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Double blind comparison of omeprazole (40 mg od) versus cimetidine (400 mg qd) in the treatment of symptomatic erosive reflux oesophagitis, assessed endoscopically, histologically and by 24 h pH monitoring

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Abstract

This double blind, double dummy study compares the rate of healing of erosive reflux oesophagitis, assessed endoscopically, with four and eight weeks treatment using omeprazole or cimetidine, and the effect of four and eight weeks treatment of reflux oesophagitis with omeprazole or cimetidine on reflux symptoms, microscopic healing, and in a subgroup of patients, oesophageal pH measurements. Omeprazole 40 mg once daily achieves (i) greater and more rapid symptom relief, (ii) more rapid and sustained endoscopic and histological healing, and (iii) greater reduction of oesophageal acid exposure than cimetidine 400 mg four times daily.

The treatment of reflux oesophagitis by histamine H_2-receptor blockers is unsatisfactory because approximately 50% of patients remain not only symptomatic, but also unhealed endoscopically after six to eight weeks' treatment.[1-3] Omeprazole, a powerful proton pump inhibitor, has been shown to be more effective than ranitidine[4-6] and placebo[7] in the short term treatment of reflux oesophagitis and in the treatment of reflux oesophagitis resistant to longterm high dose cimetidine therapy.[8] No study has compared the efficacy and rates of healing of oesophagitis in patients receiving omeprazole and the recommended dose of cimetidine. In addition, the present study has assessed therapy not only by symptom scoring and endoscopy, but also by histology and 24 h ambulatory pH measurements.

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Methods

PATIENTS

Sixty seven outpatients, aged between 18 and 80 years, with symptomatic, gastro-oesophageal reflux, confirmed both endoscopically and histologically, were randomised to receive eight weeks of continuous treatment with omeprazole 40 mg once daily or cimetidine 400 mg four times daily using a double blind, double dummy technique.

STUDY PROTOCOL

Oesophagitis was graded endoscopically as grade I (erythema), grade II (isolated round and linear erosions incompletely involving the lower 2 cm of oesophagus), grade III (erosions above 2 cm or involving the entire circumference), grade IV (benign ulcer), and grade V (stricture). Oesophageal biopsies were also graded: grade I (basal cell hyperplasia without inflammatory infiltration), grade II (I plus extension of papillae and mild inflammatory infiltration), grade III (massive polymorpho-nuclear infiltration), grade IV (III plus ulceration). Grade II or greater was considered to be indicative of oesophagitis. Patients were included in the study when both endoscopic oesophagitis was grade I or worse and pre-entry oesophageal biopsies were histologically grade I or worse. Exclusion criteria were as follows: oesophageal stricture (inability to pass GIF Q endoscope), age below 18 or above 80 years; pregnancy and women of childbearing potential; previous oesophageal or gastric surgery; active hepatic, renal or peptic ulcer disease, scleroderma or Barrett's oesophagus; administration of H_2-blockers for more than two days in 14 days before inclusion; use of investigational drugs; administration of drugs known to interact with H_2-blockers; clinically important haematological or biochemical laboratory results; evidence of any malignancy; alcoholism or drug abuse. Figure 1 illustrates the study design. Before entry and during the study patients were given supplies of antacid tablets (Rennie, Nicholas Lab) for additional symptom relief. Patients were seen at two weekly intervals, when symptoms of heartburn, regurgitation and dysphagia were assessed and graded: none, mild, moderate, and severe. Diary cards (to record day and night time reflux symptoms and daily antacid consumption) and the trial medication remaining were collected. New diary cards and drug supplies were then issued. Endoscopy, by the same endoscopist, was undertaken before entry and after four weeks of treatment. This was repeated at eight weeks if, at the four week examination, healing (defined as complete re-epithelialisation) was incomplete or histological grades ≥ 2 were reported. At each endoscopy pinch biopsies were obtained from each quadrant of inflamed epithelium and a reference biopsy taken from normal epithelium at least 5 cm proximal to the upper margin of the inflamed epithelium.

