

Measurement of gastric emptying in dyspeptic patients: effect of a new gastrokinetic agent (cisapride)

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SUMMARY Symptoms suggesting gastroparesis in patients without gastric outlet obstruction are very common but their relation to an objective delay of gastric emptying has been poorly investigated. A dual isotopic technique was used to evaluate patients with non-obstructive dyspepsia (idiopathic and secondary) (part 1) and to assess the effects of a new gastrokinetic agent: cisapride, on gastric emptying in such patients (part 2). Sixty patients with postprandial dyspeptic symptoms (vomiting, nausea, gastric bloating or full feeling) and without lesions at upper endoscopy were studied. They were distributed into three groups: idiopathic dyspepsia (n=31), postvagotomy dyspepsia (n=16) and dyspepsia secondary to medical disorders (n=13). All patients ingested the same ordinary meal; ^{99m}Tc sulphur colloid tagged egg white was the solid phase marker and ¹¹¹In chloride was the liquid phase marker. In part 1, evaluation of gastric emptying in the first 50 patients shows a delay of gastric emptying rate of solids and liquids as compared with controls. Striking differences separate the three groups of patients, however, percentages of delayed gastric emptying rate of solids and or liquids averaged 90% in postvagotomy or secondary dyspepsia groups whereas it was 44% in idiopathic dyspepsia group. Moreover, liquid emptying rate was often the only one impaired in idiopathic dyspepsia, and in 12 of the 27 patients of this group the faster emptying rate of liquids as compared with that of solids (always found in normal subjects), could not be evidenced. In part 2, 10 patients entered a double blind cross over study of cisapride (8 mg intravenously). A significant increase of solid (p<0.01) and liquid (p<0.05) emptying rates was found in patients with initial gastric emptying delay. This study emphasises the importance of an objective evaluation of gastric emptying in the presence of symptoms of gastric stasis and suggests that specific local acting therapy may be useful in patients with identified abnormal gastric emptying.

A gastric emptying delay without any gastric outlet obstruction has recently been shown in several diseases including diabetes,¹⁻³ postgastric surgical states,^{4,5} gastric ulcer and chronic gastritis,^{6,7} reflux oesophagitis,⁸ and systemic neuromuscular disorders.⁹ In most of these diseases, gastric stasis is insidious and devoid of specific symptoms.^{5,6,8,10} On the other hand, chronic dyspeptic symptoms suggesting gastroparesis often occur without any

organic disorder (idiopathic dyspepsia); surprisingly, their relationship with a specific functional disorder of the upper gastrointestinal tract and particularly with an objective gastric emptying delay remains poorly investigated.

If chronic dyspeptic symptoms are associated with an objective stasis, a drug enhancing specifically gastric motility could give these patients an opportunity for better therapeutic management. Metoclopramide and domperidone relieve dyspeptic symptoms and enhance gastric motility,¹¹⁻¹⁵ however, these drugs also act on brainstem centres by their antidopaminergic

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properties and this could account, at least partially, for their beneficial effects on symptoms. Dissociation between symptom improvement and absence of gastric emptying enhancement found in several works³⁻¹⁶ stresses this last point. Cisapride, is a new gastrokinetic drug devoid of antidopaminergic effect and seems to act directly at gastric level by facilitating acetylcholine release at the myenteric plexus site without cholinomimetic secretory or side effect¹⁷, however, the effect of this drug on gastric emptying of food has not been evaluated in man.

In this study, we measured gastric emptying rate of the solid and liquid phases of a meal, by a dual isotopic technique, in patients with chronic dyspepsia (idiopathic and secondary to non-obstructive disorders), (a) to evaluate the frequency of an objective gastric emptying delay in such patients, and (b) to test the acute effect of cisapride on gastric emptying in a double blind cross over study.

