Gut, 1990, 31, 653–656

Double blind comparative study of omeprazole and ranitidine in patients with duodenal or gastric ulcer: a multicentre trial

Cooperative Study Group

Abstract

We studied omeprazole and ranitidine in promoting duodenal ulcer healing in a multicentre trial by comparing the proportion of healed ulcers after two, four, and eight weeks of treatment. Altogether, 194 patients (143 men) were randomly allocated according to a prearranged treatment schedule to either drug and were treated double blind. Each received 40 mg omeprazole in the morning and a ranitidine placebo morning and evening or 150 mg ranitidine morning and evening with an omeprazole placebo in the morning. A total of 188 patients (94 taking omeprazole, 94 taking ranitidine) completed the trial. Sixty four (68%) omeprazole treated and 45 (48%) ranitidine treated patients had healed ulcers at two weeks, 91 (99%) omeprazole treated and 79 (88%) ranitidine treated had healed ulcers by four weeks, and 91 (100%) omeprazole treated and 86 (97%) ranitidine treated patients had healed ulcers by eight weeks. The overall difference in healing rates was significant ($p=0.0008$, Mantel-Haenszel test). The differences were significant also at two weeks (20%, 95% confidence interval 5·6 to 34·4, $p<0.01$) and at four weeks (11%, 95% CI 3·7 to 17·3, $p<0.01$), but not at eight weeks (3%, 95% CI −0·5 to +7·3, $p=0.25$), using the χ^2 statistic, the study having a power to detect a 20% difference on 90% of occasions. After two weeks of treatment complete symptom relief was observed in 70 (74%) patients receiving omeprazole and in 58 (62%) receiving ranitidine. Diary cards showed a significantly lower percentage of days with pain in the omeprazole treated group (7·4% *v* 21·4%, $p<0.02$) when assessed over either the first two weeks or over weeks three and four of treatment. A total of 144 patients with healed duodenal ulcer were followed up, with no treatment, for six months. At the end of this period 19 (26%) of 74 patients healed with omeprazole and 17 (24%) of 70 patients healed with ranitidine were still in remission. A similar protocol was used for 46 patients (25 men) with gastric ulcer who were randomly allocated to treatment with omeprazole or ranitidine as described above. Forty patients (16 omeprazole, 24 ranitidine) completed the trial. Thirteen (81%) omeprazole treated and 14 (58%) ranitidine treated patients had healed ulcers at four weeks; at eight weeks 14 (93%) omeprazole treated and 20 (87%) ranitidine treated patients had healed ulcers. These differences were not significant at four weeks ($p=0.25$) or eight weeks ($p=0.96$). Twenty seven gastric ulcer patients were followed up for six months and seven (58%) of the 12 omeprazole healed and five (33%) of the 15 ranitidine healed patients were in remission at six months. Unwanted adverse events were trivial except for one fatality in a 67 year old woman, who died from bronchopneumonia and myocardial ischaemia while receiving treatment with omeprazole, which was judged to be unrelated to her death.

Histamine H_2 receptor antagonists decrease gastric acid secretion and increase the healing rate of duodenal and gastric ulcers. The healing rates expected for ranitidine 150 mg twice daily are about 50% at two weeks and 80% at four weeks.[1,2] Omeprazole inhibits gastric acid secretion by an action on the proton pump of the parietal cell and produces a greater, more prolonged inhibition than ranitidine. In an open trial doses of 20 mg, 30 mg, 40 mg, and 60 mg omeprazole daily healed almost every duodenal ulcer in four weeks.[3] We have now compared omeprazole 40 mg once daily with ranitidine 150 mg twice daily in a multicentre double blind randomised trial and assessed cumulative duodenal ulcer healing at two, four, and eight weeks and gastric ulcer healing at four and eight weeks.

