Digestive Diseases and Sciences, Vol. 37, No. 7 (July 1992), pp. 1136–1140

CASE REPORT

Reversal of Gastric Electrical Dysrhythmias by Cisapride in Children with Functional Dyspepsia

Report of Three Cases

SALVATORE CUCCHIARA, MD, RAFFAELE MINELLA, MD, GIUSEPPE RIEZZO, MD, GIANFRANCO VALLONE, MD, PAOLO VALLONE, MD, FRANCESCO CASTELLONE, MD, and SALVATORE AURICCHIO, PhD

KEY WORDS: dysrhythmias; functional dyspepsia; gastric emptying; prokinetic drugs.

Functional or nonulcer dyspepsia (NUD) is an ill-defined condition characterized by the presence of chronic intermittent symptoms of epigastric pain and fullness, early satiety, nausea and/or vomiting, without mucosal lesions and structural abnormalities of gastrointestinal tract (1, 2). Recently, a growing number of studies in adults as well as in pediatric patients have indicated that functional dyspepsia might be due to disordered gastrointestinal motility (3–6); furthermore, the fact that prokinetic drugs seem to have a beneficial effect in at least some NUD patients, strengthens the hypothesis of a primary gut motor disorder in functional dyspepsia.

We report here the cases of three children with unexplained upper gastrointestinal symptoms, in whom diagnostic work-up revealed presence of gastric electrical abnormalities. The effects of prokinetic therapy on clinical symptoms and gastric electrical activity are discussed.

CASE REPORTS

Case 1. A 7.6-year-old girl was admitted to our Unit with a six-month history of recurrent postprandial vomiting. Vomiting was very common in the late postprandial period and not infrequently was preceded by a feeling of fullness and an inability to finish a normal meal. Episodes of burping and belching were also present. Dyspeptic symptoms occurred two times a week on average and were usually present for a whole day. On admission weight was 22.000 kg (25th–50th percentile), height was 123 cm (50th percentile). The rest of the physical examination was unremarkable.

Case 2. A 5-year-old boy had a 10-month history of epigastric pain and postprandial vomiting occurring characteristically in the late postprandial period. Symptoms recurred one to two times a week on average. The patient had also anorexia, irritability, early satiety, and epigastric pain. No abdominal distension was reported. Physical examination revealed an apparently healthy boy. His weight and height were at the 50th and 75th percentile for age, respectively. The abdominal examination was negative.

Case 3. An 8-year-old boy was referred to our unit with a history of recurrent epigastric pain and vomiting. These episodes started 12 months prior to the visit in our unit and recurred every one to two weeks. Abdominal pain was relieved by vomiting. He had been suffering also from nausea, occasional episodes of regurgitation, and loss of appetite. During the four weeks prior to admission, he had had a 2-kg weight loss. There was no history of abdominal distension or bilious vomiting. The patient's weight was at the 25th percentile and the height was at the 75th percentile; the weight–height ratio was at the 10th percentile. Physical examination was unremarkable.

In all three patients laboratory studies did not reveal signs of malnutrition or inflammation and upper gastrointestinal x-ray examination with barium was negative for mucosal pattern and transit; furthermore, in all of them endoscopy excluded focal mucosal lesions of the esophagus, stomach, and duodenum, as well as *Helicobacter pylori* infection. In the first patient, 24-hr intraesophageal pH monitoring showed an abnormal esophageal acid

Manuscript received April 8, 1991; revised manuscript received October 23, 1991; accepted November 12, 1991.

From the Department of Pediatrics and **Institute Radiologic Sciences, 2nd School of Medicine, University of Naples, *Scientific Institute of Gastroenterology of Castellana Grotte, Bari, Italy.

Address for reprint requests: Dr. Salvatore Cucchiara, Dipartimento di Pediatria, II Facoltà di Medicina, Via S. Pansini 5, 80131 Naples, Italy.

0163-2116/92/0700-1136$06.50/0

exposure (percentage of reflux: 8.5); the latter was normal in the other two cases; normal values of prolonged intraesophageal pH test have been published elsewhere (7). Gastric emptying time was determined in the three patients by ultrasonography, according to the method of Bolondi et al (8), by measuring the cross-sectional area of the antrum at a level corresponding to the scanning plane passing through the superior mesenteric vein. The patients were examined after an 8-hr fast in an upright supine position using a high-resolution machine. Following the baseline scan, a standard mixed solid–liquid meal test consisting of bread, ham, butter, and fruit juice (300 calories) was given over a period of 10–15 min. Gastric emptying time (minutes) was prolonged in all subjects (case 1: 205; case 2: 240; case 3: 210; upper normal value for children in the range age of 6–12 years: 150 min).

