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THE EFFECT OF ANTIHISTAMINE SUBSTANCES ON GASTRIC SECRETION IN MAN

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At the time when the experiments to be described here were started, there were few reports regarding the action of antihistamine substances on gastric secretion, and these were contradictory. Thus Loew, MacMillan, and Kaiser (1946) found the response to histamine in three out of four dogs reduced by benadryl, and McGavack, Elias, and Boyd (1946) reported a depressant effect of benadryl on the gastric acidity following alcohol administration to normal human beings. On the other hand, Sangster, Crossman, and Ivy (1946) found no effect of benadryl on histamine-stimulated secretion in dogs, while McElin and Horton (1946) obtained variable results in patients with multiple sclerosis, and Moersch, Rivers, and Morlock (1946) adduced evidence that gastric acidity usually *increased* after the use of benadryl. It seemed therefore of interest to investigate further the action on gastric secretion in human subjects of the three antihistamine substances in common clinical use. Since previous results (Ashford, Heller, and Smart, 1949) indicated that pepsin secretion is also stimulated by histamine, the effects of these substances on both acid and pepsin output were examined.

METHODS

These have been described in a previous paper (Ashford, Heller, and Smart, 1949). The subjects, with two exceptions, were healthy medical students of both sexes, and the same dose of histamine acid phosphate (1.5 mg. = 0.54 mg. base) was given by subcutaneous injection throughout. Each subject was used twice with an interval of at least one week between the experiments: on one occasion histamine was given followed or preceded by a control injection of normal saline (0.9 g. NaCl/100 ml. H_2O); on the other the antihistamine substance was given by subcutaneous injection either before or after the injection of histamine. Controls were performed also, in which either the saline solution alone or a solution of an antihistamine substance alone was injected.

The antihistamine substances studied and the doses used were:

1. β-dimethylaminoethyl benzhydryl ether hydrochloride ("Benadryl"). 50 mg. (= 44 mg. base) in 1 ml. normal saline per subject.

2. N-phenyl-N-benzylaminomethyl imidazoline sulphate ("Antistin"). 100 mg. (= 85 mg. base) in 2 ml. normal saline per subject.

3. N-*p*-methoxybenzyl-N-dimethylaminoethyl-2-aminopyridine maleate ("Neoantergan" = "Anthisan"). 100 mg. (= 72 mg. base) in 1 ml. normal saline per subject.

RESULTS

Figs. 1, 2, and 3 compare the secretion of free hydrochloric acid, total hydrochloric acid, and pepsin respectively in the stomachs of healthy subjects who received a subcutaneous injection of histamine and of an antihistamine substance in one experiment and a subcutaneous injection of histamine only in another. Concentrations of free acid, total acid, and pepsin are shown in Figs. 1A, 2A, and 3A respectively. Output of free acid, total acid, and pepsin per 15 min. are shown in Figs. 1B, 2B, and 3B respectively.

Ten experiments with antihistamine substances were performed on five groups of two subjects. Group I consisted of two subjects to whom 50 mg. of benadryl per person had been administered 15 min. before the standard dose of histamine. In Group II 50 mg. benadryl was injected 30 min. after histamine. The subjects in Group III received 100 mg. antistin 15 min. before histamine. Group IV and V each comprised two subjects who received 100 mg. anthisan (=neoantergan) 15 min. after histamine. The points in Figs. 1, 2, and 3 marked I, II, III, IV, and V represent mean values for the gastric secretion in the respective groups during the period of 15 min. before and five periods of 15 min. after the injection of histamine. It will be seen that

