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Domperidone is more effective than cisapride in children with diabetic gastroparesis

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SUMMARY

Background: Disorders of gastrointestinal motility are commonly detected in patients with insulin-dependent diabetes mellitus and are associated with significant morbidity. They contribute to poor metabolic control of diabetes.

Aim: To assess the effect of an 8-week course of domperidone or cisapride on gastric electrical activity, gastric emptying time and dyspeptic symptoms in children with insulin-dependent diabetes mellitus and gastroparesis.

Methods: Dyspeptic symptoms were assessed by a score system, gastric emptying time was measured by ultrasonography and gastric electrical activity was obtained by electrogastrography. Fourteen children received domperidone and 14 received cisapride. The median (range) ages were 11.6 years (5–15 years) and 12 years (6–16.9 years), respectively. Symptom assessment, ultrasonography and electrogastrography were repeated at the end of the trial. Fasting and fed (180 min after feeding) glycaemia and haemoglobin A, C (HbA_{1c}) levels were also measured.

Results: At the end of the trial both groups showed a significant decrease in symptomatic score; however, the score was markedly lower in the domperidone group than in the cisapride group ($P < 0.01$). Domperidone was significantly more effective than cisapride in reducing the gastric emptying time ($P < 0.05$), normalizing gastric electrical activity ($P < 0.05$) and decreasing the prevalence of episodes of gastric dysrhythmia ($P < 0.01$). Domperidone was also more effective than cisapride in improving diabetic metabolic control. No potentially drug-related adverse effects occurred.

Conclusions: In children with insulin-dependent diabetes mellitus complicated by dyspeptic symptoms and gastroparesis, domperidone is superior to cisapride in reversing gastric emptying delay and gastric electrical abnormalities, as well as in improving dyspeptic symptoms and diabetic metabolic control.

INTRODUCTION

Disorders of gastrointestinal motility commonly occur in patients with insulin-dependent diabetes mellitus.[1–4] They are usually associated with dyspeptic symptoms, such as nausea, vomiting, fullness and epigastric discomfort, and are an important cause of morbidity; they may also contribute to poor metabolic control of diabetes through a mismatch between duodenal nutrient load and onset of insulin action.[3, 5]

The presence of gastric motor and electrical abnormalities in diabetic patients supports the use of prokinetic drugs. Metoclopramide and domperidone, which are dopamine D_2 receptor antagonists, and cisapride‡, which is a 5-hydroxytryptamine-4 agonist that facilitates acetylcholine release at the level of the myenteric

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‡Cisapride has recently been removed from the Italian market following an order by the Public Health Minister.

plexus, have been used in adult diabetic patients with gastroparesis,[6, 7] but the presence of central nervous system effects precludes the use of metoclopramide despite its efficacy in relieving dyspeptic symptoms.[8] Domperidone and cisapride are the most commonly used prokinetics in adult diabetic patients with dyspepsia and several studies have evaluated their effect.[9–15]

There are only a few reports available on gastrointestinal motility disorders in children with insulin-dependent diabetes mellitus,[16–19] and no controlled therapeutic studies have been performed in this population. The aim of this study was to compare the effect of an 8-week course of domperidone or cisapride on gastric electrical activity, gastric emptying time and dyspeptic symptoms in children with insulin-dependent diabetes mellitus and gastroparesis.

MATERIALS AND METHODS

Patients

The study was performed on 31 children (13 males, 18 females; age range, 6–16.9 years) with insulin-dependent diabetes mellitus and recurrent symptoms of upper gastrointestinal dysfunction. The duration of insulin-dependent diabetes mellitus was 5.0 years (0.6–10.8 years) (median and range). No patient had received antisecretory or prokinetic drugs for at least 12 weeks before the study. Barium and/or upper endoscopy studies had excluded in all patients mechanical obstruction and peptic ulcer disease of the gastrointestinal tract, respectively. No patient had a history of hypoglycaemic unawareness. Evaluation of autonomic nerve function was performed in all patients by standard cardiovascular reflex tests.[18] Sympathetic function was assessed by the change in systolic blood pressure when standing up (orthostatic hypotension defined as a drop in systolic pressure of > 30 mmHg upon standing). Parasympathetic function was assessed by the variation of the R–R interval in the electrocardiogram both during deep breathing and in response to standing.

