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Symptomatic, Radionuclide and Therapeutic Assessment of Chronic Idiopathic Dyspepsia

A Double-Blind Placebo-Controlled Evaluation of Cisapride

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Twenty-eight patients with chronic idiopathic dyspepsia defined by the presence of chronic unexplained symptoms suggestive of gastric stasis and directly related to food ingestion were included in this prospective study. Gastric emptying of the liquid and solid phases of a meal was quantified by a dual-isotope method, and symptoms were evaluated by a diary and a visual analog scale. Delay in gastric emptying was evidenced in 59% of the dyspeptic patients; it occurred with liquids in more cases than solids. Quantitative and qualitative evaluation of symptoms was of no practical value in predicting the presence of objective stasis. The dyspeptic patients were included in a double-blind randomized controlled trial of cisapride, a new gastrokinetic drug devoid of central antiemetic effects. After six weeks of cisapride treatment, all patients with initially abnormal gastric emptying rates for liquids, and all but one for solids returned to normal ranges, and significant differences between cisapride and placebo groups were observed for half emptying times of both solids (136 ± 16 min vs 227 ± 32 min; $P < 0.02$) and liquids (61 ± 4 min vs 132 ± 37 min; $P < 0.01$). Cisapride also significantly improved dyspeptic symptom scores at weeks 3 and 6 of treatment as compared to those measured before treatment. Nevertheless, the decrease in global diary score was significantly higher than that seen with placebo at week 3 (−16 ± 6 vs −1 ± 9; $P < 0.05$), but not at week 6 (−18 ± 5 vs −10 ± 8). The symptomatic effect of cisapride at week 3 was significantly more pronounced in patients with abnormal initial gastric emptying than in those with normal gastric emptying (−30 ± 7 vs −4 ± 6; $P < 0.02$). These results underline the importance of objective evaluation of gastric emptying in the detection of patients with gastric stasis who exhibited the best symptomatic response to cisapride.

KEY WORDS: gastric emptying; radioisotopes; gastroparesis; dyspepsia; gastrokinetics; cisapride.

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Chronic idiopathic dyspepsia (CID) is a very common but loosely defined entity that usually covers all kinds of unexplained upper abdominal symptoms (1, 2). However, a more restrictive definition can be proposed, according to which CID is characterized by the presence of symptoms that are suggestive of gastric stasis and are directly related to food inges-

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tion. On the basis of using these criteria, CID can mostly be differentiated on clinical grounds from other functional digestive disorders such as the irritable bowel syndrome or unexplained epigastric pains. We previously showed that some CID patients do have the delayed gastric emptying their symptoms suggest and that this anomaly can be corrected by acute administration of cisapride (3). This drug is of interest because of its potent specific action on gut motility and because it has no central antiemetic effect (4).

However, to improve the understanding and therapeutic management of CID, three points require clarification: (1) the predictive value of the dyspeptic symptoms for the presence of an objective gastric stasis; (2) the persistence of the gastrokinetic effect of a drug during prolonged treatment, and (3) the symptomatic efficacy of a drug during prolonged administration, in the presence or absence of an objective delay in gastric emptying.

To elucidate these points, we evaluated the symptoms and gastric emptying rates of patients with CID and included them in a double-blind placebo-controlled study of the gastrokinetic and symptomatic effects of cisapride administration lasting for six weeks.

MATERIALS AND METHODS

We evaluated gastric emptying in 28 patients comprising 10 men and 18 women [mean age: 39 ± 17 years and mean weight: 59 ± 11 kg (SD)] and in 17 healthy control volunteers comprising 9 men and 8 women (mean age: 27 ± 4 years, and mean weight: 61 ± 13 kg). Informed consent was obtained from all subjects, and the study was approved by the ethics committee.

