

Postprandial antropyloroduodenal motility and gastric emptying in gastroparesis – effects of cisapride

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Abstract

There is little information about the organisation of antroduodenal contractions or pyloric motility in patients with gastroparesis. The mechanisms responsible for the acceleration of gastric emptying by cisapride in patients with gastroparesis are also poorly understood. Simultaneous manometric and scintigraphic recordings were performed in 12 patients with gastroparesis and nine healthy volunteers before and after cisapride administration. Antropyloroduodenal pressures were recorded with a sleeve/sidehole manometric assembly and gastric emptying with a scintigraphic method. Thirty minutes after the solid component of the test meal had begun to empty from the stomach all subjects received 5 mg cisapride intravenously over 10 minutes and recordings continued for a further 60 minutes. In the 30 minutes before cisapride there was no significant difference in the number of antral pressure waves (median 20 *v* 33, NS), basal pyloric pressure, or the number of isolated pyloric pressure waves between patients and volunteers, but the number of antral waves of extent ≥ 6 cm (median 1 *v* 5, $p < 0.05$) was less in the patients, as was gastric emptying (8% *v* 20%, $p < 0.05$). In the patients, there was no change in the number of antral waves after cisapride, but there was an increase in the number of antral waves ≥ 6 cm in extent (median 7 *v* 1, $p < 0.05$) and in the rate of gastric emptying (26% *v* 8%, $p < 0.01$). In the healthy subjects, cisapride increased gastric emptying (31% *v* 20%, $p < 0.05$), but reduced the number of antral waves (10 *v* 33, $p < 0.05$). Cisapride had no significant effect on the number of antral waves of extent ≥ 6 cm (11 *v* 5, NS). The number of isolated pyloric pressure waves decreased after cisapride (4 *v* 11, $p < 0.05$). There was a relationship between gastric emptying and the number of antral pressure waves of extent ≥ 6 cm in both the patients ($r = 0.38$, $p < 0.05$) and healthy subjects ($r = 0.50$, $p < 0.01$). There was no significant relationship between gastric emptying and the number of antral waves. It is concluded that disturbance of the relationship between antral, pyloric, and duodenal pressure waves is a major abnormality of postprandial gastric motor function in patients with gastroparesis. The stimulation of antral pressure waves of extent ≥ 6 cm may contribute to the acceleration of gastric emptying produced by cisapride in patients with gastroparesis and in normal subjects.

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Gastroparesis is now known to occur frequently and may result in upper gastrointestinal symptoms such as anorexia, nausea, vomiting, and abdominal pain.¹ There is limited information about the motor dysfunctions which lead to abnormally delayed gastric emptying. Although gastric emptying is probably dependent on the relationship between contractions in the proximal stomach, antrum, pylorus, and proximal small intestine,^{1,2} there is a paucity of information about the function of any motor component other than the antrum in patients with abnormally slow gastric emptying.³⁻⁷ It has been suggested that antral hypomotility is the major cause of delayed gastric emptying.³ However, it is clear that many patients with severe gastroparesis have both fasting and postprandial antral hypomotility,^{3,7} an increased frequency of antral contractions⁸ and abnormalities of pyloric⁹ and small intestinal^{6-8,10} motility have also been reported in gastroparetic patients. Analysis of antral motility has usually been done with a motility index which takes into account contraction frequency and amplitude.^{7,11} Such an approach gives no information about the pattern of space-time organisation of contractions, derangement of which might contribute to slow gastric emptying.

Drugs have proved to be the most effective way for acceleration of emptying in gastroparetic patients. Cisapride increases gastric emptying in many forms of gastroparesis,¹²⁻²⁰ but the mechanical effects responsible for this improvement are poorly understood. In dogs, cisapride increases antral contractions,²¹⁻²³ decreases the number of contractions which are localised to the pylorus,²¹ and increases the number of temporally associated antroduodenal pressure waves.^{22,23} In humans, cisapride increases the antral motility index.^{5,24} No studies have examined the effects of cisapride on the organisation of antral contractions or pyloric motility in gastroparesis, factors that have been examined in the present study.

