# EFFECT OF INTRAVENTRICULAR HISTAMINE ON GASTRIC ACID SECRETION

*By*

B. B. GAITONDE, S. V. SHALIGRAM AND S. K. DAMLE

*From the Department of Pharmacology, Grant Medical College, Bombay*

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The effect of intraventricular (lateral) administration of histamine on gastric acid response in the cat was studied and compared with the results of corresponding amounts given by slow intravenous infusion. A definite rise in acid secretion was noted following even a small dose of 10 $\mu$g of histamine base put in the lateral ventricles. The effect was comparable to intravenous administration of histamine. It is suggested that histamine while putting in the lateral ventricles of anaesthetised cats produces its effect on gastric secretion by its escape in the general circulation.

Histamine is a strong stimulant of parietal cells secreting hydrochloric acid, and believed by Code (1956) to play a humoral role in the gastric acid secretion. Using the technique described by Feldberg and Sherwood (1953), Bhawe (1958) described the effects of 500 $\mu$g of histamine put in lateral ventricles of cat on gastric acid secretion. The rate of escape of histamine into systemic circulation was calculated and he concluded that the amount of histamine escaping into circulation was responsible for stimulation of gastric acid secretion. On the other hand Porter *et al.*, (1953) had postulated a direct central action of histamine which involved a participation of pituitary-adrenal axis.

It was thought necessary to study the effect of small amounts of histamine on gastric acid response. In the present paper the effect of intraventricular administration of varying doses of histamine on gastric response was studied and compared with those responses obtained by equal amounts given as slow intravenous infusion over a period of fifteen minutes.

## METHODS

In all the experiments domestic cats of either sex weighing 2·5 to 5 kg were used. Cats were anaesthetized by ether and maintained on chloralose 80 mg/kg i. v. A cannula was fixed in the lateral ventricle by the method discribed by Feldberg and Sherwood (1953). Through a midline epigastric incision, gastrostomy was performed following pylorus ligation, and a glass cannula was fixed. Gastric contents were drained every fifteen min and their free acidity was estimated against N/250 sodium hydroxide using methyl red

as indicator. At the end of every experiment, position of intraventricular cannula was ascertained and the pooling of secretions, if any, behind the cannula in stomach was looked for.

In 7 cats the spinal cord was transected and vagotomy was done. Blood pressure records were taken as usual in most of the cats.

Gastric acid response is expressed in terms of mEq/litre. Average of three responses before drug administration was compared with that obtained immediately after the drug, and the difference expressed as percentage of the change over initial values.

Histamine dissolved in 0.2 ml of saline was administered and was followed by 0.2 ml saline wash. Histamine values were in terms of the base.

## RESULTS

*Control Experiments.*—Table No. 1 shows gastric acid response following O·4 ml of saline intraventricularly. It may be seen that in all the 13 cats there was a drop in concentration of acid, immediately following the saline injection, and in 6 of them there was a fall in volume of juice secreted. When these cats were observed for three hrs there was a progressive decline in acid concentration.

TABLE I

*Effect of 0.4 ml of saline (intraventricularly) in anesthetised cats*

| Sr. No. | Sex. | Wt. (kg) | Volume of gastric secretion | | Milli. Eq. of HEl/litre | | % Fall |
|---|---|---|---|---|---|---|---|
| | | | Initial (ml) | Final (ml) | Initial | Final | |
| 1 | M | 4.2 | 0.07 | 0.07 | 60.00 | 27.30 | 54.50 |
| 2 | F | 2.5 | 0.18 | 0.21 | 52.00 | 1.36 | 97.40 |
| 3 | M | 4.6 | 0.03 | 0.03 | 40.00 | 0.0 | 100.00 |
| 4 | F | 2.5 | 0.14 | 0.15 | 2.25 | 0.0 | 100.00 |
| 5 | F | 2.5 | 4.00 | 4.00 | 8.00 | 0.0 | 100.00 |
| 6 | M | 2.5 | 0.17 | 0.20 | 6.80 | 1.36 | 80.00 |
| 7 | M | 4.0 | 0.04 | 0.06 | 0.00 | 0.00 | 0.00 |
| 8 | M | 4.0 | 0.06 | 0.05 | 31.40 | 22.00 | 29.90 |
| 9 | M | 4.0 | 0.18 | 0.04 | 1.18 | 0.00 | 100.00 |
| 10 | F | 3.2 | 0.22 | 0.09 | 64.00 | 52.00 | 18.75 |
| 11 | M | 3.5 | 0.05 | 0.04 | 27.10 | 8.14 | 69.96 |
| 12 | M | 3.5 | 0.15 | 0.08 | 23.20 | 9.03 | 61.07 |
| 13 | M | 4.2 | 0.02 | 0.07 | 60.00 | 28.40 | 52.70 |

