Comparison of omeprazole and cimetidine in reflux oesophagitis: symptomatic, endoscopic, and histological evaluations

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Abstract

Symptomatic patients with endoscopically verified reflux oesophagitis were randomised to a double blind trial in which they received either omeprazole (20 mg once daily) or cimetidine (400 mg four times daily) for four, and if necessary, eight weeks. In an 'intention to treat' analysis, oesophagitis was found to have healed after four weeks in 77 of 137 (56%) in the omeprazole group and in 34 of 133 (26%) in the cimetidine group ($p < 0.001$). By eight weeks these values were 71% and 35% respectively; $p < 0.001$. Histological assessments were available for 73% of the patients. At entry, 63% (66 of 104) in the omeprazole group and 60% (56 of 94) in the cimetidine group (ns) had abnormal histology. After the study, the proportions of patients who initially had had abnormal histology but who then progressed to normal were 67% (44 of 66: omeprazole) and 48% (27 of 56: cimetidine) respectively ($p < 0.001$). All patients had reflux symptoms at entry. After four weeks, 46% in the omeprazole group and 22% ($p < 0.001$) in the cimetidine group were asymptomatic. Diary cards completed for the first two weeks showed that patients treated with omeprazole experienced fewer reflux symptoms by day and night and used fewer antacids. Omeprazole, 20 mg once a day for four to eight weeks, healed a greater proportion of patients with reflux oesophagitis than cimetidine, 1.6 g per day, assessed endoscopically and histologically, and relieved more patients' symptoms.

Omeprazole (Losec, Astra), in doses of 20–60 mg once daily heals a greater proportion of reflux oesophagitis lesions than ranitidine 150 mg twice daily within four to 12 weeks.¹⁻⁴ In this study, we compared 20 mg omeprazole once daily with the relatively high dose of 1.6 g cimetidine daily (400 mg four times a day) using endoscopic and histological assessments of the resolution of reflux oesophagitis coupled with symptoms elicited at clinic visits and recorded by the patients on diary cards. This combined approach in comparing healing and symptom relief with omeprazole and an H_2 receptor antagonist has not been reported before and we believe that it represents a critical way of assessing the possible benefit of omeprazole compared with an established treatment.

Methods

TRIAL DESIGN

Patients aged 18 years and over were eligible if they had symptomatic oesophagitis of grade I-IV verified endoscopically within the week before randomisation to this trial. Exclusion criteria were: oesophageal stricture or varices; pregnancy or lactation; upper gastrointestinal surgery; oesophageal dilatation within eight weeks; use of antireflux drugs within one week; use of any investigational drug within four weeks; severe concomitant disease; use of anti-coagulants, theophylline, or phenytoin; or previous randomisation in this trial.

The trial was a randomised, double blind (double dummy) comparison of two oral treatments – omeprazole, 20 mg once a day, and cimetidine, 400 mg four times a day – in 17 centres in the British Isles. Details of recruitment are given at the end of the paper. Compliance was assessed by tablet counts, inquiry by the physician, and by patients confirming that they had taken the tablets and capsules each day on the diary cards. Ethics committee approval was obtained at each centre, and patients gave written informed consent. The initial treatment period was four weeks but if symptoms remained after this period or oesophagitis was still present at endoscopy, treatment continued for a total of eight weeks.

CLINICAL ASSESSMENTS

Endoscopy. Oesophagogastroduodenoscopy was carried out at entry (up to seven days before to randomisation), after four weeks (25–33 days),

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Accepted for publication
1 December 1989

Figure 1: Healing of oesophagitis after four and eight weeks' treatment with omeprazole (20 mg om) or cimetidine (400 mg qds). Small bars show 95% confidence intervals.

TABLE I Patient characteristics at entry to the study

	Omeprazole group	Cimetidine group
Total number (M:F)	138 (88:50)	134 (82:52)
Age (yrs), mean (SD)	53 (15)	52 (16)
Smokers (%)	20	29
Alcohol consumers (%)	42	34
Duration of reflux symptoms (%)		
≤ 2 years	57	58
2–5 years	22	22
> 5 years	20	20
Grade of oesophagitis (% (no))		
1	12 (16)	13 (18)
2	36 (49)	39 (52)
3	50 (69)	42 (56)
4	3 (4)	6 (8)
Extent of oesophagitis (% (no))		
1–4 cm	46 (64)	49 (66)
5–9 cm	44 (61)	42 (56)
≥ 10 cm	9* (11)*	9 (12)
Barrett's oesophagus	7 (10)	3 (4)

*1 missing.

and where necessary after eight weeks (50–64 days). Grading was as follows:

Grade 0=Normal oesophageal mucosa;

Grade 1=Erythema and friability with spontaneous or contact bleeding;

Grade 2=Isolated round or linear erosions affecting the lower 2 cm of the oesophagus and not the entire circumference;

Grade 3=Erosions extending above 2 cm or affecting the entire circumference;

Grade 4=Frank benign ulcer;

Group 5=Stricture.

