

## CLINICAL TRIAL

# Treatment of refractory peptic ulcer with omeprazole or continued H<sub>2</sub> receptor antagonists: a controlled clinical trial

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## Abstract

We tested the hypothesis that the gastric H<sup>+</sup>/K<sup>+</sup> adenosine triphosphatase inhibitor, omeprazole, because of its different mode of action and pronounced inhibitory effect on gastric acid secretion, may be more effective in peptic ulcer that is refractory to histamine H<sub>2</sub> receptor antagonist treatment than continuing the same therapy. Altogether 107 patients (duodenal ulcer, n=88; prepyloric ulcer, n=14; gastric ulcer, n=3; mixed sites, n=2) with refractory peptic ulcer – that is ulcer unhealed after at least two months' treatment with cimetidine 0.8 g or 1 g daily or with ranitidine 0.3 g daily – were randomly allocated to receive either omeprazole 40 mg daily (n=54) or to continue treatment with the same H<sub>2</sub> receptor antagonist and at the same dose (n=53) for up to eight weeks. The patients in the two treatment groups were well matched demographically. Healing by 'intent to treat' analysis was as follows: at four weeks, omeprazole 46 of 54 (85%), H<sub>2</sub> receptor antagonist 18 of 53 (34%) (p<0.0001); and at eight weeks, 52 of 54 (96%) and 30 of 53 (57%) respectively (p<0.0001). One patient was lost to follow up but of the 22 patients whose ulcers were shown to be unhealed at endoscopy after receiving continued H<sub>2</sub> receptor antagonist treatment, 21 healed in four to eight weeks when changed to omeprazole. Daytime epigastric pain cleared at four weeks in 43 of 47 (91%) patients on omeprazole and in 32 of 46 (70%) on H<sub>2</sub> receptor antagonists (p=0.01) and relief of all dyspeptic symptoms occurred in 39 of 47 (83%) and 23 of 45 (51%) (p=0.0009) patients respectively. Adverse events occurred in 11 of 54 (20%) patients on omeprazole and in 12 of 35 (34%) on cimetidine but in none on ranitidine. The events were mild and none required treatment withdrawal. The commonest event in patients on omeprazole was loose stools or diarrhoea (n=5). Omeprazole was significantly better than continued H<sub>2</sub> receptor antagonist treatment for the short term management of refractory peptic ulcer as judged by healing rate and pain relief, and it was safe.

About 5–10% of peptic ulcers do not heal quickly (within two to three months) when treated with

standard doses of histamine H<sub>2</sub> receptor antagonists and are considered to be refractory. The optimal management of these patients is unknown. One explanation for delayed or non-healing in these patients is that acid suppression with H<sub>2</sub> receptor antagonists is insufficient in them.<sup>1,2</sup> In contrast, omeprazole, at a daily dose of 40 mg, causes assured and profound acid reduction, the 24 hour acidity being reduced by over 90%,<sup>3-5</sup> and is thus potentially valuable in the treatment of patients in whom H<sub>2</sub> receptor antagonists fail. Open studies with omeprazole in these patients have given promising results.<sup>6,7,8</sup> We have conducted a controlled study to assess if omeprazole 40 mg daily is better than cimetidine or ranitidine continued at the same dose in patients with peptic ulcers that are refractory to H<sub>2</sub> receptor antagonist treatment.

## Patients and methods

### DEFINITION

A refractory peptic ulcer was defined as one that was still present after at least two months' treatment with standard doses of cimetidine or ranitidine.

### PATIENT SELECTION

Patients with duodenal bulb, pyloric channel, or gastric ulcer, either prepyloric or in the body (corpus), who still had an ulcer crater of 0.5 cm diameter or more after at least two months' treatment with cimetidine 0.8 g or 1 g daily or ranitidine 0.3 g daily were entered into the study, provided they did not have pain so severe that they would be unable to complete the study if they were randomised to continued treatment with H<sub>2</sub> receptor antagonists.

