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Double-blind placebo-controlled multicentre studies of rebamipide, a gastroprotective drug, in the treatment of functional dyspepsia with or without Helicobacter pylori *infection*

N. J. TALLEY*, D. S. RIFF†, H. SCHWARTZ‡ & S. P. MARCUARD§

**Department of Medicine, The University of Sydney, Nepean Hospital, Sydney, Australia; †Advanced Clinical Research Institute, Anaheim, CA, USA; ‡Miami Research Associates, Inc., Miami, FL, USA; and §Carolina Physicians, Greenville, NC, USA*

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SUMMARY

Background: Functional dyspepsia is a problem that is difficult to treat in clinical practice.

Aim: To evaluate the efficacy and safety of rebamipide (a cytoprotective drug) in functional dyspepsia.

Methods: Patients with functional dyspepsia ($n = 557$) were divided a priori into two studies by *Helicobacter pylori* status, and enrolled in a 2-week baseline evaluation period. Ninety-nine patients with *Helicobacter pylori* and 173 patients without *Helicobacter pylori*, continuing to have at least moderate upper abdominal pain or discomfort, were randomly assigned to rebamipide 100 mg, rebamipide 200 mg or placebo, three times a day, in a double-blind design for 8 weeks.

Results: There was significant improvement of individual symptom scores from baseline in all the treatment arms. No significant improvement of individual symptom scores was observed in either rebamipide group at the end of the studies compared to placebo, although the belching score was significantly reduced in the rebamipide 100 mg and 200 mg groups at week 2 ($P = 0.017$ and $P = 0.012$, respectively) in the *Helicobacter pylori*-positive patients. The ratio of patients who requested usage of the study medication again was greater in the rebamipide 100 mg (85%) and 200 mg (96%, $P = 0.020$) groups compared with the placebo group (72%) among *Helicobacter pylori*-positive patients. There were no serious study medication related adverse events.

Conclusions: Rebamipide was not superior to placebo in terms of individual symptoms at the end of treatment.

INTRODUCTION

Functional (or non-ulcer) dyspepsia is one of the most common clinical problems encountered by primary internists and gastroenterologists.[1] Functional dyspepsia is characterized by chronic or recurrent symptoms arising from the upper gastrointestinal tract, including postprandial upper abdominal pain or discomfort, nausea, vomiting, belching, bloating and early satiety, with no identifiable organic or systemic disease.[2] The pathogenesis of functional dyspepsia is not well defined and appears to be multifactorial.[3–5]

The results of studies in functional dyspepsia with H_2 receptor antagonists have been conflicting,[6, 7] whereas studies with antacids have been universally negative.[6–8] Proton pump inhibitors appear to be superior to placebo, but not in dysmotility-like dyspepsia.[9] Several reports have suggested that abnormal motility may play a role in the pathogenesis of functional dyspepsia.[10, 11] Cisapride is considered to be effective in improving some functional dyspepsia symptoms and, in particular, dysmotility-like dyspepsia,[12, 13] but others have reported that cisapride is not superior to placebo in functional dyspepsia.[14]

Correspondence to: Dr N. J. Talley, Professor of Medicine, Clinical Sciences Building, Nepean Hospital, P.O. Box 63, Penrith 2747, Australia.
E-mail: ntalley@med.usyd.edu.au

Therefore, it seems likely that acid-suppressing agents and prokinetic agents are, at best, only effective in a subclass of patients with functional dyspepsia.

Rebamipide is a cytoprotective anti-ulcer drug[15–17] launched in Japan in 1990 and in Korea in 1993, and has been used by more than one million patients per year suffering from gastric ailments.[18] Preclinical studies indicate that rebamipide contributes to the enhancement of the defence mechanism in gastric mucosa, which results from increasing gastric mucus[19, 20] and the stimulation of the production of endogenous prostaglandins.[21, 22] Additionally, rebamipide is known to suppress gastric mucosal inflammation, which is thought to be related to its activity in inhibiting superoxide anion production from neutrophils,[23–25] scavenging hydroxyl radicals[26, 27] and inhibiting interleukin-8 production.[28] A clinical study in patients with gastritis reported the relief of individual gastrointestinal symptoms with rebamipide comparable to that with cimetidine, as well as healing of gastric lesions.[18] The aim of the present study was to evaluate the efficacy and safety of rebamipide in relieving functional dyspepsia symptoms in patients with or without *Helicobacter pylori* (*H. pylori*), and to determine whether subgroups of patients are more responsive to rebamipide therapy.

MATERIALS AND METHODS

Patients

Functional dyspepsia patients, male and female, between 18 and 80 years of age, with upper abdominal pain/discomfort rated by the patient as at least moderate in intensity, which had been present at least three times per week for 12 weeks, was unrelated to exercise and for which no focal lesions or systemic disease was present, were initially invited to participate in this study from 44 centres in the USA. All patients were recruited from gastroenterologists. Patients could also have other symptoms, including heartburn, nausea, vomiting, bloating, belching and early satiety. All patients were required to give their written informed consent before entering the study. The protocol was approved by the Ethics Committee of each investigational centre.

