

Effect of cimetidine on 24-hour intragastric acidity in normal subjects

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SUMMARY The effect of H₂-receptor blockade on intragastric acidity was studied in nine normal males. The pH of their gastric contents was measured at hourly daytime and two hourly night-time intervals for 48 hours. The subjects ate identical meals, drank identical volumes of fluid, and smoked the same number of cigarettes during the two study days. Their physical activity was unrestricted in a ward environment. Blood cimetidine and plasma gastrin were measured in serial blood samples. The nine subjects were treated in random sequence with cimetidine 0.8-1.0 g on one day and placebo capsules on the other. The drug was given in four divided doses: four subjects received it before, and five after, the three main meals. All took the fourth dose at bedtime. Replicate studies in an additional subject given placebo on both study days showed good reproducibility ($r = 0.80$, $P < 0.01$). Cimetidine therapy decreased intragastric acidity in all nine subjects. The decrease was similar in the two groups taking the drug before or after meals, mean 24 h intragastric hydrogen ion activity being lowered by 70 and 72% respectively. Nocturnal anacidity was recorded in only two of 45 samples. Administration of cimetidine before meals produced earlier and higher drug blood levels than post-prandial medication, but when it was taken after food the blood levels were highest at the time when the buffer capacity of the food was waning. Blood concentrations of cimetidine exceeded the secretory IC₅₀ level for most of the time between doses. The results show that cimetidine 0.8-1.0 g/day in four divided doses produces a striking and consistent decrease of intragastric acidity. Although variation in the timing of the dose in relation to meals did not affect the decrease of acidity, the absorption data suggest that patients should take the drug after meals.

Cimetidine is a new histamine H₂-receptor antagonist, which in man has a potency similar to metiamide for the inhibition of acid secretion stimulated by pentagastrin or food (Black *et al.*, 1972; Black *et al.*, 1973; Mainardi *et al.*, 1974; Brimblecombe *et al.*, 1975; Burland *et al.*, 1975; Pounder *et al.*, 1975a; Henn *et al.*, 1975; Richardson and Fordtran, 1975; Richardson *et al.*, 1975).

The thiourea residue in metiamide, which is thought to have been responsible for the reversible marrow depression that occurred in seven patients receiving the drug, has been replaced by a cyanoguanidine moiety in cimetidine.

In order to determine the optimal time of medication before starting clinical trials of the new com-

pound, we have studied the effect of oral cimetidine on the intragastric acidity of fully ambulant normal subjects eating a normal diet, under conditions similar to ordinary daily activity.

Methods

Ten normal male volunteers were admitted for 48 h to an especially allocated hospital ward at 7 a.m. after an overnight fast. A 10 FR nasogastric tube was positioned under x-ray control so that the tip was in the most dependent part of the stomach. The subjects ate identical meals, consumed the same volume of identical fluids, and smoked the same number of cigarettes at the same times on both days of the study (Table 1). The menu was settled by prior discussion with the subjects, to ensure that it was palatable to all. No food or fluid was taken between the meals. Detailed individual logs of *ad lib* cigarette

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Received for publication 10 November 1975

Time	Meal	Protein (g)	Fat (g)	CHO (g)	Energy value (kJ)
08.30	Breakfast				
	Cereal				
	Gammon and tomato				
	Toast and marmalade				
	Tea	46	42	105	4 068
11.00	Coffee	2	2	3	166
13.00	Lunch				
	Roast chicken and sausage				
	Vegetables				
	Apple and custard				
	Tea*	51	32	76	3 301
16.00	Tea	1	1	1	83
18.30	Dinner				
	Grilled steak				
	Vegetables				
	Jelly and cream				
	Tea*	33	34	53	2 716
22.00	Nightcap				
	Cheese and biscuits	11	32	10	1 577
	Meat extract drink				
		144	143	248	11 911

Table 1 Daily food intake

*Plus 284-568 ml beer, dependent on individual preference, but the same amount each day.

and fluid consumption were kept by the subjects during the first study day and the same intake was repeated on the second day by reference to the records. The subjects were fully ambulant, ate their meals at a table, were entertained by reading, television, and films, and played games ranging from dominoes to table tennis.

