The effect of cimetidine on the maintenance of healing of gastric ulceration

J. D. KINLOCH* F.R.C.P.
I. L. WOOLF† M.A., M.R.C.P.

A. J. G. PEARSON† M.R.C.P.
P. H. YOUNGS B.Sc.

*Chase Farm Hospital, Enfield, †Barnet General Hospital, Barnet, ‡North Middlesex Hospital, Edmonton, London and §Smith Kline & French Laboratories Ltd, Welwyn Garden City, Herts

Summary
The rate of endoscopically confirmed gastric ulcer relapse was compared in two groups of patients with newly healed benign gastric ulcers, receiving either cimetidine 400 mg nocte or matching placebo, over a period of 1 year. Six of 24 (25%) patients on cimetidine and 16 of 27 (59%) patients on placebo had endoscopically confirmed relapse. These included two patients in each group with asymptomatic relapses. The difference in the rate of relapse between the two groups was statistically significant (P = 0.01).

KEY WORDS: gastroscopy, gynaecomastia.

Introduction
The place of cimetidine in the healing of gastric ulceration is now well established. There are few placebo controlled trials, however, of its use in the maintenance of healing of gastric ulcers. In this study, we have followed up patients, with previously healed gastric ulcers, for a year on either cimetidine 400 mg nocte or placebo, using gastroscopy at 6 monthly intervals to assess progress.

Materials and methods
Seventy-nine patients with benign gastric ulceration confirmed by endoscopy were treated initially with cimetidine 1 g/day.

Patients with prepyloric ulcers and with both gastric and duodenal ulcers were excluded. Routine biopsies and cytology were performed on all ulcers to exclude malignancy. Sixty-three patients, in whom endoscopy demonstrated healing after 6 or 12 weeks on this regimen were entered to the maintenance study, the remainder being excluded because of non-healing (10), failure of compliance (4) and adverse events (2).

Patients were randomly allocated on a double-blind basis to either cimetidine 400 mg nocte or matching placebo, all other ulcer medication being discontinued, except for a standard antacid to be taken as required. They were seen at 2-monthly intervals for clinical assessment and biochemical and haematological studies. Endoscopy was performed at 6 months, 12 months or when symptoms suggested relapse. A patient with recurrence of ulceration was designated a treatment failure and discontinued maintenance therapy. Persistent failure to take medication or adverse events resulted in a patient's withdrawal from the trial.

Results
Fifty-one patients completed the trial, eight patients defaulting, one dying of unrelated disease and three being withdrawn because of adverse events. The total number of patients, the sex ratio, the ages (mean 60 years; range 33–85) and the number of patients withdrawn from the trial, were similar for both treatment groups.

The duration of symptoms before initial treatment (mean 5–8 months) was similar for both groups, but the duration of ulcer disease showed a wide range (range 0–43 years) and the cimetidine group (mean 9·3 years) had twice the mean duration of the placebo group (mean 4·2 years). Six of 24 (25%) patients on cimetidine and 16 of 27 (59%) patients on placebo had ulcer recurrence during maintenance treatment. Relapse occurred after a mean of 7·2 months (range 3–12 months) in the cimetidine group and after a mean of 5·6 months (range 1–12 months) in the controls. Two patients in each group had asymptomatic relapses, the ulcers being detected on routine endoscopy at 12 months in the cimetidine patients, and at 6 months in one of the placebo patients and by barium meal (done for an exceptional indication) after 3 weeks in the other. When the relapse rate was
compared at each month, the difference between the two treatment groups using the generalised Wilcoxon test was statistically significant in favour of cimetidine ($P = 0.01$).

Three of the cimetidine treated patients who relapsed had evidence of refractory ulcer disease, as they required 12 weeks of full dosage cimetidine before initial healing occurred, but four other patients who required 12 weeks initial treatment remained healed throughout the maintenance phase. One of the three placebo-treated patients who required initial treatment for 12 weeks remained healed. There was no statistically significant influence of time taken to heal on subsequent relapse rates in either group (Fisher's exact test).

During maintenance treatment with cimetidine two patients developed gynaecomastia. In one this necessitated withdrawal after 6 months, but in the other, in whom treatment was continued, the condition was mild, onset occurring after 9 months and resolution 1 month after completing the trial. The two other withdrawals because of adverse events occurred in the placebo group.

**Discussion**

The initial gastric ulcer healing of 63% of patients after 6 weeks and 87% after 12 weeks' treatment with cimetidine at a dose of 1 g daily is comparable with other reports in the literature (French Multicentre Trial, 1977; Frost et al., 1977; Clarke, Lee and Tasman-Jones, 1980; Landecker et al., 1979; Ciclitira et al., 1979; Akdamar et al., 1981).

