

A COMPARISON OF FIVE MAINTENANCE THERAPIES FOR REFLUX ESOPHAGITIS

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Abstract Background. Patients with reflux esophagitis have a high rate of relapse within one year after therapy is discontinued.

Methods. We enrolled 175 adults with endoscopy-confirmed reflux esophagitis in a prospective study comparing five maintenance therapies. All the patients were initially treated with omeprazole (40 mg orally once a day) for four to eight weeks, and healing was confirmed by endoscopy. Participants were then stratified according to their initial grade of esophagitis and randomly assigned to 12 months of treatment with one of the following: cisapride (10 mg three times a day), ranitidine (150 mg three times a day), omeprazole (20 mg per day), ranitidine plus cisapride, or omeprazole plus cisapride. Endoscopy was repeated after 6 and 12 months of treatment; the endoscopists were blinded to the treatment assignments. Remission was defined as the absence of esophageal lesions on scheduled or unscheduled follow-up endoscopy.

Results. In an intention-to-treat analysis, the num-

bers of patients in continued remission at 12 months were 19 of 35 (54 percent) in the cisapride group, 17 of 35 (49 percent) in the ranitidine group, 28 of 35 (80 percent) in the omeprazole group, 23 of 35 (66 percent) in the ranitidine-plus-cisapride group, and 31 of 35 (89 percent) in the omeprazole-plus-cisapride group. Omeprazole was significantly more effective than cisapride ($P=0.02$) or ranitidine ($P=0.003$), and combination therapy with omeprazole plus cisapride was significantly more effective than cisapride alone ($P=0.003$), ranitidine alone ($P<0.001$), or ranitidine plus cisapride ($P=0.03$). Ranitidine plus cisapride was significantly better than ranitidine alone ($P=0.05$).

Conclusions. For maintenance treatment of reflux esophagitis, omeprazole alone or in combination with cisapride is more effective than ranitidine alone or cisapride alone, and the combination of omeprazole and cisapride is more effective than ranitidine plus cisapride. (N Engl J Med 1995;333:1106-10.)

REFLUX esophagitis is often a chronic disease. There is a high rate of relapse within one year after therapy is discontinued.¹⁻⁹ Results with maintenance therapy have often been disappointing. We compared three single-drug maintenance treatments (cisapride, ranitidine, and omeprazole) and two combined-drug maintenance treatments (ranitidine plus cisapride and omeprazole plus cisapride) in patients with erosive reflux esophagitis.

METHODS

We recruited patients from January through December 1991. Follow-up was completed by December 1992. Initially, 324 consecutive adult outpatients were screened. Forty-two patients were excluded because they did not fulfill the eligibility criteria, which included one or more esophageal erosions involving the distal esophagus; a grade of 1, 2, or 3 according to the Savary-Miller classification¹⁰; and one or more of three symptoms: heartburn, pain, and regurgitation. Fifty-three patients were excluded for other reasons. The main criteria for exclusion were the presence of esophageal stenosis and ulcer, Barrett's esophagus, peptic ulcer, cancer, or serious renal, cardiac, hepatic, or pulmonary disease; previous gastric surgery or vagotomy; age under 18 years; pregnancy; and expected poor compliance with treatment. Patients using drugs that might damage the gastroduodenal mucosa (i.e., nonsteroidal antiinflammatory drugs) or that might affect esophageal motility and lower-esophageal-sphincter tone (i.e., calcium-channel blockers) were also excluded. Finally, 54 patients refused to participate before or immediately after the prerandomization procedures were completed, either because they were unwilling to give informed consent or because they did not wish to undergo endoscopy again.

All the remaining 175 patients had relapse of reflux esophagitis, as indicated by symptoms and the findings on endoscopy. Their previous

maintenance therapy, if any, was stopped, and they were treated with omeprazole (40 mg orally once a day for four to eight weeks). Patients then underwent endoscopy to confirm healing and were stratified, according to their initial grade of esophagitis, into one of the three Savary-Miller groups (grade 1, 2, or 3). Therapy was randomly assigned, by means of a computer-generated list, on the basis of this stratification.

