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THE EFFECT ON GASTRIC SECRETION OF DIFFERENT RATES OF HISTAMINE INFUSION AND OF "NEOANTERGAN"

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In acute experiments on lightly anaesthetized cats, a quantitative study has been made of the gastric secretory response to continuous intravenous infusion of histamine solutions. This is a necessary preliminary to the use of the method in the investigation of the effects of various substances on gastric secretion. The use of an infusion of a low concentration of histamine as a gastric secretory stimulant is not new. Ivy and Javois (1924), Gutowski (1924), Teorell (1932, 1933), Emmelin *et al.* (1941), Uvnäs (1943), Emmelin (1945), Emmelin and Frost (1947), and Öbrink (1946) have reported experiments using this method. However, the earlier workers did not maintain a constant rate of infusion for more than a short period. Emmelin (1945) used a "special device" and Öbrink (1946) used the apparatus described by Lindgren (1943) for the continuous delivery at a constant rate of small volumes of solution from a syringe. The apparatus used in the present work is described below.

Information was sought on the possibility of maintaining, for some hours, a steady output of gastric juice and acid in the anaesthetized cat. It was also desired to find out what rate of histamine infusion would give a submaximal stimulation of the secretory cells, such as would be necessary if the method were to be useful for the investigation or assay of inhibitory substances. Some guidance was given by the results of previous workers. Figures for infusion rates have been calculated approximately from data given in their publications and are presented for convenience in Table I. The rate of infusion is given in terms of μg. of histamine base per kg. of body weight per minute. Where the weight of the animal was not recorded (marked *), average weights of 10 and 3 kg. have been arbitrarily assumed for dog and cat respectively.

TABLE I

Source	Animal	Anaesthetic	Infusion μg./kg./min.	Remarks
Gutowski (1924)	dog*	decerebrate	2	
Ivy and Javois (1924)	pouch dog	none	2.7	submaximal (30–45 min.)
Teorell (1933)	cat*	chloralose and urethane	2.2 (approx.	submaximal (15 min.)
Emmelin *et al.* (1941)	cat	decerebrate	0.5–1.5	
	pouch dog	none	0.5–0.6	
Björkman *et al.* (1943)	cat	chloralose and urethane	5.1	maximal
			1.7	submaximal
Öbrink (1946)	pouch dog	none	2.2	maximal
Emmelin and Frost (1947)	cat	chloralose	2–7 usually 2–3	

From all these reports it seemed likely that an infusion rate of about 2 to 3 μg. histamine base per kg. of body weight per minute would stimulate a submaximal gastric secretion in most anaesthetized cats.

The part played by histamine as a natural gastric secretory stimulant under normal and pathological conditions in man is still undecided; however, the fact that histamine can stimulate gastric secretion has led many workers to investigate the action of antihistamine substances on this response to histamine. Such substances might be useful in the investigation of the exact role of histamine in normal gastric secretion, apart from a possible therapeutic application. There have been conflicting reports on the effects of such substances on gastric secretion, and the position has recently been summarized in the review by Loew (1947). Present

opinion (Grossman and Ivy, 1946; Loew, 1947) is that none of the antihistamine substances so far tested has any significant inhibitory effect on histamine-induced gastric secretion.

The potent antihistamine substance, β-dimethylaminoethyl-N-*p*-methoxybenzyl-α-aminopyridine ("neoantergan," 2786 R.P.), has recently been introduced in this country as "anthisan." Bovet and Walthert (1944) reported that it did not inhibit gastric secretion induced by histamine in the rat, and this was confirmed in man by Decourt (1945).

Some experiments have been made, using the method described below, to study the effect of neoantergan on the gastric secretory effect of histamine in the anaesthetized cat.

