Effect of gastrin heptadecapeptide (G17) on oesophageal contractions in patients with diffuse oesophageal spasm

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SUMMARY An intravenous bolus of pentagastrin significantly increased the amplitude and duration of oesophageal body contractions in seven patients with diffuse oesophageal spasm (DES) when compared with five normal subjects ($P > 0.05$). In order to determine whether this stimulation also occurred at physiological gastrin concentrations, the effect of an intravenous infusion of gastrin heptadecapeptide (G17), 25 pmol/kg-h, on oesophageal contractions was studied in DES patients. G17 had no significant effect on the amplitude and duration of oesophageal contractions compared with a saline control. This dose of G17 was near the D50 for gastric acid secretion and produced a rise in serum gastrin concentration comparable with a meal. G17 infusions at doses of 100 and 200 pmol/kg-h increased the amplitude and duration of oesophageal contractions, but the corresponding serum gastrin concentrations were higher than postprandial levels. Thus, endogenous fluctuations in serum gastrin heptadecapeptide, alone, are unlikely to alter oesophageal contractions in DES patients.

Gastrointestinal hormones have diverse effects on smooth muscle of the gut, but the physiological role of these effects is uncertain. It was suggested that in certain clinical disorders an exaggerated motor response to enteric hormones may produce symptoms (Cohen, 1975). Gastrointestinal hormone supersensitivity has been reported in three motor disorders: lower oesophageal sphincter supersensitivity to gastrin in achalasia (Cohen *et al.*, 1971); colonic supersensitivity to cholecystokinin in the irritable bowel syndrome (Harvey and Read, 1973); and, most recently, oesophageal body supersensitivity to pentagastrin in diffuse oesophageal spasm (Eckhardt *et al.*, 1975). In the latter instance, it was demonstrated that a bolus injection of pentagastrin significantly increased the amplitude and duration of oesophageal contraction in patients with diffuse oesophageal spasm (DES), but not in normal subjects (Eckhardt *et al.*, 1975). The purpose of our investigation was to determine whether an intravenous infusion of synthetic human heptadecapeptide gastrin (G17), in a dose that produced serum

concentrations similar to those found after a meal, exacerbated the abnormal oesophageal motility pattern in patients with DES; and it was concluded that it did not.

Methods

Studies were performed in seven patients with DES. There were four men and three women with a mean age of 58 years (range 34-81 years). All patients were symptomatic: six complained of intermittent dysphagia, five noted intermittent chest pain, and four had both symptoms. Barium swallow was considered normal in three patients, demonstrated tertiary contractions in two, and distal oesophageal diverticula in two.

The diagnosis of DES was based on the following manometric findings: (1) the lower oesophageal sphincter pressure and relaxation with swallowing were normal in each case; (2) simultaneous and/or repetitive contractions of increased amplitude accompanied an average of 59% of swallows (range 40-80%) in these patients. This frequency of abnormal contractions is similar to that previously reported in DES patients (DiMarino and Cohen, 1974). Five healthy adult male subjects (mean age 43 years), with no history of gastrointestinal disease,

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served as controls. Informed consent was obtained from both DES and normal subjects, and studies were approved by the Research Committee at Wadsworth Veterans Hospital.

In order to confirm the observation that DES patients are sensitive to pentagastrin (Eckhardt *et al.*, 1975), DES and normal subjects were given pentagastrin, 0.04 µg/kg by rapid intravenous injection over 30 seconds. The amplitude and duration of oesophageal contractions were compared during the five minutes before and after pentagastrin injection. On another day, to determine the effect of a 'physiological' dose of gastrin on oesophageal contractions in the DES patients, an infusion of G17, 25 pmol/kg-h, for 40 minutes was compared with a saline infusion in a random double-blind crossover fashion. In a previous study in humans, this dose of G17 was approximately a half maximal dose, or D50, for gastric acid secretion (Walsh *et al.*, 1976). On a third day, to study the effect of pharmacological doses of G17, three DES patients were given infusions of G17 at 50, 100, and 200 pmol/kg-h for 30 minutes each. Venous blood for serum gastrin determination was obtained basally and at the end of each infusion period. After clotting at room temperature, serum was obtained by centrifugation and stored at -20° until assayed. Gastrin was measured by radioimmunoassay (Yalow and Berson, 1970; Jaffe and Walsh, 1974). Synthetic human gastrin 1 was used as the standard. Normal serum gastrin for the assay was < 120 pg/ml.