Methods

SUBJECTS

Simultaneous manometry and gastric emptying studies were performed in 12 patients (three men and nine women) with gastroparesis. The median age of the patients was 43 years (range 26-69) and their median body weight was 71 kg (range 51-100). The aetiology of the gastroparesis was type 1 diabetes mellitus (3), associated with gastroesophageal reflux disease (3), and idiopathic (6). Information about the

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patients is given in Table I. In all subjects, gastric outlet obstruction had been excluded by upper gastrointestinal endoscopy. Gastroparesis was diagnosed before entry to the study by demonstration of the retention of >61% of the solid component of a radioisotopically labelled mixed solid/liquid meal at 100 minutes after meal completion.^{14,15} In the patients the median amount of the solid meal remaining in the stomach at 100 minutes was 82% (range 65–100%). All medication, apart from insulin, was stopped 48 hours before the study and smoking was prohibited on the day of the study. Studies were also performed in nine healthy subjects (six men and three women), median age 26 years (range 18–32), median body weight 69 kg (range 54–91), who were on no medication and had no evidence of gastrointestinal disease. The patients were older than the healthy subjects ($p < 0.05$), but there was no difference in body weight between the two groups.

Written informed consent was obtained from each subject. The protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

PROTOCOL

In the morning, after each subject had fasted from solids from 1900 hours and liquids from 2400 hours the previous day, a manometric assembly was passed transnasally and its position across the pylorus was verified with dual point transmucosal potential difference (TMPD) measurements.^{25–27} In the first two patients studied, an endoscopic technique was used to place the manometric assembly. After intravenous sedation with diazepam (5 mg), the assembly, stiffened with a removable guidewire, was towed into the duodenum under direct vision with an endoscope. After correct positioning, the guidewire was removed from the assembly. In both of these patients a recovery period of four hours was observed after the procedure and before eating the meal. In all other subjects the catheter was positioned by posture and with the aid of a weighted tip, as described previously.^{25–27} Subjects ingested the radioisotopically labelled test meal at approximately 1300 hours. About 30 minutes after the solid component of the meal had started to empty from the stomach, each subject was given cisapride (Janssen Pharmaceutica) 5 mg intravenously over 10 minutes via an indwelling venous cannula. The cisapride was dissolved in 10 ml of 5% dextrose. Manometric and scintigraphic recordings were continued for 60 minutes after the intravenous injection. In all diabetic patients, the venous blood glucose concentration was monitored at least every 30 minutes throughout the study, and maintained at between 6 and 10 mmol/l. In each patient gastrointestinal symptoms^{14,15} and autonomic nerve function²⁸ were evaluated formally on enrolment into the study.

MEASUREMENT OF ANTROPYLORODUODENAL PRESSURES

The manometric technique was similar to that

described in other studies.^{25,27} Pressures were measured with a 10 lumen perfused manometric catheter, which incorporated a 4.5 cm sleeve sensor in parallel with an array of sideholes. Sideholes at each end of the sleeve recorded intraluminal pressure and the transmucosal potential difference (TMPD) simultaneously. These sideholes are referred to as the antral and duodenal TMPD sideholes.^{25–27} Pressures from the TMPD sideholes, taken in conjunction with those recorded by two sideholes along the sleeve, allowed discrimination of isolated pyloric contractions (IPPWs) from short antropylic pressure waves. The evaluation of the space-time organisation of pressure waves was done not only for pressures recorded at 1.5 cm intervals along the sleeve, but also from the pressures recorded by the four sideholes located at 1.5 cm intervals proximal to the sleeve, and the sidehole 1.5 cm distal to the sleeve.

