Digestive Diseases and Sciences, Vol. 38, No. 8 (August 1993), pp. 1518–1524

Electrogastrography in Patients with Gastroparesis and Effect of Long-Term Cisapride

ROBIN D. ROTHSTEIN, MD, ABASS ALAVI, MD, and JAMES C. REYNOLDS, MD

Abnormalities in the gastric pacemaker potentials occur in patients with impaired gastric emptying. It is unclear if treatment effects the underlying rhythm or if normalization of dysrhythmias is important. We examined the effect of cisapride using surface electrogastrograms and radionuclide gastric emptying studies of patients with idiopathic and diabetic gastroparesis. Twelve of 14 patients had abnormal baseline electrogastrograms. After six months of cisapride, four patients had normalization of their electrical activity and six had improvement. Patients with idiopathic gastroparesis had an increase in gastric emptying at 120 min from 48.9 ± 3.8% (baseline) to 70.9 ± 6.0% (six months), P *= 0.009. Patients with diabetes mellitus had a similar improvement. Patients who had normalization of the electrogastrogram had a greater gastric emptying rate than patients with continued dysrhythmias. Thus, dysrhythmias are important in the etiology for gastroparesis, but other factors need to be examined.*

KEY WORDS: electrogastrography; gastroparesis; cisapride; myoelectric.

Gastroparesis is a common disorder of the gastrointestinal tract, resulting in significant morbidity. The underlying pathophysiology of delayed gastric emptying remains poorly understood, but disturbances in the normal slow-wave rhythm and rate have been observed (1). Surface recording of the myoelectrical activity of the stomach has been demonstrated to correlate with serosal electrodes and potentially may provide insight into the understanding of the mechanisms of dysrhythmias. Electrogastrography may therefore be a useful technique for the evaluation of gastroparesis and may help to establish whether pharmacologic intervention has an effect on gastric arrhythmias.

Treatment of gastric dysmotility disorders is difficult, and currently available medications may not offer substantial relief of symptoms. In addition, the effect of prokinetic agents on gastric dysrhythmias has not been well established. Domperidone has been shown to normalize dysrhythmias in patients with diabetic gastroparesis (2). Cisapride accelerates gastric emptying in patients with gastroparesis, possibly by enhanced acetylcholine release from the myenteric plexus (3–5). It is unclear what effect cisapride has on dysrhythmias in patients with gastroparesis.

The aims of this present study were to evaluate the myoelectrical activity in patients with diabetic and idiopathic gastroparesis by electrogastrography

Manuscript received January 20, 1992; revised manuscript received February 22, 1993; accepted February 25, 1993.

From the Departments of Medicine and Radiology, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

Dr. Reynolds current address is: Division of Gastroenterology and Hepatology, University of Pittsburgh Medical Center, M2, Desoto at O'Hara Streets, Pittsburgh, Pennsylvania 15213.

This work was in part supported by the Measey Foundation, by NIH grant R01-DK389641-01 A1, and by the Janssen Research Foundation.

Address for reprint requests: Dr. Robin D. Rothstein, Department of Gastroenterology, 3 Dulles, Hospital of the University of Pennsylvania, 3400 Spruce St., Philadelphia, Pennsylvania 19104.

and to determine if cisapride effects the rate or rhythm of the electrical signal.

MATERIALS AND METHODS

Patients. Fourteen patients with diabetic or idiopathic gastroparesis as determined by a delay in gastric emptying during solid-phase radionuclide gastric emptying studies were included in this study. All patients had a minimum of six months of symptoms of decreased gastric emptying, including anorexia, early satiety, nausea, vomiting, abdominal pain, or bloating. Patients enrolled had previously failed to respond to metoclopramide therapy or had experienced a side effect from the medication.