Inclusion and Exclusion Criteria. Inclusion criteria consisted of the presence of at least two of the following symptoms: early satiety during meal ingestion; sensation of postprandial epigastric pressure; postprandial epigastric bloating; nausea and/or vomiting; and prolonged digestion defined by the sensation of the persistence of the meal in the stomach for more than 2 hr after its ingestion. These symptoms had to be related to meal ingestion (ie, almost no symptoms in the fasting state), to have persisted for more than three months, and to occur at least three days a week. Other complaints such as pyrosis, belching, abdominal pain, or constipation were sometimes also present but not as presenting symptoms. An endoscopic examination of the upper digestive tract was always performed to exclude subjects with macroscopic lesions, whatever their location. Patients with dyspeptic symptoms secondary to an identified disease evidenced by a careful clinical examination and routine laboratory tests, those taking drugs affecting gastrointestinal motility, and subjects with previous digestive surgery or with a characterized psychiatric disorder were also excluded. Previous treatment of dyspeptic symptoms, whatever its efficacy, was not taken into account for inclusion.

Experimental Design. Before the period of treatment, the patients selected underwent symptomatic evaluation for one week (week 0) and a gastric emptying test. They were then randomized and included in a double-blind study: 15 patients (5 men and 10 women, mean age 41 ± 17 years, mean weight: 60 ± 12 kg) were given 10 mg cisapride *per os*, 15 min before the three main meals, and 13 others, (5 men and 8 women, mean age 36 ± 17 years, mean weight 59 ± 10 kg) were given placebo tablets identical in appearance to the cisapride tablets. The therapeutic period lasted six weeks. Symptoms were assessed during the third and sixth weeks of treatment (weeks 3 and 6); 13 patients (six on cisapride and seven on placebo), who at week 0 had gastric stasis defined by values above or in the upper range of normal for at least one of the three parameters characterizing gastric emptying of the meal ($t1/2$ of liquid emptying curve, $t1/2$ and β coefficient of solid emptying curve), underwent a second gastric emptying evaluation at the end of the treatment period. No concomitant drug likely to influence gastric motility was allowed during the whole study.

Gastric Emptying Measurement. Gastric emptying rates for the solid and liquid phases of a meal were measured isotopically with the same protocol in patients and control subjects. Patients who had a second gastric emptying evaluation at week 6 were given their allocated treatment (10 mg of cisapride or placebo) 15 min before the beginning of the gastric emptying measure.

Fasted subjects ingested a meal that included 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 water (440 kcal; 38% carbohydrate, 36% fat, 26% protein). The solid-phase marker was ^{99m}technetium colloid (800 μCi ^{99m}Tc) mixed with the egg white before cooking, and the liquid-phase marker was ^{111}indium diethylenetriaminepentacetic acid (150 μCi [^{111}In]DTPA) added to the water. The stability and specificity of the labeling with these markers had been previously checked (5, 6). Immediately after the meal, patients were placed in front of a gamma camera for simultaneous detection of both markers; every 20 min, anterior and posterior images were recorded for one minute over a period of 3 hr. Geometric means of anterior and posterior counts were calculated for each image. Radiation dosimetry, was of 0.04, 1.4, and 1 rads for exposures of the total body and upper and lower large intestine, respectively (5–7).

Data were stored on disks and processed by a digital computer (Informatek, France): an area of interest corresponding to the stomach was outlined, and the radioactivity in this area was counted on each image. All counts were corrected for background activity, for scatter of ^{111}In activity into the ^{99m}Tc window using phantom sources, and for physical decay of the markers. They were expressed as a fraction of the gastric activity measured at the first acquisition, at time 0. The percent emptying curves were analyzed using a simple exponential model for liquids and a power exponential model for solids (8). Half emptying times of the simple exponential function, and half emptying time and the β coefficient of the power exponential function were estimated from the

fitted curves using the computed programs of Reedy and Elashoff (9).

