Healing of benign gastric and prepyloric ulcers: A prospective, endoscopy-controlled, randomized, double-blind, Canadian multicentre study of omeprazole 20 and 40 mg daily and ranitidine 150 mg twice a day

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ABSTRACT: A double-blind, randomized study was conducted in 118 patients with benign gastric or prepyloric ulcers to compare the efficacy of omeprazole 20 or 40 mg daily with ranitidine 150 mg twice daily. The healing rates at four weeks were 67, 79 and 54% and at eight weeks increased to 90, 97 and 71% for the omeprazole 20 and 40 mg groups and the ranitidine group, respectively ($P<0.03$ for the differences between each of the omeprazole groups and the ranitidine group at eight weeks). Multivariate analysis showed influence on healing rate for ulcer size but not for smoking status, sex or ulcer site. Symptomatic relief was excellent and similar in the three groups. Ulcer recurrence during the six month follow-up off treatment after initial ulcer healing did not differ between the three groups. No serious adverse events could be attributed to the drugs. The authors conclude that treatment with omeprazole 20 or 40 mg daily for a period of four to eight weeks is safe and significantly more effective in ulcer healing than a standard dose of ranitidine. **Can J Gastroenterol 1990;4(1):7-12** *(pour résumé, voir page 8)*

Key Words: *Gastric ulcer, Omeprazole, Prepyloric ulcer, Ranitidine*

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OMEPRAZOLE, A SUBSTITUTED benzimidazole, is a gastric proton pump inhibitor producing potent inhibition of gastric acid secretion (1,2). Its efficacy in healing duodenal ulcers has been shown in comparison to cimetidine (3,4) and ranitidine (5). In patients with gastric ulcers, its efficacy has also been evaluated with doses of 20 and 30 mg (6,7). The efficacy of a drug regimen producing marked acid suppression, as can be achieved with omeprazole 40 mg daily, was the object of this investigation.

This study compares two doses of omeprazole, 20 and 40 mg daily, producing different degrees of suppression of intragastric acidity, with a standard dose of ranitidine in the treatment of benign gastric ulcer. The report deals with 118 patients enrolled by six Canadian centres according to the protocol used in an international multicentre randomized study, and is the only North American contribution to

La guérison des ulcères gastriques et prépyloriques bénins: Une étude canadienne multicentrique prospective, randomisée, à double insu et contrôlée par l'endoscopie comparant l'oméprazole 20 et 40 mg par jour et la ranitidine 150 mg deux fois par jour

RESUME: Une étude randomisée à double insu a été effectuée sur 118 patients atteints d'ulcères gastriques ou prépyloriques bénins afin de comparer l'efficacité de l'oméprazole à 20 ou 40 mg par jour et celle de la ranitidine administrée à 150 mg deux fois par jour. Les taux de guérison à quatre semaines étaient de 67, 79 et 54% et, à huit semaines, ils ont atteint 90, 97 et 71% pour les groupes traités par l'oméprazole (20 et 40 mg) et la ranitidine, respectivement (P<0,03 pour les différences entre chacun des groupes traités par l'oméprazole et le groupe recevant de la ranitidine à huit semaines). Une analyse multifactorielle a révélé une influence sur les taux de guérison en ce qui concerne le diamètre de l'ulcère, mais non pas pour le tabagisme, le sexe du patient ou le site de l'ulcère. Le soulagement symptomatique fut excellent et similaire dans les trois groupes. L'observation pendant six mois après la fin du traitement a démontré que la récidive ulcéreuse n'était pas différente entre les trois groupes. Aucun effet secondaire sérieux n'a été observé pendant l'étude. Les auteurs concluent que le traitement par l'oméprazole à 40 ou 20 mg par jour pendant une période de quatre à huit semaines est sécuritaire et significativement plus efficace pour guérir l'ulcère gastrique, qu'une dose standard de ranitidine.

the study. Earlier reports have implicated a difference in the healing rates between North America and Europe (2,4).

PATIENTS AND METHODS

Patients included in the study had one or more active ulcers in the stomach with a greater axis of at least 5 mm, verified by endoscopy within four days of beginning treatment with the study drug. Prepyloric ulcers were included and classified as such to allow separate analysis, but not stratified into the various treatment groups. Ulcers localized within 3 cm of the pyloric ring were defined prepyloric, and those localized more than 3 cm from the pylorus were considered gastric.