Five treatment groups, made up of 35 patients each, were assigned the following oral drug treatments: group 1, cisapride (10 mg three times a day); group 2, ranitidine (150 mg three times a day); group 3, omeprazole (20 mg once a day); group 4, ranitidine (150 mg three times a day) plus cisapride (10 mg three times a day); and group 5, omeprazole (20 mg once a day) plus cisapride (10 mg three times a day).

Patients were enrolled no later than one week after the endoscopic confirmation of healing. Follow-up visits were at intervals of 8 weeks, for 12 months. Patients were also contacted by telephone midway between visits to obtain information about their health status and symptoms. Endoscopy was performed at 6 and 12 months, and when clinically indicated. The endoscopists were blinded to the patients' treatment assignments. Routine hematologic and biochemical tests (complete blood counts and measurements of serum creatinine, aminotransferases, bilirubin, and alkaline phosphatase) were performed on entry into the study and at 6 and 12 months. Serum gastrin was measured at base line and at 12 months. After overnight fasts, blood samples were obtained and immediately stored at 4°C. Serum was separated and stored at -20°C. Gastrin was measured by radioimmunoassay (Sorin Biomedica, Saluggia, Italy). The normal range was 29 to 154 pg per milliliter (13.8 to 73.4 pmol per liter).

Patients were instructed not to take antacids unless their symptoms persisted. No changes in patients' lifestyles (diet, smoking habits, or level of physical activity) were requested. All the patients gave written informed consent. The study protocol was reviewed and approved by the ethics review committee at each participating institute or department.

Endoscopic Grades

Esophagitis was graded by endoscopy according to the "new" Savary-Miller classification¹⁰: grade 0 indicates no lesions; grade 1, single or multiple erosions on a single fold, with erosions that may be very erythematous or erythematous and exudative; grade 2, multiple erosions affecting multiple folds, with erosions that may be confluent; grade 3, multiple circumferential erosions; grade 4, ulcer, stricture, or

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esophageal shortening; and grade 5, Barrett's epithelium. Only patients with grade 1, 2, or 3 esophagitis were included in the study.

Symptoms

Symptoms (heartburn, pain, and regurgitation) were assessed by telephone and at patients' visits. Patients were also asked to keep a diary of symptoms. The severity of symptoms was classified as follows: grade 0, no symptoms; grade 1, mild symptoms with spontaneous remission and no interference with normal activity or sleep; grade 2, moderate symptoms with spontaneous but slow remission and mild interference with normal activity or sleep; and grade 3, severe symptoms without spontaneous remission and marked interference with normal activity or sleep.

The frequency of symptoms was classified as follows: grade 0, absent; grade 1, occasional (symptoms present less than two days a week); grade 2, frequent (symptoms present two to four days a week); and grade 3, very frequent (symptoms present more than four days a week). A score for each symptom and a total symptom score were calculated. The score for each symptom was calculated by multiplying the severity grade by the frequency grade, with a possible range for each score of 0 to 9. The total symptom score (range, 0 to 27) was calculated by adding up the scores for each symptom.

Remission was defined as the absence of esophageal lesions on follow-up endoscopy, either scheduled or unscheduled. When reflux symptoms recurred for more than four consecutive days, patients were told to notify their physicians. Endoscopy was repeated. If at least one esophageal erosion was found, a patient was considered to have relapsed and was withdrawn from the study.

Statistical Analysis

Statistical analysis was performed with the use of chi-square test-for-frequency tables with more than four cells, Fisher's exact test for two-by-two tables with small expected values, and a test for linear trend for two-by-n tables.¹¹ The Mantel-Haenszel procedure was used for the weighted combination of risks from different strata. The Mann-Whitney test or the Kruskal-Wallis test with the test for multiple comparisons was performed to compare scores. The proportions of patients in remission remaining in each group were calculated by the Kaplan-Meier method.¹¹ To estimate independent risk factors for relapse, Cox's proportional-hazards regression analysis was used.¹² The proportional assumption was graphically verified by plotting log [-log (survivor function)] against time in the various groups identified by each covariate to check parallelism.¹² A likelihood-ratio test was used to assess the probability of significance of each variable to be entered or removed, with all variables included in the regression model at the start of the analysis. The Wald test was used for hypoth-

esis testing. All P values were two-tailed, with statistical significance indicated by a value of $P < 0.05$. Default parameters of the BMDP statistical package (Los Angeles) were used for the analysis.¹³