Patients and methods

DUODENAL ULCER STUDY

Outpatients with at least one duodenal ulcer crater not less than 5 mm in diameter verified by endoscopy not more than three days before the start of treatment were recruited. Ulcer size was measured by comparison with biopsy forceps of known size and the site of the ulcer and any associated duodenitis were noted. We excluded patients under 18 or over 80 years of age, pregnant, breast feeding, or potentially fertile women, and patients with pyloric stenosis, active upper gastrointestinal bleeding, and a history of definitive acid lowering operation, those taking ulcerogenic drugs, those with significant abnormalities on laboratory testing or alcohol or drug abuse, and those who had taken H_2 receptor antagonists or anticholinergic drugs for more than two days in the fortnight before endoscopy.

Patients were given written and verbal information about the study and gave written consent. Approval for the studies was obtained from local ethics committees and the United Kingdom regulatory authority (Department of Health and Social Security).

Patients were randomised to treatment with omeprazole, two 20 mg capsules each morning, or ranitidine, 150 mg twice daily, using a double

The names of the members of the cooperative study group appear at the end of the paper.

Correspondence to:
M J Daly, Astra Clinical Research Unit, 10 York Place, Edinburgh EH1 3EP.

Accepted for publication 29 August 1989

TABLE I *Demographic data*

Variable	Duodenal ulcer		Gastric ulcer	
	Omeprazole	*Ranitidine*	*Omeprazole*	*Ranitidine*
No	96	98	21	25
Male:female	72:24	71:27	9:12	16:9
Age (years) (mean (SD))	47·2 (15·2)	47·5 (15·2)	57·3 (8·4)	60·5 (9·0)
Height (cm) (mean (SD))	169·7 (9·3)	169·6 (9·7)	168·1 (9·1)	165·4 (8·9)
Weight (kg) (mean (SD))	71·5 (13·3)	69·4 (14·2)	65·1 (13·4)	60·7 (11·2)
Non-smokers	31 (32%)	33 (34%)	8 (38%)	8 (32%)
Non-drinkers	33 (34%)	36 (37%)	12 (57%)	12 (48%)
Median (range) duration of ulcer history (months)	60 (0–720)	48 (0–360)	21 (0–479)	24 (0–336)

blind double dummy technique. A supply of standard antacids (Rennie) was also provided. The patients were given simple diary cards and were questioned about the presence or absence of day and night pain as well as antacid use. The occurrence of ulcer pain between going to bed in the evening and arising at the normal time next morning was defined as night pain and pain at other times in each 24 hour period was defined as day pain. Day and night pain were analysed separately.

Endoscopy was carried out in all patients after two weeks and if the ulcer was not healed, at four and eight weeks. Patients with a healed ulcer(s), defined as re-epithelialisation at any visit, stopped treatment and entered an untreated follow up with visits at two, four, and six months. Endoscopy was carried out at six months or earlier if recurrence of an ulcer was suspected. Patients left the trial at six months or earlier if an ulcer recurred. Routine haematological and biochemical investigations were carried out at each visit during active treatment. Thyroid function (triiodothyronine, thyroxine, and thyroid stimulating hormone) was also measured before and after treatment.

GASTRIC ULCER STUDY

Five centres recruited patients with gastric ulcer using a similar protocol except that endoscopy was not carried out at two weeks. Biopsies were taken from each patient to ensure that the gastric ulcer was benign. If malignancy was detected the patient was excluded from the trial. Continued use of non-steroidal anti-inflammatory drugs was allowed if the treatment was to remain unchanged. Such patients were put in a stratified group.

Statistics

Comparisons of healing, demographic characteristics, and laboratory investigations were made using the Mantel-Haenszel test and χ^2 statistic. Symptom relief and antacid consumption were compared using the Wilcoxon rank sum test. A value of $p<0·05$ was taken to be significant.

Assessments were made within ±1 day, ±2 days, and ±4 days for the two, four, and eight week visits respectively. Analyses were made on a per protocol basis and patients unavailable for one visit could be included for valid analysis at other scheduled assessments; consequently the numbers of patients in the tables may vary slightly for different visits.

Results

DUODENAL ULCER STUDY

Table I shows the demographic characteristics of the 194 patients who entered the study; 96 were randomised to omeprazole treatment and 98 to ranitidine treatment. Six patients failed to reattend, leaving 188 with an evaluable healing end point. There were no significant differences between the groups with respect to any variable.

