Inhibition by secretin of the gastric acid responses to meals and to pentagastrin in duodenal ulcer patients

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SUMMARY The inhibitory effects of intravenous secretin on the gastric acid responses to a meal and to pentagastrin were studied in seven duodenal ulcer patients.

A test meal of 10% peptone adjusted to pH 5.0 was introduced into the stomach and the Fordtran and Walsh method was used to measure the gastric acid output by monitoring the rate at which a solution of 0.3 M sodium bicarbonate had to be added to keep the pH of the gastric content constant at the value of 5.0. A constant dose of secretin (1 U/kg-hr) significantly depressed the serum gastrin response to a meal and produced an inhibition of acid secretion by about 70% of the control level. Secretin inhibited the acid response induced by pentagastrin by about 60% and simultaneously provoked a pancreatic bicarbonate output sufficient to neutralize about 60% of the gastric acid output to pentagastrin. We conclude that secretin is a strong inhibitor of gastric secretion in duodenal ulcer patients induced by a meal and by pentagastrin.

Previous studies in man (Wormsley, 1968; Konturek, 1970; Berstad and Petersen, 1970) showed that secretin does not invariably inhibit the gastric acid response to various stimuli, and it has been concluded that the gastric inhibitory action of this hormone is fairly weak. No study, however, has been made of the action of secretin on gastric acid secretion induced by a meal in duodenal ulcer patients.

The present study explored the effect of exogenous secretin on meal-stimulated gastric acid secretion measured by the intragastric titration method of Fordtran and Walsh (1973), and compared this effect with the action of secretin on pentagastrin-induced gastric secretion in the same duodenal ulcer patients.

Methods

Seven patients with well established chronic duodenal ulcer disease were studied, the mean age being 36 years (range 22 to 46 years) and mean weight

71 kg (range 50 to 78 kg). Each patient gave informed consent.

Two series of secretory tests were performed on each subject, one with meal-induced and the other with pentagastrin-induced gastric acid secretion.

In tests with meal-induced secretion the Fordtran and Walsh technique was applied. After an overnight fast, the patient was intubated with a 16 Fr gauge Levin tube, to which was attached a small polyvinyl tube (internal diameter 1 mm). The Levin tube was used for sampling the gastric content, and the polyvinyl tube for infusing sodium bicarbonate. The opening of the polyvinyl tube was 10 cm proximal to the most proximal opening of the Levin tube. The tubes were positioned under fluoroscopic control, so that the Levin tube openings were in the distal portion of the stomach and the opening of the polyvinyl tube was in the upper part of the fundus.

After the tubes were in place the residual gastric content was removed and basal secretion was measured by a standard aspiration technique for two 15-min periods. Then 2 to 3 ml of gastric content was removed, its pH measured by a pH meter (Radiometer, Copenhagen, Denmark), and returned to the stomach through the Levin tube. If

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the pH was below 5.0, the sodium bicarbonate infusion was begun. The gastric contents were sampled repeatedly once every three minutes, the pH was read quickly and the sample then returned to the stomach. After the rate of bicarbonate infusion had been adjusted to achieve a stable gastric pH of 5.0, the subjects were given the test meal through the Levin tube. The subjects rested in the recumbent position throughout the test and the gastric content was sampled about every three minutes, the pH read and the sample quickly returned to the stomach. In order to facilitate mixing of gastric content the subject was shaken manually as in gastric cytological examination for about five seconds before the collection of each sample. About 50 ml of gastric content was collected by aspiration into a bulb syringe, mixed thoroughly by agitation, and after taking 2-3 ml for pH determination, it was quickly returned into the stomach.

The 0.3 N sodium bicarbonate was infused by a peristaltic pump (Unipan, Poland). The rate of infusion could be varied from 0.5 to 248 m-equiv of bicarbonate per hour. The cumulative volume of bicarbonate solution infused was recorded every 15 minutes by noting the residual volume in the volumetric cylinder which served as a reservoir for the sodium bicarbonate infusion. The exact normality of the sodium bicarbonate solution was determined after each test by titrating with an acid standard, and the results of each experiment were then calculated in terms of milliequivalents of bicarbonate infused each 15-min period throughout the three-hour examination.

The standard meal was 500 ml of 10% peptone (Bacto-peptone, Difco Laboratories, Detroit, Michigan), adjusted to pH 5.0 by adding 0.5 M sodium bicarbonate.

