Br. J. Pharmac. (1982), **76,** 551–555

THE EFFECT OF CIMETIDINE ON BASAL GASTRIC ACID SECRETION IN THE RAT

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1 The effect of cimetidine on the basal gastric acid secretion of the rat has been investigated in an anaesthetized lumen-perfused preparation.

2 Six rats previously given large doses of cimetidine orally showed no significant difference in basal gastric acid secretion when compared with six control rats.

3 Intravenous administration of 1 mg and 8 mg of cimetidine failed to inhibit significantly basal gastric acid secretion.

4 Although rats with a basal gastric acid secretion above 2.5 μEq/10 min showed a consistent small reduction in basal gastric acid secretion after intravenous cimetidine, this was not seen in rats with a basal gastric acid secretion below 2.5 μEq/10 min.

5 These results contrast sharply with the pronounced inhibition of basal gastric acid secretion by cimetidine in man and the possible reasons for this are discussed.

6 The results are also contrasted with previous work on gastric fistula rats which showed higher basal gastric acid secretion and significant inhibition by cimetidine.

Introduction

There have already been many studies of the effect of the H_2-receptor antagonists on gastric acid secretion in animals previously stimulated with pentagastrin or histamine (Black, Duncan, Durant, Ganellin & Parsons, 1972; Wyllie, Ealding, Hesselbo & Black, 1973; Grossman & Konturek, 1974; Thjodleifsson & Wormsley, 1974; Konturek, Biernat & Oleksy, 1974; Magee, 1975; Fielding, Chalmers, Stafford & Lei, 1976; Holstein, 1976; Parsons, 1977; Bunce & Parsons, 1978). However, there are fewer studies on the effect of H_2-receptor antagonists on basal gastric acid secretion in animals (Harris, Smy, Reed & Venables, 1975; Brimblecombe, Duncan, Durant, Ganellin, Parsons & Black, 1975; Longstreth, Go & Malagelada, 1976; Bunce & Parsons, 1976; Bajaj & Hirschowitz, 1976; Barbezat & Bank, 1977; Parsons, 1977).

This study investigates the effect of cimetidine on basal acid secretion. The basal gastric acid secretion in rats pretreated by oral administration of cimetidine was first determined; the effects of intravenous administration of cimetidine during the monitoring of basal acid secretion were then investigated.

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Methods

Effect of oral cimetidine on gastric acid secretion

Wistar rats (12) weighing 200–350 g were housed singly. Six were offered distilled water to drink, the other six were offered only 2.5 mg/ml cimetidine solution for 48 h. All rats were deprived of food for 24 h before assessment of acid output but were allowed free access to the fluid offered. One hour before assessment, 2 ml of distilled water or 15 mg cimetidine in 2 ml distilled water was given through a peroral gastric cannula to control and cimetidine-treated groups respectively.

The lumen perfusion preparation was basedonthat of Ghosh & Schild (1958) and Lai (1964). Rats were anaesthetized by intramuscular urethane, a 5 mm diameter polythene cannula was inserted into the stomach via a duodenotomy and tied in place by a light ligature around the pylorus. A 2 mm polythene tube was passed through the mouth into the stomach. The stomach was then washed out with, but not overdistended by, 30 ml saline (0.9% w/v NaCl solution) at 37°C. The stomach was perfused via the peroral tube with normal saline at 37°C at 40 ml/h and the effluent collected from the duodenal cannula in 10 min aliquots. The acid secretion in successive 10 min aliquots was determined. When a steady basal acid secretion had been achieved, 125 μg pentagastrin, the minimum dose known to achieve maximal

0007-1188/82/080551-05 $01.00

stimulation of gastric acid in the rat (Barrett, Raventos & Siddall, 1966) was injected intravenously. Peak acid output was calculated as the mean of the two highest 10 min acid output measurements obtained after pentagastrin.

Effect of intravenous cimetidine on gastric acid secretion

A further 16 rats were deprived of food for 24 h with free access to tap water, then anaesthetized and prepared for measurement of gastric acid secretion as described above. When a steady basal acid secretion had been achieved, each rat was given an intravenous injection of 0.2 ml fluid which comprised (a) saline; (b) 1 mg cimetidine dissolved in distilled water; or (c) 8 mg cimetidine dissolved in distilled water. Measurement of gastric acid secretion was continued for 1 h. The average secretion of gastric acid between 20 min and 60 min after injection was calculated. Preliminary studies had shown that any decrease in acid secretion was most marked in the period up to 60 min after cimetidine injection and that prolongation of the period of measurement resulted in no further reduction in acid secretion. One hour after injection of cimetidine or saline, 125 μg pentagastrin was injected intravenously and the pentagastrin-stimulated peak acid output calculated as before.

