Effect of Atropine on Gastrin and Gastric Acid Response to Peptone Meal

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ABSTRACT The action of intravenous atropine on meal- and pentagastrin-induced gastric acid secretion was studied in six duodenal ulcer patients.

A test meal of 10% peptone solution adjusted to pH 5.0 was maintained in the stomach at at distention pressure of 15 cm H_2O, and a modification of the intragastric titration method of Fordtran and Walsh was used to measure gastric acid output by monitoring the rate at which a solution of 0.5 M sodium bicarbonate had to be added to keep the pH of the gastric content constant at the initial (pH 5.0) value. Serum gastrin concentrations were measured simultaneously by radioimmunoassay. The dose of 25 μg/kg-h atropine inhibited meal-induced acid secretion by about 70% and that evoked by pentagastrin by about 30%. The serum gastrin response to the test meal was not significantly altered by atropine.

We conclude that atropine is a very strong inhibitor of meal-induced gastric acid secretion and does not significantly change serum gastrin response to feeding in duodenal ulcer patients when postprandial gastric acidity (pH 5.0) and intragastric pressure (15 cm H_2O) are kept constant.

INTRODUCTION

Earlier studies have shown that atropine reduces gastric acid secretion under basal conditions (1–4) and in response to pentagastrin (4–6), histamine (4, 5, 7), and insulin (5). The effect of atropine on food-induced acid secretion has never been measured in humans; only changes in postprandial gastric acidity have been determined (2, 3, 8, 9).

Although extensive investigations on the effect of atropine on gastric functions have been made, no study has been undertaken to determine simultaneously the effect of atropine on gastric acid secretion and serum gastrin response to a meal in duodenal ulcer patients.

The present study was designed to explore the effect of atropine on meal-induced serum gastrin response and gastric acid secretion measured by a modification of the intragastric titration method of Fordtran and Walsh (10), and to compare this effect with the action of atropine on pentagastrin-evoked gastric acid secretion in the same duodenal ulcer patients.

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METHODS

The study group consisted of six patients with chronic duodenal ulcer disease with a mean age of 46 yr (range, 37–53 yr) and mean weight 73 kg (range, 57–88 kg). All patients were well accustomed to the secretory test procedure and gave informed consent. The patients received no anticholinergics for 48 h before secretory studies were made. Two series of tests were performed on each patient, one of meal-induced and the other of pentagastrin-induced secretion.

Meal-induced gastrin response and gastric acid secretion. In the tests of meal-induced secretion, a modification of the Fordtran and Walsh method (10) was applied. After an overnight fast and the collection of basal secretion by simple suction, each patient was intubated with a 16 FR Levin-type stomach tube, to which was attached a small polyvinyl tube (ID 4 mm), a large polyvinyl tube (ID 7 mm), and the glass tip of the combined glass-calomel electrode (type GK 282C/o, Radiometer Co., Copenhagen, Denmark). The tip of the large polyvinyl tube and glass electrode were about 5 cm distal to the most distal opening of the Levin tube and the tip of the small polyvinyl tube was about 10 cm proximal to the most proximal opening of the Levin tube. The distance between the tips of the small infusion tube and glass electrode was about 20 cm. The tubes were positioned under fluoroscopic control so that the tip of the large polyvinyl tube and the glass electrode were in the distal portion of the stomach and the opening of the smaller polyvinyl tube was in the upper portion of the body of the stomach.

The Levin tube was used for continuous suction of gastric content; the small polyvinyl tube was used for reinfusion of the test meal into the stomach as well as for intragastric

infusion of sodium bicarbonate from an autoburet; the large polyvinyl tube was connected to a barostat; the glass-calomel electrode was connected to a pH-meter (PHM 26, Radiometer) which in turn was connected to a recording pH-stat assembly (titrator, TTT-11, autoburet ABU13, recorder SBR2c, all from Radiometer), which recorded the cumulative amount of titrant (0.5 M $NaHCO_3$) against time.

Continuous mixing of the gastric content was accomplished by a peristaltic pump (Unipan, Poland) connected to the Levin tube and the small polyvinyl tube. The pump was set at a delivery rate of about 600 ml/15 min. The small polyvinyl tube had a T-shaped glass part to which the tubing infusing bicarbonate from the autoburet was connected. The autoburet constantly maintained gastric pH at pH 5.0. The rate of acid secretion by the stomach was calculated in terms of milliequivalents of bicarbonate infused in each 15-min period.

The barostat had a volume much larger (about 2,000 ml) than the stomach, so that any change in volume of the stomach due to contraction or relaxation had little effect on the level of fluid in the barostat. The patients rested in the recumbent position throughout the test. The tip of the xiphoid process was taken as zero reference for pressure measurement. The distention pressure was expressed as the difference in height between their point and the fluid level in the barostat.