The amplitude and duration of all oesophageal contractions initiated by wet (5 ml bolus of H₂O) or dry swallows every 30 seconds, or occurring spontaneously, were recorded by a polyvinyl catheter assembly (outside diameter 4 mm) with recording orifices 3, 8, and 13 cm proximal to the lower oesophageal sphincter. Each catheter was perfused with water (0.5 ml/min) using a hydraulic infusion system with negligible compliance and a frequency response of greater than 200 mm Hg/s (Arndorfer *et al.*, 1977). Oesophageal intraluminal pressure was transmitted from the catheter assembly to Statham P23AA external transducers, and their outputs were recorded on a multichannel recorder (Electronics for Medicine). All swallows were recorded through another transducer using a belt pneumograph placed over the larynx.

Oesophageal contraction amplitude and duration were measured from continuous recordings. The mean amplitude and duration of the three largest contractions (mean peak amplitude and duration) before and after bolus pentagastrin injections were compared in normal subjects and DES patients. For the 40 minute G17 (25 pmol/kg-h⁻¹) and placebo infusions, the amplitude and duration of the three

largest contractions were averaged for a 10 minute basal period and for 10 minute periods during the 40 minute infusion time. These tracings were analysed in coded fashion. For the pharmacological G17 infusions, the three largest contractions basally and during each infusion period were analysed for mean amplitude and duration. Since DES patients have oesophageal contractions which are not initiated by swallows—that is, spontaneous—or are repetitive, these were analysed separately and expressed as total duration of spontaneous, repetitive contractions during each study period. Student's paired *t* tests were used to analyse the data (Snedecor and Cochran, 1967).

Results

BOLUS INJECTION OF PENTAGASTRIN

In the five normal subjects, 0.04 µg/kg pentagastrin had no effect on either oesophageal contraction amplitude or duration. In the seven DES patients, mean peak (±SEM) amplitude increased significantly from 140±17 to 167±15 mm Hg (*P* < 0.05), and mean peak (±SEM) duration increased significantly from 6.4±1.1 to 10.2±1.6 seconds (*P* < 0.01) after pentagastrin injection. Mean (±SEM) total duration of spontaneous, repetitive contractions per five minute period increased from 25±9 to 75±20 seconds in DES patients (*P* < 0.05).

PHYSIOLOGICAL INFUSION OF G17

Although a bolus injection of pentagastrin significantly increased the amplitude and duration of oesophageal contraction in the seven DES patients, G17 infusion at 25 pmol/kg-h had no significant effect when compared with a placebo infusion. There was also no significant increase in the total duration of spontaneous, repetitive contractions in these patients during G17 infusion. Mean (±SEM) serum gastrin increased to 56±13 pg/ml during G17 infusion compared with 25±4 pg/ml during saline (Table 1).

PHARMACOLOGICAL INFUSION G17

Graded infusion of G17 in three DES patients produced an increase in contraction amplitude and

Table 1 Effect of G17 (25 pmol/kg-h) and saline on oesophageal contractions (mean±SEM) in seven DES patients

	G17	Saline
Amplitude (mm Hg)	157±25	158±23
Duration (s)	8.2±1.6	8.4±1.6
Spontaneous and/or repetitive contractions (s)	201±66	173±80
Serum gastrin (pg/ml)	56±13	25±4

Table 2 Effect of varying doses of G17 on oesophageal contractions (mean $\pm$ SEM) in three DES patients