Exclusion criteria

Exclusion criteria included pregnancy or lactation, history of substance abuse (within 1 year of screening visit), regular consumption of greater than 2 fluid ounces of beverage alcohol per day and regular use of NSAIDs, other than aspirin at a dose of 100 mg/day or less for cardiovascular prophylaxis. At the judgement of the investigator, patients requiring treatment with medications that might confound the evaluation of functional dyspepsia symptoms or the response to the study drug, or with any existing medical condition that would put them at unacceptable risk, were also excluded. Patients who demonstrated, on upper gastrointestinal endoscopy, gastric ulcer or greater than six gastric erosions, duodenal ulcers or erosions, oesophagitis, Barrett's oesophagus, gastrointestinal malignancy or hiatal hernia 5 cm or greater in diameter, or who had occult blood in the faeces, were excluded. Patients who had any history of documented gastric or duodenal ulcer within 1 year of screening were excluded; 15 of 173 patients in the *H. pylori*-negative study and five of 99 patients in the *H. pylori*-positive study had a medical history of ulcer > 1 year prior to the study. Those with any documented history of oesophageal stricture, pyloric stenosis, Crohn's disease, ulcerative colitis, gastrointestinal malignancy, proven or suspected relapsing pancreatitis, irritable bowel syndrome, diabetes mellitus requiring insulin or oral medication for glycaemic control, symptomatic lactose intolerance, gastrointestinal surgery or cholelithiasis were also excluded. Patients unwilling to or expected to be unable to tolerate the absence of treatment with proton pump inhibitors, H_2 receptor antagonists, pro-motility agents, antispasmodics or other gastrointestinal pharmacotherapy for the period of time from 1 week (4 weeks for proton pump inhibitors) prior to the screening endoscopy and through the 8 weeks of the double-blind treatment were also excluded. Antacids (other than allowed by the protocol) were prohibited from the beginning of the baseline evaluation period.

Study design

At screening, upper gastrointestinal endoscopy was performed for all patients to confirm the absence of focal lesions, and *H. pylori* status was evaluated by histology, rapid urease test and serology. The presence or absence of *H. pylori* was determined from six biopsy specimens (three corpus and three antrum within 5 cm of the pylorus), using the CLO Test (Tri-Med Specialties, Inc.) for two specimens (one corpus and one antrum) and histological assessment for four specimens (two corpus

and two antrum). The results were considered to be positive if at least two of the three tests were positive. There was total concordance among the three tests in 233 of the 272 (86%) patients randomized to the study. In all but one case of a negative histology in an *H. pylori*-positive patient, the discordance was due to the serology test result.

Within 2 weeks of successful completion of screening, patients with or without *H. pylori* separately entered a baseline evaluation period of 2 weeks (Figure 1). During the 2-week evaluation period, patients were treated with antacids (Gelusil, Warner-Lambert Company) only and recorded their symptoms of functional dyspepsia and the use of antacids daily. At the end of this baseline evaluation phase, patients continuing to have at least moderate upper abdominal pain or discomfort were randomized to treatment with identical placebo (2 tablets t.d.s.), rebamipide at 100 mg t.d.s. or rebamipide at 200 mg t.d.s., daily for 8 weeks. Upper abdominal pain/discomfort was selected as the basis for eligibility because it was considered to be the central symptom of functional dyspepsia.[29] Treatment assignment was randomized centrally in a 1:1:1 ratio, in blocks of three. The randomization code was generated by the Statistics and Data Management Department of Otsuka America Pharmaceutical, Inc. and maintained thereby until all data had been collected and the study was unblinded. Neither the investigators nor the patients were aware of the treatment assignments in either of the studies.

Assessment of dyspepsia

The efficacy criteria were patient assessment of upper abdominal pain/discomfort, daytime heartburn, nighttime heartburn, belching, nausea, vomiting, bloating and early satiety, which were recorded at screening, randomization (week 0), week 2, week 4, week 6 and week 8 (the end of the studies). All of these symptoms were rated by patients on a seven-point categorical scale (0, none; 1, slight; 2, mild; 3, moderate; 4, severe; 5, very severe; 6, worst possible), based on a previously validated questionnaire.[30] The protocol-defined primary efficacy evaluation was the patient assessment of upper abdominal pain/discomfort. Patients also recorded the following on a diary card: the presence and frequency of symptoms, the number of antacid tablets ingested daily and compliance with study medication. At the end of the treatment, patients answered the following self-report questions: whether study medication relieved the patient's symptoms and whether the patient would use the drug if it were available.