Outpatient 24 hour ambulatory oesophageal pH monitoring was undertaken in a subgroup of the patients studied, before entry and during the fifth week of treatment (Oxford Medilog 1000

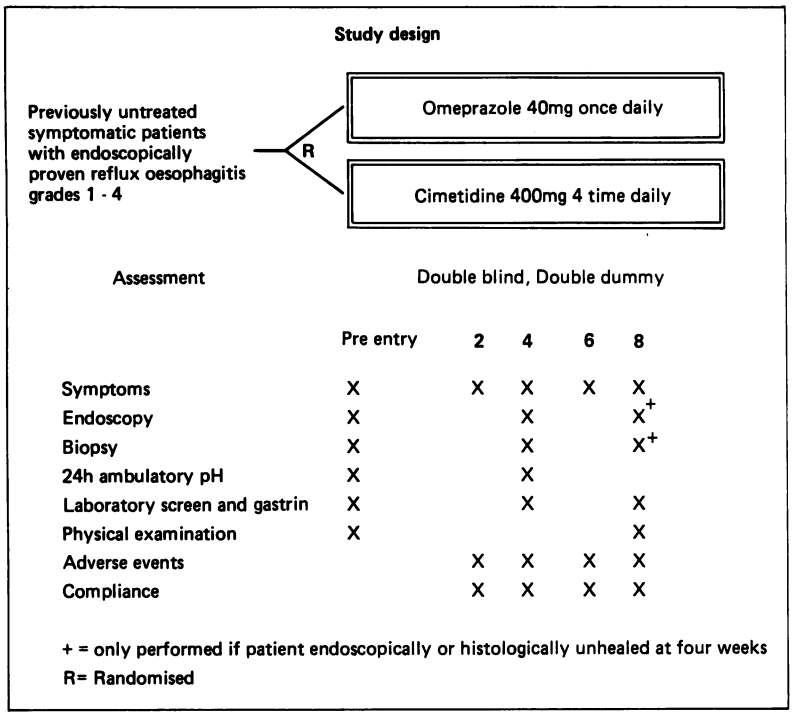

Figure 1: Study design.

recorder and radiotelemetry capsule (RTC) (Remote control systems, London). At the second recording the RTC was positioned at the same distance from the incisor teeth used in the pre-entry study and patients were requested to attempt to maintain the same degree of activity as during the pre-entry recording. Patients were helped by the use of activity cards. Parameters recorded were time (and % time) of oesophageal acid exposure (≤pH4) during day and night (night=time between retiring to bed and rising in the morning), number of reflux episodes, episode duration and longest episode.

Ethical approval was obtained from the ethical committees of each of the participating hospitals and verbal informed consent obtained from each patient.

STATISTICAL ANALYSIS

Statistical analyses were performed on a per protocol basis. Endoscopic evaluations were compared between treatments using the Mantel Haensel test. Symptom assessments, histology scores, and laboratory values were compared between treatments using the Wilcoxon's sum-ranks test. The 24 hour ambulatory pH results were compared between treatments using Student's *t* test.

Results

Between November 1985 and September 1987 a total of 67 patients were studied: 37 from Oxford, 17 from Winchester, and 13 from Portsmouth. Table I illustrates the pre-entry characteristics of these patients: 31 were randomised to receive omeprazole and 36 cimetidine. During the course of the study two patients (one omeprazole; one cimetidine) were withdrawn for protocol violations, one patient (cimetidine) for lack of compliance, and three patients (one omeprazole; two cimetidine) for adverse events (vomiting, secondary to development of oesophageal stricture; diarrhoea; malaise and lethargy): thus the per protocol analysis at four weeks included 28 patients on omeprazole and 31 patients on cimetidine.

All patients had one or more symptoms of heartburn, regurgitation, or dysphagia. Table II illustrates the severity score for heartburn. After two weeks' treatment with omeprazole, heartburn was completely relieved in 18/25 (72%) compared with 12/30 (40%) patients on cimetidine (p=0·0061) in whom this symptom was noted at presentation. After four weeks, heartburn was relieved in 23/25 (92%) and 16/30 (53%; p=0·001) of patients respectively and remained substantially unchanged at the eight week assessment. There was no significant difference between treatments in the relief of symptoms of either regurgitation of dysphagia. Table II also illustrates the pre-entry occurrence of symptomatic regurgitation and dysphagia. At the four week assessment, regurgitation was present in three of 28 (11%) of patients on omeprazole and nine of 31 (29%) on cimetidine (p=0·09): dysphagia was present in four of 28 (14%) and six of 31 (19%; p>0·2).