Patients with erosive or ulcerative oesophagitis of grade 1, 2, 3, or 4 entered the study. Healing was defined as complete re-epithelialisation of the lesion – that is, grade 0. The presence and extent of Barrett's oesophagus – that is columnar lined epithelium above the gastro-oesophageal junction – was recorded.

Histology. Biopsy specimens were taken from the mucosa with oesophagitis before and at the end of treatment. Haematoxylin and eosin stained sections were graded by one histopathologist (Dr Geraint Williams) who was blind to the treatment the patient received. The most severe of four specimens on each occasion were graded as follows:

Grade 0=Normal mucosa;

Grade 1=Minor abnormalities, either scanty intraepithelial polymorphs, or submucosal vascular dilatation, or basal epithelial cell thickening;

Grade 2=Conspicuous intraepithelial polymorphs;

TABLE II Percentage healing of reflux oesophagitis after four and eight weeks' omeprazole or cimetidine, by grade of severity assessed endoscopically at entry

Time, grade at entry	% Healed	
	Omeprazole	Cimetidine
Four weeks:		
Grade 1	56	50
Grade 2	63	31
Grade 3	51	16
Grade 4	50	0
Eight weeks:		
Grade 1	75	56
Grade 2	76	48
Grade 3	66	20
Grade 4	75	0

For proportions in each group at entry, see Table I.

Grade 3=Ulcer slough present.

Symptoms at clinic visits. Patients were asked to grade their reflux symptoms both overall (none, mild, moderate, severe) and for specific symptoms (heartburn, regurgitation, dysphagia). They were asked to report any other symptoms and possible adverse events.

Diary cards. Patients recorded the presence or absence of daytime and night time reflux symptoms and the number of antacid tablets (Rennies, Nicholas: taken as required) used each day.

ANALYSES

Analyses of endoscopically assessed healing were carried out on an 'intention to treat' basis: in accordance with the protocol, one patient in each group in whom malignancy was detected was excluded. The target number of 240 patients gave a power of 80% to detect a true difference in healing rates of 20 percentage points at $p < 0.05$ (2 tailed test). Cumulative healing rates at four and eight weeks were compared using Mantel-Haenszel test with stratification by entry endoscopic grade. In addition, a multivariate analysis using a logit model to assess the importance of various factors that were prognostic of healing was carried out.

Histology and clinical symptom data were analysed by Wilcoxon rank tests stratified by entry grade. Diary card data were analysed for the first two weeks of treatment by Kolmogorov-Smirnov tests. Correlations between endoscopic and histological grades at entry and of endoscopic grade and healing rate were carried out using Spearman's rank test.

Data are expressed as mean (SD) or with 95% confidence intervals (CI). Therapeutic gain is the percentage healed in the omeprazole group minus the percentage healed in the cimetidine group.

Results

PATIENTS AT ENTRY

Of 272 patients, 138 were randomised to receive omeprazole and 134 cimetidine. The two groups were comparable in all respects at entry; details are given in Table I. Two patients (one in each

Figure 2: Resolution of heartburn in patients with reflux oesophagitis treated with omeprazole or cimetidine. The significance of differences between treatments is shown.

group) were excluded from all analyses because of malignancy reported after randomisation.

