

# Cisapride restores the decreased lower oesophageal sphincter pressure in reflux patients

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**SUMMARY** The effect of the new prokinetic drug cisapride on the resting lower oesophageal sphincter pressure and on the strength of peristaltic contractions was studied in 10 healthy controls and in 10 reflux patients with abnormally low (<10 mm Hg) basal lower oesophageal sphincter pressure. A slow intravenous injection of cisapride 10 mg significantly increased the sphincter pressure in the controls but even more in the patients in whom it almost doubled the resting lower oesophageal sphincter pressure of 8.7 (0.5) mm Hg to between 15 and 20 mm Hg for at least 90 min. Results are expressed as mean (SE). Cisapride also significantly increased the amplitude of peristaltic contractions in controls and reflux patients. Therefore, cisapride might be useful in the treatment of reflux.

It is well known that a decreased lower oesophageal sphincter (LOS) pressure and an impaired oesophageal clearance are important factors in the pathogenesis of reflux disease.<sup>1-9</sup> Therefore, various motor stimulating drugs such as bethanechol, metoclopramide and domperidone, which may increase LOS tone and/or the efficiency of oesophageal peristaltic contractions, have been proposed for the treatment of gastro-oesophageal reflux disease.<sup>10-16</sup> Bethanechol and metoclopramide, however, may have significant side effects, while domperidone hardly increases LOS pressure in reflux patients. Cisapride is a novel gastrointestinal prokinetic drug, devoid of antidopaminergic and direct cholinergic effects acting mainly by the release of acetylcholine at the myenteric plexus site.<sup>17</sup> The present study examined in a double blind, crossover manner the effect of cisapride (*versus* placebo) on lower oesophageal sphincter pressure and oesophageal peristalsis in normal controls and in patients with reflux symptoms and an abnormally low basal LOS pressure.

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## Methods

### PATIENTS AND SUBJECTS

Studies were undertaken in 10 subjects (six men, aged 22 to 61 years; mean age 45) complaining of typical symptoms of gastro-oesophageal reflux, who were selected on the basis of a mean maximal LOS pressure of less than 10 mm Hg (1 mm Hg=133 Pa). Ten healthy volunteers without any digestive symptoms were studied as a control group (eight men; aged 21-35 years; mean age 26). Informed consent was obtained from each subject. The protocol for this study was approved by the Ethical Committee of the Medical Faculty of the University of Leuven.

Oesophageal manometry was performed with a catheter assembly, 5 mm in diameter and consisting of seven polyvinyl chloride catheters (0.8 mm ID; 1.5 mm OD), connected to external transducers (E 0333E - E154E; Siemens, Elema, Sweden). Pressures were recorded on an eight channel polygraph (Mingograph 82, Siemens). All catheters were continuously perfused with distilled water through a low compliance capillary tube infusion pump (Arndorfer Medical Specialists, Greendale, Wis, USA) at a rate of 0.6 ml/min. The four distal

recording orifices were located at the same level but were oriented in four different radial directions, 90° apart. The three other catheters were spaced at 5 cm intervals. The catheter assembly was passed through the nose. Deglutitions were signalled by means of a cutaneous EMG electrode placed over the region of the suprahyoid muscle.

Lower oesophageal sphincter pressure was measured by a stationary pull through technique (0.5 cm increment per step). The highest mean pressure of the four radially oriented orifices was taken as the LOS pressure. Oesophageal body motility was evaluated at 5, 10, and 15 cm above the LOS after wet swallows (5 ml water). The amplitude, duration and progression velocity of the deglutitive peristaltic contractions were expressed as the mean value of five consecutive swallows but also as a mean value for the three levels (5-10-15 cm above LOS). Amplitude (mm Hg) of the contraction was measured from baseline to peak; duration (sec) was measured as the time between onset and end of the pressure peaks determined by the intersection of the extrapolation of the wave at the highest slope with the baseline; progression velocity (cm/sec) of the peristaltic wave was calculated from the time laps between the onset of the pressure peak at 15 cm and at 5 cm above the LOS.

Studies were carried out after an overnight fast. The study design was of the double blind crossover type. On two different days, and in a random order, each subject received a slow intravenous injection of 10 mg cisapride or placebo. Values for mean LOS pressure and for the different parameters of the contraction waves were determined every 15 min, starting 30 min before and lasting until 90 min after drug administration. The results for the two periods (-30 min and -15 min) before drug administration were pooled and considered as the basal values. Manometric tracings were coded and evaluated blindly. Results were expressed as mean (SE).

For statistical evaluation, the results in the two crossover groups were first subjected to Koch's analysis of a two period change over design, which is valid even if assumptions on the normality and variance homogeneity may not apply.<sup>18</sup> This method uses the Mann-Whitney U-test and tests the equality of period, residual or treatment effects. The analysis of the results showed that no statistically significant period or residual effects occurred, thus warranting combination of the data obtained during respectively the two cisapride and the two placebo phases. The merged data were subsequently subjected to the Student's paired *t* test for evaluation of intratreatment changes in the various parameters *v* the pre-injection period, and differences in these changes with cisapride and placebo.