Between days 0–15 the median number (±½ interquartile range) of diary card reports of daytime reflux symptoms were 0·21 (0·14) (omeprazole) and 0·38 (0·37) (cimetidine; p= NS). After four weeks of treatment there was a significant reduction between treatment groups in the diary card record of daytime reflux symptoms to 0·0 (0·12) (omeprazole) and 0·32 (0·27) (cimetidine) (p=0·004): night time relux symptoms were also significantly reduced in omeprazole patients but not in the cimetidine group. Between days 0–15 median daily antacid tablet consumption was 0·23 (0·23) (omeprazole) and 0·65 (0·55) (cimetidine; p=NS): between days 16–29 median daily consumption fell to 0·0 (0·14) (omeprazole) and 0·48 (0·45) (cimetidine) (p=0·0005). The differences between treatment groups were sustained through the remaining four weeks of therapy.

Figure 2 illustrates the endoscopic grading of oesophagitis before entry, and after four and eight weeks therapy. After four weeks' treatment with omeprazole and cimetidine, healing (complete re-epithelialisation) had occurred in 16/28 (57%) and nine of 31 (29%) respectively (p=

TABLE I *Patient demographics*

	Omeprazole (n=31)	*Cimetidine (n=36)*
Sex M:F	21:10	28:8
Age, yr: mean (range)	54 (21–74)	39·6 (24–78)
Duration of reflux symptoms (months)	24 (2–600)	36 (1–600)
Smokers	29 (93·5%)	36 (100%)
Alcohol drinkers	31 (100%)	34 (94·4%)
Previous gastrointestinal haemorrage/oesophageal stricture	3 (9·6%)	6 (16·6%)
Previous antireflux/antacid therapy	13 (41·9%)	23 (63·8%)
Pre-entry endoscopy		
Grade 1 oesophagitis	2 (6·5%)	5 (13·8%)
2 oesophagitis	10 (32·2%)	8 (22·2%)
3 oesophagitis	16 (51·6%)	21 (58·3%)
4 oesophagitis	3 (9·7%)	2 (5·5%)
Pre-entry symptoms		
Heartburn	89%	97%
Regurgitation	75%	74%
Dysphagia	46%	35%

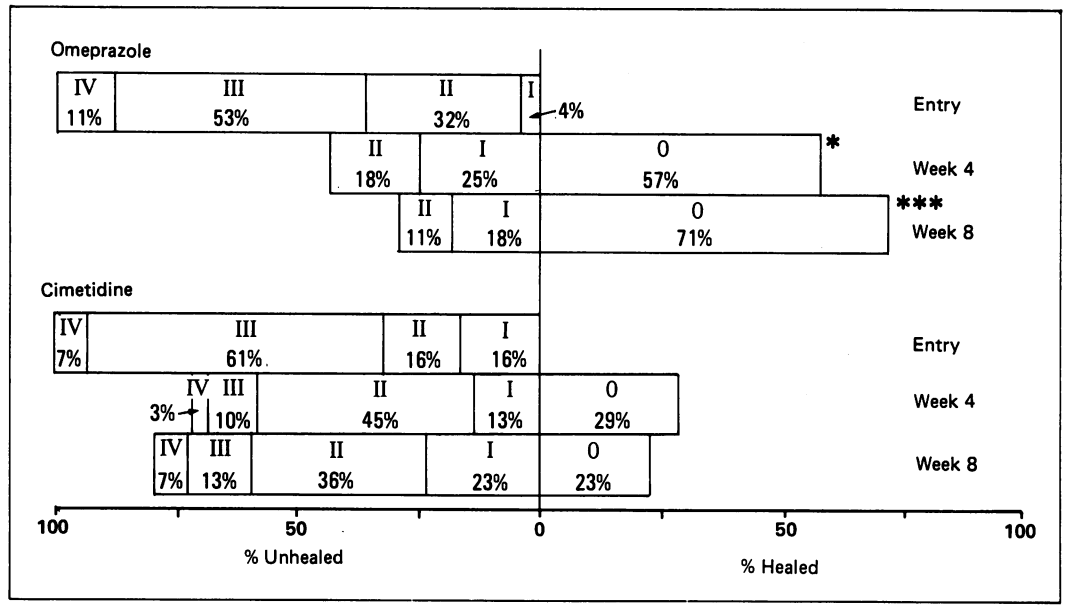

*Figure 2: Cumulative endoscopic grading scores at entry and after four and eight weeks' treatment with omeprazole or cimetidine. The percentage of patients for each endoscopic grade (roman numerals) is shown. Significance between treatments at four and eight weeks is indicated; *p=0·029, ***p<0·001.*

0·029). After eight weeks, the cumulative healing rates were 20/28 (71%) and seven of 31 (23%; p=0·0001). Over the eight week treatment period, endoscopic appearances remained unchanged in two patients on omeprazole and five on cimetidine. The endoscopic grade worsened during treatment in five patients receiving cimetidine.