Symptom Evaluation. During the three weeks of evaluation (weeks 0, 3, and 6), the severity of symptoms was graded daily by the patient for the two main postprandial periods (0 = absent; 1 = moderate; 2 = severe). At the end of each week of evaluation, each patient's diary card was checked at a clinical consultation so as to detect any misunderstanding. Specific symptom scores, ie, the sum of the 14 numbers on the card (2 quotations/day × 7 days) for a given symptom, and the global diary score (GDS), ie, the sum of all specific symptom scores were calculated. During the consultations, patients also gave a general assessment of their dyspeptic symptoms on a 10-cm-long visual analog scale (VAS). During the first consultation (week 0) patients were graded according to the Hamilton anxiety rating scale (10) and side effects of treatment were checked during the therapeutic period at the other consultations.

Side Effects and Compliance. Side effects were observed in six patients during cisapride treatment (soft stools, $N = 3$; belching, $N = 1$; constipation, $N = 1$; and flush, $N = 1$) and in four during placebo treatment (nausea, $N = 1$; headaches, $N = 2$; and constipation, $N = 1$). All these side effects were mild, and none of them led to interruption of the treatment. All patients completed the three week study period. Four of those in the cisapride group (pretreatment gastric emptying: normal in two, delayed in two) stopped their treatment during the fifth week, two for family reasons not related to the results of the treatment, and two because their symptoms did not improve. One patient in the placebo group (pretreatment gastric emptying delayed) stopped his treatment during week 5 because of the absence of improvement.

Statistical Analysis. The results were subjected to nonparametric statistical analysis. Within-group changes were evaluated by the Wilcoxon matched pairs signed ranks test. The Mann-Whitney U test was used for intergroup comparisons. Correlations between symptom scores and gastric emptying rates were assessed by the Spearman rank correlation coefficient. The frequency of gastric stasis was evaluated from the range of values obtained in the control group. All results were expressed as means ± SEM.

RESULTS

Evaluation of Gastric Emptying. Gastric emptying results were available for 27 of the 28 CID patients and for all 17 controls. A delay in gastric emptying was evidenced in the CID patients (Figure 1), whose half emptying time for the liquid marker was significantly higher than that of the controls (94 ± 9 min vs 56 ± 4 min; $P < 0.01$). The power exponential model used to characterize the gastric emptying of solids also evidenced a longer emptying time in CID patients than in controls (185 ± 29 min vs 120 ± 8 min; $P < 0.05$). The β coefficient of CID patients was not different from that of the controls

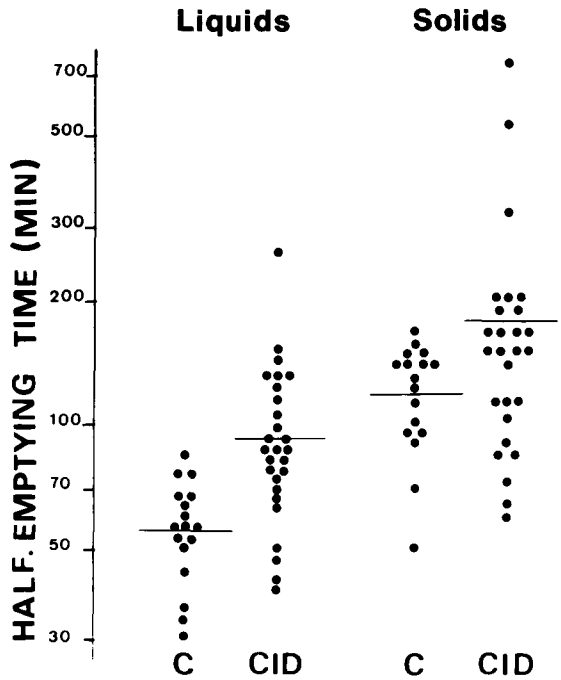

Fig. 1. Mean (lines) and individual half emptying times for the liquid and solid phases of the meal. C: controls; CID: patients with chronic idiopathic dyspepsia. Mann-Whitney test showed significant difference between C and CID for liquids ($P < 0.01$) and for solids ($P < 0.05$).

