Clinical trial

Effect of cimetidine treatment in the prevention of gastric ulcer relapse: a one year double blind multicentre study

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SUMMARY One hundred and forty six gastric ulcer patients were given open treatment using 1 g cimetidine daily to heal their ulcers. Of 130 who completed the acute treatment period of eight weeks, 112 (86%) had healed ulcers. Of these 112 patients with healed ulcers, 108 entered a one year double blind study to compare the effect of cimetidine maintenance therapy (400 mg at night) with placebo. Of the 84 patients available for assessment at the end of one year, 86% in the cimetidine treated group were in remission compared with 45% in the placebo treated group ($\chi^2=15.03$; $p<0.001$). There were similar losses from non-compliance and drop out in both groups. The incidence of untoward effects and significant drug related laboratory abnormalities was low. The results indicate that cimetidine heals nearly 90% of acute gastric ulcers within eight weeks and that subsequent low dose maintenance treatment at night offers a considerable benefit over placebo therapy.

Although the efficacy of cimetidine in the healing and prevention of recurrence of duodenal ulceration has been well documented,¹⁻⁷ the evidence for similar efficacy in the treatment of gastric ulcer is less clear. There is now good evidence to suggest that gastric ulcers can be healed using cimetidine 1g daily for four to eight weeks.⁸⁻¹⁰ The documentation covering maintenance treatment is rather sparse, however, and based on a variety of doses in relatively small patient populations.¹¹⁻¹⁵ In two studies cimetidine was compared with carbenoxolone and deglycerinised liquorice respectively.^{15 16} The results appear to show similar recurrence rates, but the studies were limited to six months only.

This multicentre study was designed to investigate in a one year double blind placebo controlled study the effect of prophylactic therapy with cimetidine on gastric ulcer recurrence.

Methods

PATIENTS

Patients who had healed gastric ulcers after treatment for four to eight weeks treatment with cimetidine 1 g daily were included in the study. Malignancy was excluded by biopsy before the initial healing treatment and only patients without concurrent duodenal ulceration and with an intact stomach were included. Patients were randomly allocated to treatment with either cimetidine 400 mg (two tablets) at night, or matching placebo. Patients were seen every two months for up to one year unless there was clinical deterioration which required an earlier visit. At each visit symptoms, untoward events and changes in medication were recorded. At the six and 12 month visit or whenever symptoms suggested a recurrence, endoscopy was performed. Blood samples were obtained before entry, and at all of the bimonthly visits. The following parameters were investigated: red and white cell count, haemoglobin, haematocrit, platelets, and reticulocyte counts, bilirubin, SGOT, SGPT, alkaline phosphatase, LDH, BUN,

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creatinine, uric acid, and serum electrolytes. At each endoscopy where an ulcer was demonstrated, material for histological and cytological examination was obtained.

STATISTICAL METHODS

Results were analysed by Wilcoxon's rank sum test for comparison of age, duration of ulcer disease, and ulcer size. All other comparisons of frequencies and results were done by chi square test or Fisher's exact test in case of small numbers.

Results

Of the 146 patients who began treatment, 112 patients had a healed ulcer after four or eight weeks treatment with open cimetidine. Three of these patients refused to continue into the double blind prophylactic phase and one patient was referred for surgery because of primary hyperparathyroidism. The remaining 108 patients were randomly allocated either to cimetidine prophylaxis (400 mg at night) or to placebo treatment. During the one year's treatment 12 patients (22.2%) in each group were lost to follow up, the reasons for drop out being listed in Table 1. Four patients died during the one year follow up, (cimetidine treatment: one congestive cardiac failure; one myocardial infarction; one bleeding from oesophageal varices. Placebo treatment: one congestive cardiac failure), the cause of death being considered unrelated to either ulcer disease or the drug therapy. One placebo treated patient underwent a portocaval shunt operation. Eight cimetidine and seven placebo patients failed to attend the clinic, and all contact was lost despite follow up letters, so that the reason for non-compliance is unknown.

Of the 108 patients who were available for analysis during the maintenance phase there was no significant difference with respect to age, sex, duration of ulcer disease, or time to healing of ulcer between the two treatment groups (Table 2). Patients allocated to placebo, however, had significantly more ulcers located in the antrum than those on cimetidine ($\chi^2=8.04$; $p<0.05$). This

Table 2 Demographic data for patients followed up during maintenance trial

	Cimetidine Group	Placebo Group	Significance
Men:women	20:22	20:22	NS
Mean age in years (range)	63.5 (28-80)	58 (26-82)	NS
Mean duration of ulcer disease in years (range)	3.0 (<1-30)	2.5 (<1-45)	NS
Time to heal ulcer			
4 weeks	25	27	
8 weeks	15	17	
Site of ulcer			
Corpus	27	20	$(\chi^2=8.04)$ $p<0.05$
Angulus	15	10	
Antrum	6	18	

NS = Not significant ($p>0.05$). As some patients had two or three ulcers the total number of ulcers is higher than the total number of patients.

difference was already present at the beginning of the maintenance phase and not altered by subsequent drop outs ($\chi^2=9.16$; $p<0.05$). Forty two patients in each treatment group completed the one year maintenance study or suffered an endoscopically proven relapse.