### EXCLUSION CRITERIA

The following groups of patients were excluded: those under 18 or over 80 years of age; women of childbearing potential (unless on oral contraceptives or fitted with an intrauterine coil) or who were lactating; patients taking mucosal protective drugs such as sucralfate or colloidal bismuth subcitrate, or those on intensive antacid treatment; those taking anticoagulants, theophylline,

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or phenytoin, because of possible interaction; patients found to have clinically important abnormalities in laboratory studies carried out before the start of the trial treatment; patients suspected of or confirmed to have malignant disease, either in the ulcer or elsewhere; and those who were likely to be non-compliant such as alcoholics. Finally, patients with a Zollinger-Ellison syndrome, with current complications such as serious bleeding or perforation that required immediate surgery, or those with pyloroduodenal stenosis that made duodenal examination at endoscopy difficult were also excluded.

#### DRUG ALLOCATION

The treatment was double blind and was started within four days of the endoscopy examination that confirmed non-healing. The patients were randomised either to continue their pretrial H<sub>2</sub> receptor antagonist at the same dose plus omeprazole placebo or to take omeprazole 40 mg each morning (two capsules, each of 20 mg strength) plus placebo cimetidine or ranitidine. Cimetidine was continued either at a dose of 400 mg twice daily or 800 mg at bedtime (two tablets, each of 400 mg strength) or 1 g daily (tablets of 200 mg strength, one three times a day after meals and two at bedtime); ranitidine was continued at a dose of 300 mg at bedtime or 150 mg twice a day (two tablets, each of 150 mg strength). Supplementary Rennie's antacid tablets were given to control residual symptoms.

#### TRIAL DESIGN

The double blind phase of treatment lasted up to eight weeks. Endoscopy was done at four weeks ( $\pm$  five days) and if the disease was still active the treatment was continued and endoscopy was repeated at eight weeks ( $\pm$  seven days). Those patients whose ulcer(s) was still present then received open treatment with omeprazole 40 mg daily for a further four weeks, without the treatment code being broken, and endoscopy was repeated. Healing was defined as the complete epithelialisation of the ulcer(s). At each endoscopy, biopsy specimens were taken from patients with gastric and prepyloric ulcers to exclude malignancy.

At each visit patients were asked if they had had any ulcer symptoms in the previous two days (daytime and night time epigastric pain, heartburn, nausea, vomiting, bleeding) and inquiries were made of any adverse events (patients were told at the time of trial inclusion to report any such event immediately). Antacid consumption over the previous two days was noted. The unused trial drugs were collected and counted to provide a guide to compliance (non-compliance being defined as using less than 75% of the H<sub>2</sub> receptor antagonist or omeprazole) and fresh drugs were issued. Finally, a physical examination was done at the start and at the end of the trial.

#### STATISTICAL ANALYSIS

In effect, there were three subgroups of patients

randomised according to whether before trial entry they were on ranitidine or on cimetidine, the latter used in two doses. For analysis of the results, however, the data have been pooled to compare the outcome of continued H<sub>2</sub> receptor antagonist treatment with that of omeprazole.

Based on a previous open study, we assumed that healing after a further four weeks' treatment with cimetidine or ranitidine would occur in about 30% of patients.<sup>9</sup> We assumed also that on omeprazole, healing would be approximately 60%. With a fixed sample size of 107 patients and true healing rates of 30% and 60% in the two treatment groups, the test power of rejecting the null hypothesis is 80% and 85% with a two sided test at the 5% significance level.

Healing rates were assessed according to patients randomised (intent to treat analysis) and of those who completed the study according to the protocol (per protocol analysis). Patients with unknown healing status were classified as unhealed for the intent to treat analysis. Confidence intervals were calculated by standard methods. Healing rates were compared by Mantel-Haenszel test: the impact on healing of possible prognostic factors was assessed by a logit model (multiple logistic regression). Pain relief was assessed by per protocol analysis and tested with a ridit analysis.

