Effect of cisapride on delayed gastric emptying in gastro-oesophageal reflux disease

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Abstract

Some patients with gastro-oesophageal reflux disease have delayed gastric emptying. This study investigates the effect of cisapride on gastric emptying in 34 patients with proved reflux and delayed gastric emptying of solids. They were enrolled in a double blind controlled crossover study. Placebo or cisapride (10 mg) tablets were given three times a day for three days followed by further assessment of gastric emptying. The protocol was repeated with the crossover tablet. Gastric emptying was assessed by a dual radionuclide technique. The percentage of a solid meal remaining in the stomach at 100 minutes (% R_{100} minutes) and the time taken for 50% of the liquid to empty (T_{50} minutes) were calculated and analysed by the Wilcoxon matched pairs signed ranks test and expressed as medians (ranges). For gastric emptying of solids the initial % R_{100} minutes (70 (60-100)%) was not significantly different from placebo (71 (35-100)%). After cisapride treatment a significant acceleration ($p < 0.001$) in gastric emptying occurred (% R_{100} minutes, 50.5 (28-93)%). Similarly with gastric emptying of liquids, the initial T_{50} minute value was 26.5 (12-82) minutes, after placebo the value was 28 (11-81) minutes, but this was significantly accelerated with cisapride ($p < 0.03$) to 22.5 (6-61) minutes. The acceleration in gastric emptying occurred in the proximal portion of the stomach for gastric emptying of both solids and liquids suggesting that this is the principal site of action of cisapride. We conclude that cisapride significantly accelerates gastric emptying of both solids and liquids in patients with gastro-oesophageal reflux disease and delayed gastric emptying.

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It is now established that some patients with gastro-oesophageal reflux disease have delayed gastric emptying of liquids or solids, or both. The relative proportions of patients with delayed emptying, however, and the importance of any delay remain controversial.¹ Because gastric emptying is a complex process and many factors influence it, some of the differences that have been recorded are probably related to the different assessment techniques being used.

Cisapride is a prokinetic agent that has been shown to enhance gastric emptying in normal patients² and in those with dyspepsia.³ The aim of this study was to assess the effect of cisapride on gastric emptying in patients with delayed gastric emptying and gastro-oesophageal reflux disease.

Methods

PATIENTS

The subjects were patients referred to our unit for the investigation of symptoms of gastro-oesophageal reflux disease. Thirty four patients were enrolled in the trial. There were equal numbers of men and women (median age 51 years, range 18-81 years). Three of the patients had undergone previous gastro-oesophageal surgery but none was taking any medication known to alter gastric emptying or acid production. All patients entered in the study had been shown to have delayed solid gastric emptying according to criteria previously published⁴ - 21 patients had delay in solid emptying alone and 13 patients delay in both liquid and solid emptying. All patients gave informed consent and the study was approved by the Ethics Committee of the Royal Adelaide Hospital.

ASSESSMENT OF REFLUX DISEASE

All patients underwent oesophageal manometry with pH studies or 24 hour pH assessment, or both. In the absence of endoscopic evidence of oesophagitis, only those showing a pH of less than 4 for more than 7% of the 24 hour period were classified as suffering from unequivocal gastro-oesophageal reflux disease.⁵ Endoscopy was performed in 30 patients. Endoscopic appearances were graded according to the degree of oesophagitis as absent, mild, moderate, or severe. Patients with gastric or duodenal ulcers, achalasia, scleroderma, or diabetes were excluded from the study.

MEASUREMENT AT GASTRIC EMPTYING

This test simultaneously measures gastric emptying of a solid meal (100 g of cooked ground beef containing 1-1.5 mCi of in vivo labelled ^{99m}Tc

Figure 1: Solid (left) and liquid (right) gastric emptying from the total stomach before and after treatment with placebo. There is no significant difference between the groups. Short horizontal bars are median values. T_{50} = time taken for half of liquid to empty. % R_{100} min = % of solid meal remaining at 100 minutes.

sulphur colloid-chicken liver) and a liquid meal (150 ml of 10% dextrose in water labelled with 0.75–1.0 mCi of ^{113m}In -diethylenetriamine penta-acetic acid). The details of the test have been documented previously.^{4,6} Several parameters were derived from the data in relation to solid and liquid emptying (expressed as a percentage of the total meal remaining within the stomach *v* time). For the solid component of the meal these were the lag period before food left the stomach, the percentage remaining at 100 minutes (% R_{100} minutes), and the linear emptying after the lag period. The 50% emptying time for the solid meal was not used because some patients did not reach 50% emptying during the study period of two hours. For the liquid component the time for 50% emptying (T_{50} minutes) was obtained.

In 27 of the studies, analysis of the distribution of the meal within the stomach was undertaken.⁷ This was performed by dividing the gastric region into proximal and distal regions of interest. The proximal stomach was defined as that part which was filled by the initial solid meal bolus at the end of the meal. The region defined by this bolus was designated the proximal stomach and the remaining area the distal stomach.

