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The effect of cisapride on gastro-oesophageal dysfunction in systemic sclerosis: a controlled manometric study

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1 Cisapride is a novel prokinetic drug which facilitates or restores motility throughout the gastrointestinal tract. Its mechanism of action is thought to involve enhancement of acetylcholine release in the myenteric plexus of the gut.

2 The effect of intravenous cisapride 10 mg on gastro-oesophageal dysfunction was investigated in 20 patients with systemic sclerosis, using a double-blind, randomised, cross-over, placebo-controlled manometric study design.

3 The increase in lower oesophageal sphincter pressure was significantly higher after cisapride (mean ± s.e. mean, 8.3 ± 2.1 cm H_2O) than after placebo (mean ± s.e. mean, 0.1 ± 0.3 cm H_2O) ($P < 0.001$). The increase in the number of fundic gastric contractions during the 30 min study period was significantly higher after cisapride (mean ± s.e. mean, 7.7 ± 2.3) than after placebo (mean ± s.e. mean, 0.9 ± 0.6) ($P < 0.01$).

4 No serious clinical adverse effects were observed.

5 The study demonstrates that intravenous cisapride induces a significant increase in lower oesophageal sphincter pressure and in the number of fundic gastric contractions, which may be beneficial in the treatment of scleroderma gastro-oesophageal dysfunction. Further long-term studies of the effect of oral cisapride in patients with systemic sclerosis are warranted.

Keywords cisapride gastro-oesophageal dysfunction systemic sclerosis manometry

Introduction

Oesophageal involvement occurs in up to 90% of patients with systemic sclerosis (Atkinson, 1976; Myers, 1979; Poirier & Rankin, 1972). Oesophageal manometric studies often demonstrate abnormalities in the distal portion of the oesophagus, with diminished amplitude or absence of peristaltic waves, and a decrease or absence of pressure in the lower oesophageal sphincter (Clements *et al.*, 1979; Saladin *et al.*, 1966; Treacy *et al.*, 1963). These abnormalities may lead to dysphagia, heartburn, and reflux oesophagitis, which are noted in approximately half of the patients (LeRoy, 1985; Medsger, 1985; Zamost, *et al.*, 1987). Delayed gastric emptying also occurs frequently in this disorder and may contribute to upper gastro-intestinal symptoms (Maddern *et al.*, 1984; Rees *et al.*, 1982).

Cisapride is a novel prokinetic agent which enhances motility along the length of the gastro-intestinal tract (McCallum *et al.*, 1988). The drug has no effect on gastro-intestinal secretion. In healthy volunteers and in patients with gastro-intestinal motility disorders, cisapride has been shown to increase lower oesophageal sphincter pressure, oesophageal motility, and gastric emptying (Ceccatelli *et al.*, 1988; Gilbert *et al.*, 1987; McCallum *et al.*, 1988).

Cisapride appears to exert its effects through indirect mechanisms thought to involve enhancement of the physiological release of acetylcholine from postganglionic nerve endings of the myenteric plexus in the gut; it is devoid of central depressant or antidopaminergic effects (McCallum *et al.*, 1988; Schuurkes *et al.*, 1985). Intravenous cisapride is generally well tolerated in healthy subjects and patients with systemic sclerosis (Horowitz *et al.*, 1987; Stacher *et al.*, 1986).

In the present manometric study, we assessed the effects of intravenous cisapride on gastro-oesophageal dysfunction in patients with systemic sclerosis, using a double-blind, randomised, cross-over, placebo-controlled protocol.

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Methods

Patients

Twenty patients with systemic sclerosis (according to the American College of Rheumatology criteria: Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee, 1980) were studied. There were 16 women and four men (mean (± s.e. mean) age 50 ± 3 years; mean (± s.e. mean) disease duration 7 ± 1 years). All drugs that could modify manometric findings, particularly calcium channel blockers (Kahan *et al.*, 1985), had been stopped for at least 2 weeks before the study. Alcohol, coffee and cigarettes were not permitted for 48 h before the study and until completion of the last manometric recording. The study was performed according to the recommendations of the declaration of Helsinki. All patients gave informed consent for all procedures.