ENDOSCOPIC HEALING

After four weeks, 77 patients in the omeprazole group and 34 in the cimetidine group had healed oesophagitis (56% *v* 26%, $p < 0.001$; therapeutic gain 31%, CI=19 to 42%). The corresponding cumulative figures at eight weeks were 97 (omeprazole) and 46 (cimetidine) patients (71% *v* 35%, $p < 0.001$; therapeutic gain 36%, CI=24 to 48%). Details are shown in Figure 1, and healing rates analysed by endoscopic grade at entry in Table II. In the omeprazole group, healing rates were consistent after four weeks, irrespective of endoscopic grade at entry ($r = -0.65$; ns), while in the cimetidine group, there was a significant inverse correlation between endoscopic grade at randomisation and healing rates ($r = -0.99$; $p = 0.001$). The same pattern was seen after eight weeks (omeprazole, $r = -0.28$, ns; cimetidine, $r = -0.98$, $p < 0.02$). A further analysis was carried out to examine whether healing rates were related to the linear extent of the oesophagitis at endoscopy: the reported lengths affected were grouped as ≤ 4 , 5–9, and ≥ 10 cm. At four weeks, the healing rates in the omeprazole group were 59%, 56%, and 45% and in the cimetidine group 29%, 23%, and 17%. At the end of the study, the figures were 75%, 70%, and 54% (omeprazole) and 37%, 36%, and 17% (cimetidine). Healing rates for both the omeprazole and cimetidine groups were significantly negatively correlated with the linear extent of the oesophagitis (all $p < 0.001$). The differences between healing rates in the omeprazole and cimetidine treated groups were statistically significant ($p \leq 0.001$) except for the ≥ 10 cm groups in which the numbers of patients were too small for detection of any difference ($n = 11$ and 12 respectively: Table I).

A second analysis, including only those patients known to have complied with the protocol, produced equivalent results. At four weeks 55 of 95 (58%) patients on omeprazole and 23 of 84 (27%; $p < 0.001$) patients on cimetidine had healed oesophagitis; after eight weeks, the figures were 78% and 44% ($p < 0.001$). The therapeutic gain for omeprazole over cimetidine was 31% (CI 16 to 45%) at four weeks and 34% (CI 20 to 48%) at eight weeks. The main reasons for excluding patients from this analysis were late attendance for endoscopy (20 patients), the return of tablets and capsules indicating that less than 75% of the prescribed trial medication had been taken (31 patients), or the use of antisecretory drugs in the seven days before randomisation (17 patients).

Too few patients (Table I) had Barrett's oesophagus for a useful subgroup analysis to be carried out. In three of 10 patients in the omeprazole group and one of four in the cimetidine group, Barrett's oesophagus was recorded at the start of the study but not at the end.

HISTOLOGICAL HEALING

Histological data were available for 198 patients (73% of randomised patients). At entry, 66 of

Figure 3: Proportion of patients with oesophagitis recording reflux symptoms by day during the first two weeks of treatment with omeprazole 20 mg om or cimetidine 400 mg qds.

104 (63%) of these patients who received omeprazole had abnormal oesophageal histology (grade I and above). In the cimetidine group, the proportion was 56 of 94 (60%). At entry, histological and endoscopic grades were significantly correlated ($r = 0.26$; $p < 0.001$).

After treatment, 33% (22 of 66) of those receiving omeprazole continued to have abnormal histology compared with 52% (29 of 56) of those receiving cimetidine ($p < 0.001$).

HEALING: MULTIVARIATE ANALYSIS

There was no evidence that age, smoking, alcohol consumption, or hiatus hernia predicted healing. Treatment (omeprazole favouring healing over cimetidine) was the only significant predictor of healing at both four and eight weeks ($p < 0.001$). Histology grade at entry predicted healing at four weeks ($p = 0.037$) and the endoscopy grade at entry predicted healing at eight weeks ($p = 0.05$).

SYMPTOMS AT CLINIC VISITS

All patients had symptoms at entry but after four weeks, 46% of those receiving omeprazole compared with 22% on cimetidine were asymptomatic ($p < 0.001$). By the end of the trial, these figures had risen to 66% and 41% respectively ($p < 0.001$). The most common single symptom was heartburn, but there was no correlation between the severity of heartburn with either endoscopic grading ($r = 0.04$; $p = 0.49$) or histological grading ($r = 0.02$; $p = 0.76$) at entry. Heartburn resolved in a significantly greater proportion of patients receiving omeprazole than

Figure 4: Night time symptoms of reflux during the first two weeks of the study. Presentation as in Figure 3.

cimetidine by four and eight weeks ($p < 0.001$, (Fig 2)). Regurgitation was reported by 78% in the omeprazole group and 77% in the cimetidine group at entry but after four weeks' treatment, these figures had fallen to 30% and 48% respectively ($p < 0.01$).

OVERALL OUTCOME: ALL CLINICAL ASSESSMENTS

Endoscopy and symptoms. After four weeks, 50 (38%) patients in the omeprazole group compared with 15 (12%) in the cimetidine group ($p < 0.001$) were both asymptomatic and had healed oesophagitis as assessed by endoscopy. A further 27 (21%) in the omeprazole group and 19 (16%) in the cimetidine group had healed oesophagitis but residual symptoms, and 10 (8%) and 12 (10%) patients respectively had relief of symptoms but still had oesophagitis. Forty four patients (34%) on omeprazole and 75 (62%) on cimetidine were neither healed nor had relief of symptoms.

