0021-972X/99/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 84, No. 7
Printed in U.S.A.

Cisapride *Versus* Placebo for 8 Weeks on Glycemic Control and Gastric Emptying in Insulin-Dependent Diabetes: A Double Blind Cross-Over Trial*

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ABSTRACT

In insulin-dependent diabetes mellitus, slow gastric emptying may make absorption unpredictable and foster glycemic instability. Cisapride accelerates emptying, but controlled long term studies are scarce, and effects on glycemic control unknown. We investigated, in patients with insulin-dependent diabetes mellitus and unstable glycemia, the effects of 10 mg cisapride 4 times daily for 8 weeks *vs.* placebo on glycemic control and gastric emptying under random, cross-over, double blind conditions. In 14 patients with delayed and 9 with nondelayed emptying, blood glucose variability over 2 8-week treatment periods separated by a 4-week wash-out and gastric emptying of a semisolid 1168-kJ meal immediately after the treatment periods were assessed. Cisapride did not affect glycemic control [SD of within-patient mean blood glucose, 4.2 mmol/L ± 0.1 (±SEM) *vs.* 4.0 ± 0.1 mmol/L after placebo; hemoglobin A_{1c}, 8.3 ± 0.2% *vs.* 8.5 ± 0.2%]. Emptying was faster after cisapride than after placebo in 8 of 14 patients with delayed *vs.* 7 of 9 with nondelayed emptying (P = NS) and in 11 of 15 without *vs.* 4 of 8 with cardiovascular autonomic neuropathy (P = NS). Autonomic neuropathy prevailed in 7 of 14 patients with delayed and 1 of 9 with nondelayed emptying. Blood glucose immediately before and during assessment of emptying was unrelated to the emptying rate, whereas blood glucose increases over fasting levels were greater with faster emptying ($P < 0.002$). In conclusion, cisapride's effects were not different from those of placebo on glycemic control and gastric emptying, it did not differently affect patients with delayed *vs.* nondelayed emptying, and it slightly accelerated emptying (P = NS) in patients without, but not in those with, cardiovascular autonomic neuropathy. Blood glucose levels before and during assessment of emptying did not affect emptying, but the glucose rise over fasting levels was greater with faster emptying. (*J Clin Endocrinol Metab* **84:** 2357–2362, 1999)

IN PATIENTS with insulin-dependent diabetes mellitus (IDDM), unstable glycemia may be caused by slow gastric emptying, which renders the time of ingesta absorption unpredictable and the ensuing blood glucose levels unlikely to be matched by the administered insulin. Slow emptying, at least of liquid meal components, has been found to result in a slow increase in the blood glucose concentration over fasting levels (1–3). On the other hand, abnormal gastric emptying may also result from high blood glucose levels, such as those encountered in patients with poor glycemic control. The latter is suggested by studies in healthy subjects as well as in patients with diabetes that showed that acute increases in blood glucose, even in the physiological range, slow gastric emptying (4–6). Under the assumption that agents enhancing the delivery of ingesta from the stomach to the small intestine would facilitate and improve glycemic control, a series of investigations was carried out to evaluate their effects in patients with diabetes. Most of these studies assessed the action of cisapride (Propulsid, Janssen Pharmaceutica, Beerse, Belgium), which enhances gastric motility via a facilitation of cholinergic transmission in the myenteric plexus (7). In uncontrolled, single dose investigations, cisapride was found to accelerate emptying (8–10), whereas uncontrolled (11, 12) and placebo-controlled but open (8) long term studies yielded equivocal results. Controlled trials on the long term effects of cisapride on gastric emptying in IDDM patients are scarce, and their results are predominantly negative. In two double blind, cross-over studies extending over 4 (13) and 8 weeks (14), respectively, the effects of 10 mg cisapride three times daily (TID) on the emptying of solid and liquid meal components did not differ from those of placebo; 1 of these investigations was carried out in 10 patients with delayed emptying (13), and the other was performed in 19 patients, 6 of whom had delayed emptying (14). Two 6-week studies were carried out under double blind, parallel group conditions (15, 16). In 1 (15), the emptying of solids as well as of liquids in 8 patients with diabetic and 3 with idiopathic gastroparesis was no more accelerated by 10 mg cisapride TID than by placebo; in the other (16), in which 4 diabetic patients received 20 mg cisapride TID and 3 patients received placebo, cisapride accelerated emptying, whereas placebo did not. The effect of cisapride administered

Received February 3, 1999. Revision received March 26, 1999. Accepted April 7, 1999.