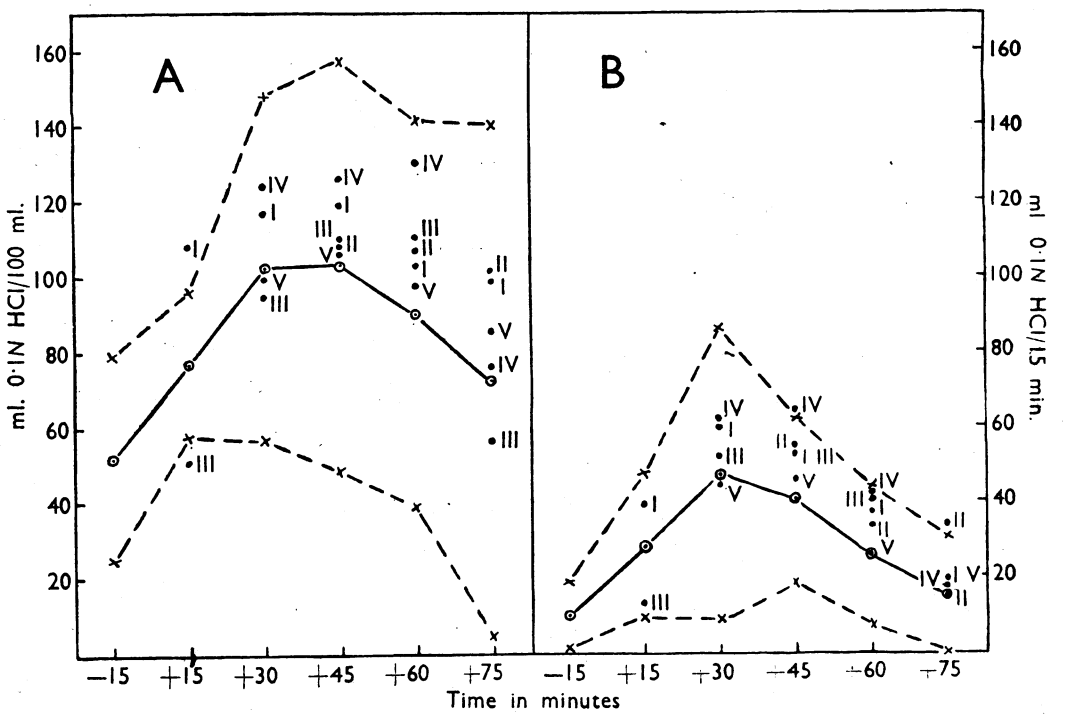

FIG. 1.—Effect of injections of antihistamine substances on histamine-provoked *free* hydrochloric acid secretion. A = ml. 0.1 *N* HCl/100 ml. B = ml. 0.1 *N* HCl/15 min. Each of the points accompanied by a Roman numeral represents the mean response to histamine plus antihistamine substance in each group of two subjects (for definition of groups see text, p. 157). ⊙——⊙ = mean line which represents the average response to histamine *alone* in the 10 subjects investigated. ×---× = the 1/40 Fiducial Limit for the average response of the subjects, calculated by multiplying the average range in the response in each group by a factor which transforms the average range into 1.69 times the standard deviation (see Herdan, 1948). 0.54 mg. histamine per subject was injected at the end of the period marked as "−15 min."

the points in Figs. 1 and 2 with few exceptions lie above the line indicating the mean response to histamine alone (which was calculated by pooling the results of the 10 control experiments on the same subjects). There was therefore no evidence that the concentration or output of hydrochloric acid decreased after the injection of the antihistamine substances. The distribution of the points in Fig. 3 is somewhat different in that a number of pepsin values are lower than the mean figures for the control experiments, though they are not low enough to reach the broken line which represents the Fiducial Limit of 1/40 for average results of two subjects. These decreases cannot therefore be regarded as significant. It will be noted, however, particularly in Fig. 3A, that quite a number of pepsin values are significantly *higher* than the mean level in the control experiments, suggesting that in some instances histamine plus antihistamine produced more pepsin than histamine alone. Figs. 1 and 2 indicate that the same applies to hydrochloric acid secretion. Thus in our series of experiments antihistamine substances not only failed to decrease histamine-provoked gastric secretion but, on the contrary, occasionally increased it.

The Table shows the results of experiments on normal subjects who received subcutaneous injections of the standard doses of antihistamine substances (100 mg. anthisan or 100 mg. antistin or 50 mg. benadryl per subject) alone and also the results of control experiments (subcutaneous injection of normal saline). It shows, first, that acid and pepsin secretions *before* the injection were much the same in the two series, and, secondly, that the doses of antihistamines used had no pronounced effect on "resting" gastric secretion—i.e., the secretion of hydrochloric acid and pepsin was neither considerably depressed nor considerably raised.

