STIMULATORY EFFECT OF METOCLOPRAMIDE ON THE ESOPHAGUS AND LOWER ESOPHAGEAL SPHINCTER OF PATIENTS WITH PSS

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Metoclopramide has been shown to stimulate motility of the gastrointestinal tract, including the esophagus. The authors therefore tested the effect of intravenous injections of metoclopramide on the sphincteric pressure and esophageal motility in 14 patients with esophageal dysfunction due to progressive systemic sclerosis (PSS). Isotonic saline similarly injected in a control period in 7 of the patients showed no effect. None of the 14 patients had a detectable pressure zone at the sphincteric area in basal conditions, but following the injection of metoclopramide, one appeared in 7 patients. Metoclopramide also caused the appearance of pressure waves in 5 of 11 patients who had aperistalsis, and caused up to a threefold increase in the amplitude of the pressure waves in the 3 patients who had hypomotility of the esophagus.

There is no known treatment for the diminished or absent contractibility of the esophagus which occurs in patients with progressive systemic sclerosis (PSS). This functional abnormality may cause severe dysphagia. Concurrent hypotonicity of the lower esophageal sphincter also permits acid regurgitation.

Metoclopramide is a procaine amide derivative (methoxy-2-chloro-5-procainamide), which is to a marked extent nontoxic and exerts an effect upon the trigger zone of the medulla oblongata as well as a stimulatory effect on the contractility of the gastrointestinal tract (1-3), including the esophagus (4-6). The authors studied the effect of intravenous injection of metoclopramide on the intraluminal manometric recording of patients who suffered from esophageal dysfunction due to PSS.

MATERIALS AND METHODS

Patients

Fourteen patients with PSS known to have esophageal motor disturbance by means of previous manometric studies were included in the study. All but 3 were females. Their ages ranged from 31 to 66 years (mean: 46.4), and duration of illness ranged from 3 to 19 years (average: 8.0). All but 2 had dysphagia and all had esophageal roentgenographic changes characteristic of PSS. None had esophageal hiatal hernia as detected by roentgenographic study. All patients had been found to have the uracil-specific anti-RNA serum antibody that seems characteristic of scleroderma (7,8), and none had the high titers of serum antibodies to ribonucleoprotein that are found in mixed connective tissue disease (9). Informed consent was granted by all patients.

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Methods

A triple lumen water-filled polivinyl catheter P.E. 240 with open tips 5 cm apart was passed into the stomach. The tubes were connected to Statham transducers P-23 Dc, and these were connected to a Grass polygraph, model 7 B. Water was continuously infused at a rate of 1.91 ml per minute by means of a Harvard infusion pump, model 931. This rate of infusion was found to give optimal results in this system, a factor that has been shown to be important (10).

With the patient supine, the tube was withdrawn until the distal tip was at the level of the lower sphincter, as detected by the pneumographic recording which showed respiratory reverse. Thus placed, the other two open tips became located in the body of the esophagus 5 and 10 cm above the area of the sphincter respectively. The tubes remained fixed in these locations throughout the study.

In the first 7 patients a control tracing was taken for an average of 10 minutes while the patient was instructed to make repeated dry swallows. Twenty milligrams of metoclopramide in 2 ml of solvent were then injected into a catheter previously placed in the antecubital vein in a single bolus lasting 20–35 seconds. Manometric recording was continued for 10 more minutes, during which the patient continued to make dry swallows. After this time the tube was withdrawn gradually. Manometric recording was done at 2-cm intervals.

A modification of this procedure was introduced in the second group of 7 patients. Its purpose was to rule out possible changes of the esophageal manometric tracing induced by the previous needle puncture itself or by the stress of the study. To achieve this, the initial 10-minute control period was followed by the intravenous injection of 2 ml of isotonic saline at the same rate as metoclopramide. Recording was done during a 10-minute period with repeated dry swallows throughout. Metoclopramide was then injected and recording in the same fixed position was continued for another 10 minutes. Recording during the withdrawal of the tubes was also done in these 7 patients.