The three patients underwent recording of electrical activity of the stomach by surface silver–silver chloride electrodes (Red Dot 2256, 3M Co.) attached to the skin of the epigastric region over the antrum and connected to a rectilinear recorder (R611, Sensormedics) through nystagmus couplers (N. 9859, Sensormedics), with lower and upper cutoff frequencies of 0.16 and 30 Hz, respectively, and a time constant of 10 msec. This recording technique is defined as electrogastrography (EGG). Because of interindividual anatomical variations, we used various recording leads and the lead with the best signal-to-noise ratio was chosen for analysis. The EGG signals were digitized and transmitted to an IBM PC for fast Fourier transform (FFT) analysis to obtain power spectra of the time signals. Spectra were obtained as follows: every 64 sec a power spectrum was computed from the preceding 256 sec of the electrogastrographic time signal, to which a Hamming window had been applied to reduce leakage (9). This procedure generates a series of overlapping spectra graphed as running spectra and makes both frequency and time analysis possible (10). Normal gastric electrical signals in man occur approximately every 20 sec, three times a minute, equivalent to 0.05 Hz. Recordings were carried out for 1 hr during fasting and for 1 hr after feeding the same meal given during gastric ultrasonography. The EGG tracings were compared with those from age-matched controls previously described (11), in whom episodes of electrical dysrhythmias were recorded for no more than 10% of both fasting and fed recording sessions (Figure 1). Electrical dysrhythmias were defined as episodes with a frequency between 4 and 9 cycles per minute (cpm) with regular rhythm (tachygastria), or below 3 cpm (bradygastria), or between 4 and 9 cpm with irregular rhythm (tachyarrhythmia), lasting for at least 1 min, or as a flatline pattern (12). Analysis of the EGG recordings in our patients revealed significant changes of fasting and/or fed electrical activity, such as flatline pattern and bradygastria (Figure 2), tachygastria (Figure 3), or a variety of peaks ranging from 1–2 cpm to 5 cpm with periods of absence of 3 cpm activity (Figure 4). In case 1 bradygastria was associated with nausea and epigastric distress.

The three patients were treated with oral cisapride (syrup, 0.6 mg/kg/day, three times a day) for eight weeks. A clinical assessment performed after four weeks of therapy showed a significant symptomatic improvement,

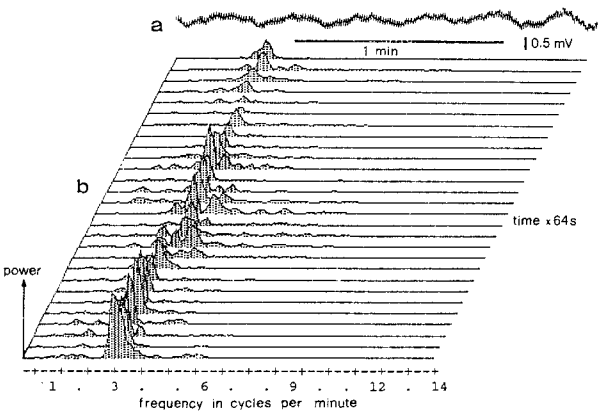

Fig 1. Example of EGG tracing (a) and running spectral analysis (b) from a fasting control child. A regular 3 cpm activity is seen. The spectral analysis shows approximately 30 min of EGG data. The running spectral analysis represents consecutive segments of EGG data, of which each is overlapped with the preceding segment. Thus, each line represents 64 sec of new data added to the previous 192 sec of EGG data for a total of 256 sec of EGG data per line.

that was just evident by the second week of therapy in the case 1 and by the third week of therapy in the cases 2 and 3. At the end of the treatment period, patients were asymptomatic and gastric emptying time (minutes) decreased significantly (case 1: 150; case 2: 135; case 3: 150); furthermore, the 24-hr intraesophageal pH monitoring revealed the absence of pathologic gastroesophageal reflux in the first patient. In all patients the EGG showed normal fasting and fed gastric electrical frequency (Figure 5). Both EGG and gastric emptying time measurement were repeated while the patients were still taking cisapride. The patients were essentially asymptomatic and taken off prokinetic therapy at a six-month clinical follow-up.

