Cimetidine in the prevention of gastric ulcer relapse

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Summary

Twenty-five patients with healed gastric ulcers completed an 11-month double-blind controlled trial comparing cimetidine 1 g daily with placebo in the prevention of ulcer relapse. Ulcers recurred in 14 patients, 12 on placebo, 2 on cimetidine. In 11 patients, 9 on cimetidine, 2 on placebo, the ulcers remained healed at the end of the trial ($P < 0.002$).

Cimetidine 1 g daily significantly reduces the relapse rate in gastric ulceration.

Introduction

It has been established that the histamine H_2 -receptor antagonist, cimetidine, promotes healing of duodenal ulcers (Bodemar and Walan, 1976; Blackwood *et al.*, 1976; Haggie, Fumont and Wyllie, 1976). The role of cimetidine in the treatment of gastric ulceration is less clear, although healing does occur in 60 to 80% of cases with a 4- or 6-week course of treatment (Ciclitira *et al.*, 1977; Multicentre Trial, 1977; Frost *et al.*, 1977; Dyck *et al.*, 1978).

The high incidence of subsequent recurrence, however, remains a major problem in the long-term medical management of both gastric and duodenal ulcers (Leading Article, 1977). Recent studies (Gray *et al.*, 1978; Blackwood, Maudgal and Northfield, 1978) have shown that maintenance cimetidine therapy is effective in preventing duodenal ulcer relapse in the majority of cases.

The efficacy of cimetidine in the prevention of gastric ulcer relapse has been studied in a double-blind controlled trial.

Patients and methods

Patients with endoscopically-proved benign gastric ulcers were initially treated with cimetidine or placebo in a 4-week trial. The protocol of this trial has previously been published (Ciclitira *et al.*, 1977). When endoscopic confirmation of complete healing had been obtained, either after the initial 4 weeks' treatment or, in some instances, following a further 4-week course of cimetidine the patients were entered, within 4 days of endoscopy, into the maintenance trial which continued for 11 months. All patients gave their informed consent.

The patients were randomly allocated into 2 groups, one receiving cimetidine 200 mg 3 times daily, with 400 mg at night, and the other identical placebo tablets containing lactose.

Both groups were supplied with unmarked antacid tablets (Rennies, Nicholas Laboratories) with instructions to take them as required.

Follow-up was at monthly intervals, when symptoms, antacid consumption, the number of trial tablets taken, and the occurrence of any adverse reactions were recorded. Blood samples were taken before entry to the trial and at each follow-up visit for a full blood count, plasma electrolytes, urea and creatine, uric acid and liver function tests. Endoscopy was repeated at 5 and 11 months when the trial ended, or at any stage in the event of symptomatic recurrence. Patients were withdrawn from the trial if ulcer relapse was confirmed.

Fisher's exact probability test was used to compare the frequency of ulcer relapse and the χ^2 test to assess the occurrence of pain in the 2 groups.

Results

Thirty-one patients entered the trial and 25

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TABLE 1. Comparison of cimetidine and placebo groups

No	Treatment	Male	Female	Smokers	Age (years)	Length of ulcer history (years) mean(± s.d.)
11	Cimetidine	6	5	6	59.1±9.4	7.1(10.1)
14	Placebo	8	6	8	59.5±11.0	7.9(8.1)

completed the study. Five patients defaulted from follow-up all within a few weeks. One 61-year-old man, a known hypertensive, receiving cimetidine died from a cerebro-vascular accident. No side-effects were observed and there were no significant alterations in the haematological and biochemical parameters assessed.

Of the 25 patients who completed the study, 24 originally had lesser curve ulcers and one a pre-pyloric ulcer. The 2 treatment groups were comparable with regard to age, sex, smoking habits and duration of ulcer disease (Table 1). Eleven patients received cimetidine, 14 placebo. Gastric ulcers recurred during the trial period in 14 patients 12 on placebo, 2 on cimetidine. In 11 patients, 9 on cimetidine, 2 on placebo, the ulcers remained healed at the end of the 11-month trial period ($P<0.002$).

FIG. 1. Progress of patients in the trial.
■ Placebo group (14 patients); ▨ cimetidine group (11 patients).
S Recurrent symptomatic gastric ulcer.
A Recurrent asymptomatic gastric ulcer.
H Remains healed after 11 months.
● Recurrent symptomatic gastric and duodenal ulcers.

The timing of relapse is shown in Fig. 1. The mean time to relapse in the placebo group was 5.75 months. One patient on placebo who relapsed at 7 months had a duodenal ulcer as well as a recurrent gastric ulcer.

Return tablet counts demonstrated that both patients on cimetidine who relapsed had omitted to take the correct number of tablets.

Nine out of 11 patients on cimetidine remained free from ulcer pain during the trial as compared to 5 out of 14 patients on placebo ($P<0.05$). Cimetidine-treated patients consumed less antacid tablets throughout the trial than those treated with placebo, although the difference was not significant.

Discussion

This study, over 11 months, demonstrates that cimetidine 1 g daily significantly reduces the incidence of gastric ulcer relapse.

Twenty-two of the 25 patients who completed the study had originally healed their gastric ulcer with cimetidine before entry into this trial. Of the 11 patients whose ulcers originally healed on placebo, 2 remained healed on maintenance cimetidine and one patient relapsed on cimetidine. The risk of relapse appeared unrelated to whether the original ulcer had healed on cimetidine or placebo tablets.

In this maintenance trial the high rate of ulcer recurrence in the placebo-treated group (12 of 14 patients) suggests that the majority of patients will have recurrent gastric ulcers within 6 months of the initial healing. This is similar to the experience with cimetidine in duodenal ulceration (Haggie *et al.*, 1976; Blackwood *et al.*, 1978).

This study included a single patient with a pre-pyloric ulcer, which remained healed on cimetidine. As ulcers at this site are often, like duodenal ulcers, associated with increased gastric acid secretion, it can be argued that cimetidine might be expected to be more effective in preventing relapse of this type of ulcer. If this patient is excluded from the analysis the results remain highly significant ($P=0.002$).

In the United Kingdom, gastric ulceration is principally a disease of the elderly and the morbidity and mortality associated with complications such as haemorrhage is high. In many such patients, particularly those with intercurrent disease, ulcer surgery is also associated with significant risk (Allan and Dykes, 1976).

Maintenance treatment with cimetidine offers a safe and effective alternative to surgery in the prevention of gastric ulcer relapse and would appear to have an important role in this disease. There is, however, no evidence that prolonged treatment will alter the ulcer diathesis.

It remains to be seen whether a lower dose of cimetidine will also prove effective in preventing gastric ulcer recurrence.

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