RESULTS

Base-line characteristics of the 175 randomized patients are shown in Table 1. The median duration of esophagitis since the first endoscopic diagnosis was four years. At the time of relapse, 129 patients were receiving maintenance therapy with H₂-receptor antagonists. During follow-up, 16 patients were withdrawn because of medication side effects, lack of compliance, or other reasons (Table 1).

Endoscopy

The percentages of patients in remission remaining in the five treatment groups at 12 months are shown in Figure 1. In an intention-to-treat analysis, the numbers of patients in remission were 19 (54 percent) in the cisapride group, 17 (49 percent) in the ranitidine group, 28 (80 percent) in the omeprazole group, 23 (66 percent) in the ranitidine-plus-cisapride group, and 31 (89 percent) in the omeprazole-plus-cisapride group. There were significant differences in the rates between the omeprazole and cisapride groups ($P = 0.02$), the omeprazole and ranitidine groups ($P = 0.003$), the omeprazole-plus-cisapride and cisapride groups ($P = 0.003$), the omeprazole-plus-cisapride and ranitidine groups ($P < 0.001$), the ranitidine-plus-cisapride and ranitidine groups ($P = 0.05$), and the omeprazole-plus-cisapride and ranitidine-plus-cisapride groups ($P = 0.03$).

Rates of recurrence of symptoms and endoscopic signs after 12 months, according to the initial grade of esophagitis, are shown in Table 2. No relapses were seen in patients with grade 1 esophagitis treated with either omeprazole or omeprazole plus cisapride, or in patients with grade 2 disease treated with omeprazole plus cisapride.

Univariate analysis showed that patients who re-

Table 1. Base-Line Characteristics of the 175 Patients and Reasons for Withdrawal from the Study, According to Treatment Group.

VARIABLE	ALL PATIENTS (N = 175)	CISAPRIDE (N = 35)	RANITIDINE (N = 35)	OMEPRAZOLE (N = 35)	RANITIDINE PLUS CISAPRIDE (N = 35)	OMEPRAZOLE PLUS CISAPRIDE (N = 35)
Characteristic*						
Sex — M/F	117/58	21/14	26/9	25/10	23/12	23/12
Age — yr	45.4±13.7	44.8±12.2	42.4±12.8	43.4±13.0	48.9±14.7	47.2±15.1
Cigarette smoker — no. (%)	80 (46)	13 (37)	17 (49)	14 (40)	20 (57)	16 (46)
No. of cigarettes daily	—	21.0±8.7	22.3±10.3	18.5±5.9	20.6±10.3	20.4±9.9
Years of smoking	—	26.0±12.7	22.6±11.9	23.9±12.4	27.7±11.5	23.9±15.9
Coffee drinker — no. (%)†	130 (74)	27 (77)	26 (74)	24 (69)	26 (74)	27 (77)
Alcohol drinker — no. (%)‡	52 (30)	15 (43)	12 (34)	7 (20)	10 (29)	8 (23)
Severity of esophagitis — no.						
Grade 1	63	12	11	14	12	14
Grade 2	71	14	14	14	14	15
Grade 3	25	5	5	5	5	5
Reason for withdrawal — no. (%)						
Lack of compliance	2 (1)	1 (3)	0	0	1 (3)	0
Medication side effects	5 (3)	2 (6)	2 (6)	0	1 (3)	0
Pregnancy	1 (1)	0	1 (3)	0	0	0
Other§	8 (5)	1 (3)	2 (6)	2 (6)	2 (6)	1 (3)

*Plus-minus values are means ±SD. There were no significant differences in base-line characteristics among the five treatment groups.

†Includes patients who drank more than five cups of coffee a week.

‡Includes patients who drank up to 20 units of alcohol weekly (1 unit = 60 ml of liquor, 170 ml of wine, or 330 ml of beer). The other patients did not drink alcohol.