TABLE

COMPARISON BETWEEN THE EFFECT OF INJECTION OF ANTIHISTAMINE SUBSTANCES AND OF 0.9 PER CENT NaCl SOLUTION ON THE GASTRIC SECRETION OF NORMAL FASTING SUBJECTS. THE FIGURES SHOWN AS "BEFORE INJECTION" ARE MEAN VALUES FOR THREE 15-MIN. PERIODS, THOSE AS "AFTER INJECTION" ARE MEAN VALUES FOR FOUR 15-MIN. PERIODS. THE FIGURES IN BRACKETS ARE THOSE OBTAINED IN THE CONTROLS—I.E., AFTER THE INJECTION OF 0.9 PER CENT NaCl SOLUTION

Subject	Antihistamine injected s.c. per subject	Secretion collected before or after injection	ml. 0.1 *N* HCl/100 ml.		ml. 0.1 *N* HCl/15 min.		Pepsin units	
			free	total	free	total	per ml.	per 15 min.
To.	100 mg. anthisan	Before	30 (18)	53 (54)	3.6 (2.3)	6.3 (7.0)	100 (100)	1200 (1275)
		After	55 (29)	72 (53)	12.0 (3.5)	15.5 (6.6)	110 (100)	2150 (1220)
		Difference	+25 (+11)	+19 (−1)	+8.4 (+1.2)	+9.2 (−0.4)	+10 (0)	+950 (−55)
Sp.	100 mg. anthisan	Before	20 (16)	30 (30)	5.4 (4.9)	8.0 (9.1)	60 (40)	1620 (1200)
		After	27 (9)	38 (20)	6.5 (2.5)	9.3 (2.5)	70 (20)	1740 (550)
		Difference	+7 (−7)	+8 (−10)	+1.1 (−2.4)	+1.3 (−6.6)	+10 (−20)	+120 (−650)
Du.	100 mg. anthisan	Before	19 (24)	39 (37)	2.3 (1.2)	4.6 (1.9)	20 (40)	235 (200)
		After	6 (10)	24 (28)	0.3 (1.0)	1.5 (2.7)	60 (40)	270 (255)
		Difference	−13 (−14)	−15 (−9)	−2.0 (−0.2)	−3.1 (+0.8)	+40 (0)	+35 (+55)
El.	50 mg. benadryl	Before	55 (58)	67 (75)	14.0 (3.5)	17.0 (4.5)	150 (125)	3850 (750)
		After	55 (83)	70 (101)	6.8 (9.6)	8.5 (11.3)	130 (125)	1590 (1540)
		Difference	0 (+25)	+3 (+26)	−7.2 (+6.1)	−8.5 (+6.8)	−20 (0)	−2260 (+790)
Ew.	100 mg. antistin	Before	18 (12)	29 (15)	6.0 (2.7)	9.7 (4.7)	10 (20)	355 (430)
		After	14 (20)	25 (28)	3.2 (4.4)	6.2 (6.2)	20 (30)	510 (600)
		Difference	−4 (+8)	−4 (+13)	−2.8 (+1.7)	−3.5 (+1.5)	+10 (+10)	+155 (+170)

