification of the disease would not have influenced the results.

Little is known about the natural history of reflux esophagitis. Furthermore, it is not clear whether relapse of esophagitis can be prevented by long-term administration of drugs that are effective in promoting healing. Recently, 150 mg of ranitidine given once daily as maintenance treatment was found not to influence the relapse rate after healing as compared with placebo (3). Koelz et al. (3) found a high relapse rate after cessation of treatment, an observation confirmed also by the present results. This observation highlights the importance of evaluating a medical regimen as an effective maintenance treatment for patients with reflux esophagitis, particularly in those not suitable for surgical treatment. Although several patients with esophagitis will manage on short-term medical treatment, preferentially with omeprazole (23), most will probably require long-term treatment. The design and safety of such a maintenance regimen must be explored in prospective, randomized studies.

We conclude that omeprazole in a dose of 20 mg daily can be administered for 4 to 8 weeks without any side effects and is superior to ranitidine in endoscopic healing of esophagitis and in relieving symptoms. There is apparently a great clinical demand for long-term medical treatment of gastroesophageal reflux disease, and the place for omeprazole in this clinical setting is being evaluated.

Received 2 December 1987
Accepted 21 January 1988

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