Assessment of safety

Overall safety was assessed by the patients and investigators at all study visits, and by telephone contact 30 days following termination of the administration of the double-blind study drug. At all study visits or early termination, weight and vital signs (oral temperature,

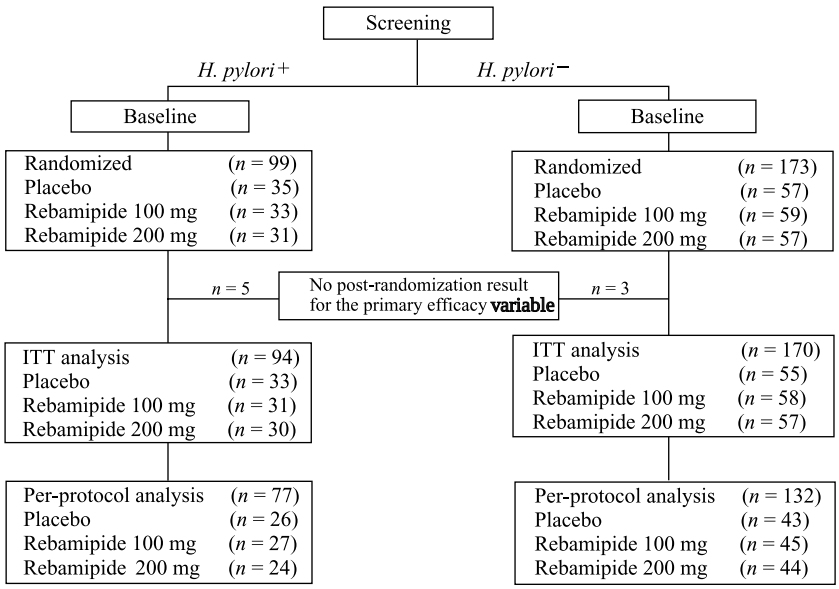

Figure 1. Flow chart representing the study design. ITT, intention-to-treat.

heart rate, respiratory rate and blood pressure) were measured. Additionally, at screening, randomization, week 2 and week 8 or early termination, the following safety evaluations were performed: haematology, blood chemistries and urinalysis. Physical examination and 12-lead electrocardiogram were performed at screening and at week 8 or early termination.

Statistical analysis

The analyses were by intention-to-treat. All values were expressed as the mean ± standard deviation (s.d.). In order to evaluate the improvement of individual symptom scores within each group during the treatment period, statistical analysis was carried out for repeated measures. Individual symptom scores for every 2 weeks, the number of antacid tablets used daily and the end-of-treatment questionnaire were evaluated by the Kruskal–Wallis test between the placebo group and each of the active treatment groups. The Bonferroni correction for multiple comparisons (placebo vs. rebamipide 100 mg and 200 mg) was applied; the level of significance was $P < 0.025$ (two-tailed).

It was originally projected that a sample size of 100 patients per treatment group would be sufficient to detect a difference in response rate of approximately 20% between the rebamipide treatment group and the placebo treatment group with 80% power at the 0.05 significance level, based on a two-sample, two-tailed normal approximation to the binomial test for equal proportions. Because of slow patient recruitment and unexpected budget constraints, the trial was stopped prior to completion of enrolment. Based on an enrolled population of approximately 50 patients per arm in the *H. pylori*-negative study and 30 patients per arm in the *H. pylori*-positive study, the detectable differences would be 30% and 40%, respectively, at a 0.05 significance level and 80% power.

RESULTS

Patient disposition

As shown in the flow diagram of patient disposition (Figure 1), 557 patients were screened for eligibility and for evaluation of *H. pylori* status. The two most common

Table 1. Baseline characteristics of patients in *H. pylori*-positive and *H. pylori*-negative functional dyspepsia groups in the intention-to-treat analysis

	H. pylori-positive			*H. pylori*-negative		
	Placebo ($n = 33$)	Reb 100 mg ($n = 31$)	Reb 200 mg ($n = 30$)	Placebo ($n = 55$)	Reb 100 mg ($n = 58$)	Reb 200 mg ($n = 57$)
Age (year*)	42.1 ± 10.3	42.8 ± 13.0	44.1 ± 14.3	42.8 ± 15.2	43.3 ± 14.9	43.7 ± 12.5
Male:female	7:26	11:20	13:17	22:33	22:36	11:46
Alcohol use	6 (18%)	12 (39%)	15 (50%)	27 (49%)	34 (62%)	31 (54%)
Smoker	14 (42%)	13 (42%)	15 (50%)	24 (44%)	23 (40%)	26 (46%)
Aspirin use	0	1 (3%)	0	1 (2%)	3 (5%)	1 (2%)
Race						
White	11	8	12	41	46	40
Black	7	5	4	4	4	6
Hispanic	15	17	13	7	4	8
Asian	0	0	0	2	0	2
Others	0	1	1	1	4	1
Pain/discomfort	3.6 ± 0.8	3.7 ± 1.0	3.7 ± 0.9	3.4 ± 0.7	3.5 ± 0.7	3.4 ± 0.8
Heartburn (day)	2.2 ± 1.5	2.0 ± 1.8	2.4 ± 1.5	1.9 ± 1.6	2.1 ± 1.4	2.1 ± 1.4
Heartburn (night)	2.5 ± 1.7	1.9 ± 1.9	2.4 ± 1.8	1.8 ± 1.6	2.1 ± 1.5	1.9 ± 1.7
Belching	2.7 ± 1.3	2.7 ± 1.3	2.5 ± 1.6	2.6 ± 1.5	2.6 ± 1.4	2.5 ± 1.6
Nausea	1.5 ± 1.5	1.7 ± 1.6	1.6 ± 1.5	1.7 ± 1.5	1.9 ± 1.5	1.8 ± 1.6
Vomiting	0.8 ± 1.4	0.2 ± 0.6	0.5 ± 1.1	0.4 ± 1.0	0.5 ± 1.2	0.5 ± 1.2
Bloating	2.9 ± 1.5	2.8 ± 1.7	2.8 ± 1.8	2.7 ± 1.4	2.9 ± 1.6	3.0 ± 1.6
Early satiety	2.8 ± 1.2	2.8 ± 1.6	2.7 ± 1.7	2.7 ± 1.4	2.7 ± 1.7	2.7 ± 1.5

