Supersensitivity to pentagastrin in diffuse oesophageal spasm

V. ECKARDT¹ AND H. WEIGAND

From the Departments of Medicine (I) and of Radiology, University of Mainz, Germany

SUMMARY A 38-year-old patient, complaining of dysphagia and substernal pain of nine months' duration, was found by manometric studies to have diffuse oesophageal spasm. As has similarly been reported for cholinergic agents in achalasia and in some cases of diffuse oesophageal spasm the oesophageal body responded in a hypersensitive fashion to subcutaneous and intravenous injections of pentagastrin. This effect was inhibited by the intravenous administration of atropine and completely abolished by nitroglycerine. When pentagastrin was subcutaneously injected before a barium examination a distortion of the oesophageal contour, described as curling or corkscrew oesophagus, regularly appeared.

Diffuse oesophageal spasm is a clinical syndrome characterized by substernal pain and dysphagia. Manometric recordings of the oesophagus reveal exaggerated repetitive, simultaneous, non-peristaltic contractions, which occur spontaneously and following a dry swallow (Roth and Fleshler, 1964). Since manometric investigations are presently performed only in a few medical centres diagnosis depends on the radiological demonstration of localized segmental spasms, giving the so-called corkscrew oesophagus appearance. However, the disorder tends to be episodic and symptoms may not occur during radiographic study (Fleshler, 1967; Gillies, Nicks, and Skyring, 1967) so that many patients' symptoms are ascribed to hysteria or angina on the basis of apparently normal radiographic studies. Several but not all, patients suffering from diffuse oesophageal spasm, respond in a hypersensitive fashion to a subcutaneous injection of cholinergic agents (Kramer, Fleshler, McNally, and Harris, 1967), thus allowing tertiary contractions to appear during a barium swallow. An increase of spontaneous activity of the oesophageal musculature is also observed in achalasia, which eliminates this test as a differential diagnostic tool. In addition, cholinergic agents might be contraindicated in patients with concomitant cardiac disease, so that radiological confirmation of the diagnosis remains difficult.

We have recently observed a patient with diffuse oesophageal spasm in whom subcutaneous and intravenous injections of pentagastrin were followed by powerful spontaneous irregular contractions as demonstrated by radiographic and manometric studies. To our knowledge a stimulatory effect of gastrin, though well documented for the lower oesophageal sphincter (Castell and Levine, 1971; Cohen, Lipshutz, and Hughes, 1971; Giles, Mason, and Humphries, 1969) has not yet been demonstrated for the musculature of the oesophageal body in man.

Case History

The 38-year-old male patient was well until nine months previously, when he began to experience retrosternal pain, which occurred periodically and would regularly awake him from sleep at night. The pain was sharp and usually described as a burning sensation radiating directly through to the back. Most of the time the pain subsided spontaneously after four or five minutes or was relieved by drinking large amounts of fluid. He also complained about dysphagia which predominantly was felt when he was tense and upset. He denied nausea, vomiting, or weight loss, and symptoms were not aggravated by physical exertion. Radiographic examination in October 1973 disclosed a narrowed lower oesophageal segment which was initially felt to be consistent with achalasia. On endoscopic examination no signs of oesophagitis or other abnormalities were found.

¹Present address: Lemuel Shattuck Hospital, Gastroenterology Dept., 170 Morton Street, Boston, Mass. 02130.

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Manometric Studies

METHOD

For the manometric studies we used three constantly perfused polyvinyl catheters with an internal diameter of 1.4 mm. Each catheter had a side hole of 1.2 mm. The recording catheters were arranged to measure intraluminal pressure at three points 5 cm apart. Each catheter was perfused with a constant flow of 0.5 ml/min. The pressures were traced directly on a Hellige multichannel recorder. All studies were performed after a 12-hour fasting period on several different days between October and December 1973.

Manometric studies on 29 October disclosed a high lower oesophageal sphincter pressure of 30 mm Hg, which relaxed normally with swallowing, thus excluding the diagnosis of achalasia. Following deglutition the pressure complex recorded from the oesophageal body was greatly increased in duration. Contraction waves occurred simultaneously and repetitively, lasting for periods up to 30 seconds.

Following a subcutaneous injection of pentagastrin (6 μ g/kg body weight) the lower two-thirds of the oesophageal body responded with an overall rise in the mean resting pressure and an increase in spontaneous activity (fig 1) similarly to the wave

pattern observed in achalasia when cholinergic agents are given. During periods of spontaneous activity of the oesophageal body musculature a simultaneous increase in pressure in the lower oesophageal sphincter to levels up to 60 mm Hg was recorded. At the same time the patient experienced a retrosternal burning sensation typical of the pain he felt clinically. This effect would last for periods up to 30 minutes, but when the same test was performed on a different day, tertiary waves and the increase of oesophageal resting pressure were abolished within four minutes after the sublingual application of 0.8 mg nitroglycerine.