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* This work was supported by Janssen Research Foundation (Beerse, Belgium).

over longer periods on glycemic control has not been adequately assessed.

The failure of cisapride to enhance gastric emptying in the majority of the long term studies referred to may be attributable to various factors. High blood glucose levels as well as the presence of autonomic neuropathy in the patients studied may have precluded stimulatory effects. Up until now, however, the impact of neither of these two factors on the effects of cisapride has been studied. Even the relationship between cardiovascular autonomic neuropathy (CANP) and delayed gastric emptying is unclear. Whereas some investigators reported that emptying was slower with more severe CANP (17–20) or delayed more often in patients with than without CANP (21–24), others reported that disordered gastric and small intestinal motility was not significantly associated with CANP (25–27). Finally, the rate of emptying prevailing in individual patients studied may have blunted the effects of cisapride; there is evidence that cisapride has marked accelerative effects on delayed but only minor effects on normal emptying (28).

The present study therefore was aimed at determining, in patients with IDDM and unstable glycemia, 1) the effects of 8-week oral administration of cisapride *vs.* placebo on glycemic control and gastric emptying under random, crossover, double blind conditions; and 2) the effects of cisapride, with respect to the prevailing blood glucose levels, on the presence of CANP and on delayed *vs.* nondelayed gastric emptying (for definition, see *Materials and Methods*).

Materials and Methods

Design

The study was designed as a randomized, cross-over, double blind trial. The design accounted for two strata: patients with delayed and patients with nondelayed emptying (for definition, see below). Half of the patients in each stratum were to receive oral doses of 10 mg cisapride four times daily (QID) for 8 weeks, then placebo QID during a 4-week washout period, and finally placebo QID for another 8 weeks; the other half of the patients were to receive placebo in the first 8 weeks, as well as in the 4-week washout period and cisapride in the second 8 weeks. The randomization plan was generated by Janssen Research Foundation. The code was kept there and broken when all data were listed in Case Record Forms, in which no treatment assignments were entered. The medication was provided as identically appearing cisapride and placebo tablets. For each patient, the investigators received a sealed envelope to be opened in case of emergency only, which contained the individual treatment code. The study was monitored throughout by Janssen.

For the detection of a difference between the treatment effects on the primary outcome measure, *i.e.* the SD of the within-patient mean blood glucose level over an 8-week treatment period, the target sample size was projected assuming a between-subject SD of glycemic variability of 11% in placebo-treated patients (Slama, G., personal communication). As the intraindividual SD can be expected to be about half as high as the interindividual SD, it was estimated that six patients were required for each treatment sequence in each stratum to detect a difference between the treatment effects as indicated by an intraindividual SD of 0.555 mmol/L blood glucose or more with a power of at least 80% and an error probability of less than 5% using a two-tailed test.

The study was conducted in accordance with the Declaration of Helsinki as revised in 1996. It was approved by the joint ethical committee of the Faculty of Medicine, University of Vienna, and the General Hospital of the City of Vienna. All patients gave written informed consent to participate.