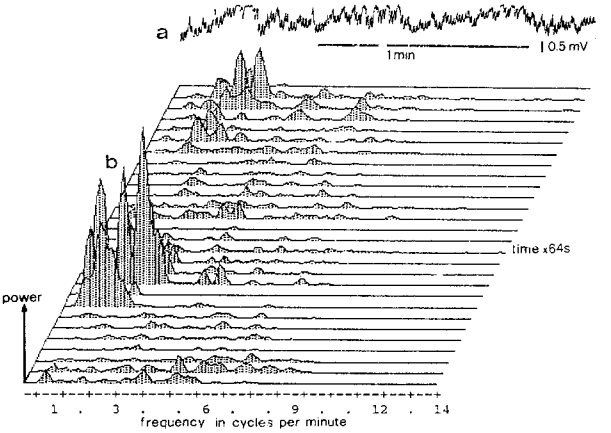

Fig 2. Case 1; recording in the fasting state. The EGG tracing (a) shows 1–2 cpm waves. The spectral analysis (b) shows the absence of 3 cpm activity and 1–2 cpm peaks.

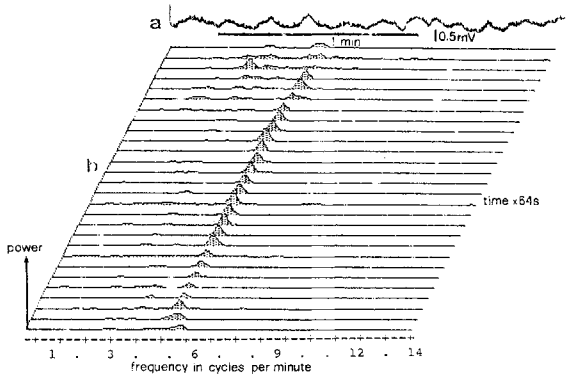

Fig 3. Case 2; recording in the fasting state. The EGG tracing (a) shows a tachygastria pattern at approximately 5 cpm. The spectral analysis (b) shows that a clear peak at 5 cpm predominates.

DISCUSSION

A large proportion of patients are referred to pediatric gastroenterologists with nonspecific recurrent functional gastrointestinal symptoms such as vomiting, anorexia, abdominal pain, nausea, and early satiety, in the absence of structural disorders or focal mucosal lesions of gastrointestinal tract. Routine diagnostic tests commonly fail to reveal significant abnormalities in these subjects. Several motor abnormalities of the stomach and proximal portions of the small intestine have been identified in pediatric and adult patients with chronic functional gastrointestinal disease (4–6, 13). They include decreased antral and/or antroduodenal contractile response to the ingestion of a meal and uncoordinated and/or nonpropagated duodenojejunal motor waves. These motor irregularities are often associated with delay in gastric emptying (14).

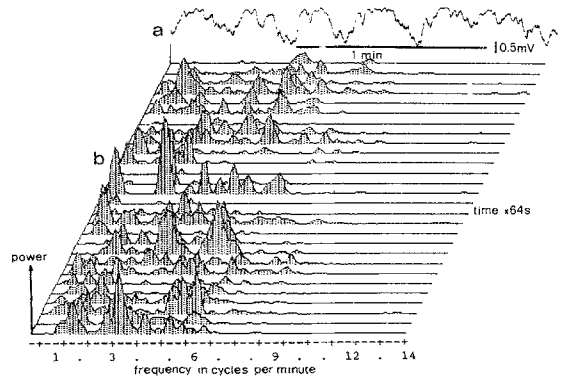

Fig 4. Case 3; recording in the fed period. The EGG tracing (a) shows waves ranging from 1.5 to 6 cpm. The running spectral analysis (b) shows a variety of peaks ranging from 1–2 to 6 cpm.

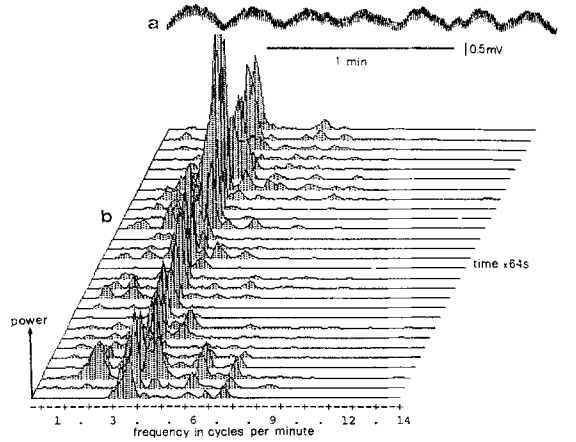

Fig 5. Case 1. Example of posttreatment EGG tracing (a) and spectral analysis (b) in the fasting state. Regular slow waves and a clear peak at 3 cpm are seen.