The standard meal (Bactoprotone, Difco Laboratories, Detroit, Mich.), consisting of 10% peptone and adjusted to pH 5.0, was allowed to flow continuously into the stomach from a reservoir-barostat with a diameter of 15 cm, open to the atmosphere. The volume of the test meal was about 300 ml, and distention pressure was adjusted by the barostat to a constant level of about 15 cm. This barostat level was selected as a constant position and used in all tests.

Venous blood was withdrawn before the infusion of the test meal and every 30 or 60 min afterwards. After the blood was allowed to clot, serum was obtained by centrifugation and was stored at −20°C until assayed.

Throughout each test, an infusion of 154 mM NaCl was delivered into an arm vein at 80 ml/h by a peristaltic pump. In test experiments, atropine sulfate in a constant intravenous dose of 25 μg/kg-h was added to the infusion at the beginning of the sixth 15-min period after the test meal was started. Atropine infusion was continued for four 15-min periods. In the control studies, 154 mM NaCl alone was infused throughout the study.

The concentration of gastrin in serum was determined radioimmunochemically (11). The routine detection limit of the assay, as employed in the present study, was 5 pg eq synthetic human gastrin (SHG)[1]/ml serum. The antiserum used (2604) was raised in a rabbit against SHG (2–17), covalently coupled to bovine serum albumin. The production and characteristics of the antiserum have been reported previously (12). Monoiodinated SHG (1–17) was used as tracer (13), and SHG (1–17) was used as standard.

Pentagastrin-induced gastric secretion. In tests with pentagastrin, a double-lumen Dreiling tube was positioned under fluoroscopic control with the tip at the junction of the third and fourth parts of the duodenum. A pediatric endotracheal tube cuff mounted over the Dreiling tube was placed midway between the gastric and duodenal orifices. At the beginning of each study, the cuff was inflated with 20 ml of air to prevent reflux of duodenal content into the stomach. Inflation did not cause any sensation or discomfort.

Gastric and duodenal contents were aspirated separately by a vacuum pump at a negative pressure of about 20 mm Hg and collected at 15-min intervals. The suction was interrupted every 2 min for 10 s and air was injected into the tube to ensure constant patency. Saliva was continuously collected by a dental aspirator.

Throughout each study an infusion of 154 mM NaCl was delivered into an arm vein at 80 ml/h by a peristaltic pump. After two basal collections, 2 μg/kg-h pentagastrin was added to the NaCl infusion for 13 15-min periods. In separate dose-response tests (4, 7) on the same patients, in which pentagastrin was given intravenously in graded doses ranging from 0.5 to 8.0 μg/kg-h, the mean highest observed acid output was attained at the dose of 2.0 μg/kg-h and was about 9.0±1.42 meq HCl/15 min. In test experiments, atropine, in a constant dose of 25 μg/kg-h, was added to the intravenous infusion at the beginning of the sixth 15-min period of pentagastrin infusion and continued for 1 h. In the control studies, pentagastrin alone was infused throughout the study.

The volume of gastric aspirate was recorded. The duodenal content was usually negligible in volume and was not analyzed. The acidity of the gastric aspirate was measured by titrating 0.2-ml samples with 0.1 N NaOH to pH 7.0 (Autoburet, Radiometer). The output of acid was expressed in milliequivalents per 15 minutes.

The percentage of inhibition of gastric acid output by atropine was calculated from the difference between the mean acid output during the control studies with either a meal or pentagastrin taken as 100% and the mean acid output during two 15-min periods of the strongest inhibition by atropine. The results were expressed as means±SEM. The Student *t* test for paired values was used in the statistical analysis of the data.

RESULTS

Fig. 1 shows the acid secretion rate in six duodenal ulcer patients under basal conditions and in response to a test meal adjusted to pH 5.0 and kept at a distention pressure of 15 cm H_2O. Mean basal secretion was 3.35± 1.05 meq/15 min. Acid secretory response to the peptone meal alone (control studies) measured by intragastric titration reached a peak in the sixth 15-min period after the test meal was infused. Peak secretion rate in control experiments was 9.1±2.30 meq/15 min and in the test experiments was 9.0±1.30 meq/15 min. In control experiments, acid secretion was relatively well sustained throughout the study, except in the last three 15 min periods, when it showed a gradual tendency to diminish towards the basal level. Intravenous administration of 25 μg/kg-h atropine resulted in almost immediate inhibition of acid response to the meal. The maximal inhibitory effect of atropine occurred in the second and third periods after the start of its infusion; secretion rate during this time was about 33% of the control level. After withdrawal of atropine infusion, the acid output returned to a level not significantly different from the control value.

[1] *Abbreviation used in this paper:* SHG, synthetic human gastrin.

