*Clinical trial***Treatment of 'cimetidine-resistant' chronic duodenal ulcers with ranitidine or cimetidine: a randomised multicentre study***

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SUMMARY Forty patients with endoscopically proven persistent duodenal ulcer who had been treated for six weeks with cimetidine (1 g/day) were randomly allocated to receive a further six weeks' treatment with cimetidine (1 g/day) or ranitidine (300 mg/day). Ulcers healed in 12 of 19 patients given cimetidine (63%) and in 13 of 21 given ranitidine (62%); two patients on cimetidine and two on ranitidine dropped out. In the unhealed ulcer group the ulcer size was reduced in most patients. There was no change in basal acid output, peak acid output, plasma gastrin and pepsinogen I levels after either treatment. Clinical data, gastric function tests, and endoscopic features did not predict ulcer healing. Both treatments were effective in the relief of pain: 72% of patients with unhealed ulcers were asymptomatic at the end of the trial.

The histamine H₂-receptor antagonist cimetidine usually heals 70–80% of chronic duodenal ulcers in four to six weeks' treatment.¹ Some of the unhealed peptic ulcers can be successfully treated by prolonging the cimetidine administration for up to three months.² In recent uncontrolled trials, ranitidine has been reported to give better results in the management of these ulcers unhealed by cimetidine.^{3–6}

In order to evaluate the effect of ranitidine in the treatment of such ulcers, we performed a randomised clinical trial comparing ranitidine with cimetidine in patients with chronic duodenal ulcers unhealed by six weeks' cimetidine treatment (1 g/day).

Methods**PATIENTS**

This multicentre study was performed at 10 centres by physicians who had all received their post-

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graduate training at the Coordinating Centre which standardised all procedures used and carried out periodic checks. Patients were recruited on the basis of endoscopically and/or radiologically proven duodenal ulcer diagnosed at or referred to the centres where they were treated for six weeks with only cimetidine (200 mg tid + 400 mg at bedtime) and possibly also low dose antacids. Patients who continued to attend the centres were submitted to endoscopy after six weeks' cimetidine treatment and if the ulcer was still present and the patient's compliance judged to be good, he was enrolled in the study. Forty patients (34 men, six women; mean age 43 years, range 18–70 years) were admitted.

Patients with endoscopically documented pyloric stenosis, chronic illnesses, on treatment with steroids or anti-rheumatic drugs, with creatinine plasma concentrations >260 µmol/l, with concomitant gastric ulcer, and pregnant women were excluded.

The patients were allocated according to a randomisation schedule for 60 patients to further treatment for six weeks with cimetidine (200 mg tid after meals and 400 mg at bedtime) or ranitidine (150 mg bid). Antacids (Maalox tablets) could be taken as needed and consumption was recorded. H₂ antagonist treatment was continuous. In view of the difficulties in recruiting patients, a preliminary evaluation of the results was performed at 40 patients, when the results of the two treatments

were found to be practically identical and enrolment was therefore closed.

Family history of proven or probable peptic ulcer, duration of dyspeptic symptoms, and the previous year's daily alcohol, coffee, and cigarette consumption were recorded for each patient. At treatment randomisation, patients were asked about the presence of day and/or night pain in the preceding week, and the subjective wellbeing was expressed on a linear scale from 0 (absence) to 10 (wellbeing). The same evaluation was performed at three and six weeks with the aid of a card completed daily by each patient recording pain episodes during the day and night, and the antacid consumption.

At entry into the trial and within three days of completion of the treatment schedule, endoscopic examinations were performed on each patient. The operators were unaware of the treatment given. The morphological aspects of the ulcers were assessed as well as their approximate size computed in mm² by multiplying their two major axes as observed with an ACMI measuring probe after pharmacological duodenal hypotonisation. Ulcers were considered unhealed if the ulcer crater persisted.

Two or three days after the first and second endoscopies (at trial entry and completion respectively), after an overnight fast, blood samples were taken for routine haematologic and biochemical tests, radioimmunological assays (Sorin Biomedica, Saluggia, Italy) of plasma gastrin (normal values 36±6 pg/ml) and pepsinogen I (normal values 62±8 ng/ml), and pentagastrin tests (6 µg/kg/body weight) were performed, the results being expressed as basal acid output (BAO, mmol H⁺/h) and peak acid output (PAO, mmol H⁺/h).

Research procedures were in accordance with the ethical standards of the Helsinki declaration of 1975.

Statistical analysis was performed with correlation analysis, χ^2 test, Fisher exact test, Wilcoxon's signed rank test and Mann-Whitney U test, as appropriate; two sided $p<0.05$ was used as the significance level throughout.