*Data represented as mean ± s.d.
Reb, rebamipide.

causes of protocol-defined exclusions occurring during the screening and baseline evaluation periods were low patient self-assessments for continuing upper abdominal pain and gastrointestinal abnormalities diagnosed at endoscopy, such as oesophagitis, gastric ulcer and duodenal ulcer. Ninety-nine patients with *H. pylori* and 173 patients without *H. pylori* were randomized between March 1998 and November 1998 to receive rebamipide 100 mg, 200 mg or placebo three times a day for 8 weeks. The three groups in each study were comparable in terms of patient demographics and symptoms at the start of the double-blind treatment, with the exception of gender in the *H. pylori*-negative study ($P = 0.029$) (Table 1).

Relief of individual symptoms

In the *H. pylori*-positive study, individual symptom scores in all three treatment groups declined significantly from baseline during the study period ($P < 0.001$), except vomiting ($P = 0.330$). There were no significant differences for any individual symptoms in comparisons between the placebo and active treatment groups at week 8. In the *H. pylori*-positive study, 13% in the placebo group, 14% in the rebamipide 100 mg group and 10% in the rebamipide 200 mg group had complete relief of upper abdominal pain/discomfort. The belching score was significantly reduced at week 2 in the rebamipide 100 mg group (31.9% reduction vs. placebo group, $P = 0.017$), with a trend at week 4 (30.6% reduction vs. placebo group, $P = 0.027$). The belching score was also significantly reduced in the rebamipide 200 mg group (36.6% reduction vs. placebo group, $P = 0.012$) at week 2 (Figure 2).

In the *H. pylori*-negative study, all individual symptom scores in all treatment groups declined significantly from baseline during the study period ($P < 0.001$). Complete relief of upper abdominal pain/discomfort was reported by 16% in the placebo group, 13% on rebamipide 100 mg and 9% on rebamipide 200 mg. There were no significant differences for any individual symptoms in comparisons between the placebo group and each of the active treatment groups by the analysis at each visit.

Consumption of antacid tablets

In the *H. pylori*-positive study, the mean number of antacid tablets used daily per patient at the baseline evaluation period was 4.6 ± 3.0 in the placebo group, 4.1 ± 2.8 in the rebamipide 100 mg group and 4.0 ± 2.5 in the rebamipide 200 mg group, and was reduced during the study period to 2.9 ± 3.0 (31% reduction), 2.1 ± 2.5 (55%) and 2.5 ± 2.1 (42%), respectively, at the last visit. There was no significant difference in the change in antacid tablet consumption between any of the groups during the active treatment period.