(2.3 ± 0.2 vs 2.2 ± 0.2), and did not alter (2.4 ± 0.7), even when only patients with an abnormally prolonged emptying time for solids were considered. When the upper limits of normal values were defined by the ranges of half emptying times for liquids, and half emptying times and coefficient for solids (30–83 min, 51–172 min, and 1.4–3.3, respectively) measured in the 17 healthy subjects studied under similar conditions, 16 of the 27 CID patients (59%) had gastric stasis. The latter concerned liquids only in eight cases, solids only in one, and both phases in seven.

When symptom scores at entry were compared for CID patients with and without delayed gastric emptying, there was no significant difference between the two groups for either of the two global scores (GDS and VAS), and only one of the five specific symptom scores (prolonged digestion) displayed such a difference (Table 1). A slight but significant correlation ($r = 0.38$, $P < 0.05$) was evidenced between the symptom score "prolonged digestion" and the gastric emptying rate of the liquid phase marker; however, a marked overlap of this symptomatic score was present between patients with and without gastric stasis. Anxiety

TABLE 1. ENTRY SYMPTOM SCORES IN PATIENTS WITH (ST +) AND WITHOUT (ST −) OBJECTIVE GASTRIC STASIS ON PRETREATMENT SCINTIGRAPHY (MEAN ± SEM)

	St + (N = 16)	*St − (N = 11)*
Early satiety	3.1 ± 1.1	3.4 ± 1.9
Epigastric pressure	11.4 ± 2.6	8.1 ± 2.6
Postprandial bloating	11.8 ± 2.2	12.9 ± 2.2
Nausea and/or vomiting	6.3 ± 1.8	9.9 ± 3.5
Prolonged digestion	14.3 ± 2.4	6.6 ± 1.4*
Global diary score	46.8 ± 7.0	37.4 ± 7.3
Visual analog score	56.9 ± 6.0	64.6 ± 6.4

*Comparison of St + and St −: $P < 0.01$

scores were similar in patients with and without gastric stasis (8.9 ± 2.1 vs 9.3 ± 1.9).

Effect of Chronic Administration of Cisapride on Gastric Emptying. Of the 28 CID patients, 13 with at least one parameter evidencing gastric stasis before the study were investigated before treatment began (week 0) and after its completion (week 6). Individual results are shown in Table 2. At week 6, mean gastric half emptying times for both liquids and solids (Figure 2) were significantly lower in the cisapride group than in the placebo group (61 ± 4 min vs 132 ± 37 min, $p < 0.01$ and 136 ± 16 min vs 227 ± 32 min, $p < 0.02$, repectively), whereas they were comparable before treatment. However, no significant difference between cisapride and placebo groups was evidenced for the β coefficient of the power exponential function characterizing the emptying of solids (2.8 ± 0.7 vs 1.8 ± 0.4).

TABLE 2. EFFECT OF CISAPRIDE AND PLACEBO ON GASTRIC EMPTYING OF LIQUIDS AND SOLIDS IN SUBGROUP OF PATIENTS TESTED TWICE BEFORE TREATMENT (WEEK 0) AND AFTER 6 WEEKS OF TREATMENT (WEEK 6)

	Liquids		*Solids*			
	*t1/2 (min)**		*t1/2 (min)*		*β†*	
Patient number	*Week 0*	*Week 6*	*Week 0*	*Week 6*	*Week 0*	*Week 6*
Cisapride						
1	87	71	165	145	3.1	3.4
2	61	48	165	116	3.9	5.7
3	69	64	141	188	3.3	1.7
4	85	69	172	139	1.9	2.5
5	150	53	333	155	1.4	2.3
6	256	63	522	74	0.5	1.2
Placebo						
1	143	101	201	371	5.7	0.9
2	83	86	769	320	0.5	0.8
3	90	106	181	178	1.6	1.8
4	89	93	193	154	3.6	1.4
5	100	88	151	168	2.0	1.6
6	120	99	188	180	3.2	2.6
7	129	348	185	220	1.9	2.4

*Exponential regression (normal range: 30–83).
†Power exponential regression (normal ranges: $t1/2$ = 51–172; β = 1.4–3.3).

