Cisapride vs Metoclopramide
An Acute Study in Diabetic Gastroparesis

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Radionuclide gastric solid-phase emptying was studied in 10 subjects with diabetic gastroparesis comparing the acute intravenous administration of cisapride (2.5, 5, 10 mg), placebo, and metoclopramide (10 mg). No hemodynamic or electrocardiographic changes were noted. While both cisapride and metoclopramide normalized impaired solid emptying, cisapride at its highest dosage (10 mg) resulted in significantly faster gastric emptying ($P = 0.003$) than metoclopramide. The effects of cisapride were dose related and correlated well ($r = 0.48, P < 0.01$) with the plasma drug levels. Clinical studies of chronic oral usage must take into account the dose-related response and factors affecting blood levels.

KEY WORDS: diabetic complications; diabetic gastroparesis; cisapride; metoclopramide; antral dysfunction.
with diabetic gastroparesis. Digestible solid was employed.

**MATERIALS AND METHODS**

The study was approved by the Human Experimentation Committee at the University of Toronto. Ten diabetic subjects (four males, six females, age range 21–73 years, mean age 39.7 years) with gastroparesis were recruited through endocrinologists at affiliated teaching hospitals. The criteria for inclusion in this study were: insulin dependent diabetes for >6 months; endoscopic exclusion of peptic ulcer disease and bezoars; absence of concomitant interfering medications including phenothiazines, drugs with anticholinergic action, and H₂ blocking agents; a serum creatinine <170 μmol/liter; upper gastrointestinal symptoms compatible with the diagnosis of DGP; and either evidence of retained gastric content after a 12-hr fast and before radiological or endoscopic examination or an abnormal radionuclide gastric emptying study. Subjects were excluded if they could become pregnant during the study or had concomitant illnesses that would interfere with completion of the study.

The 10 diabetic subjects had diabetes for 16.1 ± 9 (SD) years. Symptoms compatible with a diagnosis of diabetic gastroparesis were present for 3 ± 1 years at the time of entry into the study. Laboratory data were consistent with the expectations of this disease population. The mean Hgb A1C value was 12.1%, compared to a normal value of less than 7%.

Diabetic complications were common: retinopathy (seven subjects), nephropathy (two subjects), peripheral neuropathy (six subjects), impotence (three of four males), orthostatic hypotension (six subjects), peripheral vascular disease (four subjects), and fecal incontinence (eight subjects). Symptoms compatible with gastroparesis varied in severity and frequency in the diabetic subjects. Nausea was present in all subjects but only seven experienced significant vomiting. A sense of fullness or abdominal bloating (nine subjects), early satiety (nine subjects), and a variable amount of abdominal pain or discomfort was reported by eight of the 10 subjects.

The subjects were studied single-blind on five separate occasions separated by at least four days. Patients were asked not to smoke on the day of the testing. The experimental medication was given 15 min prior to eating a test meal. Cisapride diluent as placebo, metoclopramide (10 mg), or cisapride (three dosages: 2.5, 5, 10 mg) were administered intravenously according to a randomized 5 × 5 Latin square schedule. Blood pressure, heart rate, and ECG were monitored at 30-min intervals throughout the 2 hr of each study.

The test meal consisted of 30 mg raw beef liver that was injected at multiple sites with 150 μCi Tc-99, chopped, cooked, and then mixed with 240 cc of canned chicken stew. Subjects consumed the meal in less than 5 min and, reclining at 45 degrees, underwent continuous scintographic scanning (Pho/Gamma camera connected to M.D.S. A2 computer) for >120 min. Gastric emptying was expressed as both the percentage of activity remaining in the gastric window at 60, 90, and 120 min and the time for 50% emptying. Subjects took their usual daily insulin dosage 15 min before ingesting the test meal.

Serum samples were drawn from each subject 60 min after administration of the experimental medication. In each sample, the cisapride level was determined using high-pressure liquid chromatography (<2.0 ng/ml) by Janssen Pharmaceutica Inc. (Belgium). The subjects were interviewed the day after each experimental situation to determine whether they had experienced either any adverse effects or changes in their gastrointestinal symptoms in the intervening 24-hr period.

Twenty healthy control subjects (12 males, 8 females, mean age 32 years) were recruited through the University Placement Office to undergo a single untreated gastric emptying study. Exclusion criteria were the presence of any gastrointestinal complaints, systemic disease, or use of medications that could affect the upper gastrointestinal tract. The results of the healthy subjects established the normal range of gastric emptying.

Statistical analysis was performed using SAS (Statistical Analysis System, Version 5.08; Johnson & Johnson Computer facilities, installation 01147001, Raritan, New Jersey). The gastric emptying half-times, the residual activity, and the lag times were analyzed by regression analysis using the general linear models procedure to partition the variance sums of squares. Orthogonal comparisons were computed for the drug effect. On each parameter where the contrast of placebo versus all active medications was significant, multiple comparisons were performed using the least-squares means and a Bonferroni adjusted alpha = 0.0125. Heart rate and blood pressure were subjected to a split plot analysis of variance also using the general linear models procedure. Symptomatic data were summarized by descriptive measures only. All means are ± 1 SD.

**RESULTS**

**Gastric Emptying.** The normal range for solid-phase gastric emptying half-times (t½), as determined in the healthy control subjects, was 55 ± 18 min. Figure 1 shows the gastric emptying half-times for each experimental situation and Figure 2 shows the actual solid-phase gastric emptying as a function of time. The t½ was significantly prolonged in the diabetic subjects (88 ± 27 min) compared to the normal controls (P < 0.001) and against all active drug administrations (P = 0.0006, placebo vs active). All dosages of cisapride and the 10-mg dose of metoclopramide decreased mean gastric emptying times over placebo: t½ = 63 ± 29 min (cisapride 2.5 mg); t½ = 64 ± 26 min (cisapride 5 mg); t½ = 51 ± 19 min (cisapride 10 mg); and t½ = 75 ± 29 min (metoclopramide). The gastric emptying t½ was significantly (P = 0.003) shorter after cisapride 10 mg (51 ± 19 min) than after metoclopramide 10 mg (75 ± 29 min). The percentage of residual gastric