These patients represent the first 14 patients enrolled in a long-term trial of cisapride therapy. Mechanical and inflammatory causes of delayed emptying were ruled out by endoscopy. All patients had normal electrolytes, thyroid function tests, and calcium levels. Patients with idiopathic gastroparesis had normal serum glucose levels, in contrast to patients with diabetes who had mild elevations of the serum glucoses (<200 mg/dl). In patients with diabetes mellitus, HbA1c levels were obtained at baseline and at the completion of the study. Patients with eating disorders, collagen vascular diseases, renal disease, malignancies, or prior gastric surgery were excluded.

Patients received 10 mg of cisapride three times daily for six months. If a clinical response did not ensue or if deterioration occurred, the dose of cisapride was increased to 20 mg three times daily after one month of therapy.

Measurement of Gastric Emptying. Solid-phase gastric emptying studies were performed prior to entry into the study and after six months on cisapride as previously described (6). After an overnight 12-hr fast, patients ingested a solid meal containing 300 μCi of technetium-99-sulfur colloid-tagged egg whites cooked in butter and served with bread (150 cal, 40% carbohydrate, 40% protein, 20% fat). The patients then were positioned in front of a large-field gamma camera (GE 2000 Starcam, General Electric, Milwaukee, Wisconsin). Anterior and posterior images were obtained every minute for at least 2 hr after ingestion of the meal. Data were stored on an on-line computer for subsequent analysis.

The area of the stomach was outlined as the region of interest on each scan. Counts for each frame within the area of interest were determined and corrected for attenuation (by obtaining the geometric means of anterior and posterior image counts) and for radioactive decay. The data are expressed as the percentage of radioactivity remaining in the stomach at a given time compared to time zero. The $T_{1/2}$ emptying was not used as some patients did not achieve 50% emptying within 2 hr. Gastroparesis was defined as retention of activity greater than 28% at 2 hr. This value was based on previously determined gastric emptying in normal, healthy controls in the Nuclear Medicine Department at the University of Pennsylvania (6).

Electrogastrography. Four standard silver–silver chloride electrodes (ResTest Pregelled electrodes, NDM Corp., Dayton, Ohio) were placed on the upper abdominal wall over the region of the stomach (two in a transverse line halfway between the umbilicus and the lower end of the sternum and two additional in a vertical line 2 and 6 cm below the lower sternum), and two electrodes were placed on the right forearm as grounds. The output was then connected to a chart recorder (Beckman Dynograph R711, Sensormedics, Yorba Linda, California) for subsequent analysis. To reduce electric signals from the heart, only activity between 0.5 cpm and 10 cpm were examined using nystagmus couplers.

Studies were performed after an overnight fast before entry into the study and after six months on cisapride. A 20-min baseline recording was obtained. Recordings were continued for 1 hr following a meal of eggs with bread and butter (150 calories, 40% protein, 40% carbohydrate, 20% fat).

The electrogastrogram rhythm was determined by visual inspection of the raw signal. Normal electrical activity was defined as 3-cpm activity occurring. Tachygastria was defined by the presence of ≥4 cpm and bradygastria by 1- to 2-cpm activity (2). Postprandial recordings were used only for analysis, as the amplitude of the signal was much greater than the preprandial recordings. Electrogastrograms were read in a blinded fashion, without knowledge of whether the tracing represented a baseline or follow-up study.

Symptom Evaluation. Clinical response was determined by symptom assessment (nausea, vomiting, anorexia, bloating, early satiety, and abdominal pain) before and after six months of open-label cisapride therapy. The severity of symptoms was graded from 0 (none) to 10 (most severe). The final score represents the addition of the individual scores with total possible score of 60.

Compliance was assessed by counting the number of tablets returned at the end of the study.

Statistical Analysis. All statistical analysis was performed using the Student's paired *t* test, the Wilcoxon signed-rank test, or the Kendall correlation test when appropriate. Data are expressed as mean values ± SEM. Probability values at the 0.05 level or less were considered statistical significance.

This study was approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania. All patients gave written and informed consent prior to entry into the study.

