

Effect of chronic administration of cisapride on gastric emptying of a solid meal and on dyspeptic symptoms in patients with idiopathic gastroparesis

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SUMMARY In a double blind crossover comparison with placebo, the effects of cisapride (10 mg tid for two weeks), a non-antidopaminergic gastrointestinal prokinetic drug, on gastric emptying times and on symptoms were evaluated in 12 patients with chronic idiopathic dyspepsia and gastroparesis. Gastric emptying was studied by a radioisotopic gamma camera technique. The test meal was labelled in the solid component (^{99m}Tc -sulphur colloid infiltrated chicken liver). Nine symptoms (nausea, belching, regurgitations, vomiting, postprandial drowsiness, early satiety, epigastric pain or burning, heartburn) were graded weekly on a questionnaire. Cisapride was significantly more effective than placebo in shortening the $t_{1/2}$ of gastric emptying ($p_2=0.04$), but no significant difference was observed between the two treatments with regard to the improvement of total symptom score ($p_2=0.09$). No side effects were reported during the study.

Functional disorders of the gastrointestinal tract are common, and represent the most frequent diagnosis in western gastroenterological practice.¹

The syndrome of functional dyspepsia is characterised by non-specific postprandial symptoms in the absence of organic disease. Traditional diagnostic tests often fail to reveal any significant abnormality. Consequently, the pathogenesis is still unclear.

Recent studies using more sophisticated techniques, however, suggest possible gastrointestinal motor abnormalities in some patients. Gastrointestinal manometric studies² and myoelectric recordings³⁻⁴ have documented abnormalities in some patients with unexplained dyspeptic symptoms. Delayed gastric emptying of both solids⁵ and liquids⁶ have been shown in these patients.

The presence of gastrointestinal motor abnormalities and, specifically, of delayed gastric emptying has formed the basis for use of prokinetic drugs in the treatment of dyspeptic syndromes. Metoclopramide⁷⁻⁸ and domperidone⁹ have been shown to enhance antral contractions, accelerate gastric

emptying and relieve dyspeptic symptoms. Both drugs, to some degree, exert their effects by peripheral dopaminergic receptor blockade. Central dopaminergic receptor blockade with metoclopramide, less so with domperidone, however, can produce side effects.^{7,9}

Cisapride is a new gastrokinetic drug devoid of antidopaminergic properties.¹⁰ The drug appears to act by directly facilitating acetylcholine release from myenteric plexus, without muscarinic or nicotinic receptor stimulation.¹¹ Acute administration of this drug has been shown to accelerate gastric emptying in experimental animals¹¹⁻¹³ and in man.^{6,14}

The aim of the present study was to assess the effect of chronic administration of cisapride on gastric emptying in dyspeptic patients with idiopathic gastroparesis and furthermore to test whether improvement in gastric emptying would correlate with improvement in symptoms.

Methods

PATIENTS

Twelve consecutive dyspeptic outpatients, five men and seven women, aged between 22 and 52 years (median: 34.5 years) and with body weights ranging

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from 50 to 75 kg (median: 56.5 kg) participated in this study, after having given informed consent. The following criteria had to be met for inclusion in the study: (a) Absence of digestive organic diseases, systemic diseases, previous major abdominal surgery, severe irritable bowel syndrome, important personality disorders and, in women, abnormalities of the menstrual cycle. These were all ruled out by extensive history taking and physical examinations, gastroscopy, ultrasonography, and appropriate biochemical tests. (b) Evidence of delayed gastric emptying. (c) Presence of dyspeptic symptoms with a weekly score >5 (see below), for at least one year.

GASTRIC EMPTYING STUDIES

Gastric emptying was evaluated using a gamma camera radioisotopic technique. The subjects were given a solid liquid meal (caloric value: 568 Kcal; composition: 41% carbohydrate, 21% protein, 38% fat). The solid component of the meal consisted of 20 g fresh chicken liver, 60 g ground beef, 100 g potatoes, 10 g white bread and 160 g cream caramel. The liquid component consisted of 10 g olive oil and 200 cc water. The meal was labelled in the solid phase according to a modification of the method proposed by Wright *et al*¹⁵: 750 μCi $^{99\text{m}}\text{Tc}$ sulphur colloid ($^{99\text{m}}\text{Tc}$ SC) were infiltrated by a tuberculin syringe into the chicken liver. The liver was then cooked to a firm consistency, separated from any juices produced during cooking, finely diced, mixed with the ground meat and cooked again, to form a hamburger. The validity of this labelling procedure was tested *in vitro*, as described below.

