Clinical trial

Effect of omeprazole and cimetidine on prepyloric gastric ulcer: double blind comparative trial

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SUMMARY We conducted a six week double blind randomised study of 176 patients with prepyloric gastric ulcer to determine whether the proton pump inhibitor, omeprazole 30 mg daily would accelerate healing and pain relief, as compared with cimetidine 1 g daily. At two, four, and six weeks after entry ulcers healed in a larger percentage of patients treated with omeprazole (54, 81, and 86%) than of those treated with cimetidine (39, 73, and 78%) ('intention to treat' cohort; $p < 0.05$ at two weeks). A higher proportion of patients on omeprazole became free of pain during the first week of treatment ($p < 0.05$). No major clinical or biochemical side effects were noted. Omeprazole is an efficient treatment for patients with prepyloric gastric ulcers.

Treatment of patients with prepyloric gastric ulcers remains a therapeutic challenge. Clinical trials have shown that healing rates are lower than among patients with ulcers located in the duodenum¹ or gastric corpus.^{2,3} Reducing the failure rate is desirable, as unhealed ulcers may cause pain and complications. It is generally believed that prepyloric ulcers resemble duodenal ulcers with regard to acid secretory pattern.⁴ Omeprazole, a substituted benzimidazole which is a potent proton pump inhibitor, has been shown to reduce intragastric acidity more effectively than cimetidine.⁵ It might be expected, therefore, that omeprazole would heal prepyloric ulcers more rapidly.⁶ To test this we have carried out a double blind randomised trial of omeprazole (30 mg once daily) and cimetidine (1 g daily in four doses).

Methods

ENTRY CRITERIA

Outpatients from five centres fulfilling the following

entry criteria were selected for the study: (1) at least one active prepyloric ulcer seen at endoscopy not more than four days before the start of treatment (a visible crater was required, and patients with erosions or punctate ulcers were not included). All stomach ulcers below the angulus were considered as prepyloric, but only ulcers that could be seen endoscopically from the gastric side were to be included; (2) no treatment with H_2 -receptor antagonists during the preceding two weeks; (3) no previous gastric surgery, except for simple closure; (4) no pyloric stenosis necessitating surgical intervention; and (5) no concurrent therapy or disease complicating the evaluation of the drug – for example, liver or kidney disease. Laboratory investigations included haemoglobin; leucocyte and platelet counts; serum creatinine, electrolytes, bilirubin, alkaline phosphatase, aspartate aminotransferase and albumin; urinary albumin and glucose. Patients below 18 or above 80 years of age were excluded, as were women who were pregnant or lactating and those who were able to bear children and were not using oral contraception or an intrauterine device. Patients with concurrent gastric ulcers were also excluded. Multiple biopsy specimens from the ulcer area were taken in order to exclude

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malignancy. Each patient gave informed consent, and the trial was approved by the regional ethics committees.

STUDY DESIGN

Patients were randomly assigned to six weeks of treatment with either cimetidine (200 mg tablets), one tablet three times a day and two at bedtime, or omeprazole (30 mg capsules), one capsule in the morning. Inactive tablets and capsules, identical in appearance to the active ones, were prepared so that all patients received the same number of tablets or capsules. The patients were given diary cards and asked to record the hours each day when they felt pain.

The patients were seen after two weeks (± 2 days), after four weeks (± 2 days), and after six weeks (± 2 days) for clinical assessment, endoscopy with biopsies, and repeat laboratory tests. Endoscopy was omitted at four and six weeks if the ulcer was found to be healed – that is, complete epithelialisation of the ulcer site, at the preceding endoscopy. The number of returned tablets and capsules was recorded, and patients who were later found not to have taken the active drug for three days or more per fortnight were regarded as ineligible for 'per protocol' analysis. The patients were allowed but not encouraged to take antacid medication.

STATISTICAL CONSIDERATIONS

In planning the trial we estimated a healing rate of 60% after four weeks in the cimetidine group¹ and to increase this rate to 85% or more was considered clinically meaningful. It was calculated that roughly 150 patients (75 in each group) were needed to ensure that the risk of overlooking such a difference was less than 10%.⁷ To obviate inclusion of more patients than necessary the O'Brien and Fleming procedure⁸ was applied as a stopping rule and the results of the trial were analysed by statisticians, independent of clinicians, when one third (55) and when two thirds (110) of the patients planned for inclusion had completed four weeks of treatment.