	Basal	G17 infusion (pmol/kg-h)		
		50	100	200
Amplitude (mm Hg)	79 $\pm$ 5	87 $\pm$ 7	107 $\pm$ 15	141 $\pm$ 39
Duration (s)	6.6 $\pm$ 0.7	6.9 $\pm$ 0.7	10.2 $\pm$ 1.8	11.2 $\pm$ 3.8
Serum gastrin (pg/ml)	96 $\pm$ 4	313 $\pm$ 10	460 $\pm$ 41	872 $\pm$ 41

duration only at the 100 and 200 pmol/kg-h doses. These infusion doses produced average serum gastrin concentrations of 460 and 872 pg/ml respectively compared with a mean basal concentration of 96 pg/ml (Table 2).

Discussion

The findings of this study confirmed the observation that most patients with DES, but not normal subjects, were sensitive to a bolus injection of pentagastrin (Eckhardt *et al.*, 1975). One DES patient developed chest pain after pentagastrin, but this was mild and transient discomfort differing in character from her usual attacks of retrosternal pain. The lack of typical symptoms after pentagastrin in our patients is in accord with the recent experience of Eckhardt (Eckhardt *et al.*, 1975). Although a pentagastrin bolus increased lower oesophageal sphincter pressure, it had no effect on the amplitude and duration of oesophageal peristalsis in normal controls (Hollis *et al.*, 1972). Pentagastrin injection may be a useful and safe provocative test to assist in confirming the diagnosis of DES and in differentiating it from achalasia. Additional study, however, is necessary to establish its sensitivity and specificity.

Despite the response to bolus pentagastrin injections, there was no discernible effect of G17 infusion in a dose that mimicked postprandial gastrin concentrations. The 25 pmol/kg-h dose of G17 is known to be submaximal for gastric acid secretion (Walsh *et al.*, 1976). The mean increase in serum gastrin of 31 pg/ml after this infusion is similar to the reported G17 increment of 38 pg/ml produced by a meal (Dockray and Taylor, 1976). Pharmacological doses of G17 were required to produce increases in oesophageal contraction amplitude and duration similar to those observed after pentagastrin bolus injections. Chest pain was not induced during any of the G17 infusions. It is, therefore, unlikely that endogenous fluctuations of G17 alone affect the abnormal contractions of patients with DES.

The predominant postprandial molecular form of gastrin is big gastrin (G34) (Walsh *et al.*, 1976). Equimolar exogenous doses of G34 and G17 produce similar increases in lower oesophageal sphincter

pressure in man (Jensen *et al.*, 1977) but these initial studies do not suggest G34 as a physiological regulator of lower oesophageal sphincter pressure. There are no studies on the effect of G34, either alone or in combination with G17, on the amplitude and duration of oesophageal body contractions.

The mechanism of increased sensitivity to gastrin in DES patients is unknown. In normal subjects, pentagastrin, at doses which markedly increase lower oesophageal sphincter pressure, had no effect on primary oesophageal peristalsis (Hollis *et al.*, 1972). DES patients probably acquire hypersensitivity to pharmacological doses of gastrin. This hypersensitivity to pharmacological agents in DES may also be reflected in the manometric changes after methacholine (mecholy) injection (Kramer *et al.*, 1967). The explanation of these sensitivities is unclear, but may be related to the hypertrophic oesophageal muscle and degenerative vagal nerve afferent fibres reported in DES (Cassella *et al.*, 1965). However, it may be that the sensitivity to gastrin in DES patients is related to the raised basal amplitude of contractions, and studies in asymptomatic individuals with contraction amplitudes comparable with DES patients would be relevant to that hypothesis.

It is concluded that, in DES patients, infusion of G17 in the physiological dose range did not alter oesophageal contractions known to be sensitive to bolus doses of pentagastrin. Thus, endogenous fluctuation in G17 alone is unlikely to alter oesophageal contractions or induce symptomatic episodes in patients with diffuse oesophageal spasm.

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