There was a significantly higher rate of healing with omeprazole 40 mg every morning than with ranitidine 150 mg twice daily ($p=0·0008$, Mantel-Haenszel test). Significant differences between the treatments were also seen after two weeks (68% *v* 48%, $p<0·01$) and after four weeks (99% *v* 88%, $p<0·01$). At eight weeks almost every ulcer had healed and there was no significant difference (100% *v* 97%, $p=0·25$) (Table II). Most patients smoked – 68% in the omeprazole group and 66% in the ranitidine group, but this had no significant effect on healing by either drug (Table III).

The effect of initial ulcer size and site on healing was also evaluated (Table IV). The range of initial ulcer size was similar in both treatment groups. A significant number of small ulcers were healed compared with large ulcers in the omeprazole group at two weeks ($p<0·03$) and in the ranitidine group at four weeks ($p<0·05$). Anterior or posterior location had no significant effect.

At each endoscopy the presence or absence of duodenitis was noted. In the omeprazole treated group the incidence was 60% at the beginning and 44% at the end of treatment ($p=0·018$). Ranitidine treated patients showed a 50% incidence of duodenitis before and at the end of treatment (not significant).

More patients in the omeprazole group were symptom free when questioned at two and four weeks (Table V). Analysis of the diary cards showed a significantly lower percentage of days with pain in the omeprazole group compared with the ranitidine group in the first two weeks

TABLE II *Ulcer healing*

Assessment time (weeks)	Proportion (%) of patients healed: Duodenal ulcer					Gastric ulcer				
	Omeprazole	*Ranitidine*	*Difference (%)*	*95% confidence interval*	*p*	*Omeprazole*	*Ranitidine*	*Difference (%)*	*95% confidence interval*	*p*
2	64/94 (68)	45/94 (48)	20·0	5·6 to 34·4	0·008	NA	NA			
4	91/92 (99)	79/90 (88)	11·0	3·7 to 17·3	0·007	13/16 (81)	14/24 (58)	23	−6·7 to 52·6	0·25
8	91/91 (100)	86/89 (96·6)	3·4	−0·5 to 7·3	0·25	14/15 (93)	20/23 (87)	6	−13·5 to 26·1	0·96

NA = not assessed at this visit.

TABLE III *Effect of tobacco intake on ulcer healing*

Assessment time (weeks)	Tobacco consumption (g/day)	Proportion (%) of patients healed: Duodenal ulcer Omeprazole	Duodenal ulcer Ranitidine	Gastric ulcer Omeprazole	Gastric ulcer Ranitidine
2	0	21/29 (72)	17/31 (55)	Not	Not
	1–10	14/21 (67)	12/22 (55)	assessed	assessed
	11–20	25/37 (68)	13/26 (50)	at this	at this
	>20	4/7 (57)	3/9 (33)	visit	visit
4	0	27/27 (100)	29/30 (97)	4/5 (80)	4/8 (50)
	1–10	20/21 (95)	16/21 (76)	1/1 (100)	5/7 (71)
	11–20	37/37 (100)	22/25 (88)	6/7 (86)	4/7 (57)
	>20	7/7 (100)	9/9 (100)	1/2 (50)	1/2 (50)
8	0	27/27 (100)	30/30 (100)	4/5 (80)	6/8 (75)
	1–10	20/20 (100)	19/20 (95)	1/1 (100)	6/6 (100)
	11–20	37/37 (100)	24/25 (96)	7/7 (100)	6/7 (86)
	>20	7/7 (100)	9/9 (100)	1/1 (100)	2/2 (100)

(median 7·4% *v* 21·4% respectively, $p<0·02$). This difference was maintained in the second two weeks of treatment ($p<0·01$). Antacid consumption was significantly ($p<0·02$) lower in omeprazole treated patients in the first two weeks of treatment.

