

Effect of Burimamide on Histamine- and Pentagastrin-Stimulated Acid and Pepsin Secretion in the Pig

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SUMMARY

Burimamide, a specific histamine H₂-receptor antagonist, is an effective inhibitor of histamine and pentagastrin-stimulated gastric acid secretion in the innervated pig stomach. Pepsin secretion, and acid secretion from

denervated gastric pouches, were not significantly depressed by burimamide in the dose used in this study. Atropine inhibited pentagastrin- but not histamine-stimulated gastric acid secretion from the innervated and denervated portions of the pig stomach.

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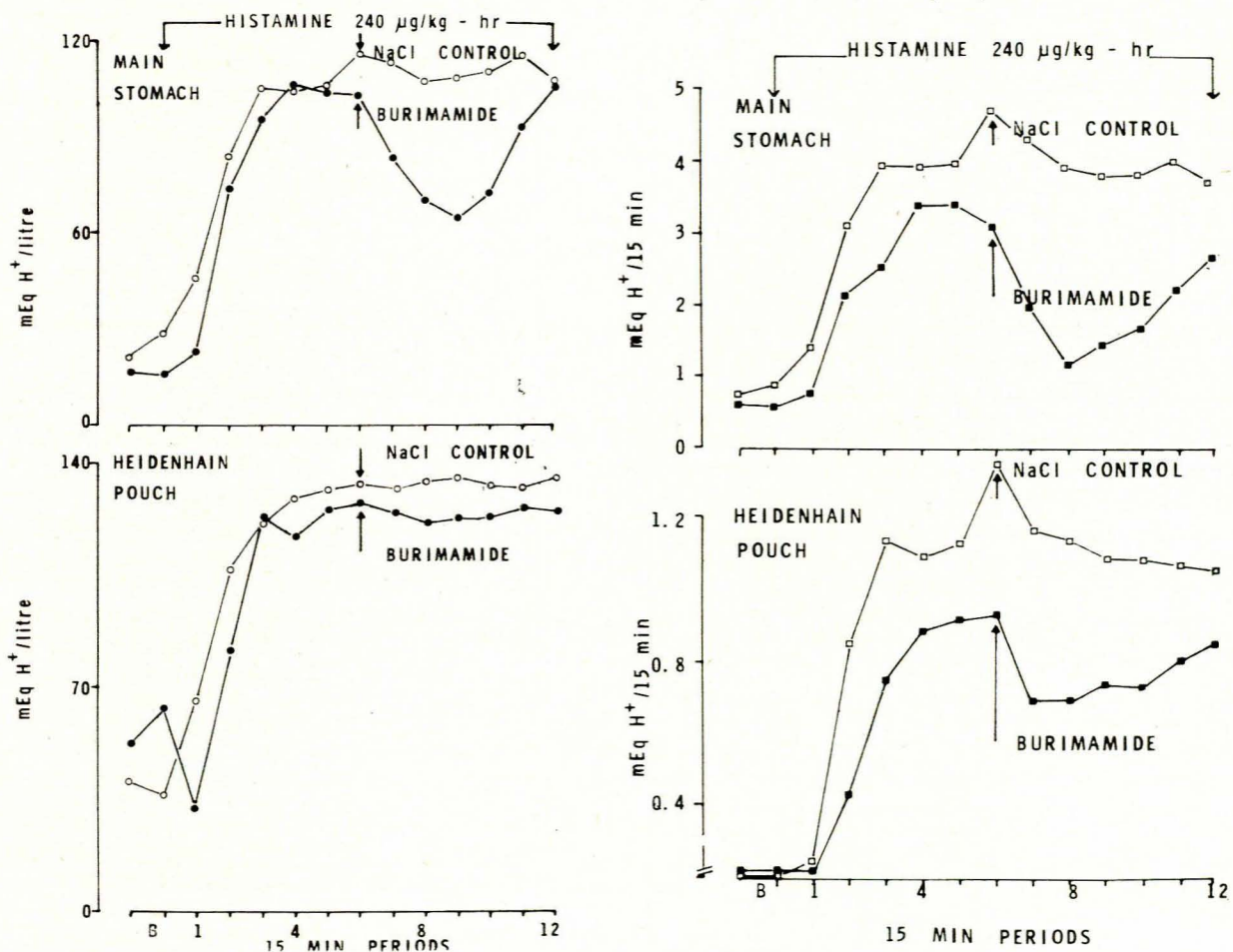


Fig. 1. Effect of burimamide or control saline on histamine-stimulated acid concentration and output from the main stomach or Heidenhain pouch.