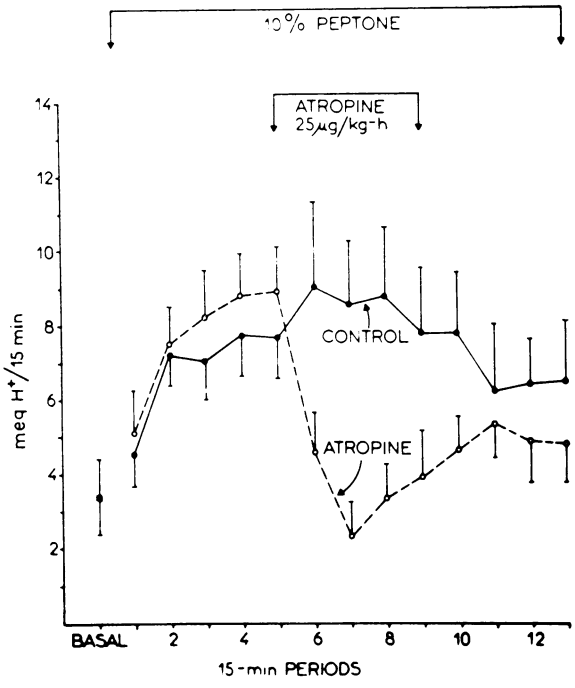

FIGURE 1 Rate of acid secretion during a 10% peptone meal with and without atropine infusion in six duodenal ulcer patients. Mean±SEM. The rate of basal secretion was measured by standard aspiration technique. The response to the meal was determined by the intragastric titration method.

The serum gastrin concentration with the test meal at pH 5.0 is shown in Fig. 2.; After the infusion of the meal gastrin concentration increased to a level which was approximately three times as high as the fasting value. In control tests the gastrin level fell somewhat by the end of the test meal. Serum gastrin concentration during a peptone meal was suppressed by atropine in three patients, unchanged in two others and elevated in one patient. The difference in the serum gastrin level between control and atropine experiments was not significantly different.

In control studies with infusion of pentagastrin in a dose of 2 μg/kg-h, acid output reached a peak of 10.0± 0.80 meq/15 min in the third 15 min period after the start of the infusion of pentagastrin and then showed a tendency to decline, reaching about 83% of the initial peak at the end of the test (Fig. 3). Atropine caused about 30% inhibition of pentagastrin-induced secretion. The inhibition of acid output after atropine reached the maximum during the last two periods of atropine infusion and was statistically significant. After the withdrawal of atropine, the acid output showed a tendency to return towards the control level.

In tests with atropine, all patients showed the symptoms of dryness of the mouth, increase in pulse rate,

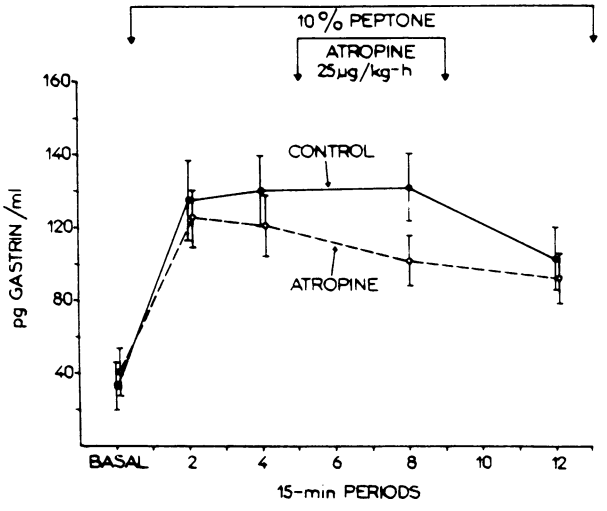

FIGURE 2 Serum gastrin level in tests as in Fig. 1.

dilatation of the pupil, and occasionally blurring of vision.

DISCUSSION

These studies provide evidence that atropine strongly inhibits meal- and pentagastrin-induced gastric acid secretion but does not significantly affect serum gastrin level when gastric pH is maintained constant at pH 5.0.

Previous investigations on the effect of atropine on gastric acid response to a meal have been performed