Patients were excluded from participation in the study for the following reasons: age below 18 or above 80 years; pregnant or breastfeeding; treatment with therapeutic doses of anti-ulcer drugs for more than three days during the 14 days preceding endoscopy; presence of erosive reflux esophagitis, pyloric stenosis, concurrent duodenal ulcer or bleeding ulcers; history of gastric surgery except for simple ulcer closure; other significant concurrent disease; and chronic alcoholism. Patients on treatment with non-steroidal anti-inflammatory drugs (NSAIDs) were included but advised not to change dose; these patients were classified but not stratified into the various treatment groups.

The study was conducted in accordance with the Declaration of Helsinki and was approved by each institution's research and ethics review committee. Written informed consent was obtained from all patients.

Six centres participated in the study. The patients were randomly assigned to double-blind treatment with omeprazole 20 or 40 mg in the morning, or ranitidine 150 mg bid. All patients received the medication for four weeks. Patients whose ulcers had not healed after four weeks received a further four week treatment course. Ulcer healing was assessed by endoscopy at four and, if necessary, eight weeks in patients with gastric ulcers and at two and, if necessary, four and eight weeks in patients with prepyloric ulcers. Complete re-epithelialization of the ulcer site or sites was used as the criterion of ulcer healing. Gastric biopsies were taken from the ulcer area in order to exclude malignancy.

Before treatment, the ulcer and general medical histories were recorded for each patient, along with a history of drug, tobacco and alcohol use. During treatment, patients were assessed after two and four weeks and if necessary after eight weeks with an ulcer symptom severity rating, physical examination, adverse event evaluation, drug accountability, and laboratory tests (hemoglobin, white blood cell count, platelets, serum creatinine, electrolytes, bilirubin, alkaline phosphatase, alanine transaminase, aspartate transaminase, and urine protein and sugar).

After completion of the ulcer healing study phase, healed patients were followed for a period of six months. Patients were reviewed at three and six months and an endoscopy performed at six months or earlier if ulcer symptoms recurred.

The healing data were analyzed with standard χ^2 tests and confidence intervals for the healing probabilities. In addition, a multivariate analysis of treatment regimen, ulcer size and site, smoking status, sex and NSAID use, was conducted to adjust for possible imbalances in one or more of these factors in the comparison between treatments. Unknown healing status was classified as 'not healed'. Safety analysis included data from all patients who received study drugs. The laboratory tests were performed in each individual centre, and thus varying units and reference ranges were used for variables.

RESULTS

A total of 118 patients entered the study. Table 1 shows the pre-entry characteristics of the patients in the three groups. None of the differences observed between the treatment groups were statistically significant. Five patients were withdrawn during the study (Table 2).

The cumulative proportions of patients healed at four and eight weeks are shown in Table 3. The omeprazole 20 mg regimen achieved significantly higher healing rates than ranitidine 150 mg bid after eight weeks of treatment (P=0.03). With omeprazole 40 mg daily, the healing rates at four and eight weeks were significantly higher than the rates observed with ranitidine (P=0.02 and P=0.001). Analysis of pos-

TABLE 1
Characteristics of patients

	Omeprazole 20 mg	Omeprazole 40 mg	Ranitidine 150 mg bid
Total number of patients	39	38	41
Age (years, mean±SD)	52.5±13.0	56.2±12.5	55±14.5
Male/female ratio	18/21	14/24	19/22
Smoker/nonsmoker ratio	21/18	19/19	24/17
Alcohol/no alcohol ratio	20/19	12/26	15/26
Number taking NSAIDs	9	8	4
Duration of ulcer disease (years, mean±SD)	8.7±13.0	6.7±8.4	5.6±7.7
Duration of current episode (days, mean±SD)	93.1±110.5	94.5±125.0	194.7±490.8
Patients with previous ulcer complication	3	5	2
Number with gastric ulcer	28	24	28
Number with prepyloric ulcer	11	14	13
Ulcer size (mm, mean±SD)	11.7±6.0	10.7±5.0	12.5±8.9

