Serum gastrin and gastric acid responses to meals at various pH levels in man

S. J. KONTUREK,¹ J. BIERNAT, AND J. OLEKSY

From the Institute of Physiology, Medical Academy, Kraków, Poland, and the District Hospital, Kraków, Poland

SUMMARY Serum gastrin and gastric acid responses to a test meal of 10% peptone were measured in six duodenal ulcer patients using intragastric titration at pH levels ranging from 5.5 to 1.0. In this way the pH profile for inhibition of serum gastrin release and gastric acid secretion was established. A peptone meal adjusted to pH 5.5 produced gastric acid similar to the maximal response to histamine. A graded decrease of pH of the peptone meal to 1.0 resulted in the progressive inhibition of the gastric acid secretion and the concomitant suppression of the serum gastrin level. Exogenous secretin given in graded doses ranging from 0.25 to 2.0 U/kg-hr caused a dose-related inhibition of gastric acid secretion and the suppression of serum gastrin level. The results of the study indicate that gastric acid secretion and the rise in serum gastrin levels in response to an experimental meal are less when the gastric contents become more acid. The mechanism may involve release of secretin from the small intestine by acid.

The introduction of acid into the duodenum is known to elicit in man and animals several integrated processes among which are the inhibition of gastric acid secretion and the stimulation of pancreatic secretion.

Although pH-dependence of these processes is generally recognized in dogs (Andersson and Elwin, 1972; Elwin and Uvnäs, 1966), little information is available concerning gastrin release and the gastric acid response to food at various pH values in patients with duodenal ulcer disease in which the loss of acid inhibition of gastrin release has been suspected (Berson and Yalow, 1971).

In this study the modified Fordtran and Walsh (1973) method has been applied to examine serum gastrin and gastric acid response to a standard peptone meal adjusted to various pHs and to compare the changes obtained with these induced by exogenous secretin in duodenal ulcer patients.

Methods

PATIENTS

The study group consisted of six patients with well

established chronic duodenal ulcer disease with a mean age of 22 years (range 20 to 24 years) and mean body weight 66 kg (range 62 to 69 kg). All patients were well accustomed to secretory test procedures and gave informed consent. The patients received no anticholinergics for 48 hours before the secretory studies were started.

INVESTIGATIVE PROCEDURE

Three series of test meals were performed on each patient using: (1) a peptone meal adjusted to pH 5.5; (2) a peptone meal adjusted to pH levels varying from pH 5.5 to 1.0; and (3) a peptone meal adjusted to pH 5.5 during which intravenous secretin was given in graded doses doubling from 0.25 to 2.0 U/kg-hr.

In the tests of meal-induced secretion a modification of the method of Fordtran and Walsh (1973) was applied. After an overnight fast and the collection of basal secretion by simple suction, the patients were intubated with a 16 FR Levin-type stomach tube, to which were attached a small polyvinyl tube (internal diameter 4 mm), a large polyvinyl tube (internal diameter 7 mm), and a combined glass-calomel electrode (type GK 282C/o, Radiometer, Copenhagen, Denmark). The tip of the large polyvinyl tube and glass-calomel electrode were about 5 cm distal to the most distal aspiration hole of the Levin tube and the tip of the small polyvinyl tube

¹Please address correspondence to: Prof. dr Stanisław J. Konturek, Institute of Physiology, ul. Grzegorzewska 16, 31-531 Kraków, Poland.

Received for publication 4 April 1974.

was about 10 cm proximal to the most proximal aspiration hole of the Levin tube. Thus the aspiration holes in the Levin tube were placed distally to the tip of the small polyvinyl tube but proximally to the glass electrode. The distance between the tips of the small infusion tube and glass-calomel electrode was about 20 cm. The tubes were positioned under fluoroscopic control so that the tip of the large polyvinyl tube and the glass-calomel 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. Such an arrangement allowed us to measure the pH of the peptone meal in the antral portion of the stomach just before its entry into the duodenum. The infusion of bicarbonate in the fundic portion of the stomach permitted of a thorough titration of gastric acid without interference with the measurement of the peptone meal pH.

The Levin tube was used for continuous suction of gastric content; the small polyvinyl tube 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 Radiometer) which recorded the cumulative amount of titrant (0.5 M NaHCO_3) against time.