*Effects of intraventricular histamine.*—Table No. II shows gastric acid response in 13 cats following 2 μg of histamine intraventricularly. It would be seen that in all the cats there was a rise in acid concentration in terms of mEq/litre. Thus, on an average, there was a rise of 75·6 per cent over the initial reading. The rise was seen immediately *i.e.* in the first 15 min. sample and was maintained in the subsequent 15 min. sample. Acid concetration dropped thereafter. Inspite of rise in acidity a fall in volume of secretion was noted. Thus the initial average volume was 0·139 ml and final volume dropped to 0·08 ml. It may be appreciated that final reading showed less of actual acid secreted during the 15 min period following administration of histamine, but compared to control cats. reduction was much less.

TABLE II

*Effect of 2 μg of histamine (intraventricularly) in anesthetised cats*

| Sri. No. | Sex. | Wt. (kg) | Volume of gastric secretion | | Milli.. Eq. of HCl/litre | | % Rise |
|---|---|---|---|---|---|---|---|
| | | | Initial (ml) | Final (ml) | Initial | Final | |
| 1 | M | 3.0 | 0.25 | 0.30 | 4.64 | 5.73 | 23.5 |
| 2 | M | 3.0 | 0.30 | 0.10 | 32.76 | 46.40 | 41.6 |
| 3 | M | 4.2 | 0.33 | 0.27 | 34.67 | 54.40 | 56.9 |
| 4 | M | 2.5 | 0.06 | 0.03 | 46.40 | 100.00 | 115.5 |
| 5 | F | 3.0 | 0.03 | 0.02 | 40.13 | 59.00 | 47.0 |
| 6 | F | 3.0 | 0.05 | 0.06 | 60.00 | 140.00 | 133.3 |
| 7 | M | 5.0 | 0.06 | 9.02 | 21.00 | 30.80 | 46.7 |
| 8 | M | 3.7 | 0.03 | 0.01 | 49.00 | 139.00 | 183.6 |
| 9 | M | 5.0 | 0.10 | 0.02 | 63.40 | 99.60 | 57.1 |
| 10 | M | 4.2 | 0.04 | 0.01 | 60.00 | 109.20 | 82.0 |
| 11 | M | 3.7 | 0.04 | 0.06 | 57.30 | 81.40 | 42.0 |
| 12 | M | 4.5 | 0.07 | 0.02 | 52.20 | 122.80 | 135.2 |
| 13 | M | 4.0 | 0.45 | 0.12 | 121.50 | 145.20 | 19.5 |

Table III shows (7 cats) the effect of 10 μg of histamine on gastric acid response given in the venricle. It may be seen that on an average there was a rise in volume of secretion from 0·163 to 0·349 ml. There was a rise in acid concentration from 15·9 mEq litre to 26·2 mEq litre. This latter represents (excluding cat No. 6) an average rise of 82·4 over the initial, in acid concentration. Thus following 10μg of histamine there was a definite and appreciable increase in gastric secretory response. Fig. 1 Illustrates the result.

