Inhibitory effect of cimetidine on gastric acid secretion vagally activated by physiological means in duodenal ulcer patients

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SUMMARY Vagal activation of gastric acid secretion by modified sham feeding in six patients with duodenal ulcer produced a peak acid response amounting to 52% of the peak acid output after pentagastrin stimulation (PAO_{pg}). Cholinergic reflex stimulation of gastric acid secretion by fundic distension in another six patients with duodenal ulcer produced a peak acid response of 45% of PAO_{pg}. Intravenous infusion of cimetidine in a dose of 100 mg/h markedly inhibited the acid sham feeding response by 90-100% and almost abolished the acid response to fundic distension. The results suggest that gastric acid secretion evoked by physiological vagal activation in man is profoundly inhibited by H₂-receptor blocking agents.

The existence of two types of histamine receptors, —H₁ and H₂—has been established (Black *et al.*, 1972). The H₂-receptor antagonists of thiourea configuration (burimamide and metiamide) markedly inhibited gastric acid secretion stimulated by histamine or gastrin but seemed less effective in inhibiting the acid secretion evoked by cholinergic stimuli (Black, 1973). Metiamide inhibited by 40% at 1 mg/kg intravenously and by 90% at 10 mg/kg the acid response to electrical vagal stimulation in cats (Bauer and Brooks, 1976). Metiamide furthermore inhibited by 70-80% at the dose of 1 mg/kg intravenously the acid response to sham feeding in the dog (Sjödén, 1976). The mode of action of H₂-receptor antagonist on acid secretion produced by stimuli other than histamine is poorly understood. Metiamide did not inhibit acetylcholine-induced acid secretion in the isolated kitten fundic mucosa (Tepperman *et al.*, 1975). In the cat the H₂-receptor blockade with metiamide was additive to the inhibitory effect of atropine on maximal acid secretion evoked by pentagastrin (Thompson *et al.*, 1975). The antagonism of metiamide on pentagastrin-stimulated acid secretion in man seemed to be of both competitive and non-competitive type (Thjodleifsson and Wormsley, 1975). The acid secretion evoked by local chemical stimulation of the oxyntic cell area could not be abolished by metiamide (Konturek *et al.*, 1976). Acid secretion stimulated by theophylline or by dibutyryl cAMP was not inhibited by H₂-receptor

antagonists in animals (Shoemaker *et al.*, 1974). A H₂-receptor antagonist has, however, been shown to abolish caffeine-stimulated gastric acid secretion in man (Cano *et al.*, 1976).

A non-thiourea H₂-receptor antagonist, cimetidine, has been introduced (Brimblecombe *et al.*, 1975). It seems to have the same antisecretory properties as burimamide and metiamide, including the property of being less effective against cholinergic stimuli (Brimblecombe *et al.*, 1975). Cimetidine is effective after both intravenous and peroral administration and it may be slightly more potent on a molar basis than metiamide, possibly because of a longer circulating half-life (Brimblecombe *et al.*, 1975). In man cimetidine has been shown markedly to inhibit basal acid secretion and the acid responses to pentagastrin, histamine, and a meal (Burland *et al.*, 1975; Henn *et al.*, 1975; Hollander *et al.*, 1975; Cano *et al.*, 1976; Richardson *et al.*, 1976). Cimetidine also inhibited by 75% the acid response to pharmacological vagal activation by insulin hypoglycaemia in man (Carter *et al.*, 1976).

The present study aimed at determining the effect of cimetidine on acid secretion evoked by physiological vagal reflex stimulation in duodenal ulcer patients.

Methods

SUBJECTS

Six men aged 29 to 54 (mean 44) years, all with a long history of recurrent duodenal ulceration, were sub-

jected to vagal stimulation of gastric acid secretion by modified sham feeding. Endoscopy or x-ray examination immediately before the study confirmed duodenal ulceration in four patients, a prepyloric ulcer in one patient, and duodenal erosions in one patient.

Another group of six male patients, aged 27 to 56 (mean 45) years, with previously confirmed duodenal ulceration, were subjected to stimulation of gastric acid secretion by fundic distension. The patients gave consent to the study after receiving detailed information. The study was approved by the Ethical Committee at the Faculty of Medicine, University of Göteborg.

ADMINISTRATION AND DETERMINATION OF CIMETIDINE

In separate experiments on each patient an intravenous infusion of either cimetidine or saline was administered in a randomised order. After four 15 minute periods of determination of the basal acid secretion, saline or 200 mg cimetidine was intravenously infused at a constant rate for the following 120 minutes. The mean dose of cimetidine was $1.4 \text{ mg kg}^{-1} \text{ h}^{-1}$ (range 1.2–1.6). Venous blood samples were taken in heparinised tubes for determination of plasma cimetidine concentration. Blood samples were taken twice in the basal period at 0 and 30 minutes before starting the intravenous infusion of cimetidine and then at 90, 120, 180, and 210 minutes. After centrifugation the samples were frozen and stored at -20°C before assay. The determination of cimetidine concentration was carried out by the Biochemistry Department of the Research Laboratories of Smith Kline & French laboratories. Plasma cimetidine concentration ($\mu\text{g/ml}$) was determined using high pressure liquid chromatography.