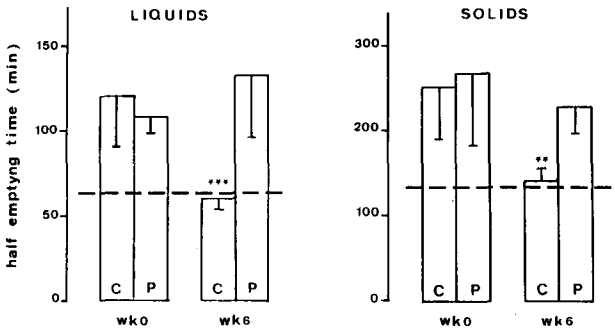

Fig. 2. Effect of chronic administration of cisapride (C) and placebo (P) on half emptying time of liquids (exponential regression) and solids (power exponential regression). Cisapride (10 mg) was given 15 min before ingestion of the marked meal. Data are means ± SEM; dotted line represents mean of control values. Comparisons between C ($N = 6$) and P ($N = 7$): $***P < 0.01$; $**P < 0.02$.

Overall Evaluation of Symptoms. Before treatment (week 0) the VAS and GDS were not different in the cisapride and placebo groups. At weeks 3 and 6, these two scores were significantly improved by cisapride, whereas placebo had no significant effect (Figure 3). The shifts induced by cisapride at weeks 3 and 6 compared to pretreatment scores were also compared to those seen with placebo (Figure 4):at week 3, cisapride was found to have a statistically significant effect on both VAS and GDS beyond that of placebo (−17 ± 4 vs −4 ± 4; $P < 0.01$, for VAS and −16 ± 6 vs −1 ± 9 for GDS; $P < 0.05$). This effect persisted at week 6 but was not significant compared to that of placebo (−24 ± 5 vs −8 ± 7 for VAS and −18 ± 5 vs −10 ± 8 for GDS).

Specific Evaluation of Symptoms. The specific symptom scores recorded before (week 0) and during treatment (weeks 3 and 6) are indicated in Figure 5: cisapride induced a significant improvement for epigastric pressure, bloating, and prolonged digestion ($P = 0.06$) and a borderline improvement for early satiety and nausea and/or vomiting ($P = 0.08$). Placebo only significantly improved nausea and/or vomiting.

Correlation between Therapeutic Effect on Symptoms and Other Parameters. The shifts in global symptomatic scores (Table 3) and specific symptom scores (Figure 6) were evaluated separately in the subgroups of patients with and without an initial delay in gastric emptying of liquids and/or solids. Despite the small number of patients in each subgroup, the decrease in the symptomatic score evidenced with cisapride at week 3 for patients with an

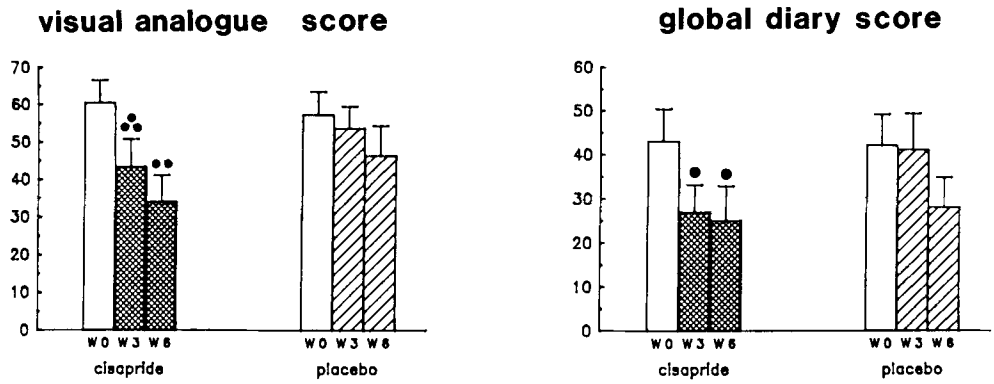

Fig. 3. Effect of chronic administration of cisapride and placebo on global scores (mean ± SEM). Comparisons between scores before and during treatment: $^{***}P < 0.01$; $^{**}P < 0.02$; $^{*}P < 0.05$.