Manometric channels were perfused with degassed liquid at 0.3 ml/minute with an adapted pneumohydraulic pump. The antral and duodenal TMPD channels were perfused with normal saline from separate reservoirs; all other channels were perfused with distilled water from a third reservoir.^{25–27} Pressures were recorded with pressure transducers (catalogue number 38/8000/1: Deseret Medical Inc, Sandy, Utah) interfaced to a 12 channel chart recorder (model 7D; Grass Inc, Quincy, Mass), which was run at a paper speed of 100 mm/min. The transmucosal potential difference was measured via the saline columns that perfused the antral and duodenal TMPD sideholes. Measurements were recorded continuously on the chart recorder throughout the experiment. Records were analysed only when the sleeve was positioned correctly across the pyloric TMPD gradient. The definition of correct positioning was antral TMPD ≤ -20 mV, duodenal TMPD ≥ -15 mV, with a difference between the two of at least 15 mV.^{25,27} On these criteria the assembly was positioned correctly for more than 95% of the total recording time during the experimental period. Records were divided into 15 minute periods for 30 minutes before and 60 minutes after cisapride, with time 0 being the start of the intravenous injection. Pressure waves were counted if their amplitude was ≥ 10 mm Hg.²⁷ Because the manometric technique was designed to record basal pyloric pressures, we were unable to measure the peak amplitude of all pressure waves, as the pen recorder went off the marked scale when pressure was >45 mm Hg.

The pressure waves recorded in the antral TMPD sidehole were counted to provide a simple motility index.^{25,27} Waves recorded by the sleeve spanning the pylorus were classified as isolated pyloric pressure waves (IPPWs), when they occurred in the absence of any discernible pressure wave in the antral or duodenal sidehole and were seen in no more than one sidehole along the sleeve.²⁵ As in previous studies basal pyloric pressure was referenced to distal antral pressure.^{25,27} Basal pyloric pressure was sampled from the tracing by deriving a visual mean value for the first 30 seconds of each minute of each study. Duodenal motility was evaluated by counting the number of pressure

waves recorded by the distal duodenal sidehole.²⁵ Antral and duodenal pressure waves were judged to be associated in time if the onset of the pressure wave recorded in one sidehole occurred within 5 seconds of the onset of a pressure wave recorded in an immediately adjacent sidehole.²⁷ The luminal distance over which associated waves occurred was determined from the spacing of sideholes on the manometric assembly.²⁷ The number of associated antral pressure waves of extent ≥ 6 cm was determined for each 15 minutes of the study.²⁷

MEASUREMENT OF GASTRIC EMPTYING

Gastric emptying was measured with a previously described technique.²⁹⁻³¹ Each test meal was ingested at approximately 1300 hours. The study was performed in the sitting position with a scintillation camera behind the subject. The solid meal consisted of 100 g cooked ground beef mixed with chicken liver labelled in vivo with ^{99m}Tc sulphur-colloid. The total caloric content of the solid meal was approximately 270 kcal (25 g protein, 21 g fat). The unlabelled liquid component of the meal was 150 ml of 10% dextrose. Corrections were made for patient movement, gamma ray attenuation, and radionuclide decay.^{29,30} Gastric emptying curves were derived for the solid component of the meal and expressed as the percentage remaining within the stomach over time. Calculations were made from these curves of duration of the lag phase (before any of the solid meal emptied from the stomach) and the amount of the solid meal which emptied from the stomach in the 30 minute interval before and the two 30 minute intervals immediately after injection of cisapride.

TABLE I Characteristics of the patient group

Patient no	Age (y)	Sex	Aetiology of gastroparesis	Autonomic nerve function score*	Gastric symptom score†
1	69	M	Diabetes mellitus	6	8
2	33	F	Diabetes mellitus	3	4
3	33	F	Idiopathic	0	15
4	36	F	Idiopathic	0	13
5	31	F	Idiopathic	0	18
6	51	F	Associated with gastroesophageal reflux disease	6	6
7	26	M	Idiopathic	0	15
8	49	F	Associated with gastroesophageal reflux disease	1	2
9	66	M	Diabetes mellitus	4	0
10	61	F	Idiopathic	4	13
11	32	F	Idiopathic	0	10
12	67	F	Associated with gastroesophageal reflux disease	3	0

*Maximum score 6, autonomic neuropathy present if score ≥ 2 .
 †Maximum score of 18 derived from six symptoms.