Methods

SUBJECTS

Patients with dyspeptic symptoms and without lesions at endoscopy were referred for evaluation of gastric emptying. At least one of the following criteria was required for inclusion in this study: inability to finish a meal, full feeling after a meal, postprandial bloating, nausea, and vomiting; symptoms had to occur after small or normal meals, disappear when fasting, be present for at least three months; at the time of the study no patient was receiving drugs known to influence gastric emptying. Sixty such patients were selected: 40 men, 20 women; 16-73 years old (44 ± 15 , SD); mean body weight: 58 ± 10 kg. Symptoms occurred without any organic disease in 31 (idiopathic dyspepsia), after vagotomy in 16 (postvagotomy dyspepsia) 11 truncal vagotomy and five proximal gastric vagotomy; they were associated with miscellaneous disorders including diabetes scleroderma and amyloidosis in 13 (secondary dyspepsia). The three groups were comparable for sex ratio, age, and weight. None of these patients (apart from two in the secondary dyspepsia group) had weight loss or important nutritional deficiencies.

Ten healthy volunteers without digestive symptoms were studied as a control group: eight men and two women; 20 to 63 years old (39 ± 10 , mean \pm SD); mean weight: 67 ± 12 kg.

All subjects gave informed consent to participate to this study, which was approved by the local human research committee.

TEST MEAL AND MARKERS

All fasted subjects ingested the same meal, prepared with 70 g coarsely ground steak, 40 g bread, 10 g butter, 10 g sugar, one egg white (30 g), 200 ml skimmed milk and 150 ml of water (440 cal; 38% carbohydrate, 36% fat, 26% protein). ^{99m}TcTechnetium sulphur colloid (^{99m}Tc: 800 μ Ci) mixed with the egg white before cooking was the solid phase marker and ¹¹¹InIndium chloride (¹¹¹In: 150 μ Ci) added to the water was the liquid phase marker. The stability and the specificity of these labellings were previously checked.¹⁸

PROTOCOLS

In part 1 of this study the frequency of gastric emptying delay was evaluated in the 50 first patients selected (Table 1) by comparison with the control group. The labelled meal was eaten sitting in front of the gamma camera positioned over the stomach. Immediately after ingestion of the meal, both markers (^{99m}Tc, ¹¹¹In) were detected simultaneously for two minute periods at 5 minute intervals for 90 minutes. In the 10 last patients selected (part 2), the effect of cisapride on gastric emptying was evaluated (Table 1). Each patient was studied twice (seven to 15 day intervals) in a double blind study with cisapride (8 mg) or a placebo given in randomised order intravenously five minutes before eating. Immediately after the meal, patients were placed in front of the gamma camera for simultaneous detection of both markers; anterior and posterior images, of one minute periods were taken at 20 minute intervals for three hours. Geometric means of anterior and posterior counts were calculated for each image. Radiation dosimetry of these examinations have been previously estimated.¹⁸

ANALYSIS OF DATA

Data were stored on discs and processed by a digital computer (Informatek, France): an area of interest corresponding to the stomach was outlined, and radioactivity was counted in this area on each image. All counts were corrected for scatter of ¹¹¹In activity into the ^{99m}Tc window using phantom sources, and for physical decay of the

Table 1 Number of patients included in the two parts of the study

	Part 1	Part 2
Idiopathic dyspepsia	27	4
Postvagotomy dyspepsia	11	5
Secondary dyspepsia	12	1
Total	50	10

markers. All counts were expressed as a fraction of ingested activity (gastric activity measured just after the ingestion of the meal); slopes of individual emptying curves were determined (1) for the solid marker by linear regression analysis and expressed by the emptying rate (a , % min^{-1}) and (2) for the liquid marker by exponential regression analysis and expressed by half emptying time ($t_{1/2}$, min). In part 1 comparisons between groups were performed by the Mann Whitney test; the evaluation of frequency of gastric stasis was based on the 95% confidence interval of the 10 control subjects. In part 2 comparisons between cisapride and placebo were performed by analysis of variance.