The statistical methods used were Fisher's exact test, the Cochran-Mantel-Haenszel test, the Mann-Whitney test, the two-sample *t* test, the sign test, and the χ^2 test, as indicated in the text and tables. Only two-tailed tests were used. Values of $p < 0.05$ were considered significant. The 95% confidence limits for differences in healing between the two treatment groups were also calculated.⁹

The primary efficacy variable was endoscopic ulcer healing and the data were subjected to both a 'per protocol analysis' – that is, including only patients who completed an assessment period according to the protocol and an 'intention to treat' analysis – that

is, including all patients who entered the study except those that did not have the disease, such as patients in whom entry biopsies showed a carcinoma. Patients lost to follow up were considered unhealed. The trial was stopped temporarily as all other omeprazole trials¹⁰ (see Discussion) and it was decided that patients who stopped medication after two or four weeks because of this trial suspension were considered ineligible for analysis beyond the time of withdrawal.

Results

DESCRIPTION AND COMPARISON OF TREATMENT GROUPS

The interim analyses did not result in any early stopping of recruitment and a total of 176 patients entered the trial – 31 from centre 1 (Glostrup), 13 from centre 2 (Herlev), 109 from centre 3 (Odense), six from centre 4 (Ribe), and 17 from centre 5 (Bispebjerg). Three additional patients fulfilled the entry criteria but did not wish to participate. Two patients were excluded from all analyses (one was included a second time and one had a carcinoma, as shown by entry biopsies; both patients were withdrawn after six and nine days, respectively). Eighty nine patients were allocated to receive omeprazole (13 from centre 1, eight from centre 2, 54 from centre 3, four from centre 4, and 10 from centre 5) and 85 to receive cimetidine. The treatment groups were well matched for selected patient characteristics (Table 1). Because of the temporary trial stop four patients in the omeprazole group and one patient in the cimetidine group were withdrawn after week 2 (all had unhealed ulcers), and another four patients in the omeprazole group and two in the cimetidine group (all had healed ulcers) were withdrawn after week 4. In the omeprazole group three patients were withdrawn during weeks 1 and 2 (one because endoscopy could not be performed because of laryngeal spasm, one because of urticaria, and one

Table 1 Selected characteristics of patients treated with omeprazole or cimetidine*

	Omeprazole	Cimetidine	p Value
Sex ratio (M:F)	36:53	44:41	NS†
Mean age – yr	57.0 (25–80)	57.6 (34–78)	NS‡
Mean length of history – yr	6.0 (0–42)	8.1 (0–43)	NS‡
Ratio of smokers to non-smokers	64:25	64:21	NS†
Mean ulcer size – mm	9.7 (3–30)	10.7 (3–40)	NS‡

*Unless otherwise noted, values represent numbers of patients, and values in parentheses are ranges. NS denotes not significant ($p > 0.05$).

†Fisher's exact test; ‡Two-sample *t* test.

Table 2 Recruitment, loss, and withdrawals of patients distributed by treatment group and the composition of two cohorts used in the analysis

	Omeprazole				Cimetidine			
	Entry Patients (n)	Week 2	Week 4	Week 6	Entry Patients (n)	Week 2	Week 4	Week 6
Recruited	90				86			
Ineligible according to entry criteria	1				1			
Withdrawn at temporary trial stop			4	4			1	2
Evaluable 'intention to treat' cohort		89	85	81		85	84	82
Withdrawn or lost to follow up		3		1		2	1	2
Ineligible at single study days because of protocol violations		4	4	7		5	8	8
Evaluable 'per protocol' cohort		82	78	70		78	73	69

Table 3 Healing rates for two analytical cohorts, tabulated by treatment groups

Cohort	Cumulative healing rates Weeks	Omeprazole Patients (n) (%)	Cimetidine Patients (n) (%)	Omeprazole v Cimetidine	p Value*
				Observed difference (%) 95% confidence limits	
'Per protocol' cohort	Two	45/82 (55)	33/78 (42)	13	NS
	Four	66/78 (85)	56/73 (77)	8	NS
	Six	62/70 (89)	59/69 (86)	3	NS
'Intention to treat' cohort	Two	48/89 (54)	33/85 (39)	15	0.04
	Four	69/85 (81)	61/84 (73)	8	NS
	Six	70/81 (86)	64/82 (78)	8	NS

*Cochran-Mantel-Haenszel test using centre as a covariable. NS denotes not significant ($p > 0.05$).