## Results

#### NUMBERS OF PATIENTS ENTERED AND EXCLUSIONS FROM ANALYSIS (TABLE I)

One hundred and seven patients were entered into the study from three centres (40, 34, and 33 patients from each of the centres). In one centre (UK) patients were predominantly on cimetidine 1 g daily before trial entry, but cimetidine 0.8 g and ranitidine 0.3 g daily were used in the other two. Fifty three patients continued their H<sub>2</sub> receptor antagonist treatment (cimetidine n=35, ranitidine n=18) and 54 were assigned to omeprazole treatment.

All 107 patients were included in the intent to treat analysis at four weeks and eight weeks but for per protocol analysis, 93 and 99 patients' data were analysed at these times respectively. The reasons for excluding 15 patients from per protocol analysis (14 at week four and eight at week eight) are shown in Table I: the commonest reason was that clinical assessments were done outside the time limits.

#### DEMOGRAPHY (TABLE II)

Patients allocated to omeprazole or ranitidine were compared separately with those allocated to omeprazole or cimetidine, and then all omeprazole assigned patients were compared with all H<sub>2</sub> receptor antagonist allocated patients. The patients were comparable with regard to mean age, sex ratio, length of ulcer history, smoking and drinking habits, previous ulcer complications, duration of pretrial H<sub>2</sub> receptor antagonist treatment, and ulcer size. Eighty eight (82%) of the 107 patients had duodenal ulcer and 14 (13%) had prepyloric ulcer; three had gastric ulcers in the corpus area and two had ulcers in two

TABLE I Numbers of patients analysed

Pretrial treatment:	Ranitidine		Cimetidine	
	Omeprazole	Ranitidine	Omeprazole	Cimetidine
Randomisation to:				
No randomised	18	18	36	35
Per protocol analysis:				
No analysed at 4 weeks	17	18	30	28
No analysed at 8 weeks	18	17	34	30
Reasons for exclusion from per protocol analysis (n=15):				
Entry criteria violated			1	1
Lost to follow up immediately after entry				1
Examination outside time limits		1	5	4
Withdrawn for non-compliance			1	1
Withdrawn because of major abnormality at baseline/adverse events	0	0	0	0

TABLE II Demography of study subjects

Pretrial treatment:	Ranitidine		Cimetidine		Pooled data	
	Ome	Ran	Ome	Cim	Ome	H <sub>2</sub> RA
Randomised to:						
No randomised	18	18	36	35	54	53
Ulcer type:						
Duodenal (DU)	15	16	29	28	44	44
Prepyloric (PPU)	3	2	3	6	6	8
Gastric (GU)	0	0	2	1	2	1
Mixed (DU/PPU/GU)	0	0	2	0	2	0
Age (mean, yrs)	46.6	47.9	45.7	50.0	46.0	49.3
Sex M/F	13/5	13/5	24/12	24/11	37/17	37/16
Length of history (median, years)	10	10	10	6	10	7
Smoker: no/yes	8:10	8:10	10:26	10:27	18:36	18:37
Smoking (g/day) (mean (SD))	9.4 (9.9)	9.3 (15.0)	10.9 (9.7)	11.9 (8.8)	10.4 (9.7)	11.0 (11.2)
Drinking (U/week) (mean (SD))	9.8 (23.9)	5.6 (9.7)	9.6 (15.9)	13.0 (17.9)	9.0 (18.6)	10.5 (15.9)
Previous surgery (perforation repair)	0	0	1	3	1	3
Previous complications	0	3	5	6	5	9
Duration H <sub>2</sub> RA treatment pre-entry (median, mths)	4	4	5	4	4	4
Ulcer diameter (median, mm)	7	7	10	10	9	8

Ome=omeprazole; Ran=ranitidine; Cim=cimetidine; H<sub>2</sub>RA=H<sub>2</sub> receptor antagonist. U=units.

locations. Their allocation to the treatment groups was also balanced.