From analysis of the proximal and distal regions of interest it was possible to determine the percentage of solid remaining in the proximal stomach at 55 minutes (% R_{55} minutes), and the time taken until 90% of the maximum distal stomach counts were reached (DT_{90}). A measure of retention in the distal stomach was derived by subtracting the DT_{90} value from the total stomach lag period.⁷ Proximal gastric liquid emptying was measured by taking the percentage of the liquid meal remaining in the proximal stomach at 20 minutes (% R_{20} minutes), and an identical set of measures to those used for solid emptying were taken for distal gastric retention of liquid (a liquid DT_{90} and liquid lag – DT_{90}).

SYMPTOMS

Symptoms were recorded at the time of enrolment into the study using a symptom score to

assess severity.⁸ This assessment was applied to symptoms of regurgitation, heartburn, vomiting, nausea, dysphagia, epigastric fullness and also appetite, constipation, and diarrhoea. In addition antacid ingestion was recorded. These assessments were repeated before each subsequent gastric emptying test.

STUDY DESIGN

Medications known to affect gastric motility were stopped by the patient 48 hours before beginning the study. A double blind placebo controlled crossover design was used for the study with 10 mg cisapride or placebo given three times a day for three days, with a week between each test period.

Placebo or cisapride was given one hour before breakfast and lunch and on going to bed at night. A further tablet – that is placebo or cisapride – was taken one hour before a gastric emptying test that was undertaken at the end of the three day period. All patients kept a record of their symptoms and antacid ingestion during the treatment period. Patients were encouraged to report any untoward symptoms during the two study periods and they were also questioned directly about side effects at the time of the gastric emptying studies at the end of the three day period.

STATISTICS

Data were analysed using Wilcoxon matched pairs signed ranks test.

Results

MANOMETRY

Thirty patients underwent oesophageal manometry. The median (range) lower oesophageal sphincter pressure was 12 (0–44) mmHg. Seventeen patients underwent 24 hour pH assessment and the median (range) percentage time of acid exposure was 15.5 (5.6–79.4)%. Endoscopic findings were available for 30 patients; 10 showed no evidence of oesophagitis, seven showed mild, five moderate, and eight severe oesophagitis.

GASTRIC EMPTYING

The % R_{100} minutes solid meal emptying values were not significantly different between the pretreatment and placebo studies (Fig 1). These values were significantly less, however, in the cisapride treated group compared with either the placebo or the pretreatment groups ($p < 0.0003$, $p < 0.0002$ respectively) (Figs 2 and 3). There were also significantly shorter lag periods ($p < 0.001$) for the cisapride group compared with the pretreatment or placebo groups (Table). Similarly, the rates of solid emptying after the lag period were more rapid ($p < 0.001$) in the cisapride group. The liquid emptying results showed a similar pattern (Figs 1, 2, and 3).

In three patients the proximal stomach region was not clearly enough defined to allow delineation of a proximal and distal region of interest.

Figure 2: Solid (left) and liquid (right) gastric emptying from the total stomach before and after treatment with cisapride. Emptying was significantly faster after cisapride for both solids and liquids. Short horizontal bars are median values. T_{50} = time taken for half of liquid to empty. % R_{100} min = % of solid meal remaining at 100 minutes.

Figure 3: Comparison of solid (left) and liquid (right) gastric emptying from the total stomach after completion of the drug treatment – that is placebo or cisapride. Emptying was significantly faster after cisapride than after placebo for both solids and liquids. Short horizontal bars are median values. T_{50} = time taken for half of liquid to empty. $\% R_{100}$ min = % of solid meal remaining at 100 minutes.

Figure 4: Amount of a solid meal remaining in the proximal stomach at 55 minutes ($\% R_{55}$ min) both before treatment and after cisapride (left), and cisapride compared with placebo (right). The amount remaining after cisapride is significantly less for both comparisons. Horizontal bars represent median values.

Figure 5: The time taken for a solid meal to reach 90% of the maximum distal stomach both before treatment and after cisapride (left) and cisapride compared with placebo (right). The time is significantly shorter after cisapride for both comparisons. Horizontal bars represent median values.

Emptying parameters for solid gastric emptying assessed before and after placebo or cisapride. Values are mean (range)

	Initial study	Placebo	Cisapride
Lag (min)	63 (25–112)	58 (19–120)	47 (21–87)
Rate (%/min)	0.77 (0.1–1.5)	0.71 (0–1.43)	0.92 (0.45–1.6)
$\% R_{100}$ mins	70 (60–100)	71 (35–100)	50.5 (28–93)

$\% R_{100}$ mins = % of meal remaining in stomach at 100 minutes.

Furthermore, as a result of misadventure in transferring data several other studies were lost after carrying out total emptying analysis. The gastric regions of interest were suitably defined to allow distributional analysis in 27 of the solid and liquid gastric emptying studies.