Throughout each meal, an infusion of 154 millimolar NaCl was delivered into an arm vein at 80 ml/hr by a peristaltic pump. In test experiments, secretin in a dose of 1 U/kg-hr was added to the constant intravenous infusion at the beginning of the fifth 15-minute period, and continued for one hour. In the control tests 154 mM NaCl alone was infused.

In the experiments in which acid output was measured by controlling gastric pH at 5.5, venous blood was collected before, and every 30 minutes after, the test meal was given. After the blood was allowed to clot, serum was obtained by centrifugation and was stored at -20°C until assayed. Serum gastrin concentration was measured by radioimmunoassay (Yalow and Berson, 1970), with synthetic human gastrin I as the standard. All samples were assayed in duplicate. The sensitivity of the assay was sufficient to measure a gastrin concentration of 1 pg/ml, and at the 1:10 dilution of

serum used in the assay, a serum gastrin concentration of 10 pg/ml could be measured.

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

Gastric and duodenal juices were aspirated separately by a vacuum pump at a negative pressure of about 20 mm Hg and collected in 15-minute batches. The suction was interrupted every two minutes and air injected into the tube to ensure constant patency. Saliva was continuously collected by a dental aspirator. All subjects were well accustomed to the secretory test procedures and were comfortable throughout the examination. The interval between tests varied from five to 10 days.

The volumes of gastric and duodenal aspirates were recorded. The acidity of gastric juice was measured by titrating 0.2 samples with 0.1 N NaOH, using an automatic titrator (Autoburet, Radiometer, Copenhagen). Acid output was expressed in milliequivalents per 15 minutes.

Bicarbonate concentration of the duodenal aspirates was measured in 0.5 samples by adding 1.0 ml of 0.1 N HCl, boiling, and backtitrating with 0.1 N NaOH to pH 7.0 (Autoburet, Radiometer). The output of bicarbonate was expressed in milliequivalents per 15 minutes.

The gastric and duodenal contents were collected under basal conditions and in response to pentagastrin. Throughout each study an infusion of 154 mM NaCl was delivered into the arm vein at 80 ml/hr by peristaltic pump. After two basal 15-min collections of gastric and duodenal contents, 2 $\mu\text{g/kg-hr}$ pentagastrin was added to the NaCl infusion and maintained for 12 15-min periods. In test experiments secretin in a dose of 1 U/kg-hr was added to the intravenous infusion at the beginning of the fifth period and continued for one hour. In the control test pentagastrin alone was infused.

Pentagastrin was given by Dr J. A. Waycott from Imperial Chemical Industries, England, and pure natural secretin was obtained from the Gastro-Intestinal Hormonal Research unit, Karolinska Institutet, Stockholm, Sweden.

The percentage of gastric acid inhibition resulting from secretin was calculated by expressing the mean acid output during the last two periods of secretin infusion as a percentage of the mean acid output during a control test with either a meal or penta-

gastrin. The results were expressed as means, plus and minus standard errors of the means. The significance of the mean difference between paired values was calculated by a paired *t* test.

Results

Figure 1 shows the acid secretion rate in the seven duodenal ulcer patients under basal conditions and in response to the test meal. Average basal secretion measured by the standard aspiration technique was 4.55 m-equiv/15 min. Acid secretion after the meal measured by bicarbonate titration reached a peak at one to half an hour. Peak secretion rate was 12.7 and 11.6 m-equiv/15 min in the test and control experiments, respectively. In control tests acid secretion was relatively well sustained one hour after reaching the peak, and then gradually diminished towards the basal level. By the end of the second hour the stomach usually contained only a small amount of the test meal. The intravenous administration of 1.0 U/kg-hr of secretin resulted in almost immediate inhibition of the gastric acid response to

the meal. The maximal inhibitory effect of secretin occurred during the last two periods of infusion, reaching about 70% of the control level. After the end of the secretin infusion, acid output returned to a level not significantly different from the control level.

During a test meal kept at pH 5.0 serum gastrin showed an abrupt rise above fasting level (fig 2).

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

Fig 1 Rate of acid secretion after standard meal with and without secretin infusion in seven duodenal ulcer patients (mean $\pm$ SEM). The rate of basal secretion was measured by a standard aspiration method. The response to a meal was determined by an intragastric titration technique.

Peak gastrin concentration occurred one hour after the meal, and was approximately twice the fasting level. In control tests the gastrin level fell to basal levels at the end of the third hour after the meal. Secretin caused a marked suppression of the serum gastrin response in all subjects. The gastrin response to food plus secretin was significantly smaller than that to the meal alone.

