EFFECT OF LARGE DOSES OF HISTAMINE ON GASTRIC SECRETION OF HCl

AN AUGMENTED HISTAMINE TEST

BY

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In the routine histamine test of gastric secretion the dose of histamine advised has been determined arbitrarily as being generally sufficient to provoke an acid response and generally free from liability to cause untoward symptoms. It is thus a compromise, and fails to take account of individual variations in susceptibility. This defect can be overcome by utilizing the group of synthetic drugs known as the antihistaminics.

These compounds have been shown to antagonize all histamine effects save that on gastric secretion. This interesting anomaly has been well demonstrated by the work of Halpern (1948). He has shown that, although guinea-pigs could be protected against the systemic effects of as much as 1,500 lethal doses of histamine, many animals died within a day or two as a result of gastric perforation.

The purpose of this paper is to describe the parietal cell response in man to large doses of histamine, the systemic effects of the drug being prevented by the use of an antihistamine. It will be shown that in this way it is possible to give a maximum stimulus to the parietal cells. An augmented histamine test of gastric secretion, based on this principle of maximum stimulation, is described and an analysis made of the results of 148 such tests performed on normal subjects and on patients with peptic ulcer.

Secretion of HCl after Increasing Doses of Histamine

Dosage.—Throughout this investigation histamine has been given subcutaneously as histamine acid phosphate in multiples of the usual body-weight (B.W.) dose of 0.1 mg. per 10 kg. body weight. Mepyramine hydrogen maleate ("anthisan") was chosen as the antihistamine. In a series of preliminary experiments it was found that, in order to protect the patient against the systemic effects of histamine, each body-weight dose of histamine had to be covered by 1 ml. of mepyramine (25 mg.). It was also found that the antihistamine should be given intramuscularly 30 minutes before giving the histamine injection. Thus, a patient about to be given four B.W. doses of histamine would have an intramuscular injection of 4 ml. of mepyramine 30 minutes previously.

Secretion Studies.—Secretion tests were begun at 9 a.m. following a 12-hour fast. A constant size of stomach-tube, having multiple perforations at its tip, was used throughout. The fasting juice was first aspirated by syringe, the position of the patient and the position of the tube being altered until the "residual pool" of gastric juice had been tapped. This achieved, the tube was fixed to the side of the face and the patient made comfortable in this position—usually reclining on the left side. Subsequent collection of gastric juice was made by continuous aspiration, using the suction provided by an electric pump. The spontaneous secretion was withdrawn for a control period of 45 minutes before giving mepyramine, and thereafter aspiration was continued for 30 minutes until the histamine injection was made. The volume of the gastric juice withdrawn in the 45-minute period after histamine was measured and the titratable free hydrochloric acid estimated. The weight of HCl secreted in this time was then calculated and expressed in milligrams of HCl. All saliva was expectorated during these tests.

Effects of Increasing Dosage of Histamine.—With these standard conditions, one, two, three, or more B.W. doses of histamine covered by the requisite amount of antihistamine were given to each subject on successive days. The order in which the different doses was given was varied in each subject. This series of experiments was made on five "normal" males (hernia cases without history of dyspepsia) and on five male patients with clinical and radiological evidence of duodenal ulcer. In all, 77 separate secretion tests were made. The largest single injection of histamine given was the equivalent of 12 B.W. doses; thus one ulcer patient was given 6.8 mg. and one normal subject 7.1 mg. without untoward effects. Headache and flushing were not more severe after large doses of histamine than after the usual single B.W. dose uncovered by antihistamine. The latter often induced drowsiness, which enabled the subjects to endure more readily a trying succession of secretion tests.

Results.—The weights of HCl secreted in 45 minutes in response to various doses of histamine have been plotted as ordinates on a graph, with the dose of histamine along the abscissa: in both groups of patients an S-shaped curve was produced (Figs. 1 and 2). It will be seen that maximum HCl output follows the giving of four B.W. doses of histamine and that any further increase in histamine dosage is not followed by appreciable change in acid output. It seems probable that, with increasing doses of histamine, an increasing number of parietal cells are stimulated until the entire parietal cell population is functioning. This is in agreement with the findings of Card (1952).