Experimental Methods

Cats weighing from 1.75 to 4.72 kg. (average, 2.67 kg.) were used after preliminary withholding of solid food for 18 to 24 hours. In a few animals anaesthesia was induced with chloroform and continued with cyclopropane and oxygen. The depth of anaesthesia could be readily varied from complete surgical anaesthesia during the operative procedure to a light plane of narcosis during the remainder of the experiment. The main disadvantage apart from the slight danger of explosion is that of expense. In most animals anaesthesia was produced by intraperitoneal injection of sodium pentobarbitone, small maintenance doses being given intravenously when required later. The anaesthetized animal was prepared for collection of gastric secretion by the method of Lim (1923) as recently modified by Roth and Ivy (1944).

The stomach and duodenum are approached by a midline abdominal incision and a cannula is inserted into the stomach through the pylorus from an opening in the first part of the duodenum. The duodenum is ligated just proximal to the entry of the bile duct and the cardio-oesophageal junction is also tied, the vagi being excluded from the ligature. The cannula is a piece of perforated soft rubber tubing about 7 cm. long and of about 0.4 cm. bore. It is tied on to a short length of glass tubing around which the pyloric ligature is tied, the local blood vessels being carefully preserved. From the other end of the glass tubing another short rubber tube passes to the exterior through a stab wound in the right side of the abdominal wall, at the level of the pylorus. The animal is arranged slightly tilted on its right side so that the gastric juice flows readily from the stomach, without stasis. In only two of some seventy animals have more than a few drops (<0.5 ml.) been found in the stomach at the end of 6–7 hours of collection of juice. The stomach is gently rinsed out with warm saline via the pyloric cannula, and after closure of the abdominal incision the animal is left for an hour before the infusion is commenced. The whole procedure takes only a few minutes, and under the conditions described the rate of secretion at the end of one hour is basal and of the order of one or two drops in ten minutes, no free acid being detected. It is important that the animal be kept warm during the whole of the experiment.

The infusion apparatus was designed and made by Dr. E. H. J. Schuster; it incorporates a cylinder with close-fitting reversible piston, originally a small hydraulic jack. This apparatus delivers a constant slow flow of liquid paraffin to a vessel from which the infusion fluid is displaced into the cat. By means of an electric gramophone motor and a variable reversible gear, a continuous infusion can be maintained indefinitely at a rate variable from 0.19 to 6.0 ml. per min. Histamine acid phosphate is made up in normal saline, and the infusion of 0.75 ml. of saline per min. easily replaces the fluid and chloride lost in the gastric juice. (Throughout this paper doses of histamine are doses of the base.) In control animals infusion of saline alone did not cause any secretion greater than the basal rate. The total volume of juice and the amounts of free and total acid were measured, samples being collected at intervals of 10 to 30 minutes for up to 7 hours. For acid titration *N*/50 or *N*/20 sodium hydroxide was used with thymol blue as the usual indicator for the two endpoints. Peptic activity of the juice has not been measured.

In most of the experiments with neoantergan it was infused with histamine in the same solution. In three other experiments, after an initial period of two hours during which 5 μg. histamine per min. was infused, the infusion was rapidly changed to a mixture of 5 μg. histamine and 15 μg. neoantergan per min. for 1½ to 2 hours. Finally the original solution of histamine was substituted for the mixture. The solutions were changed with only a momentary interruption of the flow since it was arranged that the pump could deliver liquid paraffin to either of two bottles by changing a number of clips.

Results

The average volumes of juice and of free acid secreted by groups of 6 or 7 cats during successive 30-min. periods of histamine infusion are shown in Fig. 1. The four groups of cats received histamine infusions of 2.5, 5, 10, and 20 μg. per min. respectively for 5–6 hours. After an initial delay varying from about 30 to 90 minutes, during which there is a steady increase in secretion, a reasonably constant rate of secretion is maintained for some 5 hours at least. The initial delay is less at the higher rates of infusion, as might be expected. The groups receiving 10 and 20 μg. histamine per min. achieve much the same peak rate of secretion. When the average hourly secretion rates are compared with the rate of infusion as in Table II and Fig. 2, it can be seen that although there is a wide variation between the responses of individual cats there is a relation between the mean rate of secretion in a group of cats and the rate of histamine infusion. It is certain that in most cats secretion is not maximally stimulated by an infusion of 5 μg. histamine per min. and probably not by 10 μg. per min. If the rates