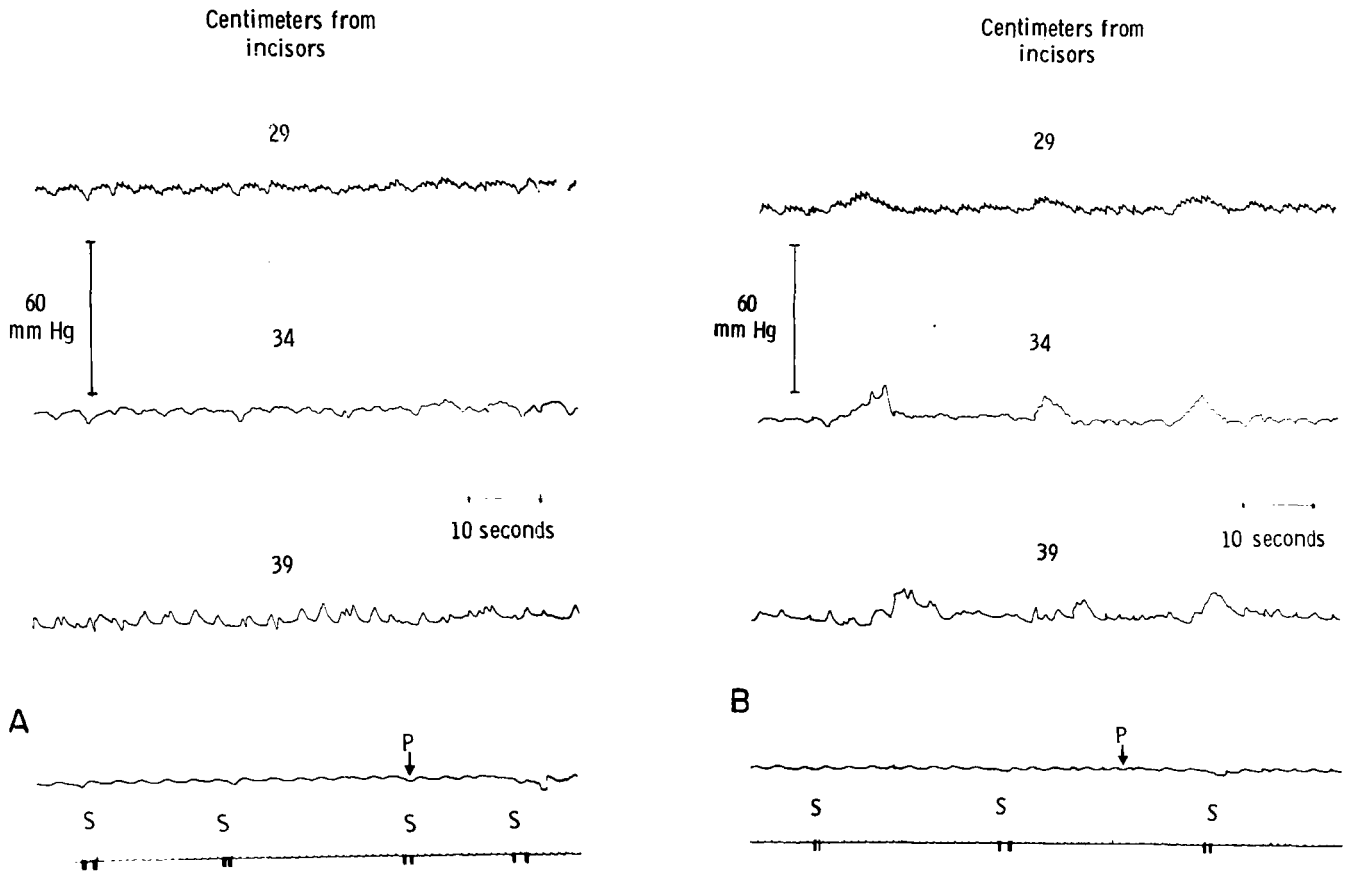

Fig 1. *Esophageal manometric recording in a patient with PSS before and after metoclopramide injection. The distal catheter (39 cm from incisors) is located at the site of the lower esophageal sphincter. The other tips are located 5 and 10 cm above this area respectively.* **A.** *Control period. No contractions follow commanded swallows* (**S**). **P** *indicates pneumographic recording.* **B.** *Following metoclopramide administration, contractions are noticeable in the same segments of the body of the esophagus.*