FIG. 1.—Dose-response curves in five cases of duodenal ulcer.

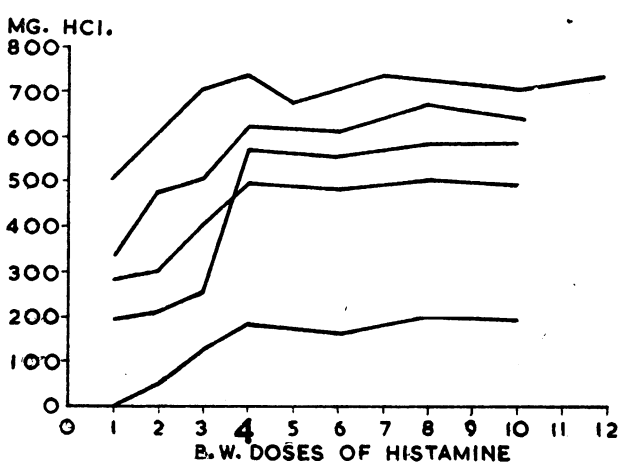

FIG. 2.—Dose-response curves in five normal subjects.

Duration of Maximum HCl Secretion after Four Body-weight Doses of Histamine

The following observations were made to determine the duration of the secretory response to large doses of histamine with a view to standardizing an augmented histamine test.

Eight male patients with duodenal ulcer were selected for study. Each patient was given a single test in which the subcutaneous administration of four B.W. doses of histamine was preceded by an intramuscular injection of 4 ml. of mepyramine. The juice was again collected by continuous suction, but the collecting vessel was changed every five minutes for a period of one hour. The weight of HCl secreted in each five-minute period was expressed in milligrams of HCl.

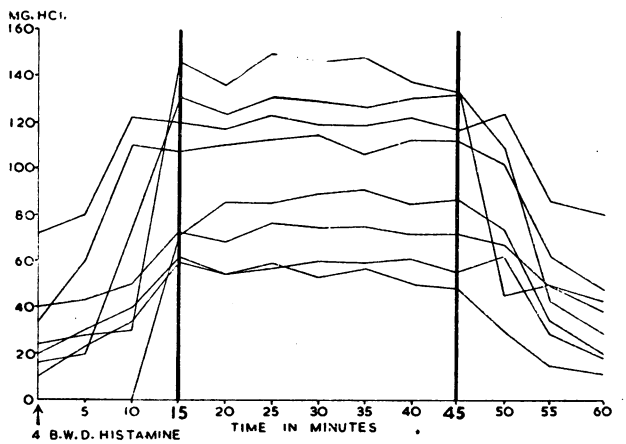

FIG. 3.—Gastric output of HCl (mg.) in response to four B.W. doses of histamine. Continuous aspiration—five-minute specimens from eight patients.

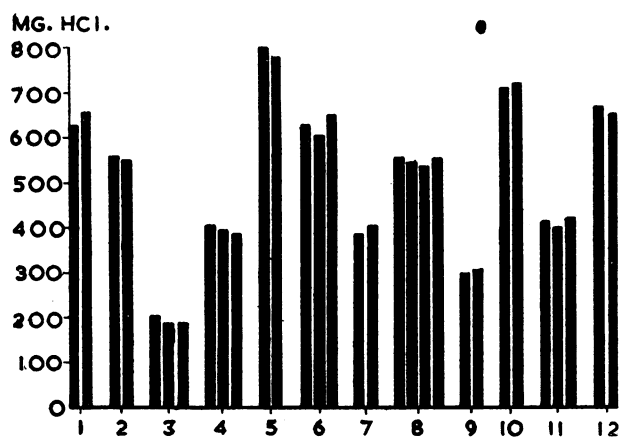

FIG. 4.—Gastric HCl output after histamine (four B.W. doses). Repeated estimations in 12 patients.