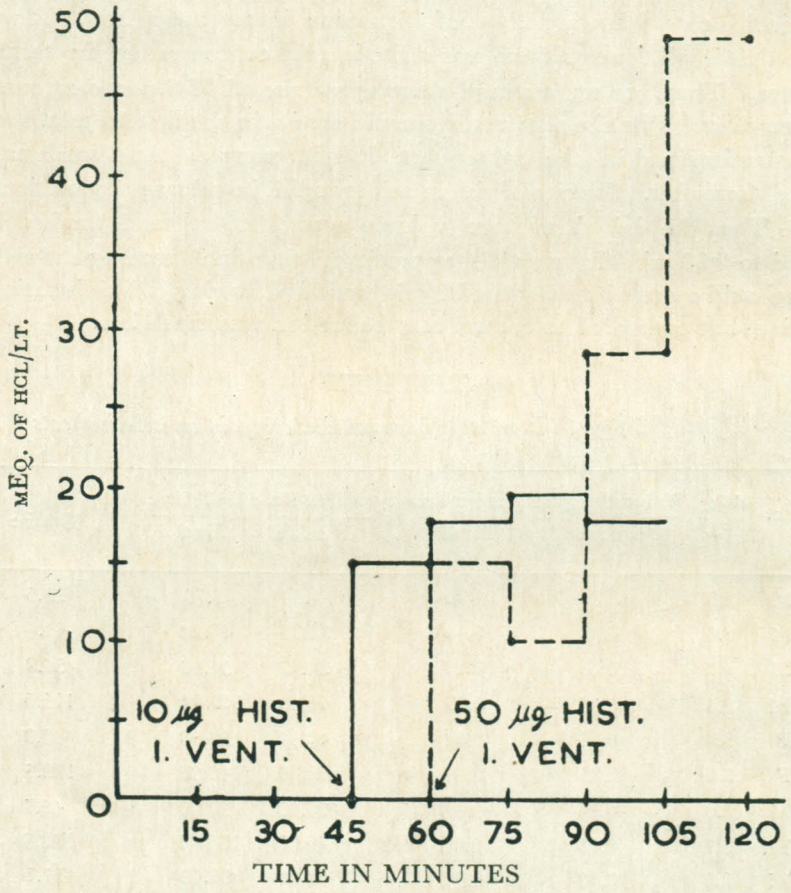


Fig. 1. Effect of histamine (base) on gastric acidity.
——cat O, 2.5 kg, effect of 10 µg histamine (intraventicularly).
——cat Q, 4.7 kg, effect of 50 µg histamine (intraventicularly).

## TABLE III

*Effect of 10 µg of histamine (intraventricularly) in anesthetised cats*

| Sr. No | Sex. | Wt. (kg) | Volume of gastric secretion | | Milli. Eq. of HCl/litre | | % Rise |
|---|---|---|---|---|---|---|---|
| | | | Initial (ml) | Final (ml) | Initial | Final | |
| 1 | M | 3.0 | 0.20 | 0.30 | 4.90 | 11.40 | 132 6 |
| 2 | M | 3.5 | 0.25 | 0.30 | 27.30 | 33.30 | 22.0 |
| 3 | M | 4.5 | 0.35 | 1.30 | 2.18 | 4.90 | 124.7 |
| 4 | M | 3.0 | 0.10 | 0.25 | 27.30 | 54·60 | 100.0 |
| 5 | M | 5.0 | 0.03 | 0.02 | 35.20 | 52.68 | 49.7 |
| 6 | F | 2.5 | 0.11 | 0.17 | 0.00 | 17.08 | - |
| 7 | F | 2.5 | 0.10 | 0.10 | 8.73 | 14.46 | 65.6 |

Table No. IV shows gastric acid response following 50 μg of histamine and 100 μg in 2 cats. It may be seen that there was an average increase in volume of secretion from 0·29 ml initial to 0·33 ml final. There was a considerable increase in acid concentration. In 2 animals there was no free acidity initially but this dose of histamine produced a marked rise in acid secretion.

## TABLE IV

*Effect of histamine (intraventricularly) in the dose of 50 or 100 μg*

| Sr. No. | Sex. | Wt. (kg) | Dose ug. | Volume of gastric secretion | | Milli. Eq. of HCl/litre | | % Rise |
|---|---|---|---|---|---|---|---|---|
| | | | | Initinl (ml | Final (ml) | Initial | Final | |
| 1 | M | 3.5 | 100 | 0.15 | 0.55 | 8.4 | 15.0 | 78.5 |
| 2 | M | 4.5 | 100 | 0.10 | 0.30 | 0.0 | 10.0 | ∞ |
| 3 | M | 4.5 | 50 | 0.40 | 0.35 | 4.9 | 33.2 | 577.6 |
| 4 | M | 3.5 | 50 | 0.50 | 0.10 | 20.0 | 30.0 | 50.0 |
| 5 | M | 4.7 | 50 | 0.30 | 0.35 | 0.0 | 16.8 | ∞ |

*Effect of histamine (intraventricular) in spinal cord transected and vagotomised animals.*—Table No. V shows effect of intraventricular histamine in 4 spinal cord transected and vagotomized animals 3 of which were administered 10 μg of histamine. All 3 showed rise in acid concentration after 10 μg of histamine although 2 showed some fall in volume of secretion. There was a considerable rise in both volume and acid concentration in the cat (No. 3) given 50 μg of histamine intraventricularly.