was lost to follow up); a fourth patient was withdrawn after week 4 at his own wish (he had pain, but a healed ulcer). In the cimetidine group, one was withdrawn during weeks 1 and 2 because of acute meningitis and another was withdrawn from 'per protocol' analysis because biopsies at week 6 revealed a carcinoma; one patient was lost to follow up after week 2; and after week 4 two patients were withdrawn (one symptom free with an unhealed ulcer refused to take more medicine, and another, with a healed ulcer, suffered severe pain and was referred for surgery which revealed an occlusion of the coeliac and mesenteric arteries). Finally, a number of patients in both treatment groups were ineligible for 'per protocol analysis' at one or more assessment periods because of protocol violations, in most cases because they had not taken the stipulated number of capsules or tablets, or came too early or late for the scheduled endoscopies; two patients in the cimetidine group were ineligible on all visit days because, in retrospect, it was discovered that five days had passed between entry endoscopy and start of treatment. Table 2 summarises the recruitment, loss, and withdrawals of patients.

ULCER HEALING

Table 3 shows the healing rates in the two treatment groups for each of the two analytical cohorts, in

addition to the 95% confidence limits for the differences in healing rates between the groups. In both analytical cohorts and on all study days the cumulative healing rates were higher in the omeprazole group than in the cimetidine group. The difference in healing rates was more marked after two weeks than after four or six weeks and was statistically significant in the 'intention to treat' cohort. Because time to healing is a survival type end point the Cochran-Mantel-Haenszel test was used on the 'intention to treat' cohort to cover all three time points ($\chi^2_{CMH} = 3.47$; $df = 1$; $p = 0.06$).

Table 4 shows the healing rates in relation to

Table 4 Healing rates for 'per protocol' cohort after two weeks, according to smoking status and ulcer size

	Omeprazole Patients (n) (%)	Cimetidine Patients (n) (%)
Smoking status		
Smokers	30/58 (52)	23/58 (40)
Non-smokers	15/24 (63)	10/20 (50)
p value*	NS	NS
Ulcer size		
<9 mm	28/41 (68)	20/37 (54)
≥9 mm	17/41 (41)	13/41 (32)
p Value*	0.03	NS

*Cochran-Mantel-Haenszel test using centre as a covariable. NS denotes not significant ($p > 0.05$).

smoking status and ulcer size. In both treatment groups healing rates were lower among smokers but neither difference was statistically significant. By contrast, ulcer size seemed to be a predictor of healing. The influence of sex and length of ulcer history was also analysed, and no significant differences were found.

ULCER PAIN

Table 5 compares the duration of pain in the two groups. Twenty one patients in the omeprazole group and 12 patients in the cimetidine group had no ulcer pain during the trial. In the omeprazole group 13 patients became free of pain during the first week, as compared with four patients in the cimetidine group (Fisher's exact test, $p < 0.05$). No significant difference was found, however, in symptomatic effect by actuarial analysis of the whole treatment period (Cochran-Mantel-Haenszel test; $\chi^2_{CMH} = 1.98$; $df = 1$; $p > 0.05$).

Table 6 shows the average number of hours of pain in the two treatment groups during the trial. No significant differences were found (Mann-Whitney test, $p > 0.05$). The high mean values in both treatment groups during the last weeks are explained by a large number of hours of pain reported by a few patients.

Ulcer healing after two weeks was not well corre-

lated with the presence or absence of pain (Fisher's exact test; $p = 0.22$).

UNEXPECTED SYMPTOMS AND LABORATORY FINDINGS

Four patients (one in the omeprazole group) were withdrawn because of intercurrent disease, as mentioned above. Among the omeprazole treated patients each of the following complaints was reported in a single case: headache, fatigue, transient diarrhoea, gastroenteritis, and muscle pain. Among the cimetidine treated patients two complained of impotence, two of dizziness, one of headache, and one of dry mouth.

The laboratory values were analysed for changes in levels from the entry to the last day of treatment by the sign test and the pattern of change between treatment groups was compared by the χ^2 test. Apart from an increase in serum creatinine concentrations in the cimetidine group ($p < 0.05$) no significant differences were found.

In several cases a single value fell outside the reference range for the laboratory concerned, but such abnormalities occurred at random in both treatment groups and only one case deserves special mention. In a 40 year old woman treated with cimetidine concentrations of aspartate aminotransferase increased to 122 IU/l after six weeks' treatment (reference interval: 10–35). A liver biopsy revealed an acute hepatitis of viral or toxic type. She fully recovered after treatment was stopped.