Endoscopy, histology and symptoms. In a subgroup of 170 patients (93 in the omeprazole and 77 in the cimetidine group), all three types of assessment were complete at entry and at the end of the study. Of these, 42 (45%) in the omeprazole group were healed endoscopically and histologically and were asymptomatic, a significantly greater proportion than in the cimetidine group (17 (22%) patients: $p < 0.01$).

DIARY CARDS

Diary card data were analysed for days two to 14 inclusive. Data were available for 84% (omeprazole group) and 81% (cimetidine group) of randomised patients. Results are shown in Figures 3, 4, 5, and 6. The differences between treatments were all significant ($p < 0.001$), with fewer omeprazole recipients having reflux symptoms by day or night, or taking antacids. Over the first two weeks, 121 patients taking omeprazole also took 1029 antacids (average 8.5 each) while 109 patients taking cimetidine also took 1642 antacids ($p < 0.001$; average 15.1 each). A significantly greater proportion of patients in the omeprazole group satisfied the strict criteria of having no daytime or night time reflux symptoms and taking no antacids: after two weeks, 74% of patients treated with omeprazole satisfied these criteria for symptom relief compared with 51% who received cimetidine.

SAFETY

Blood tests performed at the beginning and end of the trial did not show any trends for increased numbers of out of range values in either group.

Adverse events were reported during the study by 29 (21%) patients receiving omeprazole and 24 (18%) receiving cimetidine. Reporting did not imply a causal relation with the blinded trial medication. Nine (7%) patients on omeprazole and 11 (8%) on cimetidine were withdrawn because of adverse events. In all, 15 patients in the omeprazole group and 31 in the cimetidine group failed to complete the study.

Three adverse events were classified as serious. One patient (taking omeprazole) lost conscious-

Figure 5: Proportion of patients taking antacids in addition to omeprazole or cimetidine for the treatment of reflux oesophagitis during the first two weeks of the study.

ness and had left-sided weakness after alcohol ingestion. The possible diagnoses were epilepsy with Todd's paralysis or transient cerebral ischaemic attack, thought to have been precipitated by the alcohol. A second patient (taking omeprazole) had a myocardial infarction, which was not judged to be related to the trial drug. The third patient had urticaria that was judged to be causally related to cimetidine.

Discussion

Omeprazole has been shown in other studies to be effective in relieving reflux oesophagitis. A greater proportion of patients on omeprazole have healed oesophagitis, when assessed endoscopically, and symptom relief within four and eight weeks than those receiving ranitidine.¹⁻⁴ This study extends these observations to cimetidine given four times daily in a total dose of 1.6 g/day and to three types of assessment (symptomatic, histological, and endoscopic) in the same study. The advantage of omeprazole is not the result of poorer compliance with the four times daily regimen of cimetidine, for the therapeutic gain after four weeks was 30% in favour of omeprazole whether non-compliant patients and other protocol violators were included or excluded. Overall, twice as many recipients of omeprazole than of cimetidine had endoscopically healed oesophagitis at four and eight weeks. At entry, endoscopic and histological grades were correlated, but there was no correlation between symptoms and endoscopic or histological gradings, emphasising the importance of reliable measurements of each.⁵ In the

Figure 6: Proportion of patients free of reflux symptoms by day and by night and taking no antacids during the first two weeks of treatment with omeprazole or cimetidine.

omeprazole group, healing, assessed endoscopically, occurred at roughly the same rate irrespective of severity at entry, whereas with cimetidine, the healing rates for patients with more than mild oesophagitis were low (Table II). Moreover, there were only small increases in the healing rates when the duration of treatment with cimetidine 1.6 g/day was increased from four to eight weeks: the therapeutic gain for omeprazole over cimetidine showed no sign of decreasing after eight weeks (31% at four weeks, 36% at eight weeks). Healing rates were correlated with the linear extent of the oesophagitis at entry – the healing rate for cimetidine in extensive oesophagitis (≥ 10 cm) was 17% at the end of the study and that for omeprazole was 54%. A measurement of the linear extent of oesophagitis may be complementary to the more conventional endoscopic grading of severity in comparing drug effects.⁵

More rapid healing of the lesion, assessed endoscopically or histologically, is not the sole criterion for success of treatment. The speed of relief of symptoms is important for the patient and cannot be assessed solely at monthly clinic visits.