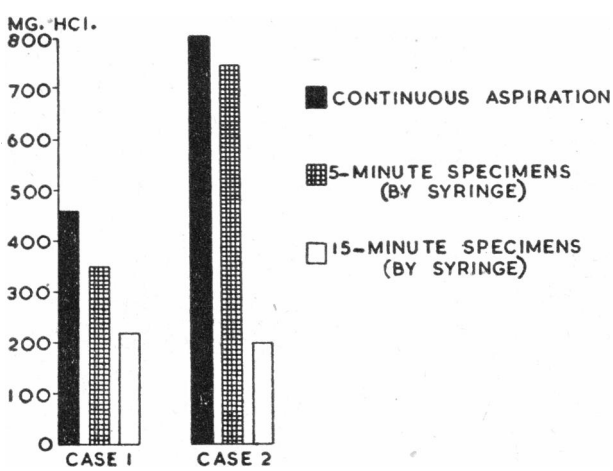

FIG. 5.—Gastric output after histamine (four B.W. doses).

In all cases maximum output was reached in about 10–15 minutes and persisted for the next 30–35 minutes (Fig. 3). The best measure of output, therefore, is based on the secretion during the half-hour period from 15 to 45 minutes after administration of histamine.

Adopting this half-hour period of continuous aspiration, each of 12 patients was given two or more tests on successive days. The consistency of consecutive estimations is shown in Fig. 4. The error occurring between separate tests was about 5%.

That it is essential to collect the gastric juice by continuous aspiration has been shown by a simple experiment in which the histamine test was repeated on three successive days on each of two patients. The method of aspiration was the only variable factor in the three tests: continuous aspiration was used on the first day, syringe removal at five-minute intervals on the second day, and syringe removal at 15-minute intervals on the third day. It will be seen that the "maximum" HCl output of the stomach appears to fall when interval aspiration is employed (Fig. 5). This fall is due to the reduction in the volume of juice aspirated from the stomach, a considerable amount having been lost through the pylorus in the intervals between aspiration.

The Augmented Histamine Test

The test to be described is based on the conclusions reached in the foregoing studies. It provides two single results expressed in milligrams of HCl. The first figure indicates the basal secretion, and the second gives an expression of maximum parietal cell activity. The test is made as follows:

(1) The test is preceded by a 12-hour fast.

(2) A No. 9 stomach tube is introduced into the stomach and the fasting juice aspirated by means of a 50-ml. syringe. It is essential to alter the position both of the tube and of the patient until the tip of the tube reaches the most dependent part of the stomach and permits aspiration of the residual pool of fluid. This position of the tube is now maintained by fixing it to the side of the face and by insisting that the patient does not alter his posture until completion of the test. This will usually mean that he will lie comfortably on his left side.

(3) The spontaneously secreted gastric juice is now collected for a period of 45 minutes and the basal secretion expressed in milligrams of HCl produced in this time interval.

(4) 4 ml. of mepyramine is now given by intramuscular injection.

(5) The gastric juice is aspirated for the next 30 minutes and is discarded.

(6) A subcutaneous injection of a 4 B.W. dose of histamine acid phosphate is now made.

(7) The histamine-provoked secretion is continuously aspirated and the volume secreted in the half-hour from 15 to 45 minutes after injection is measured and its titratable free HCl estimated. The weight of HCl produced in this 30-minute period is the figure expressing the maximum parietal cell response.

This test of gastric secretion has certain advantages over other gastric-function tests. It is simple to do and lasts only two hours. The systemic effects following the administration of a large dose of histamine are prevented and the main subjective sensation is the drowsiness due to the antihistamine. More than 200 such tests have now been made in this unit without incident. It provides two figures—one expressing basal secretion and one maximum secretion of HCl.