Gastric emptying times from the proximal stomach for solids, determined by the $\% R_{55}$ minutes values, were significantly less in the cisapride group than in the pretreatment ($p < 0.0003$) and placebo groups ($p < 0.02$) (Fig 4). The DT_{90} values were also reduced in the cisapride group compared with placebo ($p < 0.03$) and pretreatment ($p < 0.002$) results (Fig 5). The lag periods minus DT_{90} values, which are indicators of distal stomach retention, did not, however, show a significant difference between the cisapride and the placebo groups (Fig 6). Proximal liquid gastric emptyings ($\% R_{20}$ minutes) were enhanced in the cisapride group compared with placebo and pretreatment patients ($p < 0.05$). As in the solid emptying studies, however, the liquid lag period minus the DT_{90} values were not smaller – that is there was no significant difference between groups with regard to the retention of liquid in the distal stomach.

SYMPTOMS

A significant improvement in symptom scores was recorded for dysphagia, regurgitation, and heartburn ($p < 0.01$) after both placebo and cisapride, with cisapride also showing a significant lessening of a feeling of epigastric fullness ($p < 0.01$).

There was no significant difference between the placebo and cisapride response and the remaining symptoms. No troublesome side effects were reported during the cisapride treatment period. There was no significant alteration in antacid ingestion between the placebo and cisapride period and bowel habit was not significantly altered, although four patients in the cisapride group complained of mild diarrhoea.

Discussion

When gastric emptying is assessed in patients with gastro-oesophageal reflux disease it seems that all groups find patients who have delayed emptying of solids. Some groups, however, have found no significant delay overall in emptying compared with control subjects,^{9–11} and some have found significant delay in patients compared with controls.^{6,12–17} Two groups have found that patients with delayed emptying are more likely to have endoscopically proved oesophagitis than patients with normal emptying, suggesting that the emptying problem may have a patho-

Figure 6: Lag periods minus time taken for 90% of distal stomach counts ($\text{lag}-DT_{90}$ is a parameter which reflects the retention time of the solid meal in the distal stomach both before treatment compared with cisapride (left) and placebo compared with cisapride (right). There is no significant difference between the groups for either comparison. Horizontal bars represent median values.

genetic role in the development of reflux disease.^{6,17}

Furthermore, it has been found that the delay in solid emptying in patients with reflux disease occurs in the proximal rather than in the distal stomach.¹⁸ Morphological abnormalities have been described in both the antrum and body of the stomach in patients with reflux disease.¹⁹⁻²¹ The retention of food in the proximal stomach introduces the potential for a greater number of transient lower oesophageal sphincter relaxations to occur.²² An increase in the number of these transient sphincter relaxations in patients with reflux disease has been reported,²³ but it has not been correlated with gastric emptying.

Cisapride is a drug that has been shown to enhance gastric emptying of both solids and liquids in normal subjects and patients with dyspepsia. Its effect on gastric emptying in patients with gastro-oesophageal reflux disease and delayed emptying has not been reported, and it was the aim of this study to examine cisapride's effects in these patients. We have found previously that symptoms of gastro-oesophageal reflux disease are improved by the gastric prokinetic agents, metaclopramide and domperidone, but the improvement in symptoms was not significantly different from that obtained with placebo.²⁴ Cisapride has been reported to accelerate gastric emptying in patients with dyspepsia,³ although another group reported no such effect.²⁵

Our study shows that in patients with gastro-oesophageal reflux disease and delayed solid gastric emptying, three days of low dose cisapride (10 mg, three times a day) caused a significant acceleration in total gastric emptying of solids and liquids. In the case of the solid meal this acceleration was associated with a significant shortening of the redistribution time within the stomach, as measured by the time of retention in the proximal stomach and the time taken for the meal to move into the distal stomach. Cisapride

could effect these changes either by enhancing proximal gastric motor activity or by decreasing distal gastric retropulsion of food. Either or both of these mechanisms could have led to the results we obtained in these patients. Retropulsion was not observed, however, and so it seems more likely that cisapride had its effect on the proximal stomach.

On the other hand, the distal stomach does not seem to be emptying more rapidly once the bolus of food is delivered to it. If cisapride has led to an alteration in antral capacity, we are unsure how this would have affected our measurements. It could have led to an acceleration in gastric emptying but presumably would not have altered the redistribution time. Thus it seems more likely that the action of cisapride is on the proximal rather than the distal stomach in patients with gastro-oesophageal reflux and delayed gastric emptying.

It is of interest that the regulation of solid emptying from the stomach is often ascribed mainly to the antrum, although emptying is undoubtedly a complex process.²⁶ Our results support the concept that the fundus and body of the stomach may play a more fundamental role in emptying of solids than is usually acknowledged.⁷ As was expected, both placebo and cisapride led to amelioration in patients' symptoms.²⁴ Because of the short time course of treatment, however, symptomatic outcome was not a major aim of this study.

These results provide encouragement for further studies to determine if prolonged administration of cisapride to patients with gastro-oesophageal reflux disease and delayed gastric emptying will have a beneficial effect on the course of the disease.

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