The meal was consumed at 1 pm, after at least a five hour fast. No attempt to control the rate or extent of mastication was made. Immediately after eating the meal, the patients laid supine under the 140 Kev diverging multihole collimator head of a gamma camera (PHO/gamma IV Searle, Nuclear Chicago), with the head 30° elevated.

Imaging started immediately after ingestion of the meal (time=0). Data were collected continuously for 120 minutes, summed at one minute intervals and stored on discs for later analysis.

On completion of the emptying study, the stored data were processed by a digital computer (Digital PDP 11/34). A video monitor permitted selection of an area of interest, representing the isotope contained in the stomach. The counts occurring within this area were obtained for each of the 120 frames collected. Decay factors were used to compensate for the decline in radioactivity of $^{99\text{m}}\text{Tc}$.

The gastric emptying curves were plotted as percentage of isotope still present in the stomach against time. These curves were then fitted using a power exponential function¹⁶ and results were calculated

using a BASIC program on a separate computer (M20-Olivetti-Italy) and expressed as $t^{1/2}$.

The non-linear least-square computer program used to obtain the fitted power exponential curves also provides a measure of goodness of fit, expressed as R^2 (1-residual sum of squares/total sum of squares).

Gastric emptying was evaluated by this method in 15 healthy volunteers without a history of digestive disorders: 12 men and three women, aged 32.3 ± 8.7 years ($M \pm SD$) and weighing 66.2 ± 10.7 kg. The 95% confidence interval (70–125 min) served to determine the presence of gastric stasis in the dyspeptic patients we examined. Only patients with gastric emptying $t^{1/2}$ longer than 125 min were included in the present study.

DYSPEPTIC SYMPTOMS SCORING

Each patient was instructed to complete weekly a questionnaire listing nine symptoms: nausea, belching, regurgitations, vomiting, postprandial headache, postprandial drowsiness, early satiety, epigastric pain or burning, heartburn. Each symptom was graded, on a weekly basis: 0=absent; 1=occasionally, slight; 2=moderately often, moderately severe; 3=very often, markedly severe. Two hundred and eighteen healthy volunteers, 130 men and 88 women, aged 41.1 ± 10.3 years ($M \pm SD$), had previously completed this questionnaire and served as controls. In this group we obtained weekly scores ranging from 0 to 5, which were considered normal values. A total weekly symptom score greater than 5 was therefore required for entry into the study.

EXPERIMENTAL DESIGN

All patients considered eligible for the study on the basis of symptoms were included. All medication was withdrawn and patients entered into a one week drug free run in phase. At the end of this week, gastric emptying was measured. Only patients with delayed gastric emptying were admitted to the trial.

The patients were then randomised and treated with cisapride 10 mg tid orally, 15 minutes before the meal, and matching placebo, each given for two weeks, under double blind conditions. Six patients received cisapride first (CP group), six placebo (PC group). At the end of each treatment period, gastric emptying tests were carried out. In order to evaluate gastric emptying in steady-state conditions of the test drugs, the last tablet of each treatment was administered 15 minutes before ingestion of the labelled meals.

STATISTICAL ANALYSIS

Non-parametric statistical tests were used and 2-tailed p values were computed.

(a) Comparability of treatment groups

The pretreatment comparability of the PC and CP groups was evaluated by means of the Fisher exact test (for sex) and the Mann-Whitney U-test (other variables).

(b) Crossover analysis

Intermedication differences of changes in $t_{1/2}$ values and changes in symptom scores were evaluated by means of the Mann-Whitney U-test in an analysis for the two period crossover design.¹⁷ This analysis discriminates between treatment effects, period effects, and residual effects. As an interperiod wash-out was impracticable and, in order to minimise any possible carryover effects, only the symptom scores of the second week of each period was taken into account for statistical analysis.

(c) Intraindividual changes of $t_{1/2}$ and total symptom score

As no significant residual or period effects occurred regarding either $t_{1/2}$ values or the total symptom score, as evidenced by application of the two period crossover analysis, results of both sequence groups were merged according to the treatment (cisapride period 1+2, placebo period 1+2). Intraindividual changes (post- pretreatment) were calculated and evaluated using Wilcoxon's matched-pairs signed-ranks test.