TABLE 2
Patients withdrawn during study

Treatment group	Reason for withdrawal (time)	Healing status
Omeprazole 40 mg	Worsening of symptoms (8 days)	Unknown
Ranitidine	Adverse events (9 days)	Unknown
Ranitidine	Adverse events (14 days)	Healed
Ranitidine	Concurrent disease (16 days)	Not healed
Ranitidine	Increase in ulcer size (29 days)	Not healed

TABLE 3
Cumulative healing rates (number and percentage of patients)

Treatment	Four weeks	95% CI	Eight weeks	95% CI
O_{20}	26/39 (67%)	50 to 81%	35/39 (90%)	76 to 97%
O_{40}	30/38 (79%)	63 to 90%	37/38 (97%)	86 to 100%
R	22/41 (54%)	37 to 69%	29/41 (71%)	54 to 84%
$\Delta(O_{20}-R)$		−8 to 34%		2 to 36%
$\Delta(O_{40}-R)$		5 to 45%		11 to 41%
$\Delta(O_{40}-O_{20})$		−8 to 32%		−4 to 18%

CI Confidence interval; O_{20} Omeprazole 20 mg daily; O_{40} Omeprazole 40 mg daily; R Ranitidine 150 mg twice daily; Δ Difference

sible prognostic factors showed that ulcer site, smoking status and sex did not influence healing; ulcer size was the only prognostic factor of statistical significance (P=0.018). However, the logit analysis, taking into consideration the imbalance of more patients with large ulcers in the ranitidine group, did not change the statistical results (at eight weeks, omeprazole 20 mg group versus ranitidine group, P=0.03 and omeprazole 40 mg group versus ranitidine group, P=0.01). Differences in healing rates between the omeprazole 20 mg group and the omeprazole 40 mg group were not statistically significant.

In the small subgroup of patients taking NSAIDs, there was a significantly higher healing rate in omeprazole- versus ranitidine-treated patients; after eight weeks of treatment, six of nine, eight of eight, and one of four patients were healed in the omeprazole 20 mg, omeprazole 40 mg and ranitidine groups, respectively (P=0.02). Healing rates after two weeks in prepyloric ulcer patients were six of 11, four of 14 and four of 13 in the omeprazole 20 mg, omeprazole 40 mg and ranitidine groups, respectively (not significant).

At pre-entry, all patients reported symptoms. After two weeks, the proportion of patients free from symptoms or mildly symptomatic was 86% in the omeprazole 20 mg group, 83% in the omeprazole 40 mg group and 86% in the ranitidine group; after four weeks, the corresponding figures were 97, 91 and 94%, respectively.

Complaints during the study were reported by 10 patients in the omeprazole 20 mg group, three patients in the omeprazole 40 mg group and 14 patients in the ranitidine group (Table 4). None of the complaints was clinically important. However, the adverse events caused the withdrawal of two patients in the ranitidine group (headache, sleepiness and unsteady gait in one patient whose side effects disappeared completely on open treatment with the same drug; nausea and dizziness which disappeared one day after stopping the trial medication in the other patient). In addition, one patient in the ranitidine group was withdrawn when a concurrent disease (pancreatic carcinoma) was clinically diagnosed. During the study, there was no significant change in the mean values for the laboratory tests.

The cumulative proportions of the initially enrolled patients who were still in remission verified by endoscopy, after the follow-up of six months, were 62% in the omeprazole 20 mg group, 62% in the omeprazole 40 mg group and 47% in the ranitidine group (Figure 1); no statistically significant difference was observed between the three groups.

DISCUSSION

Healing of benign gastric ulcers is a slow process; indeed, on placebo, reported healing rates are in the range of 25 to 54% after observation for six to eight weeks (8-12). For the same period

TABLE 4
Complaints during the study (number of patients)

Complaint	O_{20}	O_{40}	R
Nausea, vomiting	3	0	2
Diarrhea	2	1	3
Dizziness	3	1	1
Headache	1	0	2
Tiredness	2	0	0
Blurred vision	0	1	1
Unsteady gait	0	0	1
Metallic taste	0	0	2
Skin rash	1	0	0

O_{20} Omeprazole 20 mg daily; O_{40} Omeprazole 40 mg daily; R Ranitidine 150 mg twice daily

of treatment, clinical trials using drugs acting to control gastric acid report healing rates in the range of 67 to 70% with antacids (8,11), 65 to 89% with cimetidine (6,8,9,13,14) 78 to 94% with ranitidine (13-16) and 65 to 80% with famotidine (12). However, comparisons of these results may not be appropriate since the initial ulcer size, a major factor in determining the healing time course (17), was not taken into consideration. Furthermore, the strong relationship shown between degree of acid suppression and healing rate in duodenal ulcers (18) is not observed in clinical trials of acid-inhibiting drugs in the treatment of gastric ulcer (19).