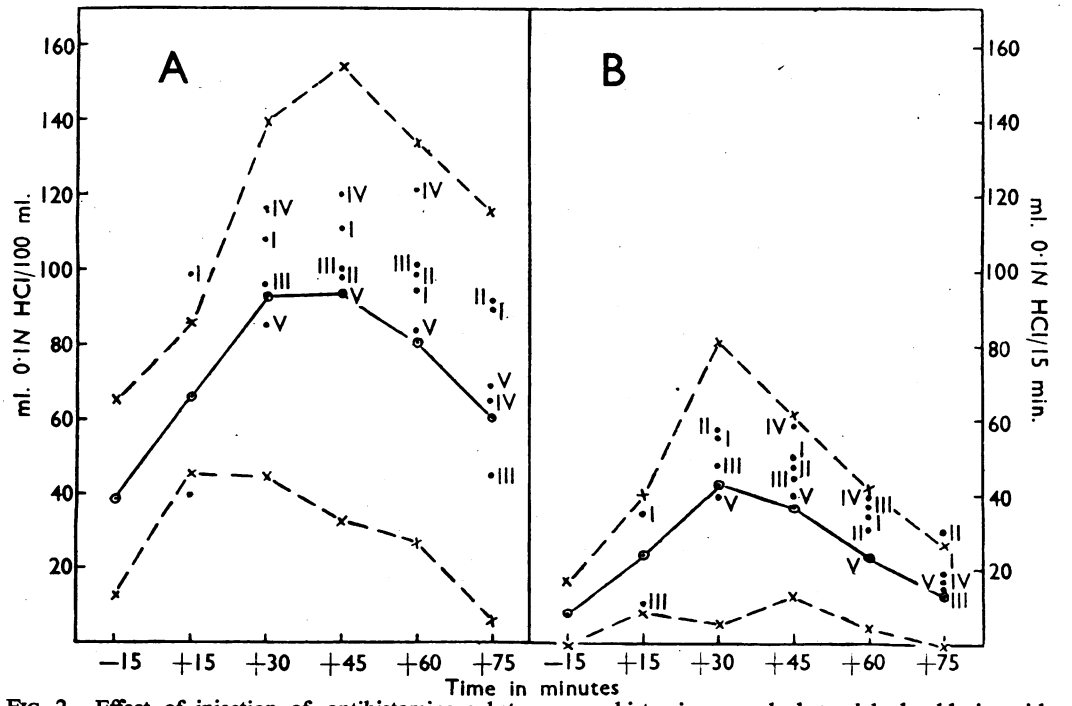

FIG. 2.—Effect of injection of antihistamine substances on histamine-provoked *total* hydrochloric acid secretion. A = ml. 0.1 *N* HCl/100 ml. B = ml. 0.1 *N* HCl/15 min. For further description see Fig. 1.

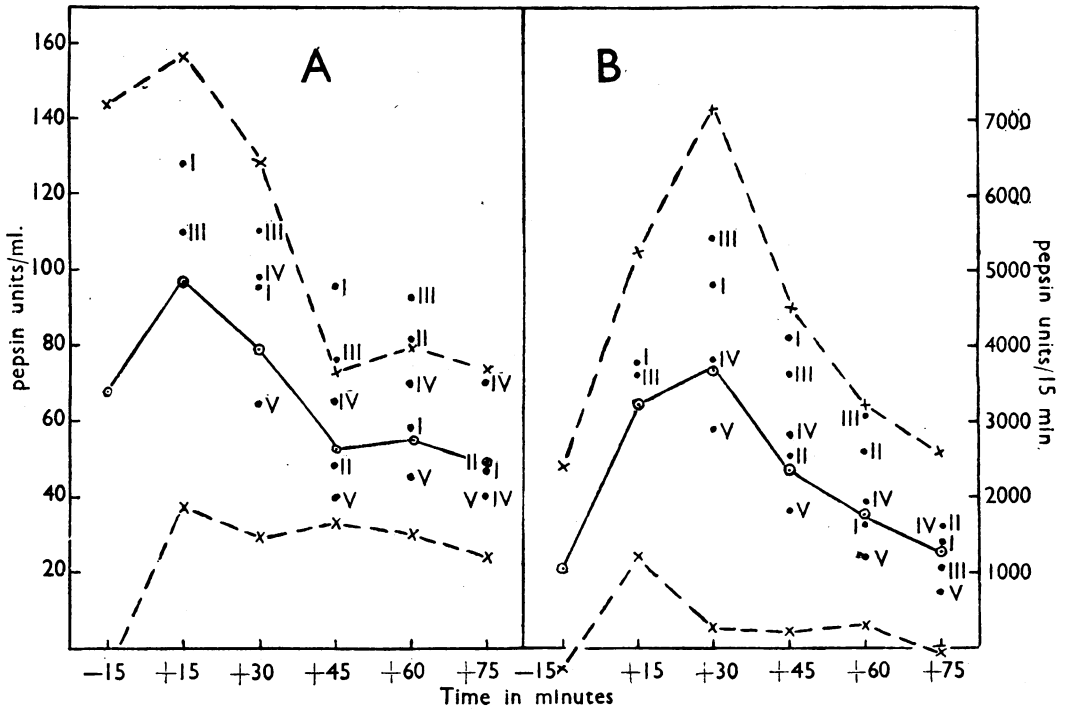

FIG. 3.—Effect of injection of antihistamine substances on histamine-provoked pepsin secretion. A = pepsin units/ml. B = pepsin units/15 min. For further description see Fig. 1.