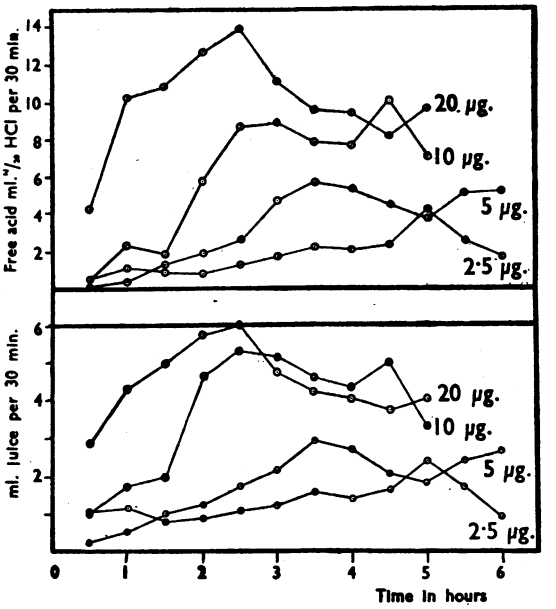

FIG. 1.—Mean volumes of juice and free acid secreted in successive 30-minute periods by groups of cats receiving different rates of histamine infusion. 2.5, 5, 10, and 20 μg./min. (equivalent to range of 0.74 to 1.25, 1.4 to 2.3, 3.4 to 4.5, and 5.3 to 9.8 μg. histamine/kg./min.) in groups of 6, 7, 6, and 6 cats respectively. Infusion started at zero time. Abscissae, time in hours. Ordinates ml., juice and *N*/20 HCl in 30 min.

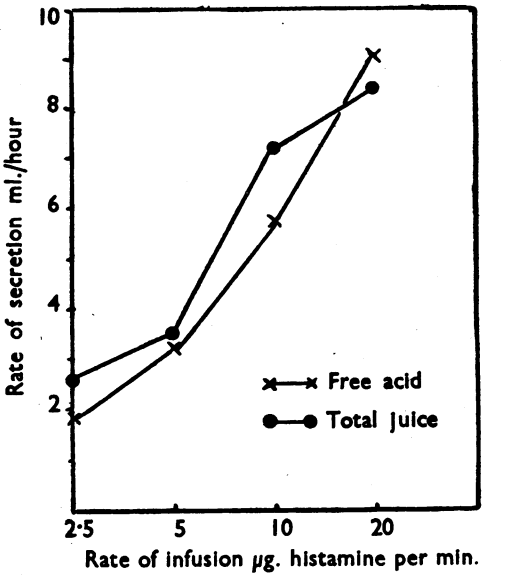

FIG. 2.—Average hourly secretion rates (gastric juice and free acid) over a period of 5–6 hours in groups of cats, at different rates of histamine infusion. Abscissae: rate of histamine infusion (logarithmic. scale). Ordinates: rate of secretion.

of infusion are correlated with the weights of the individual animals it is found that a rate of histamine infusion in excess of 4 μg. per kg. per min. causes maximal secretion in most animals. The secretion due to 2 to 3 μg. histamine per kg. per min. is usually submaximal.