## TABLE V

*Effect of different doses of histamine (intraventricularly) in spinal and vagotomised cats*

| Sr. No. | Sex. | Wt. (kg) | Dose ug | Volume of Gastric Secretion | | Milli. Eq. of HCl/litre | | % Rise |
|---|---|---|---|---|---|---|---|---|
| | | | | Initial (ml) | Flnal (ml) | Initial | Final | |
| 1 | M | 3.25 | 10 | 0.08 | 0.09 | 54.5 | 55.1 | 1.1 |
| 2 | M | 3.5 | 10 | 0:09 | 0.06 | 9.09 | 21.5 | 136.3 |
| 3 | M | 4.0 | 50 | 0.09 | 0.23 | 6.80 | 60.7 | 792.5 |
| 4 | M | 3.7 | 10 | 0.04 | 0.02 | 57.3 | 98.2 | 71.3 |

*Effect of intravenous infusion of 2 and 10 μg of histamine.*—Table No. VI shows the effect of intravenous infusion of 10 μg of histamine completed over a period of 15 min on gastric acid response in 5 cats. It may be seen that in 5 cats given infusion of 10 μg of histamine, on an average, the volume of secretion rose from initial 0·34 ml to 0·54 ml and acid concentration rose

from initial 4·8 mEq/litre to final 8·2 mEq/litre. Out of 4 cats (not shown in the table) given a slow infusion of 2 μg, 2 have shown an increased response in acid concentration while the other 2 showed a fall. Response following 10 μg of histamine intravenously was comparable to that seen after intraventricular administration of the same dose.

TABLE VI

*Effect of intravenous infusion of 10 μg of histamine on gastric acid response*

| Sr. No. | Sex | Wt. (kg) | Volume of gastric secretion | | Milli. Eq. of HCl/litre | | % Rise |
|---|---|---|---|---|---|---|---|
| | | | Initial | Final | Initial | Final | |
| 1 | M | 3.0 | 0.75 | 1.2 | 7.0 | 12.0 | 71.4 |
| 2 | F | 2.5 | 0.45 | 0.8 | 3.2 | 7.3 | 128.1 |
| 3 | M | 4.0 | 0.07 | 0.07 | 10.4 | 17.0 | 63.4 |
| 4 | M | 3.5 | 0.3 | 0.37 | 1.4 | 2.4 | 71.4 |
| 5 | M | 3.5 | 0.15 | 0.29 | 2.1 | 2.9 | 38.1 |

*Effects on blood pressure.*—Effects of 0·4 ml of saline and various doses of histamine given intraventricularly did not produce marked change in blood pressure. There was an occasional rise.

## DISCUSSION

Following the administration of 0·4 ml of normal saline in lateral ventricles of cat, a fall in volume of secretion and in acid concentration in some cats was seen. Partly, this fall in secretary response could be atributed to the natural tendency of gastric secretion to decline with time in anaesthetised cat as was observed in control experimenents. Response to 2 μg of histamine put in lateral ventricles showed a dissociation between volume of secretion and acid concentration. Thus in most of the cats there was a reduction in volume secreted during a given time, as against a rise in acid concentration in terms of mEq/litre. There was a slight fall in amount of acid secreted during the given time following administration of 2 μg of histamine. This response could be explained by assuming a small effect of histamine superimposed on the type of response obtained in control cats. Rate of secretion by itself might have also affected the acid concentration. When 10 μg of histamine were introduced in ventricles there was a slight but distinct stimulation of gastric acidity. Both volume of secretion and acid concentration rose. In a personal communication, Feldberg has stated that he had observed a barely perceptible acid response following introduction of 10 μg of histamine in cat's lateral ventricles. In the present experiments the lowest dose which produced a response was 2 μg.

When histamine was given by a slow intravenous infusion, 2 and 10 μg being administered over a period of 15 min, it was observed that 2 μg had an equivocal effect, while 10 μg produced a definite rise in gastric comparable with the effect produced on intraventicular administration. Bhawe (1958) reported that the amount of histamine escaping into blood following administration of 500 μg in lateral ventricle was 1 to 12 μg per min. There was, however, no figures available stating the amount of histamine escaping into the blood following the lower doses. We have studied the histamine levels in blood extracted by Code's method (1952), after administration of the intraventricular histamine. But the results were variable. It is believed on the basis of our experiments reported here that a major part of histamine has slowly escaped in blood which may account for rise in gastric acidity observed. There is thus no need to postulate a purely central action for histamine response under the conditions of these experiments.

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