PAPERS AND SHORT REPORTS

Does treatment with cimetidine extended beyond initial healing of duodenal ulcer reduce the subsequent relapse rate?

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Abstract

Cimetidine 1 g daily is often continued for a fixed period beyond the time of healing of duodenal ulcer on the assumption that it might reduce the subsequent relapse rate. To test this, 194 patients whose ulcers had healed after one month of cimetidine 1 g daily were allocated at random to three groups for further treatment with cimetidine 1 g daily for two months ($n=63$) or five months ($n=66$) or placebo ($n=65$). Thereafter all patients received placebo. Endoscopy was done routinely every three months, or earlier if symptoms recurred. During follow-up in the placebo phase, which lasted for up to 25 months, the estimated total proportions of patients in the three groups with symptomatic recurrences of ulcer were 80%, 90%, and 77%, respectively; the corresponding proportions with silent plus symptomatic relapses were 92%, 90%, and 100%. The relapse rates were also similar in all three groups. Statistical analysis showed a significant variation in relapse rate but the differences were regarded as clinically unimportant.

These findings show that full-dose cimetidine continued for several months beyond the time of healing of duodenal ulcer does not decrease the risk of subsequent relapse.

Introduction

Three treatment regimens with cimetidine are used in the longer term management of duodenal ulcer *after* healing. The first is long-term, low-dose maintenance treatment to prevent relapse¹;

the second is intermittent treatment, in which symptomatic attacks are treated with a short course of cimetidine²; and the third is extended "full-dose" treatment. The rationale of this last approach is that by extending treatment after healing the course of the disease might be changed, resulting in a reduced relapse rate when the drug is stopped. This method would avoid the disadvantages of the other two—namely, that a quarter of patients are unsuitable for intermittent treatment (for reasons such as risk of haemorrhage or perforation in the elderly) and that prolonged maintenance treatment over several years (the effectiveness and safety of which remain to be established) can be avoided.

Extended full-dose treatment is commonly used in practice but the value of the policy had not been investigated. We therefore undertook such a study.

Patients and methods

The study was approved by the ethical committee of the Rotherham Area Health Authority. Patients with duodenal ulcer proved by endoscopy and who had not received cimetidine within the past six months were eligible for the study, which lasted from September 1977 until February 1980. They were treated with cimetidine 1 g daily (three doses of 200 mg during the day, one of 400 mg at night) for one month; unmarked 200 mg tablets were used. Those who healed were entered into the second phase of the study. Healing was defined as the complete disappearance of the ulcer(s) and erosions and their replacement by intact mucosa which was normal or inflamed on endoscopy.

The second phase lasted five months and was double blind. Patients were allocated at random to treatment with either cimetidine 1 g daily for five months, cimetidine 1 g daily for two months followed by placebo for three months, or placebo for five months. They were seen for interview after two months and again at five months. Those who did not have a symptomatic recurrence were entered into the third phase, in which all patients received "single-blind" treatment with placebo. This lasted for a maximum of 25 months. Endoscopy and interview were performed at the end of the second phase and then every three months in the third phase (if asymptomatic) to detect silent recurrence of ulceration or whenever symptoms arose. Recurrence was defined as the return of an ulcer(s) or erosions or both, with or without symptoms.

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At each interview the prescription was renewed and the pharmacy counted returned tablets. All patients were supplied with antacid tablets (magnesium trisilicate *BPC*) to relieve trivial symptoms. At every visit the patients were reminded to contact the clinician (KDB) immediately if there was any increase in or recurrence of symptoms. Because of the possibility that some patients would not follow these instructions and go on to develop severe symptoms, or suffer these when away from the area, all were given a sealed reserve supply of cimetidine (Tagamet) for emergency use. Again it was emphasised that should they need to use the reserve cimetidine they were to report back as soon as possible. Only one patient failed to do so.

Thus we compared the relapse rate of duodenal ulcer, both symptomatic and silent, of three groups of patients during placebo treatment who had healed within one month with cimetidine and in total had received either one, three, or six months of cimetidine.