The use of cimetidine in the maintenance of patients with healed gastric ulcers has been studied using doses of cimetidine 800 mg or 1 g, or placebo over a 6 to 24 month period, in four small controlled trials. Birger Jensen et al. (1979) showed no relapse in 10 patients on cimetidine compared with five out of nine on placebo treated for 1 year. Barr et al. (1983) found five relapses in 24 patients on cimetidine compared with 12 relapses out of 25 patients on placebo during the first year of a 2-year study. A statistically significant benefit of cimetidine over placebo was demonstrated after 1 year, but not after 2 years, by which time three more cimetidine patients and one more placebo patient had relapsed. In both these trials endoscopy was not always repeated in asymptomatic patients, so asymptomatic relapses could have been missed.

Machell et al. (1979) found only two non-compliant patients relapsed out of 11 patients on cimetidine compared with 12 of 14 patients on placebo. Endoscopy was performed routinely twice during maintenance treatment or if symptoms developed. La Brooy et al. (1980) however found no difference in the relapse rate of the cimetidine and placebo treatment groups (endoscopically confirmed relapses in two of 15, and three of 14 patients respectively).

Morgan et al. (1983) carried out a 2-year maintenance study after gastric ulcer healing in 41 patients given 400 mg cimetidine at night and in 34 patients, Caved-S two tablets daily. In the first year 9.8% of the cimetidine group and 14.3% of the Caved-S group had an ulcer recurrence. In the second year, this rose to 14.3% for cimetidine and 18.5% for Caved-S. In this follow-up study, routine endoscopy was performed on admission and at 6 months and only, thereafter, if there were dyspeptic symptoms.

Hentschel et al. (1983) assessed maintenance treatment after gastric ulcer healing for 1 year in a double blind controlled trial, with endoscopy at 6 months and 1 year, or if symptoms developed. Eighty-four patients were treated with 400 mg cimetidine at night or placebo. Fourteen percent (6 of 42) of the cimetidine treated patients relapsed compared with 55% (23 of 42) on placebo. Two of the six relapsed cimetidine patients and five of the 23 relapsed placebo patients were asymptomatic. Most of the relapses occurred during the first 6 months of treatment. These figures are similar to a small double-blind trial by Boyd, Wilson and Wormsley (1982) using ranitidine 150 mg at night or placebo over 1 year, with a 17.5% relapse rate for 27 ranitidine patients and 56% for 18 placebo treated patients.

In the present study cimetidine 400 mg nocte was compared with placebo for the maintenance of 51 patients with healed gastric ulceration over the period of a year, or until endoscopically proven relapse. Only six of 24 (25%) cimetidine treated patients relapsed compared with 16 of 27 (59%) placebo patients, a statistically significant difference.

Six patients had to be excluded from the study in the early phase of the trial because of malignant ulceration. The malignancy was shown on the first biopsy in four patients, but in the two other patients, the ulcers healed and symptoms resolved before repeat biopsy of the ulcer site demonstrated malignancy. Although cimetidine may delay the diagnosis, one study suggests this may not influence the prognosis adversely (Scotcher, Sikora and Freedman, 1981). There is clearly need for care in excluding gastric carcinoma before treatment with an ulcer healing agent.

Recurrence of gastric ulcer is common and because a more elderly population is involved, a higher morbidity and mortality might be expected. Hanscom and Buchman (1971) in a follow up study of 377 healed gastric ulcer patients found a 42% incidence of recurrence within 2 years, with complications of gastric ulcer occurring in 22 patients and three ulcer-associated deaths. Morgan et al. (1978)
found a similar ulcer recurrence rate of 44% after 2 years in patients on no specific therapy, using endoscopy in symptomatic patients.

In 1972, Bonnevie (1978) analysed the survival of 1905 peptic ulcer patients diagnosed between 1963 and 1968. He analysed the total of 235 deaths that occurred and also carried out an independent actuarial analysis of their life expectancy. Seventy gastric ulcer patients died, 18 also having duodenal ulcer disease, and of these there were 10 ulcer related deaths. The 9-year cumulated risk of dying from peptic ulcer was 1-8%, with no significant difference between gastric and duodenal ulcer, although three-quarters of the ulcer specific deaths were in the first year. The total risk of dying over the same period was 18%. The observed cumulated survival rates were less than the expected survival rate, attributed to the excess of deaths during the first 2 years after ulcer diagnosis. The prognosis was influenced by age, patients under 50 having the expected survival rate, but those over 50 showed a greater than expected rate of death, increasing with the age at diagnosis (median age at death was 72 years).

Cimetidine in low dosage (400 mg nocte) has been shown to maintain ulcer healing and it would seem justified to recommend long-term maintenance treatment in elderly patients (i.e. over the age of 70 years) or in patients with concomitant disease, where the risk of developing ulcer complications or proceeding to surgery would be unacceptably high.

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References


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J. D. Kinloch, A. J. Pearson, I. L. Woolf and P. H. Young

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