# Scintigraphic Detection of Metaclopramide Esophageal Stimulation in Progressive Systemic Sclerosis

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Supine radionuclide esophageal scintigraphy (RES) and manometry were used to prospectively evaluate metaclopramide effect on esophageal function and pressure amplitudes in 14 patients (12 females and two males; median time since diagnosis: 2 yr) with progressive systemic sclerosis (PSS). Quantitation of RES included calculation of percent emptying at 30 sec, and standard manometric measurements were obtained. RES and manometry were performed before and 10 min following the i.v. administration of metaclopramide. RES showed a significant increase in mean percent emptying from 36% to 46% after drug administration ($p < 0.01$), while mean lower esophageal pressure (end-expiratory) increased from 2 to 11 mm of Hg ($p < 0.001$). Manometry failed to reveal a significant increase in either distal or proximal mean esophageal contractile amplitude, and no correlation was found between the increase in percent emptying at RES and the change in lower esophogeal pressure in the individual patient. RES is the only quantitative method presently available to evaluate bolus propagation in the esophagus, and it documented improved esophageal function after metaclopramide administration in a PSS population. When drug therapy is directed at augmentation of esophageal emptying, RES is an ideal method to evaluate drug response.

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Radionuclide esophageal scintigraphy (RES) is a sensitive test for esophageal dysfunction (*1–4*). Because of its quantitative nature, a major use of RES should be evaluation of the effectiveness of therapeutic interventions. However, there have been few reports of its use to document drug effects on the diseased esophagus (*5*).

Metaclopramide is a stimulant of gastrointestinal (GI) motility, and the drug has been used to accelerate gastric emptying in both diabetic gastroparesis and in progressive systemic sclerosis (PSS) with documentation by nuclear gastric emptying studies (*6,7*). The drug also stimulates esophageal contractility, and has been used to treat reflux esophagitis (*8*). Because of its actions, it may have a role in the therapy of esophageal disease in PSS, a disorder characterized by decreased amplitude of contractions in the distal esophagus. We report our use of RES to study the effect of metaclopramide on esophageal function in patients with PSS.

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## MATERIALS AND METHODS

The study population was composed of patients with PSS under the care of the Division of Rheumatology at our institution. The only exclusion to enrollment was a choice by the patient not to participate. This study was approved by the Scientific Review Committee and the Committee for the Protection of Human Subjects at our institution, and informed consent was obtained from all patients.

PSS in these patients was diagnosed using the criteria of the American Rheumatism Association. A total of 14 patients were studied. Six of these 14 patients have the CREST syndrome. A summary of the findings in this patient population is given in Table 1. There were 12 females and two males, and the age range was 33–69 yr (mean 49.8 yr; median 45 yr). The duration of symptoms ranged from 6 mo to 30 yr. Since time of onset of symptoms is a relatively subjective assessment in this population and the duration of individual symptoms in a given patient is different, the time since diagnosis was used as

**TABLE 1**
Clinical Findings

| | |
|---|---|
| Raynaud's phenomenon: | 13/14 |
| Calcinosis: | 6/10 (4:N.A.*) |
| Sclerodactyly: | 13/14 |
| Telangiectasia: | 11/14 |
| Restrictive lung disease: | 3/14 |
| Myositis: | 4/14 |
| Arthritis: | 10/14 |
| Xerostomia: | 5/14 |
| Anti-nuclear antibody: | 10/13 (1:N.A.*) |
| Anti-centromere antibody: | 5/11 (3:N.A.) |
| Dysphagia: | 10/14 |
| Heartburn: | 11/14 |

*N.A. = not available

a more objective indicator of duration of disease. The median time since diagnosis was 2 yr (mean 5.3 yr; range 6 mo–29 yr).

RES and manometry were performed in no particular scheduling sequence, with performance at the time of scheduling convenience. RES was performed within 4 wk of manometry in all patients. All drugs known to interfere with gastrointestinal motility were discontinued 48 hr before the time of examination. All 14 patients underwent RES, and manometry was performed in 12 of these 14 patients. The two other patients did not wish to participate in manometric evaluation.