Diary cards have previously been shown to be a sensitive way of detecting differences in the speed of ulcer healing between omeprazole and H_2 receptor antagonists.⁶⁻⁸ In this study, the differences were even more noticeable than in peptic ulcer disease: differences in symptom relief and antacid consumption became apparent after the first three days of treatment.

Both 24 hour oesophageal acid exposure⁹ and clinical dose finding¹⁰ studies indicate that 20 mg once daily omeprazole is appropriate for the treatment of reflux oesophagitis. Where the oesophagitis remains unhealed after longterm, full dose H_2 receptor antagonist treatment, 40 mg omeprazole daily is more effective than high dose ranitidine.¹¹ The present study shows that a dose of 20 mg/day omeprazole is more effective by symptomatic, endoscopic, and histo-

logical assessment than 1.6 g/day cimetidine in treating reflux oesophagitis, and that omeprazole heals oesophagitis irrespective of the severity of the disease.

Patients were recruited as follows: C M Bate (53), P W N Keeling (36), C O'Morain (24), S P Wilkinson (20), D N Foster (20), R A Mountford (19), J M Temperley and S A Cairns (18), R F Harvey (17), D G Thompson and V Mani (17), M Davis (17), I C Forgacs (12). The authors thank Drs Mani (Leigh) and Cairns (Preston) for their help, and also the following who contributed to this study: J H B Saunders, Bedford (6), M Al-Najar, Doncaster (5), A C B Wicks, Leicester (4), D N Clarke, Stirling (3), M Z K Rana, Bournemouth (1). We are particularly grateful to Dr Geraint Williams, UHW Cardiff, who carried out all of the histological examinations. Alison Scrimgeour and Eva Hammarström analysed the study, and Carol Richardson prepared the manuscript.

- 1 Havelund T, Laursen LS, Skoubo-Kristensen E, *et al.* Omeprazole and ranitidine in treatment of reflux oesophagitis: double-blind comparative trial. *Br Med J* 1988; **296**: 89–92.
- 2 Van Trappen G, Rutgeerts L, Schurmans P, Coenegrachts J-L. Omeprazole (40 mg) is superior to ranitidine in short-term treatment of ulcerative reflux oesophagitis. *Dig Dis Sci* 1988; **33**: 523–9.
- 3 Klinkenberg-Knol EC, Jansen JMBJ, Festen HPM, Meuwissen SGM, Lamers CBHW. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. *Lancet* 1987; **i**: 549–1.
- 4 Sandmark S, Carlsson R, Fausa O, Lundell L. Omeprazole or ranitidine in the treatment of reflux oesophagitis. *Scand J Gastroenterol* 1988; **23**: 625–32.
- 5 Funch-Jensen P, Kock K, Christensen LA, *et al.* Microscopic appearance of the esophageal mucosa in a consecutive series of patients submitted to upper endoscopy. *Scand J Gastroenterol* 1986; **21**: 65–9.
- 6 Crowe JP, Wilkinson SP, Bate CM, Willoughby CP, Peers EM, Richardson PDI. Symptom relief and duodenal ulcer healing with omeprazole or cimetidine. *Aliment Pharmacol Therap* 1989; **3**: 83–91.
- 7 Bate CM, Wilkinson SP, Bradby GVH, *et al.* Randomised, double blind comparison of omeprazole and cimetidine in the treatment of symptomatic gastric ulcer. *Gut* 1989; **30**: 1323–8.
- 8 McFarland RJ, Bateson MC, Green JRB, *et al.* Omeprazole provides quicker symptom relief and duodenal ulcer healing than ranitidine. *Gastroenterology* 1990; **98**: 278–83.
- 9 Robinson MG, Humphries TJ, McIntosh D, Allen ML, Gagliola AJ, Broadstreet TE. Omeprazole dose response effect on 24 hour esophageal acid exposure in patients with symptomatic gastroesophageal reflux disease. *Gastroenterology* 1989; **96**: A420.
- 10 Hetzel DJ, Dent J, Reed WD, *et al.* Healing and relapse of severe peptic esophagitis after treatment with omeprazole. *Gastroenterology* 1988; **95**: 903–12.
- 11 Lundell L, Westin IH, Sandmark S, *et al.* Omeprazole or high dose ranitidine in the treatment of patients with reflux oesophagitis not responding to standard doses of H_2 -receptor antagonists. *Gastroenterology* 1989; **96**: A310.