None of the volunteers had a history of dyspepsia. A pentagastrin test (0.6 mg subcutaneously) before the study had demonstrated that all the subjects secreted acid (Table 2).

Five millilitre samples of gastric contents were aspirated from every subject every hour from 8 a.m. to midnight and every two hours from 2 a.m. to 8 a.m. Immediately after collection, the pH of gastric aspirates was measured to the nearest 0.1 pH unit using a combined glass electrode and pH meter (Radiometer, Copenhagen). Aspirates collected within 2 h of medication were replaced in the stomach in order to ensure complete absorption of the drug. The pH electrode was calibrated with standard buffers of pH 2.0, 4.0, and 7.0. The calibration was checked immediately before each batch of measurements. The result of each pH measurement of hydrogen ion activity was converted to mmol/l for analysis.

Medication consisted of cimetidine or identically appearing placebo capsules; one subject received the placebo on both days of the study. Five subjects received cimetidine on the first day and four on the second day, the order of treatment being allocated

	Drug after meals (n = 5)	Drug before meals (n = 4)	Placebo both days (n = 1)
Age (yr)	34.2 ± 5.0 (19-45)	33.5 ± 2.9 (25-37)	27
Weight (kg)	82.9 ± 3.7 (75.8-95.5)	76.2 ± 8.1 (53.8-90.9)	76.5
Acid output (mmol/h) basal	3.1 ± 1.4 (1.2-9.2)	3.0 ± 0.8 (1.2-5.2)	2.4
MAO _{FG}	29.4 ± 3.5 (22.2-42.3)	38.5 ± 8.4 (21.3-54.0)	15.6
Cigarette smokers (no)	3	3	0

Table 2 Details of the normal volunteers (mean ± SEM (range))

randomly. Independently of that randomization, the subjects were divided into two comparable groups based on the results of their pentagastrin test and cigarette consumption (Table 2); four subjects received the capsules 30 min before and five subjects 30 min after, the three main meals of the day. All received the last dose 30 min after the night-time snack. The dose of cimetidine was 200 mg four times a day, except that in four subjects one 200 mg dose was replaced by 400 mg: in two subjects before, and in two after, dinner. As the gastric acidity levels after the 400 mg dose were similar to those after 200 mg, the results were pooled for analysis. Because the numbers in each group of this study are small, the results have not been subjected to statistical analysis.

Fasting venous plasma gastrin concentrations were determined by radioimmunoassay (Russell *et al.*, submitted for publication). Whole blood cimetidine concentrations were measured by high-pressure liquid chromatography (Smith, Kline and French Laboratories, Philadelphia). Detailed studies of cimetidine absorption in relation to breakfast or dinner were performed once during the study in each of the nine subjects receiving the drug: indwelling cannulae were used for repeated venous sampling. Haematological and biochemical safety tests were performed before and after the study.

The subjects were unaware of the nature of medication taken on a particular day. They all gave their informed consent to the study, which was approved by the appropriate ethical committees.

Results

The study was well tolerated by all the subjects, who reported no unwanted effects associated with the drug. No abnormalities were detected in the safety profiles. The various sampling procedures did not interfere with appetite, eating, or recreational arrangements. Beer and cigarette consumption

	Drug after meals (n = 5)	Drug before meals (n = 4)	Placebo both days (n = 1)
Beer intake (ml/24 h)	965 ± 114 (568-1136)	909 ± 57 (852-1136)	852
Urine output (ml/24 h)	1482 ± 231 (955-2325)	1787 ± 204 (1200-2130)	1600
Cigarettes (24 h)	7.4 ± 3.1 (0-14)	13.0 ± 5.5 (0-27)	0

Table 3 Beer intake, urine output and cigarette consumption (mean ± SEM (range))