Analysis of Results of 148 Augmented Histamine Tests

The histamine test described, unlike other tests of gastric secretory function, has been shown to impose a maximum load on the secretory cells whose function it is designed to test. Furthermore, the consistency of consecutive estimations has been demonstrated. In an attempt to establish standards of normality for the test and note deviations from these

standards in patients with peptic ulcer, 148 subjects have been examined. This group comprises 25 normal subjects, 103 duodenal ulcer cases, and 20 patients with gastric ulcer. All were males. The normal group consisted of patients awaiting operation for hernia; in none was there a history of dyspepsia and none were febrile. The diagnosis in the ulcer patients was confirmed at operation in every case.

Results.—In the normal group the average basal output of HCl was 70 mg. and the average maximum output 422 mg.; in patients with duodenal ulcer the basal output averaged 265 mg. and the maximum output 837 mg.; in patients with gastric ulcer the means were 113 mg. and 478 mg. respectively. The occurrence of a wide variation on either side of these mean volumes is shown in the frequency distribution charts (Figs. 6 and 7).

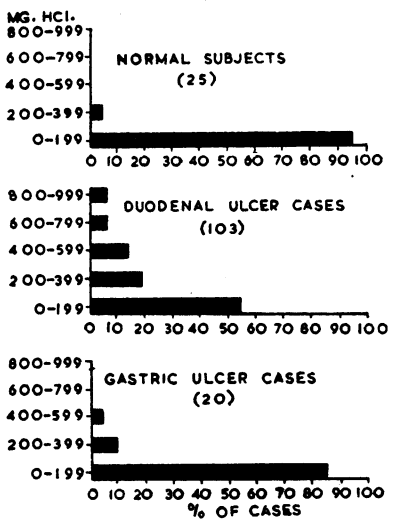

FIG. 6.—Frequency distribution of basal acid output (males).

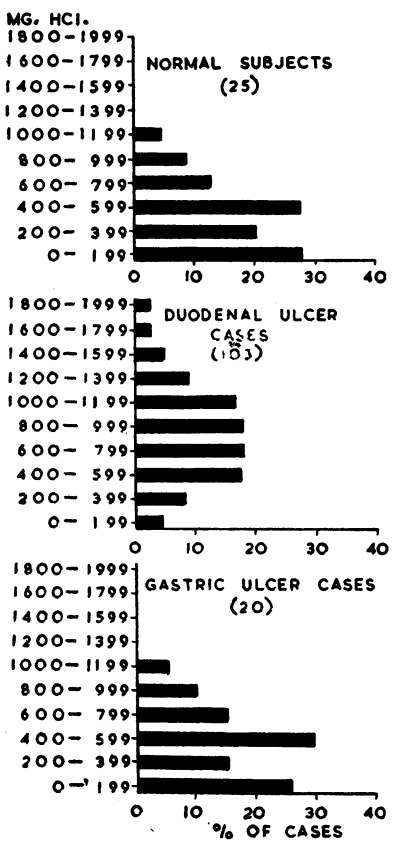

FIG. 7.—Frequency distribution of maximum acid output (males).

Three normal subjects and three gastric ulcer patients were found to have basal anacidity. All showed an acid response after histamine. The presence of stenosis did not appreciably influence either the basal or the maximum acid output in the duodenal ulcer group; a reduction in concentration was compensated by an increase in the volume of juice secreted, so that the actual amount of HCl produced was similar to that in the uncomplicated cases.

Discussion

The gastric secretory response to the commonly employed stimuli of food, alcohol, or small doses of histamine is known to vary greatly from day to day in any one individual. Indeed, the stomach has come to be regarded as capricious in its behaviour. That this is not so has been demonstrated by administering increasing doses of histamine. Four or more B.W. doses of histamine will result in an output of HCl which is constant for an individual and which represents the maximum parietal cell output of acid.