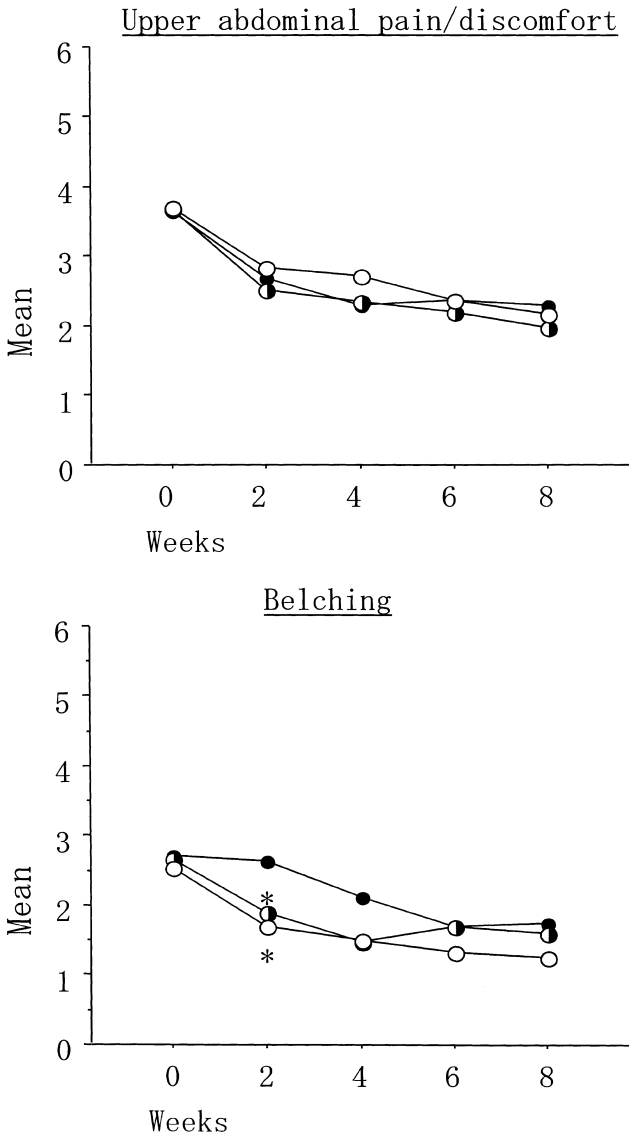

Figure 2. Time course of symptom scores of upper abdominal pain/discomfort and belching recorded at randomization and every 2 weeks during treatment in the *Helicobacter pylori*-positive study. Placebo group (●), rebamipide 100 mg group (◑) and 200 mg group (○). Data represent the mean values of the individual symptom scores. *$P < 0.025$ vs. placebo group by Kruskal–Wallis test.

In the *H. pylori*-negative study, the mean number of antacid tablets used daily per patient was 3.2 ± 3.0 in the placebo group, 3.1 ± 2.1 in the rebamipide 100 mg group and 3.5 ± 2.5 in the rebamipide 200 mg group at the baseline evaluation period, and was reduced during the study period to 2.1 ± 3.2 (36% reduction), 1.5 ± 1.9 (50%) and 1.8 ± 2.6 (49%), respectively, at the last visit. There were trends for reduced antacid tablet consumption in the rebamipide treatment groups at the end of the first 3 weeks of the active treatment period (placebo group, 0.6 ± 1.9 tablet decrease from baseline; rebamipide 100 mg group, 1.3 ± 1.4 tablet decrease, $P = 0.042$; rebamipide 200 mg group, 1.6 ± 2.0 tablet decrease, $P = 0.032$).

End-of-treatment questionnaire

In the *H. pylori*-positive study, analysis of the end-of-treatment questionnaire revealed that patients thought the study medication relieved the symptoms of functional dyspepsia in 62% of the placebo group, 78% of the rebamipide 100 mg group and 83% of the rebamipide 200 mg group ($P = 0.087$), while there were no significant differences between treatment groups (Table 2). The percentage of patients who responded positively when asked whether they would take the study medication again if available was 72% of the placebo group, 85% of the rebamipide 100 mg group and 96% of the rebamipide 200 mg group, which was significantly different for the placebo group vs. the rebamipide 200 mg group ($P = 0.020$).

There were no significant differences in responses to these questions between treatment groups in the *H. pylori*-negative study (Table 2).

Safety assessment

Forty-nine (49%) and 122 (71%) patients experienced treatment-emergent adverse events in the *H. pylori*-positive and *H. pylori*-negative studies, respectively. The

Table 2. Patient end-of-treatment questionnaire on whether study medication relieved the symptoms and whether the patient would use the drug if it were available

	H. pylori-positive			*H. pylori*-negative		
	Placebo ($n = 33$)	Reb 100 mg ($n = 31$)	Reb 200 mg ($n = 30$)	Placebo ($n = 55$)	Reb 100 mg ($n = 58$)	Reb 200 mg ($n = 57$)
Symptom relief by the study medication						
Yes	18 (62%)	21 (78%)	20 (83%)	27 (61%)	29 (54%)	33 (63%)
No	11	6	4	17	25	19
P value		0.201	0.087		0.446	0.832
Request for the study medication again						
Yes	21 (72%)	23 (85%)	24 (96%)	27 (61%)	32 (59%)	38 (73%)
No	8	4	1	17	22	14
P value		0.224	0.020		0.832	0.133

Reb, rebamipide.

Table 3. Drug-related treatment-emergent adverse events

	H. pylori-positive			*H. pylori*-negative		
	Placebo ($n = 35$)	Reb 100 mg ($n = 33$)	Reb 200 mg ($n = 31$)	Placebo ($n = 57$)	Reb 100 mg ($n = 59$)	Reb 200 mg ($n = 57$)
Side-effects	10 (29%)	5 (15%)	6 (19%)	23 (40%)	14 (24%)	12 (21%)
Diarrhoea	1 (3%)	0	2 (6%)	3 (5%)	2 (3%)	3 (5%)
Constipation	0	1 (3%)	1 (3%)	0	0	0
Nausea	4 (11%)	1 (3%)	0	2 (4%)	1 (2%)	0
Abdominal pain	3 (9%)	1 (3%)	1 (3%)	3 (5%)	3 (5%)	1 (2%)
Headache	4 (11%)	0	1 (3%)	2 (4%)	2 (4%)	1 (2%)
Rash	2 (6%)	0	1 (3%)	2 (4%)	0	1 (2%)

Occurring in ≥ 2% of all patients. Statistical testing was not performed on the incidence of adverse events.
Reb, rebamipide.