Continuous mixing of the gastric content was performed throughout the test meal using a peristaltic pump (Unipan, Poland) connected to the Levin tube and to the small polyvinyl tube. The pump was set at a delivery rate of about 600 ml/15 min and the peptone meal aspirated from the stomach by the Levin tube was infused into the stomach through the small polyvinyl tube. The latter tube had a T-shaped glass part to which the tubing infusing bicarbonate from the autoburet was connected. The rate of intragastric infusion of bicarbonate from the autoburet was automatically adjusted by such titration as was necessary to maintain the gastric pH constant at pH 5.5. The rate of acid secretion by the stomach was calculated in terms of milliequivalents of bicarbonate infused in each 15-min period.

The barostat was connected through the large polyvinyl tube with the stomach and had a volume much larger (about 2000 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 distension pressure was

expressed as the difference in height between this point and the fluid level in the barostat.

The test meal used for intragastric titration consisted of 10% peptone (Bactoprotone, Difco Lab, Detroit, Michigan) and was allowed to flow continuously into the stomach from a reservoir-barostat. The initial volume of the test meal in the stomach and in the barostat was about 300 ml and the distension pressure was adjusted by the barostat to a constant level of about 15 cm. The meal solution was either adjusted to a constant pH 5.5 or to a selected pH varying from 5.5 to 1.0 and then introduced into the stomach, where, by intragastric titration, it was held at this same pH for 30 minutes. In both types of test the meal was removed from the stomach and replaced by a fresh meal at the same pH (5.5) or at another pH (from 5.5 to 1.0). In the latter instance the order of change of pH was sequential from 5.5 to 1.0.

In tests with exogenous secretin, the test meal was adjusted to pH 5.5 and introduced every 30 minutes after emptying the stomach of the residues of the previous meal. Secretin (Gastrointestinal Hormone Research Unit, Karolinska Institutet, Stockholm, batch number 17351) was infused intravenously in graded doses doubling every 30 minutes from 0.25 to 2.0 U/kg-hr.

For comparison of gastric secretory responses a histamine infusion test was performed. A dose of 40 $\mu\text{g/kg-hr}$ of histamine dihydrochloride was infused intravenously and gastric juice was collected by a simple aspiration technique. The acidity of gastric juice was measured by titration of 0.2 ml samples with 0.1 N NaOH using an automatic titration (Autoburet, Radiometer). Acid output was expressed in milliequivalents per 15 minutes.

Blood samples for serum gastrin determinations were obtained from a peripheral vein during the basal period and every 45 minutes after the introduction of the test meal into the stomach. Each sample was allowed to clot at 40°C, was centrifuged within one hour, and the serum was aspirated and then maintained frozen at -20°C until assayed.

In tests with a peptone meal, the gastrin concentration in serum was determined radioimmunochemically (Yalow and Berson, 1970). The routine detection limit of the assay, as employed in the present study, was 5 pg equiv. synthetic human gastrin (SHG) per ml serum. Serum gastrin concentration of 10 pg/ml or greater could be measured.

CALCULATIONS

The percentage of the decrease of gastric output by secretin or decreasing pH levels was calculated from the difference between the mean acid output during the peptone meal at pH 5.5 (taken as 100%) and the

mean acid output during last two 15-min periods at a given dose of secretin or a selected pH value of the peptone meal. The results were expressed as means, plus and minus standard error of the mean (SEM). The significance (*P*) of the mean difference between paired values was calculated by paired *t* test.

Results

The introduction into the stomach of a 10% peptone meal adjusted to pH 5.5 resulted in an abrupt rise of gastric acid secretion reaching the level of maximal acid response to histamine (fig 1). In control experiments when the peptone meal was held in the stomach at the same pH 5.5, acid secretion was relatively well sustained throughout the study.

Fig 1 Gastric acid outputs in response to a peptone meal at pH levels varying from 5.5 to 1.0 or at constant pH 5.5. For comparison the maximal acid response to histamine is presented. In this and subsequent figures each point is the mean of six tests on each of six duodenal patients. The vertical lines are the standard errors of the mean.

When a peptone meal was adjusted to pH levels ranging from 5.5 to 1.0 there was a significant decrease of gastric acid response at pH 4.0. With a further fall in the meal pH, acid output showed a progressive reduction and it was almost completely inhibited at pH 1.0 (fig 1).

