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Metoclopramide response in patients with early diffuse systemic sclerosis. Effects on esophageal motility abnormalities

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ABSTRACT

Objective. *To assess the metoclopramide response in patients with early diffuse systemic sclerosis (dSSc) and the acute effects of intravenous (IV) metoclopramide on the lower esophageal sphincter (LES).*

Methods. *Twenty-one patients with early dSSc (mean age 41.4 ± 9.8 yrs., mean disease duration 2.47 ± 0.75 yrs.) were prospectively evaluated. Six patients with late dSSc (mean age 52.6 ± 9.1 yrs., mean disease duration 9.5 ± 2.5 yrs.) were used as control group. All underwent solid-state esophageal manometry at rest and 15 minutes later received 10 mg of metoclopramide in an intravenous single bolus.*

Results. *We found that the mean LES pressures measured by the station pull-through technique significantly increased in both early and late dSSc patients after metoclopramide administration ($p < 0.05$). While early dSSc patients did improve the mean residual pressures ($p < 0.05$), late dSSc patients did not ($p > 0.05$). In the esophageal body (EB), the mean contractions amplitude at 18, 13, 8, and 3 cm above the LES was <20 mm Hg for both groups. However, peristaltic contraction velocitiy was significantly higher in early dSSc patients (< 0.05) than in that with late dSSc ($p > 0.05$). Our study did not show any major differences when comparing both groups. No side effects were seen.*

Conclusions. *The results of our study show that metoclopramide may improve LES pressures in patients with early and late dSS. Metoclopramide improve the mean residual pressure in patients with early dSSc, but not in late dSSc patients. Although esophageal contractions amplitude were significantly improved, they did not achieve a pressure >20 mm Hg. Because metoclopramide can be used orally, it may mitigate both dysphagia and heartburn.*

Introduction

Systemic sclerosis (SSc) commonly involves the esophagus. Regardless of the disease subtype, the esophagus is involved in approximately 75% to 85% of all patients with SSc, by either manometric or radiographic criteria (1). Esophageal dismotility results from smooth muscle atrophy and fibrosis (2) in the distal esophagus and lower esophageal sphincter (LES). These pathologic changes give rise to a diminished to absent lower esophageal peristalsis and an incompetent LES. Thus, the most common esophageal symptoms attributed to SSc are heartburn and regurgitation, which result from gastroesophageal reflux (GER). Prokinetic drugs commonly used for gastrointestinal (GI) involvement are metoclopramide, cisapride and erythromycin.

The aim of our study was to evaluate the metoclopramide response in patients with early diffuse SSc (dSSc) using computerized solid-state manometry.

Materials and methods

Patient population

Between 2002 and 2004, twenty-one dSSc patients (19F, 2M) were referred to the Medicine Department of the Hospital General Mexicali, ISESALUD and Clínica-Hospital No. 28, IMSS, Mexicali, Baja California, Mexico because of Raynaud's phenomenon, induration of the hands or arthralgias/arthritis. All patients fulfilled SSc diagnosis criteria (3) and were affected by the diffuse subset of the disease (4). At the time of the examination the mean age was 41.4 ± 9.8 years and mean disease duration was (2.4 ± 0.75 years). The onset of disease was calculated from either the first symptom/sign ascribable to SSc (Raynaud's phenomenon or skin thickening). All patients underwent manometric examination and upper GI endoscopy after obtaining informed consent. Only 2 patients were receiving oral metoclopramide before the study. Drugs that might affect esophageal motility such as calcium channel blockers and oral metoclopramide were discontinued 2 weeks before inclusion.

Esophageal manometric study

Esophageal motility was investigated after an overnight fasting period by solid-state manometry (Polygraph HR, Synectics Medical, Sweden). For the procedure, a four channnel nasophar-

ingeal polyvinyl catheter was placed transnasally into the esophagus. LES pressure was measured by station pull-through (SPT) technique. Contractions in the esophageal body (EB) were measured with the four proximal openings positioned 18, 13, 8, and 3 cm above the LES. Fifteen wet swallows were given, separated by 30-second intervals. The wet swallows were then followed by fifteen dry swallows, separated by 30-second intervals. After obtaining a basal manometric recording 10 mg of intravenous metoclopramide in a single dose was administered. Fifteen minutes later a new manometric recording was done.