Before treatment there was no difference in the results of the median (range) worst histological scores taken from oesophageal biopsies: 4 (1–4) in both treatment groups (p=NS). At four weeks the median worst scores were 1 (0–4) omeprazole *v* 3 (0–4) cimetidine (p=0·0028). At the final endoscopy the median worst scores were 1 (0–4) omeprazole *v* 2 (0–4) cimetidine (p=NS).

Eighteen patients (nine omeprazole; nine cimetidine) completed 24 hour oesophageal pH measurements both pre-entry and after four weeks treatment. The results of these recordings are illustrated in Table III and Figure 3. There were no significant differences in the recorded pH parameters at the pre-entry tests. Both total and daytime oesophageal acid exposure were significantly less at four weeks in the omeprazole treated patients. There was no significant difference between treatments in night time oesophageal acid exposure after four weeks, although all but two of the omeprazole treated patients recorded a decrease in nocturnal acid exposure (Fig 3).

Both day and night time oesophageal acid exposure was abolished in the six patients on omeprazole in whom endoscopic oesophagitis had healed. In those five patients with endocopic healing after four weeks' cimetidine treatment, a daytime acid (pH<4) exposure in excess of 5% was recorded in three and night time exposure in excess of 2% persisted in two patients.

In the three endoscopically unhealed patients receiving omeprazole, mean daytime oesophageal acid exposure fell from 20·7 to 2·1%, but remained >5% in only one patient. Mean night time acid exposure did not change (19·4% *v* 21·3%), remaining above 2% in all three patients and being reduced in only one patient. In the four endoscopically unhealed patients receiving cimetidine, daytime oesophageal acid exposure increased in three patients and night time exposure increased in three of the four patients. There was no consistent relationship between endoscopic grading at pre-entry with recorded acid exposure.

Haematological and biochemical results remained within normal ranges throughout the study period. Gastrin serum concentrations were measured at entry (median (range): omeprazole: 5 (3–20) pmol/l: cimetidine: 8 (3–35) pmol/l) and after four (omeprazole: 9 (2–51) pmol/l: cimetidine: 10 (4–19) pmol/l) and eight (omeprazole: 11 (5–17) pmol/l: cimetidine: 7 (4–19) pmol/l) weeks of treatment, were well with the normal range (omeprazole 2–51 pmol/l; cimetidine 3–35 pmol/l) and there was no significant difference between treatment groups.

Discussion

The patients in our study were well matched before entry, in all aspects of their oesophageal reflux disease although slightly more patients in the cimetidine group had previous gastrointestinal complications and had received previous medical therapy. The proportion of patients, however, with grade 2–4 endoscopic oesophagitis was slightly greater in the omeprazole group. Of note is the fact that only seven of 67 (10%) patients had endoscopic grade I oesophagitis and that the remaining 90% had erosive or ulcerative oesophagitis.

Our results, in common with other studies comparing omeprazole and ranitidine[2-6] have shown that the symptom of heartburn is relieved not only more rapidly, but also to a greater extent with omeprazole than with histamine H_2-receptor blocker therapy and, moreover, in our

TABLE II *Effect of omeprazole and cimetidine treatment on symptoms of heartburn, regurgitation and dysphagia*

	Patients n (%)					
	Heartburn		Regurgitation		Dysphagia	
	Om	Cim	Om	Cim	Om	Cim
Entry						
None	3 (11%)	1 (3%)	7 (25%)	8 (26%)	15 (54%)	20 (65%)
Mild	7	13	11	14	4	7
Moderate	9	9	9	7	4	2
Severe	9	8	1	2	6	2
	NS		NS		NS	
Week 2						
None	21 (75%)	13 (42%)	24 (86%)	21 (68%)	24 (86%)	29 (94%)
Mild	7	14	4	7	0	0
Moderate	0	4	0	3	0	0
Severe	0	0	0	0	0	0
	p=0·0064		NS		NS	
Week 4						
None	26 (93%)	17 (55%)	25 (89%)	22 (71%)	24 (86%)	25 (81%)
Mild	2	11	3	8	4	5
Moderate	0	3	0	1	0	1
Severe	0	0	0	0	0	0
	p=0·011		NS		NS	
Week 6						
None	24 (96%)	19 (63%)	22 (88%)	21 (70%)	24 (96%)	28 (93%)
Mild	0	8	3	8	1	2
Moderate	1	3	0	1	0	0
Severe	0	0	0	0	0	0
	p=0·0054		NS		NS	
Week 8						
None	23 (92%)	17 (59%)	23 (92%)	27 (93%)	24 (96%)	27 (93%)
Mild	2	11	2	1	1	2
Moderate	0	1	0	1	0	0
Severe	0	0	0	0	0	0
	p=0·0056		NS		NS	

study 41% of patients receiving cimetidine had no relief of this symptom throughout the study period.