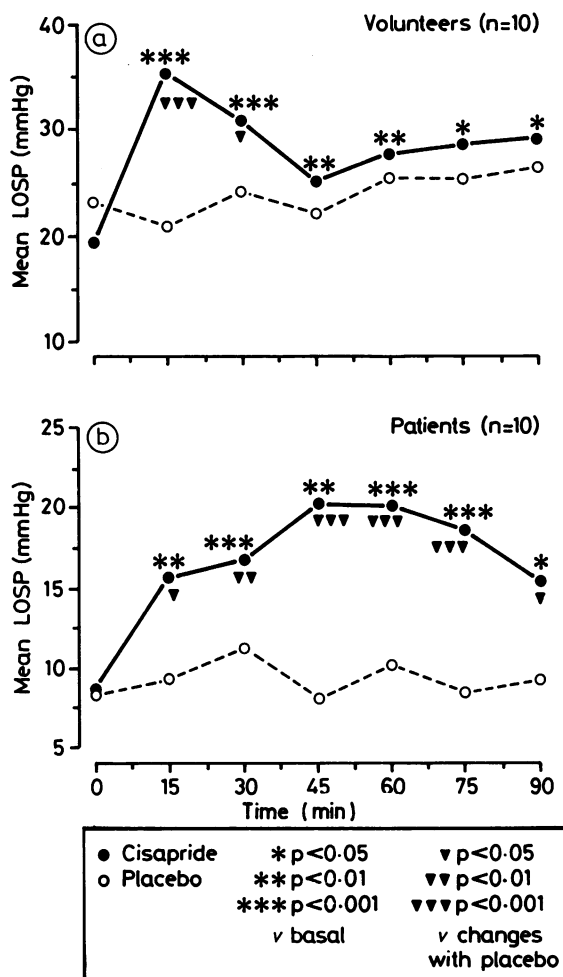


Fig. 1 Effect of cisapride on resting LOS pressure in normal volunteers (Fig. 1a) and in reflux patients with a low basal LOS pressure – that is, less than 10 mm Hg (1 mm Hg = 133 Pa) (Fig. 1b).

## Results

### LOS PRESSURE

The mean basal LOS pressure was 19.3 (1.0) mm Hg in the control subjects and 8.7 (0.5) mm Hg in the reflux patients. No significant change in LOS pressure was noticed after placebo, either in the controls or in the reflux patients. Cisapride induced a significant (*v* basal values and *v* placebo) rise in LOS pressure in both the controls and the patients. In the control subjects the LOS pressure increased to a peak value of 34.2 (2.8) mm Hg at 15 min after drug administration [% change: +90% (20%)] (Fig. 1a). In the reflux patients with low basal LOS pressure the

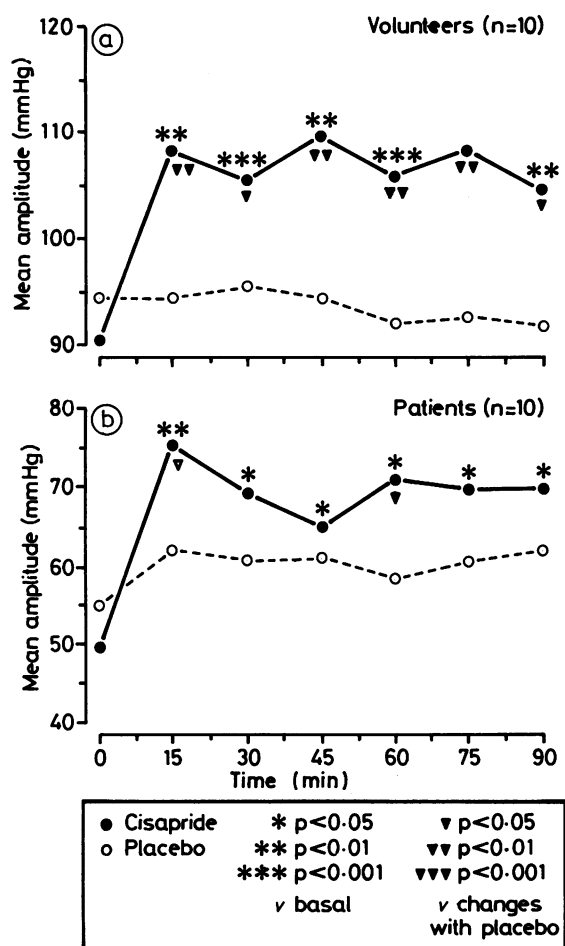


Fig. 2 Effect of cisapride on amplitude of peristaltic oesophageal body contractions in normal volunteers (Fig. 2a) and in reflux patients with a low basal LOS pressure – that is, less than 10 mm Hg (1 mm Hg = 133 Pa) (Fig. 2b).

effect of cisapride was even more pronounced: LOS pressure began to rise within the first 15 min period, reached a peak value of 20.35 (2.3) mm Hg at 45 min after drug administration [% change: +145% (37%)] and remained significantly increased throughout the 90-min study period ( $p < 0.05$ – $0.001$ ) (Fig. 1b).