Six patients with dSSc with a disease duration > 5 years (9.5 ± 2.5 yrs., mean age 52.6 ± 9.1 yrs.) who were seen at the same period served as a control group. All of these patients had also been performed upper gastrointestinal endoscopy.

Laboratory investigations

Routine laboratory, chest x-ray, thorax CT scan, and anti-topoisomerase I antibodies (ELISA) were performed.

Statistics

Statistical analysis was performed by means of Student's t-test for comparison of the mean ± SD of age, disease duration, and manometry records. All data were expressed as mean ± SD. The statistical significancy was considered when $p < 0.05$.

Results

Table I shows the principal clinical characteristics of the 27 patients studied. Table II and Table III summarises the results found pre-and post-administration of metoclopramide in early and late dSSc patients. At baseline, twenty out of 21 patients with early dSSc had a LES pressure 10 mm Hg, The mean LES pressures were 5.9 ± 2.1 mm Hg. The percentage of relaxation was found to be normal (> 90%). The mean amplitude pressure at 18, 13, 8, and 3 cm above the LES was less than 20 mm Hg. Both duration and propagation velocity of esophageal contractions also were found reduced. After intravenous metoclopramide the mean LES pressures increased significantly ($p < 0.05$). Thirteen out of 20 patients with a LES pressure lesser than 10 mm Hg, achieved a LES pressure of ≥ 10mm Hg. The mean residual pressure and the mean propagation velocity also showed a significant difference ($p < 0.05$). However, esophageal contractions amplitude did not achieve pressures ≥ 20 mm Hg. No side effects were seen after administrating metoclopramide.

In control group (disease duration > 5 years, n = 6), the mean LES pressures also significantly increased following metoclopramide administration ($p < 0.05$). The residual pressure showed no changes ($p > 0.05$). In the EB, metoclopramide significantly improved the mean contraction amplitude, but all records were < 20 mm Hg (Table III). Our study did not find any major differences when comparing both groups (Table IV).

Table I. Characteristics of the 27 dSSc patients included in our study.

	Early dSSc (n = 21)	Late dSSc (n = 6)
Sex (F/M)	19/2	6/0
Age, yrs	41.4±9.8	52.6±9.1
Raynaud's phenomenon	20 (95%)	5 (83%)
Digital ulcerations	5 (23%)	1 (16%)
Pulmonar fibrosis	6 (28%)	1 (16%)
Erosive esophagitis	5 (23%)	1 (16%)
Disease duration,years	2.4± 0.7	9.5± 2.5
Anti-topo-isomerase 1	10 (47%)	2 (33%)
Kidney involvement	0/21	0/6
Pulmonar arterial hypertension	1 (4.7%)	0/6
Pericardial effusion with tamponade	1 (4.7%)	0/6
Dysphagia	9 (42.4%	2 (33%)

Table II. Manometric asessment pre-and post-administration of metoclopramide in early dSSc (n=21).

	Pre	Post	P			
Lower esophageal sphincter pressure (mmHg)	5.9 ±2.1	9.6 ± 2.6	0.001			
Residual pressure (mmHg)	0.64±0.5	0.93± 0.5	0.03			
Esophageal body peristaltic wave	Dry swallows			Wet swallows		
	Pre	Post	P	Pre	Post	P
Duration above the lower esophageal sphincter (s) at						
3 cm	3.1 ± 0.5	3.2± 0.48	0.263	3.1 ± 0.6	3.1 ± 0.5	0.434
8 cm	3.0 ± 0.5	3.1± 0.4	0.378	2.9 ± 0.7	3.1 ± 0.6	0.001
13 cm	2.9 ± 0.3	2.9± 0.4	0.616	2.7 ± 0.5	2.7 ± 0.4	0.53
18 cm	2.7 ± 0.4	2.8± 0.4	0.23	2.5 ± 0.5	2.5 ± 0.5	0.93
Propagation velocity (cm/s)	2.6 ± 0.5	2.9± 0.5	0.024	2.2 ± 0.6	2.6 ± 0.6	0.024
Amplitude above the lower esophageal sphincter (mmHg) at						
3 cm	13.8 ± 2.2	14.5± 2.4	0.0001	13.2 ± 1.8	13.8 ± 2.1	0.103
8 cm	12.2 ± 2.5	13.1± 2.7	0.0001	13.0 ± 2.1	13.3 ± 1.8	0.432
13 cm	11.0 ± 2.2	12.1± 2.2	0.0001	11.2 ± 1.7	11.8 ± 1.6	0.001
18 cm	9.8 ± 2.2	10.6± 2.2	0.0004	10.0 ± 2.2	11.5 ± 2.3	0.0001