Statistics—Comparability of the three age groups of patients was assessed by analysis of variance (for age and duration of symptoms) and by χ^2 tests (for sex distribution and smoking). Discriminant analysis was used to verify the results by examining whether it was possible to discriminate between the three groups on the basis of these four variables. The incidence and rates of relapse were assessed with Gehan's modified Wilcoxon test,³ the groups being tested in pairs. The probability of relapse in any month was estimated by life-table analysis.⁴

Results

Out of 248 patients given cimetidine 1 g daily for duodenal ulcer, 194 (78%) were healed within one month. These patients were therefore allocated at random to the three groups for double-blind treatment. Table I shows the comparability of the groups. The groups were similar in all but mean age, which was significantly higher in the group allocated to cimetidine for a further two months.

Fifteen patients were withdrawn during the second phase for various reasons (table I). The remaining 179 patients, including five who were found to have a silent relapse at the end of six months of cimetidine (table II), entered the third (placebo) phase.

Table III shows the estimated probabilities of and median times to relapse during the placebo phase, and figs 1 and 2 show the estimated rates of relapse. The probability and rate of relapse, both symptomatic and silent plus symptomatic, were similar in each of the three groups of patients. The symptomatic relapse rate was highest in the first six months and then decreased noticeably (fig 1). At six months about half the patients were likely to relapse, at 12 months about a further quarter might be affected, but over the next year only a further 10% would be expected to have a recurrence. Adding silent relapse to the

TABLE I—Comparability of treatment groups

	Total duration of cimetidine 1 g/day		
	1 Month	3 Months	6 Months
No of patients at entry	65	63	66
Mean age (years)	45.4	52.4*	47.4
Duration of symptoms (years)	12.4	13.2	12.0
No (%) of men	52 (80)	50 (79)	49 (74)
No (%) of smokers	48 (74)	50 (79)	43 (65)
No withdrawn during second phase†	4	2	9

*Compared with other two groups $p < 0.01$.

†Reasons for withdrawal: poor compliance (5), pregnancy (1), severe facial herpes zoster (1), defaulted (4), symptomatic relapse during cimetidine (4).

TABLE II—Relapse during cimetidine 1 g/day in second (double-blind) phase after three and six months of treatment

	Total duration of cimetidine 1 g/day	
	3 Months	6 Months
No beginning treatment	63	66
No (%) with symptomatic relapse*	1 (1.6)	3 (4.5)
No (%) with silent relapse	0	5 (7.6)†
Total (%)	1 (1.6)	8 (12.1)

*Patients with symptomatic relapse withdrawn from trial.

†Patients with silent relapse (detected at routine endoscopy at end of cimetidine treatment) continued trial and entered third (placebo) phase. They were followed up till symptoms occurred. Their data were used in calculating later incidence of symptomatic relapse during placebo but not of silent relapse.

TABLE III—Estimated proportions of relapses and median times to relapse during placebo phase

Total duration of treatment with cimetidine	Symptomatic relapse		Silent plus symptomatic relapse	
	% Incidence	Median time (months)	% Incidence	Median time (months)
1 Month (n = 61)	77	6.3	100	5.5
3 Months (n = 61)	80	5.5	92	3.5
6 Months (n = 57)	90	5.0	90*	3.9

*Fifty-two patients included in analysis (see footnote to table II).

Incidence of silent plus symptomatic relapse in patients after cimetidine for one month significantly different from that after cimetidine for three months (Gehan test: silent plus symptomatic relapse $Z = 2.0806$; $p = 0.038$).

FIG 1—Estimated probability of symptomatic relapse during placebo treatment.

FIG 2—Estimated probability of symptomatic plus silent relapse during placebo treatment.

symptomatic ones (fig 2) made this pattern even more pronounced; at six months two-thirds of patients were likely to relapse, at 12 months about a further fifth, and during the succeeding year about an additional 10% of patients might relapse.

