# PAPERS AND ORIGINALS

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## Prophylactic effect of cimetidine in duodenal ulcer disease

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### Summary and conclusions

**Fifty-seven symptom-free patients with duodenal ulcer entered a double-blind trial to assess the prophylactic effect of cimetidine. Patients were randomly allocated to receive cimetidine 400 mg twice daily (29 patients) or placebo (28 patients). The trial was designed to imitate daily clinical practice, so duodenal ulcer disease was diagnosed by means of *x*-ray examination. Three patients from each group withdrew from the trial. All remaining patients continued to receive treatment for 12 months or until symptoms recurred. Three out of 26 patients suffered relapses during cimetidine treatment, compared with 20 out of 25 receiving placebo. No side effects were attributable to cimetidine. Long-term cimetidine treatment had no curative effect as relapses occurred soon after treatment was stopped. The estimated chance (cumulative remission rate ±2 SE) of remaining symptom-free 13 weeks after one year's cimetidine treatment had been completed was 47±21%.**

**Maintenance treatment with cimetidine is a suitable alternative to elective surgery in patients with duodenal ulcer subject to frequent relapses. Further study is needed to establish the optimal duration and safety of prolonged cimetidine treatment.**


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### Introduction

In most patients with active duodenal ulcer disease cimetidine treatment promotes rapid healing and relief of symptoms,[1 2] but symptoms often recur shortly after treatment is completed.[3] Patients who suffer repeated relapses may be eligible for maintenance treatment with cimetidine, but the efficacy and safety of such treatment cannot be reliably predicted. In patients with active disease the healing process may have begun before the start of treatment, and it could not be assumed that cimetidine would also effectively prevent the onset of a relapse.

Preliminary findings suggested that long-term treatment with the $H_2$-receptor antagonist metiamide reduced the relapse rate in patients with duodenal ulcer, but the results were not conclusive.[4] We therefore decided to study the relapse rate in patients with duodenal ulcer treated with cimetidine (400 mg twice daily) or placebo for one year. The trial was designed to imitate the expected future use of cimetidine in clinical practice. Consequently, a radiological diagnosis was accepted as evidence of duodenal ulcer disease and a relapse was recorded when ulcer symptoms recurred.

### Patients and methods

Patients were included in the trial if they fulfilled the following criteria. (*a*) Deformity of duodenal cap or duodenal crater shown by barium-meal examination. Patients with an ulcer in the prepyloric region of the stomach were excluded. (*b*) An episode of epigastric pain within the previous three months, but absence of pain for at least one week before entry. (*c*) No previous gastric or biliary surgery. (*d*) No clinical or biochemical evidence of renal, hepatic, or cardiac disease. Laboratory tests performed before entry included measurements of haemoglobin concentration, red and white cell counts, differential count, platelet count, serum aspartate transaminase, alkaline phosphatase, bilirubin, urate, and creatinine; urine microscopy; and analysis of urine for protein and glucose. (*e*) Informed consent. Children aged less than 16 years, and pregnant or lactating women were excluded.

Out of the 57 patients who entered the study, 38 had recently participated in a short-term trial of the therapeutic effect of cimetidine: seven had become symptom-free during placebo treatment and 31 during cimetidine treatment.[2] The remaining 19 patients had received no treatment before entering the prophylactic trial, and had been symptom-free for an average of five weeks (range 2-12 weeks).

Patients were randomly allocated to receive treatment with cimetidine (200-mg tablets) or identical inactive placebo tablets, and were instructed to take two tablets in the morning and two at bedtime, the treatment period being 12 months. No other treatment or dietary advice was given. All patients were seen at the outpatient clinic at four-week intervals and questioned about ulcer symptoms and possible side effects. Laboratory investigations were repeated, blood pressure measured, new supplies of the drug were issued, and returned tablets counted.

A relapse was recorded when a patient had suffered either moderate or severe epigastric pain on at least five days within a fortnight, or had had complications. Such patients were withdrawn from the trial and offered "open" cimetidine treatment. Treatment was stopped after 12 months if no relapse had occurred, but the patients continued to visit the outpatient department regularly, and relapses occurring in the post-trial observation period, which varied from 0 to 33 weeks, were recorded. The patients were not informed which treatment they had received during the trial. Six patients did not complete the trial: in the cimetidine group one patient developed diarrhoea, one found the four-weekly visits too time-consuming, and one feared possible side effects of the new drug; in the placebo group one patient complained of impotence, one was symptom-free and stopped taking the tablets, and one feared possible side effects. No patient had ulcer symptoms when withdrawing from the trial. The study was double-blind and the code remained closed until the last patient had completed treatment.

To use all available information, especially from the important post-trial period, the cumulative rates of continued remission were calculated with the use of life tables.[5] This method allows full use of the information from each patient until relapse, withdrawal, or last visit to the outpatient department. The standard error (SE) was calculated according to the method of Peto *et al*,[5] the remission rate ±2 SE being a rough estimate of the 95% confidence limits.

