

Twice daily cimetidine in the initial treatment of chronic gastric ulcer – a double-blind placebo-controlled trial

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Summary

Thirty-one patients with endoscopically proven chronic gastric ulcer completed a randomised double-blind trial comparing the effects of cimetidine and placebo on ulcer healing. Seventeen patients received cimetidine 400 mg bid and 14 patients received placebo. Repeat endoscopy at six weeks showed that the ulcer had healed in 12 patients (71%) receiving cimetidine and in four patients (29%) receiving placebo ($p=0.032$). Non-smokers healed their ulcers better than smokers (83% vs 35%, $p=0.023$). The use of cimetidine was not associated with any adverse effects.

Introduction

Although cimetidine has been shown to be efficacious in healing duodenal ulcers, early studies on gastric ulcer yielded conflicting results.¹⁻⁵ More recently, larger studies from the United States have confirmed that cimetidine, given four times daily, is superior to placebo in accelerating the healing of gastric ulcers.^{6,7} The purpose of the present study was to compare the use of cimetidine 400 mg bid with placebo in the treatment of chronic gastric ulcer patients.

Materials and method

Adult patients with benign chronic gastric ulcer confirmed endoscopically and histologically were included in the study. The following categories of patients were excluded:

- pregnant and lactating women and females likely to conceive
- patients with severe concomitant diseases
- patients treated with histamine H₂-receptor antagonists or ulcer therapy other than antacids in

the month prior to diagnosis

- patients with concomitant oesophageal or duodenal ulceration and
- patients who had undergone previous gastric surgery.

Informed consent was obtained. All patients were free to withdraw from the study at any time. The trial was conducted in accordance with the Declaration of Helsinki.

Patients received either cimetidine 400 mg bid or an identical placebo tablet bid according to a randomised code. They were also given a supply of antacid tablets (Rennie, Nicholas Lab Ltd each containing calcium carbonate 680 mg and light magnesium carbonate ph Eur 80 mg) to take as required for pain. Diary cards were kept to record pain and antacid usage. The patients were assessed at two, four and six weeks. After six weeks endoscopy was repeated and the ulcer assessed as healed or not healed. Compliance was assessed by the use of tablet counts. Gastric secretory testing, as well as pre and post treatment haematological and biochemical evaluation were performed.

Numerical data were analysed by student's t-test. Categorical data were analysed by Fisher's exact probability test. All p values less than 0.05 (two-tailed) were considered significant.

Results

Twenty of the 51 patients who were entered into the trial did not complete the protocol. Of these, 10 defaulted follow up, six were excluded because of malignancy, diagnosed after entry (it is our practice that treatment is instituted before histology is available) one because of gastrointestinal bleeding, and three because of uncontrolled abdominal pain despite taking the trial medication and antacids. Therefore 31 patients were available for analysis: 17 of them received cimetidine 400 mg bid and 14 received placebo one tablet bid. There was no significant difference between the two groups with respect to their sex, age, weight, duration of disease, history of previous gastrointestinal haemorrhage, smoking, alcohol consumption, initial size and location of index ulcer, basal acid output (BAO), and peak acid output (PAO) (Table 1).

Table 1

Patient characteristics

	Cimetidine	Placebo
Number	17	14
Sex (M:F)	14:3	8:6
Age: mean year (range)	52 (19-81)	57 (35-76)
Weight: mean kg (range)	53 (39-66)	54 (40-69)
Duration of disease in years: median (range)	2 (<1-10)	6 (<1-30)
Previous gastrointestinal bleeding (%)	2 (12)	0 (0)
Smokers (%)	11 (65)	9 (64)
Drinkers (%)	5 (29)	3 (21)
Initial ulcer diameter: mean mm (range)	10 (3-20)	10 (6-30)
Location of ulcer: prepyloric	1	1
corpus	16	13
BAO mean mEq/hr (range)	5 (<1-23)	5 (<1-8)
PAO mean mEq/hr (range)	24 (5-52)	22 (15-31)

At six weeks 12 of 17 patients (71%) treated with cimetidine 400 mg bid healed their ulcers compared to four of 14 patients (29%) treated with placebo ($p=0.032$) (Table 2). Various patient characteristics were analysed to see if they influenced ulcer healing. Only smoking was found to affect treatment outcome. Overall, non-smokers healed their ulcers better than smokers [9/11 (82%) vs 7/20(35%), $p=0.023$]. See Table 3. The initial ulcer size was larger in patients whose ulcers did not heal (mean = 12mm) compared with those whose ulcers healed (mean =9 mm). However, this difference was not statistically significant ($p=0.072$). Similarly, gastric secretory capacity did not influence the treatment outcome.

Table 2

Incidence of gastric ulcer healing on cimetidine and placebo

	Cimetidine	Placebo
Healed	12 (71%)	4 (29%)
Not Healed	5 (29%)	10 (71%)
Total	17	14

$p = 0.032$

The two treatment groups were comparable in terms of pain experienced prior to entry into the trial. Pain relief during the day was similar in the two groups except during the sixth week in which patients who had placebo experienced more pain ($p=0.044$). Night-time pain improved equally in both groups during the six weeks of treatment (Figure 1). There was a trend towards a greater reduction of antacid usage in the cimetidine group but this did not reach statistical significance (Figure 2).

