Lower oesophageal sphincter response to intravenous infusions of pentagastrin in normal subjects, antrectomised and achalasic patients¹

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SUMMARY Lower oesophageal sphincter response to infusion of graded doses (0.003 - $0.050 \mu\text{g kg}^{-1}\text{min}^{-1}$) of pentagastrin was evaluated in four antrectomised patients as well as in six healthy subjects and seven achalasic patients in whom inhibition of antral gastrin release was maintained by continuous acidification ($\text{HCl } 0.1 \text{ N}$) and aspiration of gastric antrum. In normal subjects and in antrectomised patients doses of pentagastrin required for half-maximal gastric acid secretion ($0.012 \mu\text{g kg}^{-1}\text{min}^{-1}$) produced statistically significant increases of LES pressure. In achalasic patients, the infusion of pentagastrin did not affect LES pressure. These data seem to indicate that gastrin plays, at least in some degree, a physiological role in the regulation of LES tone. Insensitivity of LES to pentagastrin in achalasia suggests that the raised sphincter pressure in this disorder can not be attributed to gastrin.

Gastrin and its analogue pentagastrin (PG) have been shown to increase lower oesophageal sphincter (LES) pressure (Giles *et al.*, 1969; Castell and Harris, 1970). This effect has been reported to be enhanced in patients with achalasia (Cohen *et al.*, 1971). Other studies, however, did not confirm these data (Farrell *et al.*, 1974; Sturdevant and Kun, 1974; Goyal and McGuigan, 1976; Walker *et al.*, 1975), and the role of the hormone in maintaining LES tone has yet to be determined.

In previous investigations little consideration has been given to possible variations in endogenous serum gastrin levels during basal and stimulation periods. It might well be that variable endogenous serum gastrin levels interact at receptor sites with exogenous gastrin or pentagastrin, thus altering the resulting data. The aim of the present study was to evaluate the LES pressure response to graded doses of PG in subjects during maximal inhibition of antral gastrin release. Normal subjects and achalasic patients in whom the antral mucosa was continuously bathed with $\text{HCl } 0.1 \text{ N}$ solution (Walsh *et al.*, 1975), as well as antrectomised patients, were investigated.

Methods

Six normal volunteers (four males and two females), four male patients, previously operated upon for duodenal ulcer with antrectomy and gastrojejunal anastomosis, and seven achalasic patients (four males and three females), were investigated. Diagnosis of achalasia was made on the basis of radiological, endoscopic, and manometric findings. None of the normal and antrectomised subjects had symptoms related to the gastrointestinal tract and particularly clinical, radiological, and pH-manometric evidence of gastro-oesophageal reflux was lacking; none was taking drugs of any kind.

Three water-filled, polyvinyl catheters, 1 mm internal diameter, were used to transmit intraluminal pressures to Elema-Schönander external transducers. Manometric variations were then recorded on a multichannel Hellige polygraph. The catheters had side openings, 1.2 mm in diameter, arranged to measure intraluminal pressures at three points, 5 cm apart. The pressure recording tubes were perfused with distilled water at a constant rate of 0.750 ml/min using a Braun syringe pump.

Constant $\text{HCl } 0.1 \text{ N}$ infusion (6 ml/min) and aspiration was done through two additional catheters (1.8 mm internal diameter). These had multiple perforations over the 8 cm distal segments and were positioned in the gastric antrum under fluoroscopic

¹This work was presented in part to the American Gastroenterological Association, May 1977, Toronto, Canada.

Received for publication 8 June 1978

control. The five polyvinyl catheters were joined into a single unit with an external diameter of 6.2 mm. The middle recording orifice was 16 cm proximal to the distal tips of the multiperforated catheters.

All subjects were studied in the supine position after overnight fasting. The recording assembly was positioned with all the orifices in the stomach. After a 15 minute rest-period LES pressure was measured by a 0.5 cm interval pull-through of the catheters. The assembly was then positioned again in the stomach and during a second pull-through the catheters were anchored so that the middle recording orifice recorded from the highest pressure point in the lower oesophageal sphincter. Pressures were simultaneously recorded from the oesophagus and the stomach. LES pressure was continuously recorded during a 10 minute intravenous saline infusion and for five successive 10 minute periods of graded doses of intravenous pentagastrin infusion (0.003; 0.006; 0.012; 0.025; 0.050 $\mu\text{g kg}^{-1}\text{min}^{-1}$). In the normal subjects and in the achalasic patients, after preliminary gastric emptying, continuous acidification of the gastric antrum and continuous aspiration of gastric contents was performed for 30 minutes before, and for the duration of, the intravenous infusion period.

LES pressure was recorded as cm H₂O with the mean gastric fundic pressure as the zero reference. The middle inspiratory pressure was reported as the sphincter pressure. LES pressure was measured at one minute intervals or, if the subject happened to swallow, 20 seconds after the end of sphincter inhibition.

Manometric tracings were coded and evaluated blindly at the end of the entire study. Student's *t* test analysis of variance (two-way classification), and Duncan's test were used to evaluate data.

Results

Mean basal LES pressure in normal subjects was 27.8 ± 5 cm H₂O ($M \pm \text{SEM}$) compared with 22.4 ± 2 cm H₂O in the antrectomised patients ($P > 0.05$) and 43.7 ± 6.2 cm H₂O in the patients with achalasia ($P > 0.05$). During the first 30 minute period of antral acidification, LES pressure increased to 36.3 ± 7 cm H₂O in normal subjects and decreased to 42.4 ± 7.2 cm H₂O in the achalasic patients. Neither change was statistically significant ($P > 0.05$).