Results

PART 1: GASTRIC EMPTYING IN DYSPEPSIA

A significant delay of both liquid and solid gastric emptying was found in the 50 dyspeptic patients: $t_{1/2}$ of the liquid marker was 155 ± 14 min, mean \pm SEM (control group: 79 ± 6 min; $p < 0.001$) and the solid marker emptying rate was 0.35 ± 0.03 % min^{-1} (controls 0.47 ± 0.03 % min^{-1} ; $p < 0.01$). There were striking differences, however, between the three groups of patients: as far as the liquid marker is concerned (Fig. 1) a significant delay of gastric emptying was evidenced in all three groups, but it was less pronounced in the idiopathic dyspepsia group than in the postvagotomy dyspepsia and the secondary dyspepsia groups where dyspepsia can be related to an identified pathology: $t_{1/2} = 127 \pm 15$ min (idiopathic dyspepsia) and 187 ± 22 min (postvagotomy dyspepsia + secondary dyspepsia) ($p = 0.01$); for the solid marker (Fig. 2) no significant delay was found between the idiopathic dyspepsia group and the control group (0.43 ± 0.04 % min^{-1} and 0.47 ± 0.03 % min^{-1} respectively) whereas a significant stasis was evidenced in the postvagotomy dyspepsia group (0.20 ± 0.06 , $p < 0.01$) and the secondary dyspepsia group (0.27 ± 0.06 , $p < 0.02$).

Percentages of patients with an objective delay of gastric emptying (emptying rate $\leq m - 2$ SD from controls) are given in Table 2. The idiopathic dyspepsia group again differed from the secondary dyspepsia and postvagotomy groups: less than 50% of idiopathic dyspepsia patients had an objective delay of gastric emptying whereas this was the case in more than 80% of postvagotomy dyspepsia and secondary dyspepsia patients ($p < 0.02$).

The mean difference between solid and liquid gastric retention (solid-liquid discrimination) at 90 minutes was $6 \pm 3\%$ in the idiopathic group versus $16 \pm 7\%$ in controls ($p < 0.01$); no significant difference was found for that parameter between

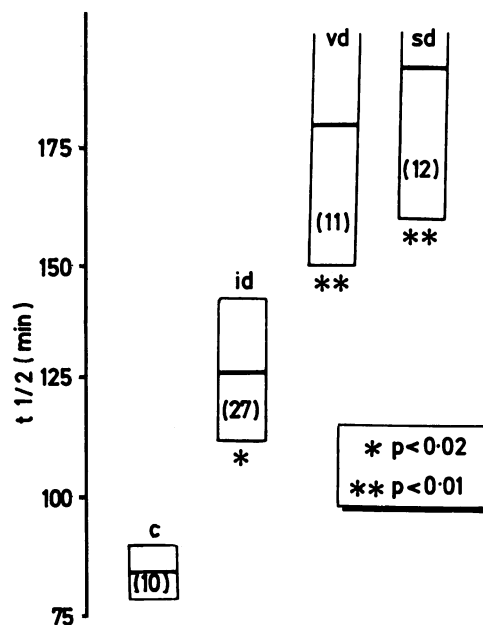


Fig. 1 Gastric emptying of liquids expressed by half emptying time (exponential regression); means \pm SEM, (n) = number of subjects studied. c = controls, id = idiopathic dyspepsia, vd = postvagotomy dyspepsia, sd = secondary dyspepsia. Statistical comparisons with controls performed with the Mann Whitney test.