DETERMINATION OF ACID SECRETION

The experiments were carried out after an overnight fast. The subjects were placed in a semi-recumbent position. A double lumen nasogastric tube (Salem Sump Tube No. 14) was placed with its tip in the antral part of the stomach under fluoroscopic control. The gastric contents were continuously aspirated using a suction pump giving negative pressure (90 mm Hg) once per second. Throughout the experiments the stomach was continuously perfused with a phenol red solution (8 mg/l) at a rate of 225 ml/15 min via a thin polyethylene tube with its tip 5–10 cm below the cardia. The rather high perfusion volume was used to facilitate the mixing of marker solution and gastric content. The volume and pH of the collected gastric contents was determined for each 15 minute period by potentiometric titration of 100 ml to pH 7.0. The phenol red concentration in the gas-

tric contents was determined spectrophotometrically at wave length 565 nm after filtration (Millipore filter 1.2μ) and alkalisation with 0.4 ml of concentrated (10%) NaOH. The known percentage loss of phenol red, assuming that the same percentage of acid had been lost via the pylorus, allowed the amount of acid secreted to be calculated.

MODIFIED SHAM FEEDING

After two 15 minute periods of intravenous infusion (cimetidine or saline) the patients were given hamburgers and omelette to chew. The patients were not allowed to swallow the food and were encouraged to spit out the morsel and to rinse the mouth with water. The modified sham feeding was extended over 15 minutes. Thereafter acid secretion was followed for nine further 15 minute periods, including four 15 minute periods after the end of cimetidine or saline infusion. Peak acid output was defined as the sum of the two highest consecutive 15 minute periods.

FUNDIC DISTENSION

A thin-walled rubber balloon connected to a thin polyethylene tube was tied to the nasogastric sump tube with the balloon 20 cm above the intragastric tip of the tube. The correct position of the balloon was frequently checked by fluoroscopy during the test. To avoid pooling of gastric contents above the distended balloon another aspiration hole was cut in the nasogastric tube at this point. After two 15 minute periods of intravenous infusion (cimetidine or saline) the balloon was slowly filled with 650 ml of air over a period of 15 minutes. The distension was maintained for five further 15 minute periods after which distension was released and acid secretion was determined for four further 15 minute periods.

MAXIMAL ACID RESPONSE TO HUMORAL STIMULI

The peak acid output after stimulation with penta-

Table 1 Individual peak values of maximal acid responses to pentagastrin (PAO_{pg}) and to modified sham feeding (PAO_{sh}) in six duodenal ulcer patients

Subjects	PAO_{pg} (mmol/30 min)	PAO_{sh} (mmol/30 min)	$\text{PAO}_{sh}/\text{PAO}_{pg}$ (%)
1	34.6	23.8	69
2	26.7	6.8	26
3	29.0	14.1	49
4	33.3	15.8	47
5	24.5	8.6	35
6	21.2	19.9	94
Mean	28.2	14.8	52
SEM	± 2.1	± 2.7	

gastrin (Peptavlon, ICI) or betazol (Histalog, Lilly) was determined in each patient. Pentagastrin was intravenously infused in a dose of 90.8 $\mu\text{g/h}$ for 45 minutes, followed by 298 $\mu\text{g/h}$ for a further 60 minutes in 11 patients. Histalog was given as a subcutaneous injection (2 mg/kg body weight) and acid secretion was determined for 2½ hours in one patient. Peak acid output was defined as the sum of the two highest consecutive 15 minute periods.

STATISTICAL EVALUATION

The Wilcoxon matched-pairs' signed-ranks test was used (Siegel, 1956).

Results

EFFECT OF CIMETIDINE ON ACID RESPONSE TO MODIFIED SHAM FEEDING

The mean peak acid output after modified sham feeding was 14.8 mmol/30 min, amounting to 52% of mean peak acid output after pentagastrin or Histalog stimulation in the six duodenal ulcer patients (Table 1). Cimetidine markedly inhibited the basal acid secretion in the second 15 minute period of infusion as well as the acid response to modified sham feeding (Fig. 1). In each individual the cimetidine infusion significantly inhibited the acid response ($P < 0.025$) and abolished the acid secretion in the last 15 minute period of cimetidine infusion. Acid secretion reappeared after stopping the cimetidine infusion. The plasma cimetidine concentrations showed a mean concentration of 0.67 $\mu\text{g/ml}$ at 30 minutes after starting the infusion and the mean concentration levelled off to 0.98–1.08 $\mu\text{g/ml}$ during the infusion (Fig. 1).