## Results

Of the 57 patients who entered the trial, 29 received cimetidine and 28 placebo. The two groups were comparable in sex ratio, age, length of history, and pretrial treatment (table I). Three patients from each group were withdrawn for the reasons mentioned above. Three of the remaining 26 patients in the cimetidine group suffered a relapse, compared with 20 of the remaining 25 patients in the placebo group

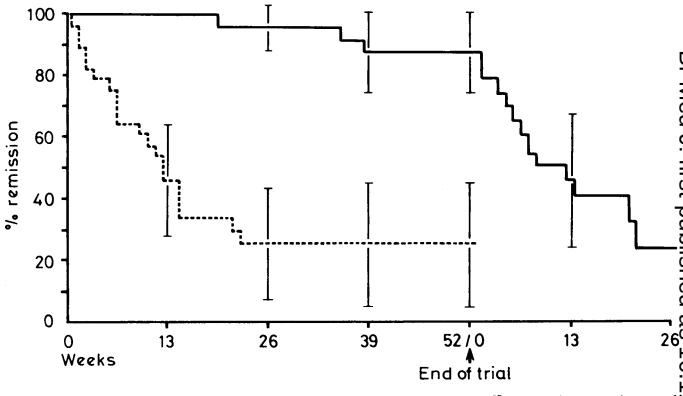
TABLE I—*Distribution of patients who received prophylactic cimetidine treatment or placebo according to age, sex, history of duodenal ulcer disease, and pretrial treatment*

| | Cimetidine group | Placebo group | Significance |
|---|---|---|---|
| Men : women | 23 : 6 | 20 : 8 | NS |
| Mean age in years (range): | | | |
| Men | 48 (20-69) | 49 (30-73) | NS |
| Women | 49 (42-56) | 48 (37-57) | NS |
| Mean length of history in years (range): | | | |
| Men | 14 (0-40) | 15 (0-40) | NS |
| Women | 13 (1-30) | 8 (1-15) | NS |
| Pretrial treatment: | | | |
| Cimetidine | 14 | 17 | NS |
| Placebo | 5 | 2 | NS |
| None | 10 | 9 | NS |

NS = Not significant (P>0·05).

TABLE II—*Retrospective analysis of factors that may have influenced outcome in patients who received cimetidine or placebo*

| Prognostic factors | Cimetidine group | | Placebo group | |
|---|---|---|---|---|
| | No of relapses | No of patients | No of relapses | No of patients |
| Sex: | | | | |
| Men | 2 | 22 | 14 | 17 |
| Women | 1 | 4 | 6 | 8 |
| Length of history: | | | | |
| <5 years | 0 | 7 | 6 | 7 |
| ≥5 years | 3 | 19 | 14 | 18 |
| Pretrial treatment: | | | | |
| Cimetidine | 2 | 14 | 12 | 16 |
| Placebo | 0 | 4 | 2 | 2 |
| None | 1 | 8 | 6 | 8 |
| Total | 3 | 26 | 20 | 25 |




Life-table analysis according to method of Peto *et al*[5] showing estimated % probability (±2 SE) of continued remission during and after cimetidine treatment for one year (solid line) and during placebo treatment for one year (broken line). Absolute numbers of patients in cimetidine group not in relapse at entry and after subsequent intervals of 13 weeks were 29, 26, 25, 23, 9, and 2. Corresponding numbers in placebo group were: 28, 13, 6, and 5.

TABLE III—*Differences in blood-pressure readings and results of laboratory investigations at beginning and end of treatment with cimetidine or placebo. Values are means*

| Variables | Cimetidine group | | | Placebo group | | |
|---|---|---|---|---|---|---|
| | Beginning | End | Difference | Beginning | End | Difference |
| Blood pressure (mm Hg)* | 98·3 | 104·2 | 5·9 | 105·1 | 107·4 | 2·3 |
| Haemoglobin (g/dl) | 14·3 | 14·8 | 0·5 | 14·3 | 14·8 | 0·5 |
| Erythrocytes (×10¹²/l) | 4·7 | 4·8 | 0·1 | 4·7 | 4·8 | 0·1 |
| Leucocytes (×10⁹/l) | 7·5 | 7·5 | 0 | 8·0 | 8·2 | 0·2 |
| Platelets (×10⁹/l) | 514 | 435 | −79 | 614 | 506 | −108 |
| Alkaline phosphatase (U/l)† | 166 | 170 | 4 | 197 | 171 | −26 |
| Aspartate transaminase (U/l)‡ | 22 | 21 | −1 | 20 | 21 | 1 |
| Serum urate (mmol/l) | 0·31 | 0·32 | 0·01 | 0·32 | 0·28 | −0·04 |
| Serum creatinine (μmol/l) | 97 | 95 | −2 | 81 | 82 | 1 |

*Mean of systolic and diastolic pressure.
†Normal range 70-271 U/l.
‡Normal range 10-40 U/l.
*Conversion: SI to traditional units*—Urate: 1 mmol/l ≈ 16·8 mg/100 ml. Creatinine: 1 μmol/l ≈ 0·01 mg/100 ml.