RESULTS

Six of the 7 patients included in the first study group and 5 of those in the second protocol showed aperistalsis of the lower portions of the esophagus during the control period. The other 3 patients had markedly diminished contractions in the same area. Although the patients were not selected, the high pressure zone of the lower esophageal sphincter was not detectable in any of the 14 patients, possibly because of the long duration of their illness.

First Study Group

Following the injection of metoclopramide, 4 of the 7 patients in this group had an increase in pressure at the lower sphincter area which ranged from 2 to 7 mm/Hg (average: 4.4 mm/Hg). In 5 of the 6 patients who showed aperistalsis during the control period, contractions of variable amplitude appeared after the injection of metoclopramide (Figure 1). These contractions lasted throughout the 10-minute study period. Metoclopramide injection resulted in a threefold increase in the amplitude of contractions in the patient who had hypoperistalsis during the control period (Figure 2).

Upon withdrawl of the tubes, 3 patients in this group were found to have spontaneous, rhythmic contractions at the upper third of the esophagus which were not transmitted to lower segments (Figure 3). These contractions were probably induced by metoclopramide because previous manometric studies in these patients had not shown them.

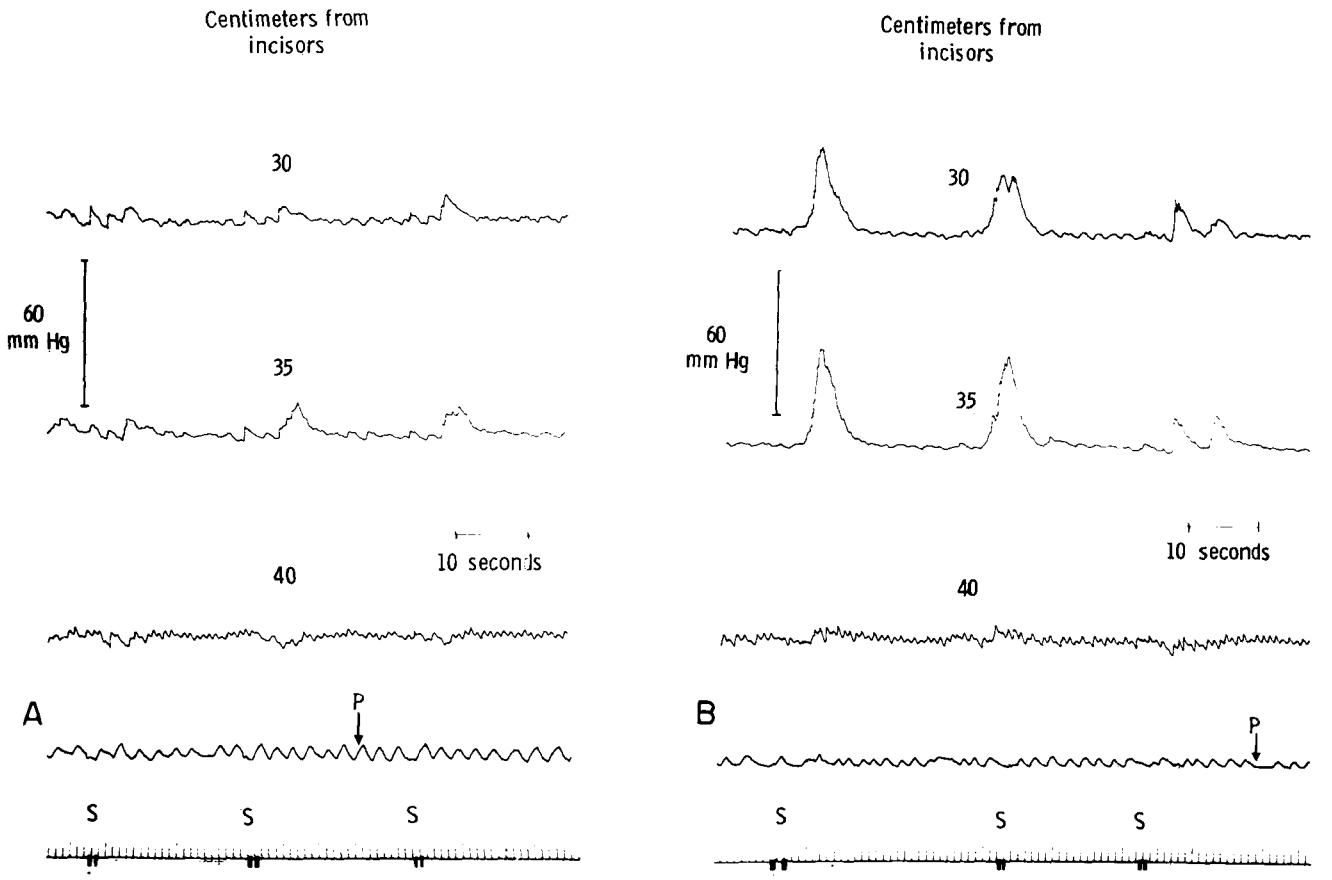

Fig 2. *Esophageal manometric recording in a patient with PSS who showed low contractions in the distal esophagus during the control period* (**A**). *Following metoclopramide injection* (**B**), *contractions increased markedly. In this particular case there was only a minor increase in pressure at the lower esophageal sphincter which is not apparent in the figure.* **P** *indicates pneumographic recording.*