A potential role for gastric electrical abnormalities in patients with functional gastrointestinal symptoms is currently under investigation (15). The electrical activity of the stomach consists of cyclic depolarization of the membrane potential of smooth muscle cells, called slow waves or electrical control activity. Slow waves emanate from a pacemaker area located along the greater curvature and propagate in an aboral direction toward the pylorus, at a frequency of 3 cpm in man. They are not associated with gastric mechanical activity but are believed to set motor contractions spatially and temporally (16). When slow waves show an increase in plateau depolarization with superimposed electrical spikes, the stomach exhibits motor contractions that are involved in mechanical trituration and propulsion of ingested food (16).

There is some suggestion that gastric dysrhythmias can impair gastric motility either by inhibiting the strength of antral contractions or by destroying the aboral propagation of electrical potential and peristalsis (17); therefore, normal gastric propulsion is impaired, and gastric stasis, distension, and nausea can ensue.

We recorded the electrical activity of the stomachs in our patients by means of surface electrodes attached to the abdominal skin. This noninvasive method, known as electrogastrography, has been shown to be as reliable as intraluminal recording of myoelectrical activity (18).

Myoelectrical abnormalities of the stomach have been described in patients with functional dyspepsia (19, 20); furthermore, they have been detected following intravenous administration of drugs such

as epinephrine, met-enkephaline, PGE_2, and glucagon (21–23). There is also experimental evidence that smooth muscle cells of the stomach can exhibit an abnormal slow-wave frequency after inhibition of cholinergic activity (24).

It is commonly believed that the gastric threshold to dyshythmias is increased after ingestion of food: this is probably due to the effect of postprandial mechanical and neurohormonal changes on gastric smooth muscle (25). However, gastric dysrhythmias including tachygastria, bradygastria, and flatline patterns were detected in our patients during fasting as well as postprandially. Moreover, normalization of both myoelectrical activity and gastric emptying time was achieved after a therapeutic course of cisapride, a prokinetic drug known to enhance cholinergic transmission from the myenteric plexus to the smooth muscle cells (26).

Our observations suggest that gastric stasis, which is common in patients with symptoms of functional gastrointestinal disease, could be due to development of gastric electrical dysrhythmias and that prokinetic drugs such as cisapride can be effective in these patients through reestablishing a normal gastric electrical rhythm. In a recent study, domperidone, a peripheral antidopaminergic agent, has been shown to be effective in normalizing both gastric electrical rhythm and symptoms in adults with diabetic gastroparesis (27). Since gastric emptying time was unchanged, the authors concluded that mechanisms other than gastric dysrhythmias could be involved in the occurrence of gastroparesis in their patients.

SUMMARY

Three children (ages 5, 7.6, and 8 years), with recurrent unexplained upper abdominal symptoms such as vomiting, epigastric pain, anorexia, early satiety and without structural or mucosal abnormalities of gastrointestinal tract, underwent electrogastrography (EGG)—recording of gastric electrical activity using cutaneous electrodes positioned on the epigastric region and connected to a recording polygraph. Frequency of EGG signals was analyzed by fast Fourier transform. Significant changes of fasting and fed gastric myoelectrical activity (tachygastria, bradygastria, flatline pattern) were recorded in the three patients; furthermore, gastric emptying (GE) of a solid–liquid mixed meal, measured by ultrasonography, was significantly prolonged in them. A follow-up study was carried out after an eight-week course with oral cisapride: in all patients symptoms improved, GE time normalized, and EGG analysis showed normal electrical rhythm. It is suggested that gastric dysrhythmias can play a pathogenetic role in patients with functional gastrointestinal symptoms and that symptomatic improvement is accompanied by normalization of gastric electrical rhythm.