We defined endoscopic healing of oesophagitis as complete circumferential re-epithelialisation. Endoscopic healing rates of oesophagitis in patients treated with omeprazole for four weeks have been reported to vary between 76% and 85%,[4-6] although two reports[4 6] included the presence of endoscopic erythema as evidence of healing and Vantrappen[5] defined healing as the disappearance of oesophageal ulceration. The latter definitions and the higher dose of omeprazole (60 mg) used by Klinkenberg-Knol[4] would explain the difference in endoscopic healing rates reported between this and the other studies. Further advantages of omeprazole therapy are shown by the fact that, during the period of the present study, no patient receiving omeprazole had worsening of the grade of endoscopic oesophagitis and, moreover, the endoscopic grading remained unchanged in only two patients. In contrast, of the 31 patients receiving cimetidine, the endoscopic grading worsened in five and remained unchanged in five.

Havelund *et al*[5] and Whitehead *et al*[9] have shown respectively that histological grading of oesophagitis is improved to a greater extent with omeprazole therapy compared with ranitidine and placebo. Our study confirms these findings but also has demonstrated that after eight weeks of therapy histological gradings are similar in the two therapeutic groups. This implies that administration of both drugs produces histological healing of oesophagitis, but omeprazole, at 40 mg daily, achieves healing more rapidly.

A major factor in the cause of a reflux oesophagitis is inappropriate exposure of the distal oesophagus to gastric acid.[10] Oesophageal pH monitoring provides a useful indicator of the degree and pattern of this acid exposure[11] although caution must be used in interpreting the results because of variation within individuals.[12] In order to minimise the variability of this investigation the methods that we used for performing repeated recordings of oesophageal pH were as standardised as possible. The results of the 24 h oesophageal pH measurement show that omeprazole is far more effective in increasing the pH of gastro-oesophageal refluxate by comparison to cimetidine. Moreover, omeprazole treatment completely abolished acid reflux in six of the nine patients receiving that drug who underwent pH recordings.

In those patients in whom endoscopic healing was recorded omeprazole reduced oesophageal acid exposure to a much greater degree than cimetidine (Table III).

Nocturnal acid reflux, because of its prolonged contact with and poor clearance[13] from the distal oesophagus is believed to be extremely injurious to the oesophageal epithelium.[8 14] This view is supported by the fact that in three of the four patients receiving cimetidine, and without endoscopic healing, nocturnal acid exposure increased substantially. In only one of three patients receiving omeprazole, and in whom endoscopic oesophagitis persisted, did nocturnal

TABLE III *Effect of omeprazole and cimetidine treatment on percentage total acid exposure below pH 4·0. Values are mean and (range)*

		Total acid exposure % – All patients						
		Daytime		Night time		Overall		
		Day 0	Day 29	Day 0	Day 29	Day 0	Day 29	n
All patients								
Cimetidine	Mean	10·48	10·50	7·66	11·56	9·51	10·78	9
	Range	(3·25–21·98)	(2·97–34·00)	(0–30·94)	(0–40·23)	(1·91–21·19)	(2·38–36·42)	
Omeprazole	Mean	11·25	0·74*	11·31	7·10	11·43	3·37*	9
	Range	(2·07–36·10)	(0–5·89)	(0–40·56)	(0–55·07)	(1·83–37·86)	(0–23·10)	
Healed patients								
Cimetidine	Mean	8·74	5·28	7·00	7·44	8·11	5·95	5
	Range	(3·25–12·52)	(2·97–7·29)	(0–30·94)	(0–32·00)	(1·91–19·94)	(2·38–16·37)	
Omeprazole	Mean	6·53	0·08†	7·25	0·00	6·99	0·05†	6
	Range	(2·07–11·23)	(0–0·25)	(0–16·08)	(0–0·02)	(1·83–11·23)	(0–0·14)	
Unhealed patients								
Cimetidine	Mean	12·66	17·02	8·48	16·70	11·27	16·81	4
	Range	(4·35–21·98)	(8·26–34·00)	(2·29–19·93)	(1·64–40·23)	(3·98–21·19)	(7·82–36·42)	
Omeprazole	Mean	20·70	2·07	19·42	21·28	20·30	10·01	3
	Range	(5·85–36.10)	(0·04–5·89)	(5·15–40·56)	(2·95–55·07)	(8·35–37·86)	(1·07–23·10)	

Asterisks signify a statistical significance between treatments: *p<0·0001; †p<0·05.