#### HEALING

Omeprazole was significantly better than continued H<sub>2</sub> receptor antagonist treatment in healing refractory peptic ulcer at four weeks and eight weeks as judged by intent to treat analysis (four weeks – omeprazole 85%, H<sub>2</sub> receptor antagonist 34%; eight weeks – 96% *v* 57% respectively) and by per protocol analysis (four weeks – 87% *v* 39%; eight weeks – 98% *v* 60%) (all *p* values <0.0001) (Table III). When the subset of 88 duodenal ulcer patients was considered separately, the same pattern persisted (intent to treat analysis: four weeks – 36 of 44 (82%) *v* 17 of 44 (39%), *p*=0.0001; eight weeks – 42 of 44 (95%) *v* 27 of 44 (61%), *p*=0.0004. After eight weeks' continued H<sub>2</sub> receptor antagonist treatment, 22 patients underwent endoscopy and were found to have unhealed ulcers. They received omeprazole for four weeks and healing was observed in 19 of 22 (86%). In two of the remaining three patients with unhealed ulcers, healing occurred with a further four weeks' omeprazole treatment but the third did not continue with the treatment.

Within individual centres there was a close similarity in healing rates on omeprazole but on

TABLE III Healing\* of refractory peptic ulcer

	Intent to treat analysis		Per protocol analysis	
	4 weeks	8 weeks	4 weeks	8 weeks
Omeprazole (n=54)	46 (85%)	52 (96%)	41 (87%)	51 (98%)
H <sub>2</sub> RA (n=53)	18 (34%)	30 (57%)	18 (39%)	28 (60%)
<i>p</i>	<0.0001	<0.0001	<0.0001	<0.0001
95% CI of differences	+35–	+25–	+31–	+23–
	+67%	+53%	+65%	+53%

\*Healing status unknown; at 4 weeks – omeprazole *n*=2, H<sub>2</sub>RA *n*=4; at 8 weeks – omeprazole *n*=1, H<sub>2</sub>RA *n*=1. H<sub>2</sub>RA=H<sub>2</sub> receptor antagonist.

H<sub>2</sub> receptor antagonists there were considerable differences, the lowest healing rates being observed in Sweden. Thus, by intent to treat analysis the healing rates on omeprazole at four weeks in Rotherham, Linköping and Milan were 86%, 88%, and 82%, and on H<sub>2</sub> receptor antagonists the rates were 47%, 12%, and 41% respectively.

Healing rates on cimetidine and ranitidine were roughly similar. Thus, by per protocol analysis, at four weeks healing rates (and 95% confidence intervals for the difference in true healing rates) were: omeprazole 13 of 17 (76%) *v* ranitidine 6 of 18 (33%) (CI+13%–+73%); and at eight weeks: 18 of 18 (100%) *v* 12 of 17 (67%) (CI+5%–+54%) respectively. The corresponding figures for patients on omeprazole *v* cimetidine were: at four weeks, 28 of 30 (93%) *v* 12 of 28 (43%) (CI 30%–70%); and at eight weeks, 33 of 34 (97%) *v* 16 of 30 (53%) (CI 25%–63%), respectively.

Neither ulcer size or drinking habits were found to have an influence on ulcer healing. No appreciable differences were observed in omeprazole treated patients, but among patients who continued with H<sub>2</sub> receptor antagonist treatment, healing was higher in smokers than in non-smokers (48% *v* 20%) and lower in those with an ulcer history of ≤12 months than in those with a history >12 months (29% *v* 41%) but the differences were not significant. The only factor which had a significant bearing on the outcome was the drug used.

#### SYMPTOM RELIEF

The degree and rapidity of pain relief was not a primary objective in this study; indeed a relatively high proportion of patients were symptom free at entry. Daytime epigastric pain was the commonest symptom. It was absent at randomisation in 16 of 53 (30%) patients allocated to omeprazole and in 23 of 52 (44%) assigned to H<sub>2</sub> receptor antagonists. At four weeks; these proportions were: omeprazole 43 of 47 (91%), H<sub>2</sub> receptor antagonists 32 of 46 (70%) (*p*=0.01). Only a few patients on omeprazole required treatment beyond this point; at eight weeks, only one of the seven patients treated in this way reported pain compared with five of 31 patients on continued H<sub>2</sub> receptor antagonist treatment.