Methods

To define the severity of dyspeptic symptoms during the 2 weeks before the study, children and parents were interviewed about the following symptoms: abdominal (epigastric and mesogastric) pain, early satiety or anorexia, feeling of abdominal fullness (or bloating) and regurgitation (or vomiting or heartburn). Symptoms were scored as follows:[18, 20] 0, absent; 2, occasionally (1–3 days per week), slight; 4, occasionally (1–3 days per week), moderately severe; 6, often (> 3 days per week), markedly severe. Anorexia or early satiety was scored by the percentage of daily caloric intake during the week before starting the study in relation to the ideal caloric intake (0, > 75–100%; 2, 50–75%; 4, ≥ 25–50%; 6, < 25%). Parents were asked to record the frequency and intensity of symptoms on a diary card.

Fasting glucose (mg %) and the haemoglobin A, C (HbA_{1c}) concentration (%) were measured before a test meal was given for the measurement of the gastric motility. Blood glucose concentration measurement was also repeated in all patients 180 min after feeding. HbA_{1c} was measured by a high performance liquid chromatography autoanalyser.

Gastric motility was recorded after an overnight fast by simultaneous measurement of the gastric emptying time and the gastric electrical activity. The gastric emptying time was measured by ultrasonography of the gastric antrum using a real-time apparatus with a 5-MHz linear array transducer applied with minimal compression. Subjects received a mixed solid–liquid meal based on the caloric intake at breakfast for children of different age groups (Table 1) and sat at a 30° angle to the horizontal plane of the examination couch. Scanning was performed by the same operator in the fasting state, every 30 min for the first post-prandial hour and at 15-min intervals afterwards. The cross-section of the gastric antrum was measured at the level of the sagittal plane passing through the superior mesenteric vein taken as a point of reference. At this level, the cross-section of the gastric antrum has an elliptical shape and

Table 1. Test meals for the measurement of the gastric emptying time in diabetic children and control subjects

Age (years)	Bread (g)	Raw ham (g)	Butter (g)	Fruit juice (mL)	Kilocalories
3–6	75	30	5	170	384
> 6–9	60	45	7.5	212.5	423
> 9–12	100	53	8.75	127	500
≥ 13	120	45	12.5	212.5	608

its area was calculated using $\pi \times A \times B/4$ (cm^3) (A, longitudinal diameter; B, anteroposterior diameter). The stomach was considered to be empty when the antral area returned to the baseline value without food particles in the lumen and remained unchanged for at least 30 min.[20]

The gastric electrical activity was measured by electrogastrography, which was performed by placing two Ag–AgCl bipolar surface electrodes (Commed Andover Med, Haverill, MA, USA) on the epigastric skin, after reduction of the cutaneous impedance by a skin preparation paste (OmniPrep, D.O. Weaver, Aurora, CO, USA). One electrode was located on the midline of the abdomen, several centimetres cephalad from the umbilicus, after sonographic localization of the antrum; the second electrode was located on the subject's left side, just below the lower rib and above the level of the first electrode. A reference electrode was placed in the left iliac fossa. The electrogastrograph was recorded for 1 h fasting and 1 h after a meal. The electrodes were connected to a 96-kb portable battery-operated recorder (Synectics-Medtronic Medical, Milan, Italy). All recordings were performed at a sampling frequency of 4 Hz; high and low cut-off frequencies were set at 0.01 and 0.5 Hz, respectively. The signals were digitized and processed by means of an appropriate software program (Synectics-Medtronic Medical, Milan, Italy). The electrogastrograph signals were subjected to running spectral analysis. In this technique, spectra are obtained as follows: every 64 s, a power spectrum is computed from the preceding 256 s of the electrogastrograph time signal to which a Hamming window has been applied to reduce leakage;[21] this procedure generates a series of overlapping spectra graphed as running spectra and makes both frequency and time analysis possible.[22] Gastric electrical activity consists of cyclic depolarizations ('slow waves') at the level of the membranes of smooth muscle cells, propagating from a pacemaker area (located along the great curvature in the upper third) towards the distal parts of the stomach. The aboral propagation of slow waves determines the aboral propagation of gastric mechanical contractions. Normally, the human stomach depolarizes at a frequency of 3 cycles per minute (cpm) (0.05 Hz). A rhythmic activity of 2.0–4.0 cpm is defined as the normal frequency range. The following parameters were measured: (i) percentage of normal gastric electrical rhythm; (ii) percentage of tachygastria, i.e. the percentage of time during which the spectrum has a dominant peak in the 4.0–9.0 cpm range; a dysrhythmic episode had to be recorded for at least 2 min, with the normal signal simultaneously absent; (iii) fed-to-fasting ratio of the dominant electrogastrograph power (power ratio), i.e. the power of the electrogastrograph at the dominant frequency. The power was calculated on a linear scale. Gastric motility variables were compared with a control population described previously.[18]

Study design

After the baseline study, the patients were allocated in a randomized fashion to an 8-week therapeutic trial with either cisapride (0.8 mg/kg daily) or domperidone (0.9 mg/kg daily) in three pre-prandial daily doses. Measurement of the gastric emptying time and electrogastrography and symptomatic assessment were repeated at the end of the treatment period by investigators unaware of the treatment groups. Subjects were followed up as out-patients every 2 weeks. The study was approved by the ethical committee of the faculty, and informed written consent was given by parents of the subjects.