Oesophageal manometry

Oesophageal motility was recorded with a multilumen manometric tube (external diameter 4.5 mm, Dentsleeve, Arndorfer Medical Specialties Inc, Greendale, Wisconsin, USA) which featured an orifice for measuring gastric pressure, a sleeve device (5 cm in length and 5 mm in width) for measuring lower oesophageal sphincter pressure, and two orifices at 1 and 7 cm above the sleeve sensor for recording pressure activity in the oesophageal body. Each catheter was continuously perfused with bubble free water (22° C) at 0.5 ml min^{-1} by means of a pneumohydraulic system (Arndorfer Medical Specialties Inc). The recording catheters were connected to pressure transducers (Statham P23ID, Gould Electronics, Ballainvilliers, France). The pressures were recorded on a four channel polygraph (Beckman R 511; Sensormedic, Gagny, France).

Experimental design

The study was performed using a double-blind, randomised, placebo-controlled, cross-over protocol. The subjects were studied twice, with cisapride and placebo, at 3 day intervals, after a 12 h overnight fast, and in a supine position. The manometric assembly was passed through the nose into the stomach. The sleeve sensor was positioned across the highest pressure zone which showed relaxation upon swallowing. Cisapride 10 mg or placebo were infused intravenously over 2 min into an antecubital vein. The patients were instructed to swallow 3 ml water at 1 min intervals for 10 min before drug administration (baseline period) and for 30 min after the end of cisapride or placebo infusion.

Manometric recording analysis

All tracings were interpreted without knowledge of the infused substance and the patients' clinical history. The lower oesophageal sphincter pressure was calculated every minute by taking into account the corresponding fundic pressure. Relaxation of the lower oesophageal sphincter was calculated as the maximum reduction in sphincter pressure after swallowing and was expressed as a percentage of the resting pressure. For each wet swallow, the amplitude (cm H_2O; from the oesophageal baseline to the peak of the complex) and the duration (s; calculated as the interval from the upstroke of the complex to its return to baseline) of contractions were measured. Propagation velocity (cm s^{-1}) was measured between the tube orifices located 1 and 7 cm above the lower oesophageal sphincter. Fundic gastric contractions were recorded by the most distal catheters.

Statistical analysis

In each patient, the mean value for all oesophageal manometric parameters was calculated for the two 10 min baseline periods, as well as for the 30 min periods following cisapride or placebo administration. In each patient, the variation in these parameters was calculated as the difference between the mean value after cisapride or placebo administration and the respective mean baseline value. Student's *t*-test for paired data was used to evaluate the significance of the differences between the two baseline values, as well as between the variations after placebo and cisapride administration. P values < 0.05 were considered significant.

Results

The results are shown in Table 1. For all manometric parameters studied, the baseline values obtained before placebo or cisapride administration did not differ significantly.

The mean (± s.e. mean) baseline value of the lower oesophageal sphincter pressure was 9.6 ± 2.2 cm H_2O

Table 1 Results of manometric variations after intravenous cisapride 10 mg or placebo administration

	Variation after placebo administration	*Variation after cisapride administration*
LOSP	0.1 ± 0.3	8.3 ± 2.1**
Waves		
Amplitude, 1 cm	0.6 ± 3.0	6.0 ± 5.3
Amplitude, 7 cm	3.2 ± 4.6	13.9 ± 5.9
Duration, 1 cm	0.4 ± 0.1	0.5 ± 0.2
Duration, 7 cm	0.7 ± 0.4	0.6 ± 0.2
Velocity	−0.1 ± 0.1	−0.5 ± 0.2
Number of fundic gastric contractions	0.9 ± 0.6	7.7 ± 2.3*

Results are means ± s.e. mean.
Variations of manometric parameters (differences between the values after placebo or cisapride and their respective baseline values) are shown.
LOSP = Lower oesophageal sphincter pressure (cm H_2O).
Waves: amplitude in cm H_2O, duration in seconds (1 and 7 cm above lower oesophageal sphincter), velocity in cm s^{-1}.
* $P < 0.01$, ** $P < 0.001$.