RESULTS

Description of Study Subjects. Fourteen patients with gastroparesis were entered and completed the study. One patient with diabetic gastroparesis did not have a six-month follow-up electrogastrogram. Seven patients had insulin-dependent diabetes (mean age, 40 ± 6 years), and seven had no other known significant medical problems (mean age, 37 ± 6 years). There was no statistical difference in the HbA1c levels (6.6 ± 1.2 mg/dl at baseline and 7.0 ± 0.5 mg/dl at six months). Three of the 14 patients with idiopathic gastroparesis and six of the seven patients with diabetes mellitus required 60 mg of

cisapride daily for relief of symptoms. The remaining patients had significant symptomatic improvement on 30 mg of cisapride daily.

Compliance was considered good, with less than 10% of the medication returned in all subjects.

Baseline Electrogastrograms. Baseline electrogastrograms were abnormal in 12 of the 14 patients. Two patients (one with idiopathic gastroparesis and one with diabetic gastroparesis) had normal electrogastrograms at baseline. Five patients had tachygastria, including three patients with idiopathic gastroparesis and two patients with diabetes mellitus. Seven patients had bradygastria during their baseline examinations, including three patients with idiopathic disease and four with diabetes mellitus.

Baseline Gastric Emptying. Baseline gastric emptying was similarly delayed in both the diabetic and the idiopathic groups of patients. There was no difference between the two groups in the percentage of gastric emptying at any time after meal ingestion. There was no difference between the gastric emptying results of the two patients with normal electrogastrograms and those with baseline abnormal electrogastrograms.

Baseline Symptoms. Patients with diabetic and idiopathic gastroparesis had similar degrees of severity of symptoms (16.7 ± 2.3 vs 20.8 ± 2.1).

Electrogastrograms Following Six Months of Treatment with Cisapride. One patient with a normal baseline electrogastrogram had an unchanged rate at six months. A second patient with a normal baseline electrogastrogram developed bradygastria at six months despite therapy. A third patient with baseline tachygastria had persistence of the rapid rate at six months (Table 1).

After six months of cisapride therapy, four patients with abnormal baseline patterns developed normal 3-cpm activity (Figures 1–3). Two of these patients had baseline tachygastria and two had bradygastria. At six months, the five patients with normal electrogastrograms included four patients with idiopathic gastroparesis and one with diabetic gastroparesis.

Six patients had incomplete normalization of the electrical signal (decrease in the duration of the arrhythmia) on the follow-up electrogastrogram. At baseline, two patients had tachygastria and four had bradygastria. At six months, the abnormal rhythm persisted, but there was 3-cpm activity for 40–80% of the period studied.

There was no follow-up electrogastrogram in one patient with diabetes mellitus who had bradygastria at baseline.

TABLE 1. ELECTROGASTROGRAMS AT BASELINE AND AT SIX MONTHS

Patient and type of gastroparesis	*Electrogastrogram*	
	Baseline	*Six months*
1. Idiopathic	Tachygastria	Improved
2. Idiopathic	Bradygastria	Improved
3. Idiopathic	Normal	Normal
4. Idiopathic	Bradygastria	Normal
5. Idiopathic	Bradygastria	Normal
6. Idiopathic	Tachygastria	Normal
7. Idiopathic	Tachygastria	Improved
8. Diabetes	Bradygastria	Improved
9. Diabetes	Tachygastria	Normal
10. Diabetes	Bradygastria	Improved
11. Diabetes	Bradygastria	Improved
12. Diabetes	Tachygastria	Tachygastria
13. Diabetes	Bradygastria	No follow-up
14. Diabetes	Normal	Bradygastria