initial gastric emptying delay was significantly larger than that for patients with normal emptying; thus, consequently, the symptomatic effect of cisapride mainly concerned patients with an initial gastric emptying delay. A similar trend was evidenced at week 6, but did not reach the significance level; no such difference was seen in placebo-treated patients. At week 3, a significant symptomatic improvement was achieved by cisapride when compared to placebo in the group of patients having an initial gastric emptying delay, whereas no significant effect was evidenced in patients having normal gastric emptying before treatment (Table 3).

DISCUSSION

This work was designed to improve the understanding and management of chronic idiopathic dyspepsia (CID). This term refers to chronic symptoms that are suggestive of gastric stasis and are strictly related to meal ingestion in patients devoid of any other identified disorders that could explain them. As previously found in another group of CID patients selected on the same criteria (3), the pres-

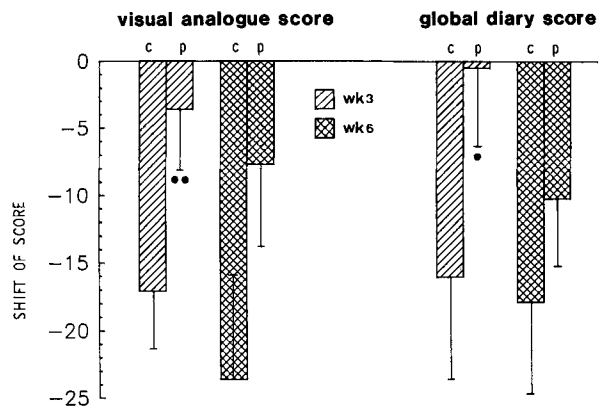

Fig. 4. Effect of chronic administration of cisapride (c) and placebo (p) on shifts in global scores (means ± SEM). Comparisons between cisapride and placebo. $^{**}P < 0.01$; $^{*}P < 0.05$.

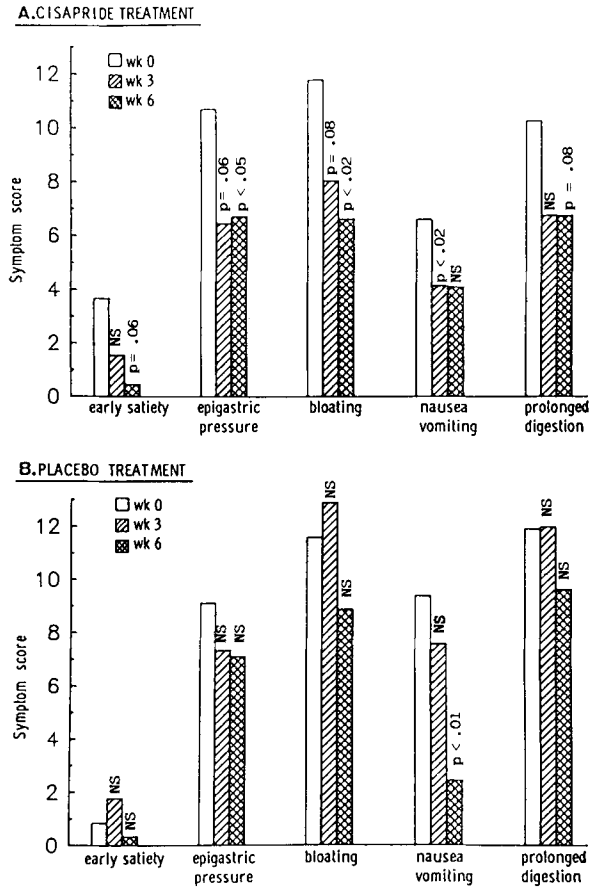

Fig. 5. Evolution of specific symptom scores during cisapride (A) and placebo (B) treatments; statistical evaluation of differences between before and during treatment results are depicted.

