

## The effect of cisapride on dyspepsia symptoms and the electrogastrogram in patients with non-ulcer dyspepsia

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### SUMMARY

**Background:** The electrogastrogram (EGG), which records gastric myoelectrical activity, is abnormal in one-third of adult patients with non-ulcer dyspepsia (NUD). **Aim:** To observe the effects of cisapride on EGG in adults with NUD.

**Methods:** Twenty-seven NUD patients who had undergone a pre- and post-prandial EGG were entered into an open study. All patients completed a dyspepsia symptom questionnaire and were then treated with cisapride 10 mg t.d.s. The dyspepsia questionnaire was repeated in all those completing 4 weeks of treatment. Those with an initial abnormal EGG (< 70% of slow wave

activity at 2–4 cycles per minute) had a repeat EGG at the end of the study.

**Results:** Treatment with cisapride was associated with a significant improvement in the post-prandial EGG ( $P = 0.007$ ). After 4 weeks of treatment, 7 of 13 abnormal EGGs normalized. Symptom scores improved significantly in the 13 patients with an abnormal EGG who completed treatment ( $P < 0.0003$ ), but not in NUD patients with a normal EGG ( $P = 0.48$ ).

**Conclusion:** In this open study, treatment of NUD with cisapride was associated with significant symptom improvement in patients with an abnormal pre-treatment EGG, but not those with a normal EGG, with a significant improvement of the post-prandial EGG.

### INTRODUCTION

Non-ulcer dyspepsia (NUD) is characterized by persistent or recurrent epigastric symptoms including pain and fullness, early satiety, nausea, and/or vomiting that are not explained by structural or biochemical abnormalities.<sup>1</sup> Recent studies have indicated that NUD might be a result of abnormalities in gastric physiology. NUD patients demonstrate a reduced sensory threshold to gastric distension compared to controls.<sup>2–4</sup> Motor abnormalities include a decreased antral and/or antroduodenal contractile response to the ingestion of a meal or uncoordinated and/or non-propagated duodenal-jejunal motor waves.<sup>5, 6</sup> These abnormalities of gastric motor physiology are often accompanied by delayed

gastric emptying<sup>7–10</sup> and maldistribution of food in the stomach.<sup>11</sup> The maldistribution of food may also be related to impaired gastric accommodation,<sup>2</sup> resulting in increased food loading of the antrum following a meal.

The electrogastrogram (EGG) is a non-invasive test used to measure gastric myoelectrical activity. Normal gastric myoelectrical activity consists of a slow wave and spike potentials. The EGG accurately records the slow wave, which controls the velocity and propagation of gastric contractions. Previous studies have demonstrated that the EGG is reproducible and stable over time.<sup>12</sup> In addition, the EGG is not affected by age or gender.<sup>13</sup> The EGG detects gastric dysrhythmias, either fast frequency waves (tachygastria) or slow frequency waves (bradygastria). Studies using serosal transducers and manometry have shown that tachygastrias correlate with absent antral contractions<sup>14</sup> and bradygastrias are associated with both strong and or absent antral

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contractions.<sup>14–17</sup> The EGG may therefore be used as an indirect marker of abnormal antral motility in NUD. Up to 30% of patients with NUD have an abnormal EGG.<sup>18</sup> Nausea has been shown to be the most common symptom associated with an abnormal EGG. Repeating the EGG in symptomatic patients has indicated that the gastric dysrhythmias remain abnormal.<sup>19</sup>

Clinical trials of the prokinetic agent cisapride have shown that this agent is effective in relieving symptoms of NUD.<sup>20</sup> In addition, there are reports that gastric dysrhythmia in children with NUD improve after treatment with cisapride.<sup>21, 22</sup> Cisapride has also been reported to improve gastric dysrhythmias in idiopathic and diabetic gastroparesis.<sup>23</sup> However, there are no reports of the effect of cisapride on the EGG in adults with NUD.

The aims of this study were to assess whether standard doses of cisapride affect abnormal EGG in adults with NUD, and to assess symptom response in NUD patients with normal and abnormal EGGs.

#### MATERIALS AND METHODS

Non-ulcer dyspepsia was diagnosed according to standard criteria. All the patients presented with persistent or recurrent pain or discomfort localized to the epigastrium, which may or may not have been related to meals. All the patients had a normal upper gastrointestinal endoscopy, haematology and biochemistry and no other disorder to account for the epigastric symptoms. Seventeen consecutive adult patients with NUD and an abnormal EGG, and 10 consecutive patients with NUD and a normal EGG were invited to enter into an open, prospective therapeutic trial. The study protocol was supported by the hospital ethics committee and all subjects gave informed consent.