Two experiments only were performed on patients suffering from gastric ulcers. The response to 0.54 mg. histamine injected subcutaneously was first investigated. Anthisan in doses of 100 mg. three times daily was subsequently given by mouth for 17 days to patient Hi. and for 20 days to patient Da. and the histamine test then repeated. The response of patient Hi. was found to be almost identical with that in the preliminary experiment. In the second patient (Da.) the acid concentration did not reach higher values than on the first occasion but remained at the maximum level for a longer period of time (60 as compared with 15 min.). Clinically patient Hi. showed no improvement during or immediately after the "treatment" with anthisan. Patient Da. was definitely worse, a finding which was borne out by radiological re-examination after the administration of anthisan had been terminated. It was therefore thought unjustifiable to prolong the experiments or to investigate the effects of antihistamine substances in other patients with gastric or duodenal ulcers.

DISCUSSION

The results presented show clearly that neither benadryl, antistin, nor anthisan in the dosages given decrease acid or pepsin secretion provoked by histamine in healthy human beings. In some of the subjects studied the output of acid and pepsin in fact rose above that resulting from the injection of histamine alone. Deutsch (1947), who administered 0.5 mg. histamine and 100 mg. "bridal" (=antergan) or 200 mg. antistin intravenously, appears to have obtained similar results, as also did Moersch and his co-workers (1946) in patients suffering from duodenal ulcer. Gordonoff (1948), in a small series of experiments on healthy subjects injected with 50 mg. neoantergan and 0.5 mg. histamine, failed to observe an increase of hydrochloric acid secretion.

Administration to healthy subjects of 50 mg. benadryl, 100 mg. antistin, or 100 mg. anthisan alone had no pronounced effect in our series of experiments. Doran (1947) and Deutsch (1947), however, using higher doses of antihistamine substances reported increases in hydrochloric acid concentration.

The results of these "acute" experiments are in apparent contrast with those of McGavack *et al.* (1946), who administered 200–400 mg. benadryl by mouth daily to healthy subjects for periods of two to six weeks and observed a marked depression of acid secretion. Their results are not in accord with

our findings in two ulcer patients who had received 300 mg. anthisan by mouth daily for periods of 17 and 20 days : neither a reduction of the high acid secretion nor any amelioration of clinical symptoms was obtained.

It would thus appear from our results that beneficial effects of antihistamine substances on patients suffering from gastric or duodenal ulcers may not be expected. On the contrary, the administration of these substances would seem to be contraindicated in these and similar conditions.

It is perhaps surprising that the antihistamines which antagonize all other actions of histamine whether stimulant or depressant (Dews and Graham, 1947 ; Gaddum, 1948) have no effects on the action of histamine on glandular tissues. However, since the mechanism of the action of histamine on the gastric glands is as yet imperfectly understood, it would seem unprofitable at present to speculate on the reasons for the failure to influence this particular action.

Summary

1. Subcutaneous injection of 50 mg. benadryl, 100 mg. antistin, or 100 mg. anthisan failed to lower the concentration and output of hydrochloric acid and pepsin in 10 healthy subjects to whom 0.54 mg. histamine had been administered ; on the contrary, an increase of gastric secretion was noted in some subjects.

2. Injection of the same doses of the antihistamine substances alone produced no marked alteration of acid or pepsin secretion.

3. Two patients with gastric ulcers were given 300 mg. anthisan by mouth daily for 17 and 20 days. Gastric secretion of acid was not reduced after these periods and the clinical state of the patients did not improve.

4. It is suggested that the use of antihistamine substances is contraindicated in patients suffering from gastric ulcer and similar conditions.

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