Gastric Emptying Following Six Months of Treatment with Cisapride. Gastric emptying significantly improved after six months of cisapride in both groups of patients at all time intervals measured except for the initial 15 min after meal ingestion. The percentage of gastric emptying in patients with idiopathic gastroparesis at 60 min increased after six months from 21.0 ± 3.8% to 42.8 ± 5.4%, P = 0.006, and at 120 min from 48.9 ± 3.8% to 70.9 ± 6.0%, P = 0.009. Patients with diabetes mellitus demonstrated an increase in the percentage of gastric emptying at 60 min from 15.4 ± 4.6 to 33.7 ±

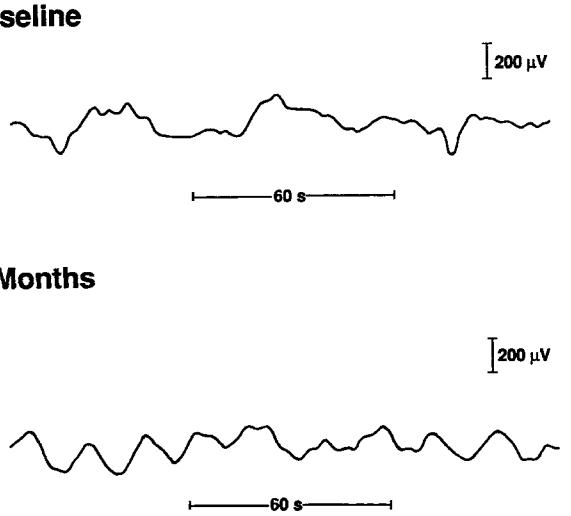

Fig 1. This is a representative section of a baseline and six-month electrogastrogram. This patient at baseline had 1–2 slow waves per minute. At six months, there was an increase towards normal in the rate of myoelectrical activity.

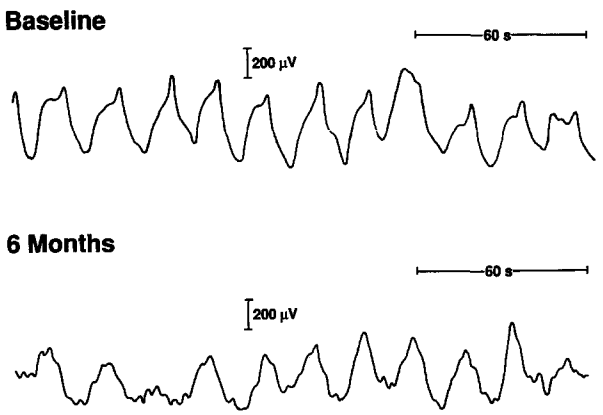

Fig 2. This patient had tachygastria at baseline with a very rapid rate of 7–8 cpm. The slow-wave activity at six months had decreased to normal.

7.3, $P = 0.031$, and at 120 min from 40.4 ± 6.9 to 65.6 ± 7.3, $P = 0.029$ (Figure 4). There was no significant difference in the emptying results between patients with idiopathic and diabetic gastroparesis.

Relationship Between Electrogastrography and Emptying. The baseline 2-hr gastric emptying was similar between the group of patients with subsequent normal electrogastrograms at six months and patients who continued to have abnormal electrogastrograms at six months. However, at six months, the five patients that had normal 3-cpm activity had a greater percent emptying at 60 min (50.7 ± 4.9% vs 31.3 ± 5.6%, $P = 0.037$) and a significantly greater rate of emptying at 120 min (82.0 ± 5.2% vs 60.6 ± 5.0%, $P = 0.017$) than patients whose electrogastrograms did not normalize.

Correlation Between Symptoms and Electrogastrography and Gastric Emptying. There was improvement in the overall symptom scores after six months of cisapride in both the idiopathic and diabetic groups of patients. For all patients, the initial symptom score was 18.9 ± 2.4 and decreased to 10.9 ± 3.1, $P = 0.045$ after six months of cisapride (Figure 5).

The severity of symptoms and percentage of gastric emptying did not correlate at baseline or at six months. There was also no relationship between electrogastrogram results and symptom scores. Patients with normal electrogastrograms did not have less severe symptoms than patients with abnormal electrogastrograms at six months.