Discussion

These findings indicate that prescription of omeprazole 30 mg once daily to patients with prepyloric gastric ulcer is superior to prescription of cimetidine 1 g daily in four doses in accelerating ulcer healing and bringing pain relief. Although this potential benefit was obtained without serious side effects we advise caution in interpreting the results. First, one needs to consider whether the observed differences in healing rates and frequencies of patients without pain are of clinical significance. Second, the relevance of the findings for defining the role of omeprazole in the treatment of prepyloric ulcers in a general population should be debated. The 95% confidence limits for the therapeutic gain observed in the healing rates after two weeks may be considered clinically important and the results show that more pronounced acid inhibition also benefits patients with prepyloric ulcers although this benefit is less discernible than in patients with duodenal ulcers.¹⁰ The present results differ from those reported in the only other published comparative trial on omeprazole in patients with gastric ulcers.¹¹ In that trial healing rates among

Table 5 Duration of pain during trial ('intention to treat' cohort)

No pain	Omeprazole Patients (n)	Cimetidine Patients (n)
From start	21	12
Only after week 1	13	4
Only after week 2	9	9
Only after week 3	4	5
Only after week 4	4	10
Only after week 5	2	9
*No diary-proven 'no pain' the last week of medication	36	36
Total	89	85

*That is, a symptomatic treatment failure on the 'intention to treat' basis.

Table 6 Number of hours of pain in the omeprazole and cimetidine groups of 'per protocol' cohort

Week	Omeprazole mean hour (range)	Cimetidine mean hour (range)
1	17.1 (0–137)	19.4 (0–91)
2	10.7 (0–140)	13.9 (0–96)
3	7.9 (0–138)	11.5 (0–70)
4	8.2 (0–135)	12.9 (0–148)
5	8.9 (0–168)	11.0 (0–106)
6	7.5 (0–168)	10.5 (0–95)

patients treated with omeprazole 20 mg once daily were almost identical to healing rates among patients treated with ranitidine 150 mg twice daily. Several factors may explain the different results in the two trials. First, the difference may reflect a dose response effect. The decrease in 24 hour intragastric acidity after omeprazole treatment shows considerable interindividual variation and this variation is more pronounced on omeprazole 20 mg daily than on a dose of 30 mg daily.¹² Possibly a lower failure rate in the omeprazole group could be obtained by increasing the dose – for example, to 40 or 60 mg daily, and this question calls for settlement in a clinical trial, at least in patients who do not heal after four weeks' treatment. Second, the present trial comprised patients with prepyloric gastric ulcers only and these patients may be more prone to benefit from acid inhibition, as their acid secretory pattern resembles that of duodenal ulcer patients.⁴ Finally, the German trial¹¹ comprised more patients with small ulcers than the present trial, and in both trials small ulcers healed more rapidly.

The present results also showed that omeprazole relieves pain more rapidly than cimetidine, although this effect was less pronounced than the effect on ulcer healing. This may be explained by the modest correlation between pain and ulcer healing, in addition to methodologic problems in the assessment of pain. The poor correlation between symptomatic response and ulcer healing, which is a well known finding in clinical trials on peptic ulcer disease, illustrates the fact that the mechanism of ulcer pain and the pathways through which the pain is mediated is poorly understood.¹³ The method of recording pain by counting hours of pain each week is attractive from a compliance point of view, but may give misleading results. Thus other causes of abdominal discomfort, such as an irritable bowel syndrome, will also be recorded as 'ulcer pain'. This may account for a major proportion of patients seemingly experiencing pain in the last weeks of the trial period despite ulcer healing.

The present trial was temporarily suspended because of a report that large doses of omeprazole administered in rats for two years had resulted in the development of gastric carcinoid tumours consisting of enterochromaffin like cells.¹⁴ The trials were restarted when available data suggested that these effects were not the direct result of omeprazole, but due to a gastric neuroendocrine response to profound and sustained acid suppression and subsequent hypergastrinaemia in rats given high doses of omeprazole for almost their whole life span.^{15 16} Short term treatment of omeprazole has not been shown to cause any changes in endocrine cell density,¹⁷ but further

studies are needed to elucidate the possible consequences of prolonged acid inhibition in man.

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