§Three patients felt well and refused to repeat the endoscopic examination; five patients did not return for follow-up visits.

lapsed had a higher frequency of grade 3 esophagitis (49 percent, $P < 0.001$) and alcohol intake (54 percent, $P < 0.001$) than patients who did not relapse. On evaluation of risk factors (sex, age, alcohol and coffee intake, smoking, grade of esophagitis, and treatment), only the grade of esophagitis before healing ($P < 0.001$) and the maintenance treatment ($P < 0.001$) independently influenced the likelihood of relapse. No significant interaction was found between these two variables.

Symptoms

The symptom scores, a measure of the severity and frequency of symptoms before and after the study, were compared. For continued relief of heartburn, omeprazole alone or omeprazole plus cisapride gave better results than did cisapride alone or ranitidine alone ($P < 0.001$) (Fig. 2). Ranitidine plus cisapride was better than ranitidine alone ($P < 0.001$).

Patients treated with omeprazole alone or in combination with cisapride had less pain at the end of treatment than patients treated with cisapride alone or ranitidine alone ($P < 0.001$). Ranitidine plus cisapride was more effective than ranitidine alone ($P < 0.001$) (Fig. 2). After 12 months, regurgitation was reduced in the omeprazole and omeprazole-plus-cisapride groups as compared with the cisapride and ranitidine groups ($P < 0.001$ for both comparisons).

Overall Symptoms

Recurrence of symptoms at 12 months in the five treatment groups is shown in Table 2. The mean (\pm SD) total symptom scores for the cisapride group at the be-

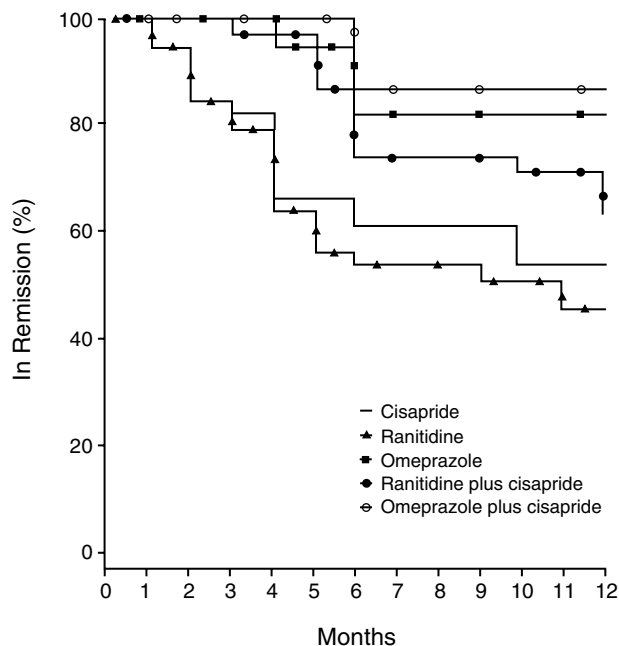


Figure 1. Kaplan-Meier Plot of Patients with Reflux Esophagitis Remaining in Remission, According to Treatment Group. In each treatment group, there were 35 patients included in the analysis throughout the study.

Table 2. Recurrence of Symptoms and Endoscopic Signs at 12 Months in the Five Treatment Groups, According to the Initial Grade of Esophagitis.

TREATMENT GROUP*	GRADE 1†	GRADE 2‡	GRADE 3‡
	number of patients (percent)		
Cisapride (n = 35)			
Endoscopic signs	3 (20)	4 (27)	5 (100)
Symptoms	2 (13)	6 (40)	5 (100)
Ranitidine (n = 35)			
Endoscopic signs	4 (27)	4 (27)	5 (100)
Symptoms	4 (27)	5 (33)	5 (100)
Omeprazole (n = 35)			
Endoscopic signs	0	2 (13)	3 (60)
Symptoms	0	0	1 (20)
Ranitidine plus cisapride (n = 35)			
Endoscopic signs	1 (7)	3 (20)	4 (80)
Symptoms	2 (13)	1 (7)	3 (60)
Omeprazole plus cisapride (n = 35)			
Endoscopic signs	0	0	3 (60)
Symptoms	0	0	0

*Initial numbers of patients in each group are given. Some patients were withdrawn (see Table 1).

