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Cisapride provides symptomatic relief in functional dyspepsia associated with gastric myoelectrical abnormality

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SUMMARY

Objective: We evaluated the effects of cisapride (10 mg t.d.s. and 20 mg b.d.) on gastrointestinal symptoms and gastric myoelectrical activity in patients with functional dyspepsia. Myoelectrical activity was measured by electrogastrography.

Methods: Patients with functional dyspepsia, defined as discomfort in the epigastrium, a negative endoscopy, and clinical symptoms of dyspepsia, were enrolled. A total of 38 patients participated in the study (23 female; 15 male; 24–72 years of age). Screening electrogastrography identified those with a normal electrogastrogram (14 subjects) and those with an abnormal electrogastrogram (24 patients). Patients were randomly assigned to 2 weeks of placebo or 2 weeks of cisapride (10 mg t.d.s.); both groups then received 2 weeks of cisapride (20 mg b.d.). Electrogastrograms were repeated at the end of each 2-week treatment period.

Results: Cisapride 10 mg t.d.s. significantly improved symptoms in all patients. An additional 2 weeks of treatment with cisapride 20 mg b.d. led to continued improvement in symptoms in all patients, with significant improvement in the group with abnormal baseline electrogastrograms. Cisapride significantly improved postprandial bloating and discomfort in patients with abnormal baseline electrogastrograms. Cisapride also significantly improved postprandial gastric myoelectrical activity as measured by electrogastrography in patients with abnormal baseline electrogastrograms.

Conclusion: Cisapride provides symptomatic relief and improves gastric myoelectrical abnormalities in patients with functional dyspepsia.

INTRODUCTION

Dyspepsia, or abdominal distress, is a common but loosely defined clinical syndrome. Symptoms of dyspepsia affect as many as 25% of the United States population.[1, 2] Symptoms are often vague and patient-dependent and there is no clear-cut definition.[3] Efforts have been made to specifically quantify symptoms and to distinguish dyspepsia from other syndromes of abdominal discomfort, such as irritable bowel syndrome, gastro-oesophageal reflux disease (GERD), and peptic ulcer disease.[2, 3]

In 1989 the International Ad Hoc Working Party proposed the following definition of dyspepsia: 'episodic or persistent abdominal symptoms, often related to feeding, which patients or physicians believe to be due to disorders of the proximal portion of the digestive tract'.[3] In 1991 an International Working Team suggested that functional dyspepsia be classified into three subtypes, based on combinations of several symptoms: dysmotility-like, ulcer-like, and non-specific dyspepsia.[4]

Functional dyspepsia may be defined as episodic or continual abdominal symptoms originating in the upper abdomen (oesophagus, stomach, and small bowel) or attributed to patient perception of distress in these

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structures.[5] Symptoms include vague epigastric or periumbilical discomfort, early satiety and fullness after meals, bloating, regurgitation, and nausea and vomiting.[5] Standard clinical investigations, including laboratory tests and conventional imaging studies, do not detect an apparent cause, such as peptic ulcer disease, GERD, or pancreatitis; nor are the symptoms drug- or alcohol-induced. Upper abdominal symptoms distinguish dyspepsia from irritable bowel syndrome, in which symptoms are referable to the lower gut, but there is much clinical overlap.[5] *Helicobacter pylori* infection does not appear to correlate with gastric dysmotility, but studies are conflicting.[2, 5–7]

The pathophysiology of functional dyspepsia is unclear. Most studies support the hypothesis that functional dyspepsia represents an underlying motility disorder, with a likely neuropathic source. If present, motor abnormalities tend to be varied, changeable, and not time-related to symptoms.[5] Antral hypomotility has been noted, and its association with decreased vagal tone supports the role of extrinsic nerve dysfunction in functional dyspepsia. Approximately 40% to 50% of patients with dysmotility-type dyspepsia have delayed solid-phase gastric emptying. Bloating symptoms are associated with a dilated gastric antrum. Abnormal myoelectrical gastric slow waves—tachydysrhythmias, tachygastrias, and bradygastrias—are seen in patients with chronic idiopathic nausea and vomiting.[8]