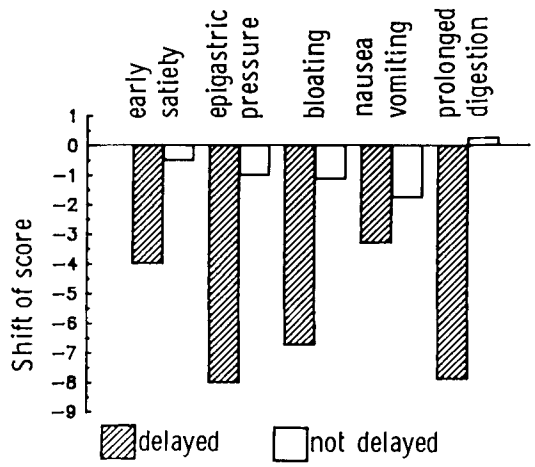

Fig. 6. Shifts in specific symptom scores induced by cisapride at week 3 in subgroups of patients with gastric emptying delay (N = 7) and without such delay (N = 8) (Negative values indicate score reductions induced by cisapride).

ent study shows that about half these patients do have objective gastric stasis. Other authors noted gastric stasis in CID (11–15) but did not simultaneously assess gastric emptying of the two main phases of a normal meal. The individualization of the CID syndrome in relation to other functional disorders is also supported by the fact that in the irritable bowel syndrome, no such delay could be seen (16–18).

This work was not designed to determine the substratum of the gastric stasis found in some of our CID patients. However, in patients with severe dyspeptic symptoms, electrophysiological (13, 15, 19) and manometric disturbances were recently reported (20, 21). In fact, more extensive studies, conducted simultaneously with gastric emptying assessments, are needed to explain: (1) why some CID patients have a selective delay in gastric emptying of liquids [in this connection, a methodological problem seems unlikely, since in patients with secondary dyspepsia—postvagotomy or in diabetes—the delay in gastric emptying, assessed under similar conditions, was seen to affect both phases of the meal (3)], and (2) why the β coefficient of the power exponential function characterizing the emptying of solids, a parameter closely related to antral motility (22, 23), did not significantly alter in our CID patients, even when only those with a delayed half emptying time of the solid marker were considered. All these points suggest that besides antral motility disturbances, other postprandial motility disorders involving relaxation of the proximal stomach, antroduodenal coordination, or duodenojejunal motor activity may be responsible for gastric emptying anomalies evidenced in CID patients.

It is not known whether gastric stasis originates in the gut itself or in the central nervous system. The high frequency of psychiatric disorders in patients with CID (20) and the evidence of stress-induced gastric motor disturbances, at least under acute conditions (24), suggest the latter, whereas the identification of intrinsic myoelectric abnormalities of the gastric muscular cells (19) supports the former. The efficacy of cisapride, which has no central antiemetic effects, in improving dyspeptic symptoms strengthens the possibility that a peripheral disorder is at least partly responsible for the complaints of CID patients.

