Effect of Cisapride on Gastric Dysrhythmia and Emptying of Indigestible Solids in Type-II Diabetic Patients

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Background: Abnormal gastric slow-wave frequencies have been observed in diabetic gastroparesis. To evaluate the effect of cisapride on gastric dysrhythmia and emptying of indigestible solids, 20 type-II diabetic patients with symptoms suggestive of gastroparesis were enrolled in this study. *Methods:* Cutaneous electrogastrography, gastric emptying of radiopaque markers, and evaluation of upper gastrointestinal symptoms were performed before and after administration of an 8-week course of cisapride. *Results:* The fasting-state percentages of dominant frequency in normal and tachygastric ranges improved significantly after an 8-week course of cisapride treatment ($P < 0.01$ and $P < 0.05$, respectively). The post-meal percentages of dominant frequency in the tachygastric range also improved significantly after cisapride treatment ($P < 0.05$). The upper gastrointestinal symptoms score decreased significantly, and gastric emptying of radiopaque markers also increased significantly after 8 weeks of cisapride treatment ($P < 0.01$). *Conclusions:* In conclusion, this study showed that cisapride can improve gastric dysrhythmia during both fasting and post-meal phases in patients with diabetic gastroparesis. In addition, upper GI symptoms and gastric emptying of indigestible solids may also show significant improvement after 8 weeks of cisapride treatment.

Key words: Cisapride; diabetic gastroparesis; electrogastrography; indigestible solids

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Gastric motility disorder is a serious complication of diabetes mellitus that may produce significant morbidity from indigestion, nausea, vomiting, dehydration, or electrolyte disturbances (1). Characteristic motor and myoelectric disturbances have been observed in diabetic gastroparesis (2). Generally, delayed solid- and/or liquid-phase gastric emptying is observed in association with reduced postprandial antral contractions and impaired cycling of the migrating motor complex (3). Motor activity in the stomach is regulated by electric pacemaker activity known as the slow wave (4). Abnormally high (tachygastric) or low (bradygastric) gastric slow-wave frequencies have been observed in diabetic gastroparesis and are associated with impaired antral motor activity (5, 6).

The use of radiopaque markers (ROMs) has been proposed as an easy, non-invasive technique to assess gastric emptying (7, 8). ROMs have been used to evaluate the effects of diabetes mellitus (9, 10) and the effects of prokinetic agents (11). Cisapride has been reported to be effective in patients with diabetic gastroparesis by improving solid and/or liquid emptying and ameliorating gastric dysrhythmia (12). However, there have been few reports about the effect of cisapride on both gastric dysrhythmia and emptying of indigestible solids in diabetic patients. In this study we evaluated the effect of cisapride on gastric dysrhythmia and indigestible solid emptying in diabetic patients with symptoms suggestive of gastroparesis.

MATERIALS AND METHODS

Patient population

Twenty type-II diabetic patients with symptoms suggestive of delayed gastric emptying and with abnormal gastric emptying of ROMs were included in this study. Symptoms included nausea, vomiting, upper abdominal discomfort, early satiety, bloating, and anorexia. There were 14 men and 12 women, with ages ranging from 41 to 78 years (mean, 63.5 ± 10.8 years). The duration of diabetes mellitus ranged from 3 to 15 years (mean, 7.4 years). All patients showed evidence of autonomic neuropathy as assessed by a standard series of cardiovascular reflex tests (13). Upper gastrointestinal (GI) endoscopy was performed to rule out the possibility of organic obstruction or peptic ulcer disease. None of the subjects had undergone previous surgery of the GI tract or were taking any medications known to cause nausea, vomiting, or dyspepsia (for example, non-steroidal anti-inflammatory drugs, digoxin). None of the postmenopausal women were receiving hormone replacement therapy. In addition to their daily oral hypoglycemic agents, all patients received 5 mg cisapride before meals three times daily for 8

weeks. Informed consent was obtained from all subjects, and the study protocol was approved by the ethics review committee of Taichung Veterans General Hospital.

Assessment of gastrointestinal symptoms

Upper gastrointestinal symptoms were evaluated before and after an 8-week course of cisapride treatment by means of a standard questionnaire. Anorexia/nausea, early satiety, upper abdominal discomfort or distention, vomiting, and abdominal pain were scored in accordance with the following scheme: 0 = none, 1 = mild (symptom could be ignored if the patient did not think about it), 2 = moderate (symptom could not be ignored but did not influence daily activities), 3 = severe (symptom influenced daily activities). The maximum possible total score was 15.