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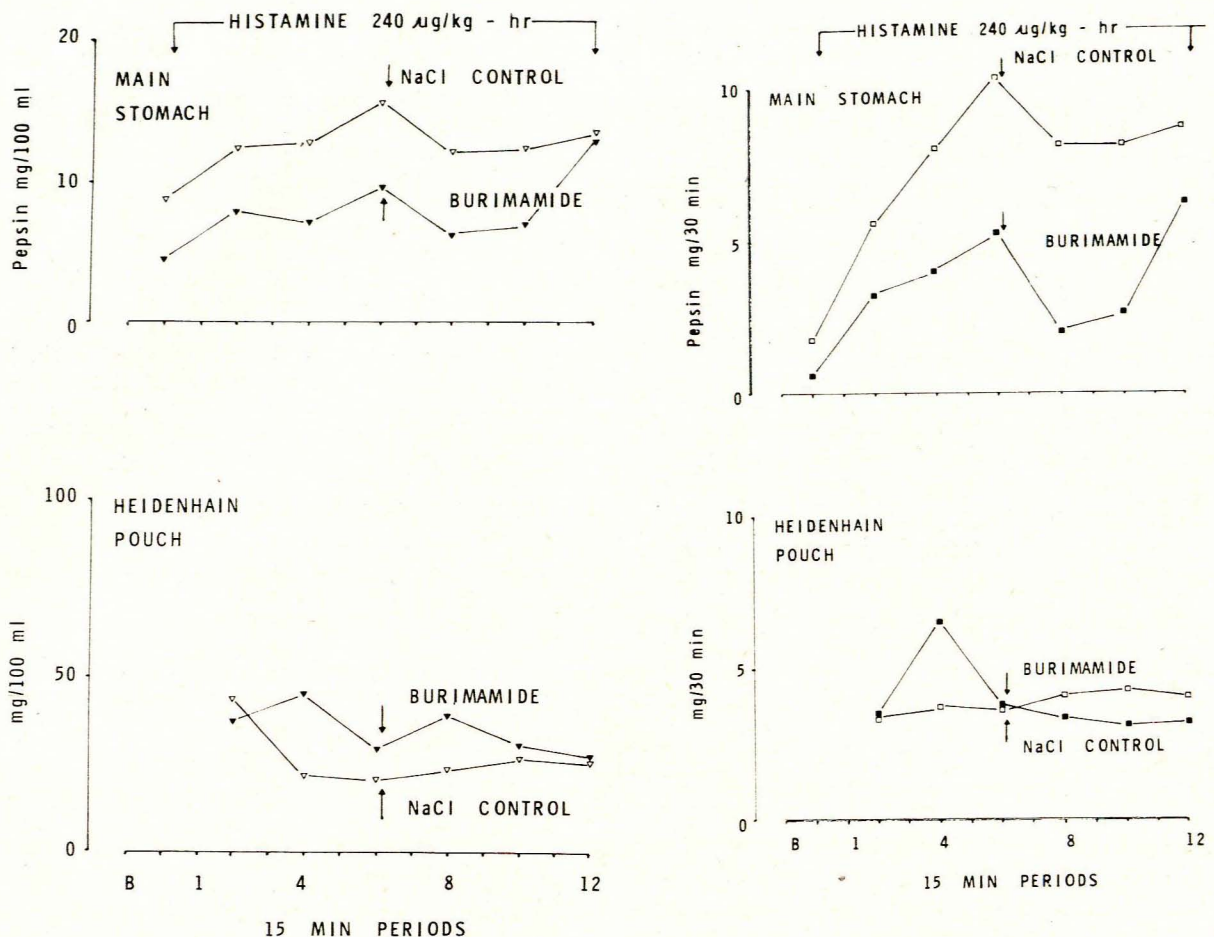


Fig. 2. Effect of burimamide or control saline on histamine-stimulated pepsin concentration and output from the main stomach or Heidenhain pouch.