Results

Rats which were offered 2.5 mg/ml cimetidine solution in place of drinking water did not have a significantly different fluid intake from rats offered distilled water. The volume of fluid drunk in ml/100 g body wt. daily was 11.6 ± 2.0 (mean ± s.d.) by controls and 12.7 ± 2.4 by rats drinking cimetidine solution. This fluid intake resulted in the cimetidine-treated group receiving 200–400 mg/kg cimetidine daily for the two days before the assessment of gastric acid secretion. One hour before the acid secretion was measured the rats also received an intragastric bolus of 40–70 mg/kg cimetidine.

Table 1 The effect of oral and intravenous cimetidine on basal and pentagastrin-stimulated peak gastric acid secretion (μEq/10 min) in rats

(a) *Oral*

	Control		*Cimetidine-treated*	
Animal	Basal	Peak	Basal	Peak
1	1.6	8.7	1.8	2.5
2	2.1	13.8	2.7	3.5
3	2.6	8.4	4.4	8.5
4	2.7	10.4	4.9	9.5
5	3.0	10.2	5.2	11.7
6	3.9	11.5	6.3	8.5
Mean	2.7	10.5*	4.2	7.4†
±s.d.	±0.8	±2.0	±1.7	±3.6

Significantly different from basal: * $P < 0.001$; † $P < 0.05$.

(b) *Intravenous*

	Control			*Cimetidine 1 mg*			*Cimetidine 8 mg*		
Animal	Basal	After saline	Peak	Basal	After cimetidine	Peak	Basal	After cimetidine	Peak
1	2.5	2.8	9.2	1.5	1,5	3.4	2.1	2.6	4.7
2	3.6	3.7	10.1	1.6	1.9	4.1	2.4	2.9	3.9
3	4.2	4.2	11.2	2.5	1.9	4.4	2.6	2.3	2.8
4	5.6	5.2	11.6	3.0	2.2	4.4	5.0	2.9	4.6
5	8.6	8.6	19.1	5.4	3.9	6.4	5.2	3.8	4.5
6				9.4	5.6	13.1			
Mean	4.9	4.9	12.2*	3.9	2.8	6.0*†	3.5	2.9	4.1*†
±s.d.	±2.4	±2.2.	±3.9	±3.0	±1.6	±3.6	±1.5	±0.6	±0.8

Significantly different from basal: * $P < 0.01$.
Significantly different from peak acid output in controls: † $P < 0.01$.

Effect of 48 h oral cimetidine on gastric acid secretion

The results of the estimation of basal gastric acid secretion and peak acid output after pentagastrin stimulation in both control and cimetidine-treated rats are shown in Table 1. The average basal gastric acid secretion in cimetidine-treated rats (4.2 ± 0.7 μEq/10 min; mean ± s.e.mean) was not significantly lower than that in the control group (2.7 ± 0.3 μEq/10 min); indeed four of the six rats in the cimetidine-treated group showed a higher basal acid secretion than any of the rats in this control group. From the data for controls in the second experiment as well as the first experiment it is clear that cimetidine had no effect on the basal gastric acid secretion.

In the control group, pentagastrin produced a peak acid output which was 2.9–6.6 (average 4.2) times the basal acid output ($P < 0.001$). The response in the cimetidine group, although significant ($P < 0.05$) was smaller in extent (1.3×–2.3×; average 1.7×). The augmentation of acid output in the cimetidine group (average + 3.2 μEq/10 min) was significantly less than in the control group (+ 7.9 μEq/10 min) ($P < 0.05$).

Effect of intravenous cimetidine on gastric acid secretion

The basal gastric acid secretion was not altered by intravenous injection of normal saline. Intravenous injection of 1 mg cimetidine (3–5 mg/kg) and 8 mg cimetidine (24–40 mg/kg) did not significantly reduce the average basal acid output.

Study of the data for individual animals shows that only in those animals with higher (> 2.5 μEq/10 min) basal acid secretion is there any reduction in basal acid output after cimetidine administration. Indeed, in the three animals with basal gastric acid secretion less than 2.5 μEq/10 min, injection of cimetidine was associated with an increase in gastric acid output. Combining the data from all rats given intravenous injections of 1 and 8 mg cimetidine, therefore, shows no significant reduction of basal acid output after intravenous cimetidine. However, a significant ($P < 0.05$) reduction in basal acid secretion is seen in those animals with a basal acid secretion of 2.5 μEq/10 min or more (basal 5.1 ± 1.0 (mean ± s.e.mean) basal after cimetidine 3.5 ± 0.5).