Gastric emptying of radiopaque markers

Gastric emptying of indigestible solids was evaluated before and after an 8-week course of cisapride treatment by means of ROMs. A gelatin capsule with 10 rod-shaped ($2 \times 2 \times 8$ mm) radiopaque polyurethane markers containing 40% barium sulfate was ingested along with the test meal for the electrogastrography (EGG) study. A supine plain abdominal radiograph was taken 4.5 h after ingestion of the solid meal to count the number of markers emptied from the stomach. According to established normal values, all markers should have been emptied from the stomach 4.5 h after ingestion (14).

Electrogastrography

Cutaneous EGG was performed before and after administration of an 8-week course of cisapride. Patients were studied in the morning after an overnight fast, for 30 min in the fasting state and for an additional 30 min after consumption of a mixed solid and liquid meal. The test meal consisted of two fried eggs, two slices of toast, and 500 ml of 5% glucose water. The total meal contained 412 kcal and consisted of 28% protein, 15% lipids, and 57% carbohydrates. The patient was positioned comfortably in a chair and requested to remain as still as possible to reduce motion artefacts. After gentle skin abrasion to enhance electric conditions, three Ag-AgCl electrodes (Accutac Diaphoretic ECG Electrodes; NDM, Dayton, Ohio, USA) were affixed to the abdomen. The first electrode, for one of the active EGG leads, was placed on the patient's left side about one-third of the distance from the ventral to left axial midline and 1 cm below the bottom rib. The second electrode, for the other active EGG lead, was placed on the patient's ventral midline about halfway between the umbilicus and the xyphoid process. The third electrode, for the reference lead, was placed on the patient's abdomen, forming a triangle with three equal sides.

EGG was performed with a portable EGG recorder (Synetics Medical Inc, Irving, Tex., USA). All recordings in the study were made at a sampling frequency of 4 Hz. After the measurement the EGG data were digitized, fed into a personal computer, and analyzed by means of a commercially available software program (ElectroGastroGram Version 6.30, Gastrosoft Inc., Synetics Medical). The data were obtained by running spectrum analysis. Using a fast Fourier transform (FFT) algorithm of a 256-sec 'window' of the raw data, power spectra of overlapping stretches of the electric signal were computed and displayed as a function of time, yielding frequency and amplitude information over the course of the study (15). Several variables, including dominant frequency (DF), the percentages of DF in the defined normal frequency range (2.4–3.7 cycles per minute (cpm)), bradygastric range (<2.4 cpm) and tachygastric range (3.7–10 cpm), dominant frequency instability coefficient (DFIC), dominant power instability coefficient (DPIC), and postprandial to fasting power ratio (PR), were analyzed. DFs higher than 10 cpm were separated from tachygastria because they were assumed to arise from outside the stomach. DF was calculated as the highest peak of the mean FFT line during the recording time. DFIC was used to ascertain the changes in DF during the period of data acquisition. It was defined as the coefficient of variation (standard deviation, mean DF × 100%) of DF.

Table I. Fasting blood sugar and electrogastrography (EGG) variables before and after an 8-week course of cisapride treatment

	Before	After	*P* value
Blood sugar (mg/dl)	148.8 ± 37.8 (94–245)	151.9 ± 38.8 (95–252)	>0.05
Fasting EGG			
DF (cpm)	3.12 ± 1.16 (1.17–6.33)	3.03 ± 0.3 (2.58–3.98)	>0.05
DF in normal range (%)	46.0 ± 24.0 (3.7–85.2)	66.0 ± 23.9 (25.9–96.3)	<0.01*
Bradygastria (%)	23.5 ± 20.7 (0–88.9)	16.5 ± 14.3 (0–44.4)	>0.05
Tachygastria (%)	28.5 ± 24.4 (0–96.3)	17.0 ± 15.5 (0–48.1)	<0.05*
DFIC (%)	37.5 ± 18.1 (12–89)	29.5 ± 18.5 (8–69)	>0.05
DPIC (%)	81.8 ± 39.6 (29–168)	65.7 ± 29.6 (39–147)	>0.05
Post-meal EGG			
DF (cpm)	2.74 ± 0.53 (1.64–3.52)	2.91 ± 0.53 (1.64–3.28)	>0.05
DF in normal range (%)	44.3 ± 21.6 (7.4–96.3)	60.0 ± 19.0 (10–96.3)	>0.05
Bradygastria (%)	25.6 ± 21.9 (3.7–77.8)	15.6 ± 11.8 (0–40.7)	>0.05
Tachygastria (%)	30.5 ± 19.8 (0–74.1)	19.4 ± 12.1 (0–44.4)	<0.05*
DFIC (%)	40.3 ± 20.3 (10–106)	32.3 ± 19.2 (4–93)	>0.05
DPIC (%)	98.5 ± 64.2 (43–278)	107.3 ± 38.4 (43–172)	>0.05
PR	1.9 ± 2.2 (0.4–8.8)	1.9 ± 1.3 (0.2–6.1)	>0.05

cpm = cycle per minute; DF = dominant electric frequency; DFIC = dominant frequency instability coefficient; DPIC = dominant power instability coefficient; PR = postprandial to fasting power ratio.