The usual interpretation of an S-shaped curve such as is shown in Figs. 1 and 2 is that the dose-response relationship is of an all-or-none nature. Therefore, with regard to the gastric secretion of HCl, this means that there is no secretion by a parietal cell until an effective stimulus is applied to it; then the parietal cell secretes maximally. The entire population of acid-secreting cells can be stimulated by giving four or more B.W. doses of histamine. Several investigators have attempted to make actual counts of the parietal cells in the gastric mucosa. As accurate counting necessitates detailed examination of the entire stomach, this method can rarely be applicable to human material. Furthermore, the visualization of a parietal cell under the microscope does not necessarily mean that it had been a functioning parietal cell. It would seem reasonable, however, to regard the maximum acid output of a stomach as an index of its parietal cell population.

The routine use of test meals is futile; in selected cases it is of value to determine the presence or absence of HCl. The failure of the stomach to yield gastric juice which was acid to Töpfer's reagent in response to a gruel meal was formerly taken to imply achlorhydria. Until recently, absence of free acid in response to histamine acid phosphate (0.1 mg. per 10 kg.) was regarded as a satisfactory criterion. Palmer and others have shown, however, that, although acid may be absent in several histamine tests, subsequent tests may reveal its presence. In short, the available tests, though satisfactory in most cases, cannot be relied upon to decide the presence or absence of complete achlorhydria. In several of a series of cases believed to have achlorhydria, as indicated by the ordinary histamine test, reinvestigation by the test described here has revealed an appreciable acid response. It should be emphasized that *p*H measurements should be employed in addition to titration methods if small changes in acidity are expected. The application of this test to cases of proved pernicious anaemia has regularly shown a true achlorhydria to be present. The advantages claimed for this augmented histamine test are that it imposes a uniform stimulus which exerts a full load on the acid-secreting cells, and that the results of the test are capable of repetition.

Although the test provides accurate data, its application, like that of all gastric secretory tests, is limited. No narrow standards of normal can be established, and it is consequently difficult to interpret the findings in disease. The observation that duodenal ulcer is associated with a higher range of acid output than normal is in agreement with the accepted work of Bloomfield (1932–3) and Polland (1933). Similarly, the results of the present analysis, which show that the acid output in patients with gastric ulcer varies but little from the output in normal subjects, are not at variance with present beliefs. There is clearly no place for "hypoacidity" and "hyperacidity" as aids to diagnosis. Pernicious anaemia is the only common pathological condition having a characteristic secretory response.

Vanzant *et al.* (1932) found a considerable incidence of "unexplained anacidity" in a study of normal subjects, but not all of these were tested with histamine. Polland (1933) quoted a 9.3% incidence of anacidity to histamine in normals. There were no cases of anacidity to large doses of histamine in the present study. Although the group was a small one, it seems likely that extensive use of the augmented histamine test will reveal a much lower incidence of this "unexplained anacidity."

As no true correlation can be shown between variations in output and pathological states, the main fields of usefulness for the augmented histamine would seem to be in physiological study, in certain anaemias, and in those rare and controversial cases in which peptic ulcer is claimed to exist in the presence of achlorhydria.

Summary

The effects of increasing doses of histamine on the gastric secretion of hydrochloric acid have been studied

in normal subjects and in patients with duodenal ulcer. The dosage required to effect maximum acid output has been established and the duration of this response determined.

An augmented histamine test of gastric secretion, based on these findings, is described.

This test, which imposes a uniform and maximum stimulus on the acid-secreting cells, gives consistent results on repeated estimations in any one individual.

An analysis has been made of the results of the test in 25 normal subjects, 103 duodenal ulcer cases, and 20 patients with gastric ulcer.

I am indebted to Professor C. F. W. Illingworth for his direction and helpful criticism throughout this investigation, to Mr. Gabriel Donald for preparing the charts, and to May and Baker Ltd. for presenting generous supplies of anthisan.