Following a 6 h fast, all patients underwent a standard EGG. All medication that might have influenced gastric motor or secretory function was discontinued at least 48 h before the recording. The EGG was performed with the patients in a semi-reclining position and the subjects were asked to avoid major movements and talking. Two bipolar skin electrodes were placed on the abdomen; one midway between the xyphoid process and umbilicus and the other 5 cm to the left, just below the costal margin. A reference electrode was placed on the right side of the abdomen. The electrodes were connected to an EGG recording unit (Synectics, Stockholm, Sweden). A 45 min fasting recording was performed following which the patient ate a standard cheese sandwich

(500 kcals, 50% carbohydrate, 25% fat and 25% protein) with 150 mL of water. This was followed immediately by a further 1 h recording. The EGG data was analysed by the 'multigram' Synectics software package running on a personal computer. Visual inspection of the wave form detected any major movement artefact, which was deleted from the analysis. The dominant frequency of the EGG throughout the recording was calculated by running spectral analysis. Normal electrical activity is defined as more than 70% of cycles at a frequency of 2–4 cycles per min.<sup>24</sup> Activity of 0–2 cycles per min is termed as bradygastria, and 4–9 cycles per min, tachygastria. An abnormal EGG was defined as less than 70% of slow wave activity (2–4 cycles/min) either before or after the standard meal.<sup>24</sup>

All patients completed a questionnaire measuring symptom severity. The Glasgow dyspepsia severity score was used as a global measurement of the severity of dyspepsia.<sup>25</sup> This records frequency of symptoms, effect on routine activities, time off work, frequency of medical consultations, clinical investigations and use of over-the-counter and prescribed medications. The maximum score is 18 and the minimum score is 0. The seven commonest symptoms in non-ulcer dyspepsia (epigastric pain, bloating, early satiety, anorexia, nausea, vomiting and heartburn) were evaluated according to the Likert scale, measuring the timing, severity and frequency of the symptoms giving maximum and minimum scores of 84 and 0, respectively.<sup>26</sup>

All patients were requested to take cisapride 10 mg three times daily, half an hour before meals for 4 weeks. If the initial EGG was abnormal, the test was repeated after the 4-week treatment period, with the final dose on the morning of the test. If the initial EGG was normal, the EGG was not repeated. In patients with normal and abnormal EGGs, the dyspepsia questionnaire was repeated following the course of cisapride.

Statistical analysis was performed using paired and unpaired Student's *t*-test (statistical significance =  $P < 0.05$ ).

#### RESULTS

Of the 27 patients recruited for the study, 17 patients had an abnormal EGG. Four of these patients were unable to tolerate cisapride due to side-effects and did not complete the 4-week treatment period. Of the 10 patients with a normal EGG, two had cisapride related

Table 1. Mean symptom scores in NUD patients before and after cisapride

	Abnormal EGG		Normal EGG	
	Glasgow score	Likert score	Glasgow score	Likert score
Pre-cisapride	8.21	29.3	7.6	21.3
Post-cisapride	6.09	22.6	7.66	16.8
P-value	0.0003	0.038	0.48	0.89

side-effects and a further patient was lost to follow-up. Side-effects included diarrhoea, headache and worsening of abdominal pain. *Helicobacter pylori* prevalence was similar in patients with an abnormal EGG (four out of 17) and normal EGG (two out of 10).

Symptoms

Patients with an abnormal EGG had no significant difference in their symptoms scores compared to those with a normal EGG prior to treatment ( $P = 0.59$ ). Following treatment, patients who had an abnormal EGG had a significant reduction in their symptom scores ( $P = 0.0003$ ) whilst this was not observed in patients with a normal EGG (Table 1).

Electrogastrography

Following 4 weeks of treatment with cisapride, the abnormal EGG normalized in 7 out of 13 (54%)

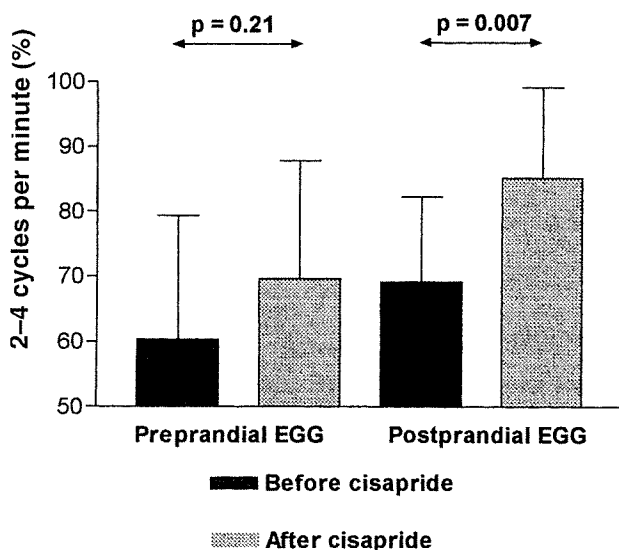


Figure 1. Electrogastrography in NUD patients (with an abnormal initial electrogastrogram) before and following treatment with cisapride.

patients. Considering the patients with an abnormal EGG as a group, there was an improvement in the mean pre-prandial EGG recordings following cisapride, but this did not reach statistical significance (Figure 1). In