#### OE SOPHAGEAL PERISTALSIS

The administration of placebo had no significant effect upon amplitude, duration, and progression velocity of the deglutitive peristaltic contractions.

After cisapride, however, a significant ( $v$  basal values and  $v$  placebo) increase in amplitude of the peristaltic contractions was observed in the control subjects and in the patients with reflux disease. In the

control group, the mean amplitude significantly increased throughout the 90 min registration period from 90.5 (9.8) mm Hg during the basal period to a maximum mean value of 109.59 (12.40) mm Hg 45 min after drug administration [% change: 21% (2%)] (Fig. 2a). In the reflux patients, the increase in amplitude was even more pronounced, from 49.7 (5.0) mm Hg during the basal period to a maximum mean value of 75.4 (8.8) mm Hg 15 min after drug administration [% change: +47% (8%)] (Fig. 2b) and remained significantly increased throughout the 90 min period.

After cisapride, there was a trend for the duration of the contraction waves to increase and for their progression velocity to decrease, but these effects did not reach statistical significance. No side effects were observed after the administration of cisapride.

#### Discussion

The results of the present study clearly show that cisapride, administered iv in a dose of 10 mg, increases the resting LOS pressure not only in normal controls but also in reflux patients with an abnormally low resting LOS pressure. Cisapride also significantly increased the amplitude of the peristaltic oesophageal body contractions. Therefore, cisapride might be useful in the treatment of reflux disease.

As shown by Dodds *et al*<sup>6</sup> gastro-oesophageal reflux can occur by one of the three following mechanisms: (a) a transient complete relaxation of the LOS, (b) a transient increase in intra-abdominal pressure, and (c) spontaneous reflux associated with low resting LOS pressure. Although there is considerable overlap in mean resting LOS pressure between reflux patients and normals, abnormally low values of basal LOS pressure are almost always associated with severe reflux.<sup>2,19,20</sup> Once reflux has occurred, the bulk of the refluxed material is cleared from the oesophageal lumen by primary peristaltic contractions whereas the minimal residual acid is neutralised by the swallowed saliva.<sup>9</sup> In normal subjects, the amplitude of the peristaltic contraction is not the critical factor for acid clearing because any contraction amplitude within the broad range of normal is sufficient to obliterate the oesophageal lumen and strip all fluid from the oesophagus.<sup>8</sup> As oesophageal peristalsis is frequently impaired in patients with reflux disease, however,<sup>21–25</sup> and as oesophageal emptying is impaired in patients with reflux symptoms who have oesophageal motor dysfunction,<sup>7</sup> it is possible that the decrease in amplitude of oesophageal contractions in reflux patients contributes to the disability of the oesophagus to clear the refluxed material.

To increase LOS strength and to improve the

peristaltic performance of the oesophagus, motor stimulating drugs have been used in the treatment of reflux disease. Bethanechol has been shown to increase the resting LOS pressure and to improve oesophageal acid clearing in patients with reflux.<sup>10-11</sup> Metoclopramide also increases LOS pressure in normal subjects and in reflux patients<sup>13-14</sup> but its ability to increase oesophageal clearing awaits further documentation. Both drugs, however, may have considerable side effects. Domperidone has less side effects but hardly increases LOS pressure in reflux patients.<sup>15,16</sup>

Cisapride is a novel gastrointestinal prokinetic drug, devoid of antidopaminergic and direct cholinergic effects, acting mainly by facilitating the release of acetylcholine at the myenteric plexus site.<sup>24</sup> Cisapride has been shown to increase LOS pressure and the amplitude of the oesophageal body contractions in normal controls<sup>26-31</sup> and in patients with reflux disease,<sup>32</sup> but it has never been shown thus far whether cisapride is also able to increase LOS pressure in reflux patients with an abnormally low resting LOS pressure.

Our study clearly shows that a slow intravenous injection of 10 mg of cisapride is able to increase the abnormally low sphincter pressure [8.7 (0.5) mm Hg] to a more normal level of 15 to 20 mm Hg for at least 90 minutes. It seems logical to accept that this increase may have a beneficial effect for the prevention of reflux in these patients. To what extent the increase in amplitude of the deglutitive peristaltic contractions may contribute to a better oesophageal clearance is less well understood.

We did not correlate the effect of cisapride on the LOS pressure with the different phases of the migrating motor complex (MMC). This does not invalidate the results obtained, however, because the mixing in our study of the values of LOS pressure during different phases of the MMC could only have resulted in an increase in the standard deviation of the measured values, thus making it more difficult to reach statistical significance. Although the results of our studies present indirect evidence for a potentially beneficial effect of the drug in reflux disease, long-term controlled trials have to be carried out to fully assess the therapeutic value of cisapride in the treatment of patients with gastro-oesophageal reflux. Preliminary experience in oesophagitis patients suggests that cisapride is superior to placebo in reducing reflux symptoms and healing oesophageal mucosal lesions.<sup>33</sup>

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