The electrogastrograph, which records gastric myoelectrical activity using surface electrodes on the abdomen and thus does not disturb stomach activity, has been shown to provide accurate measurements of gastric dysrhythmia in patients with functional dyspepsia.[9–11] We have recently shown that electrogastrographic measurements—particularly the percentage of time that normal 2- to 4-cpm slow waves predominated in the postprandial state—differentiated patients with functional dyspepsia from healthy controls with a 100% specificity and 43% sensitivity. Dyspepsia patients had an abnormal gastric myoelectrical response to meals.[12]

Recent studies have shown that cisapride, an oral gastrointestinal prokinetic agent indicated for symptomatic relief of nocturnal heartburn due to GERD, can normalize gastric dysrhythmia in dogs with tachygastria-associated motor patterns.[13, 14] Rothstein *et al.* found that abnormal electrogastrograms in patients with idiopathic and diabetic gastroparesis were normalized or improved after 6 months of cisapride treatment.[15]

Several mechanisms are believed to contribute to the promotility action of cisapride. Cisapride is a serotonin-4 (5-HT_4) receptor agonist;[13] cisapride enhances acetylcholine release from postganglionic nerve endings in the myenteric plexus, thus affecting gastric motility;[16] and cisapride increases lower oesophageal sphincter pressure and lower oesophageal peristalsis, which results in reduced exposure of the oesophagus to gastric secretions and accelerates gastric emptying and oesophageal clearing.[13] In addition, cisapride stimulates salivation, which further enhances oesophageal acid clearance.[17]

In the present study, we measured the response of patients with clinical symptoms of functional dyspepsia to various doses of cisapride. We then correlated electrogastrographic findings with clinical findings to determine whether patients with functional dyspepsia and impaired gastric myoelectrical activity were more responsive to cisapride than were patients without demonstrable abnormalities on their electrogastrograms.

MATERIALS AND METHODS

Subjects

Forty-six patients with functional dyspepsia who met the entry criteria participated in the study.

All patients had a history of dyspeptic symptoms of at least 6 months duration (continuous or intermittent). The following symptoms were evaluated: nausea, vomiting, anorexia, early satiety, postprandial bloating or discomfort, upper abdominal discomfort or pain and belching. The symptoms were graded from 0 to 3 (0, absent; 1, mild; 2, moderate; 3, severe). A total score of ≥ 6 was required for the enrolment of the study. All patients underwent endoscopy to rule out organic disease as an explanation for their symptoms.

Patients were excluded if there was evidence of peptic ulcer, erosive gastritis, gastric cancer, gastric polyp, previous gastrectomy or pyloric stenosis, other known disorders of the gut such as gastro-oesophageal reflux disease, chronic intestinal pseudo-obstruction, or diabetic mellitus. Also excluded were those who took any medications other than contraceptives.

The study was approved by the Institutional Review Board at Integris Baptist Medical Center. All patients signed informed consent forms prior to entry.

Study design

This was a randomized, double-blind, placebo-controlled, prospective study.

Patients who met the criteria of functional dyspepsia (described above) were given a screening electrogastrogram to identify those with a normal baseline electrogastrogram and those with an abnormal electrogastrogram. This was repeated at the end of the first 2 weeks of treatment and again at the conclusion of the second 2-week treatment period.

Patients were randomly assigned to 2 weeks of placebo or 2 weeks of cisapride 10 mg t.d.s. Both groups then received 2 weeks of cisapride 20 mg b.d. to determine whether the higher dose was more effective. Both investigators and patients were blinded to the type of treatment. Cisapride tablets and matched placebo tablets were provided by Janssen Research Foundation.

Electrogastrography

Prior to the attachment of the surface electrodes, the abdominal surface was cleaned with a sandy skin-prep paste (Omni Prep, Weaver & Co., Aurora, CO) to lessen impedance between the pair of electrodes to below 10 $k_{\sum}$. This markedly reduced motion artefacts, and increased the signal-to-noise ratio.

Three silver/silver chloride electrodes (Red Dot, 3 M Health Care, St Paul, MN) were placed on the abdomen. Electrode 1 was placed at the midpoint between the xiphoid and the navel, electrode 2 was placed 5 cm to the left and 3 cm above this point. These two epigastric electrodes were connected to yield a bipolar signal. The third electrode was placed in the lower quadrant near the left costal margin and served as a reference.