The oesophagus responded in the same hypersensitive fashion when pentagastrin was given intravenously. On a dose of 0.04 μ g/kg body weight given as a bolus the response began within 30 seconds and fell to normal levels within five minutes. At doses above 1.0 μ g/kg body weight the onset of the pentagastrin effect was retarded and spontaneous activity was significantly less than maximal. When measurements were repeated five minutes after an intravenous injection of 0.5 mg atropine spontaneous activity of the oesophageal musculature occurred at a higher dose of pentagastrin (0.08 μ g/kg body weight) and spastic waves did not exceed a pressure of 25 mm Hg.

Fig 1 Intraluminal manometric recordings of the lower oesophagus during swallowing. Pressures are recorded at three points 5 cm apart, the upper recordings being the most proximal site.

Left Initially swallows (marked by arrows) are followed by simultaneous repetitive contractions at the three recording sites.

Centre After a subcutaneous injection of 6 γ pentagastrin/kg body weight multiple powerful, spontaneous contractions, not initiated by a swallow, appear, and the mean resting pressure of the oesophagus rises from a basal level of -2 to $+8$ mm Hg.

Right Shortly after sublingual application of 0.8 mg nitroglycerine the mean pressure of the oesophagus returns to its previous levels. Pressure response to swallowing remains simultaneous, but repetitive contractions as initially recorded are absent.

Dilatation with a Stark dilator performed on 16 November was followed by a marked improvement in the patient's dysphagia and a fall of the lower oesophageal resting pressure to 15 mm Hg. However, in response to pentagastrin the lower oesophagus exhibited the same distinctive pattern of powerful, repetitive spontaneous contractions.

As the patient was still complaining about substernal pain occurring regularly at night, a trial with a long-acting nitrite (2.5 mg) twice daily was started and examinations were repeated four weeks later. At this time the patient reported a significant reduction in the number of attacks of pain, as described previously by Orlando and Bozyski (1973). On manometric studies each swallow was still followed by simultaneous contractions, but long-lasting repetitive waves were not demonstrated. Again the oesophagus responded in a hypersensitive fashion to pentagastrin. This

distinctive pattern of hypersensitivity did not occur when 0.25 mg carbamoylcholinchloride, a cholinergic agent, was subcutaneously injected. The dose of carbamoylcholinchloride we used is capable of producing an increase in spontaneous activity in achalasia.

Radiographic Studies

Barium studies in October 1973 revealed a tapered, narrowed segment (fig 2a) at the level of the diaphragm. Abnormal peristalsis could not be demonstrated. Six minutes after the subcutaneous injection of 6 μ g pentagastrin/kg body weight the lower oesophagus exhibited irregular localized contractions alternating with areas of dilatation (fig 2b). These contractions and the increase in lower oesophageal sphincter pressure caused delayed transport and regurgitation of barium into the proximal oesophagus. The radiographic pattern now appeared

Fig 2a Radiographs taken in October 1973 show a tapered narrowed segment at the level of the diaphragm. The diagnosis of achalasia was made at this time.

Fig 2b In response to a subcutaneous injection of pentagastrin localized, powerful, non-progressive contractions occur giving the contour of the oesophagus a more irregular appearance.

characteristic for diffuse oesophageal spasm.

Discussion

In 1969 Giles *et al* reported an increase in lower oesophageal sphincter pressure after the intravenous application of hog gastrin and stimulation of endogenous gastrin in normal persons. Subsequently Cohen *et al*, in 1971 proposed that lower oesophageal sphincter hypertension in patients with achalasia is due to supersensitivity to endogenous gastrin. We think that in reporting our case we have demonstrated for the first time that oesophageal musculature in diffuse oesophageal spasm might respond in a hypersensitive fashion to subcutaneous and intravenous injections of pentagastrin. Manometric tracings following pentagastrin injection in our patient were comparable to those obtained after the administration of cholinergic agents in some patients with diffuse oesophageal spasm (Kramer *et al*, 1967). Moreover radiographically the diagnosis was confirmed only when pentagastrin was injected, whereas cholinergic agents did not produce a similar effect.

Spontaneous activity of oesophageal musculature was less marked and occurred at higher doses when atropine was given before the pentagastrin injection.

This finding suggests that the pentagastrin effect was mediated through acetyl-choline release, as has been shown for smooth muscle previously (Bennett, 1965).

Our findings in this case lead us to believe that the pentagastrin test should be considered in the diagnosis of diffuse oesophageal spasm.

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