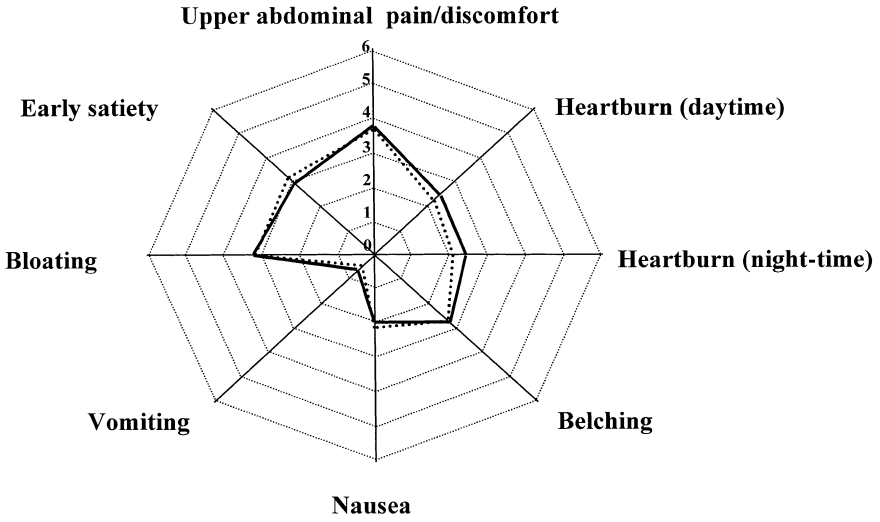

Figure 3. Comparison of various individual symptom scores (from 0–6) at screening in functional dyspepsia patients with (full line) and without (dotted line) *Helicobacter pylori* infection.

adverse events were considered by the investigator to be related to the study medication in 21 (21%) patients in the *H. pylori*-positive study and 49 (28%) patients in the *H. pylori*-negative study (Table 3). Most of these types of events were related to the digestive system or body as a whole, including headache and pain. More patients in the placebo treatment group experienced study medication-related adverse events (29%) than in the rebamipide 100 mg group (15%) or the rebamipide 200 mg group (19%) in the *H. pylori*-positive study, and also in the *H. pylori*-negative study (40% in the placebo group, 24% in the rebamipide 100 mg group and 21% in the rebamipide 200 mg group). There were no deaths or study medication-related serious adverse events in either study.

DISCUSSION

We investigated the efficacy and safety of rebamipide compared with placebo in functional dyspepsia patients with or without *H. pylori* in separate studies, and found that a significantly greater number of *H. pylori*-positive patients treated with rebamipide requested the study medication again, and that rebamipide reduced the belching score at week 2 but not at week 8 in the *H. pylori*-positive patients.

As shown in Figure 3, individual symptom scores at screening were comparable between *H. pylori*-positive and *H. pylori*-negative functional dyspepsia patients; *H. pylori* infection has not been convincingly implicated in the pathogenesis of functional dyspepsia.[31–33] On the other hand, patients with and without *H. pylori* infection may still respond to a local gastroprotective therapy in a different manner. Thus, it is meaningful to evaluate the efficacy of rebamipide in studies distinguished by *H. pylori* status. Although controversial, Thumshrin *et al.* reported that *H. pylori* infection was associated with a heightened gastric sensitivity in dyspeptics.[34] As the association between *H. pylori* infection and gastritis is well established,[35] gastric mucosal inflammation may play a key role in enhancing gastric sensitivity. Rebamipide is known to suppress gastric mucosal inflammation in experimental gastrointestinal injury models[36–39] and gastric ulcer patients infected with *H. pylori,*[40] and thus we expected that rebamipide might show more potent efficacy in *H. pylori*-positive patients with functional dyspepsia.

Based on end-of-treatment questionnaires in the *H. pylori*-positive study, the majority of patients in each group thought the study medication relieved the symptoms of functional dyspepsia. A somewhat larger proportion of patients in the rebamipide treatment groups, however, responded favourably in this subjective global assessment compared to those in the placebo group. Furthermore, at the end of treatment, a greater percentage of patients in the rebamipide treatment groups (especially the rebamipide 200 mg treatment group) compared to the placebo group responded positively when asked if they would take the medication again, if available. However, these were secondary endpoints, and rebamipide failed to show reduction in any individual symptom score at the end of the study period.

Significant reduction was seen in the belching score with rebamipide at week 2 in the 100 mg and 200 mg groups. Is there a possible mechanism for a reduction of belching by rebamipide? Nitric oxide (NO), which is

known to promote relaxation of the lower oesophageal sphincter and hence belching,[41] may be increased in inflamed gastric mucosa. Nagano *et al.* reported that rebamipide inhibited NO production derived from inducible NO synthase in cultured RAW264.7 cells stimulated by interferon gamma.[42] However, the improvement in belching was modest in the present trial and was not sustained with rebamipide, and the observation is likely to be coincidental. Indeed, the prevalence of belching at baseline was similar in the *H. pylori*-positive and *H. pylori*-negative studies. In the *H. pylori*-negative study, no individual symptoms were relieved by rebamipide compared with placebo. Rebamipide has no antisecretory activity,[15] but antacid usage tended to be reduced in the rebamipide groups during the early portion of the study. No difference among the study groups was seen in the last 4 weeks of the study.