In the placebo group, one patient developed gastrointestinal haemorrhage and three patients had uncontrolled abdominal pain while on trial medication. These four were not included in the analysis. No significant clinical, haematological or biochemical events attributable to cimetidine therapy occurred during the course of the trial. As regards compliance, all patients who completed the study had taken a minimum of 85% of the prescribed cimetidine or placebo tablets as assessed by tablet counts.

Discussion

Although cimetidine was found to be highly efficacious in the treatment of duodenal ulcer, early studies on its use in gastric ulcer yielded conflicting results. While two European studies demonstrated that cimetidine was more effective than placebo^{1,2}, one British and two American studies showed no difference between the two treatments.³⁻⁵ Two recent large multicentre trials in the United States had again confirmed the efficacy of cimetidine in gastric ulcer healing.^{6,7} It is possible that the large amount of antacids consumed in some of the earlier trials^{4,5} might have masked the beneficial effect of cimetidine. Indeed, a recent study⁸ demonstrated that even a low-

Table 3

The Effects of smoking on gastric ulcer healing

	Cimetidine	Placebo	All
Smokers	7/11 (64%)	*0/9 (0%)	**7/20 (35%)
Non Smokers	5/6 (83%)	*4/5 (80%)	**9/11 (82%)

Gastric ulcer healing rate, expressed in %

* Placebo group: Smokers vs Non-smokers $p = 0.005$

** All patients: Smokers vs Non-smokers $p = 0.023$

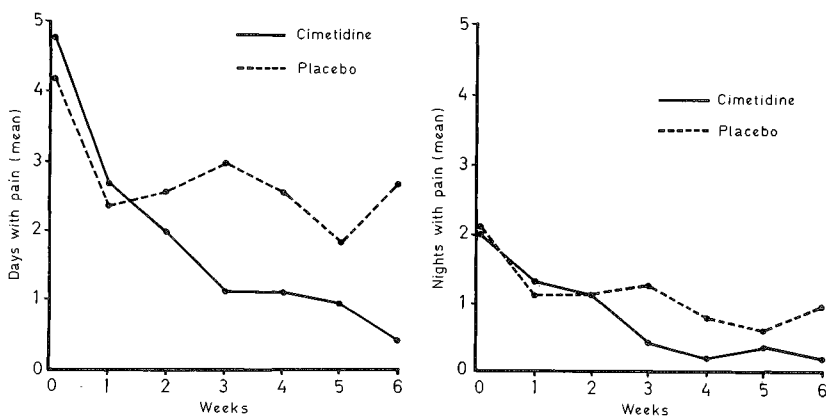


Figure 1
Mean numbers of days and nights with pain

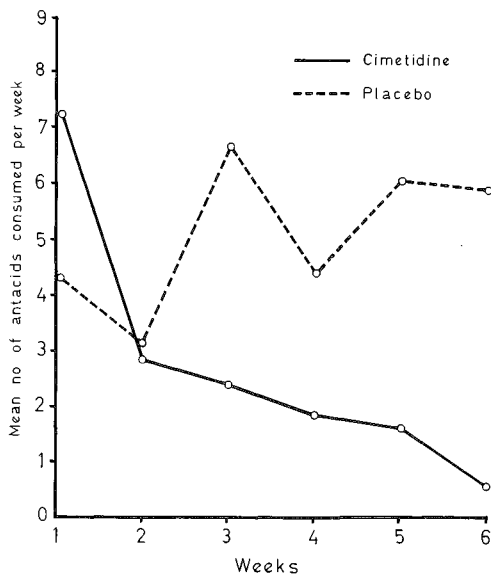


Figure 2
Antacid consumption

dose antacid regimen with total neutralising capacity of 120 mmol/day was superior to placebo in the treatment of gastric ulcer.

Daily dosages of cimetidine of one to 1.2 grams per day in four divided doses were used in previous placebo controlled studies.¹⁻⁷

A dosage of 400 mg twice daily has been compared with the four times daily regimen and found to be equally effective.^{9,10} But to our knowledge, the twice daily regimen has not previously been formerly assessed in a placebo controlled study. Our results indicate that cimetidine 400 mg bid is superior to placebo in the healing of gastric ulcer in Singaporean patients. There was a trend towards greater symptom improvement in the cimetidine group but not achieving statistical significance. It is worth stressing that all the four patients who were withdrawn from the trial either because of bleeding or uncontrolled abdominal pain were all taking placebo. They were not included in the final analysis. If they were considered as therapeutic failures, the difference between the cimetidine group and the placebo group could be even more significant statistically [12/17 (71%) vs 4/18 (22%); with $p < 0.02$].

The deleterious effect of smoking on duodenal ulcer healing had been reported by many workers.¹¹⁻¹³ However, although Doll et al¹⁴ reported in 1958 that smoking retarded gastric ulcer healing, more recent studies¹⁵⁻¹⁷ did not demonstrate such an effect. Our study, however, suggests that smoking retards the healing of gastric ulcer. This was particularly evident in the nine smokers taking placebo, none of whom healed their ulcers. As compared with placebo, cimetidine was particularly effective in smokers (Table 3). Previous authors reported that larger ulcers healed more slowly than smaller ulcers.^{7,15,18} Our results showed a similar trend, although statistical significance was not achieved.

Amongst our patients gastric secretory capacity did not influence ulcer healing. This is consistent with results from other studies.^{4,5,7} However, a recent Japanese study indicated that cimetidine was effective for gastric ulcers associated with high gastric acid production but not for those with low acid outputs.¹⁹

Twice daily cimetidine is therefore safe and effective for the treatment of gastric ulcer.

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