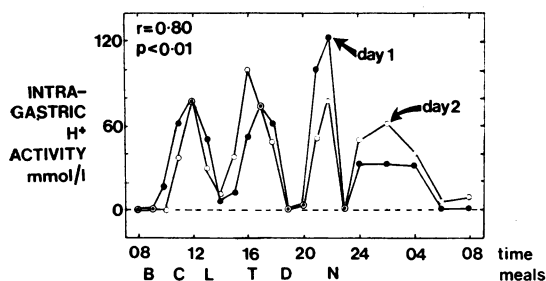


Fig. 1 The intragastric acidity of one subject receiving placebo on two successive days.

and urine output were similar in both groups of subjects (Table 3). Good reproducibility between two days of the study was demonstrated by the acidity of gastric aspirates from the subject who received the placebo on both days ($r = 0.80$, $p < 0.01$; Fig. 1). In that subject, the mean hydrogen ion activity was 35.2 mmol/l and 38.7 mmol/l during the two successive 24 h periods, an overall change of +9%.

Regardless of medication, intragastric acidity was decreased in all the subjects after each main meal, but cimetidine therapy was associated with a prolonged decrease which persisted until the next meal (Fig. 2). The decrease of mean hydrogen ion activity during each 24 h period was similar in both treatment groups, diminishing from the placebo day level of 29.1 mmol/l to 8.7 mmol/l (-70%) when cimetidine was taken before food, and from 34.1 to 9.4 mmol/l (-72%) when it was taken after food. The hourly pattern of decreased activity was similar in the pre- and post-prandially treated groups.

Absorption of cimetidine was faster and resulted in high peak blood levels in most of the subjects who received it before meals (Fig. 3). With the pre-prandial 200 mg dose, peak blood concentrations of 4.12 and 6.40 $\mu\text{mol/l}$ were attained within 1 h of administration. However, when cimetidine 200 mg was taken after the meal, absorption was delayed for 30 min and the peak blood concentrations of 2.72,

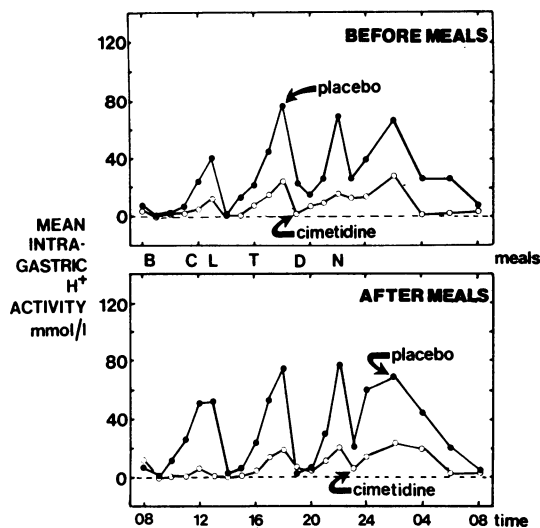


Fig. 2 Mean intragastric acidity: capsules before food in four subjects, and after food in five subjects.

B = breakfast, C = coffee, L = lunch, T = tea, D = dinner, N = nightcap.

4.32, and 4.52 $\mu\text{mol/l}$ were not reached until 1½ to 2½ h after medication. Similar absorption curves were obtained with the post-prandial 400 mg dose, although peak blood levels were somewhat higher (4.84 and 6.00 $\mu\text{mol/l}$). The very high peak level of 11.60 $\mu\text{mol/l}$ attained by one subject 1 h after pre-prandial 400 mg cimetidine was probably related to his low body weight (54 kg, dose 7.41 mg/kg). The other individual who received a 400 mg pre-prandial dose of the drug had a lower peak blood level (6.84 $\mu\text{mol/l}$, weight 84 kg, dose 4.76 mg/kg). Doubling the dose of cimetidine to 400 mg at dinner-time in four subjects did not result in a greater