Inclusion criteria and randomization

Patients with classical IDDM were eligible for inclusion if they were C peptide negative, 19–70 yr old, were receiving intensified insulin treatment (Basis Bolus Insulin Therapy), had a history of unexplained unstable glycemia, and could be expected to be compliant with drug intake, glucose monitoring, and the completion of a diary. Further, patients were eligible if hematological, biochemical, and urine analyses showed no gross abnormalities; serum creatinine levels were less than 221 μmol/L; there was no significant organic impairment; and there was no illness apart from IDDM. Patients were not eligible if they had used an investigational drug 30 days before the initial assessment; were taking medications potentially interfering with the aims of the study, *i.e.* cholinergics, anticholinergics, spasmolytics, antiemetics, dopamine antagonists, opioids, and gastroprokinetic agents including macrolide antibiotics; had undergone major gastrointestinal surgery; and were known or suspected to use illicit drugs or to abuse alcohol. Females of childbearing age had to be using adequate contraceptive control and not pregnant or lactating. Patients were included in the study if they had, during a 4-week phase (basal phase), a SD of the mean blood glucose of more than 2.78 mmol/L, *i.e.* moderate to severe glycemic instability.

Procedure

Eligible patients underwent evaluations of gastric emptying and CANP as described below and completed a symptom questionnaire. They were trained to make capillary blood glucose measurements using a monitor with automatic data storage (One Touch II, Life Scan, Ortho Diagnostic Systems, Milpitas, CA). When this was accomplished, the patients were asked to make at least four blood glucose measurements per day over a 4-week period. Half of the measurements were requested to be made just before breakfast, lunch, and supper, and the other half to be made 1.5–2 h postprandially. The mean blood glucose and the number of biological hypoglycemic ($\leq$2.78 mmol/L) and hyperglycemic ($\geq$13.88 mmol/L) events per week were determined. Patients were provided with a diary to record the incidence and severity of clinical hypoglycemic events and other relevant information, such as missed meals, sports, insulin doses, and illnesses. A clinical hypoglycemic event was classified as mild if the patient had symptoms but was able to help her/himself and as severe if she/he required assistance or coma was induced.

At the end of the basal 4 weeks, the patients were asked to register blood glucose every 3 h for at least 15 h while maintaining their daily routine. On the subsequent day and after an overnight fast, venous glucose levels were determined before as well as 30, 60, and 120 min after a standard breakfast. Patients completed a quality of life questionnaire and their hemoglobin A_{1c} (HbA_{1c}) levels were determined. During the treatment phase, patients were required to take tablets containing 10 mg cisapride QID, *i.e.* 30 min before breakfast, lunch, and supper as well as at bedtime. Further, they were instructed to make at least four glucose measurements per day, *i.e.* one just before each main meal (breakfast, lunch, and supper) and one at bedtime, and to complete their diaries daily. After each of the two treatment periods, venous glucose levels in response to a standard breakfast were evaluated again, and the patients completed a symptom and a quality of life questionnaire. Further, gastric emptying and HbA_{1c} were recorded, and hematological, biochemical, and urine analyses were performed to evaluate drug safety.

Patients

Twenty-eight out-patients entered the basal phase; 4 of them dropped out during that phase because they found the study protocol too demanding. Of the 24 patients included in the treatment phase, 1 dropped out after a short time for the same reason. Twelve females (7 postmenopausal) and 11 males completed the study; their median age was 45 yr (interquartile range, 32–53 yr), their median body mass index (BMI) was 22.8 kg/m^2 (21.2–25.4 kg/m^2), their median IDDM duration was 20 yr (12–27 yr), and their median HbA_{1c} at inclusion was 8.4% (7.5–8.9%). Nineteen patients injected ultralente insulin twice daily, *i.e.* between 0600–0800 h as well as between 1000–1100 h, and 4 injected ultralente insulin in the morning and neutral protamine Hagedorn insulin at bedtime. Before breakfast as well as at lunch and supper, all patients injected a standardized bolus of regular insulin. Seven patients had

nonproliferative retinopathy, 4 had mild nephropathy (albumin excretion, 30–300 mg/24 h); 14 had delayed and 9 had nondelayed gastric emptying (for definitions, see below).