(d) Correlation of the changes in total symptom score and the changes in gastric emptying rate of solids

Changes in gastric emptying times after two weeks of treatment relative to the condition at selection, were expressed as:

$$\frac{t_{1/2}(\text{basal}) - t_{1/2}(\text{drug})}{t_{1/2}(\text{basal}) + t_{1/2}(\text{drug})} \times 200$$

and compared with the corresponding changes in the total symptom complex (Spearman rank correlation coefficient r_s , 2-tailed probability).

IN VITRO STUDIES

To evaluate the stability of 'in vitro' labelled chicken liver, 0.5 g portions of finely diced cooked labelled liver were agitated at 37°C in tubes containing 2 ml filtrated fresh gastric juice. Solid particles and supernatant were separated by centrifugation at 540 g for 15 minutes and then counted by a scintillator well counter (gamma-counter AMSR, Abbott, USA). After a 90 minute incubation, 98±2% (M+SD; nine samples) of radioactivity was still bound to the solid. An identical technique was used to validate the stability of other radiolabelled solid foods commonly used in gastric emptying studies. When 'in vivo' ^{99m}Tc

Table 1 Mean and median $t_{1/2}$ values (min) before and at the end of 2 weeks of treatment with cisapride or placebo

	Basal	Cisapride	Placebo
Mean	285.1	143.6	264.3
SD	181.63	58.53	146.87
Median	209.5	118.0	238.0
Extremes	(131-652)	(68-250)	(113-578)

—— p=0.012 ——
 ————— p=0.52 —————
 ————— p=0.042 —————

SC labelled chicken liver¹⁸ was tested, similar results were obtained, 97±8% of the radioactivity still being found in the solid. In contrast, after incubation of ⁵¹CrCl₃ ground beef meat¹⁹ and ^{99m}Tc SC egg white,²⁰ leakage of the isotopes was significantly greater; the percentages of radioactivity still bound to the solid after 90 minutes were respectively 81±8% (p<0.01) and 69±5% (p<0.01, by Wilcoxon's rank sum test). These results are similar to those obtained by 'in vivo' validation techniques carried out using intubation in healthy volunteers.^{19,21} 'In vitro' ^{99m}Tc SC labelled chicken liver has a stability similar to 'in vivo' labelled liver which requires a particularly cumbersome preparation. Furthermore, it appeared more reliable than ⁵¹CrCl₃ ground meat and ^{99m}Tc SC egg white. For these reasons, all studies in man reported in this study were carried out using chicken liver, 'in vitro' labelled with ^{99m}Tc SC.

Results

All the patients completed the trial without reporting any side effects attributable to the treatment.

Except for the symptom 'regurgitation' which was significantly more prominent in the cisapride group than in the placebo group, the two groups were comparable at the start of the study as to be age and sex distribution, severity of dyspeptic symptoms and $t_{1/2}$.

RESPONSE OF GASTRIC EMPTYING

Gastric emptying curves of the solid component of the test meal were satisfactorily fitted by the power exponential analysis (R^2 : median=0.96; range: 0.77-0.99).

Table 1 gives the mean (±SD) and median values of $t_{1/2}$. The global curves based on median values of individual fitted curves are displayed in Figure 1.

Cisapride caused a significant acceleration of gastric emptying, the mean $t_{1/2}$ being halved, when compared with the basal values (means: 143.6 vs 285.1 min; medians: 118.0 vs 209.5 min; $P_2=0.012$). Two patients, however, had little or no improvement, whereas one emptied solids even slower than

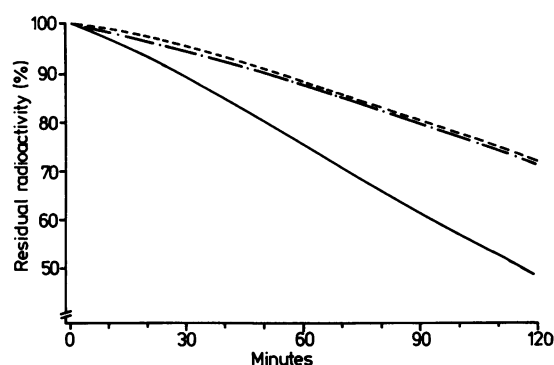


Fig. 1 Gastric emptying curves in basal conditions (---) and at the end of a two-week treatment with cisapride (—) or placebo (-·-·-). Each curve represents the median (n=12) of % of ingested marker within the stomach versus time.