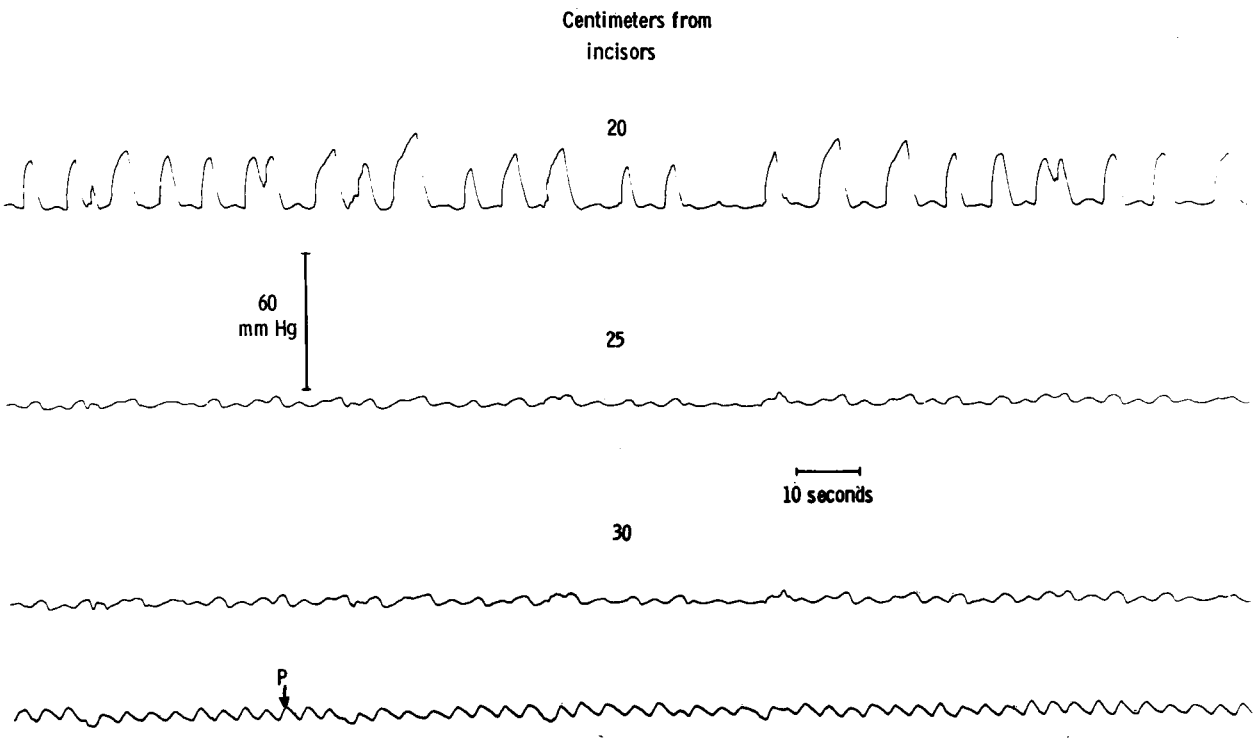

Fig 3. *Spontaneous, rhythmic contractions found in the upper third of a PSS patient's esophagus (20 cm from the incisors) which had been injected with metoclopramide. Notice the lack of transmission of these contractions to lower segments.* **P** *indicates pneumographic recording.*

Second Study Group

No changes were noticed in the esophageal manometric tracing that followed the injection of isotonic saline. Following metoclopramide there was an increase in pressure at the lower sphincter area in 3 of the 7 patients (range: 5–6 mm/Hg; average: 5.3).

Both patients who had abnormally low contraction in the lower esophagus showed an increase of their amplitude, whereas in this group none of the 5 patients with aperistalsis showed contractions induced by metoclopramide. No spontaneous contractions occurred at the upper third of the esophagus in these 7 patients during withdrawal of the tubes.

There was no apparent selection of the patients who fell into each of the two study groups, and the differences in response to metoclopramide found between them has no explanation other than the fortuitous allocation of patients. Altogether, in 7 of 14 patients a pressure zone not previously present appeared at the sphincteric area following intravenous metoclopramide injection. In 5 of 11 PSS patients who had aperistalsis in their control tracings, pressure waves became noticeable, and in all 3 who had hypomotility there was a remarkable increase in the amplitude of the pressure waves following metoclopramide injection.

No side effects were noticed following the injection of metoclopramide.

DISCUSSION

Patients with PSS characteristically have both a diminished pressure at the lower esophageal sphincter and hypo- or aperistalsis of the esophagus (11,12). Metoclopramide, a drug reported to have stimulatory effect on both sites in human subjects (4–6), is an obvious candidate for possible treatment of the esophageal dysfunction in PSS. Indeed the present findings indicate that the esophagus of some patients with PSS does respond to metoclopramide in such a way that it may be useful in their treatment.