Rebamipide had few adverse events. As shown in Table 3, the incidence of adverse events in the rebamipide treatment groups was lower than in the placebo group in both studies, and no severe adverse events were observed during the study period.

In conclusion, we could find no significant differences in individual symptoms at the end of treatment, although more patients treated with rebamipide responded that they would request the medication again, if available. Rebamipide was generally well tolerated in both doses.

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REFERENCES

1 Talley NJ, Zinsmeister AR, Schleck CD, Melton LJ III. Dyspepsia and dyspepsia subgroups: a population-based study. Gastroenterology 1992; 102: 1259–68.
2 Barbara L, Camilleri M, Corinaldesi R, *et al.* Definition and investigation of dyspepsia—consensus of an international ad hoc working party. Dig Dis Sci 1989; 34: 1272–6.
3 Talley NJ. Nonulcer dyspepsia: current approaches to diagnosis and management. Am Fam Physician 1993; 47: 1407–16.
4 Talley NJ, Colin-Jones D, Koch KL, Koch M, Nyrén O, Stanghellini V. Functional dyspepsia: a classification with guidelines for diagnosis and management. Gastroenterol Int 1991; 4: 145–60.
5 Talley NJ, Phillips SF. Non-ulcer dyspepsia: potential causes and pathology. Ann Intern Med 1988; 108: 865–79.
6 Saunders JHB, Oliver RJ, Higson DL. Dyspepsia incidence of non-ulcer disease in a controlled trial of ranitidine in general practice. Br Med J 1986; 292: 665–8.
7 Talley NJ. Drug treatment of functional dyspepsia. Scand J Gastroenterol 1991; 26: 47–60.
8 Gotthard R, Bodemar G, Brodin U, Jönsson KÅ. Treatment with cimetidine, antacid or placebo in patients with dyspepsia of unknown origin. Scand J Gastroenterol 1988; 23: 7–18.
9 Talley NJ, Meineche-Schmidt V, Pare P, *et al.* Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). Aliment Pharmacol Ther 1998; 12: 1055–65.
10 Greydanus MP, Vassallo M, Camilleri M, Nelson DK, Hanson RB, Thomforde GM. Neurohormonal factors in functional dyspepsia: insights on pathophysiological mechanisms. Gastroenterology 1991; 100: 1311–8.
11 Tucci A, Corinaldesi R, Stanghellini V, *et al. Helicobacter pylori* infection and gastric function in patients with chronic idiopathic dyspepsia. Gastroenterology 1992; 103: 768–74.
12 Eberl T, Barnert J, Dumitrascu DL, Fischer J, Wienbeck M. The effect of cisapride on dysmotility-like functional dyspepsia: reduction of the fasting and postprandial area, but not of the postprandial antral expansion. Eur J Gastroenterol Hepatol 1998; 10: 991–5.
13 Halter F, Miazza B, Brignoli R. Cisapride or cimetidine in the treatment of functional dyspepsia. Results of a double-blind, randomized, Swiss multicentre study. Scand J Gastroenterol 1994; 29: 618–23.
14 Champion MC, MacCannell KL, Thomson ABR, *et al.* A double-blind randomized study of cisapride in the treatment of nonulcer dyspepsia. Can J Gastroenterol 1997; 11: 127–34.
15 Yamasaki K, Ishiyama H, Imaizumi T, Kanbe T, Yabuuchi Y. Effect of OPC-12759, a novel antiulcer agent, on chronic and acute experimental gastric ulcer, and gastric secretion in rats. Jpn J Pharmacol 1989; 49: 441–8.
16 Yamasaki K, Sakurai K. Role of lipid peroxidation in protection of rats by rebamipide against gastric mucosal lesions induced by stress plus indomethacin. Pathophysiology 1994; 1: 251–7.
17 Yamasaki K, Arakawa T, Takaishi O, Higuchi K, Kobayashi K, Kuroki T. Influence of rebamipide on indometacin-induced gastric hemorrhage in rats under restraint stress. Arzneimittelforschung 1999; 49: 359–65.
18 Arakawa T, Kobayashi K, Yoshikawa T, Tarnawski A. Rebamipide: overview of its mechanisms of action and efficacy in mucosal protection and ulcer healing. Dig Dis Sci 1998; 43(Suppl. 9): 5S–13S.
19 Ishihara K, Komuro Y, Nishiyama N, Yamasaki K, Hotta K. Effect of rebamipide on mucus secretion by endogenous prostaglandin-independent mechanism in rat gastric mucosa. Arzneimittelforschung 1992; 42: 1462–6.
20 Song DU, Ryu MH, Chay KO, *et al.* Effect of rebamipide on the glycosaminoglycan content of the ulcerated rat stomach. Fundam Clin Pharmacol 1998; 12: 546–52.