before the treatment. Placebo treatment resulted in a slight deterioration in one, severe deterioration in two, slight improvement in six and no change in three patients. Gastric emptying times after placebo treatment were not statistically different from the pretreatment values (means: 264.3 vs 285.1 min; medians: 238.0 vs 209.5 min; $p_2=0.52$).

The difference between cisapride and placebo in improving the patients' stomach evacuation rate was significant ($p_2=0.042$).

RESPONSE OF SYMPTOMS

The effects of cisapride and placebo on the mean and median values of the weekly scores are shown in Table 2. Table 3 shows the effects of treatments on the discrete symptoms in both sequence groups. In comparison with the situation at the start, both cisapride and placebo significantly improved the total symptom scores ($p_2=0.002$; $p_2=0.012$, respectively), but no significant difference ($p_2=0.09$) was detected between the two treatments.

Table 2 Mean and median symptoms scores in the pretreatment period and during the second week of treatment with cisapride or placebo

	Basal	Cisapride	Placebo
Mean	10.2	6.1	7.3
SD	3.33	4.64	4.03
Median	9.0	4.5	6.5
Extremes	(6-16)	(1-15)	(2-16)

— p=0.002 —
 — p=0.012 —
 — p=0.09 —

CLINICAL IMPROVEMENT VERSUS ACCELERATION OF GASTRIC EMPTYING

Compared with pretreatment levels, two weeks' treatment with cisapride resulted in improvement of the clinical symptoms, as well as in a significant shortening of gastric emptying rate times. As depicted in Figure 2, the relative changes in symptom scores correlated significantly with the relative changes in gastric emptying rates ($r_s=0.69$; $p_2<0.025$). No such correlation was seen after placebo treatment ($r_s=0.12$; $p_2=0.72$); although symptoms also improved, compared with the pretreatment conditions, gastric emptying rates changed little during placebo treatment.

Discussion

The term dyspepsia includes a wide range of digestive disorders from the mild disturbance experienced by most healthy individuals after eating over large over rich meals to very severe conditions with gross abnormalities of gastrointestinal motility such as in chronic intestinal pseudo-obstruction. To consider dyspeptic patients as a whole may, therefore, be misleading, especially when the effect of a therapy is tested.

In the present study, an attempt has been made to

Table 3 Effects of treatments on the discrete symptoms (M±SD) in both sequence groups

	C-P group			P-C group		
	Basal	Cisapride	Placebo	Basal	Placebo	Cisapride
Early satiety	2.2±0.40 (6)	1.3±0.51 (6)	1.7±0.81 (6)	1.8±0.75 (6)	1.0±0.63 (5)	0.5±0.54 (3)
Belching	1.7±0.52 (6)	1.3±0.52 (6)	1.2±0.41 (6)	1.8±0.41 (6)	1.3±0.82 (5)	1.0±0.63 (5)
Epigastric pain	2.0±1.26 (5)	1.5±1.22 (4)	1.5±1.04 (5)	1.3±1.50 (3)	0.7±0.81 (3)	0.5±0.54 (3)
Drowsiness	1.7±0.51 (6)	1.2±0.98 (4)	1.8±0.75 (6)	1.7±1.21 (5)	1.0±1.26 (3)	0.8±0.98 (3)
Regurgitations	1.7±0.81 (6)	1.8±1.16 (5)	0.8±0.98 (3)	0.3±0.51 (2)	0.5±0.54 (3)	0.0 (0)
Nausea	1.0±1.54 (2)	1.0±1.54 (2)	1.0±1.26 (3)	0.8±0.75 (4)	0.0 (0)	0.0 (0)
Vomiting	0.7±1.03 (2)	0.7±1.03 (2)	0.7±1.03 (2)	0.2±0.40 (1)	0.0 (0)	0.0 (0)
Headache	0.0 (0)	0.2±0.40 (1)	0.3±0.51 (2)	0.8±1.32 (2)	0.8±1.32 (2)	0.2±0.40 (1)
Heartburn	0.0 (0)	0.0 (0)	0.2±0.40 (1)	0.5±0.83 (2)	0.2±0.40 (1)	0.2±0.40 (1)
Total	10.8±3.54	9.0±4.85	9.2±4.35	9.5±3.27	5.5±2.94	3.2±1.83

(n)= number of patients presenting the symptom.