The patient with persistent tachygastria at baseline and at six months became asymptomatic and demonstrated significant improvement in the percent of gastric emptying (2-hr emptying increased from 20% at baseline to 67% at six months). Despite deterioration of the myoelectrical rhythm from a normal 3-cpm rhythm to bradygastria in one patient, the 2-hr gastric emptying rate at six months had improved (25% to 84% at six months). Interest-

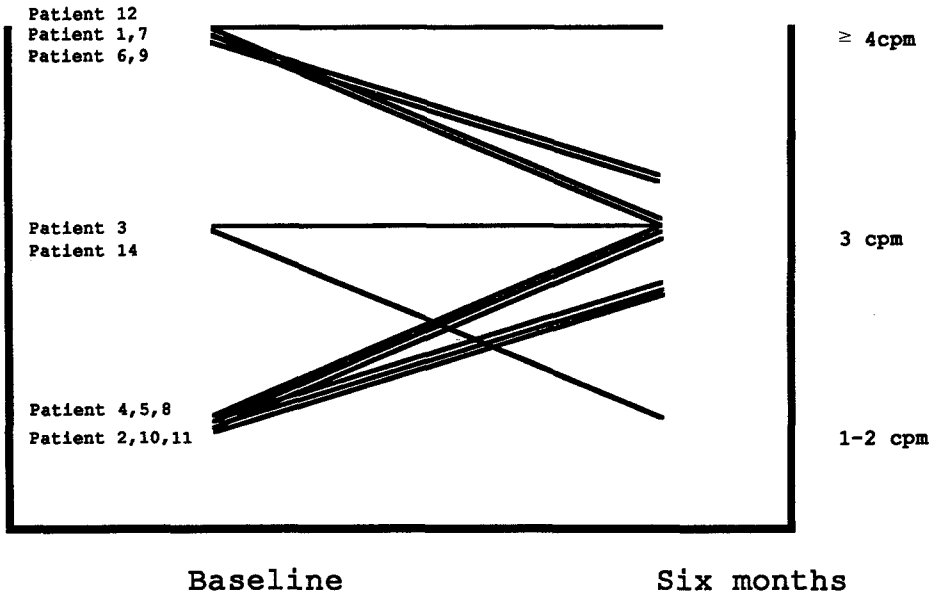

Fig 3. The number of cycles per minute on the electrogastrogram are represented before and after six months of cisapride.