Assessment of gastrointestinal symptoms and quality of life

Dysphagia, heartburn, chest pain, regurgitation, early satiety, postprandial epigastric fullness, anorexia, nausea, vomiting, and abdominal discomfort were evaluated using a standard questionnaire at the start of the basal phase as well as after each of the two treatment periods. The frequency of symptoms was scored as follows: 0, absent; 1, present rarely; 2, present frequently; 3, present very often; and 4, always present. The mean frequency was evaluated as the total symptom score. The number of bowel movements per week and day and the consistency of stools were also noted. The quality of life was assessed using the questionnaire employed in the Diabetes Control and Complications Trial (29).

Evaluation of CANP

CANP was assessed as described previously (20) by four tests, *i.e.* the resting heart rate variation, the maximum minus minimum heart rate difference, the heart rate response to standing up, and the heart rate response to a Valsalva maneuver. Further, the blood pressure response to standing up was measured. The result of each of the tests was classified as normal; borderline, *i.e.* between the 90–95% confidence limit for healthy subjects; or abnormal, *i.e.* beyond the 95% confidence limit. The overall classification was as follows: 1, normal; 2, borderline CANP, *i.e.* 1 test result abnormal or 2 borderline; 3, definite CANP, *i.e.* 2 or 3 results abnormal; and 4, severe CANP, *i.e.* 4 or 5 results abnormal.

Measurement of gastric emptying

The emptying of a semisolid 1168-kJ meal was recorded scintigraphically (30). The ingredients were 250 ml milk (9.2 g fat, 8.5 g protein, and 12.3 g carbohydrates), 15 g sugar, 14 g maize starch (11.9 g carbohydrates), and, for flavoring, cinnamon; its osmolality was 558 mmol/kg. The meal was cooked under continuous stirring until a semisolid consistency was reached and, after cooling to a temperature at which it could be eaten, was mixed with 60 MBq [^{99m}Tc]phylate in isotonic saline. The ^{99m}Tc radiolabel is bound reliably to the meal (30). Recording began at the end of ingestion and lasted 120 min. The patients sat in an armchair tilted 30° backward to avoid overprojection of stomach and small intestine. A posteriorly located, single headed γ-camera (GCA901A, Toshiba Medical Systems, Tokyo, Japan) was used. Serial images over 1 min each were acquired in the frame mode. A region of interest including the stomach was drawn. Counts in this region were corrected for the variation in tissue attenuation caused by the changing intragastric position of the meal and the use of a single headed camera (31) as well as for background activity and radionuclide decay. An activity-time curve, expressed as percentages of counts in the region immediately after ingestion, was derived. The percentage of the meal remaining in the stomach at 120 min (residual radioactivity, RRA_{120}) and the area under the emptying curve (AUC_{120}) were taken as overall measures of emptying. The shape of the emptying curves was analyzed using the power exponential and the parameter β (32). A β more than 1 characterizes an initially slow emptying followed by a more rapid emptying, whereas a β less than 1 describes a fast initial and subsequent slower emptying. The radiation burden was 1.7–5.4 milli-Sievert, *i.e.* less than from a barium contrast investigation. The capillary blood glucose concentration was measured just before meal ingestion as well as 60 and 120 min after the termination of the meal.

According to the results of the study performed in the basal phase, patients were classified as having delayed (n = 13) or nondelayed (n = 10) emptying. The criterion for delayed emptying was a residual radioactivity at 50 min (RRA_{50}) of more than 73.2%, *i.e.* more than the mean RRA_{50} + 1.5 SD (53.5 + 19.7%) of 48 healthy, symptom-free young men (median age, 25 yr (interquartile range, 23–27 yr); and a median BMI of 22.2 kg/m^2 (20.3–23.3 kg/m^2). Ten of the 13 patients with delayed emptying had an RRA_{50} greater than the RRA_{50} ± 2 SD of the healthy subjects.

Statistical analysis

Effects on the SD of the mean within-patient blood glucose level were examined by ANOVAs accounting for the influences of the random factor patient (no. 1–23), the fixed between-subject factors stratum (delayed emptying, nondelayed emptying) and CANP (normal/borderline, definite/severe), and the fixed within-subject factors treatment (cisapride, placebo) and sequence (cisapride-placebo, placebo-cisapride).