The responses of serum gastrin to the test meal at a constant pH 5.5 or at pH levels varying from 5.5 to 1.0 are shown in figure 2. In control tests the gastrin level reached the peak in the second 15-min period following the introduction of the meal in the stomach and it was approximately about twice as high as the fasting level. As with acid secretion there was a pro-

Fig 2 The responses of serum gastrin in tests as in figure 1.

gressive decline of serum gastrin as pH levels varied from 5.5 to 1.0.

In tests with a secretin infusion during a test meal gastric acid output showed a progressive decrease with increasing doses of secretin. A significant

Fig 3 Gastric acid outputs in response to a peptone meal during intravenous infusion of secretin in doses ranging from 0.25 to 2.0 U/kg-hr.

Fig. 4 The responses of serum gastrin in tests as in figure 3.

inhibition of acid secretion occurred at the dose of 0.5 U/kg-hr and it was about 90% inhibition at the dose of 2.0 U/kg-hr (fig 3).

Secretin infused in graded doses resulted in the progressive decrease of the serum gastrin level reaching about 50% of the control level at the dose of 2.0 U/kg-hr (fig 4).

Discussion

This study provides evidence that the serum gastrin level and gastric acid secretion in response to a peptone meal are pH-dependent and that exogenous secretin given in graded doses during the test meal mimics the changes in serum gastrin and gastric acid secretion evoked by the varying pH levels of the meal.

To our knowledge, no previous studies specifically determined the pH profile of serum gastrin release and gastric acid secretion in response to a meal in man. However, several reports estimated the pH dependence of gastrin release by chemical, mechanical, or vagal stimulation in animals. It was found that the pH threshold for the stimulation of gastrin release in dogs varies depending upon the type of release (Andersson and Elwin, 1972; Elwin and Uvnäs, 1966), being lower for distension or vagal stimuli (pH 1.5) than for chemical stimuli such as amino acids or peptone (pH 3.0).

The relative contribution of distension, buffering, and chemical stimulation of gastrin release in re-

sponse to a meal is difficult to determine in the intact stomach because all these factors interact. The distension of the antral gland area in dogs by itself causes a pressure-related increase in gastrin release and probably constitutes the most potent stimulant of gastrin release (Debas, Csendes, Walsh, and Grossman, 1973; Debas, Konturek, Walsh, and Grossman, 1974). Distension of the stomach in dogs also initiates cholinergic reflexes from the fundic and antral gland area to the oxyntic glands (Debas, Konturek, Walsh, and Grossman, 1974). Peptone meal provokes acid secretion by acting directly on parietal cells. Gastrin and cholinergic stimulation interact at the level of parietal cells and potentiate each other in the stimulation of acid secretion.

In our present study the degree of gastric distension was well controlled using a barostat technique, enabling a constant distension stimulus to be maintained throughout the experiment. The antral pH was also controlled by continuous intragastric titration at a selected pH value. It was found that a peptone meal held in the stomach at a constant pressure of 15 cm H₂O and at the constant pH of 5.5 provided a potent stimulation of both gastrin release and gastric acid secretion reaching the level of the maximal histamine-induced acid response. This exaggerated response to a peptone meal was well maintained throughout the test meal and was probably due to the manipulation of the gastric pH by intragastric titration preventing the natural tendency of the gastric pH to decrease. When the pH of a test meal was decreased in sequential order from 5.5 to 1.0, the gradual suppression of the serum gastrin level and inhibition of acid secretion was observed. The fall in the gastric content pH as low as pH 1.0 resulted in almost complete inhibition of the gastric acid response and the decrease of serum gastrin to the fasting level.

Since Fordtran and Walsh (1973) showed that the titration with bicarbonate below pH 2.0 may underestimate the amount of acid being secreted due to the dilution error, the values of acid output obtained at pH 1.0 may not be accurate. However, maintaining the gastric pH at low levels allowed us to determine the full pH profile of gastrin release in the intact stomach. It was found that the decrease of gastric acid secretory response to a peptone meal varying in pH was accompanied by parallel suppression of serum concentration. The pH changes of the gastric content evoked in our study may occur under natural conditions and it is reasonable to accept that in duodenal ulcer patients the gastric inhibitory mechanisms are activated during normal digestion of food. This does not support the previous suggestions that the usual suppression of gastrin release

by a low antral pH may be inadequate or absent in duodenal ulcer patients (Berson and Yalow, 1971).