The electrogastrographic signal was amplified using a portable recorder (Digitrapper EGG, Medtronic-Synectics Medical, Inc., Shoreview, MN) with a recording frequency of 1–18 cpm. Online digitization with a sampling frequency of 1 Hz was performed using an analogue–digital converter, and digitized samples were stored in the portable recording device. During the entire recording period, the patient lay in a supine position and was not allowed to talk or read, in order to minimize motion artefacts. The patient was kept alert to avoid falling asleep.

At the end of each study, the portable recording device was connected to an IBM 486 personal computer, and the data were uploaded. Motion artefacts were visually identified and deleted. Spectral analysis was used to extract the following parameters: dominant frequency; dominant power; and percentage of normal gastric slow waves.

Assessments

An electrogastrogram was recorded at baseline (prior to treatment), at the end of 2 weeks of treatment with either placebo or cisapride 10 mg t.d.s., and again at the end of the additional 2 weeks of treatment with cisapride 20 mg b.d. On each occasion, the electrogastrogram was recorded for 0.5 h in the fasting state and for 2 h after a standardized meal containing 500 kCal. The meal consisted of a turkey sandwich, potato chips, and 120 mL of orange juice (32% fat, 18% protein, and 50% carbohydrate).

Parameters extracted from the overall spectral analysis and running spectral analysis (minute-by-minute) were: (i) the percentage of 2–4 cpm slow waves; (ii) dominant frequency and dominant power; and (iii) postprandial increase in the dominant power (spectral power at 3 cpm).[18, 19]

Patients were further stratified by any abnormalities in parameters seen on the baseline electrogastrogram. An abnormal electrogastrogram was defined as: (i) < 70% 2–4 cpm slow waves in both the fasting and the fed state; or (ii) a postprandial increase in dominant power of < 0 dB.

An average total symptom score was calculated at baseline and at the end of the first and second 2-week treatment periods.

Statistical analyses

All data were expressed as mean ± s.e. Analysis of variance was used to investigate the difference among three or more variables. The paired or unpaired Student's *t*-test was used to assess the change from baseline to end-point and the difference between placebo and cisapride. *P*-values of < 0.05 were defined as statistically significant.

RESULTS

Thirty-eight patients completed the study; 23 female and 15 male patients between the ages of 27 and 72 years. Their mean age was 46.4 ± 1.8 years, and their mean body mass index was 24.4 ± 1.0 kg/m^2.

Of the 38 patients who completed the study, 14 had normal electrogastrograms at baseline, and 24 had abnormal electrogastrograms. During the first 2 weeks of the study, 18 patients (seven with normal and 11 with abnormal baseline electrogastrograms) received placebo; 20 patients (seven with normal and 13 with abnormal baseline electrogastrograms) received cisapride 10 mg t.d.s. During the second 2-week treatment period, all 38 patients received cisapride 20 mg b.d.

Cisapride 10 mg t.d.s. for 2 weeks significantly improved symptoms of dyspepsia in all patients, regardless of electrogastrogram results at baseline ($P < 0.05$; Figure 1). The improvement was further enhanced or sustained after 2 further weeks of treatment with cisapride 20 mg b.d. As shown in Figure 2, an improvement of symptoms was also observed in all patients who received placebo in the first 2 weeks ($P < 0.05$). After 2 weeks of treatment with cisapride 20 mg b.d., a further significant reduction in the symptom score was noted in the patients who had abnormal baseline electrogastrogram ($P < 0.001$), but not in those who had normal baseline electrogastrogram ($P > 0.05$).