Discussion

It has been described that esophageal manometry, scintigraphy, and cine-esophagography are approximately equivalent in their ability to detect esophageal dysfunction in SSc and measure

Table III. Manometric asessment pre-and post-administration of metoclopramide in late dSSc (n=6).

	Pre	Post	P			
Lower esophageal sphincter pressure (mmHg)	6.67± 1.9	9.33± 2.0	0.007			
Residual pressure (mmHg)	0.67± 0.5	1.0 ± 0.6	0.363			
Esophageal body peristaltic wave	Dry swallows			Wet swallows		
	Pre	Post	P	Pre	Post	P
Duration above the lower esophageal sphincter (s) at						
3 cm	3.4 ± 0.4	3.4 ± 0.5	0.792	3.2 ± 0.4	3.2 ± 0.4	1
8 cm	3.1 ± 0.2	3.2 ± 0.2	0.456	3.1 ± 0.6	3.2 ± 0.5	0.158
13 cm	2.9 ± 0.7	3.0 ± 0.5	0.225	2.9 ± 0.7	3.0 ± 0.5	0.383
18 cm	2.6 ± 0.4	2.7 ±03	0.037	2.6 ± 0.4	2.7 ± 0.4	0.11
Propagation velocity (cm/s)	3.3 ± 0.8	3.3 ± 0.5	1	3.0 ± 0.2	2.7 ± 0.4	0.174
Amplitude above the lower esophageal sphincter (mmHg) at						
3 cm	14.6 ± 2.8	15.3 ± 2.7	0.101	13.3 ± 4.8	14.5 ± 3.8	0.033
8 cm	13.5 ± 2.5	14.1 ± 2.6	0.174	12.1 ± 3.7	13.1 ±29	0.203
13 cm	12.0 ± 2.2	13.1 ± 2.5	0.0009	10.6 ± 3.3	12.0 ± 3.0	0.025
18 cm	11.0 ± 2.5	12.1 ± 2.7	0.0009	9.3 ± 3.2	10.8 ± 2.3	0.044

Table IV. Comparison between dSSc patients with disease duration > 5 years and < 5 years.

	Pre > 5 yrs.	Pre < 5 yrs.	P	Post > 5 yrs.	Post < 5 yrs.	P
Lower esophageal sphincter (mmHg)			0.43			0.8
Residual pressure (mmHg)			0.922			0.03
Esophageal body peristaltic wave	Dry swallows			Wet swallows		
	> 5 yrs. Pre vs Pre	< 5 yrs. Post vsPost		> 5 yrs. Pre vs Pre	< 5 yrs. Post vs Post	
Duration above the lower esophageal sphincter (s) at						
3 cm	0.32	0.55		0.9	0.47	
8 cm	0.56	0.56		0.56	0.68	
13 cm	0.55	0.47		0.45	0.83	
18 cm	0.62	0.67		0.68	0.39	
Propagation velocity (cm/s)	0.02	0.15		0.001	0.66	
Amplitude above the lower esophageal sphincter (mmHg) at						
3 cm	0.44	0.51		0.6	0.47	
8 cm	0.31	0.4		0.5	0.68	
13 cm	0.36	0.32		0.4	0.16	
18 cm	0.29	0.17		0.68	0.39	

its severity (5). In evaluating GI involvement in the patient with SSc, both manometry and scintigraphy are candidate variables (6). In this study, we directly used manometry.