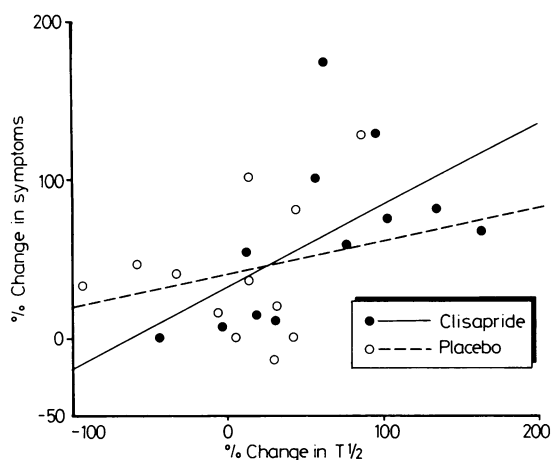


Fig. 2 Correlation between relative (vs basal) changes in symptom scores and gastric emptying $t_{1/2}$ after 2-week treatment with cisapride and placebo.

define a group of patients as homogenous as possible. Specifically, patients with secondary dyspepsia were excluded. Neither were included patients with mild, infrequent or short lived symptoms in order to minimise the chances of clinical improvements because of spontaneous fluctuations of the disease, rather than to the actual effects of the therapy. To further select a specific category of dyspeptic patients and to show objectively responses to the treatments, only subjects with symptoms associated with a proven delay of gastric emptying were included. Abnormal gastric emptying is not necessarily caused by a gastric disorder, however, recent studies showed that delay of gastric emptying²² and inhibition of postprandial antral motility²³ can be induced by centrally acting stressful stimuli in healthy individuals, *via* endocrine²⁴ and, probably, nervous²⁵ pathways. Therefore, in our study, psychiatric disorders, such as depression²⁶ and anorexia nervosa,²⁷ were excluded and efforts were made to ascertain that anxiety did not play a major role in the pathogenesis of digestive symptoms in our patients.

In 12 such carefully selected patients, cisapride produced a significant acceleration of gastric emptying of solids, compared with placebo. On the contrary, no significant difference was found between the two treatments regarding to the effects on symptoms. Both drugs induced a symptomatic improvement, compared with the pretreatment values. The symptomatic effect produced by placebo is a well recognised phenomenon in upper gastrointestinal disorders.²⁸ Cisapride might have induced a similar symptomatic improvement, compared with pretrial conditions, by a placebo effect. Statistical analysis, however, showed a significant correlation between

symptomatic improvements and increased rates of gastric emptying induced by cisapride, with respect to the pretrial conditions. This raises once again the all important question, if any exists, between digestive symptoms and objective identification of gastrointestinal motor abnormalities.

In a recent study on patients with irritable bowel syndrome, symptoms were reported to occur invariably concomitant to recognisable episodes of irregular interdigestive motility of the small bowel.²⁹ This does not seem to be the case in functional dyspepsia, as extensive evaluation often fails to reveal motility disorders in such patients.

In the present study, we excluded patients who had been referred to us complaining of dyspeptic symptoms, in whom gastric emptying times turned out to be normal. These approximately represent 50% of the patients with unexplained dyspepsia.³⁰ Other studies showed that, although the vast majority of patients with severe dyspepsia present manometric abnormalities during either fasting, or fed, or both, in approximately 20% of them no recognisable motility disorder can be detected; also, no symptomatic difference was observed between these patients with normal motility and those with gastric dysmotility, or gastric plus intestinal dysmotility.²

A relationship between gut motor abnormalities and dyspeptic symptoms is, therefore, far from being established. Gastrointestinal motor abnormalities, such as gastroparesis, may or may not represent the cause of dyspeptic symptoms.

Functional dyspepsia is a heterogenous syndrome and new diagnostic methodologies are being needed to clarify the different pathogenetic mechanisms of dyspeptic symptoms and, consequently, to indicate more specific therapeutic approaches.

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