Although the mechanism of action of metoclopramide on the gastrointestinal tract is not yet well known, it seems to be related to blockade of nonadrenergic inhibitory nerves with enhancement of the response to acetylcholine (6). The pathophysiology of the esophageal motor disturbance in PSS is not clearly

understood, but it may be due to a defect in neural function (13). Atrophy of smooth muscle and/or fibrosis are common findings at necropsy in the esophagus of subjects with scleroderma (14). The current findings with metoclopramide and those of others with metacholine (13) and reserpine (15) indicate that the esophageal dysfunction in PSS is amenable to pharmacologic improvement.

The fact that all 3 patients who had diminished (but still present) contractions responded to metoclopramide, while only 5 to 11 patients with aperistalsis responded, suggests that there may be a degree of involvement beyond which it elicits no response in the body of the esophagus. Although suggestive, at the polygraph speed used in this study it could not be clearly determined if the contractions elicited by metoclopramide were peristaltic or not.

Following metoclopramide at the dosage used and in an intravenous single bolus, half the patients had an increase in pressure, albeit small in some, at the lower esophageal sphincter. Because metoclopramide can be used orally, it may help in the relief of both dysphagia and acid regurgitation, which patients with PSS suffer. Preliminary clinical observations in these patients suggest such relief.

The finding of spontaneous, nonpropulsive, rhythmic contractions in the upper third of the esophagus, which were apparently induced by metoclopramide, is also interesting. Previous reports have dealt only with the action of this drug upon the smooth muscle sections of the gastrointestinal tract, whereas muscle in this segment of the esophagus is mostly striated. There may be, however, a metoclopramide-sensitive area in this segment of the esophagus which is capable of eliciting rhythmic contractions independent of deglutition.

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