The absence of abnormal gastric emptying in 41% of our CID patients raises several questions. Here again, lack of sensitivity of the method used seems unlikely, since under identical technical conditions, we found that more patients with secondary dyspepsia exhibited delay in gastric emptying than those with CID (3). Other authors also found a similar discrepancy between secondary dyspepsia and CID, using manometric evaluation of gastric motility (20). Although it is tempting to consider CID patients without gastric stasis as psychiatric

TABLE 3. SHIFTS IN GLOBAL DIARY SCORES RECORDED BEFORE AND AFTER CISAPRIDE TREATMENT AND PLACEBO IN PATIENTS WITH (ST +) AND WITHOUT (ST −) OBJECTIVE GASTRIC STASIS ON PRETREATMENT SCINTIGRAPHY

	St +	*St −*
Cisapride		
Week 3–week 0	−29.9 ± 7.5 (N =7)*†	−4.1 ± 5.8 (N =8)
Week 6–week 0	−24.6 ± 12.7 (N =5)	−12.5 ± 5.3 (N =6)
Placebo		
Week 3–week 0	+4.6 ± 6.4 (N =9)	−12.0 ± 98 (N =3)
Week 6–week 0	−7.3 ± 5.4 (N =8)	−16.5 ± 33 (N =3)

*Significantly different from St − (P = 0.01).
†Significantly different from placebo (P = 0.08).

cases, subjects with characterized psychiatric disorders were excluded from the present study, and our evaluation of anxiety symptoms using a well-established test (10) did not show any difference between patients with and without gastric stasis. In CID therefore, the possibility of intermittent occurrence of gastric stasis should be considered in addition to dysfunction involving other parts of the digestive tract than the stomach.

A point of important practical value for the management of CID patients was to determine whether or not evaluation of symptoms had a predictive value for the presence of objective stasis. Only one of the seven parameters tested (the symptom score "prolonged digestion") was significantly higher in patients with stasis than in those with normal gastric emptying. However, because of a marked overlap, this score did not seem to be of practical value for the detection of stasis in individual patients. Thus, like others (20, 25), we conclude that no clinical feature clearly distinguishes patients with delayed gastric emptying from those with normal emptying. This conclusion underlines the importance of an objective assessment of gastric dysfunction in CID.

Cisapride was shown to have striking effects on the gastric emptying of both phases of the meal at the end of the six-week treatment period since almost all initially delayed gastric emptying rates were brought to within normal range. Chronic administration of this drug was recently reported to have a similar effect on gastric emptying of solids after two weeks of treatment in CID patients with objective gastroparesis (26) and patients with diabetic gastroparesis (27). Thus the fading of the enhancement of gastric emptying sometimes described with other gastrokinetic drugs (28, 29) does not seem to apply to cisapride. Cisapride also improved symptoms, as shown by the significant reduction of the visual analog and global diary scores, whereas no significant effect was evidenced with placebo at either week 3 or week 6. The evolution of each dyspeptic symptom studied indicates that nearly all these symptoms were affected in various degrees by the improvement of scores achieved by cisapride. However, comparison of the global scores for cisapride and placebo showed that the effect of cisapride was more significant than that of placebo at week 3 but not at week 6. This lesser significance of cisapride versus placebo at week 6 does not seem to be due to the fading of the symptomatic effect of cisapride between weeks 3 and 6, but rather to an increase in the "placebo effect" (Figure 4) and to the decreased number of patients at this second stage of the trial. Long-term studies including more patients are now needed to reach definite conclusions about the usefulnesses of this drug in treating dyspeptic symptoms for longer than three weeks.

We previously showed that the efficacy of cisapride in improving gastric emptying mainly concerns patients with objective gastric stasis (3). On the other hand, the action of a prokinetic drug on symptoms had not until now been assessed in dyspepsia on the basis of pretreatment gastric emptying status. Our results show that the symptomatic improvement achieved by cisapride mainly concerned patients with initial gastric stasis, at least during the first three weeks, when this drug was clearly more potent than placebo. This result shows the practical importance of assessing gastric emptying in the detection of anomalies that cannot be predicted by symptom analysis, and in selecting the subgroup of patients that will electively respond to a given treatment. Obviously, further studies are required to confirm the specificity of the symptomatic efficacy of cisapride in patients with gastric emptying delay and to identify drugs that relieve symptoms of CID not related to gastric emptying disorders more effectively than the present therapy.

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