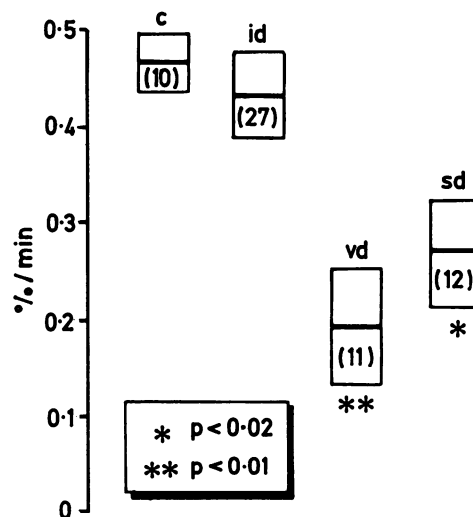


Fig. 2 Gastric emptying of solids expressed by emptying rate (linear regression); means \pm SEM, (n) = number of subjects studied. c = controls, id = idiopathic dyspepsia, vd = postvagotomy dyspepsia, sd = secondary dyspepsia. Statistical comparisons with controls performed with the Mann Whitney test.

Table 2 Percentages of patients in whom gastric stasis of liquids (L) and solids (S) was evidenced

Gastric stasis on*	L	S	L and/or S
Idiopathic dyspepsia (27)	41%	26%	44%
Postvagotomy dyspepsia (11)	73%	70%†	90%†
Secondary dyspepsia (12)	83%	64%†	83%

* Stasis of liquids: $t \frac{1}{2} \geq m + 2$ SD of controls; stasis of solids:

a $\leq m - 2$ SD of controls.

† Data not available for one patient.

controls and postvagotomy dyspepsia or secondary dyspepsia patients. Moreover this discrimination between gastric emptying of solids and liquids always found in the control subjects, cannot be objectivated in 12 of the 27 idiopathic dyspepsia patients (seven with normal and five with delayed gastric emptying rate of solids or liquids).

PART 2: DOUBLE BLIND CONTROLLED TRIAL OF CISAPRIDE VERSUS PLACEBO

The effect of cisapride on individual gastric emptying rates of solids and liquids are shown in Figure 3; cisapride enhanced gastric emptying of solids in six of the 10 patients tested and that of liquids in seven; the patients with a preexistent gastric emptying stasis of solids and/or liquids (evidenced by the placebo sequence) were those mainly concerned with this action by cisapride. A

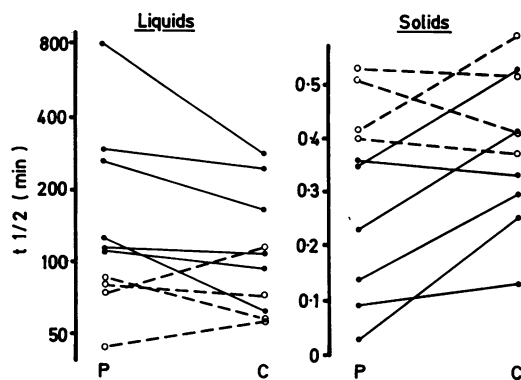


Fig. 3 Effect of cisapride (C) versus placebo (P) on gastric emptying (GE) of liquids (left) and solids (right): individual results. The enhancement of GE by cisapride is evidenced by a decrease of the half GE time (exponential regression) for liquids, and an increase of GE rate (linear regression) for solids. Dotted lines = patients with normal GE on P. Solid lines = patients with delayed GE on P.

significant ($p < 0.05$) enhancement of gastric emptying of solids by cisapride, but not of liquids ($p = 0.06$) was shown in the whole group of patients; whereas a significant increase of gastric emptying rate of both solids ($p < 0.01$) and liquids ($p < 0.05$) was evidenced in the subgroup of dyspeptic patients with preexistent delay of gastric emptying (Fig. 4). Although the number of patients in subgroups (idiopathic dyspepsia, postvagotomy dyspepsia, secondary dyspepsia) was too small to perform statistical comparisons, the gastrokinetic action of the cisapride seems to concern both postvagotomy and idiopathic patients (Table 3).