The main findings of our study were that early dSSc patients exibited mean LES pressures < 10 mm Hg, low amplitude contractions of the distal two-thirds of the esophageal body with reduction of propagation velocity of the contraction waves consistent with a myophatic process (7). After metoclopramide administration, the mean LES pressures (and residual pressures), peristaltic contraction velocitiy, and esophageal contractions amplitude significantly improved. However, esophageal contractions amplitude was not higher than 20 mm Hg.

Intravenous metoclopramide also significantly increased the mean LES pressures of patients with disease duration >5 years ($p < 0.05$). In contrast, there was no significant difference in the mean residual pressures ($p > 0.05$). All presented diminished amplitude which did not achieved pressures > 20 mm Hg. Our study did not find any major differences when comparing patients with early or late dSSc.

Metoclopramide, a cholinergic agonist, was one of the first agents used to treat GI motility disorders (8-10). Our study focused on 21 early dSSc patients (disease duration < 5 yrs.) and the results were compared with to that of six dSSc patients with a disease duration >5 years seen at the same period. Some authors reported that metoclopramide caused an increase in the LES pressure but were lesser than 10 mm Hg, possibly because of the mean duration of disease was of 8.0 years (10). Others reported improvement in the LES pressures and gastroesophageal reflux in most patients but had less consistent effect in improving esophageal body pressures (8).

The onset of prokinetic effect on the GI tract occurs within 3 minutes after an IV administration and within 60 minutes following an oral dose (7). The usual adult oral dose is 5 a 20 mg four times per day, taken 30 minutes before meals and at bedtime. (7-11). After study, we recommended to our patients an oral dose of 10 mg three times per day. At this dose, there has been improvement of their dysphagia. No dystonic reactions have been observed.

Our study confirms that SSc patients show the typical esophageal manometry pattern consistent in LES pressure and diminished amplitude with hypoperistalsis which may improve after metoclopramide. Because metoclopramide can be used orally , it may mitigate both dysphagia and heartburn, which are common in these patients.

References

1. SCOBEY MW, CASTELL DO: Secondary esophageal motility disorders. *In* CASTELL DO (Ed.): *Esophageal Motility Testing*. New York, Elsevier 1987: 172-8.
2. FITZGERALD RC, TRIADAFILOPOULOS G: Esophageal manifestations of rheumatic disorders. *SeminArthritisRheum* 1997;26:641-66.
3. MASI AT, RODNAN GP, MEDSGER TA JR *et al*.: Preliminary criteria for the classification

of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; 23: 581-90.
4. LEROY CE, BLACK C, FLEISCHMAJER R *et al*.: Scleroderma (systemic sclerosis). Classification, subset and pathogenesis. *J Rheuma - tol* 1988; 15: 202-5.
5. KLEIN HA, WALD A, GRAHAM TO *et al*.: Comparative studies of esophageal function in systemic sclerosis. *Gastroenterology* 1992; 102: 1551-6.
6. CLEMENTS PJ, BECVAR R, DROSOS AA *et al*.: Assessment of gastrointestinal involvement. *Clin Exp Rheumatol* 2003; 21 (Suppl. 29): S-15-S18.
7. LIN HC, HASLER WL: Disorders of gastric emptying. *In* YAMADA T (Ed.): *Textbook of Gastroenterology.* Philadelphia, J.B. Lippincot Co. 1995: 1318-46.
8. JOHNSON DA, DRANE WE, CURRAN J *et al*.: Metolopramide response in patients with progressive systemic sclerosis. *Arch Intern Med* 1987; 147: 1597-601.
9. MYERS AR: Progressive systemic sclerosis: Gastrointestinal involvement. *Clin Rheum Dis* 1979; 5: 115-29.
10. RAMIREZ-MATA M, IBAÑEZ G, ALARCÓN-SEGOVIA D: Stimulatory effect of metoclopramide on the esophagus and lower esophageal sphincter of patients with PSS. *Arthritis Rheum* 1977; 20: 30-4.
11. GILLILAND B: Systemic sclerosis (scleroderma) and related disorders. *In* KASPER DL, BRAUNWALD E, FAUCI AS *et al*. (Eds.): *Harrison's Principles of Internal Medicine*. 16th ed. New York; MacGraw-Hill; 2005: 1979-1990.