Clinical trials

Effect of long-term cimetidine on gastric acid secretion, serum gastrin, and gastric emptying

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SUMMARY Gastric acid secretion, gastric emptying, fasting serum gastrin and the serum gastrin response to a meal were measured in duodenal ulcer patients before, and at least five days after completing prolonged treatment with cimetidine (1 or 2 g/day for four or eight weeks followed by 600 mg twice daily for six months). Fasting serum gastrin and the gastrin response were also measured during treatment. Compared with pretreatment values, fasting serum gastrin concentrations were raised both during and five to 31 days after stopping treatment ($P \leq 0.02$). The integrated gastrin response and the rate of gastric emptying of the solid component of the meal were increased during treatment ($P < 0.001$ and $P < 0.02$ respectively) but returned to pretreatment levels after stopping therapy. No significant changes were observed in the basal or maximal acid outputs or the rate of emptying of the liquid component of the meal. The results imply that the hypergastrinaemia associated with long-term cimetidine therapy does not result in increased gastric acid secretion.

The effects of a single dose of the histamine H_2 -receptor antagonist cimetidine on gastric secretion, fasting gastrin concentrations, the serum gastrin response to a meal, and gastric emptying are well established (Heading *et al.*, 1977; Richardson, 1978). The effects of short courses of treatment on gastric secretion and basal gastrin concentrations have also been described (Bank *et al.*, 1977; Holden *et al.*, 1977; Sewing *et al.*, 1978; Winship, 1978), but information on the effects of long-term therapy is limited (Spence *et al.*, 1977; Bodemar and Walan, 1978). We have therefore examined the effect of long-term cimetidine therapy (1 or 2 g/day for four or eight weeks followed by 600 mg twice daily for six months) on gastric acid secretion, fasting gastrin concentrations, the serum gastrin response to a meal, and gastric emptying rates.

Methods

After endoscopic confirmation of an active duodenal ulcer, patients were entered into the study provided that they had not previously been treated with cimetidine. Gastric acid secretion, fasting serum gastrin concentration, the serum gastrin response to a standard meal, and gastric emptying rates of both liquid and solid components of the meal were

assessed, all drugs being stopped a minimum of 48 hours beforehand. Patients were then treated with cimetidine (1 or 2 g daily in divided doses) for four or eight weeks until there was endoscopic evidence that the ulcer had healed. They then received 600 mg of cimetidine twice daily for six months. The fasting gastrin, the gastrin response to the meal, and gastric emptying studies were repeated after three months' treatment with 600 mg twice daily, while the patients were still taking the drug. These began one to two hours after the patient had taken the 600 mg morning dose of cimetidine. All studies were repeated at least five days after completion of therapy with 600 mg twice daily.

GASTRIC ACID SECRETION

After an overnight fast, a size 14 Ryle's tube was passed and its position in the stomach checked by means of a water recovery test. Basal acid output (BAO) was measured over one hour and after the subcutaneous injection of pentagastrin (6 $\mu\text{g/kg}$ bodyweight), the maximal acid output (MAO) was determined over the subsequent hour.

SERUM GASTRIN AND GASTRIC EMPTYING STUDIES

These were carried out simultaneously. After an overnight fast, two blood samples were taken 15 minutes apart for measurement of fasting serum

gastrin concentrations. The patient then ate a meal consisting of Carnation breakfast food, milk, biscuits, and cheese (50 g protein, 55 g carbohydrate, and 40 g fat) containing indium-113m diethylenetriaminepenta-acetic acid as a radioactive marker of the liquid component and approximately 30 small paper particles labelled with 99m-technetium sulphur colloid as a marker of the solid component of the meal. Gastric emptying rates of the two markers were then determined by a scintigraphic method (Heading *et al.*, 1976). The emptying rate of the liquid marker was expressed as an emptying half-time ($T_{1/2}$); solid marker emptying being expressed as a zero order rate constant (% technetium emptied per minute) as it approximates more closely to a linear function with time than to an exponential (Heading *et al.*, 1976).

Blood samples for serum gastrin measurements were taken at intervals for three hours after meal ingestion and stored at -40°C until assayed in duplicate by radioimmunoassay. All the samples obtained from each patient's three studies were measured in the same batch. The specificity and accuracy of the assay were as previously described (Heading *et al.*, 1977).

Statistical analyses were performed using Wilcoxon's paired signed rank tests.

Results

GASTRIC ACID SECRETION

The BAO and MAO before starting treatment and a mean of 11.4 days (range: 6-28 days) after completing treatment are shown in Table 1. Although the median BAO and MAO were increased by 28% and 8% respectively after completing treatment, the changes were not statistically significant. There was no correlation between individual changes in BAO and MAO and the number of days after stopping the drug on which the second test was performed.