For the residual radioactivity determinations and the blood glucose levels in the course of the emptying studies, ANOVAs for repeated measures were carried out. They accounted for the random factor patient; the fixed between-subject factors sex, illness duration, BMI, stratum, and CANP; and the fixed within-subjects factors treatment, sequence, and period (residual radioactivity at 40, 80, and 120 min; blood glucose before meal ingestion as well as at 60 and 120 min). In addition, comparisons were performed using Student's *t* test for paired data and correlation analyses for continuous variables, and the χ^2 test for categorical variables. For the rejection of the null hypothesis, an error probability of $P < 0.05$ (two-tailed) was considered significant. Data are expressed as the mean ± SEM. To investigate the degree to which the factors patient, sex, illness duration, BMI, stratum, CANP, treatment, sequence, blood glucose before meal ingestion, and blood glucose rise over fasting levels predicted the RRA_{120}, a stepwise multiple linear regression analysis was carried out.

Results

Glycemic control

Glycemic control was unaffected by cisapride; the SD of the within-patient mean capillary blood glucose, the mean blood glucose, as well as the numbers of biological hypoglycemic, clinically mild and severe hypoglycemic, and biological hyperglycemic events did not differ from the values recorded during placebo treatment (Table 1). There was also no difference between the values recorded during cisapride and placebo treatments, respectively, and those recorded in the basal phase. The plasma blood glucose profiles in response to the standard breakfast after cisapride did not differ significantly from those after placebo and in the basal phase (Table 2). HbA_{1c} after cisapride differed neither from the HbA_{1c} after placebo nor from that in the basal phase (Table 1). After cisapride as well as after placebo, patients with delayed emptying did not differ in HbA_{1c} (8.5 ± 0.3% *vs.* 8.6 ± 0.3%) from patients with nondelayed emptying (8.2 ± 0.3% *vs.* 8.4 ± 0.2%), and patients with CANP had HbA_{1c} levels (8.3 ± 0.4% *vs.* 8.6 ± 0.4%) not different from those in subjects without CANP (8.3 ± 0.2% *vs.* 8.5 ± 0.2%).

Gastric emptying

After cisapride, emptying did not differ significantly from that after placebo [treatment factor, $F(1, 20) < 1$; Fig. 1]. The treatment effects differed neither in patients with delayed nor in those with nondelayed emptying [interaction treatment-stratum, $F(1, 20) < 1$]. The meal was emptied faster after cisapride than after placebo in 8 of the 14 patients with delayed and in 7 of the 9 with nondelayed emptying [χ^2 (1) = 1.70; P = NS]. The shape of the emptying curves, as described by the parameter β, did not differ between cisapride and placebo (Table 3) or between patients with delayed and those with nondelayed emptying.

The autonomic function tests revealed that 15 patients had no or only borderline CANP, whereas 4 had definite and 4 had severe CANP. At the initial assessment, 7 of the 8 patients with and 7 of the 15 without CANP had delayed

TABLE 1. Blood-glucose level, SD of within-patient mean blood glucose, and number of hypo- and hyperglycemic events in the basal phase and during placebo and cisapride treatments as well as HbA_{1c}, total symptom score, total quality of life score, and body weight at the initial assessment and after treatment