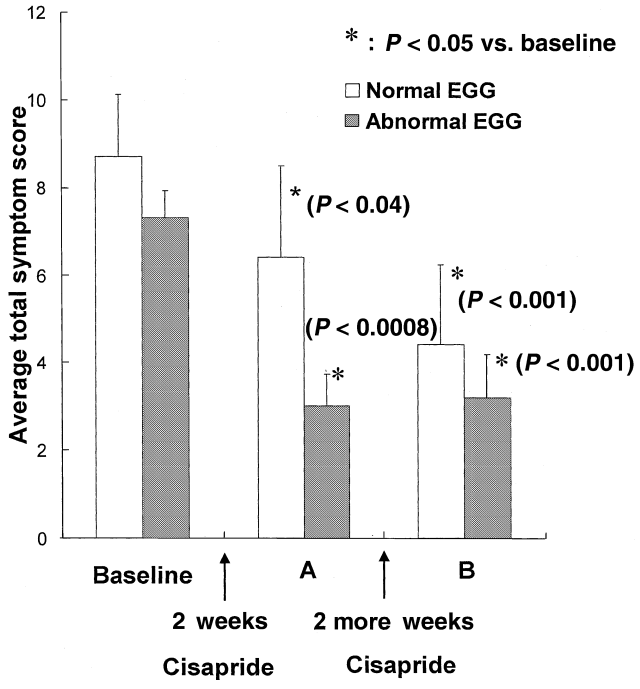

Figure 1. The average total symptom score (ATSS) for dyspepsia after 2 weeks of cisapride 10 mg t.d.s. (A), followed by 2 weeks of treatment with cisapride 20 mg b.d. (B). The greatest reduction in symptoms occurred in patients with abnormal baseline electrogastrograms (EGGs).

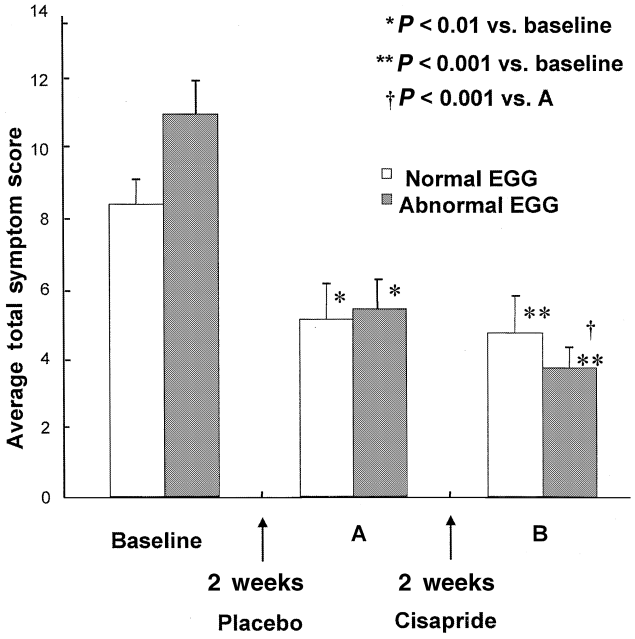

Figure 2. The average total symptom score (ATSS) for dyspepsia in patients who received placebo during the first 2 weeks of treatment (A) and cisapride during the second 2 weeks of treatment (B). Cisapride provided further reduction in the symptoms, especially in patients with abnormal baseline electrogastrograms (EGGs).

Cisapride was significantly more effective than placebo in relieving postprandial bloating and discomfort in patients with abnormal baseline electrogastrograms, as seen in Figure 3. A reduction in symptoms was noted at the end of the first 2 weeks with both placebo (1.5 ± 0.26 vs. 2.1 ± 0.15 at baseline, $P < 0.03$) and cisapride (0.8 ± 0.20 vs. 2.1 ± 0.22 at baseline, $P < 0.002$). However, cisapride was superior to placebo. The symptom score after the first 2-week treatment period was significantly lower with cisapride than with placebo (0.8 ± 0.20 vs. 1.5 ± 0.26, $P < 0.05$). Longitudinally, cisapride also provided significant improvement in postprandial symptoms. The symptom score of 1.5 ± 0.26 at the end of 2 weeks of placebo treatment was reduced to 0.7 ± 0.23 following 2 weeks of cisapride ($P < 0.05$).

Gastric myoelectrical activity in patients who had abnormal baseline electrogastrograms was significantly improved with cisapride but not with placebo. The postprandial change in electrogastrogram-dominant power was marginally enhanced (increased) after the first weeks of treatment with cisapride 10 mg t.d.s. and this enhancement became significant after 2 further weeks of cisapride 20 b.d. (Figure 4).