RES was performed in the supine position. The patient was administered 10 cc of water containing 100–300 $\mu$Ci (0.37–1.11 $\times$ $10^7$ Bq) of technetium-99m sulfur colloid. Imaging was performed anteriorly using a large field-of-view gamma camera with a high sensitivity, parallel hole collimator. Continuous computer acquisition was performed with an acquisition rate of 0.5 sec/frame. The study was acquired for a total of 50 sec. The patient was instructed to take an initial swallow, followed by a "dry" swallow at 30 sec. Using a cumulative image of esophageal activity, regions of interest (ROIs) were generated for the total, proximal, middle, and distal esophagus. Using these regions, corresponding time-activity curves were generated. This entire procedure was performed a second time after an approximate 5-min delay and upright positioning to ensure emptying of the first tracer dose. Next, each patient was administered 10 mg of metaclopramide intravenously (slowly over 1–2 min), and after a 10-min delay, two more swallows of the tracer were performed as described above.

The acquisition of each study was begun ~2–3 sec before the patient was instructed to swallow. This delay in swallowing allowed an adequate determination of baseline activity. On the first swallow, baseline activity is essentially zero. After the first study, there can be scatter in the ROIs from activity in the gastric fundus or mild retention of radiotracer in the esophagus, and baseline correction is necessary. This aspect is described in greater detail in an earlier publication from our laboratory (*4*).

The nuclear studies were analyzed with regard to several parameters. The esophageal transit time (ETT) was calculated. The ETT is the time from peak activity until 90% emptying on the total esophageal time-activity curve. As has been previously published by our laboratory (*9*), our normal values for the ETT are 6.8 ± 0.2 (s.e.m.). Our upper limit of normal is 12 sec, and as such a value of >12 sec is considered abnormal. A second parameter analyzed was the percent emptying of the esophagus after the first swallow (but prior to the "dry" swallow). This value was calculated by the following formula:

$$\text{Percent emptying} = -\frac{(\text{peak activity} - \text{baseline}) - (\text{average retained activity} - \text{baseline})}{(\text{peak activity} - \text{baseline})} \times 100\%.$$

The reported values for these two parameters are an average of the values obtained for each of the two swallows. In addition to the quantitative analysis, the dynamic computer display of each swallow and the time-activity curve patterns from the proximal, middle, and the distal esophagus were visually analyzed in regard to proper bolus propagation and for the presence or absence of significant esophago-esophageal or gastroesophageal (GE) reflux.

As previously described (*10*), manometry was performed by the following technique. A four-lumen catheter was used with lumens at 5-cm intervals and at 90° angles (diameter 4.5 mm; internal diameter of each lumen 0.8 mm). A pneumohydraulic capillary infusion system was used for continuous infusion of each lumen at a rate of 0.5 ml/min. Each manometry catheter was connected to a transducer and to a direct writing recorder. This is a low compliance system, with a pressure increase rate of 400 mmHg/sec.

After nasal passage of the catheter, a station pull-through technique was used to record lower esophageal (LES) pressure with all four orifices. The reported LES pressure is the mean of the four individually determined pressures measured from the mean gastric pressure. LES pressure was measured at both mid- and end-expiration. Following LES pressure measurement, the catheter was positioned with the distal lumen 2 cm above the LES. Ten "wet swallows" (5 cc water bolus) were administered, separated at 30-sec intervals, to assess peristaltic activity. Amplitude was measured from the mean of esophageal baseline to the peak of the peristaltic wave. The amplitude of peristalsis for each subject was the mean value of ten wet swallows. After initial evaluation, each patient was administered 10 mg of metaclopramide intravenously, and following a 10-min delay, LES pressure, esophageal motility, and pressure amplitudes were reassessed. Normal values for mean pressure amplitudes in the proximal and distal esophagus and for LES pressure are given in Table 2 (*10*).

Statistical analysis (using the paired t-test) was performed to determine the effect of metaclopramide on both the RES and manometric studies. Correlative analysis between the results of these two tests was also performed using linear regression analysis.

## RESULTS

Baseline RES was abnormal in all 14 patients prior to metaclopramide administration. All transit times were >50 sec (and not quantitated beyond this time). The average percent emptying was 36% (range 0–80%).