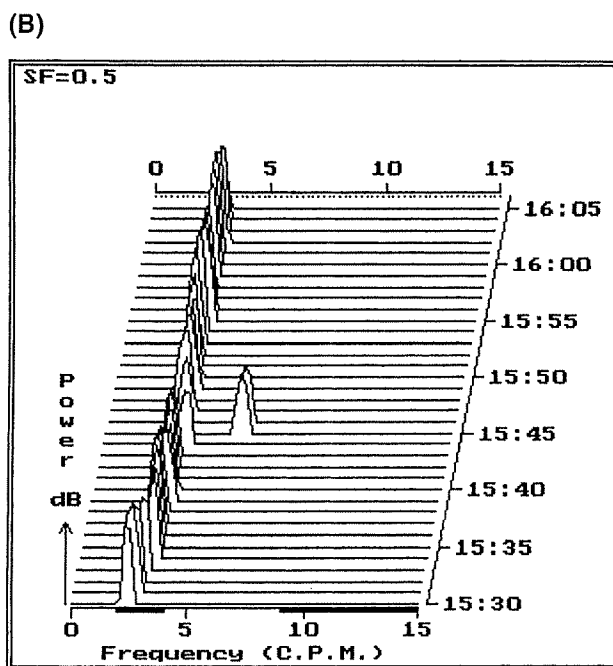
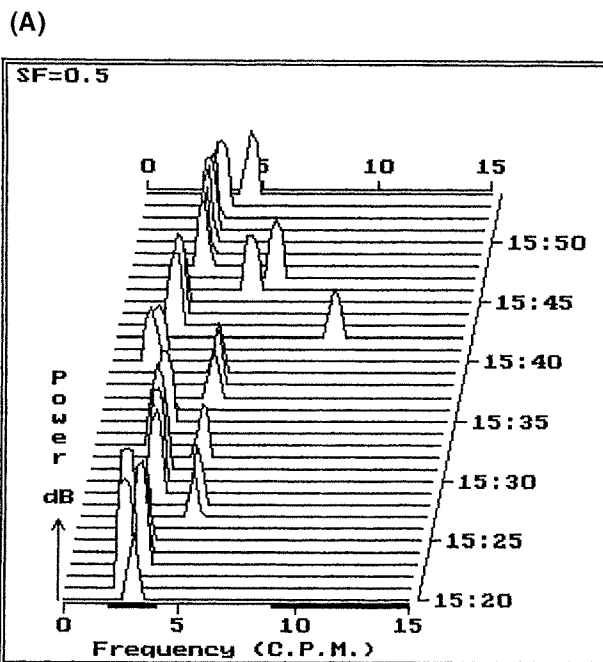


Figure 2. (A) Pseudo three-dimensional representation of the postprandial EGG in a patient before treatment with cisapride, and (B) following treatment with cisapride.

contrast, the mean post-prandial EGG recordings improved significantly ( $P = 0.007$ ) following cisapride treatment (Figure 1). Prior to treatment there was no correlation between the severity of symptoms and an abnormal EGG. However, all patients in whom the EGG normalized following treatment with cisapride had an improvement in their symptom score.

A pseudo three-dimensional representation of the post-prandial electrogastrogram in a patient before (Figure 2a) and after (Figure 2b) treatment with cisapride demonstrates normalization of post-prandial tachygastria.

## DISCUSSION

A large proportion of patients referred to gastroenterology departments have non-ulcer dyspepsia. In this group of patients routine diagnostic tests, including endoscopy, ultrasound and blood tests, fail to identify a significant abnormality. Abnormalities of gastric motility have been detected using antro-duodenal manometry and barostats, but these tests are invasive and poorly tolerated. The EGG is a simple non-invasive method of detecting abnormal gastric myoelectrical activity and an abnormal EGG is thought to reflect changes in antral motility.

Cisapride is a prokinetic agent that may act by enhancing acetylcholine release from the myenteric plexus. In this open study we explored the possible effects of cisapride in NUD patients with normal and abnormal EGGs and assessed whether treatment with this prokinetic drug influences the abnormal EGG.

After a 4-week course of treatment with cisapride, a significant improvement in dyspepsia symptom scores was only observed in patients who had an abnormal EGG prior to starting treatment. In this group of patients, following treatment with cisapride, a significant improvement in the post-prandial EGG was observed and in 54% of patients, the EGG normalized. In NUD, the presence or absence of *H. pylori* did not correlate with EGG findings.

This study suggests that in adults, cisapride has an effect on the abnormal EGG similar to that previously described in children.<sup>21</sup> This open study also suggests that symptomatic improvement is most likely in NUD patients with an abnormal EGG. Trials of treatment in NUD have usually been symptom based, although there are trials where gastric function has been incorporated in the study design.<sup>27-35</sup> Conventional classification of NUD subdivides the disorder into three groups accord-

ing to symptoms (ulcer-like, dysmotility-like, reflux-like). The development of minimally invasive tests of gastric motor physiology should provide a more satisfactory physiological classification of NUD. The EGG helps to define patients on electro-physiological criteria. Other minimally invasive tests such as gastric scintigraphy<sup>36</sup> and gastric antral ultrasonography<sup>37-39</sup> have been shown to be abnormal in some patients with NUD, and the combination of electrogastrography and gastric motor studies might add to the further classification of the disorder. On the basis of this open study, we recommend that in trials of treatment in NUD, the EGG should be used to stratify patients. In NUD the EGG may also be helpful in assessing the effect of drugs on myoelectrical activity of the stomach.

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