Infusion of neoantergan alone (15 μg./min.) did not stimulate gastric secretion in excess of the "basal" level and no free acid was detected in such juice. In Figs. 3 and 4 average secretion curves are compared for groups of cats given histamine alone and mixtures of histamine and neoantergan. Secretion in a group of cats given 5 μg. histamine and 15 μg. neoantergan per min. is greater than that due to 5 μg. histamine per min. alone (Fig. 3). This is also apparent from the average hourly secretion rates shown in Table III. From Fig. 4 it will be seen that

TABLE II

MEAN RATES OF SECRETION OF JUICE AND FREE ACID IN RELATION TO RATE OF HISTAMINE INFUSION

(Histamine doses are given in terms of free base; the acid phosphate was used)

Group rate of infusion	No. of cats	Avge. wt. (kg.)	Range of individual infusion rates μg./kg./min.	Mean rate of secretion of juice			Mean rate of acid production (*N*/10 HCl)		
				ml./hr.	σ	ϵ	ml./hr.	σ	ϵ
2.5 μg./min. ..	6	2.7	0.74–1.25	2.61	1.78	0.73	1.89	2.24	1.00
5.0 μg./min. ..	7	2.85	1.4 –2.3	3.50	2.25	0.85	3.26	3.33	1.26
10.0 μg./min. ..	6	2.52	3.4 –4.5	7.20	3.50	1.43	5.78	3.19	1.30
20.0 μg./min. ..	6	2.58	5.3 –9.8	8.42	2.41	0.98	9.07	4.47	1.83

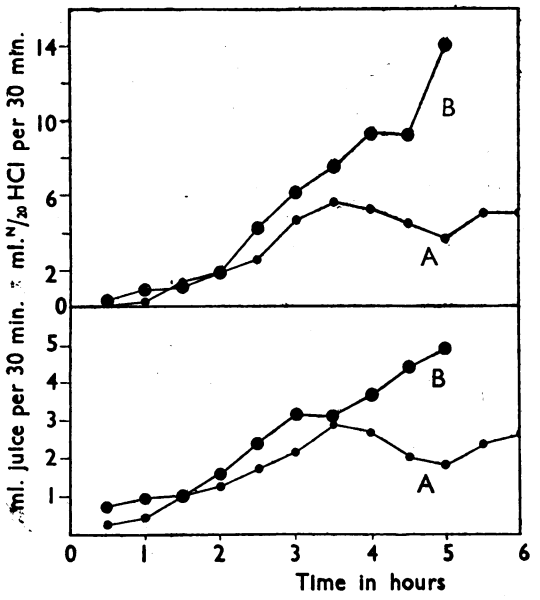

FIG. 3.—Effect of neoantergan. Comparison of secretion of gastric juice and free acid due to 5 μg. histamine/min. (A) and a mixture of 15 μg. neoantergan and 5 μg. histamine/min. (B). Secretion induced by the mixture is greater than with histamine alone. Figures are average values for groups of 7 and 6 cats respectively.

TABLE III

THE EFFECT OF NEOANTERGAN ON GASTRIC SECRETION INDUCED BY HISTAMINE INFUSION, 5 μG./MIN.

Cat No.	Weight kg.	Duration, hours	Average rate of secretion: Juice, ml./hr.	Average rate of secretion: N/10 acid, ml./hr.
A. Infusion 5 μg. histamine per min.				
28	2.75	6	5.90	5.85
34	3.25	6	1.20	0.50
35	2.80	5	5.20	6.65
36	2.50	5	0.65	0.00
37	2.90	6	1.90	0.65
45	2.18	5	3.75	3.85
58	3.60	7	5.90	5.30
Mean rate ± standard error			3.50 ± 0.85	3.26 ± 1.26
B. Infusion 5 μg. histamine + 15 μg. neoantergan per min.				
29	2.50	6	3.10	2.50
40	2.45	5	3.95	0.75
43	1.87	4	5.50	5.55
44	1.75	5	6.20	6.85
47	2.50	6	12.05	15.55
48	3.48	5	1.80	0.80
Mean rate ± standard error			5.43 ± 1.47	5.33 ± 2.08