†There were 15 patients in each treatment group.

‡There were 5 patients in each treatment group.

ginning and at the end of treatment were 3.5 ± 1.7 and 7.6 ± 6.5 , respectively. For the ranitidine group, the comparable figures were 3.5 ± 1.7 and 8.4 ± 6.8 , whereas for the omeprazole group, they were 3.5 ± 1.7 and 3.3 ± 1.9 . For the patients treated with ranitidine plus cisapride and those treated with omeprazole plus cisapride, the mean scores were 3.9 ± 2.5 and 5.4 ± 6.1 , and 3.5 ± 1.9 and 3.0 ± 0.0 , respectively. At 12 months, there were significant differences ($P = 0.001$) between the omeprazole group and the ranitidine group and between the omeprazole-plus-cisapride group and both the cisapride and ranitidine groups.

Association between Relapse and Symptoms

A strong association was found between the presence of symptoms during maintenance therapy and the risk of relapse. When the five treatment groups were combined with the Mantel-Haenszel procedure (χ^2 for homogeneity = 1.95, $df = 4$; $P = 0.74$), the risk of relapse was 22.6 times as high (95 percent confidence interval, 7.3 to 69.9) for symptomatic patients as for asymptomatic ones.

Adverse Events

Collectively, side effects occurred in 28 (16 percent) of the patients. Five patients discontinued treatment for this reason — three because of severe diarrhea and two because of abdominal pain (Table 1). These side effects went away after therapy was stopped. In the other 23 patients, side effects included an increase in the number of stools, mild diarrhea, or both (in 17 patients), abdominal cramps and flatulence (3), headache (2), and pruritus “without lesions” (1). These side effects also disappeared spontaneously; no further side effects were reported after the second week of treatment. No significant difference in the frequency of adverse events was observed among the study groups, nor were any changes in hematologic or biochemical

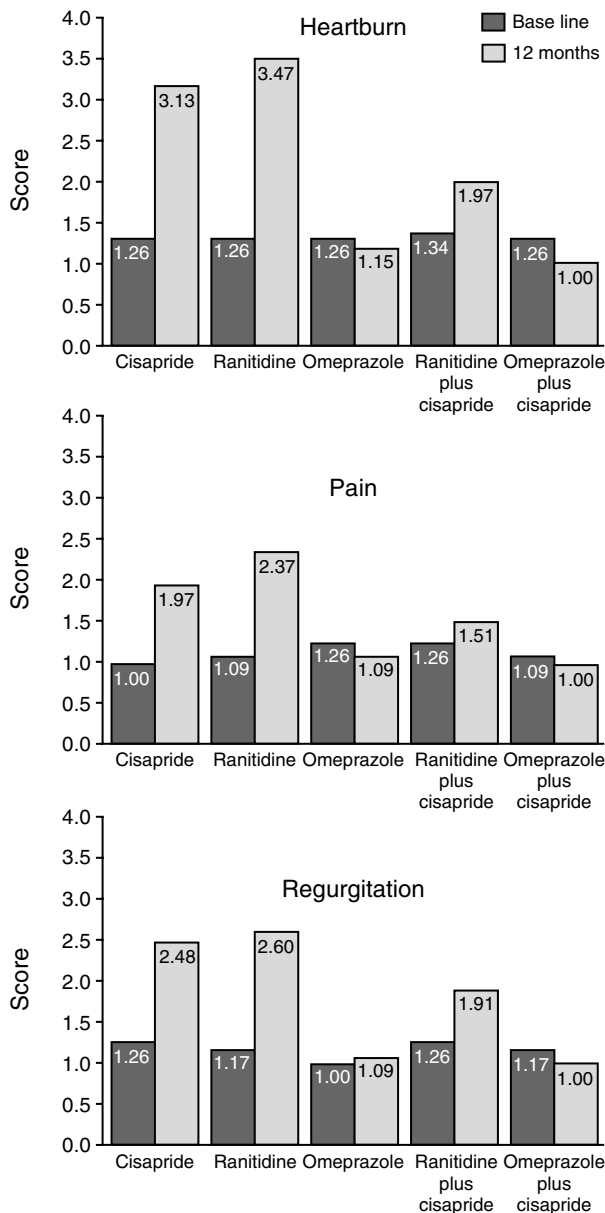


Figure 2. Scores for Heartburn, Pain, and Regurgitation at Base Line and 12 Months.