Histamine receptors have been divided into two groups, depending upon whether they are or are not blocked by conventional antihistamines such as mepyramine maleate. These have been termed H_1 and H_2 receptors respectively. An antagonist of H_2 receptors (burimamide) has recently been discovered¹ and a more potent and less toxic analogue, metiamide, was subsequently developed. These H_2 receptor antagonists inhibit gastric acid secretion stimulated by histamine, gastrin, hypoglycaemia and food in the dog² and by histamine and pentagastrin in man.³

In this study the effect of burimamide on histamine- and pentagastrin-stimulated gastric acid and pepsin secretion was measured in porcine innervated stomach and denervated gastric pouches.

METHODS

Cross-bred White-Landrace pigs weighing 15-25 kg were prepared with a gastric fistula and a Heidenhain pouch. Two weeks were allowed between surgery and the first study. Animals were fasted for 20 hours before each study.

Experiments were not done more frequently than once in 48 hours. Six studies were performed in random order on 5 pigs.

After two 15-minute basal collections, gastric secretion was stimulated by intravenous infusions of either pentagastrin (8 $\mu\text{g}/\text{kg}\cdot\text{h}$) or histamine acid phosphate (240 $\mu\text{g}/\text{kg}\cdot\text{h}$), using a Braun Unita I infusion pump, for 3 hours. The doses of histamine and pentagastrin used in this study were those previously found to stimulate maximal secretion from porcine denervated gastric pouches.⁴ Pigs receiving histamine were given mepyramine maleate intramuscularly 10 minutes before starting the infusion. Ninety minutes after the start of the infusion of stimulant, either burimamide (5 mg/kg of a solution containing 15 mg/ml) or a control 0.15M NaCl solution was injected intravenously over 60 seconds. Animals showed signs of restlessness while the burimamide was being injected. Samples were collected every 15 minutes, the volume measured, and the acid titrated with 0.2M NaOH using an automatic titrator (Radiometer, Copenhagen). Aliquots from successive pooled 30-minute samples were deep-frozen at -20°C and the pepsin content assayed 1-4 weeks later, according to the method of Berstad.⁵

