

significant prolongation of heterotopic heart allograft survival across a strong histocompatibility barrier ($\text{AgB}^2 \rightarrow \text{AgB}^1$) resulted. Urine dialysate from the same patient six days after niridazole was withdrawn failed to prolong heart allograft survival.

To avoid graft rejection high concentrations of circulating immunosuppressive drugs or drug metabolites should preferably be established in the recipient's blood by the time of operation since the process of allograft rejection begins when the graft circulation is restored. Our results suggest that the addition of niridazole to the more usual immunosuppressive regimen of azathioprine and prednisolone ensures the presence of high concentrations of such factors within 24 hours of starting treatment. A much slower accumulation of immunosuppressive factors occurs when niridazole is omitted.

The immunosuppressive potential of niridazole has received attention only recently. We⁸ and others⁹ have shown that the parent compound has no immunosuppressive activity in vitro, whereas metabolites present in serum and urine from animals treated with niridazole are potent inhibitors of lymphokine production by antigen-sensitised lymphocytes⁹ and of the human MLR,⁸ and appear to act early in the antigen-recognition phase of the in-vitro reaction.^{8, 10} While niridazole is rapidly broken down in vivo, its metabolites have a half-life of about 40 hours,¹¹ which we believe justified our use of alternate-day treatment in kidney-graft recipients. Toxic side effects prevent

the prolonged use of niridazole,¹² and we wished to identify the active metabolite(s) in the hope that these would be free from harmful side effects and might be given to transplant recipients for prolonged periods.

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Cimetidine in patients with gastric ulcer: a multicentre controlled trial

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Summary

Forty-five adult outpatients with endoscopically confirmed gastric ulceration completed a double-blind trial of either cimetidine (1 g/day) or placebo. After six weeks 18 of the 23 patients receiving cimetidine showed complete ulcer healing compared with only six of the 22 patients receiving placebo. The cimetidine group also had fewer days with pain than the placebo group but the difference was not statistically significant.

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Cimetidine therefore seems to promote healing of gastric ulcers without severe side effects, although its effect on pain is less pronounced than in patients with duodenal ulcers.

Introduction

The therapeutic effect of the histamine H₂ receptor antagonist cimetidine in duodenal ulcer is now well established,¹⁻³ whereas the drug's effect on gastric ulcer has received less attention. One early trial showed that cimetidine promoted ulcer healing,⁴ and two preliminary studies supported this finding, although the results were not conclusive.^{5, 6} We present here the results of a double-blind study set up to assess the therapeutic efficacy of oral cimetidine, 1 g/day, compared with placebo in the short-term treatment of gastric ulcer.

Patients and methods

Fifty-one consecutive outpatients (18 women and 33 men) who fulfilled the following entry criteria were admitted to the trial. Firstly, a gastric ulcer had been seen at gastroscopy not more than seven days before start of treatment. All craters located above the pylorus were regarded as gastric ulcers, whereas craters in the pyloric canal were excluded. Secondly, no patient had had gastric surgery. Thirdly, there was no clinical or biochemical evidence of renal, hepatic, or cardiac disease (the laboratory investigations before entry included haemoglobin measurement; white and red blood counts; differential count; platelet count; estimation of serum aspartate aminotransferase, alkaline phosphatase, bilirubin, and creatinine

concentrations; and urine microscopy and analysis for protein and glucose.) Finally, all patients gave their informed consent. Children below 16 years of age and pregnant or lactating women were not included.

All treatment for ulcers other than antacids was withdrawn. At gastroscopy we had distinguished between corpus ulcers (at or above the angulus) and prepyloric ulcers (below the angulus). Multiple biopsy specimens were taken to exclude malignancy.

The patients were treated for six weeks, and they visited hospital every two weeks. They were randomly allocated to treatment with cimetidine (200-mg tablets) or placebo (inactive tablets identical in appearance) and were instructed to take one tablet three times a day after meals and two tablets at bedtime. The patients were issued with diary cards and instructed to record when they felt pain. They were given a supply of commercial antacid tablets (containing 180 mg colloidal aluminium hydroxide and 60 mg magnesium hydroxide at one centre and 400 mg dihydroxy aluminium sodium carbonate at the other centres). At each visit the diary cards were reviewed, unexpected symptoms were recorded, and laboratory tests were repeated. Unused antacid tablets were counted. Gastroscopy was repeated within five days after treatment had stopped to ascertain whether or not the ulcer had healed.