(Fisher's exact test, P<0·001). Retrospective analysis of possible prognostic factors showed no significant differences (table II). The patients who suffered a relapse had pain but no complications except melaena in one patient from the cimetidine group. Three patients in the cimetidine group and two patients in the placebo group had periods of slight ulcer symptoms that did not fulfil the criteria of a relapse. The remaining patients who completed 12 months' treatment remained symptom-free during the trial.

During the post-trial period 12 relapses were observed in the 23 patients who completed 12 months' cimetidine treatment. The post-trial observation period varied from 0 to 33 weeks. In all these cases the relapse manifested itself as a recurrence of pain, but no complications occurred. Only one of the five patients who completed 12 months' placebo treatment suffered a relapse in the post-trial period.

A more complete picture is obtained by a life-table analysis of all 57 patients who entered the trial (see figure). According to this analysis, which incorporates the patients who were withdrawn during the trial, the cumulative remission rate (±2 SE)—that is, the estimated probability of not developing a relapse during the 12 months—was 88±13% in the cimetidine group and 25±20% in the placebo group. All relapses in the placebo group occurred before the 23rd week of treatment, whereas the three relapses in the cimetidine group occurred after 19, 35, and 38 weeks respectively. Soon after treatment was completed several relapses occurred in the cimetidine group, and after 13 weeks the cumulative remission rate was only 47±21%. The fall in the remission rate after the 13th post-trial week could be calculated only with great uncertainty as the observation time for most of the patients was still too short. The cumulative remission rate in the placebo group fell only slightly in the post-trial period (not shown in the figure).

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Various unexpected symptoms and signs were noted in the two groups of patients (including patients who were withdrawn). One patient in the cimetidine group developed pulmonary embolism, one oedema of fingers, one presbyopia, two diarrhoea, and one arterial hypertension. Three patients in the placebo group complained of impotence, headache, and fatigue respectively. Reduced libido was reported by one patient from each group. Laboratory screening tests showed no significantly abnormal findings. Mean blood-pressure values and results of laboratory investigations at the beginning and end of treatment (after completing one year's treatment or at the time of relapse or withdrawal) are shown in table III. During the study one of the departments was moved to another hospital, where different standards were used. This might partly explain the differences in pretrial and post-trial values. The differences between cimetidine and placebo groups, however, were not significant (Mann-Whitney U tests, P ·0·05).

## Discussion

The possibility that symptomless relapse occurred in some patients and that symptomatic relapse in others was unaccompanied by renewed ulceration cannot be excluded since no patient underwent duodenoscopy. Such possible discrepancies are, however, of limited practical consequence, and we decided that it was more important to choose a design that imitated so far as possible the conditions under which cimetidine may be used in daily clinical practice. Our findings agreed with those of a similar trial conducted by Bodemar and Walan[6] in showing that maintenance treatment with cimetidine for one year is highly effective, but we also found that the treatment had no lasting effect. Soon after treatment was completed relapses occurred at about the same rate as in patients whose ulcers had healed spontaneously or during a short course of cimetidine. Wallace *et al*[7] reported severe relapses after cimetidine treatment, but we observed no such incidents in the patients who had received cimetidine for one year or in the patients in the placebo group who had received a short course of cimetidine before entering the maintenance trial. No side effects directly attributable to cimetidine were observed during the trial.

Our results suggest that maintenance treatment with cimetidine is a realistic alternative to elective surgery in patients subject to frequent relapses, but several points still need clarification. Firstly, the optimal duration of treatment is not known. Fry[8] and Greibe *et al*[9] have shown that duodenal ulcer disease often resolves after a few years, especially in patients diagnosed in general practice, but the average ulcer history of 13·5 years in our patients also shows that prolonged treatment is needed in some cases. It remains to be proved that such treatment is safe and that patients do not acquire tolerance to cimetidine with time, though limited experience in cases of the Zollinger-Ellison syndrome suggests that this is unlikely.[10]

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Requests for reprints should be addressed to Dr H R Wulff.

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# Prolongation and enhancement of serum methotrexate concentrations by probenecid

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## Summary and conclusions

**The disappearance of methotrexate (MTX) from the serum after an intravenous bolus injection and intravenous infusion was studied over 24 hours in eight and four patients respectively. Probenecid given at the same time as the bolus injection delayed the disappearance of MTX from the serum and resulted in enhanced concentrations throughout the 24 hours studied. At 24 hours the mean concentration was four times higher than in patients not given probenecid. Overall serum concentrations were even greater than those in patients who had received MTX by intravenous infusion.**

**We suggest that smaller doses of MTX may be given and treatment costs thereby reduced if probenecid is given in addition.**

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## Introduction

Methotrexate (MTX) has been successfully used in various neoplastic diseases, and knowledge of its pharmacokinetics and metabolism has allowed it to be used at high doses when followed by folinic acid rescue.[1] MTX disappears rapidly from the blood, so that high concentrations are maintained for only short periods, even after high doses.[2] Since its rapid excretion

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