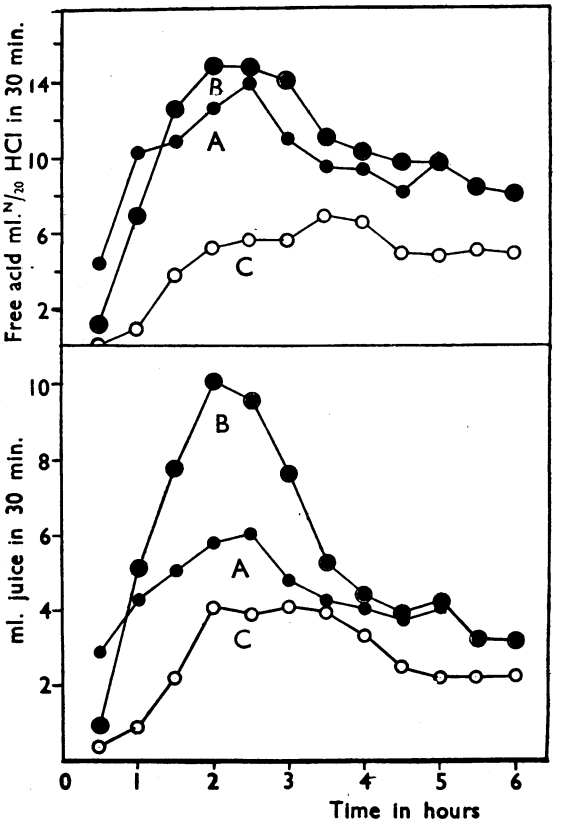

FIG. 4.—Effect of neoantergan. Comparison of average secretion curves for juice and free HCl due to 20 μg. histamine per min. (6 cats) (A) with that due to infusion of the same amount of histamine and 5 or 15 μg. neoantergan per min. (3 cats each). 15 μg. neoantergan (B); 5 μg. neoantergan (C).

the secretion produced by 20 μg. histamine and 15 μg. neoantergan per min. is probably greater than that due to histamine alone, although the secretion produced by 20 μg. histamine and 5 μg. neoantergan per min. is less than that due to histamine alone. These contrary findings may be partly due to the small number of animals tested in this group (Table IV).

In two of three other experiments, in each of which the effects of infusions of histamine and neoantergan and of histamine alone were compared in the same animal, there was a definite increase in secretion of juice and acid during the period of the mixed infusion compared with that due to histamine only (Fig. 5). The effect was absent in the third cat. Certainly no inhibition of gastric secretion was observed.

TABLE IV

THE EFFECT OF NEOANTERGAN ON GASTRIC SECRETION INDUCED BY 20 μG. HISTAMINE/MIN.

Cat No.	Weight kg.	Duration, hours	Average rate of secretion: Juice, ml./hr.	Average rate of secretion: N/10 HCl, ml./hr.
20 μg. histamine per min.				
15	2.05	4	3.65	1.05
16	2.50	5	9.10	9.80
17	2.30	6	9.20	8.85
18	2.45	6	9.85	10.05
20	2.35	7	10.15	14.80
64	3.80	5	8.50	9.90
Mean rate ± error			8.41 ± 0.99	9.08 ± 1.83
20 μg. histamine and 5 μg. neoantergan per min.				
22	2.50	6	4.35	3.50
23	3.50	6	2.80	1.50
24	2.75	6	8.85	9.05
Mean rate ± error			5.33 ± 1.82	4.67 ± 2.24
20 μg. histamine and 15 μg. neoantergan per min.				
25	1.80	6	11.80	2.15
26	1.80	6	12.90	19.20
27	2.70	6	7.70	8.95
Mean rate ± error			10.8 ± 1.58	10.1 ± 4.95