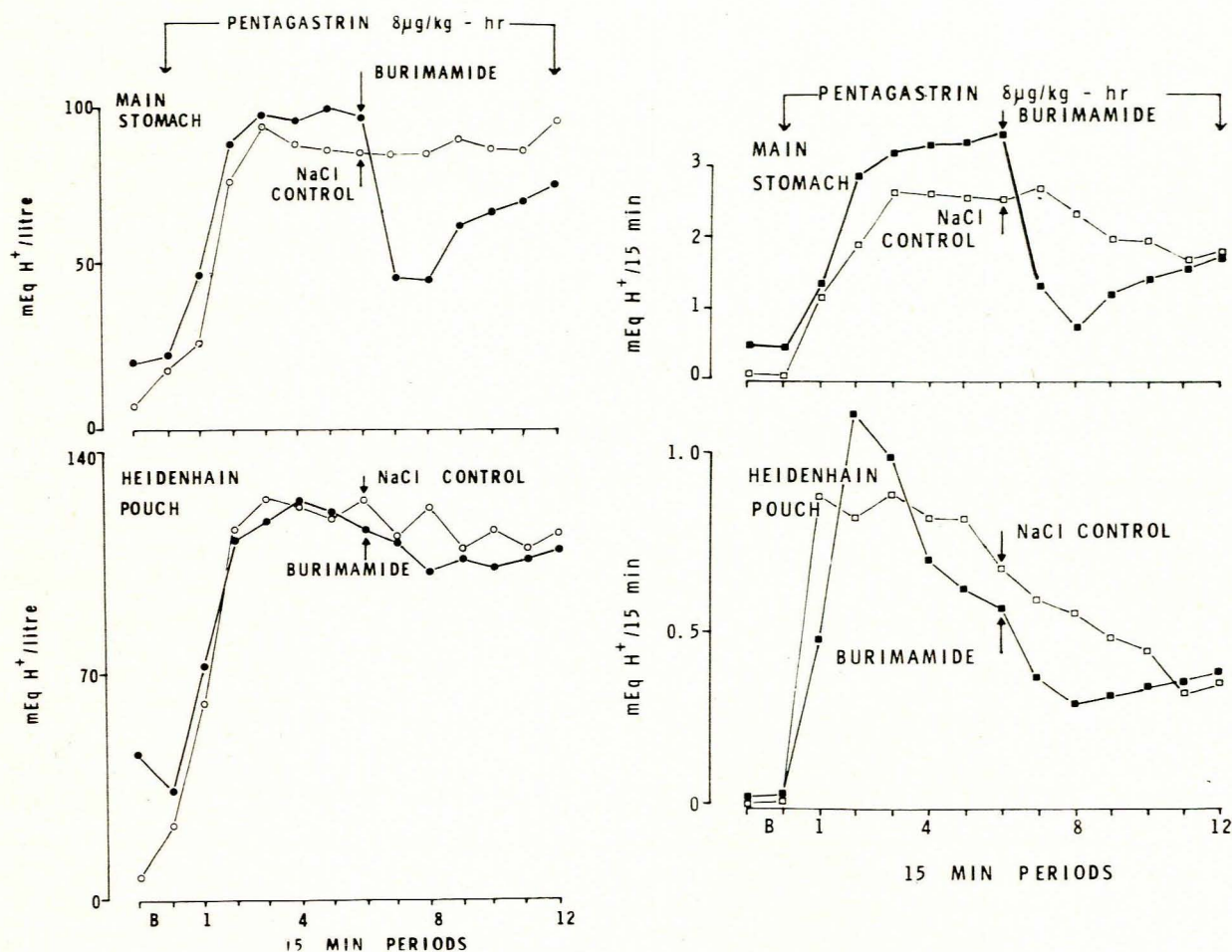


Fig. 3. Effect of burimamide or control saline on pentagastrin-stimulated acid concentration and output from the main stomach or Heidenhain pouch.

Studies were repeated in 2 pigs weighing 20 and 25 kg, using atropine (600 µg given over 60 seconds) instead of burimamide. The acid response was measured as before.

Insulin tests were performed in 3 of the 5 pigs used in these studies. Hypoglycaemia induced by soluble insulin (0.5 U/kg as an intravenous bolus) was shown to produce an acid response from the main stomach but no response from the Heidenhain pouch. Complete denervation of the pouches was thus confirmed. The 2 other pigs died (1 with pneumonia, 1 of uncertain cause) before the insulin tests could be performed.

Differences in acid or pepsin secretion between the hour before and the hour after the injection of burimamide or saline were calculated in each individual test. Differences produced by burimamide were compared with differences following saline by using the unpaired Student's *t*-test.

RESULTS

The effect of burimamide on histamine-stimulated acid and pepsin secretion was as follows:

Acid secretion (Fig. 1): Burimamide significantly inhibited acid concentration ($P < 0.005$) and output ($P < 0.02$) in the main stomach when compared with saline controls. However, the differences in acid concentration and output in the Heidenhain pouches were not significant ($P > 0.5$ and 0.3 respectively).

Pepsin secretion (Fig. 2): Histamine-stimulated pepsin concentration was unaffected by burimamide in either innervated stomach or Heidenhain pouch. Burimamide produced a drop in the mean pepsin output from the main stomach, but this was not statistically significant. Pepsin output from the Heidenhain pouch was unaltered by burimamide.