Statistical analysis of the rates and incidence of relapse, considering symptomatic and silent plus symptomatic relapse separately, showed a significant difference when the groups given cimetidine for a total of one month and three months were compared for silent plus symptomatic relapse (Gehan test: $Z = 2.0806$; $p = 0.038$). None of the other five comparisons approached statistical significance. Figure 2 shows the reason for this difference: in the first half-year of the placebo phase the rate of relapse in the group given cimetidine for a total of three months was more rapid than in the group who had been given cimetidine for only one month.

Of the patients who relapsed, two-thirds had symptoms, most of whom had an ulcer. Of those who relapsed silently, however, only half had an ulcer; the remainder had erosions only (table IV).

Adverse events during cimetidine treatment were uncommon. One

TABLE IV—Relation between first recurrence of lesions and symptoms during placebo treatment

	Erosions only	Ulcer with or without erosions	Total
Symptomatic relapse	9%	55%	64%
Silent relapse	18%	18%	36%

man noticed soreness of the breast two months after beginning cimetidine; this cleared spontaneously despite continued treatment. A second patient reported excessive sweating, which he associated with cimetidine treatment, and another complained of arthralgia while taking the drug.

Discussion

Our study shows that after healing of duodenal ulcer relapse is uncommon when cimetidine 1 g daily is continued but that once treatment is stopped there is a high relapse rate, which is not affected by previous treatment of up to six months' duration.

There was a significantly faster relapse rate after treatment with cimetidine for three months than for one month (fig 2) but we do not regard this as clinically important: we should have expected the reverse if cimetidine favourably influenced the outcome. "Rebound" is unlikely to be the cause of the greater relapse rate, for otherwise we should have expected the highest rate in the group treated for six months.

When we began this study information about the duration of cimetidine treatment and its effect on subsequent relapse rate was not available. Later two reports indicated that the relapse rate and severity of the disease were reduced after treatment for one year with cimetidine 400 mg nightly⁵ or 800 mg daily.⁶ Other investigators using cimetidine in doses of 400 mg to 1 g daily for three to 12 months, however, failed to show such benefit.⁷⁻¹⁶ Some of these studies comprised only a small number of patients; because this may produce misleading results¹⁷⁻¹⁹ we persevered with our investigation. Though it seems unlikely in retrospect that such treatment could influence the long-term outcome of a chronic relapsing disease, there are reports that short-term treatment with other drugs might have just such an effect—colloidal bismuth,²⁰ carbenoxolone,²¹ acetazolamide,²² proglumide,²³ trithiozine,^{24 25} and an antacid-anticholinergic combination²⁶; indeed, healing on placebo is followed by a lower relapse rate than healing with cimetidine.^{1 16} It was suggested that this last phenomenon might have been due to milder disease in those who healed spontaneously. A few patients relapse soon after stopping cimetidine but there is no evidence that the relapse rate is increased after cimetidine.

The high early symptomatic relapse rate after stopping cimetidine and the subsequent decrease agrees with other reports,^{1 9 11} including an earlier study from Rotherham²⁷; however, some investigators have observed a more uniform rate of relapse.¹⁶ We also obtained an assessment of the true (silent plus symptomatic) ulcer relapse rate; the early relapse rate was even higher, suggesting that silent relapse may precede the development of symptoms. In some patients with a silent ulcer who nevertheless continued with placebo, this is indeed what we observed.

An additional observation is that patients with a silent relapse stand an equal chance of having erosions only as opposed to an ulcer. The appearance of symptoms, however, generally indicates an ulcer.

Extending full-dose cimetidine beyond the time of healing of duodenal ulcer does not reduce the subsequent relapse rate, nor does it postpone the interval until relapse. Its only value is in patients selected for operation, for it keeps them in remission until then. As a routine measure in patients with ulcer such a policy confers no lasting advantage. Nevertheless, it remains to be seen whether very long-term treatment—say, for several years—can alter the outcome.

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