21 Yamasaki K, Kanbe T, Chijiwa T, Ishiyama H, Morita S. Gastric mucosal protection by OPC-12759, a novel antiulcer compound, in the rat. Eur J Pharmacol 1987; 142: 23–9.
22 Kleine A, Kluge S, Peskar BM. Stimulation of prostaglandin biosynthesis mediates gastroprotective effect of rebamipide in rats. Dig Dis Sci 1993; 38: 1441–9.
23 Ogino K, Hobara T, Ishiyama H, *et al.* Antiulcer mechanism of action of rebamipide, a novel antiulcer compound, on diethyldithiocarbamate-induced antral gastric ulcers in rats. Eur J Pharmacol 1992; 212: 9–13.
24 Suzuki M, Miura S, Mori M, *et al.* Rebamipide, a novel antiulcer agent, attenuates *Helicobacter pylori* induced gastric mucosal cell injury associated with neutrophil derived oxidants. Gut 1994; 35: 1375–8.
25 Danielsson D, Jurstrand M. Nonopsonic activation of neutrophils by *Helicobacter pylori* is inhibited by rebamipide. Dig Dis Sci 1998; 43(Suppl. 9): 167S–73S.
26 Yoshikawa T, Naito Y, Tanigawa T, Kondo M. Free radical scavenging activity of the novel anti-ulcer agent rebamipide studied by electron spin resonance. Arzneimittelforschung 1993; 43: 363–6.
27 Naito Y, Yoshikawa T, Tanigawa T, *et al.* Hydroxyl radical scavenging by rebamipide and related compounds: electron paramagnetic resonance study. Free Rad Biol Med 1995; 18: 117–23.
28 Aihara M, Azuma A, Takizawa H, *et al.* Molecular analysis of suppression of interleukin-8 production by rebamipide in *Helicobacter pylori*-stimulated gastric cancer cell lines. Dig Dis Sci 1998; 43(Suppl. 9): 174S–80S.
29 Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. Gut 1999; 45(Suppl. 2): II37–42.
30 Svedlund J, Sjödin I, Dotevall G. GSRS — a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci 1988; 33: 129–34.
31 Blum AL, Talley NJ, O'Morain C, *et al.* Lack of effect of treating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. N Engl J Med 1998; 339: 1869–74.
32 Talley NJ. A critique of therapeutic trials in *Helicobacter pylori*-positive functional dyspepsia. Gastroenterology 1994; 106: 1174–83.
33 Talley NJ, Vakil N, Ballard EDII, Fennerty MB. Absence of benefit of eradicating *Helicobacter pylori* in patients with nonulcer dyspepsia. N Engl J Med 1999; 341: 1106–11.
34 Thumshrin M, Camilleri M, Saslow SB, Williams DE, Burton DD, Hanson RB. Gastric accommodation in non-ulcer dyspepsia and the roles of *Helicobacter pylori* infection and vagal function. Gut 1999; 44: 55–64.
35 Dooley CP, Cohen H, Fitzgibbons PL, *et al.* Prevalence of *Helicobacter pylori* infection and histologic gastritis in asymptomatic persons. N Engl J Med 1989; 321: 1562–6.
36 Murakami K, Okajima K, Uchiba M, *et al.* Rebamipide attenuates indomethacin-induced gastric mucosal lesion formation by inhibiting activation of leukocytes in rats. Dig Dis Sci 1997; 42: 319–25.
37 Kokura S, Yoshikawa T, Naito Y, *et al.* Effects of rebamipide, a novel anti-ulcer agent, on gastric mucosal injury induced by platelet-activating factor in rats. Dig Dis Sci 1997; 42: 2566–71.
38 Yoshida M, Kitahora T, Wakabayashi G, *et al.* Active oxygen species in formation of acute gastric mucosal lesions induced by thermal injury in rats. Dig Dis Sci 1995; 40: 1306–10.
39 Kim CD, Hong KW. Preventive effect of rebamipide on gastric lesions induced by ischemia-reperfusion in the rat. J Pharmacol Exp Ther 1995; 275: 340–4.
40 Higuchi K, Arakawa T, Nebiki H, *et al.* Rebamipide prevents recurrence of gastric ulcers without affecting *Helicobacter pylori* status. Dig Dis Sci 1998; 43: 99S–106S.
41 Murray J, Du C, Ledlow A, Bates JN, Conklin JL. Nitric oxide: mediator of nonadrenergic noncholinergic responses of opossum esophageal muscle. Am J Physiol 1991; 261: G401–6.
42 Nagano C, Wakebe H, Azuma A, Imagawa K, Kikuchi M. IFN-gamma-induced iNOS mRNA expression is inhibited by rebamipide in murine macrophage RAW264.7 cells. Dig Dis Sci 1998; 43(Suppl. 9): 118S–24.