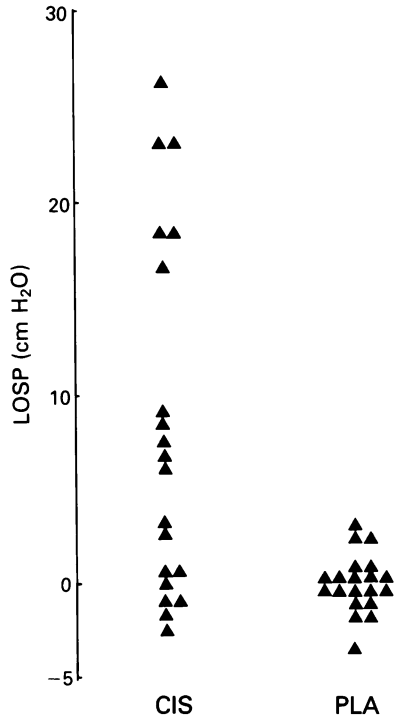

Figure 1 Individual variations in lower oesophageal sphincter pressure (LOSP, in cm H_2O) after intravenous cisapride 10 mg (CIS) and placebo (PLA) administration to 20 patients with systemic sclerosis.

before placebo and 10.8 ± 2.4 cm H_2O before cisapride administration (P not significant). The increase in lower oesophageal sphincter pressure was significantly higher after cisapride (mean ± s.e. mean, 8.3 ± 2.1 cm H_2O) than after placebo (mean ± s.e. mean, 0.1 ± 0.3 cm H_2O) ($P < 0.001$). The individual results of the variations in lower oesophageal sphincter pressure after cisapride and placebo administration are shown in Figure 1. Peak activity occurred during the 11 to 20 min period after cisapride administration and duration of significant effect continued through the 30 min study period: the increase in lower oesophageal sphincter pressure (mean ± s.e. mean) after cisapride was 7.0 ± 1.9 cm H_2O during the 1–10 min period ($P < 0.01$), 10.3 ± 3.0 cm H_2O during the 11–20 min period ($P < 0.01$), and 7.5 ± 2.1 cm H_2O during the 21–30 min period ($P < 0.01$).

The amplitude of the waves at 1 cm and 7 cm above the lower oesophageal sphincter tended to increase after cisapride administration, as compared with values after placebo administration, but the differences did not reach statistical significance (Table 1).

The variations in duration and velocity of peristaltic contractions, as well as in the lower oesophageal sphincter relaxation, did not differ significantly after cisapride or placebo administration.

The increase in the number of fundic gastric contractions during the 30 min study period was significantly higher after cisapride (mean ± s.e. mean, 7.7 ± 2.3) than after placebo administration (mean ± s.e. mean, 0.9 ± 0.6) ($P < 0.01$).

Patients were divided into two groups with a good or poor response to cisapride, defined respectively by an increase in lower oesophageal sphincter pressure higher or lower than 5 cm H_2O. The clinical differences (age, body weight, disease duration, heartburn, and dysphagia) between these two subgroups were not statistically significant.

No serious adverse effects were observed after placebo or cisapride administration. Mild and transient adverse effects were reported by three patients after placebo administration (dizziness (1), flushing (1), palpitations (1)) and by 11 patients after cisapride administration (dizziness (4), flushing (5), headache (3)).

Discussion

This study demonstrates that intravenous cisapride 10 mg significantly increases the lower oesophageal sphincter pressure and the number of fundic gastric contractions in scleroderma patients.