Both treatments were well tolerated with no significant changes in body weight, blood pressure, pulse, or laboratory results including thyroid function. No patients were withdrawn from treatment. There were no serious adverse events. Minor adverse events were reported for nine patients receiving omeprazole (headache two, influenza two, fatigue, difficulty in sleeping, loose motions, raised alkaline phosphatase, and proteinuria one each) and for nine patients receiving ranitidine (headache two, muzzy head, dizziness, tiredness, calf pains, postural hypotension, prolonged menstruation, and vomiting with diarrhoea one each).

All patients with healed ulcers were eligible to enter the untreated follow up study. Seventy four patients healed with omeprazole and 70 healed with ranitidine treatment were followed up. The other patients were not followed up because they were unable or unwilling. The

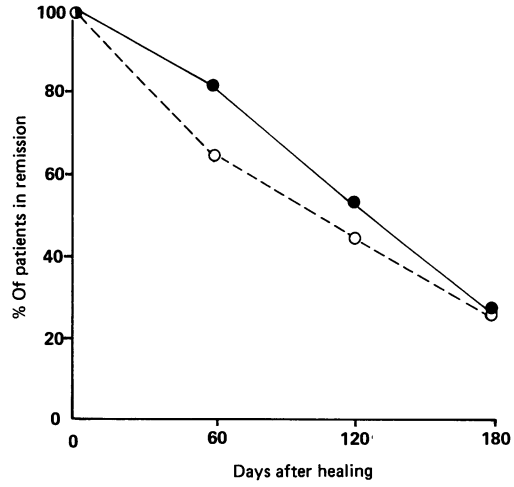
TABLE IV *Effect of initial ulcer diameter on ulcer healing*

Assessment time (weeks)	Initial ulcer size	Proportion (%) of patients healed: Duodenal ulcer Omeprazole	Duodenal ulcer Ranitidine	Gastric ulcer Omeprazole	Gastric ulcer Ranitidine
2	Small: 5–9 mm	32/43 (74)	22/37 (59)	Not	Not
	Medium: 10–15 mm	28/41 (68)	18/44 (41)	assessed	assessed
	Large: >15 mm	3/10 (30)	3/11 (27)	at this visit	at this visit
4	Small: 5–9 mm	41/42 (98)	34/37 (92)	4/4 (100)	8/9 (89)
	Medium: 10–15 mm	41/41 (100)	37/41 (90)	8/9 (89)	3/7 (43)
	Large: >15 mm	8/9 (89)	6/10 (60)	1/3 (33)	3/8 (38)
8	Small: 5–9 mm	41/41 (100)	35/36 (97)	4/4 (100)	9/9 (100)
	Medium: 10–15 mm	41/41 (100)	39/41 (95)	8/9 (89)	6/7 (86)
	Large: >15 mm	8/8 (100)	10/10 (100)	2/2 (100)	5/7 (71)

TABLE V *Patients' overall evaluation of symptoms when questioned during a visit. Figures are numbers of patients*

Assessment time (weeks)	Treatment	Duodenal ulcer Total	Evaluation* 2	1	0	−1	Gastric ulcer Total	Evaluation* 2	1	0	−1
2	Omeprazole	95	70	21	3	1	17	9	8	0	0
	Ranitidine	94	58	33	3	0	24	10	11	3	0
4	Omeprazole	28	25	2	1	0	15	11	2	1	1
	Ranitidine	45	32	11	2	0	24	9	11	3	1
8	Omeprazole	0	0	0	0	0	2	1	1	0	0
	Ranitidine	9	7	1	1	0	9	4	2	3	0

*2=symptom free, 1=improved, 0=no change, −1=became worse.



Percentage of patients in remission after duodenal ulcer healing while being treated with omeprazole (●) or ranitidine (○), starting with 74 omeprazole healed and 70 ranitidine healed patients at time 0.

relapse rate was similar regardless of the agent initially used to heal the ulcer (Figure) and by six months 19 (26%) of the omeprazole healed patients and 17 (24%) of the ranitidine healed patients were still in remission. Smoking had no clear effect, although 68% of the omeprazole treated group and 66% of the ranitidine treated group were smokers.