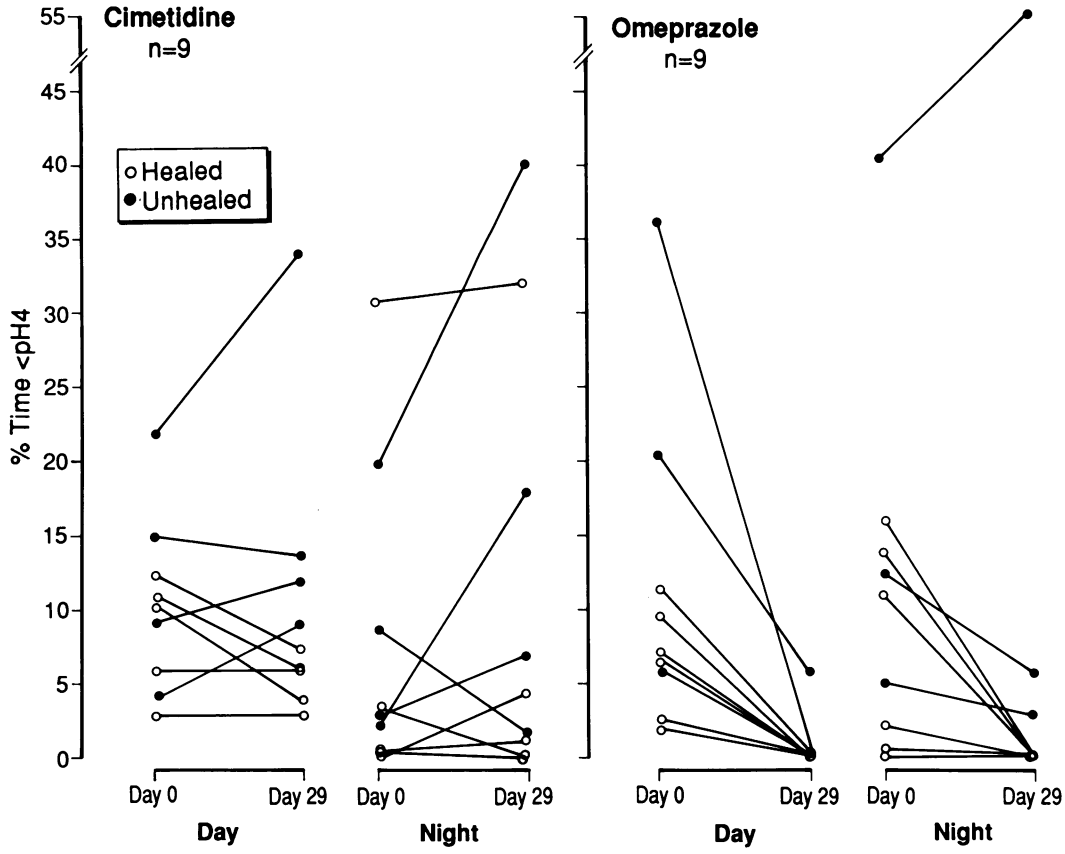

Figure 3: Percentage time per 24 h of oesophageal pH less than four in patients treated with cimetidine (n=9) and omeprazole (n=9), before (day 0) and during treatment (day 29). Patients healed endoscopically at four weeks, open symbols; patients with persistent oesophagitis, closed symbols. Night time defined as time between retiring to bed and arising.

oesophageal acid exposure fall. Thus, omeprazole does not entirely abolish nocturnal oesophageal acid exposure in all patients, even when a higher dose (60 mg) is administered.[4] Failure of this drug to control nocturnal oesophageal acid exposure may be an important cause of treatment failure in some patients with reflux oesophagitis.

This study has shown the superiority of omeprazole 40 mg once daily over cimetidine, 400 mg four times a day, in the treatment of erosive reflux oesophagitis. Use of this drug achieves substantial and rapid symptom relief, rapid and sustained endoscopic and histological healing and marked reductions in distal oesophageal acid exposure. In those few patients who prove refractory to healing use of oesophageal pH profiles may indicate a requirement for the short term administration of a higher dosage of omeprazole,[4] for more prolonged therapy at a lower dose[15] or for anitreflux surgery.

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