* Statistically significant by *t* test.

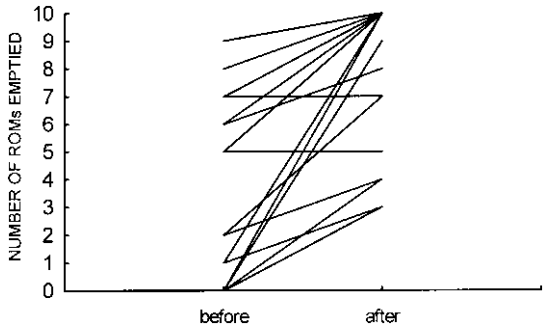

Fig. 1. Gastric emptying of radiopaque markers before and after an 8-week course of cisapride ($P < 0.01$). ROMs = radiopaque markers.

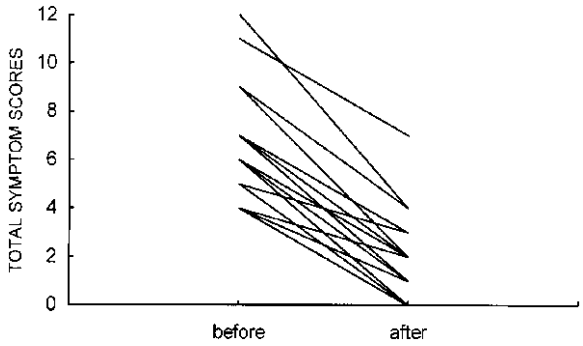

Fig. 2. Upper gastrointestinal symptom scores before and after an 8-week course of cisapride ($P < 0.01$).

Statistical analysis

The data were expressed as mean ± standard deviation. The differences in fasting and post-meal EGG variables, including DF, percentages of DF in the normal range, the bradygastric range, and the tachygastric range, DFIC, DPIC, and PR, before and after 8 weeks of cisapride treatment were evaluated by means of Student's *t* test. The correlation of between the improvement of EGG variables and the improvement of upper GI symptoms or gastric emptying of ROMs was evaluated by using the Yates correction of chi-square analysis. A *P* value < 0.05 was considered statistically significant.

RESULTS

The fasting blood sugar did not change significantly after an 8-week course of cisapride treatment (148.8 ± 37.8 versus 151.9 ± 38.8 mg/dl, $P > 0.05$). Among the fasting EGG variables there were no significant changes in the DF, percentages of DF in the bradygastric range, DFIC, or DPIC before and after 8 weeks of cisapride treatment (Table I). However, the percentages of DF in the normal range improved after an 8-week course of cisapride treatment ($46.0 \pm 24.0\%$ versus $66.0 \pm 23.9\%$ before versus after treatment, $P < 0.01$). The percentages of DF in the tachygastric range also improved significantly after cisapride treatment ($28.5 \pm 24.4\%$ versus $17.0 \pm 15.5\%$ before versus after treatment, $P < 0.05$). Furthermore, among the post-meal EGG variables there were no significant changes in DF, percentages of DF in the normal range or bradygastric range, DFIC, or DPIC before and after 8 weeks of cisapride treatment. However, percentages of DF in the tachygastric range improved after 8 weeks of cisapride treatment ($30.5 \pm 19.8\%$ versus 19.4 12.1% before versus after treatment, $P < 0.05$). PR did not change significantly after administration of cisapride (1.9 ± 2.2 versus 1.9 ± 1.3, $P > 0.05$).

All patients showed delayed gastric emptying of ROMs (mean, 3.3 ± 3.3; range, 0–9) emptied after 4.5 h before cisapride treatment. After 8 weeks of cisapride treatment the gastric emptying of ROMs increased significantly (mean, 6.35 ± 3.7; range, 0–10, before versus after treatment, $P < 0.01$) (Fig. 1). The upper GI symptoms score ranged from 4 to 12 (mean, 6.6 ± 2.2) before cisapride treatment and decreased significantly to 0–7 (mean, 1.9 ± 1.7 before versus after treatment, $P < 0.01$) after 8 weeks of cisapride treatment (Fig. 2). However, there was no correlation between the improvement of EGG variables and the improvement of upper GI symptoms or gastric emptying of ROMs ($P > 0.05$).