This study shows that treatment with omeprazole at a dose of 40 mg daily, a very powerful acid-suppressing regimen, is more effective than a standard dose of ranitidine in healing gastric ulcers. Omeprazole 20 mg daily was also more effective than ranitidine 150 mg twice a day after eight weeks of treatment. In comparison to cimetidine 1 g daily, omeprazole 30 mg daily was shown to be more effective in healing ulcers located in the antrum of the stomach (6), while ranitidine 150 mg bid and omeprazole 20 mg daily in a previous study resulted in similar healing rates (7). The present results are not due to differences between the treatment groups in demographic data, smoking status, ulcer locations or sex. In studying the total population of subjects enrolled in the three groups, ulcer size was a prognostic factor in the healing rate. However, the slightly smaller ulcer size in the omeprazole groups could not explain the differences in results since the logit statistical analysis that the authors used took into consideration the imbalance in ulcer size at the beginning of the study. It is generally assumed that prepyloric ul-

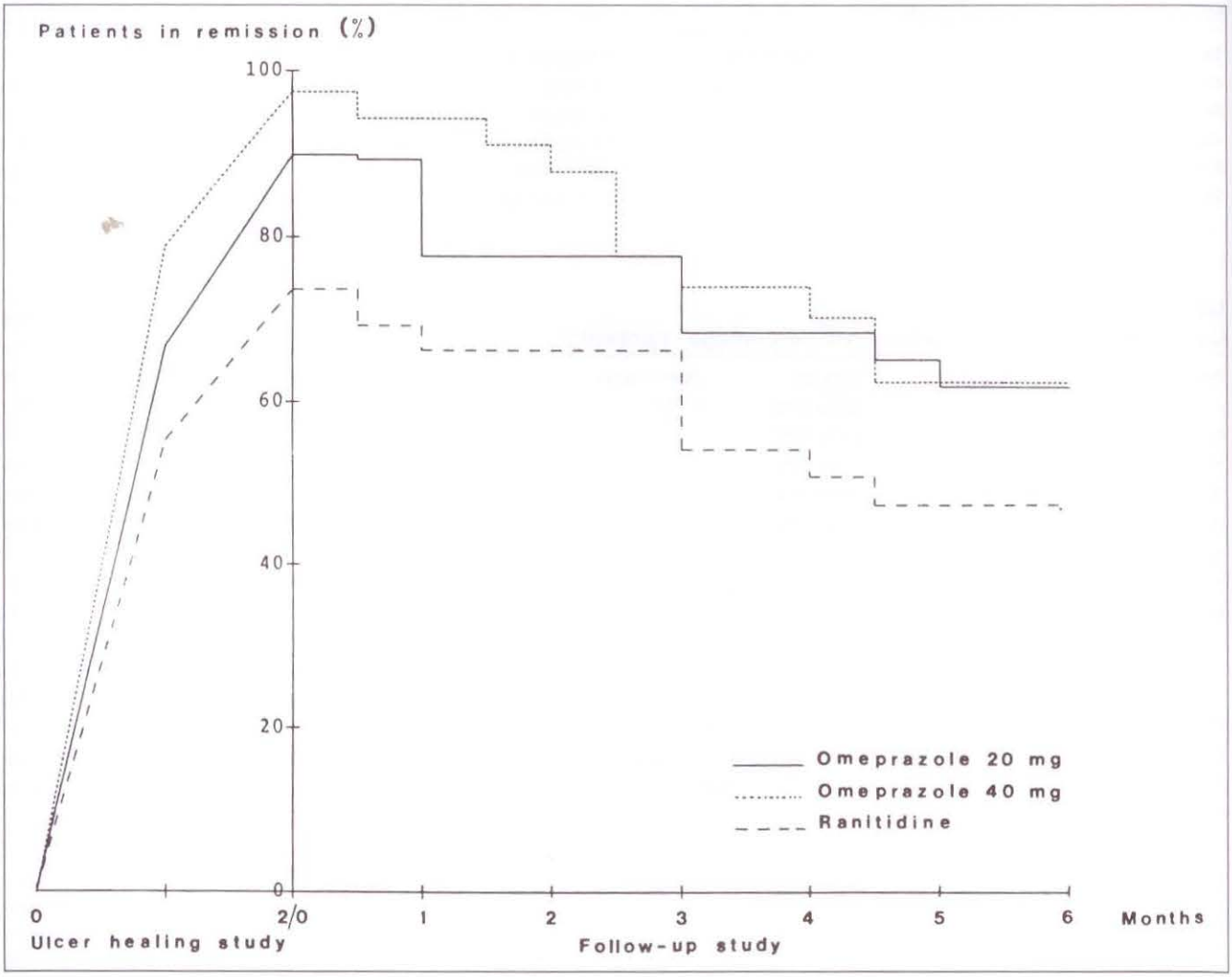

Figure 1) *Percentages of patients in remission during six months following ulcer healing with omeprazole 20 mg daily, omeprazole 40 mg daily and ranitidine 150 mg twice daily*

cers behave physiologically similarly to duodenal ulcers (20), for which omeprazole has been shown to be superior to 150 mg ranitidine twice daily in its healing capacity (5). Although studies of gastric acid secretion were not performed, the relative numbers of prepyloric over gastric ulcers did not differ between the three groups, and in each treatment group, about two-thirds of ulcers were gastric ulcers.

Even if the pathogenesis of gastric ulcers appears to be related more to abnormalities in mucosal defence mechanisms than to aggressive factors (21,22), this study nonetheless suggests that control of gastric acid is likely to be very important in the healing of gastric ulcers. Adding placebo data to the analysis of the effect of H_2 receptor antagonists in the treatment of gastric ulcers, Howden et al (19) found correlations between acid suppression and ulcer healing stronger with suppression of total 24 h versus nocturnal acidity, contrasting with duodenal ulcers for which suppression of nocturnal