Statistical analyses

Statistical analysis for significant differences was performed by Student's test for between-group comparison and by Wilcoxon's signed rank test for within-group comparison. A P value of less than 0.05 was required for significance. Data were expressed as the mean ± s.d.

RESULTS

Twenty-eight patients completed the trial; three were excluded due to poor compliance. Fourteen patients received cisapride and 14 received domperidone. The two groups were comparable at baseline in terms of the severity of symptom score, gastric motility and glycaemic parameters (Table 2). At the end of the course, a significant improvement in the symptomatic score (median and ranges) had occurred in the two groups (domperidone, post-trial: 3.14 ± 1.5; baseline: 14.21 ± 1.84; $P < 0.001$; cisapride, post-trial: 7.42 ± 1.82; baseline: 14.71 ± 1.85; $P < 0.05$). The post-trial symptomatic score in the domperidone group was markedly lower than that in the cisapride group ($P < 0.01$). Four patients who were given cisapride were still symptomatic at the end of the treatment period and received domperidone, which produced a clinical response.

Table 3 reports the effects of drug administration on gastric functional variables and serum variables of metabolic control. The post-trial gastric emptying time was significantly reduced in the domperidone group, but was not significantly changed in the cisapride group; furthermore, the post-trial gastric emptying time was significantly lower in the domperidone group than in the cisapride group (Fig. 1). At the end of the trial, significant changes in gastric electrical activity only occurred in the domperidone group; they included a higher prevalence of normal electrical rhythm (Fig. 2), a lower prevalence of tachygastria and a higher fed-to-fasting power ratio. The post-trial gastric electrical variables were not significantly improved in the cisapride group. Both the post-trial percentage of normal electrical activity and the fed-to-fasting power ratio were significantly higher in the domperidone group than in the cisapride group.

Finally, patients on domperidone showed significant post-trial improvement in the serum variables of metabolic control, such as the fasting and post-prandial glycaemia and HbA_{1c} concentration (Fig. 3). None of the patients reported potentially drug-related side-effects.

DISCUSSION

This study shows that domperidone is a safe and effective prokinetic drug for the improvement of gastric motility and metabolic control in children with insulin-

Table 2. Baseline variables of the patients who completed the trial (data as mean ± s.d.)

Variable	Cisapride	Domperidone	Cisapride vs. Domperidone	Control group*
Number of cases	14	14		15
Male/female	6/8	8/6		6/9
Age (years) (median (range))	11.6 (5–15)	12 (6–16.9)	N.S.	7.0 (4–15)
Duration of disease (years)	6.2 ± 3.1	4.2 ± 2.7	N.S.	
Clinical score	14.21 ± 1.84	14.71 ± 1.85	N.S.	
Glycaemic variables				
T_0 glycaemia (mg/dL)	170 ± 30	173.6 ± 25.6	N.S.	
T_{180} glycaemia (mg/dL)	253 ± 14	249 ± 12.8	N.S.	
HbA_{1c} (%)	8.35 ± 0.20	8.4 ± 0.27	N.S.	
EGG variables				
3 cpm (%)	67.8 ± 3.9	67.42 ± 5.09	N.S.	86 ± 7.0†
Tachygastria (%)	24.35 ± 2.3	23.92 ± 2.16	N.S.	8.4 ± 6.6†
Fed-to-fasting power ratio	0.9 ± 0.33	0.82 ± 0.32	N.S.	3.0 ± 0.6†
Gastric emptying time (min)	204.3 ± 12.22	207.9 ± 12.35	N.S.	150 ± 15

cpm, cycles per minute; EGG, electrogastrography; HbA_{1c}, haemoglobin 1c; T_0, before feeding; T_{180}, 180 min after feeding.
*Cucchiara *et al.*[18]
† $P < 0.05$ between patients and controls.

Table 3. Effects of drug administration on gastric functional variables and glycaemic variables (data as mean ± s.d.)