EFFECT OF CIMETIDINE ON ACID RESPONSE TO FUNDIC DISTENSION

Fundic distension in six duodenal ulcer patients gave a mean peak acid output of 11.2 mmol/30 minutes which was 45% of the mean peak acid output after pentagastrin stimulation (Table 2). Cimetidine almost abolished the acid response to fundic distension. The inhibition exceeded 96% in every 15 minute period. The acid secretion did not reappear during the four 15 minute periods after the end of the intravenous infusion of cimetidine (Fig. 2). The inhibition was significant ($P < 0.025$). The mean plasma cimetidine concentrations were 0.81 $\mu\text{g/ml}$ at 30 minutes after starting the infusion and then remained at 1.05–1.36 $\mu\text{g/ml}$ throughout the infusion period (Fig. 2).

Discussion

Vagal activation by adequate sham feeding in duodenal ulcer patients produces a peak acid response amounting to about 55% of the peak acid response

Fig. 1 Mean ($\pm$ SEM) plasma cimetidine concentrations during intravenous infusion of 200 mg cimetidine for two hours and its effect on mean ($\pm$ SEM) basal acid secretion and acid response to 15 minutes modified sham feeding (Sh) in six duodenal ulcer patients.

to pentagastrin stimulation (Knutson and Olbe, 1974a). Gastrin is concomitantly released (Knutson *et al.*, 1974; Mayer *et al.*, 1974) and originates mainly from the antrum (Knutson *et al.*, 1974). The released gastrin contributes to the acid sham feeding response but seems to be quantitatively of minor importance in man (Knutson and Olbe, 1974a, b). The acid response to sham feeding is abolished by proximal gastric vagotomy in duodenal ulcer patients (Knutson and Olbe, 1973). Consequently the predominating stimulus to acid secretion by sham feeding in man seems to be direct vagal activation of the oxyntic cell area. Fifteen minutes of sham feeding produces near maximal acid response to that stimulus in duodenal ulcer patients (Knutson and Olbe, 1974a). The acid response to modified

Table 2 Individual peak values of maximal acid responses to pentagastrin (PAO_{pg}) and to fundic distension (PAO_{fd}) in six duodenal ulcer patients

Subjects	PAO_{pg} (mmol/30 min)	PAO_{fd} (mmol/30 min)	PAO_{fd}/PAO_{pg} (%)
7	25.9	9.3	36
8	32.8	11.7	36
10	15.7	10.0	64
11	27.8	16.1	58
12	24.0	10.2	42
13	25.3	10.2	40
Mean	25.3	11.3	45
SEM	± 2.3	± 1.0	

sham feeding by the 'chew and spit' technique is not significantly different from the acid response to adequate sham feeding (Stenquist *et al.*, 1976). In the present study 15 minutes of modified sham feeding produced a peak acid response amounting to 52% of the peak acid response to pentagastrin stimulation.

Fig. 2 Mean ($\pm$ SEM) plasma cimetidine concentrations during intravenous infusion of 200 mg cimetidine for two hours and its effect on mean ($\pm$ SEM) basal acid secretion and acid response to fundic distension by a balloon of 650 ml in six duodenal ulcer patients.

Cimetidine profoundly inhibited the acid sham feeding response by 90-100%. Graded fundic distension is a potent stimulus to acid secretion in man. The peak acid response has been evoked by 600 ml balloon distension reaching about 50% of the peak acid response to pentagastrin stimulation (Gröttinger *et al.*, 1977a). This acid distension response is evoked by an atropine-sensitive mechanism partially dependent on intact vagal innervation without contribution of any significant gastrin release (Gröttinger *et al.*, 1977b, d). The acid response to fundic distension in man is then most reasonably mediated *via* cholinergic long vagovagal and short intramural reflex pathways that previously have been established in the dog (Grossman 1961, 1962). In the present study fundic distension by a balloon of 650 ml produced a peak acid response of 45% of the peak acid response to pentagastrin stimulation. Cimetidine almost abolished the acid response to fundic distension.

Plasma concentrations of cimetidine just above 1 μ g/ml inhibited by more than 90% the acid responses to sham feeding and fundic distension in the present study. Blood concentrations of cimetidine of 0.4-0.5 μ g/ml have inhibited by 50% the acid responses to pentagastrin and a meal in man (Burland *et al.*, 1975; Pounder *et al.*, 1976). These data seem to indicate that in man the acid secretion evoked by physiological nervous excitation of the oxyntic gland area is as sensitive to inhibition by the H_2 -receptor blocking agents as is the acid secretion produced by humoral stimulation. The inhibitory effect observed in the present experiments may not, however, be due solely to H_2 -receptor blockade, as there is some evidence that at least fundic distension in man elicits stimulatory as well as endogenous inhibitory effects on acid secretion (Gröttinger *et al.*, 1977c). The mechanism of this endogenous inhibitory action is unknown.

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