In response to intravenous pentagastrin, control rats produced a peak acid output equivalent to 2.7 (range 2.1–3.7) times the basal acid output. Stimulation by pentagastrin of rats previously given 1 mg cimetidine intravenously produced a peak acid output on average 1.8 (1.2–2.6) times basal (significantly different from controls) and similarly rats given 8 mg cimetidine produced a peak average 1.3 (0.9–2.2) times basal acid output (significantly different from controls but not from rats given 1 mg cimetidine).

Discussion

Our estimation of basal gastric acid secretion and peak acid output gives comparable results to previous work on the anaesthetized lumen-perfused rat model (Lai, 1964; Barrett *et al.*, 1966).

We have shown that oral administration of cimetidine, in a dose which will significantly inhibit pentagastrin-stimulated acid secretion, fails to inhibit basal gastric acid secretion in rats. The dose of cimetidine used was very large, equivalent in a 70 kg man to 20 g cimetidine daily with a 3.5 g bolus and far more than is necessary significantly to reduce the basal acid secretion in man (Pounder, Williams, Milton Thompson & Misiewicz, 1976; Barbezat & Bank, 1976; Hollander, Hossain & Sufi, 1976).

We have shown that intravenous cimetidine also has no significant effect on the rat basal acid secretion. One mg of cimetidine in a rat is equivalent to a 210 mg dose in a 70 kg man; this dose had little effect on the rat basal gastric acid secretion and even when the dose was increased eight fold there was still no significant inhibition of the basal acid secretion. However, as expected, the intravenous cimetidine was effective in inhibiting the response to pentagastrin stimulation.

Our results suggest a threshold cimetidine-insensitive basal acid secretion of 2.5 μEq/10 min. Only in animals with basal secretions above this level was there inhibition of acid output.

Previous work has indicated varied effects of H_2-receptor antagonists on rat basal acid secretion. Brimblecombe *et al.* (1975) using gastric fistula rats, showed that an infusion of 5 mg cimetidine per hour produced a 71% inhibition of the basal gastric acid secretion in the first hour, but no absolute values of acid secretion were given. Parsons (1977) found that an oral dose of 8 mg cimetidine produced virtually complete abolition of acid output in conscious, gastric fistula rats. However, basal gastric acid secretion as measured in the gastric fistula rat is six times greater than that in our lumen-perfused rats. Bunce & Parsons (1976) using the isolated whole stomach preparations of immature rats showed that metiamide, although a competitive antagonist of histamine, did not significantly reduce basal acid secretion. The basal gastric acid secretion in that study was comparable to ours when the animals' weight was taken into account.

Our results concur in showing that cimetidine has no effect on basal acid secretion of less than 2.5 μEq/10 min in the rat. However, it does inhibit

the much higher basal gastric acid secretion in the gastric fistula rat but not to levels lower than the basal gastric acid secretion we found in the lumen-perfused preparation. Both are referred to as 'basal'. It is not clear why the gastric fistula rat has such a high basal acid secretion, but this study indicates that the drive to 'basal' acid secretion may have at least two components.

The nature of receptors on parietal cells is still controversial (Grossman & Konturek, 1974) and the factors influencing basal acid secretion have received little attention. Basal acid secretion has been assumed to be dependent on vagal cholinergic stimuli and the basal level of serum gastrin, but this simple view has been criticized (Grossman, 1979).

Our results contrast with studies in man in which 200 mg of cimetidine or metiamide produced 77–90% reduction in the basal gastric acid secretion (Longstreth *et al.*, 1976; Bajaj & Hirschowitz, 1976; Barbezat & Bank, 1977). Man would appear to resemble the chronic fistula rat in having a large cimetidine-sensitive component to basal acid secretion.

Variation in response to H_2-receptor antagonists between species has already been demonstrated (Grossman, Beaven, Code, Duncan & Sol, 1978). Pentagastrin-induced stimulation of gastric acid secretion is uniformly inhibited, but the effect of cholinergic stimulation is variably inhibited by the H_2-receptor antagonists (Black, *et al.*, 1972; Werner, Carter, Forrest & Dozois, 1974; Carter, Forrest, Werner, Heading, Park & Shearman, 1974).

Further investigation of the factors influencing basal gastric acid secretion, which are inhibited by cimetidine in man, but not inhibited by cimetidine in rat, is indicated. Whilst major interest will inevitably be the effect of cimetidine in man, in the analysis of a complex multifactorial control system, such as appears to operate on basal acid secretion, the study of the different species may help in unravelling the factors involved.

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(*Received October 29, 1981.*
Revised February 26, 1982.)