REFERENCES

1. Lennard-Jones JE: Functional gastrointestinal disorders. N Engl J Med 308:431–435, 1983
2. Heatley RV, Rathbone BJ: Dyspepsia: A dilemma for doctors? Lancet 2:779–781, 1987
3. Mathias JR, Finelli DS: Functional diseases of the small intestine. *In* Functional Disorders of the Gastrointestinal Tract. S Cohen, R Soloway (eds). New York, Churchill Livingstone, 1987, pp 39–58
4. Malagelada JR, Stanghellini V: Manometric evaluation of functional upper gut symptoms. Gastroenterology 88:1223–1331, 1985
5. Pineiro-Carrero VM, Andres JM, Davis RH, Mathias JR: Abnormal gastrointestinal motility in children and adolescents with recurrent functional abdominal pain. J Pediatr 113:820–825, 1988
6. Hyman PE, Napolitano JE, Diego A, Patel S, Flores AF, Grill BB, Reddy SN, Garvey TQ, Tomomasa T, et al: Antroduodenal manometry in the evaluation of chronic functional gastrointestinal symptoms. Pediatrics 86:39–44, 1990
7. Cucchiara S, Staiano A, Gobio-Casali L, Boccieri A, Paone FM: Value of the 24-hour intraoesophageal pH monitoring in children. Gut 31:129–133, 1990
8. Bolondi L, Bortolotti M, Santi V, Calletti T, Gaiani S, Labò G: Measurement of gastric emptying time by real-time ultrasonography. Gastroenterology 89:752–759, 1985
9. Van der Schee EJ, Smout AJPM, Grashuis JL: Application of running spectrum analysis to electrogastrographic signals recorded from dog and man. *In* Motility of the Digestive Tract. M Weinbeck (ed). New York, Raven Press, 1982, pp 241–250
10. Van der Schee EJ, Grashuis JL: Running spectrum analysis as an aid in the representation and interpretation of electrogastrographic signals. Med Biol Eng Comput 25:57–62, 1987
11. Cucchiara S, Riezzo G, Pezzolla F, Baldassarre M, Giorgio I, Auricchio S: Study of the electrical activity of the stomach in children with non-ulcer dyspepsia (NUD). Pediatr Res 27:530, 1990
12. Koch KL, Stern RM, Vasey M, Botti JJ, Creasy GW, Dwyer A: Gastric dysrhythmias and nausea of pregnancy. Dig Dis Sci 35:961–968, 1990
13. Cucchiara S, Bortolotti M, Colombo C, Boccieri A, De Stefano M, Vitiello G, Pagano A, Ronchi A, Auricchio S: Abnormalities of Gastrointestinal motility in children with nonulcer dypepsia and in children with gastroesophageal reflux disease. Dig Dis Sci 36:1066–1073, 1991
14. Read MW, Hoaghton LA: Physiology of gastric emptying and pathophysiology of gastroparesis. Gastroenterol Clin North Am 18:369–373, 1989

15. Geldof H, van der Schee EJ: Electrogastrography. Clinical applications. Scand J Gastroenterol 24(suppl 171):75–82, 1989
16. Szursewski JH: Electrical basis for gastrointestinal motility. *In* Physiology of the Gastrointestinal Tract, 2nd ed. LA Johnson (ed). New York, Raven Press, 1987, pp 383–422
17. Dubois A: Gastric dysrhythmias: Pathophysiologic and etiologic factors. Mayo Clin Proc 64:246–250, 1989
18. Abell TL, Malagelada JR: Electrogastrography. Current assessment and future perspectives. Dig Dis Sci 33:982–992, 1988
19. You CH, Lee KY, Chey WY, et al: Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. Gastroenterology 79:311–314, 1980
20. Geldof H, 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
21. Abell TL, Malagelada JR: Glucagon-evoked gastric dysrhythmias in humans shown by an improved electrogastrographic technique. Gastroenterology 88:932–940, 1985
22. Kim CH, Zinsmeister AR, Malagelada JR: Effect of gastric dysrhythmias on postcibal motor activity of the stomach. Dig Dis Sci 33:193–199, 1988
23. Kim CH, Hanson RB, Abell TL, Malagelada JR: Effect of inhibition of prostaglandin synthesis on epinephrine-induced gastroduodenal electromechanical changes in humans. Mayo Clin Proc 64:149–157, 1989
24. Sarna SK, Daniel EE: Threshold curves and refractoriness properties of gastric relaxation oscillators. Am J Physiol 226:749–755, 1974
25. Kim CH, Malagelada JR, Azpiroz F, Zinsmeister AR: Meal reduces sensitivity of the stomach to pharmacologically induced dysrhythmia. Dig Dis Sci 32:1027–1032, 1987
26. McCallum RW: Gastric emptying in gastroesophageal reflux and the therapeutic role of prokinetic agents. Gastroenterol Clin North Am 19:551–564, 1990
27. 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 84:1069–1075, 1989