**TABLE 2**
Normal Manometric Values

| | |
|---|---|
| Mean proximal esophageal contractile amplitude | 50–80 mmHg |
| Mean distal esophageal contractile amplitude | 50–110 mmHg |
| Mid-expiratory LES pressure | 10–26 mmHg |

Following the administration of metaclopramide, the average percent emptying increased to 46% (range 0–91%) ($p < 0.01$). The individual responses to metaclopramide are shown grapically in Figure 1. One patient reverted entirely to normal after metaclopramide, with an increase in percent emptying from 52% to 91%, and the transit time decreased from >50 sec to an average of 10.5 sec (Figure 2). One of the 14 patients had a decline in esophageal emptying from 80% to 72% after metaclopramide injection. This patient also had a decrease in mid-expiratory LES pressure after drug administration.

Most patients (nine of the 12) failed to increase the amplitude of their distal contractions. The average distal esophageal pressure was 9.5 mm of Hg (range 0–28 mm of Hg), which increased to only 10.9 mmHg (range 0–40 mmHg) after metaclopramide. This response was not statistically significant. There was a statistically significant increase in end-expiratory LES pressure, rising from an average of 2.0 mmHg (range 0–8 mmHg) to 11 mmHg (range 7–15 mmHg) ($p < 0.001$), and all 12 patients exhibited this postmetaclopramide rise in pressure. Mid-expiratory LES pressure also increased (baseline average: 14 mmHg; Postmetaclopramide: 20.8 mmHg). No significant change in proximal esophageal pressure occurred. There was no evidence of significant correlation between the degree of change in LES pressure (either mid- or end-expiration) and the change in percent emptying at RES. These results are summarized in Table 3.