GASTRIC ULCER STUDY

Table I shows the demographic characteristics of the 46 patients who entered into the study. Of these, 40 reached an evaluable end point. Omeprazole healed a higher proportion of patients, with a 23% therapeutic gain at four weeks, but there was no significant difference at four or eight weeks between the two treatments (Table II). Smoking (Table III) and ulcer size (Table IV) had no significant effect on ulcer healing. Only three patients were receiving concurrent non-steroidal anti-inflammatory drugs, a number too small to permit separate analysis. Symptomatic relief was good with both treatments, with a significant difference in favour of omeprazole for night pain after two weeks ($p<0·03$) when assessed by direct questioning. There was also significantly less daytime pain ($p<0·03$) assessed by diary card and antacid consumption during weeks three and four in the omeprazole treated group.

Both omeprazole and ranitidine were well tolerated, with no significant changes in body weight, blood pressure, pulse, or laboratory results including thyroid function. No patients were withdrawn from treatment. There was one serious adverse event when a 67 year old woman died from bronchopneumonia and ischaemic heart disease nine days after starting treatment with omeprazole, which was judged to be unrelated to her death. Minor adverse events were reported for five patients receiving omeprazole (nausea, tiredness two, abdominal pain, bruised ear) and for four patients receiving ranitidine (awaking suddenly, constipation, bronchitis, cold symptoms).

Twelve omeprazole healed and 15 ranitidine healed patients were followed up without treat-

ment. Seven (58%) omeprazole healed and five (33%) ranitidine healed patients were in remission at six months. There was no difference between the two groups. Numbers were too low to evaluate the effect of smoking.

Discussion

Expected duodenal ulcer healing rates at four weeks are 78% with ranitidine and 70% with cimetidine;[2] in this study ranitidine produced healing rates of 48% at two weeks and 88% at four weeks. The cumulative healing rates at four weeks could be questioned as there was no endoscopic confirmation that ulcers healed at two weeks were still healed. Nevertheless, it was decided that for ethical reasons patients should not receive unnecessary medication after healing had been confirmed, nor should they be routinely subjected to another endoscopy within two weeks of healing. These decisions did not affect the data because the untreated follow up period showed that although some patients relapsed within a month none did so within the two week period which could have affected the cumulative four week healing results. The important finding from this study is that the rate of duodenal ulcer healing is superior with omeprazole and that the difference is apparently due to exposure to the drug in the first two weeks when there was the greatest difference in healing rates. Those patients who were unhealed at two weeks and required four weeks' treatment showed a small difference between treatments. The healing rate in duodenal ulcer patients treated with omeprazole was 68% and 99% at two and four weeks respectively, which was 20% and 11% higher than the healing rate with ranitidine. Thus this study confirms the previous data[3-5] that omeprazole produces unprecedented rates of duodenal ulcer healing after only two weeks. Overall the present findings agree with those reported in a recent review[6] of comparative studies where omeprazole was found to be consistently superior to ranitidine or cimetidine in healing duodenal ulcer.

The postulated mechanisms of healing peptic ulceration include not only suppression of gastric acid secretion but also mucosal protection by agents such as prostaglandins and colloidal bismuth. The latter has also been reported to exert a beneficial effect through an action on *Helicobacter pylori*. Excluding bismuth, the efficacy of different classes of ulcer healing agents has been clearly correlated with their ability to decrease 24 hour gastric acidity,[7] and this property alone would seem sufficient to account for the high level of healing with omeprazole after two weeks. Jones *et al*[8] also concluded that increasing the degree of gastric acid suppression accelerated duodenal ulcer healing, which agrees with the results of this study. Indeed, it has been shown that lower doses of omeprazole, such as 10 mg daily, have a smaller and more variable effect on acid secretion which parallels the inferior healing rates seen with this dose in duodenal ulcer patients.[9] In contrast, patients with gastric ulcer have lower basal and pentagastrin stimulated acid secretion, which has raised doubts about the importance of secretory inhibition on healing. This study produced gastric ulcer healing rates in accord with those obtained for omeprazole and ranitidine in a much larger study[7] where it was found that omeprazole was significantly better than ranitidine in healing gastric ulcer. It was concluded that the higher healing rates in that study were due to increased inhibition of acid secretion by omeprazole. Thus suppression of gastric acid secretion is important in improving the balance between aggressive and defensive factors so allowing healing of gastric as well as duodenal ulcer.