The relief of night time pain and of heartburn was similar for both treatments. At four weeks, however, relief of daytime epigastric pain 91% *v* 70% (*p*=0.01) and overall relief of symptoms 83% *v* 51% (*p*=0.0009) were significantly better with omeprazole.



## ADVERSE EVENTS

Eleven of 54 (20%) patients on omeprazole, 12 of 35 (34%) on cimetidine, but none of the 18 patients on ranitidine reported adverse events; and all the patients with such events were from one centre which recruited cimetidine treated patients. There were no serious adverse events and no patients were withdrawn because of them. The commonest problems on omeprazole were mild gastrointestinal disorders – diarrhoea (n=3), loose stools (n=2), and constipation (n=1). In contrast, the events seen in patients on cimetidine were more diverse with individual patients reporting one of the following: cramps, headache, orchitis, loose stools, nausea, eructation, and greasy skin.

## Discussion

Our study has shown that omeprazole (40 mg daily) was significantly better than continued treatment with standard doses of cimetidine (0.8 g or 1 g daily) or ranitidine (300 mg daily) in healing peptic ulcer that was refractory to these doses of H<sub>2</sub> receptor antagonists. Though pain control was not a primary objective and patients with extremely severe pain were not included, omeprazole gave better symptom relief than did further H<sub>2</sub> receptor antagonist treatment.

Our results support and extend the observation made in open studies<sup>6-8</sup> where healing rates of 90–100% were obtained with omeprazole 40 mg daily. They are, however, at variance with those of the multicentre trial in France<sup>10</sup> where the healing rates on omeprazole 20 mg daily and on continued ranitidine 300 mg daily were similar at two weeks – 48% and 46% and at four weeks – 80% and 75% respectively. The difference may be influenced by three factors. Firstly, although the lower dose of omeprazole (20 mg) used is capable of producing considerable acid inhibition, it does so less consistently than the 40 mg dose. Secondly, in their study resistance was defined as failure to heal after only six weeks' cimetidine treatment. Lastly, patients whose ulcers remained unhealed on cimetidine 800 mg daily were randomised to receive either omeprazole or ranitidine, which in France has previously been shown to be superior to continued cimetidine treatment.<sup>11</sup>

Consideration of the study design is relevant since we had two options for the control arm – either to extend H<sub>2</sub> receptor antagonist treatment at the same dose despite the failure of treatment at this dosage to heal ulcers in these patients or to double the dose, which would also extend the H<sub>2</sub> receptor antagonist treatment period. The latter step has attractions and is commonly used in clinical practice, although without clear evidence of its efficacy. Our experience<sup>12</sup> has shown that continuing the same dose of H<sub>2</sub> receptor antagonist but in a formal clinical trial can be associated with a considerable increase in the healing rate. Indeed, in the present study there was appreciable healing in the group receiving continued H<sub>2</sub> receptor antagonist treatment. This effect coupled with a dose increase would confound interpretation. Since our aim was to see if omeprazole was an effective treatment option in this type of patient, we avoided the confusion of

changing two variables at once by using continued H<sub>2</sub> receptor antagonist treatment as the control arm.

Medical treatment options available until recently in the management of peptic ulcer refractory to H<sub>2</sub> receptor antagonists include continued treatment with the same drug at the same dose or at a higher dose<sup>9</sup>; combining the H<sub>2</sub> receptor antagonist with the antimuscarinic, pirenzepine<sup>12-14</sup>; or changing to the mucosal protectants, sucralfate<sup>15</sup> or colloidal bismuth subcitrate. Of these measures, the only one that has given clear and unequivocal benefit is colloidal bismuth subcitrate, which in two controlled studies was shown to accelerate healing significantly compared with cimetidine treatment continued at the same dose or at a higher one.<sup>16,17</sup> We can now extend the therapeutic options by including omeprazole 40 mg daily, which heals more than 80% of refractory ulcers within four weeks, and almost all within eight weeks, is effective in relieving pain, and is safe.

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