Figure 3 demonstrates that secretin caused about 60% inhibition of pentagastrin-induced gastric acid secretion. Inhibition of acid output following secretin infusion was statistically significant during the entire period of the secretin infusion. The inhibition was due to a decrease both in volume and acid concentration of the gastric juice.

Basal pancreatic volume and bicarbonate outputs were negligible (fig 4). During infusion of pentagastrin, 2 μ g/kg-hr, a slight and insignificant increase in pancreatic secretion was observed. Secretin produced a sudden increase in volume and bicarbonate output, reaching a peak in the third 15-min period. After the end of the secretin infusion, pancreatic secretion showed a tendency to return towards the control level.

Comparison of the mean peak acid outputs to pentagastrin, with the mean peak acid responses to the meal indicates that most ulcer patients secrete

Fig 3 Rate of acid secretion in response to pentagastrin with and without secretin infusion in the same seven duodenal ulcer patients as in figure 1.

acid after a test meal at a rate slightly less than after pentagastrin. The difference did not reach statistical difference.

Fig 4 Pancreatic bicarbonate output in tests as in figure 3.

The output of bicarbonates in milliequivalents during peak pancreatic response in tests with pentagastrin plus secretin reached about 60% of peak gastric acid output in milliequivalents in these tests.

Discussion

These studies provide evidence that secretin strongly inhibits the gastric acid response to a test meal and to pentagastrin, and causes the suppression of the serum gastrin response to the meal in duodenal ulcer patients with gastric hyperchlorhydria.

Previous measurements of the gastric acid response to a meal have been made solely in animals with fundic gland area pouches. In these experiments secretin only moderately inhibited gastric acid response to feeding (Brooks, Stening, and Grossman, 1971; Sjödin, 1971). This was probably due to the fact that during gastric pouch response to food the endogenous acid could trigger antral and duodenal inhibitory mechanisms, and thus mask the potential inhibition of exogenous secretin. A similar decrease in the inhibitory action of secretin on gastrin-induced secretion was previously found in dogs with Heidenhain pouches when a gastric fistula was kept closed and acid from the main stomach was allowed to enter the duodenum and inhibit gastric acid secretion endogenously (Wormsley and Grossman, 1964).

In our present study, a new technique for measuring the rate of gastric secretion, described by Fordtran and Walsh (1973), was applied to study the effect of secretin on meal-induced acid secretion. This method involved the intragastric titration of acid by bicarbonate to keep the gastric content pH at a preselected, constant value of 5.0. Although the technique involved the manipulation of the gastric pH, thus preventing the natural tendency of the gastric pH to decrease, and is therefore not entirely physiological, the control of the gastric pH excluded the inhibition of antral gastrin and the release of secretin by endogenous acid passing from the stomach to the duodenum.

Since the effect of secretin on gastric acid was accompanied by a marked depression of the serum gastrin level, it is concluded that this action might be attributed at least in part to the prevention of gastrin release by secretin. This notion has been advanced in recent studies in which the serum gastrin response to food, with or without secretin, was measured by radioimmunoassay (Thompson *et al*, 1972). There is no doubt, however, that secretin in man blocks the action of gastrin at the level of the parietal cells (Berstad and Petersen, 1970) and our present study is in keeping with this concept. In fact, this is

probably the major mechanism by which secretin inhibits gastric secretion. A comparison of the inhibitory effect of secretin on equal rates of gastric acid secretion induced by pentagastrin or a test meal shows that the degree of inhibition in both instances was very similar.

There is now considerable evidence that the gastric acid secretion produced by a test meal is the result of the combination of gastrin release and direct cholinergic stimulation of the parietal cells. The major factor responsible for both the release of gastrin and direct cholinergic stimulation is the distension of the stomach by food. Further study is needed to determine the action of secretin on both mechanisms of food-induced gastric secretion.

Our present study supports the principle of treating duodenal ulcer in man with secretin (Grossman, 1966). As reported previously, the injection of secretin was found to relieve duodenal ulcer pain in patients with active duodenal ulcer (Holst, Høj, and Rune, 1971). The possible effectiveness of secretin in the treatment of peptic ulcer was tested in cats, in which this hormone completely prevented pentagastrin and histamine-induced peptic ulcerations in the duodenum, even though in these animals secretin inhibited acid secretion only slightly (Konturek, 1968).

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