Discussion

Radioisotopic methods are the most acceptable and accurate means of evaluating gastric emptying in a clinical diagnostic setting. Such a method was used in this prospective study of patients with chronic symptoms of dyspepsia and without gastric outlet obstruction or any other lesion at endoscopy. A double (anterior + posterior)

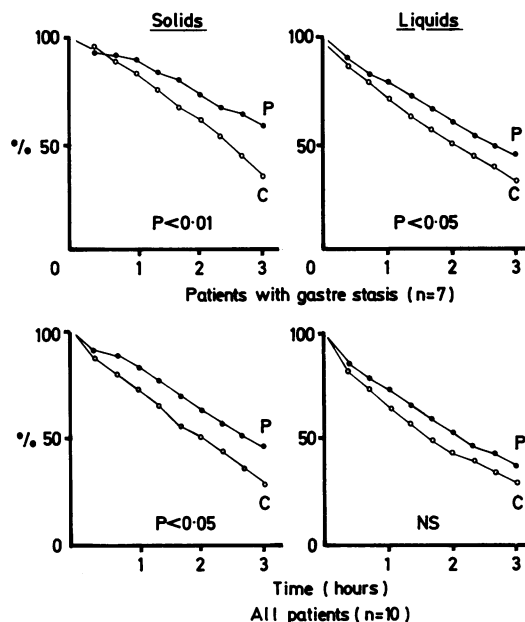


Fig. 4 Effect of cisapride (C) versus placebo (P) on GE of liquids and solids in the whole group of patients tested and the subgroup of patients with gastric emptying delay. Each curve represents % of ingested marker within stomach versus time (hour). Comparisons were performed by analysis of variance. (NS = non-significant).

Table 3 Effect of cisapride (C) versus placebo (P) on gastric emptying rates of solids and liquids ($M \pm SEM$) in 10 dyspeptic patients

	Solids (%min ⁻¹)*		Liquids (t _{1/2} , min)*	
	P	C	P	C
Whole group (10)	0.31±0.06	0.38±0.04	200±72	126±25
Idiopathic dyspepsia (4)	0.33±0.06	0.45±0.06	132±45	112±19
Postvagotomy dyspepsia (5)	0.25±0.09	0.33±0.07	285±136	151±47

* The enhancement of gastric emptying is evidenced by the increase of gastric emptying rate for solids (linear regression) and the decrease of half gastric emptying time for liquids (exponential regression)

detection, as used in part 2, is probably a more accurate way to measure gastric emptying than the single detection; this procedure was, however, used in part 1 designed to investigate on a routine basis dyspeptic patients; if it probably biases absolute values of gastric emptying, it is very unlikely that it impairs results of this study based on comparisons between groups of patients and control subjects for whom procedures were identical.

When the whole group of patients (idiopathic dyspepsia, postvagotomy dyspepsia and secondary dyspepsia) was considered, a significant delay of gastric emptying was shown for both solids and liquids, thus confirming that symptoms of dyspepsia suggesting gastroparesis do correspond to an objective delay of gastric emptying. Other studies on dyspepsia whatever the aetiology are rare, concern few patients and include subjects with obstructive lesions; they have however given similar results.¹⁹⁻²¹ The substratum of the gastric stasis found in dyspeptic patients remains to be established. A reduction of antral motor activity^{13 14 22} and anomalies of the basal electrical rhythm,²³ however, have been found in such patients; an acido peptic gastric secretion defect that could induce a gastric stasis of solids⁶ has not been investigated in our patients, but seems improbable as their gastroparesis affects both liquids and solids. Finally, central nervous disorders could be at the origin of the stasis as it has been shown that central nervous stimulations induce motor disturbances of the stomach.²⁴