Parameter	Basal phase	Placebo	Cisapride
Mean blood glucose (mmol/L)	9.3 ± 0.4	9.5 ± 0.3	9.6 ± 0.3
SD of within-patient mean blood glucose (mmol/L)	4.1 ± 0.2	4.0 ± 0.1	4.2 ± 0.1
Biologic hypoglycemic events (no./week)[a]	5 (0–25)	4 (0–25)	4 (0–23)
Clinical mild hypoglycemic events (no./week)[a]	6 (0–28)	2 (0–29)	1 (0–11)
Clinical severe hypoglycemic events (no./week)[a]	0	0 (0–2)	0 (0–3)
Biologic hyperglycemic events (no./week)[a]	29 (3–65)	22 (5–72)	28 (2–72)
HbA_{1c} (%)	8.2 ± 0.0	8.5 ± 0.2	8.3 ± 0.2
Total symptom score (smaller, lower symptom frequency)	3.2 ± 0.8	2.3 ± 0.5	2.3 ± 0.6
Total quality of life score (smaller, better quality)	92.9 ± 2.8	91.0 ± 2.9	89.3 ± 3.1
BW (kg)	68.0 ± 2.1	66.9 ± 2.0	67.4 ± 2.0

Results are expressed as the mean ± SEM or as the median with the range in *parentheses* ([a]).

TABLE 2. Blood glucose levels (millimoles per L) before (0 min) and 30, 60, and 120 min after ingestion of the standard breakfast at the end of the basal phase as well as after 8 weeks of treatment with placebo and cisapride

	0 min	30 min	60 min	120 min
Basal phase	12.9 ± 0.6	12.6 ± 0.5	14.8 ± 0.7	15.1 ± 1.0
Placebo	10.5 ± 0.8	10.6 ± 0.7	12.2 ± 1.0	12.9 ± 1.1
Cisapride	12.2 ± 0.8	12.0 ± 0.8	14.3 ± 0.9	14.0 ± 1.0

Values are the mean ± SEM.

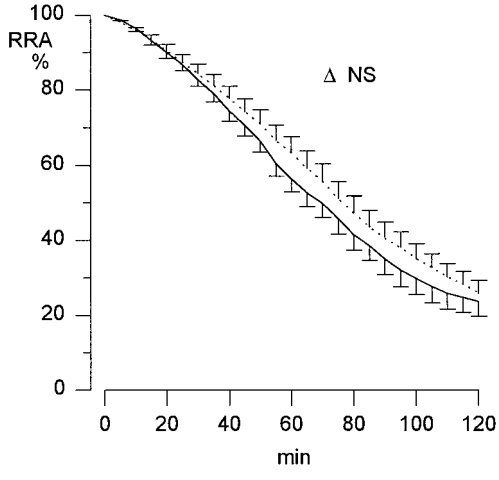

FIG. 1. Gastric emptying pattern (means ± SEM) in the 23 patients after 8 weeks of treatment with cisapride (*solid line*) and placebo (*broken line*). RRA, Residual radioactivity.

emptying [χ^2 (1) = 3.65; $P < 0.1$ (NS)]. Patients with CANP were older than those without [48.3 ± 4.2 *vs.* 39.7 ± 2.7 yr; t (21) = 5.96; $P < 0.0001$] and had a longer illness duration (24.6 ± 4.1 *vs.* 17.6 ± 2.1 yr; P = NS). In the 15 patients with no CANP, emptying was somewhat faster after cisapride than after placebo [area under the curve at 120 min, 6858 ± 335 *vs.* 7662 ± 335 U; t (14) = 1.95; $P < 0.07$ (NS)], whereas in the 8 patients with CANP, the emptying after cisapride was virtually identical to that after placebo (area under the emptying curve at 120 min (AUC_{120}), 7589 ± 698 *vs.* 7358 ± 825 U; Fig. 2). This was reflected by the F ratios for the interactions treatment-CANP [F(1, 20) = 2.11; P = NS] and period-CANP [F(2, 20) = 3.52; $P < 0.04$]. The shapes of the emptying curves did not differ between patients with and without CANP. Sex, illness duration, BMI, and treatment sequence had no influence on emptying.