Table 1 Gastric acid secretion in 22 duodenal ulcer patients before and after cimetidine therapy

	Acid output (mmol h^{-1})	
	Basal	Maximal
Before treatment	2.72	30.4
After treatment	3.49	32.7

Results are medians.

SERUM GASTRIN STUDIES

In comparison with pretreatment values, fasting gastrin concentrations were increased by 26% while patients were on treatment ($P < 0.01$) and by 21% a mean of 13.8 days (range: 5-31 days) after stopping

Table 2 Effects of cimetidine on basal serum gastrin concentrations and on the 150-minute integrated gastrin response (IGR) to a meal in 17 duodenal ulcer patients

	Basal serum gastrin conc. (pg h ml^{-1})	IGR ($\text{pg h}^{-1} \text{ ml}^{-1}$)
Before treatment	53.5	228.6
During treatment	67.5	580.8
After treatment	65.0	291.6

Results are medians.

Figure Serum gastrin concentrations expressed as % of mean basal concentrations in 17 duodenal ulcer patients given the standard meal. Bars are ± 1 S.E. $\bullet$ — $\bullet$ Before cimetidine. $\blacksquare$ — $\blacksquare$ After three months of cimetidine. $\blacktriangle$ — $\blacktriangle$ Five to 31 days after stopping cimetidine after six months' treatment.

therapy ($P = 0.02$) (Table 2). Higher concentrations were observed in 16 of the 17 patients during treatment and in 13 of the 17 patients after treatment. The serum gastrin response to the standard meal is shown in the Figure and the 150-minute integrated gastrin response (IGR) in Table 2. Compared with pretreatment values, the IGR was increased by 154% ($P < 0.001$) while on treatment with a return to pretreatment levels after completion of treatment. There were no correlations between the pretreatment BAO or MAO and the percentage rise in the IGR during therapy ($r = 0.11$ and 0.02 ; $P > 0.1$). There was no correlation between the individual changes in IGR before and after stopping treatment and the number of days after stopping the drug on which the test was performed.

GASTRIC EMPTYING

During treatment, there was a 77% increase in the

rate of emptying of the solid marker in the meal ($P < 0.02$) (Table 3); this returning to pretreatment levels after completion of therapy. There was no significant change in the emptying of the liquid marker.

Table 3 Effects of cimetidine on gastric emptying rates of indium-113m (liquid marker) and 99m-technetium (solid marker) in 16 duodenal ulcer patients

	Indium $T\frac{1}{2}$ (min)	% Technetium emptied min^{-1}
Before treatment	57.9	0.13
During treatment	61.5	0.23
After treatment	51.4	0.19

Results are medians.

Discussion

We have previously shown that a single dose of cimetidine given to normal subjects does not alter gastric emptying of either the liquid or solid components of a meal (Heading *et al.*, 1977). Although the present results show increases in mean gastric emptying rates for both components of the meal during and after completion of cimetidine therapy, the only significant change was observed in the rate of emptying of the solid component during therapy. As acid is an inhibitor of gastric emptying (Hunt and Knox, 1972), its inhibition during cimetidine therapy may result in a differential effect on the rate of emptying of the two components of the meal.

It has previously been reported that fasting serum gastrin levels are unaffected by a single dose of cimetidine (Richardson, 1978). After a short course of the drug, one investigator has reported no change in fasting gastrin levels (Bank *et al.*, 1977), and another an increase (Sewing *et al.*, 1978). We have found a significant rise in fasting serum gastrin concentrations during treatment and also after completion of six months' treatment. However, the changes were small and seem unlikely to have clinical relevance.

The demonstrations that the integrated gastrin response to a meal is enhanced by single doses of cimetidine (Heading *et al.*, 1977; Richardson, 1978) has led to concern that prolonged therapy might cause parietal cell hyperplasia and a rebound in gastric acid secretion above pretreatment levels when therapy is stopped. Our present results confirm that the IGR to food is enhanced while the drug is being given but indicate that the response returns quickly to normal when the drug is withdrawn. Basal and maximal acid secretion rates after treatment are, however, no different from values before treatment,

indicating that the hypergastrinaemia has not resulted in an increase in the parietal cell mass.

Our results of acid secretion are in agreement with those of Bodemar and Walan (1978) who found that when cimetidine was stopped there was no increase in gastric acid output over pretreatment levels. Their estimations of acid output, however, were carried out only two days after stopping therapy. The interval between withdrawal of therapy and our measurements of acid secretion approximates much more closely to the reported interval between withdrawal of therapy and severe recurrent duodenal ulceration (Wallace *et al.*, 1977). Thus, although treatment with cimetidine is associated with a hypergastrinaemia, there is no excessive rebound in acid secretion after withdrawal of the drug and recurrence of duodenal ulceration at this time cannot be due to this mechanism.

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