Burimamide had the following effects on pentagastrin stimulated secretion:

Acid secretion (Fig. 3): There was marked fade in pentagastrin-stimulated gastric acid secretion after 1½ hours in both the main stomach and denervated gastric pouches. Burimamide significantly inhibited acid concentration ($P < 0.02$) and output ($P < 0.02$) from the main stomach, but again acid concentration was unaffected and acid

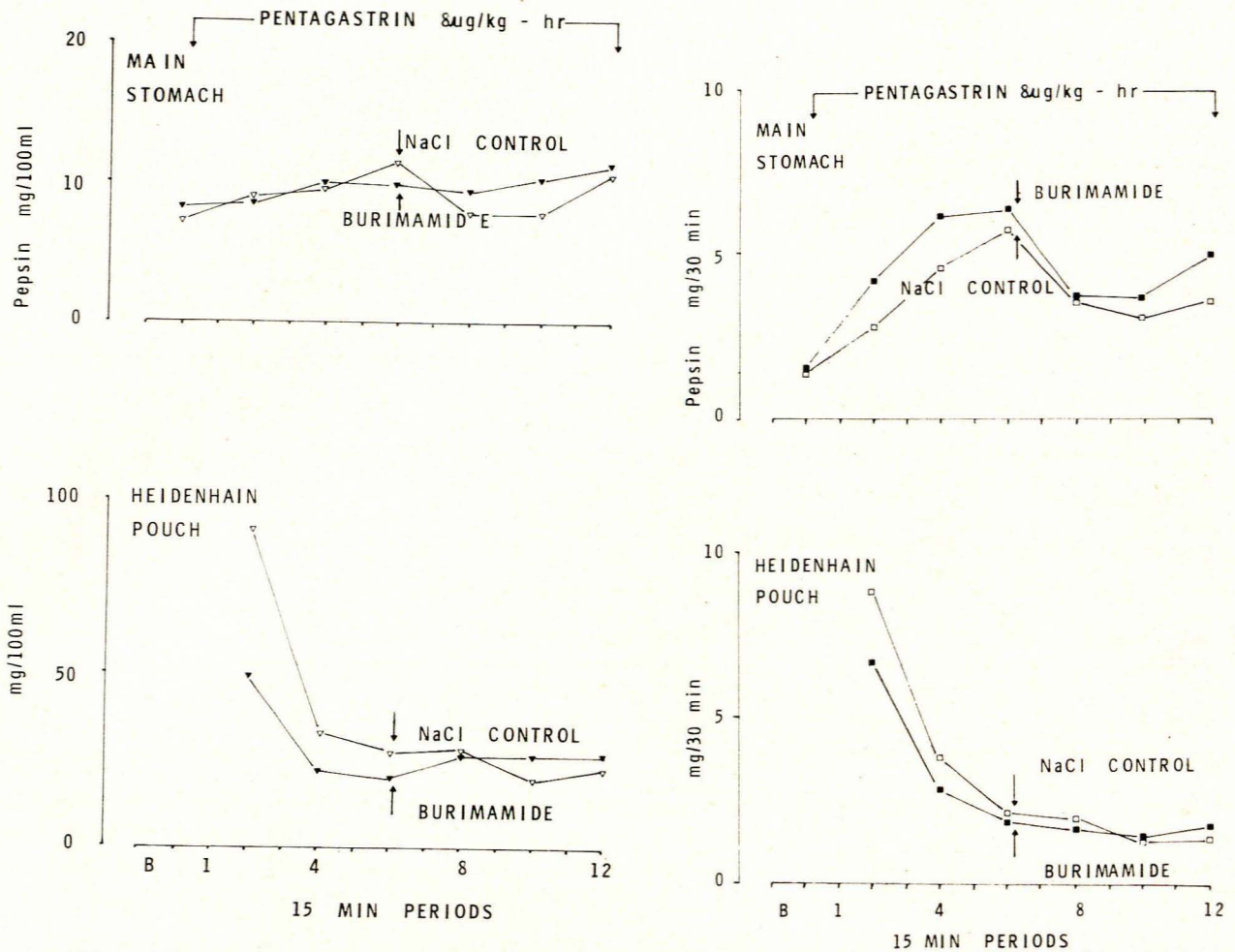


Fig. 4. Effect of burimamide or control saline on pentagastrin-stimulated pepsin concentration and output from the main stomach or Heidenhain pouch.

output insignificantly lowered in the denervated pouches ($P > 0.5$).

Pepsin secretion (Fig. 4): Pentagastrin-stimulated pepsin concentration and output in gastric secretions from the main stomach and the Heidenhain pouches were unaffected by burimamide.