Other factors affecting healing are ulcer size and smoking. Small ulcers tended to heal more rapidly with both treatments, but the distribution between groups was similar and this did not influence overall healing rates. A clear effect of smoking on ulcer healing or relapse was not shown in this trial, where most patients were smokers.

There has been speculation that the mechanism of secretory inhibition or the time taken to heal an ulcer could influence the time to relapse.[8] However, in this study the relapse rates were similar for the duodenal ulcer patients healed with the H^+,K^+ ATPase inhibitor omeprazole (mostly healed at two weeks) and with the H_2 receptor antagonist ranitidine (mostly healed at four weeks). The relapse rate for gastric ulcer was similar.

Omeprazole was significantly better than ranitidine on a number of assessments of pain relief. Both drugs were well tolerated. Overall these results suggest that duodenal and gastric ulcers heal more rapidly during omeprazole treatment, which may be explained by a more effective control of gastric acid secretion.

Members of the cooperative study group: F I Lee (Victoria Hospital, Blackpool), D G Colin-Jones, P L Golding, H T Khawaja, J Snook (Queen Alexandra Hospital, Portsmouth), J J Misiewicz, I Trotman, C Charles, R Pennagini (Central Middlesex Hospital, London), C W Venables, M Clague, W J Crisp, S Raimes (Freeman and Newcastle General Hospitals, Newcastle upon Tyne), P M Smith, A H Troughton (Llandough Hospital, Penarth), J H Baron, G Foster (St Charles Hospital, London), R Cockel (Selly Oak Hospital, Birmingham), J A H Forrest, C W Howden (Stobhill General Hospital, Glasgow), and M J Daly (Astra Clinical Research Unit, Edinburgh).

We wish to thank A B Haessle for support, Mr M Sanderson for data handling, and Mrs J Patterson for statistical analysis.

1 Bardhan KD, Bianchi-Porro G, Bose K, *et al.* A comparison of two different doses of omeprazole versus ranitidine in treatment of duodenal ulcers. *J Clin Gastroenterol* 1986; **8**: 408–13.
2 McIsaac RL, McCanless I, Summers K, Wood JR. Ranitidine and cimetidine in the healing of duodenal ulcer: meta analysis of comparative clinical trials. *Aliment Pharmacol Therapy* 1987; **1**: 369–81.
3 Co-operative Study. Omeprazole in duodenal ulceration, acid inhibition, symptom relief, endoscopic healing and recurrence. *Br Med J* 1984; **289**: 525–8.
4 Lauritsen K, Rune SJ, Bytzer P, *et al.* Effect of omeprazole and cimetidine on duodenal ulcer. A double-blind comparative trial. *N Engl J Med* 1985; **312**: 958–61.
5 Classen M, Damman HG, Domschke W, *et al.* Omeprazole heals duodenal but not gastric ulcers more rapidly than ranitidine. *Hepatogastroenterology* 1985; **32**: 243–5.
6 Walan A. Omeprazole. *Clin Gastroenterol* 1988; **2**: 629–40.
7 Walan A, Bader J-P, Classen M, *et al.* Effects of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. *N Engl J Med* 1989; **320**: 69–75.
8 Jones DB, Howden CW, Burget DW, Kerr GD, Hunt RH. Acid suppression in duodenal ulcer: a meta-analysis to define optimal dosing with antisecretory drugs. *Gut* 1987; **28**: 1120–7.
9 Prichard PJ, Rubenstein D, Jones DB, *et al.* Double blind comparative study of omeprazole 10 mg and 30 mg daily for healing duodenal ulcers. *Br Med J* 1985; **290**: 601–3.