DISCUSSION

The results of this study showed that cisapride can improve both gastric dysrhythmia and gastric emptying of indigestible solids in type-II diabetic patients. Gastric emptying depends on the coordinated action of the proximal stomach, distal antrum, pylorus, and duodenum (4). The phasic contraction of the distal stomach is regulated by a rhythmic electric depolarization, known as the pacesetter potential or gastric slow wave, which is generated in the proximal gastric body. Under normal conditions the slow wave oscillates at 3 cpm. However, certain rhythm disturbances have been observed in clinical disease, such as an overly fast rhythm (tachygastria), overly slow rhythm (bradygastria), and irregular rhythm (arrhythmia) (16). Tachygastria and bradygastria are found in many patients with severe diabetes gastroparesis (4, 5). In this study the percentages of DF in the normal range before cisapride treatment were similar to the data for type-I diabetic patients (5).

By using hyperglycemic clamping in healthy volunteers, a plasma glucose threshold of approximately 175 mg/dl was noted to inhibit postprandial phasic antral motor activity (17). With an increase in plasma glucose level to 230 mg/dl, disruption of gastric slow-wave cycling was observed, with marked increases in both tachygastric and arrhythmic activities. The authors concluded that underlying neuropathy or myopathy is not necessary for impairment of gastric function in diabetic gastroparesis. However, in this study all patients showed evidence of autonomic neuropathy. Fasting blood sugar did not change significantly after 8 weeks of

cisapride treatment in our study. Therefore, the improvement in gastric dysrhythmia in patients with diabetic gastroparesis may be due to the direct effect of cisapride on gastric myoelectric activity rather than the effect of blood sugar.

It is possible that dysrhythmia is symptomatically important in diabetic gastroparesis because correction of the slow-wave disturbance, and not the gastric emptying defect, correlates best with reduction in nausea (5). In this study the fasting-state percentages of DF in the normal and tachygastric ranges improved significantly after an 8-week course of cisapride treatment. The post-meal percentages of DF in the tachygastric range also improved significantly after cisapride treatment. The upper GI symptoms score decreased significantly after administration of cisapride. These findings are in agreement with the results of Koch et al. (18) and Rothstein et al. (12).

EGG can detect changes in activity induced by consumption of a meal, with increased frequency power reflecting increased contractility of the stomach (15). The postprandial EGG amplitude is usually at least twice as high as the preprandial EGG amplitude. It is well established that the presence of a meal in the stomach produces both an increase in afferent and efferent vagal traffic between the central nervous system and the gastrointestinal system and an increase in gastric contractile activity and numerous other hormonal and neural changes (19). Evidence indicates that the postprandial EGG changes occur owing to neurohumoral mechanisms (20). Vagal blockade or vagotomy dampened the increase of EGG 3-cpm amplitude in dogs (19, 21) and in humans (22). Although there was some improvement in the EGG variables, in our study PR did not change significantly after 8 weeks of cisapride treatment.

The gastric clearance of ROMs is an indirect measure of gastric emptying, and emptying of ROMs usually starts late in the postprandial period (23). It has been hypothesized that the gastric clearance of ROMs reflects the onset of the interdigestive migrating motor complex (MMC). The stomach empties the three components of meals—liquids, digestible solids, and indigestible solids—at different rates and in different patterns (24). Larger objects seem to be consistently retained by the food-filled stomach until the next interdigestive MMC. Since phase-III MMCs sweep the fasting stomach in cycles every 100–120 min, measuring the time taken for the postprandial stomach to empty indigestible solid markers may reflect both the time of gastric emptying of the meal and the first interdigestive phase-III MMC. Therefore, abnormal gastric clearance of ROMs may be due to delayed gastric emptying of digestible solids and/or the absence, decreased frequency, or impaired efficacy of cyclical MMCs. Some diabetic patients have been observed to empty food at an abnormally slow rate (25) and/or to show diminished or absent MMCs in the antrum (26). Cisapride has been reported to be effective in patients with diabetic gastroparesis by improving solid and/or liquid emptying and ameliorating gastric dysrhythmia (12). In this study improved gastric emptying of indigestible solids was observed after an 8-week course of cisapride treatment. However, there was no correlation between the improvement in EGG variables and the improvement in upper GI symptoms or gastric emptying of ROMs. The correlation between the EGG and gastric emptying has not yet been clarified. Since gastric myoelectric activity is only one of the factors affecting gastric emptying, it may be no one-to-one correlation between the EGG and gastric emptying (18).

In conclusion, this study showed that cisapride can improve gastric dysrhythmia, both fasting and after a meal, in patients with diabetic gastroparesis. In addition, upper GI symptoms and gastric emptying of indigestible solids may show improvement after 8 weeks of cisapride treatment. These findings may support the effects of cisapride on diabetic patients with gastric bezoars.

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