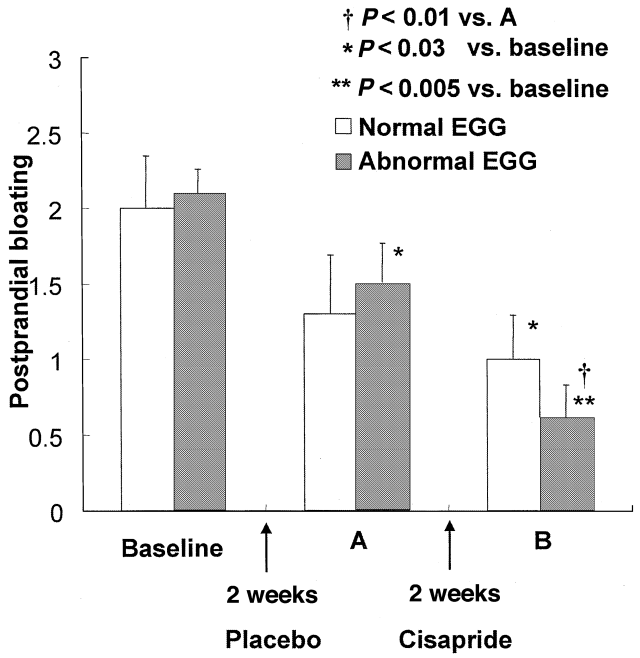

Figure 3. The mean score for postprandial bloating and discomfort in patients with abnormal electrogastrograms (EGGs) treated with 2 weeks of placebo or cisapride, followed with 2 weeks of cisapride. Cisapride demonstrated superior performance to placebo both in parallel and longitudinally.

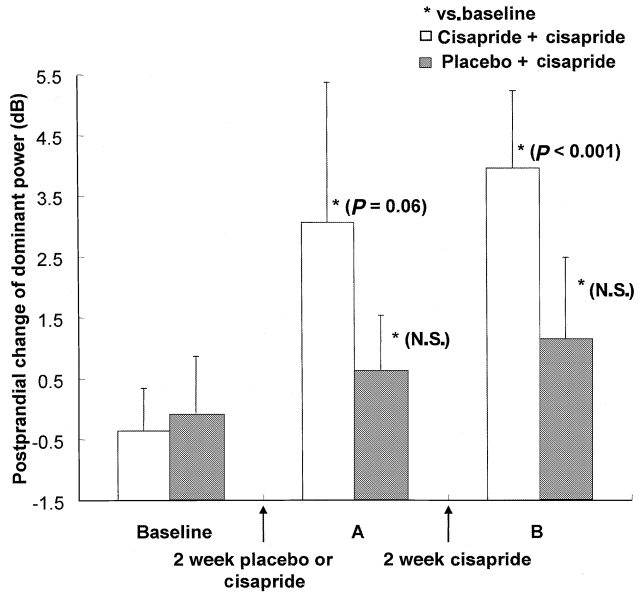

Figure 4. Mean change of dominant power after a meal in patients with abnormal baseline electrogastrograms (EGGs). There was a marginal increase after the first 2 weeks of cisapride (A) and a significant increase after the second 2 weeks (B).

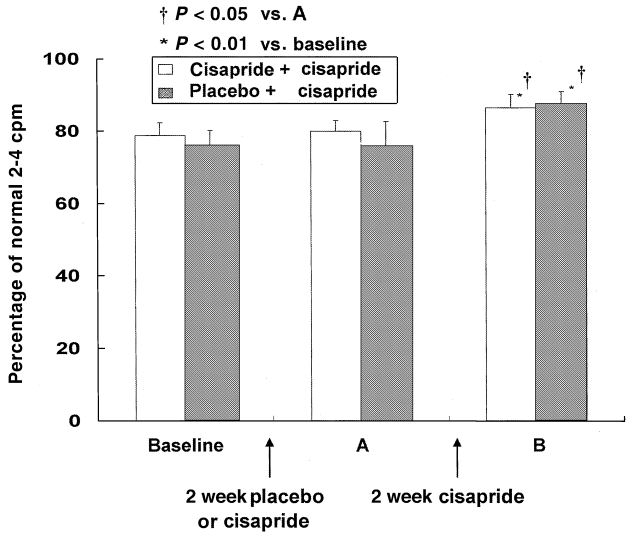

Figure 5. Postprandial gastric myoelectrical activity in patients with abnormal electrogastrograms (EGGs). Cisapride 20 mg b.d. (B) significantly improved gastric slow wave activity compared to cisapride 10 mg t.d.s. or placebo (A).