The mean score (as defined in the Methods section) is shown for each symptom in each treatment group. The score for each symptom was calculated by multiplying the severity grade (0 to 3) by the frequency grade (0 to 3); therefore, the possible range of each score was 0 to 9. The numbers of patients evaluated at 12 months were 31 in the cisapride group, 30 in the ranitidine group, 33 in the omeprazole group, 31 in the ranitidine-plus-cisapride group, and 34 in the omeprazole-plus-cisapride group.

test results, weight, blood pressure, or heart rate recorded.

At the end of the healing phase, all groups of patients had similar levels of serum gastrin. These exceeded normal values as an expected consequence of omeprazole treatment in the acute phase.⁸ At the end of follow-up, gastrin levels in the cisapride group had decreased significantly ($P < 0.001$) and were significantly lower than the levels observed in the other groups

($P < 0.001$). No significant differences were observed among the ranitidine, omeprazole, cisapride-plus-ranitidine, and cisapride-plus-omeprazole groups.

DISCUSSION

For maintenance treatment of reflux esophagitis, we found that omeprazole alone or in combination with cisapride was significantly more effective than ranitidine alone or cisapride alone in preventing lesions or symptoms of esophagitis, and the combination of omeprazole plus cisapride was more effective than ranitidine plus cisapride. Omeprazole treatment was effective in preventing the recurrence of symptoms as well as of endoscopic signs in mild-to-moderate and severe erosive esophagitis. As previously demonstrated, omeprazole is effective in complicated forms (grades 4 and 5) of esophagitis.^{6,8,9} Therefore, we believe that omeprazole is the drug of choice for the initial and maintenance treatment of severe esophagitis. Like McTavish et al.,¹⁴ we observed no serious side effects during long-term omeprazole treatment, aside from increased release of gastrin. Among patients with erosive esophagitis of grade 1 or 2, 50 to 60 percent of those treated with cisapride or ranitidine were free from recurrent symptoms or endoscopic signs at 12 months, as has been reported in short-term studies.¹⁵⁻¹⁹

The combination of cisapride with ranitidine or omeprazole is attractive and rational: in the present study, multivariate analysis showed that cisapride plus ranitidine was significantly more effective at reducing the frequency of relapses than ranitidine alone. When this combined therapy was compared with cisapride alone, no significant difference was observed, suggesting that cisapride, not ranitidine, provides the therapeutic advantage. Ranitidine plus cisapride can be an alternative to omeprazole, although the possibility of reduced compliance (because of the large number of pills that must be taken each day) should be examined in future studies.

Long-term medical treatment of reflux esophagitis must be compared with antireflux surgery. Spechler et al.²⁰ demonstrated that — for complicated esophagitis — surgery is significantly more effective than medical treatment in improving symptoms and endoscopic signs for up to two years, even if medical treatment is also effective. A comparison between these results and our findings is difficult. Spechler et al. included ranitidine in their medical treatment but not omeprazole. Most of the patients in their study had complicated esophagitis (grades 4 and 5). Since they presented their results without stratification for the esophagitis grade, it is uncertain whether surgery is better than medical treatment for patients with erosive esophagitis (grades 1, 2, and 3). Because effective drugs are available, patients with erosive esophagitis may have better options than surgery, which has a substantial number of operative and postoperative complications²⁰ and which may have poor results in 5 to 20 percent of cases.²¹ In our study, omeprazole had a low incidence of side effects, as previously demonstrated with even higher doses.²²

We believe that a clinical trial comparing omeprazole with surgery for patients with severe esophagitis is needed.

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