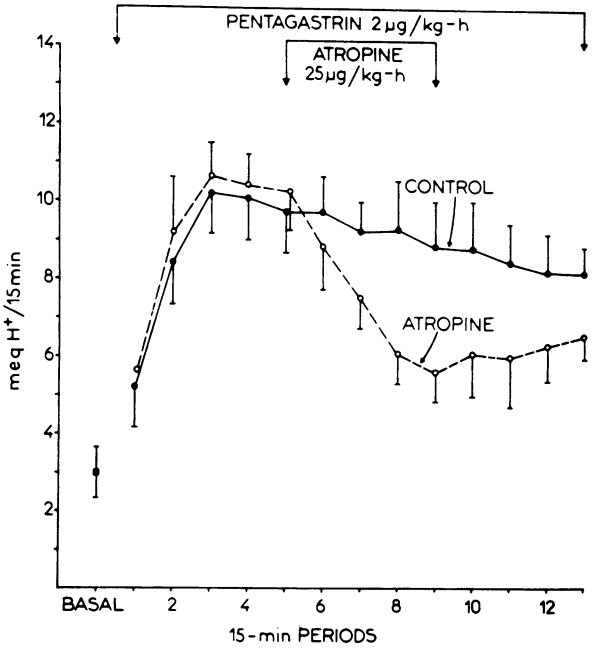

FIGURE 3 Rate of acid secretion in response to pentagastrin with and without atropine infusion in the same six duodenal ulcer patients as in Fig. 1.

solely on animals with fundic pouches (14, 15). In our present report, a new technique for measuring the rate of acid secretion, described by Fordtran and Walsh (10), was modified and applied to study the effect of atropine on meal-induced gastric acid secretion from the intact stomach. This method includes the intragastric titration of secreted acid by sodium bicarbonate to keep the gastric content pH at a constant level and the use of barostat technique to control intragastric pressure.

Although the method involves the manipulation of the gastric pH, and is therefore not entirely physiological, the accurate and continuous control of gastric pH excludes the inhibition of release of antral gastrin by a low pH and/or release of secretin by endogenous acid passing from the stomach to the duodenum. In our ulcer patients, the gastric acid response to the peptone meal was slightly smaller than the highest observed response to pentagastrin. Fordtran and Walsh (10), using single feeding with the standard meal consisting of ground and cooked beef steak, found that after eating most ulcer patients secreted acid at a rate exceeding their peak histamine response. The discrepancy in the secretory rate attained by beefsteak and by our peptone meal might be attributed to the difference in the meal stimulus applied.

Bachrach (16), after his extensive review of the literature in 1958, concluded that there is no evidence that atropine or any other anticholinergic had any inhibiting effect on the secretion of acid in response to food. Our results demonstrate that atropine can reduce food-stimulated acid secretion, but they are not necessarily applicable to the use of anticholinergic drugs clinically, since the toxic effects observed at the dose used probably could not be tolerated for more than an acute experimental procedure.

Recent studies on dogs (14, 15) in which gastric acid secretion from fundic pouches and serum gastrin response to feeding, sham feeding, and insulin hypoglycemia were determined, showed that atropine in a dosage ranging from 100 to 200 μg/kg completely suppressed acid responses to all these stimuli. Atropine had no significant effect on the rise in plasma gastrin after feeding but eliminated plasma gastrin responses to sham feeding and insulin hypoglycemia. We have shown recently (17) that atropine abolished acid and gastrin stimulation by distention as well as by vagal, cholinergic, and chemical stimuli applied to the innervated antral pouch (18). It is evident from these studies that vagal release of gastrin is atropine-resistant and probably of antral origin, whereas the increase in serum gastrin response to feeding is atropine-resistant and of unknown origin.

In our present study, the inhibitory action of atropine on meal-induced acid secretion was not accompanied by any significant change in serum gastrin level. It is therefore concluded that this action is not attributable to the inhibition of gastrin release, but instead could be attributed to the inhibition of gastrin effect on parietal cell or inhibition of cholinergic effect on acid secretion. In other studies (19, 20) in which serum gastrin response to feeding with and without atropine was measured, it was found that prior atropinization significantly enhanced serum gastrin level induced by feeding. The atropine-induced enhancement of serum gastrin level may be considered as a secondary phenomenon, probably attributable to such factors as gastric distention associated with atropine-induced delay in gastric emptying and the decrease of gastric secretion with subsequent loss of acid inhibition of the antrum. In our study gastric distention was controlled by a barostat technique, whereas antral pH was maintained constant by intragastric titration at pH 5.0. These factors may account, at least in part, for the failure of atropine to raise serum gastrin level in response to a test meal.

It is well established that under normal conditions, i.e. in response to food, cholinergic stimulation and gastrin act synergically on the oxyntic glands (21, 22, 23). The attempts to evaluate the quantitative importance of these factors were unsuccessful, but they showed that only small amounts of gastrin are needed to potentiate acid response to vagal stimulation. Atropine was shown to be a more effective inhibitor of insulin- than of pentagastrin-induced acid secretion (5), suggesting that cholinergic stimulation is more sensitive than gastrin stimulation to atropine inhibition. In our study the effects of the same dose of atropine on equipotent pentagastrin or meal stimulation in the same subjects were significantly different. Atropine inhibited meal-induced acid secretion more than pentagastrin-induced secretion, suggesting that cholinergic innervation plays an important role in the stimulation of the oxyntic glands by food.

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