Atropine produced a marked and prolonged inhibition of pentagastrin-stimulated acid secretion, both in the main stomach and in Heidenhain pouches (Fig. 5). Histamine-stimulated gastric acid secretion was unaffected by atropine in either the main stomach or denervated gastric pouches in both the pigs tested.

DISCUSSION

Histamine and pentagastrin-stimulated gastric acid secretion has been shown to be reduced by burimamide in the innervated pig stomach. Burimamide was, however, found to be ineffective in reducing acid secretion in denervated gastric pouches in the doses used in this study. Calculation

of the percentage change in acid secretion produced by the drug or placebo (Fig. 6) emphasises the difference found between innervated stomach and denervated pouches in this species. It is not known precisely how H_2 receptor antagonists reduce acid secretion, although it seems highly probable that they block histamine H_2 receptor sites. If this inhibition is competitive in type, reducing the large dose of stimulant used in this study or increasing the amount of antagonist might produce a different result in the Heidenhain pouch. It is nevertheless interesting that the sensitivity of the parietal cells to H_2 receptor antagonists is altered by denervation. This is compatible with the hypothesis proposed by Grossman and Konturek² that histamine, gastrin and acetylcholine each have a receptor site on the parietal cell and that these sites interact with one another. The controversy as to whether histamine is the final common pathway for stimulation of gastric acid secretion remains unanswered. The observation that burimamide did not significantly reduce acid secretion in denervated pouches in the pig may find practical application in that it is not known whether humans would react in the same way. Standard doses of