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AN ANTIHISTAMINE IN THE FENESTRATION OPERATION FOR OTOSCLEROSIS

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As the window in a fenestration operation is made in the vestibular part of the bony labyrinth, signs of a vestibular disturbance are to be expected after the operation. Thus vertigo, with its associated nausea and vomiting, is a constant and sometimes troublesome early sequel, and plays an important part in determining the length of stay in hospital.

In a unit where the demand for beds is always greater than the number available, there is a constant stimulus to search for some means of increasing the rate of turnover of the beds. For some years now we have employed special head and balancing exercises to overcome the vertigo following operations on the labyrinth (Cawthorne, 1946; Cooksey, 1946), but even with these it was not possible to turn a fenestration bed over in less than two weeks.

Because of the immediate post-operative vestibular disturbance it was our practice to keep patients as comfortable and quiet as possible by means of twice-daily injections of soluble phenobarbitone. The disadvantage of this treatment was that the patients were made very drowsy; and vertigo was rarely sufficiently controlled for them to be fit to move to the gymnasium for exercises in under five days. We therefore started to search for a more effective means of controlling the vertigo without causing too much drowsiness, and this brings us to "avomine" (promethazine-8-chlorotheophyllinate). This contains one of the most active of the antihistaminic drugs, promethazine hydrochloride, combined with theophylline and in a form suitable for ambulant patients. It was introduced primarily for the treatment of travel sickness, and its success in this condition suggested that it might help in our problem. Campbell (1949) has already reported on the value of another preparation, dimenhydrinate ("dramamine"), after the fenestration operation.

We first used avomine in our fenestration cases in July, 1951, and to date it has been given to nearly 300 patients. Treatment is started as soon as the patient is admitted to hospital, the day before operation. We have found that a dose of 50 mg. three times daily usually suffices, and this dosage is continued for two weeks after operation.

Results

The results of avomine therapy have been striking, and may be summarized as follows.

Post-operative Vomiting.—Formerly vomiting was often troublesome for two or three days after operation. Since the introduction of avomine vomiting is rare once the patient has recovered from the anaesthetic. With regard to the effect of the anaesthetic on the post-operative course, it has been found that the agents used rarely cause vomiting once the patient is fully conscious. The anaesthetics have been given by Dr. V. F. Hall and Dr. S. A. Mason; after premedication with "omnopon" and scopolamine, in half the cases intravenous thiopentone only was used, whilst in the other half this was supplemented with intravenous pethidine and gas-and-oxygen.

Diet.—Because of the vomiting patients rarely ate solid food for the first two or three days after operation. Now they welcome a light diet the day after operation and usually enjoy normal food the day after that.

Drowsiness.—Continued drowsiness caused by prolonged sedation with barbiturates no longer occurs.

Getting Up.—Formerly patients were reluctant to leave their beds within four days of operation, but now they get up on the second or third day.

Exercises.—The head and balancing exercises can now be started in bed the day after operation, and they go down to the gymnasium to join the class on the fourth day. Formerly they were reluctant to do this before the sixth or seventh day.

Walking.—Whereas patients were unable to walk steadily unaided for about ten days, they can do so now as a rule by the sixth day.

Discharge.—Patients are able to leave hospital on the seventh post-operative day, thus enabling a fenestration bed to be turned over each week.

Micturition.—It is not uncommon for patients to have difficulty with micturition following operations on the labyrinth. This complication has become much less frequent with avomine.

Since the introduction of avomine, and although four or five fenestrations are performed each week, not a single patient has had to be kept in hospital longer than seven days because vertigo was not sufficiently controlled. Perhaps the most convincing proof of its success is given by patients who have had a fenestration operation performed on each ear—one before and the other after we started using avomine. Almost without exception they have commented upon how much less disturbing they found the second compared with the first operation. So far we have not observed any unpleasant side-effects, and it has not been necessary to withdraw the drug in any case.

We would like to thank Messrs. May and Baker for providing the avomine used in some cases of this series.

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