Results

Six patients did not complete the trial. A man receiving cimetidine was referred for surgical treatment after 18 days because of continuing severe pain, and a man in the placebo group was treated surgically as the biopsy specimens from the ulcer showed an adenocarcinoma. A man in the cimetidine group, who was known to have arteriosclerosis of the legs, was admitted to another hospital because of incipient gangrene of two toes. Another man receiving cimetidine developed a raised serum bilirubin concentration (3.6 mg/100 ml) and slightly raised alkaline phosphatase concentration while the aminotransferase level remained normal. Treatment was stopped and the blood values returned to normal. Cholecystography showed nothing abnormal. A woman in the cimetidine group claimed that the tablets caused constipation and withdrew from the trial, and a man in the placebo group was sent to prison.

Of the remaining 45 patients who completed the trial, 23 received cimetidine and 22 placebo. Table I shows that the cimetidine group had a shorter average history of ulcer and a greater proportion of women than the placebo group.

ULCER HEALING

The ulcers healed completely in 24 patients: 18 (78%) of the 23 patients receiving cimetidine and in six (27%) of the 22 patients from the placebo group (Fisher's exact test; $P < 0.002$). Thus the

TABLE I—Comparison of cimetidine and placebo groups

	Cimetidine group	Placebo group	Significance
Sex ratio M : F	11 : 12	17 : 5	NS*
Ratio of prepyloric to corpus ulcers	13 : 10	12 : 10	NS*
Mean age in years (range)	56.7 (32-77)	56.3 (35-77)	NS†
Mean length of history in years (range)	5.6 (0-23)	10.8 (0-26)	$P < 0.05+$

NS = Not significant. *Fisher's exact test. †Mann-Whitney test.

TABLE II—Therapeutic gain—that is, difference between healing rates in cimetidine group and placebo group—in various subgroups of patients

Subgroup	No of patients	Therapeutic gain (%)	Significance*
Sex:			
Women	17	18	NS
Men	28	76	$P < 0.002$
Type of ulcer:			
Prepyloric	25	44	NS
Corpus	20	60	$P < 0.05$
Length of history of ulcer:			
< 6 years	20	48	NS
≥ 6 years	25	53	$P < 0.05$

*Fisher's test was used to test significance of therapeutic gain in each subgroup.

therapeutic gain—that is, the difference between the healing rates in the two groups—was 51% and the 95% confidence interval of this difference was 25-77%.

The result was slightly biased by the patient from the cimetidine group who was referred for surgery before completing the trial, as this patient's ulcer would probably not have healed during continued treatment. When this patient was included among those with unhealed ulcers the therapeutic gain was 48% (95% confidence limits 22-74%) and the result was still significant ($P < 0.01$).

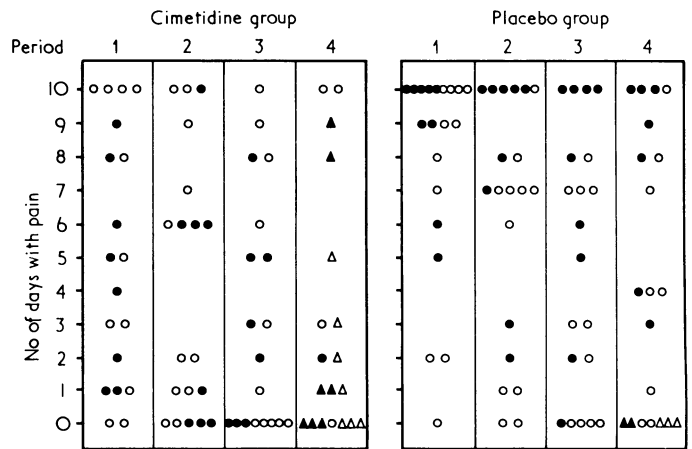
The total group of patients was subdivided according to sex, site of ulcer, and length of history of ulcer, and the therapeutic gain in each subgroup is shown in table II.

ULCER PAIN

The six-week treatment period was divided into four 10-day periods, omitting the day when treatment was started and the last day of treatment. The number of days with pain in each of these periods is shown in the figure. Four symptom-free patients—that is, patients who had had no symptoms during the week preceding the trial—and two patients who did not fill in the diary cards (one from the cimetidine group and one from the placebo group) were not included in these calculations.

The mean number of days with pain during the whole treatment period was 15.2 in the cimetidine group and 23.3 in the placebo group. This difference was not statistically significant (Mann-Whitney test; $P = 0.05$). A significant effect was observed only in the subgroup of patients with corpus ulcers, who had on average 13.6 days with pain in the cimetidine group and 29.3 in the placebo group ($P < 0.05$). In the patients with prepyloric ulcers the difference was much smaller—16.3 days in the cimetidine group and 18.4 in the placebo group. The figure also shows that some patients in the cimetidine group continued to suffer pain although the ulcer had healed completely endoscopically.