In normal subjects, the sphincter pressure progressively increased during graded doses of pentagastrin infusion with significant variation at doses of 0.012 $\mu\text{g kg}^{-1}\text{min}^{-1}$ ($P < 0.05$) and of 0.025 $\mu\text{g kg}^{-1}\text{min}^{-1}$ ($P < 0.01$) (Fig. 1). In antrectomised patients, LES pressure increased during PG administration to reach 33.1 ± 2 cm H₂O with the final

Fig. 1 LES pressure values during infusion of saline (S) and graded doses of pentagastrin (PG) in normal subjects. HCl indicates period of antral acidification. * $P < 0.05$; ** $P < 0.01$.

Fig. 2 LES pressure values during infusion of saline (S) and graded doses of pentagastrin (PG) in antrectomised patients. * $P < 0.05$; ** $P < 0.01$.

dose. The LES pressure increment was significantly different at doses of 0.006 $\mu\text{g kg}^{-1}\text{min}^{-1}$ ($P < 0.05$) and 0.012 $\mu\text{g kg}^{-1}\text{min}^{-1}$ ($P < 0.01$) (Fig. 2). In the patients with achalasia the infusion of graded doses of pentagastrin did not affect the pressure of the lower oesophageal sphincter (Fig. 3).

Discussion

It has been stated that producing a response with continuous infusion of a polypeptide at a dose calculated to give one-half the maximal response in the target organ represents one of the main criteria to establish the physiological role of a hormone (Grossman, 1977). Walker *et al.* (1975) reported that there was no statistically significant increase in LES pressure during PG infusion at doses of 0.004–12 $\mu\text{g kg}^{-1}\text{h}^{-1}$; however, examination of individual results suggested that PG might be stimulating LES pressure in some subjects and inhibiting it in others. Two further studies (Hogan *et al.*, 1974; Kaye *et al.*, 1976) showed that LES pressure increased during continuous infusion of PG at above maximal (0.04

Fig. 3 LES pressure values during infusion of saline (S) and graded doses of pentagastrin (PG) in achalasic patients. HCl indicates period of antral acidification.

$\mu\text{g kg}^{-1}\text{h}^{-1}$) or submaximal ($0.9 \mu\text{g kg}^{-1}\text{h}^{-1}$) doses for gastric acid secretion in man. In a recent study (Freeland *et al.*, 1976), the continuous infusion of gastrin heptadecapeptide I at doses within the physiological range induced a significant increase in LES pressure. Such different and contrasting results might indicate that endogenous individual factors may interfere with the exogenous stimuli at level of LES. Up until now little relevance has been given to possible interactions between the exogenous polypeptide and analogous hormone acting on the same receptor sites. It is possible that effects of hormonal substances might be difficult to evaluate due to variations of serum gastrin levels in basal conditions and during gastrin or pentagastrin administration, because of the feedback mechanism between acid secretion and antral gastrin release. Moreover, even the measurement of total gastrin immunoreactivity in serum does not correlate with LES pressure possibly because of the different biological actions of various molecular gastrin types (Higgs *et al.*, 1971; Dodds *et al.*, 1974; Morris *et al.*, 1974; Freeland *et al.*, 1976).

Data of the present study show that continuous intravenous PG infusion stimulates LES pressure in normal and antrectomised subjects. Significant increase of LES pressure was obtained with doses of pentagastrin near (Isenberg *et al.*, 1975) or equal to (Multicentre Pilot Study, 1967) those calculated to give one-half the maximal acid secretion in man. In the present study the carboxyl-terminal amino acid

sequence of gastrin stimulated LES pressure during maximal constant inhibition or absence of gastrin release from the gastric antrum; although the data do not exclude the possibility that the various molecular forms of the hormone might differ in their action upon the sphincter, they suggest that gastrin is, at least partly, involved in the regulation of LES tone in physiological conditions. The lower mean peak sphincter pressure during pentagastrin infusion in antrectomised patients as compared with normal subjects, although not statistically significant, suggests that some factor other than gastrin is responsible for lowering the resting sphincter pressure after antrectomy.

An exaggerated LES response to intravenous bolus gastrin administration has been recorded (Cohen *et al.*, 1971) in achalasia, suggesting that in these patients a gastrin supersensitivity of the LES exists. Data of the present study indicate that continuous intravenous infusion of pentagastrin does not affect LES pressure in achalasia and suggest that gastrin plays no role in the maintenance of the raised sphincter tone in this disorder.

Acidification of the gastric antrum has been reported to inhibit LES pressure in both normal subjects and in achalasic patients and this finding has suggested that sphincter pressure is determined by endogenous gastrin (Cohen *et al.*, 1971). The present study does not confirm these results and indicates that acidification of the antrum does not significantly affect LES pressure in both normal subjects and achalasic patients; unlike the study of Cohen *et al.*, however, in this investigation, continuous aspiration of gastric contents during antral acidification prevented gastric distension.

All the above findings suggest that basal endogenous gastrin does not influence LES pressure, while, more raised serum gastrin levels, as can occur after a meal, might take part in the regulation of LES tone in normal subjects.

This study was supported by CNR grant no. 76.01525 115.3329. The authors wish to thank J. H. Walsh for valuable criticism.

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