Results

Thirty six patients (31 men, five women) completed the trial, 17 on cimetidine and 19 on ranitidine.

Four patients two on ranitidine and two on cimetidine dropped out. One of the two ranitidine patients refused to have the second endoscopy and the other stopped treatment 10 days before completing the trial. The two cimetidine patients refused to continue medical treatment and decided on surgery.

The two treatment groups were comparable at trial entry for age, sex, family history of peptic ulcer,

duration of dyspeptic symptoms, night and day pain, subjective wellbeing, and daily consumption of cigarettes, coffee and alcohol, as well as for ulcer size and morphology (Table 1); they were also comparable for BAO, PAO, plasma gastrin and pepsinogen I (Table 2).

Ulcers healed in 12 patients on cimetidine (63%) and in 13 on ranitidine (62%) (Table 3). In the unhealed groups total ulcer area decreased after cimetidine and ranitidine treatment respectively from 241 and 685 to 79 and 265 mm² (Fig. 1).

Both treatments produced a similar improvement in night and day pain and subjective wellbeing. Antacids were taken only by a small percentage of patients during the first two weeks; consumption was low and similar in the two treatment groups.

After cimetidine or ranitidine treatment, no significant differences were found in either group for BAO, PAO, plasma gastrin or pepsinogen I, compared with the pretreatment values or between the two treatment groups at the end of the trial (Table 2).

Subdividing the patients into two groups according to whether their ulcers had healed or not at trial completion, these two groups were comparable for age, sex, coffee and alcohol consumption, family history of peptic ulcer, day and night pain, subjective wellbeing, and ulcer size. A longer history of dyspeptic symptoms was observed in the healed than in the unhealed ulcer patients, although the difference did not reach significance (Table 4); a positive correlation ($p<0.01$) was found

Table 1 Characteristics of patients at randomisation

	Cimetidine (1 g/day)	Ranitidine (300 mg/day)
Number of cases	19 (15♂, 4♀)	21 (19♂, 2♀)
Mean age (yr)	40 (SD 15.0)	46 (SD 13.2)
Smokers (>5 cigarettes/day)*	16	12
Coffee consumers (>2 cups/day)*	16	14
Alcohol consumers (>40 g/day)*	10	10
Family history of peptic ulcer	5	6
Median duration of symptoms, month (range)	60 (4-240)	120 (6-240)
Patients with day pain	13 (68%)	16 (76%)
Patients with night pain	7 (37%)	12 (57%)
Median wellbeing score (range)	7 (0-10)	6 (0-10)
Median ulcer size, mm ² (range)	40 (9-300)	36 (5-400)
Ulcer morphology:		
round	14	16
oval	4	4
linear	1	1

* in the previous year.

Table 2 Gastric function tests according to treatment at entry (A) and completion of (B) the trial (median values, range in parentheses)

	Cimetidine (1 g/day)		Ranitidine (300 mg/day)	
	A	B	A	B
BAO (mmol H^+ /h)	7 (2-10)	4 (0-15)	4 (0-15)	5 (0-18)
PAO (mmol H^+ /h)	38 (13-63)	35 (15-61)	40 (3-80)	41 (5-87)
Gastrin (pg/ml)	43 (14-117)	48 (10-109)	55 (20-100)	52 (35-90)
Pepsinogen I (ng/ml)	98 (69-160)	83 (65-180)	92 (69-180)	108 (92-220)

between age and duration of dyspeptic symptoms.

Smoking did not seem to affect the healing rate, but healing seemed to be favoured in subjects who stopped smoking (Table 5) although significance was not achieved. BAO, PAO and gastrin were similar in the healed and unhealed ulcer patients; pepsinogen I levels were higher in the former group (Table 6). At the first endoscopy, round ulcers were found in 20, oval in four and linear in one of the healed ulcer patients, and respectively in eight, two and one of the unhealed ulcer patients. In the 11 unhealed ulcer patients the total ulcerated area reduced from 926 to 344 mm²; in one case only was an increase in the ulcerated area found (9-25 mm²) (Fig. 1).

The percentage of patients with day and/or night pain and the average score of subjective wellbeing were similar in the healed and unhealed ulcer groups. The percentage of asymptomatic patients increased markedly in the first two weeks, and at the end of the trial two patients (8%) with healed ulcers and three patients (28%) with unhealed ulcers had symptoms (Fig. 2).

No significant modifications of routine haematologic and biochemical tests were found after either treatment; no side effects due to the treatments were reported by the patients.

Discussion

It should be noted that in this trial the total ulcer population from which our patients were drawn could not be determined, owing to the fact that the

initial diagnosis was not always established at the centres.