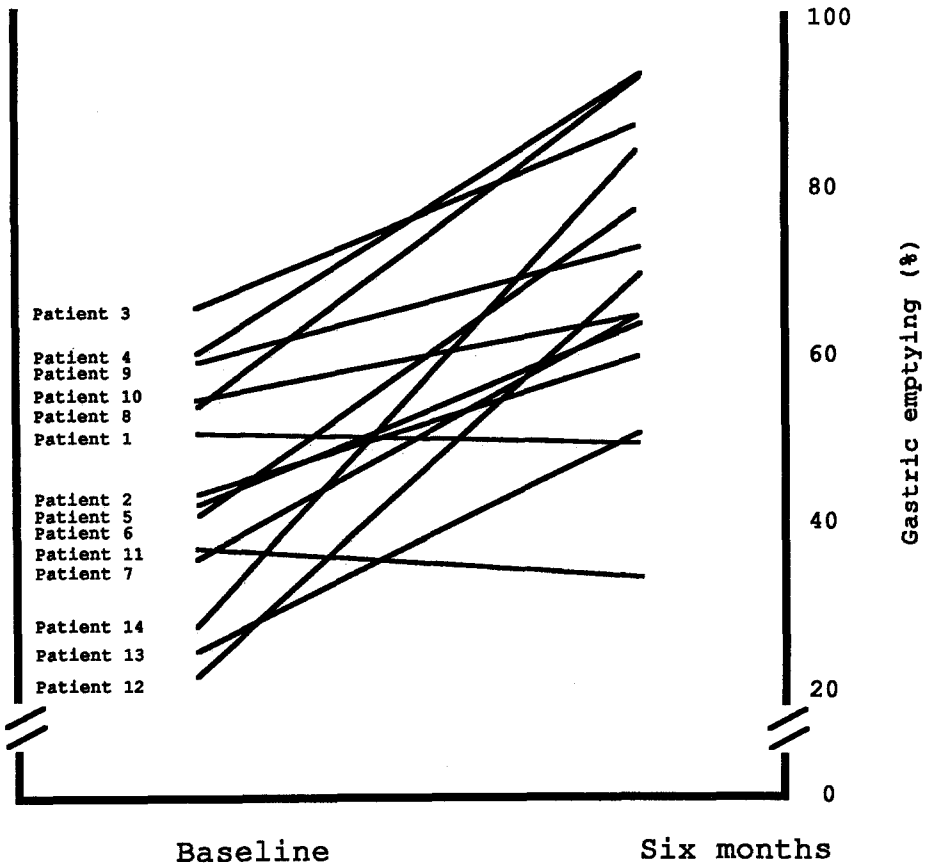

Fig 4. There was an overall increase in the percent of gastric emptying at 2 hr over six months.

ingly, however, the patient did not have any significant change in symptoms.

DISCUSSION

Gastroparesis remains a poorly understood entity. The surface electrogastrogram, which correlates well with mucosal electrodes, permits evaluation of the myoelectrical signal of the stomach, which may provide further insight into the pathophysiology of gastroparesis (7–12).

Disturbances in gastric pacemaker potentials have been described in patients with gastroparesis (1, 13–15). In our study, we noted the presence of myoelectrical abnormalities, including bradygastrias and tachygastrias in both patients with idiopathic and diabetic etiologies for their gastroparesis. The finding of both these rhythms in both groups of patients suggests potential similarity in the pathogenesis of the gastroparesis in both groups of patients. In addition, symptom scores and pharmacologic responses to cisapride were similar in both groups, further supporting a common underlying pathophysiology.

Despite these similarities, distinctions between these groups do exist. Electromyographic rhythm differences at baseline suggest considerable heterogeneity within both groups of patients. In addition, patients with idiopathic gastroparesis were more likely to have normalization of their electrogastrograms at six months.

Although gastric scintigraphy is helpful in the evaluation of patients with gastroparesis, it is not helpful in determining the etiology for delayed gastric emptying. The electrogastrogram provides an alternative methodology for examining patients with delayed gastric emptying and may help in our understanding of the pathophysiology of gastroparesis. The appearance of normal baseline electrogastrograms in two symptomatic patients with gastroparesis, however, and the lack of correlation between symptoms and electrogastrograms also suggest that additional mechanisms are important.