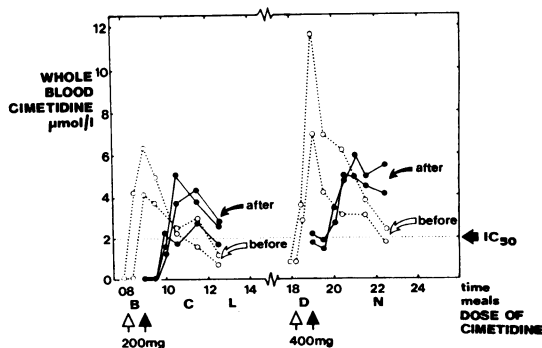


Fig. 3 Whole blood cimetidine concentrations following 200 mg at breakfast (five subjects) and 400 mg at dinner (four subjects).

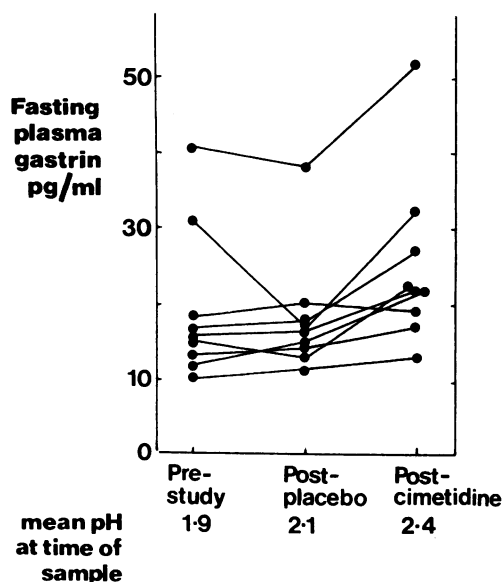


Fig. 4 Fasting plasma gastrin levels in normal volunteers on each morning of the study and mean intragastric pH at time of blood sampling.

decrease of acidity than that recorded in the five remaining subjects who received 200 mg.

Mean fasting plasma gastrin levels in the nine subjects receiving cimetidine were similar in the mornings before the study and after the placebo day ($19.54 \text{ pg/ml} \pm \text{SEM } 3.40$, range 10-41, and $18.44 \text{ pg/ml} \pm 2.43$, range 13-37, respectively). Mean fasting plasma gastrin was higher on the morning after the cimetidine than on either of the two control days ($25.55 \text{ pg/ml} \pm 4.06$, range 14-54). This increase was due to a rise of plasma gastrin in five of the nine subjects (Fig. 4) but was not related to the timing or the size of the evening dose of cimetidine.

Discussion

Serial measurements of intragastric pH are suitable for recording the effects of diet or drugs on gastric acidity (Nichol, 1939; James and Pickering, 1949; Rowlands *et al.*, 1952; Atkinson, 1954; Kasich and Agyros, 1958; Bingle and Lennard-Jones, 1960; Vakil *et al.*, 1963; Lennard-Jones and Babouris, 1965; Babouris *et al.*, 1965). The major advantage of this technique is that data can be collected during a reasonably long period in subjects whose diet and activity are similar to normal life. Experiments of the type described in this paper, with each subject acting as his own control, allow the effect of an antisecretory

compound on gastric acidity to be measured during a prolonged period, while taking into account all the variables that affect the stomach in daily life.

Moore and Scarlata (1965) published a series of activity coefficients for the conversion of hydrogen ion activity, as measured by a glass electrode, to hydrogen ion concentration or total titratable acidity. This conversion has not been applied to our results, because the coefficients do not apply to gastric juice containing food buffer. Moreover, it is possible that hydrogen ion activity may be more important than total titratable acidity in the pathogenesis of duodenal ulceration. Moore (1968) also reported that the use of commercial buffers may result in errors of pH determination when glass electrodes are used below pH 2.0: in this study, we measured pH to the nearest 0.1 unit and the described errors were well within that limit of accuracy.

Replicate measurements in the one subject who received placebo on both days of the study correlate significantly, and confirm the reliability of the technique. Intra-gastric acidity decreased after each main meal in all the subjects, supporting the observation of Lennard-Jones and Babouris (1965) that food buffers the acid secreted after a meal for approximately two hours.