Six (14%) of the cimetidine treated patients relapsed, 36 (86%) remained healed whereas with placebo treatment 23 (55%) relapsed and 19 (45%) patients remained healed, this difference being highly significant ($\chi^2=15.03$; $p<0.001$). No evidence of malignancy was shown in any of the ulcers that recurred during maintenance treatment.

Seven (24%) of 29 recurrences were asymptomatic, the proportion of asymptomatic recurrences being similar in both groups: two of six during cimetidine treatment and five of 23 during placebo treatment (Table 3).

Table 3 Recurrence of ulceration during maintenance treatment and relationship to presence or absence of symptoms

Treatment	Patients (no.)			
	Completed one year study	Endoscopically confirmed		
		Symptomatic relapse	Asymptomatic relapse	Total relapses
Cimetidine	42	4	2	6 (14%)
Placebo	42	18	5	23 (55%)

A more detailed picture of the pattern of relapses and drop out is shown in the Figure. In both groups the majority of relapses occurred in the first six

Table 1 Reasons for withdrawal from trial during maintenance therapy

Reasons	Cimetidine	Placebo
Death	3	1
Surgery	0	1
Side effect	1	3
Failure to attend clinic	8	7
Total	12	12

CIMETIDINE	54/0	50/1	48/1	47/5	46/5	45/5	42/6
PLACEBO	54/0	49/2	45/5	43/17	42/19	42/19	42/23

Figure Corrected cumulative remission rate showing patients in remission as percentage of total number of patients presenting at each bimonthly control and number of patients who had endoscopically been shown to have reulceration in the preceding months. Figures above graph separated by an oblique bar represent absolute number of patients presenting and total number of recurrences at each control.

months: five of six during cimetidine treatment, 17 of 23 during placebo treatment. It should be emphasised that the curves do not show the exact time of onset of the asymptomatic recurrences, as routine endoscopy was only performed at six and 12 months.

With the exception of one patient who originally had an antral ulcer and developed a duodenal ulcer, all recurrences of gastric ulceration occurred at or very close to the site of the presenting lesion. Ulcers recurred in the corpus in 7.4% of cimetidine patients and 40% of placebo patients, in the antrum in 39% of placebo patients and in none of the cimetidine patients. The recurrence rate in the angulus was 26% in the cimetidine patients, however, and 80% in placebo patients, a finding which indicated a trend, but did not reach statistical significance ($\chi^2=5.21$; $p<0.1$).

UNTOWARD EVENTS AND LABORATORY TEST ABNORMALITIES

During prophylactic treatment four patients were withdrawn because of suspected side effects. Three

patients receiving placebo developed chest pain, herpes zoster, or thrombocytopenia respectively. One patient receiving cimetidine requested withdrawal of the treatment because of fatigue. The following untoward events were observed without interrupting the study: three patients receiving placebo reported impotence, vertigo, and pruritus respectively, and four patients presented with gynaecomastia (due to hepatic cirrhosis), transient rash, anaemia or thrombocytopenia. Four patients receiving cimetidine reported headache, disturbed sleep, loss of libido (a female patient) or pruritus, and two patients developed transient anaemia or leucocytosis. One patient developed gynaecomastia during the eighth month of treatment, some weeks after starting therapy with spironolactone for incipient heart failure, the gynaecomastia clearing by the 12th month after withdrawal of spironolactone.

Four patients taking cimetidine and nine taking placebo had abnormal liver function tests (increased bilirubin, alkaline phosphatase and/or SGOT) on more than one occasion. In all cases this could be attributed to pre-existing alcoholic liver damage. No other significant abnormalities of laboratory data were seen.

Discussion

In a large and unselected population of patients with endoscopically proven gastric ulcer, an 86% healing

rate was achieved using cimetidine 1 g daily for four to eight weeks. This result compares favourably with others⁸⁻¹⁰ who have reported healing rates of 60 to 80% during acute therapy under controlled conditions. Trials where cimetidine was not significantly superior to placebo in healing gastric ulcers were characterised by comparatively small numbers of patients or high placebo healing rates.¹⁸⁻²⁰

The recurrence rate for gastric ulcers after healing is reported to be at least 60% without treatment.¹⁷ The need for effective drug prophylaxis, at least for selected patients, seems obvious. Only a few studies so far have dealt with maintenance treatment of gastric ulcer¹¹⁻¹⁴ reporting significantly fewer recurrences with cimetidine treatment than with placebo. This study strongly confirms these results.

In this study, after randomisation to either cimetidine or placebo maintenance treatment, the distribution of ulcer localisation turned out to be unequal. Significantly fewer ulcers of the antrum were treated with cimetidine than with placebo. The authors do not believe that this imbalance had a major influence on the final outcome of the study. It seems very unlikely that a small difference in the number of antral ulcers between the cimetidine and placebo treatment groups would have a noteworthy effect on relapse rates. This appears to be emphasised by the fact that no antral ulcers relapsed on cimetidine.

Twenty four per cent of the relapses in this trial were asymptomatic, about 80% occurring in the first six months. As this applies to both treatment groups, relapses on cimetidine do not appear to differ from those on placebo except that they occur significantly less frequently. It appears from this study that a significant improvement in remission can be expected for maintenance treatment of healed gastric ulcers with cimetidine. As decisive prognostic factors for gastric ulcer patients are not known, it is still a matter of debate who should receive long term prophylactic treatment. We would suggest that those taking ulcerogenic drugs and those at major risk from ulcer complications would benefit most from long term maintenance therapy.

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