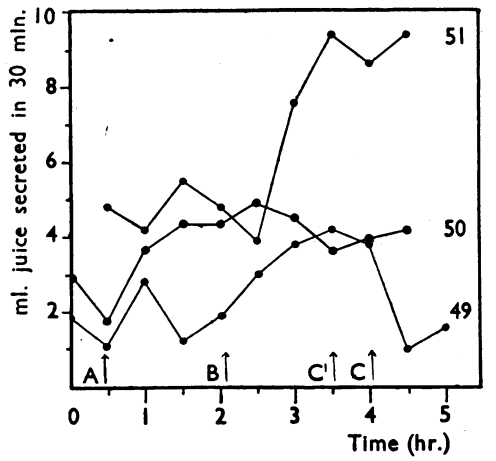

FIG. 5.—Effect of neoantergan on gastric secretion of cats 49, 50, and 51: 5 μg. histamine per min. at A and C (C′ for cat 51); 5 μg. histamine and 15 μg. neoantergan per min. between B and C (C′ for cat 51). Pentobarbitone anaesthesia.

The majority of the results suggest the probability that neoantergan may increase rather than reduce the stimulation of gastric secretion by histamine.

DISCUSSION

Continuous intravenous infusion of histamine causing submaximal secretion of gastric juice and acid has given in most animals a reasonably steady flow of juice and acid for some hours after the first 30 to 90 minutes; during this initial period the secretion is increasing to the steady level. At the highest rates of infusion used there is a tendency for the rate of secretion, which is probably maximal, to fall off after 5–6 hours. In most animals a rate of infusion of 2 to 3 μg. histamine per kg. per min. will not stimulate gastric secretion maximally, and this rate of infusion is probably suitable if it is desired to test the effect of other substances on the secretion produced by histamine. In a particular animal one can test whether the secretion is in fact submaximal by observing the effect of increasing the rate of infusion once a steady rate of secretion has been obtained. The former level of secretion is usually regained within 30 minutes of reducing the infusion rate again.

The effect of substances which antagonize histamine or histamine-induced gastric secretion can be investigated. The test substance may be injected in single doses during the histamine infusion, or average secretion curves for groups of animals receiving histamine alone can be compared with similar curves for groups receiving histamine and the antagonist. A quantitative estimation of the effect can be obtained with either method.

The finding that neoantergan did not inhibit the effect of histamine on gastric secretion was expected in view of earlier work. There seems little doubt that, like other less potent antihistamine agents, neoantergan does not decrease the gastric secretory effect of histamine. Even the much more potent thiodiphenylamine derivative, 3277 R.P., has been shown to be ineffective against the gastric ulceration produced by large doses of histamine in the guinea-pig, although protecting the animal from the immediately lethal effect of the histamine (Halpern and Martin, 1946). Clinical evidence confirms that neoantergan has no value in the control of gastric hypersecretion (Decourt, 1945). The evidence reported here strongly suggests that neoantergan may actually increase the gastric secretory response to injected histamine. Similar effects after the administration of benadryl have been reported by Emmelin and Frost (1947) in anaesthetized cats and by McElin and Horton (1946) and Doran (1947) in man.

This probable potentiation of histamine action on gastric secretion may link up with the reported aggravation of symptoms in some asthmatic patients treated with antihistamine substances (see Bovet and

Walthert, 1944, p. 38). These authors pointed out that this finding might be due to an increased "histaminaemia," and Geiringer (1947) has recently reiterated this possibility in a comment on the conclusions of Doran. Proof of such an explanation of the apparently anomalous finding awaits further experiment.

SUMMARY

1. Gastric secretion has been collected from cats, anaesthetized with sodium pentobarbitone, by a cannula tied into the stomach through the pylorus. Volumes of juice and of free and total acid secreted have been measured.

2. The mean rate of secretion of juice and of acid in a group of cats is related to the rate of infusion of histamine, although the rate of secretion obtained with a certain rate of histamine infusion varies considerably from animal to animal.

3. The infusion of 2 to 3 μg. histamine per kg. per min. causes a submaximal secretion in most cats, which remains relatively steady after the first 30 to 90 minutes for at least 5 or 6 hours.

4. The method can be used to investigate the effect of other substances on the gastric secretion induced by histamine.

5. The antihistamine substance neoantergan has been found to increase rather than to inhibit the gastric secretion induced by an infusion of histamine. The implications of this finding are discussed.

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