In patients with abnormal baseline electrogastrograms, there was no significant change in the percentage of normal 2–4 cpm slow waves during the first 2 weeks. On the other hand, cisapride 20 b.d. provided a significant improvement in gastric slow wave rhythmicity, as shown in Figure 5.

In addition to the 38 patients who completed the study, six patients entered but did not complete the study. Two patients withdrew due to personal reasons and one due to a broken leg. One patient had severe bloating while on placebo and withdrew before the end of the first 2-week placebo period. Two patients experienced mild diarrhoea during the second 2-week period of cisapride 20 mg b.d. and decided to discontinue from the study. No side-effects were reported in any other patients.

DISCUSSION

Functional dyspepsia may be caused by different aetiologies. Better treatment may be provided if the underlying aetiology is known. The existing classification of subtypes of functional dyspepsia is based on subjective assessment of symptoms and does not provide guidance regarding treatment options. In this study, we differentiated patients into two groups, those with and those without abnormal myoelectrical findings on the baseline electrogastrogram. It was found that cisapride

was more effective for the treatment of dyspeptic symptoms in patients with abnormal gastric myoelectrical findings than in those without abnormalities.

Gastric motility can be assessed by gastric manometry via an intubated catheter or by a scintigraphic method, by asking patients to take a test meal with isotopes. These methods are invasive or radioactive and their applications are usually limited to patients with suspected gastroparesis. Gastric motility is regulated by gastric myoelectrical activity which is composed of slow waves and spike/second potentials. The spike/second potential is directly associated with the occurrence of gastric contractions. The slow wave determines the maximum frequency and propagation of gastric contractions. Previous studies have shown that abnormalities in the gastric slow wave (dysrhythmias) are associated with gastric motor disorders.[18–22] The absence of normal gastric slow waves or the appearance of gastric dysrhythmias leads to gastric hypomotility or uncoordinated contractions. It has been validated that the rhythmicity of the gastric slow wave can be accurately recorded using electrogastrography.[23–25] Recently it has become clear that the appearance of gastric contractions is not only associated with superimposed spike/second potentials but is also correlated with the increased slow wave amplitude;[26] a postprandial increase in amplitude is a frequently observed phenomenon in electrogastrographic studies. Whilst there is still a debate on the interpretation of the postprandial increase of electrogastrogram amplitude, a postprandial decrease in electrogastrogram amplitude is believed to be associated with gastric motility disorders. In this study, the electrogastrogram was defined as abnormal if the percentage of normal gastric slow waves was below 70% in both fasting and fed states, or there was a decrease in postprandial amplitude.[27]

The results of the present study have demonstrated that cisapride was more effective than placebo for the treatment of overall dyspeptic symptoms and of postprandial bloating and discomfort in patients with abnormal baseline electrogastrograms. This response to cisapride may be related to improvement in gastric emptying, as reported in other studies.[28–31]

While cisapride was developed as a gastrointestinal prokinetic agent, this study also showed that it has an effect in normalization of gastric dysrhythmias; a significant increase in the percentage of normal gastric slow waves (2–4 cpm) was observed. The data seemed to indicate that the dosage of 20 mg b.d. was more effective than 10 mg t.d.s., and that 4 weeks of treatment may be necessary for a complete normalization of gastric myoelectrical activity. Improvement of gastric slow wave rhythmicity with cisapride in patients with gastroparesis has also been reported in a number of previous studies.[15–31]

A significant placebo response was observed in the treatment of symptoms, which agrees with other studies reporting a high placebo response in patients with functional dyspepsia.[2] The placebo response was however, not found in any of electrogastrogram parameters. This study clearly demonstrated that cisapride is superior to placebo for the treatment of postprandial symptoms as well as overall symptoms in patients with abnormal electrogastrograms.

In summary, the present results show the efficacy of cisapride in relieving gastrointestinal symptoms and in improving gastric myoelectrical activity in patients with functional dyspepsia. The study also suggests that electrogastrography may be used to identify a subset of patients with gastric motor disorders in whom treatment with cisapride may be especially beneficial.

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