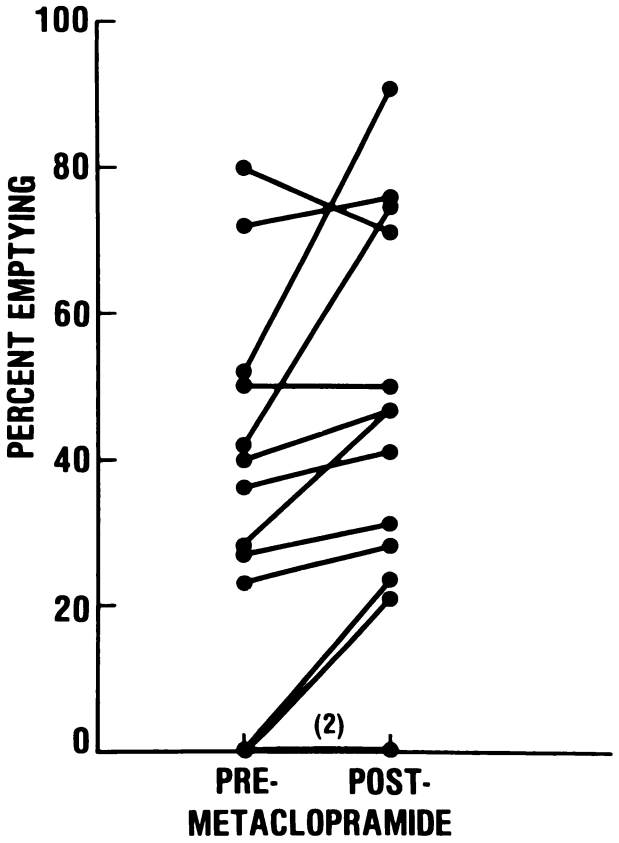


**FIGURE 1**
Percent emptying at radionuclide esophageal scintigraphy before and after metaclopramide administration.

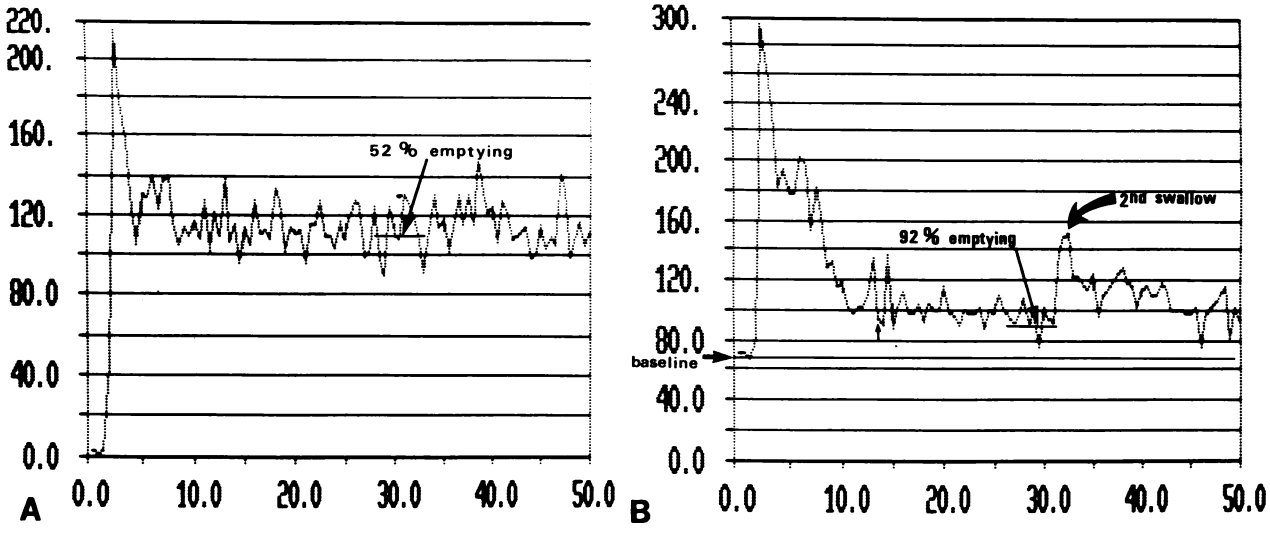


**FIGURE 2**
A: Esophageal time-activity curve prior to metaclopramide administration showing 52% emptying at 30 sec. Transit time is greater than 50 sec. B: Esophageal time-activity curve after metaclopramide injection showing 92% emptying at 30 sec. Baseline correction of scatter from the activity in the gastric fundus and any retained esophageal activity is shown. The small arrow marks 90% emptying of the esophagus, and the transit time is 10 sec.

TABLE 3
Summary of Metaclopramide Effects on Esophageal Function

| | Mean value Premetaclopramide | Mean value Postmetaclopramide | Statistical significance |
|---|---|---|---|
| Percent emptying at RES | 36% | 46% | $p < 0.01$ |
| Proximal contractile amplitude | 39.7 mmHg | 42.5 mmHg | Not significant |
| Distal contractile amplitude | 9.5 mmHg | 10.9 mmHg | Not significant |
| Mid-expiratory LES pressure | 14 mmHg | 20.8 mmHg | $p < 0.01$ |
| End-expiratory LES pressure | 2.0 mmHg | 11 mmHg | $p < 0.001$ |

## DISCUSSION

Metaclopramide (2 - methoxy - 5 - chloro - procainamide) is a stimulant of GI motility. The potential mechanisms of action of this drug include: (a) peripheral neurogenic actions, such as augmentation of cholinergic responses and antagonism of dopaminergic and tryptaminergic neurotransmission (*11–14*); (b) Direct smooth muscle effects (*15*); (c) actions on the central nervous system (*16*). Though a number of pharmacologic studies of its mechanism of action have been performed, its true mode of action is uncertain, and this uncertainty is matched by confusion concerning its indications for use in clinical medicine. This confusion has been partially explained in the past by the fact that clinical methods to measure GI motor functions have been inadequate (*17*).

Metaclopramide has prominent effects on the esophagus. It markedly increases the resting pressure of the lower esophageal sphincter, and modestly increases both the amplitude and duration of primary peristaltic contractions of the normal esophagus (*18*). Both of these actions potentially would be of benefit in the treatment of reflux esophagitis. Also, metaclopramide accelerates gastric emptying, and decreases the amount of gastric contents available for reflux, and this fact, too, makes it an attractive drug for GE reflux. In studies of metaclopramide therapy in GE reflux (*8,19–21*), there has been a decrease in the frequency and duration of reflux. All of the effects of metaclopramide on the esophagus and stomach may play a role in this improvement.

PSS is a generalized connective tissue disorder, with a very high frequency of esophageal involvement (*22*). Several manometric abnormalities are found in PSS. These include low amplitude contractions in the smooth muscle portion of the esophagus and lowered LES pressure (incompetent LES) (*23–25*). Severe reflux esophagitis is very common in PSS, presumably because the incompetent LES allows more GE reflux and the loss of contractile strength (and even peristalsis) in the distal esophagus limits clearance of refluxed acid. Also, gastric empyting is frequently delayed.