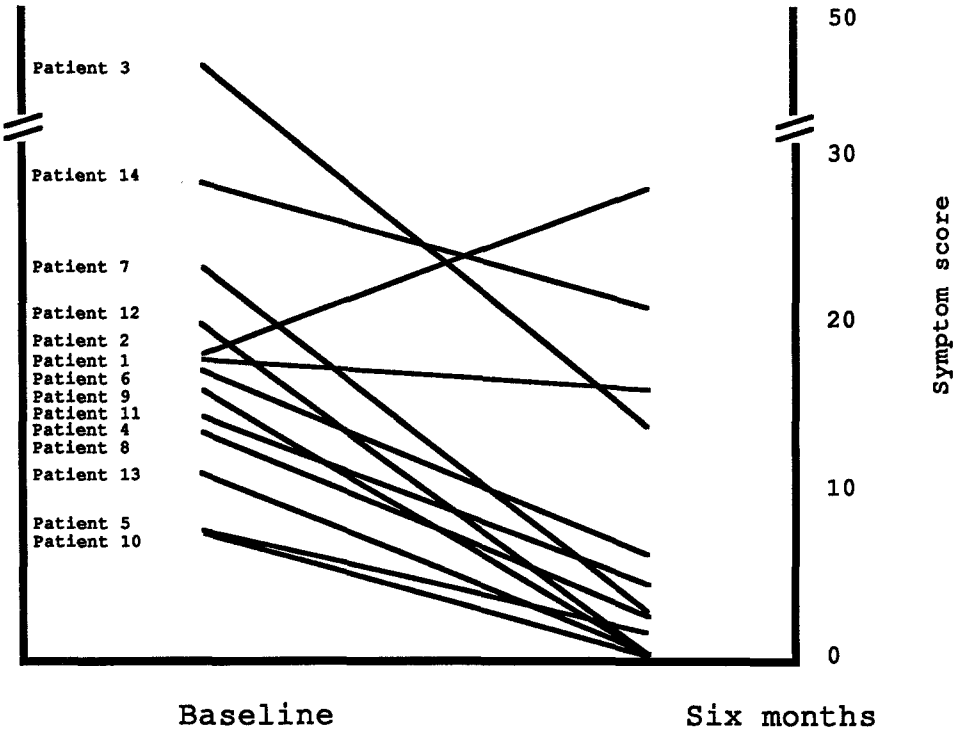

Fig 5. There was a decrease in symptom scores over six months.

Other factors that may lead to gastroparesis in patients with normal myoelectrical signals include smooth muscle dysfunction, a dissociation between the electrical signal and muscle response, pylorospasm, or incoordination of the antrum and duodenum. Patients with symptoms of gastroparesis, therefore, reflect a heterogeneous population.

In our study, we found that patients with either idiopathic or diabetic gastroparesis had a sustained beneficial effect from cisapride on the rate of emptying of solid foods from the stomach and on symptoms over the six months of open-label trial. Cisapride has been previously shown to be efficacious in the short-term treatment of patients with diabetic and idiopathic gastroparesis (16, 17). Cisapride improves both liquid and solid emptying in patients with idiopathic gastroparesis and acutely improves gastric emptying of indigestible solids in patients with diabetic gastroparesis (3, 18). Four weeks of therapy with cisapride accelerated both solid and liquid emptying in patients with insulin-dependent diabetes mellitus (5). Further confirmation of our observations will require blinded prospective protocols.

There is limited information in the long-term effect of prokinetic medications on gastric arrhythmias. Koch et al. (2) demonstrated baseline abnormalities in myoelectrical activity in six insulin-dependent diabetic patients. Six months of therapy with domperidone led to normalization of all electrogastrogram patterns to 3 cpm despite a lack of significant improvement in gastric emptying (2). In our study, 10 of 12 patients with baseline abnormal electrogastrograms had improvement in the electrical activity of the stomach.

In the present study, patients had improvement in their symptom scores. Without a placebo group, however, we cannot eliminate the possibility of spontaneous improvement in some patients, especially in those patients with idiopathic gastroparesis. Geldof et al noted that after one year, one third of patients with chronic, unexplained nausea and vomiting became asymptomatic without treatment (1).

In prior studies (19), a dichotomy between gastric emptying and symptoms has been noted. The present data not only support this previous finding but also demonstrate a similar discrepancy between electrogastrograms and symptoms. It is intriguing and puzzling why there is a lack of consistency between severity of symptoms and objective evidence of gastroparesis.

These data suggest that gastroparesis is a complex disorder with multiple factors important in the

underlying pathophysiology. In some patients, electrical disturbances may explain the delay in gastric emptying. While gastric myoelectrical activity is important, other, as yet undetermined, factors are involved in the pathophysiology of gastric emptying abnormalities.

ACKNOWLEDGMENTS

The authors thank Greg Zangari and Michelle Sample for their assistance in this work.