In the present study data of dyspeptic patients were also analysed separately according to the aetiology of their dyspeptic symptoms: secondary to medical diseases such as diabetes or neuromuscular disorders, to surgical vagotomy and idiopathic. In the former groups (secondary dyspepsia and postvagotomy dyspepsia) a

significant delay of both solid and liquid emptying rates was shown and more than 80% of these patients have an abnormally delayed gastric emptying rate (Table 2) of solids and/or liquids. This confirms the results of previous studies of diabetic dyspepsia,^{1-3 13 14} and of postvagotomy dyspepsia.^{25 26} It is a matter of interest that similar studies performed after vagotomy but in patients without dyspeptic symptoms, evidenced no or only very moderate abnormalities of gastric emptying.⁴ To our knowledge only Scarpello *et al*²⁷ did not find a significant delay of gastric emptying in diabetic patients, even in the seven with dyspeptic symptoms; methodological problems may be at the origin of this discrepancy. In patients with secondary dyspepsia simultaneous assessment of liquid and solid emptying rates were rarely done; Campbell *et al*'s results¹ indicate, as ours do, that gastroparesis concerns the two components of the meal. Results obtained in the idiopathic dyspepsia patients are more exciting and conflicting: idiopathic dyspepsia is a very common syndrome; it affects patients usually thought to have no objective anomaly and are generally labelled as having functional disorders although without any proof of functional abnormalities. Curiously, such patients were rarely investigated. In a work testing only a liquid meal²⁸ no objective delay was found. Bertrand *et al*²⁹ have shown an objective delay of gastric emptying in such patients, using non-digestible radio-opaque pellets incorporated into a standard meal and counted on radiograph series taken at hourly intervals. More recently, Cottrell and colleagues³⁰ found a delay of solid gastric emptying in five patients with severe idiopathic dyspepsia, whereas only three out of 14 patients of You *et al*²³ have a radiological stasis of a barium meal. In the present study, patients with idiopathic dyspepsia were evaluated and compared with patients with dyspeptic symptoms of known origin (postvagotomy dyspepsia and secondary dyspepsia) and to controls. A delay of gastric emptying was found in the idiopathic dyspepsia group; however, this delay concerns only one out of two of those patients (Table 2); it is significant only for gastric emptying of liquids, and is smaller than that observed in the secondary dyspepsia and postvagotomy dyspepsia group (Fig. 1). Several hypothesis could account for this: (a) a lack of sensitivity in our method for detecting an abnormal gastric emptying seems improbable because under similar conditions high percentages of abnormal results were found in the other patients studied (postvagotomy dyspepsia and secondary dyspepsia groups) although they had similar symptoms, (b) the presence of other gastrointestinal functional

disorders inducing the symptoms whatever their nature or their origin, (c) finally the symptoms may not correspond to any gastrointestinal disturbance. Another peculiarity of the idiopathic dyspepsia group is the loss of discrimination between gastric emptying of liquids and solids evidenced in 12 out of 27 patients; such a finding has already been described in elderly subjects³¹ and in asymptomatic diabetic patients.¹ Its mechanism remains unknown. Although a solid-liquid discrimination is found in the other groups, these results must be accepted with caution because the liquid markers are not entirely specific of the liquid phase but are partially adsorbed on solids.¹⁸

Cisapride, a new gastrokinetic drug, devoid of the antidopaminergic effects and acting at least in part by release of acetylcholine from terminal neurones but without secretory or parasympathomimetic side effects³² was studied in acute administration. This drug accelerates significantly gastric emptying of solids in dyspeptic patients considered as a whole. When the seven patients who exhibited gastric emptying delay during the placebo sequence were considered alone, a significant enhancement of both solid and liquid gastric emptying rates was shown. Thus as previously described with metoclopramide,^{33 34} it seems that cisapride has a gastrokinetic effect mainly in patients with gastric stasis.

In conclusion this study emphasises the importance of an objective measurement of gastric emptying in dyspeptic patients as (a) the presence of a stasis cannot be predicted by analysis of symptoms particularly in idiopathic dyspepsia patients and (b) the determination of an objective gastric stasis could lead to a better rationale of therapeutic management of these patients, as the action of the gastrokinetic drug cisapride tested in this study seems to concern mainly patients with gastric emptying delay. Trials are now needed to determine if efficacy of cisapride on gastric emptying persists during chronic administration and to correlate its effects on symptoms with those on gastric emptying rates. Such an approach would contribute to a better understanding and therapeutic management of these subjects.

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