Ranitidine (300 mg/day) and cimetidine (1 g/day) were equally effective in the healing of chronic duodenal ulcers unhealed by previous treatment with cimetidine (1 g/day) for six weeks. These results suggest that the effect of the two drugs in the treatment of 'cimetidine-resistant' ulcers do not greatly differ; however, because of the limited number of the patients studied, the confidence limits of the healing rates were wide and to exclude smaller differences larger series are needed.

Patient compliance was good on both treatment schedules. These results do not agree with previous data suggesting that the more potent H_2 antagonist ranitidine with its simpler schedule could be more effective in the treatment of 'cimetidine-resistant' duodenal ulcers.³⁻⁶

In our study, prolonged treatment, regardless of

Table 4 Characteristics of patients at trial entry subdivided according to healing of their ulcer at trial completion

	Healed ulcer	Unhealed ulcer
Number of cases	25 (21♂, 4♀)	11 (10♂, 1♀)
Mean age (yr)	40 (SD 15.0)	41 (SD 12.8)
Smokers (>5 cigarettes/day)*	17 (68%)	7 (63%)
Coffee consumers (>2 cups/day)*	20 (80%)	7 (63%)
Alcohol consumers (>40 g/day)*	13 (52%)	6 (54%)
Family history of peptic ulcer	7 (28%)	4 (36%)
Median duration of symptoms, month (range)	120 (12-240)	60 (12-144)
Patients with day pain	18 (72%)	8 (72%)
Patients with night pain	11 (44%)	4 (36%)
Median wellbeing score (range)	6 (0-10)	6 (3-10)
Median ulcer size, mm ² (range)	48 (9-300)	18 (5-400)
Ulcer morphology:		
round	20	8
oval	4	2
linear	1	1

* in the previous year.

Table 3 Healing rate according to treatment (95% confidence limits in parentheses)

	No.	Cimetidine (%)	No.	Ranitidine (%)
Healed ulcer	12	63 (85-41)	13	62 (83-42)
Unhealed ulcer	5	26 (46-6)	6	29 (48-10)
Drop outs	2	11	2	9
Total	19		21

Fig. 1 Ulcer size in patients who completed the trial; each column represents a single patient, height of clear area indicating ulcer size at treatment randomisation, that of the solid area indicating its size at trial completion. Three solid columns indicate there was no change in ulcer size.

the H₂ antagonist administered, increased the number of healed ulcers; in fact, ulcers healed in more than 62% of our cases who had previously been treated with cimetidine for six weeks. Furthermore, except for one case, the unhealed ulcers all reduced in size. These findings suggest, in line with Bardhan's observations,² that such patients should be considered slow responders rather than resistant to treatment.

There were no differences in gastric function tests after either treatment compared with values observed after the initial six weeks' cimetidine treatment. Plasma gastrin concentrations were

slightly higher than normal; this could be the effect of the previous cimetidine treatment.^{7 8}

Clinical endoscopic and laboratory data and gastric function tests of our patients at allocation did not allow us to predict ulcer healing. In our patients, smoking habits were not proved to interfere with healing, as already observed by some authors.^{9 10} A long history of dyspeptic symptoms seems favourable to healing as shown by some authors¹¹ but unlike other reports where the shorter the history the quicker the healing.¹² The morphology and size of the ulcer had no bearing on the healing rate; the observation of only one case in which an

Table 5 Ulcer healing according to smoking habit

	Healed ulcers	Unhealed ulcers
Non-smokers	8 (66%)	4 (34%)
Smokers	17 (71%)	7 (29%)
Gave up smoking for duration of trial	6 (86%)	1 (14%)
Continued smoking	11 (65%)	6 (35%)

Table 6 Gastric function tests in patients at trial entry subdivided according to healing of their ulcer at trial completion (median values, range in parentheses)

	Healed ulcers	Unhealed ulcers
BAO (mmol H ⁺ /h)	4 (0-16)	7 (0-12)
PAO (mmol H ⁺ /h)	34 (3-80)	47 (17-63)
Gastrin (pg/ml)	68 (14-100)	39 (20-117)
Pepsinogen I (ng/ml)	90 (80-180)	67 (69-104)

Fig. 2 Weekly percentage of patients with pain according to presence of healed (●—●) or unhealed (○- -○) ulcer at trial completion.

unhealed ulcer became larger confirms the observation that all ulcers reduce their area in time.¹³

Both ranitidine and cimetidine were effective in the relief of pain. Absence of pain did not indicate the healing of duodenal ulcers as already shown by Walt *et al.*¹⁴ in fact 72% of our patients with unhealed ulcers were symptom free at the end of the trial.

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