The capillary blood-glucose levels immediately before the emptying studies as well as over the time of the recording of emptying did not differ between patients who received cisapride and those who received placebo [0 min, 9.0 ± 0.7 *vs.* 9.4 ± 0.6 mmol/L; 60 min, 13.1 ± 0.8 *vs.* 13.5 ± 0.6 mmol/L; 120 min, 12.3 ± 0.8 *vs.* 12.1 ± 0.7 mmol/L; treatment, F(1, 20) < 1]. Glucose levels were also not affected differently by the two treatments in patients with delayed *vs.* nondelayed emptying and in those with *vs.* without CANP (all F ratios < 1). Sex, illness duration, BMI, and treatment sequence had no influence on blood glucose. The RRA_{120} was slightly greater with higher preprandial blood glucose [cisapride, r (21) = 0.367; $P < 0.1$ (NS); placebo, r (21) = 0.154; P = NS]. The blood glucose rise from preprandial levels to the levels at 60 and 120 min after the start of ingestion was inversely related to the residual radioactivity, *i.e.* greater with faster emptying [60 min: r (44) = −0.460; $P < 0.002$; 120 min: r (44) = −0.563; $P < 0.001$]. This relationship was linear [60 min: F(1, 44) = 11.80; $P < 0.002$; 120 min: F(1, 44) = 17.70; $P < 0.0001$]. The results of the multiple linear regression analysis pointed in the same direction: the factor blood glucose rise over fasting levels, the only factor meeting the $P < 0.1$ significance level for entering the model, explained 44% of the RRA_{120} variability. As blood glucose increases occur consecutive to the delivery of ingesta to the small intestine, this means that the emptying rate determined the increase in glucose levels.

TABLE 3. Parameters of gastric emptying at the initial assessment as well as after 8 weeks of treatment with placebo and cisapride

Parameter	Initial assessment	Placebo	Cisapride
RRA_{50} (%)	76.5 ± 2.9	71.0 ± 3.7	66.6 ± 3.1
RRA_{120} (%)	28.4 ± 4.6[a]	25.9 ± 3.3	22.9 ± 3.9
AUC_{120} (U)	7852 ± 369[a]	7556 ± 362	7112 ± 334
β	2.6 ± 0.5	2.0 ± 0.2	2.0 ± 0.2

Values are the mean ± SEM.
[a] n = 20.

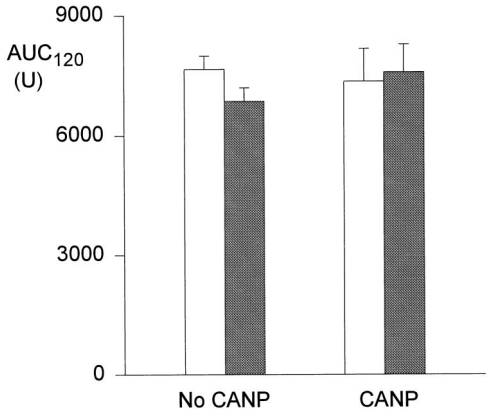

FIG. 2. Gastric emptying [mean area under the curve at 120 min (AUC_{120}) ± SEM] after 8 weeks of treatment with placebo (*empty columns*) and cisapride (*full columns*) in the 15 patients without or only borderline CANP (No CANP) and in the 8 patients with definite and severe CANP (CANP).

Gastrointestinal symptoms and quality of life

The number of patients with symptoms as well as the reported nature of the symptoms and the total symptom score (Table 1) after cisapride treatment did not differ from the respective data after placebo and at the initial assessment. The number of stools per week was greater after cisapride than after placebo in two patients, less in two, and the same as after placebo in 17. The total quality of life score after cisapride differed neither from that after placebo nor from that in the basal phase (Table 1).

Adverse effects

No potentially drug-related adverse effects occurred. One patient developed a slight facial paresis after 8 weeks of placebo treatment. She continued to participate in the study, and the paresis faded away within 3 weeks.