REFERENCES

1. Geldof M, Van Der Schee EJ, Van Blankenstein M, Grashuis JL: Electrogastrographic study of gastric myoelectrical activity in patients with unexplained nausea and vomiting. Gut 27:799–808, 1986
2. Koch KL, Stern RM, Stewart WR, Vasey MW: Gastric emptying and gastric myoelectrical activity in patients with diabetic gastroparesis: Effect of long-term domperidone treatment. Am J Gastroenterol 84:1069, 1989
3. Jian R, Ducrot F, Piedeloup C, Mary JY, Najean Y, Bernier JJ: Measurement of gastric emptying in dyspeptic patients: Effect of a new gastrokinetic agent (cisapride). Gut 26:352–358, 1985
4. McCallum RW: Cisapride: A new class of prokinetic agent. Am J Gastroenterol 86:135, 1991
5. Horowitz M, Maddox A, Harding PE, Maddern GJ, Chatterton BE, Wishart J, Shearman DJC: Effect of cisapride on gastric and esophageal emptying in insulin-dependent diabetes mellitus. Gastroenterology 92:1899–1907, 1987
6. Velchik MG, Reynolds JC, Alavi A: The effect of meal energy content on gastric emptying. J Nucl Med 30:1106, 1989
7. Hamilton JW, Bellahsene BE, Reichelderfer M, Webster JG, Bass P: Human electrogastrograms: Comparison of surface and mucosal recordings. Dig Dis Sci 31:33–39, 1986
8. Smout AJPM, van der Schee EJ, Grashius JL: What is measured in electrogastrography? Dig Dis Sci 25:179–186, 1980
9. Stern RM, Koch KL, Stewart WR, Vasey MW: Electrogastrography: Current issues in validation and methodology. Psychophysiology 24:55–64, 1987
10. Kim CH, Zinsmeister AR, Malagelada JR: Mechanisms of canine gastric dysrhythmia. Gastroenterology 92:993–999, 1987
11. Kim CH, Azpiroz F, Malagelada JR: Characteristics of spontaneous and drug induced gastric dysrhythmias in a chronic canine model. Gastroenterology 90:421–427, 1987
12. You CH, Lee KY, Chey WY, Menguy R: Electrogastrographic study of patients with unexplained nausea, bloating, and vomiting. Gastroenterology 9:311–314, 1980
13. You CH, Chey WY, Lee KY, Menguy R, Bortoff A: Gastric and small intestinal myoelectrical dysrhythmia associated with chronic intractable nausea and vomiting. Ann Intern Med 95:449–451, 1981
14. Abell TL, Camilleri M, Malagelada JR: High prevalence of gastric electrical dysrhythmias in diabetic gastroparesis. Gastroenterology 88:1300, 1985 (abstract)
15. Telander RL, Morgan KG, Kreulen DL, Schmalz PF, Kelly KA, Szurszewski J: Human gastric atony with gastric atony and tachygastria and gastric retention. Gastroenterology 75:497–501, 1978
16. Camilleri M, Malagelada JR, Abell TL, Brown ML, Hench V, Zinsmeister AR: Effect of six weeks of treatment with cisapride in gastroparesis and intestinal pseudoobstruction. Gastroenterology 96:704, 1989
17. Havelund T, Øster-Jørgensen E, Eshøj O, Larsen ML, Lauritsen K. Effects of cisapride on gastroparesis in patients with insulin-dependent diabetes mellitus. Acta Med Scand 222:339, 1987
18. Feldman M, Smith HJ: Effect of cisapride on gastric emptying of indigestible solids in patients with gastroparesis diabeticorum. Gastroenterology 92:171, 1987
19. Snape WJ, Battle WM, Schwartz SS, Braunstein SN, Goldstein HA, Alavi A: Metoclopramide to treat gastroparesis due to diabetes mellitus. Ann Intern Med 96:444, 1982