acidity is the most relevant acting factor with H_2 receptor antagonists (18). In asymptomatic duodenal ulcer subjects, omeprazole 20 mg daily has been shown to result in a 90% suppression of mean 24 h intragastric acidity (23), while ranitidine 150 mg twice daily reduced 24 h intragastric acidity by 63 to 69% (24-25). Repeated doses of omeprazole 40 mg daily have been reported to decrease 24 h median hydrogen ion activity by almost 100% in healthy volunteers (26) and 97% in duodenal ulcer patients in symptomatic remission (23). The present clinical results in healing rates follow these gradual effects on 24 h intragastric acidity increasing from ranitidine 150 mg twice a day to omeprazole 20 mg daily and omeprazole 40 mg daily.

Even if acid is a permissive factor in the development of ulcers (and the amount need not be excessive), perhaps almost complete suppression of acid over 24 h leaves the gastric mucosa under the predominant activity of the defensive mechanisms and turns off pathogenetic factors dependent on the presence of a minimum hydrogen ion concentration such as tissue protein degradation. Total absence of acid might allow the action of natural healing mechanisms at a faster pace than in circumstances of moderate acid inhibition. Higher rates of ulcer healing achieved with omeprazole 20 and 40 mg daily versus ranitidine 150 mg twice daily are consistent with the hypothesis that the degree of suppression of intragastric acid is very important in the healing phase of gastric ulcers; there are furthermore no data suggesting that omeprazole has inherent cytoprotective activity. However, pronounced inhibition of acid may also promote liberation of gastrin and favour its trophic effect on the gastric mucosa.

The authors conclude that omeprazole 20 mg daily and omeprazole 40 mg daily resulted in a significantly more rapid healing rate than ranitidine 150 mg twice daily in benign prepyloric and gastric ulcers. These results are similar to the data from the international study (27) and do not indicate a difference between North America and Europe in the reporting of healing rates. For a period of four to eight weeks, treatment with omeprazole was shown to be safe. Ulcer recurrence during the six month follow-up period was not different with either treatment used to heal the acute ulcer.

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