	Domperidone			Cisapride		
	Pre-trial	Post-trial		Pre-trial	Post-trial	
EGG variables						
3 cpm (%)	67.8 ± 3.9	82.07 ± 3.8	$P < 0.05$	67.42 ± 5.09	72.57 ± 5.5*	N.S.
Tachygastria (%)	24.35 ± 2.3	13.28 ± 3.2	$P < 0.05$	23.92 ± 2.16	20.35 ± 2.04	N.S.
Fed-to-fasting power ratio	0.9 ± 0.33	2.44 ± 0.37	$P < 0.01$	0.82 ± 0.32	1.02 ± 0.29*	N.S.
Gastric emptying time (min)	204.3 ± 12.22	164.3 ± 11.74	$P < 0.01$	207.9 ± 12.35	182.14 ± 9.55*	N.S.
Fasting glycaemia (mg/dL)	170 ± 30	123 ± 21	$P < 0.05$	173.6 ± 25	151 ± 27	N.S.
Post-feeding glycaemia (180 min) (mg/dL)	253 ± 14	196 ± 24	$P < 0.05$	249 ± 12.8	221 ± 7	N.S.
HbA_{1c} (%)	8.35 ± 0.20	7.17 ± 0.3	$P < 0.05$	8.4 ± 0.27	8.02 ± 0.17	N.S.

cpm, cycles per minute; EGG, electrogastrography; HbA_{1c}, haemoglobin 1c.
* Statistically significant difference between the domperidone and cisapride groups for the post-trial values ($P < 0.05$).

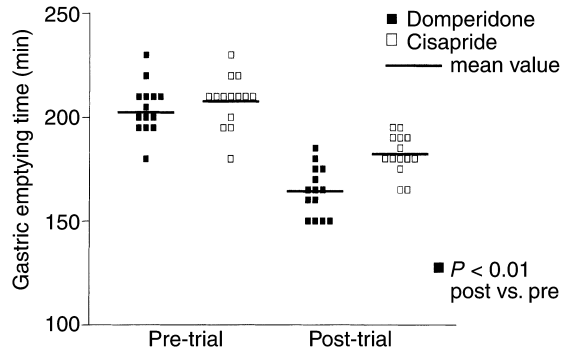

Figure 1. Pre- and post-trial values of the gastric emptying time (min) for each patient in the two groups. The post-trial gastric emptying time in the domperidone group is significantly shorter than that in the cisapride group ($P < 0.05$).

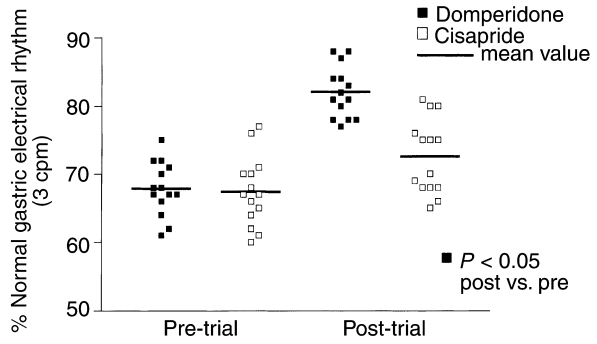

Figure 2. Pre- and post-trial values of normal gastric electrical rhythm (3 cpm) for each patient in the two groups. The post-trial percentage of normal gastric electrical rhythm in the domperidone group is significantly higher than that in the cisapride group ($P < 0.05$).

dependent diabetes mellitus and gastroparesis. Gastrointestinal motility disorders have been widely investigated in diabetic adults, but only a few reports have focused on these disorders in children with insulin-dependent diabetes mellitus. [16–19] We have previously described a paediatric population with insulin-dependent diabetes mellitus with gastroparesis and gastric electrical abnormalities.[18] Interestingly, gastroparesis in these subjects has been shown to be significantly correlated with disturbed metabolic control. Indeed, it is conceivable that delayed gastric emptying may cause asynchrony between insulin effect and the delivery of nutrients into the small intestine.[3, 23, 24] On the other hand, hyperglycaemia itself can affect the neuromuscular mechanisms regulating gastrointestinal motility and delay the gastric emptying process. [23, 25, 26] It should also be emphasized that patients with insulin-

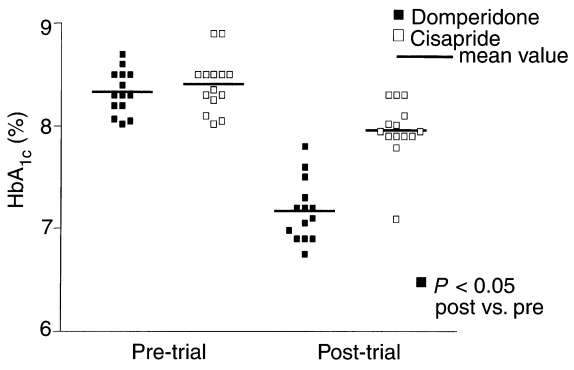

Figure 3. Pre- and post-trial values of the percentage of serum haemoglobin 1c (HbA_{1c}) for each patient in the two groups.