Discussion

The results of the present study show that cisapride (10 mg administered QID for 8 weeks) had no effect on glycemic control, as reflected by the SD of the within-patient mean blood glucose level over the treatment periods and by the HbA_{1c}, or on gastric emptying at the end of the treatment periods, which differed from the effects of placebo. Emptying was slightly, but insignificantly, faster after cisapride than after placebo in the 15 patients who had no CANP, whereas emptying was virtually identical after cisapride and placebo treatment in the 8 patients with CANP. The finding of no systematic superiority of long term treatment with cisapride over placebo treatment on the gastric emptying of IDDM patients is consonant with the results of an open study (11) as well as those of 2 double blind, placebo-controlled, cross-over trials (13, 14) and a double blind, parallel group trial (15). Our findings are at variance with a report claiming that slow emptying was unrelated to CANP (25). Although there was no statistically significant relationship in the present study, attention should be payed to the fact that of the 14 patients with definitely delayed emptying, 7 had CANP and 7 had no CANP, whereas of the 9 patients with nondelayed emptying, only 1 had CANP. A lack of CANP, however, does not exclude a neuropathy affecting enteric nerves, which may result in gastric dysfunction. The overall CANP prevalence rate of 35% found in our patients is about as high as that in patient groups studied previously (33, 34), but lower rates, *i.e.* 27% and 17%, have also been reported (35).

Previous cross-over studies showed that the rate of gastric emptying is determined in part by the prevailing blood glucose level (4–6). Fraser *et al.* (4) reported that 8 of 10 IDDM patients emptied solid and 9 of 10 patients emptied liquid meal components slower with blood glucose stabilized using a clamp technique at 16–20 mmol/L than at 8 mmol/L. Concordant findings were obtained by others (6). At 8 mmol/L, a glucose level slightly lower than the ones prevailing in the present study, the emptying of liquids as well as solids in 9 IDDM patients was slower than that at 4 mmol/L (5). Thus, hyperglycemia could have accounted for the failure of cisapride treatment to accelerate gastric emptying in the present investigation. However, in contrast to the above-mentioned studies, emptying was only slightly slower with higher preprandial blood glucose levels in our patients. This finding is consistent with earlier cross-sectional observations in patients with long standing IDDM, in whom no correlation was found between the emptying rate, on the one hand, and the glucose level before ingestion of the meal, of which the emptying was assessed (3, 36). That there is no close relationship between the blood glucose concentration during the assessment of emptying and the rate of emptying is suggested also by another cross-sectional study in 86 diabetic patients; although the emptying of liquid was slower in patients with a mean blood glucose level greater than 15 mmol/L than in those with a mean glucose level less than 15 mmol/L, the solid meal components were not emptied differently (2). The direct relationship found in the present investigation between the rate at which the semisolid meal was emptied and the postprandial increase in blood glucose above fasting levels corresponds to earlier observations made after the administration of liquid meals (1–3): the faster the emptying, the faster the rise in blood glucose. By contrast, the administration of a human amylin analog, which yields a slowing of emptying (37), resulted in a reduction of postprandial (38) as well as 24-h plasma glucose levels (39).

The finding that cisapride had no effect different from those of placebo on the frequency of occurrence and the nature of gastrointestinal symptoms is consonant with earlier observations. In two long term, double blind, cross-over trials (13, 14) cisapride failed to reduce the frequency and/or severity of symptoms more than did placebo. Beneficial effects of cisapride, by contrast, were noted in open studies (10, 11, 40).

It can be concluded that cisapride, in the number of patients studied and the dosage assessed, 1) did not affect glycemic control; 2) had no effect on gastric emptying, which differed significantly from the effect of placebo; 3) did not act differently in patients with delayed and those with nondelayed emptying; 4) slightly accelerated emptying in patients with no or only borderline CANP, but not in those with definite CANP; and 5) did not affect the frequency of occurrence or the nature of gastrointestinal symptoms or the self-rated quality of life. Further, the rate of gastric emptying

was not related to the blood glucose levels before and during the emptying studies, whereas the blood glucose rise over fasting levels was directly related to the rate of gastric emptying. In the dosage investigated, cisapride does not seem suited as a means to accelerate slow gastric emptying and thereby to improve glycemic control in patients with IDDM. It remains to be investigated whether a higher dosage, *i.e.* 20 mg cisapride QID, would be more efficacious.

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