The decrease of gastric acid response to a peptone meal at a low pH was probably due to the suppression of gastrin release and direct inhibition of parietal cells by a low pH.

Secretin infused in graded doses ranging from 0.25 to 2.0 U/kg-hr resulted in a progressive decrease of serum gastrin and gastric acid secretion induced by the meal. A significant decrease of both serum gastrin and gastric acid response occurred at the dose of 1.0 U/kg-hr secretin which was shown previously to elicit the maximal stimulation of pancreatic bicarbonate secretion (Konturek, 1970a). The similarity of the changes in the serum gastrin and gastric acid secretion induced by decreasing pH levels of a peptone meal or by increasing doses of secretin may be interpreted as indicating that the gastric inhibitory mechanisms elicited by low pH levels are mediated by secretin. Although exogenous secretin under experimental circumstances appears to suppress the release of gastrin as well as to interfere with its action at the parietal cell (Konturek, 1970b; Thompson, Reeder, Bunchman, Becker, and Brandt, 1972; Wormsley, 1968), the importance of this mechanism under physiological circumstances is not settled because the release of this hormone in response to a meal may be relatively small. Further study using immunoassay of secretin in blood is needed to determine the physiological role of secretin in gastric inhibitory mechanisms. There is no doubt that the pharmacological doses of secretin cause the suppression of gastrin release by food (Konturek,

Biernat, and Grzelec, 1973) and interfere with the action of gastrin at the parietal cells supporting the idea of treating duodenal ulcer in man with this hormone (Grossman, 1966).

References

- Andersson, S., and Elwin, C. E. (1972). Release of gastrin in relation to antral acidity and absorption of chemical stimulants. In *Gastrointestinal Hormones*, edited by L. Demling, pp. 1-6. Thieme, Stuttgart.
- Berson, S. A., and Yalow, R. S. (1971). Gastrin in duodenal ulcer. *New Engl. J. Med.*, **284**, 445-453.
- Debas, H. T., Csendes, A., Walsh, J. H., and Grossman, M. I. (1973). Release of antral gastrin. In *Proceedings of a Symposium on Recent Advances in Gastrointestinal Hormone Research*. Rochester, N.Y., edited by W. E. Chey, in press.
- Debas, H. T., Konturek, S. J., Walsh, J. H., and Grossman, M. I. (1974). Proof of a pyloro-oxynic reflex for stimulation of acid secretion. *Gastroenterology*, **66**, 526-532.
- Elwin, C. F., and Uvnäs, B. (1966). Distribution and local release of gastrin. In *Gastrin*, edited by M. I. Grossman, pp. 69-82. Butterworths, London. University of California Press, Los Angeles.
- Fordtran, J. S., and Walsh, J. H. (1973). Gastric acid secretion rate and buffer content of the stomach after eating; results in normal subjects and in patients with duodenal ulcer. *J. clin. Invest.*, **52**, 645-657.
- Grossman, M. I. (1966). Treatment of duodenal ulcer with secretin: a speculative proposal. *Gastroenterology*, **50**, 912-913.
- Konturek, S. J. (1970a). Pancreatic dose-response curves to intravenous secretin in man. *Gastroenterology*, **58**, 828-832.
- Konturek, S. J. (1970b). Effect of secretin and jejunal acidification on gastric and pancreatic secretion in man. *Gut*, **11**, 158-162.
- Konturek, S. J., Biernat, J., and Grzelec, T. (1973). Inhibition by secretin of the gastric acid responses to meals and to penta-gastrin in duodenal ulcer patients. *Gut*, **14**, 842-846.
- Thompson, J. C., Reeder, D. D., Bunchman, H. H., Becker, H. D., and Brandt, E. N., Jr. (1972). Effect of secretin on circulating gastrin. *Ann. Surg.*, **176**, 384-393.
- Wormsley, K. G. (1968). Gastric response to secretin and pancreozymin in man. *Scand. J. Gastroent.*, **3**, 632-636.
- Yalow, R. S., and Berson, S. A. (1970). Radioimmunoassay of gastrin. *Gastroenterology*, **58**, 1-14.