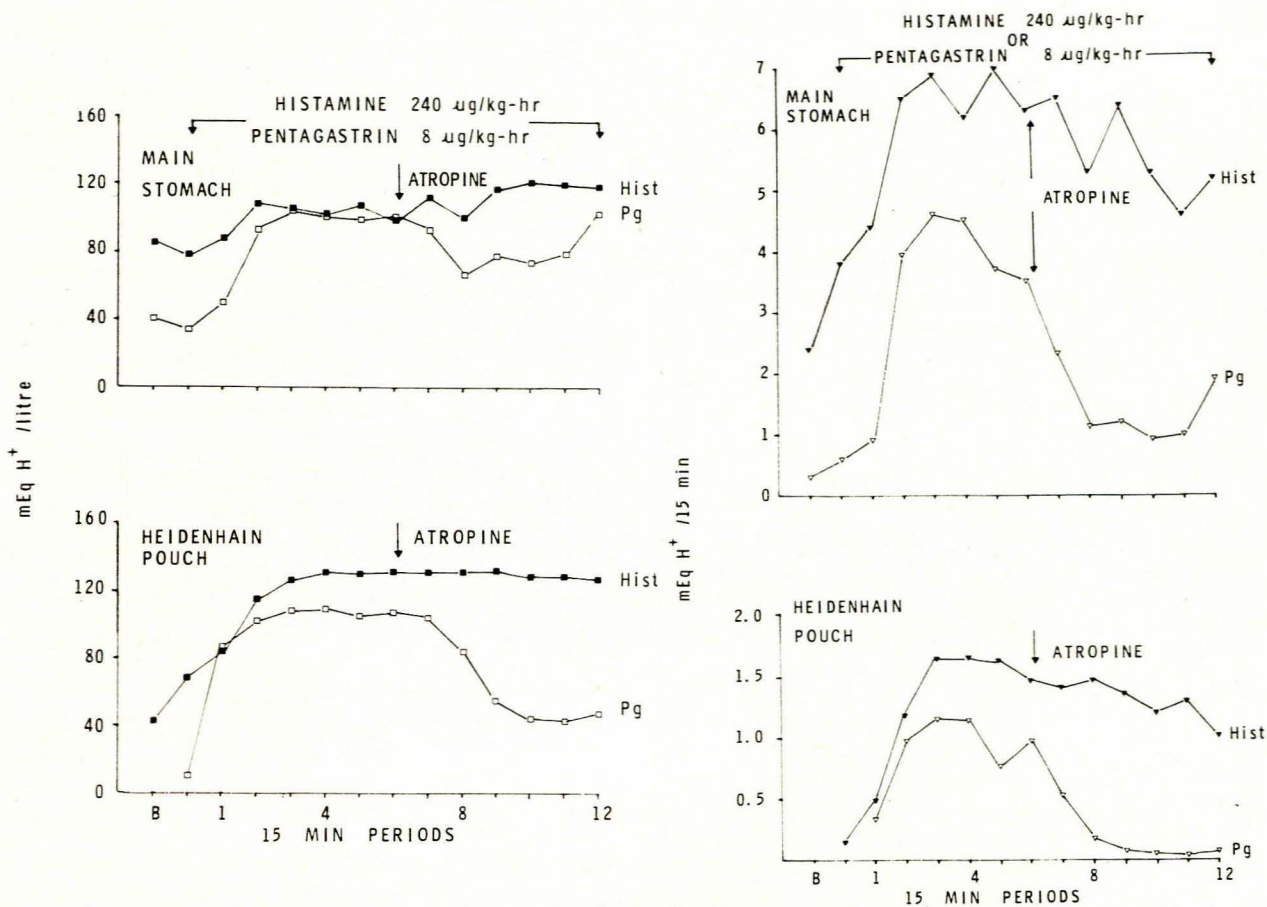


Fig. 5. Effect of atropine on histamine- or pentagastrin-stimulated acid concentration and output from the main stomach or Heidenhain pouch.

% CHANGE IN STIMULATED GASTRIC SECRETION

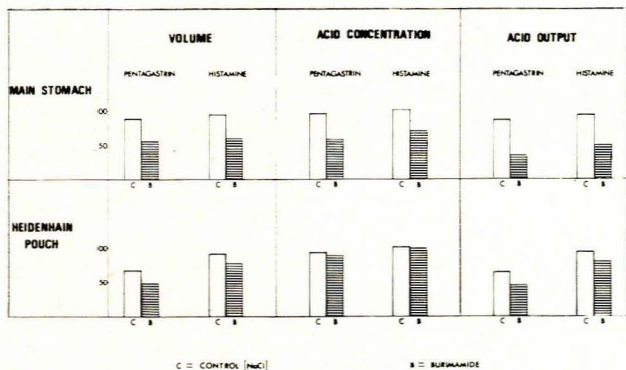


Fig. 6. Percentage change in volume output, acid concentration and acid output between the hour before and the hour after burimamide or control saline injections.

this drug may therefore be ineffective in patients with a partially or completely denervated stomach.

As expected, histamine and pentagastrin did not increase pepsin concentration in the gastric juice. Heidenhain pouch juice, in fact, initially had a high pepsin concentration

which rapidly declined with stimulation, an observation made previously in the dog.⁶ It was noted that most of the samples collected from the gastric fistulae were bile-stained, and it was thought that this might interfere quantitatively with pepsin estimation. The colour index of these samples was measured (modified from the method described by Henry *et al.*,⁷ and no significant negative correlation was found between the amount of bile discoloration and pepsin concentration ($r = -0.0568$ in 166 comparisons). Histamine-stimulated pepsin output from the main stomach was considerably reduced after the burimamide injection, but this was not statistically significant when compared with controls. The vagus and secretin are strong stimulators of pepsin secretion.^{8,9} It would be of interest to note the effect of H₂ receptor antagonists on pepsin secretion stimulated by neural and hormonal pathways.

The effect of atropine on gastric acid secretion differed from that of burimamide in that pentagastrin-stimulated secretion was markedly depressed in both the main stomach and the denervated pouches, while histamine-stimulated secretion was unaltered. These results can only be taken as qualitative, since the numbers studied were small. The failure to depress histamine-stimulated acid secretion may be a result of the large dose of stimulant

used, inhibition of histamine effect by atropine being of the competitive type.¹⁰

Studies are being conducted with H₂ receptor blockers in patients with peptic ulceration. Initial results have indicated that metiamide is associated with a significant reduction of gastric acid secretion, and symptomatic relief of ulcer dyspepsia. Prolonged double-blind trials are being conducted to accurately assess its clinical value.

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