Cimetidine decreased the overall intragastric hydrogen ion activity by 71%, with every subject responding to the drug. Pentagastrin-stimulated acid output in the nine subjects was in the upper parts of the normal range, indicating that the drug inhibited the secretory response to food of a parietal cell mass compatible with the occurrence of duodenal ulceration. Although the number of subjects so far studied is small, published data suggest that the degree of inhibition of gastric secretion by cimetidine in normal subjects and duodenal ulcer patients is similar (Pounder *et al.*, 1975a, b; Henn *et al.*, 1975).

In terms of mean intragastric hydrogen ion activity, there was no major difference between the two groups who took the drug either before or after food. This was despite the earlier and high blood concentrations of cimetidine in those who took it before meals, and the delayed peak concentrations in those who took it post-prandially. On the basis of previous studies, we suggested that cimetidine should be given with or after a meal (Pounder *et al.*, 1975a). This was because slower absorption from the gut resulted in prolonged bioavailability of the compound, particularly at the time when the buffering capacity of the meal was waning due to gastric emptying.

The results of the present study confirm that the timing of a dose of cimetidine in relation to food does affect its absorption, but this does not appear

to affect intragastric acidity under these conditions. Regular administration of 200 mg four times daily should ensure drug levels above or near the IC_{50} level of $2 \mu\text{mol/l}$ (Burland *et al.*, 1975), and a decreased acidity throughout the 24 h. In a clinical situation, when a dose of cimetidine may be delayed or omitted, medication taken after food should provide effective blood levels for a longer period, and cover the break in therapy.

In patients with duodenal ulcer a single oral dose of 400 mg metiamide profoundly inhibited nocturnal acid secretion, an acidity being recorded for several hours in eight of 11 subjects (Milton-Thompson *et al.*, 1974). In the present study, an acidity was recorded in only two of 45 nocturnal samples. As metiamide and cimetidine have comparable inhibitory activities for histamine or pentagastrin stimulated gastric acid secretion in man (Brimblecombe *et al.*, 1975), these dissimilar results could be due either to differences of technique, or more likely to the different environmental conditions of the two studies. Nocturnal acid secretion in the duodenal ulcer patients was unstimulated and measured after a five hour fast in hospitalized patients (Milton-Thompson *et al.*, 1974). By contrast, in the present study, acid secretion was almost continuously stimulated by a high protein diet and a meat extract evening drink. Physical and mental activity, smoking, and alcohol may have also played a part. The combined results of our studies suggest that, for the best control of nocturnal acid secretion, patients with duodenal ulcer might be advised to take only a light meal some time before the bedtime dose of cimetidine.

The small rise in fasting plasma gastrin after 24 h treatment with cimetidine was probably secondary to the decreased acidity during the night and early morning. This idea is in line with our previous report that cimetidine had no effect on the secretion of gastrin in response to a meal when intragastric pH was held at 5.50 (Pounder *et al.*, 1975a). It also agrees with the finding that, when the intragastric pH is not controlled, a rise in plasma gastrin follows the administration of metiamide (Barbezat *et al.*, 1975). These observations raise the possibility that prolonged treatment with H_2 -receptor antagonists may be followed by a sustained rise of plasma gastrin. The implications of this with regard to the long-term treatment of gastric or duodenal ulcer will have to be reviewed as experience with the drug accumulates.

We are grateful to the Clinical Research Group, Smith, Kline and French Laboratories, Welwyn Garden City, for supplies of cimetidine and for arranging the estimation of blood cimetidine levels. We thank Mr R. C. G. Russell, Surgical Unit,

St. Mary's Hospital, London, W2, for the radio-immunoassay of plasma gastrin. We also thank the medical officer-in-charge, the dietitian, Mrs Sutton, and the staff of the Departments of Pathology and Radiology, the Royal Naval Hospital, Stonehouse, Plymouth, for their help in arranging the study.

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