Patients in the placebo group took significantly more antacids than those in the cimetidine group (53 tablets in six weeks compared with 26 tablets in six weeks) ($P < 0.05$).



Number of days with pain during cimetidine or placebo treatment in four 10-day periods (2nd-11th day, 12th-21st day, 22nd-31st day, and 32nd-41st day of treatment).

●—Patients with corpus ulcers. ○—Patients with prepyloric ulcers. ▲ or △ in fourth period indicate that corpus or prepyloric ulcer had healed completely at endoscopy.

UNEXPECTED SYMPTOMS AND LABORATORY FINDINGS

The following unexpected symptoms and laboratory findings were noted in the patients who completed the trial: headache (in 2 patients on cimetidine and 1 on placebo); dizziness (2 on cimetidine, 1 on placebo); palpitations (1 on placebo); muscle pain (1 on placebo); transient itch (1 on cimetidine); transient rash (1 on placebo); transient increase in alkaline phosphatase (1 on cimetidine, 1 on placebo); marginally increased alkaline phosphatase (1 on cimetidine). The mean serum creatinine concentration did not increase significantly in the cimetidine group during treatment, and no patient developed an abnormal serum creatinine concentration.

Discussion

This trial showed that six weeks' treatment with cimetidine 1 g/day greatly enhanced the healing of gastric ulcers. The effect on the ulcer pain, however, was less pronounced than in the duodenal ulcer trials,³ and there was little correlation between ulcer healing and symptomatic relief in the cimetidine group.

We used a simple anatomical definition of gastric ulcer, as all ulcers located above the pylorus were included. Prepyloric ulcers are often, like duodenal ulcers, associated with an increased gastric acid production, and cimetidine might be expected to be more effective for treating this type of ulcer than for treating corpus ulcers. This trial showed the opposite trend as regards both ulcer healing and symptomatic relief, but there were too few patients to provide conclusive results. Further studies are needed to elucidate this problem.

The random allocation of the patients to the two treatments resulted in the patients in the cimetidine group including a greater proportion of women and having a shorter average ulcer history than those in the placebo group. The possible influence of this uneven distribution of the patients on the result of the trial must be considered. A retrospective stratification showed that cimetidine had less effect in women than in men and that it had almost equal effects in patients with short and long histories. We therefore concluded that the randomisation did not bias our results in favour of cimetidine.

As in previous trials, there were no serious untoward effects of cimetidine. The unexpected symptoms noticed by some patients did not differ from those usually encountered in controlled trials and cannot be ascribed to cimetidine. One patient was withdrawn from the trial because of transient hyperbilirubinaemia, which may have been caused by the treatment.

Carbenoxolone promotes the healing of gastric ulcers, and we

considered comparing cimetidine and carbenoxolone rather than cimetidine and placebo. We chose the latter design because of the frequent side effects of carbenoxolone.⁸ Carbenoxolone is not registered in Denmark and therefore we did not deprive the patients in the placebo group of an effective treatment in current use. Nevertheless, comparative studies of carbenoxolone and cimetidine are needed as it cannot be taken for granted that the two drugs are equally effective in the same subgroups of patients with gastric ulcer.

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Kinetics of indium-111 labelled lymphocytes in normal subjects and patients with Hodgkin's disease

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Summary

The distribution in the body and the circulation in the blood of autologous lymphocytes labelled with indium-111 were studied in two normal subjects and two patients with Hodgkin's disease. Four hours after injection radioactivity was identified in the spleen, liver, and bone marrow. Radioactivity, followed by imaging and whole body scanning, began to appear in the lymph nodes four to 18 hours after injection, and some, though not all, lymph node groups in the body could be readily visualised. There were no differences between the normal subjects and the patients with Hodgkin's disease. The pattern of

clearance of radioactivity from the blood was consistent with a normal circulation between blood and lymphoid tissues of the labelled lymphocytes.

Since indium-111 stays firmly attached to the cell, it seems an ideal label for studying lymphocyte kinetics, and the use of this technique may have further clinical applications.

Introduction

Studies on the circulation and distribution of lymphocytes in man have been limited by lack of a suitable isotopic label. The ideal label would remain firmly attached to the cell and permit the distribution of radioactivity in the body to be detected for at least two days. Recent results using ¹¹¹In-oxine as a lymphocyte label¹ suggest that it may satisfy these criteria. In this preliminary study we followed the distribution of ¹¹¹In-labelled autologous lymphocytes in two normal subjects and two patients with early Hodgkin's disease. Our results suggest that this lymphocyte label is suitable for further clinical studies in man.

Methods

Two patients with Hodgkin's disease were studied shortly after diagnosis. After subsequent staging laparotomies one proved to have

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