The effects of metaclopramide on esophageal function make this drug an appealing therapeutic agent in PSS. Metaclopramide effects on the esophagus in PSS have been tested using manometry alone. Ramirez-Mata et al. (*27*) studied 14 patients with a long history of PSS (average disease duration 8 yr), performing manometry before and after the i.v. administration of metaclopramide. The baseline LES was undetectable in all these patients, and metaclopramide induced a LES pressure in seven of the 14 patients. Likewise, three patients with hypomotility developed increased amplitude of their contractions after the drug. Eleven patients had aperistalsis, and five of these 11 patients developed contractions after the medication was given. The major problem with this investigation was that it was not possible to determine if the contractions elicited by metaclopramide were peristaltic in nature. This shortcoming has been corrected in our investigation. There are two primary aspects of functional data that are needed to validate metaclopramide therapy for reflux esophagitis or the dysphagia of PSS: (a) its effect on LES pressure, as has been shown using manometry by both us and by Ramirez-Mata et al. (*27*), and (b) its effect on esophageal emptying, which we have shown for the first time and could only be shown quantitatively by RES.

We have previously shown a high correlation between percent emptying at RES and distal pressure at manometry in PSS (*4*). We expected that an improvement in percent emptying after metaclopramide would be accompanied by a corresponding increase in distal esophageal pressure. However, this increase did not occur in our population. It may mean that a simple loss of distal esophageal pressure amplitude is not the only mechanism for decreased emptying in PSS, or it may be that manometry is not sufficiently sensitive to detect the improvement in function. In any regard, this finding does indicate that RES is the method of choice to document improvement in bolus propagation.

In a single patient, metaclopramide had the opposite effect on the esophagus than is to be expected. It decreased esophageal emptying and mid-expiratory LES pressure. It is known that high concentrations of metaclopramide can cause inhibition of gut mechanical activity in laboratory preparations (*13*), and this case may represent an abnormally elevated sensitivity to the drug. This finding, as well as proper dosage of metaclo-

pramide in general, is another area of research in which RES will play a role.

Metaclopramide is not without side effects. Approximately 10% of patients experience somnolence, dizziness, or faintness, and ~1% experience dystonic reactions similar to those that occur with phenothiazines (*26*), and it is of value to document a drug response in the individual patient. As shown by our population, and as occurs in diabetic gastroparesis patients treated with metaclopramide (*6*), not all patients have augmentation of their GI motility. If the therapeutic aim is to enhance esophageal motility, the use of metaclopramide can be avoided in those patients without augmentation of esophageal function at RES, and needless therapy, with its potential side effects, can be avoided.

RES studies have been performed using a number of different technical variation, including upright imaging. We use the supine technique for our initial diagnostic evaluation and also for evaluation of therapeutic drug response because supine imaging excludes the effect of gravity. In PSS, emptying of the esophagus in the supine position of RES is directly related to distal esophageal contractile amplitude (*4*). However, in the upright position, relatively prompt emptying occurs even with severe PSS involvement because of a flacid LES. When using RES as a diagnostic tool for the evaluation of dysphagia, it is frequently of benefit to study the patients in both supine and upright positions. Achalasia can resemble esophageal disease from PSS when studied supine, but with upright positioning, the PSS esophagus will empty, while the achalasia esophagus shows marked retention of activity.

Multiple variations have also been used for quantitation of RES. One problem with quantitation is that, with anterior imaging, there is varying attenuation of esophageal activity as it progresses from cervical esophagus to gastric fundus. Sophisticated methods of quantitation have been studied (*28*). Our current method is a relatively simple, yet reproducible technique, and since the patients serve as their own controls for evaluating drug response, the problem of varying attenuation is less important. As previously shown (*4*), quantitation of percent emptying using our method correlates well with quantitative manometry in PSS patients, implying that more sophisticated methods of RES quantitation may not be necessary.

The dysphagia that occurs in PSS has two components: (a) dysphagia secondary to GE reflux with esophagitis, and (b) dysphagia secondary to poor motor function. Metaclopramide is of potential benefit for both components. The effectiveness of various regimens of metaclopramide for the prevention of GE reflux can be measured by esophageal pH monitoring. Improvement in motor function by metaclopramide can only be effectively evaluated by RES. Future evaluations of various drug regimens of metaclopramide in PSS would be aided by the use of esophageal pH monitoring for GE reflux, manometry to evaluate LES pressure, and RES to evaluate motor function.

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