Dysphagia and heartburn are common findings in patients with systemic sclerosis, resulting from an impaired oesophageal clearance, a decreased lower oesophageal sphincter pressure, and gastroparesis (Atkinson, 1976; Myers, 1979; Rees *et al.*, 1982; Zamost *et al.*, 1987). The pathogenesis of scleroderma oesophageal dysfunction has not been well elucidated. Systemic sclerosis is characterized by vascular and microvascular abnormalities, excessive fibroblastic activity and collagen deposition in various organs, and numerous immunological abnormalities (Kahan *et al.*, 1989; LeRoy, 1985; Medsger, 1985). Early in the course of the disease, the oesophagus may appear normal on histological examination despite the presence of functional abnormalities on manometric study (Treacy *et al.*, 1963). In advanced disease, the most common finding in the oesophagus is smooth muscle atrophy and widespread fibrosis, whereas neural elements are generally intact (Atkinson & Summerling, 1966; D'Angelo *et al.*, 1969).

Some studies suggest that patients with systemic sclerosis have an early abnormality in cholinergic neural function, consistent with a reduced peristaltic amplitude, a reduced lower oesophageal sphincter pressure, a diminished lower oesophageal sphincter response to cholinesterase inhibitors, and a somewhat preserved response to direct cholinergic receptor stimulation with methacholine (Cohen *et al.*, 1972). Alternatively, an ultrastructural study of the oesophagus supports a primary vascular cause, rather than a neurogenic or myopathic process, of oesophageal dysfunction in systemic sclerosis (Russell *et al.*, 1982). Whatever the mechanisms involved in the pathogenesis of scleroderma gastro-oesophageal dysfunction, the prokinetic action of cisapride on the motility of the gastro-intestinal tract might be beneficial in these patients.

The manometric findings of the present study are consistent with those observed with cisapride in healthy volunteers and patients with gastro-intestinal motility disorders. When administered in single or repeated doses, cisapride increases lower oesophageal sphincter pressure in normal volunteers and in patients with reflux disease (Ceccatelli *et al.*, 1988; Gilbert *et al.*, 1987; McCallum *et al.*, 1988). Studies of the effect of oral or intravenous cisapride on oesophageal motility yielded variable results; some authors observed an increase in the amplitude,

but not the velocity, of oesophageal contractions after cisapride administration (Ceccatelli *et al.*, 1988; Gilbert *et al.*, 1987), whereas other investigators did not find any significant effect on oesophageal peristalsis (Wallin *et al.*, 1987). Our findings are also in accordance with those of others (Horowitz *et al.*, 1987) who found no significant change in oesophageal transit after cisapride administration in patients with systemic sclerosis. The increase in the number of fundic gastric contractions after cisapride administration in our patients is consistent with the findings of most studies which demonstrated that cisapride shortens gastric emptying of liquids and solids in healthy subjects, or patients with delayed gastric emptying of idiopathic, diabetic, or postsurgical origin (Feldman & Smith, 1987; Jian *et al.*, 1985; Lazzaroni *et al.*, 1987; Müller-Lissner *et al.*, 1986), or patients with systemic sclerosis (Horowitz *et al.*, 1987).

Because of its ability to enhance lower oesophageal sphincter tone and to increase the number of fundic gastric contractions, cisapride would be expected to be of value in patients with systemic sclerosis. It is noteworthy that cisapride has been shown to be useful in combination with cimetidine in patients with reflux oesophagitis (Galmiche *et al.*, 1988; McCallum *et al.*, 1988) and that the effectiveness of cimetidine in the treatment of gastro-oesophageal reflux has been demonstrated in scleroderma patients (Petrokubi & Jeffries, 1979). Long-term studies are warranted to assess the effects of oral cisapride, alone or in combination with H_2-receptor antagonists, in patients with systemic sclerosis and gastro-oesophageal dysfunction.

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