dependent diabetes mellitus and gastroparesis often complain of incapacitating dyspeptic symptoms that lead to morbidity and a poor quality of life.[4] Thus, it is of great importance to try to reverse abnormalities of gastric motility and improve gastric emptying in patients with insulin-dependent diabetes mellitus and gastroparesis. [23]

The greater efficacy of domperidone compared to cisapride might be due to the different mechanisms of action of the two drugs. Gastric emptying delay is usually due to a combination of motor defects, such as exaggerated fundic relaxation, defective antral contractility, impaired antro-duodenal co-ordination and pylorospasm;[27] furthermore, gastric motor disorders may also be sustained by electrical abnormalities, such as those detected in our patients.[3] In particular, both a reduced prevalence of normal electrical rhythm and an increased rate of episodes of tachygastria have been reported to be associated with antral hypo-contractility.[28, 29] An interesting electrical feature detected in the great majority of our patients was a low fed-to-fasting power ratio, thought to reflect post-feeding antral mechanical hypo-contractility.[28–30]

Our study indicates that domperidone has a greater ability than cisapride to affect the pathogenetic mechanisms underlying gastroparesis. Experimental evidence exists that domperidone exhibits various mechanisms of action at the level of intestinal intramural nerves, such as enhanced acetylcholine release, inhibition of cholinesterase activity and adrenergic α-1-receptor antagonism.[6] In contrast, cisapride does not antagonize the intrinsic nervous sympathetic tone.[31] It should be emphasized that increased sympathetic nervous system activity has been associated with the occurrence of gastric electrical dysrhythmias.[32] Therefore, it should

come as no surprise that domperidone is more efficacious than cisapride in improving both gastric mechanical and electrical activity in our patients.

Previous studies in adults with diabetic gastroparesis have evaluated the effects of both domperidone and cisapride on dyspeptic symptoms and the gastric emptying time; however, no studies have compared the effects of the two drugs. Placebo-controlled studies have shown the ability of domperidone to improve symptoms and quality of life in adults with diabetic gastroparesis, regardless of the patient's gastric emptying status;[10, 11] furthermore, in a double-blind comparison of domperidone and metoclopramide, both drugs were effective in relieving functional symptoms, but the side-effect profile was better in the domperidone group.[9] In two placebo-controlled studies in adults with diabetic gastroparesis, cisapride had no significant effects on symptoms and gastric emptying;[14, 15] interestingly, cisapride was also unable to improve glycaemic control, as assessed by plasma blood glucose profiles and HbA_{1c}[15] and by plasma blood glucose levels and insulin requirement.[14] Dutta *et al.* showed that cisapride was significantly better than placebo in improving symptoms and gastric emptying in a diabetic gastroparesis population with a wide age range.[13]

Although a significant correlation between gastric emptying delay and the severity of dyspepsia has not always been reported in subjects with insulin-dependent diabetes mellitus and gastroparesis,[6] dyspeptic symptoms have been shown to correlate with the presence of gastric electrical abnormalities. [12] This could explain the higher efficacy of domperidone than cisapride in improving the clinical score in our patients. It has also been reported that a normal autonomic nerve function is associated with clinical response to domperidone in patients with insulin-dependent diabetes mellitus and gastropathy.[33] Therefore, autonomic function testing has been suggested as a useful marker for the identification of subjects with insulin-dependent diabetes mellitus and gastroparesis who are likely to respond to domperidone.[9] Interestingly, none of our patients had autonomic nerve dysfunction when evaluated before the study.

In our study, we have taken into account glycaemic parameters as markers of metabolic control in addition to dyspeptic symptoms and variables of gastric motility. It is remarkable that clinical improvement and reversal of functional abnormalities of the stomach paralleled the improvement in fasting and post-prandial glycaemia as well as the serum HbA_{1c} levels. We suggest that children with insulin-dependent diabetes mellitus and poor metabolic control should be investigated for symptoms of functional dyspepsia, such as nausea, early satiety, epigastric discomfort and vomiting, and for the presence of gastric motility disorders. The latter can be investigated through non-invasive tools, such as ultrasonography of the stomach and electrogastrography. Domperidone is a valuable and safe agent in children with insulin-dependent diabetes mellitus and gastroparesis because it improves upper gastrointestinal symptoms and metabolic control of diabetes through its prokinetic and anti-arrhythmic effects on the stomach.

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