TABLE II Effect of cisapride on basal pyloric pressure*

	Basal pyloric pressure (mm Hg) at time		
	-30-0 min	0-30 min	30-60 min
Patients	1.7 (0.8-3.7)	1.3 (0.8-1.4)	0.4 (0.2-1.3)
Volunteers	0.5 (0.0-1.0)	0.4 (-0.3-0.7)	0.0 (-0.7-1.0)

*Data are median values and interquartile ranges. Cisapride was given at time 0. There are no significant differences.

ASSESSMENT OF GASTROINTESTINAL SYMPTOMS

Before each study, gastrointestinal symptoms were evaluated with an established questionnaire.^{14,15,30} Anorexia, nausea, early satiety, upper abdominal discomfort or distension, and vomiting were each scored as 0=none, 1=mild (symptom could be ignored if the patient did not think about it), 2=moderate (symptom could not be ignored, but did not influence daily activities), 3=severe (symptom influenced daily activities). The maximum possible total score was therefore 18.

ASSESSMENT OF AUTONOMIC NERVE FUNCTION

Autonomic nerve function was assessed by standard cardiovascular reflex tests.²⁸ Parasympathetic function was evaluated by heart rate variation (R-R interval) during deep breathing and the immediate heart rate response to standing (30:15 ratio). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. The result of each of the three tests was scored as 0=normal, 1=borderline, 2=abnormal (for a maximum possible score of 6) according to the criteria of Ewing and Clarke.²⁸ Autonomic neuropathy was defined as a score ≥ 2 .³⁰

STATISTICAL ANALYSIS

Data within each group were analysed using the two tailed Wilcoxon matched pairs signed-rank test, and between groups with a two way analysis of variance for each 30 minute period. Relationships between emptying and motility were evaluated using the Pearson correlation coefficient. A p value of <0.05 was considered significant in all analyses. All values are expressed as median and interquartile range.

Results

There was considerable variation in gastrointestinal symptoms among patients (Table I). The median symptom score was 9 (range 0-18). Seven patients, of whom three had longstanding diabetes mellitus, had autonomic neuropathy.

Nasogastric intubation and ingestion of the test meal were well tolerated by all subjects. Approximately 15 minutes after completion of the cisapride injection, two patients and one healthy volunteer complained of light headedness and nausea. In all instances these symptoms resolved promptly when the subjects lay flat. Data from these three subjects was excluded from analysis. The remaining 18 subjects did not report any adverse effects.

PRESSURE WAVES

There was no significant difference between the patients and healthy subjects in the number of antral pressure waves, IPPWs, or basal pyloric pressure in the 30 minute interval before cisapride (Table II, Figs 1 and 2). The median number of antral waves in the gastroparetic patients did not approach significance ($p < 0.2$). In the patients with gastroparesis there were fewer antral pressure waves of extent ≥ 6 cm

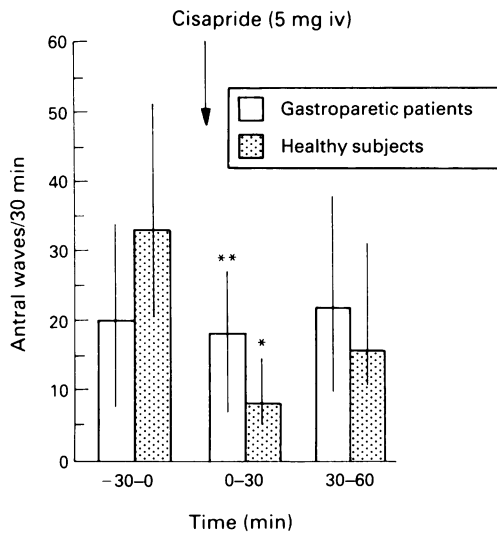


Figure 1: Group data for antral pressure waves for gastroparetic patients and volunteers (medians and interquartile range) before and after intravenous cisapride. (* $p < 0.05$ compared with values before cisapride, ** $p < 0.05$ control v gastroparetic patients.)

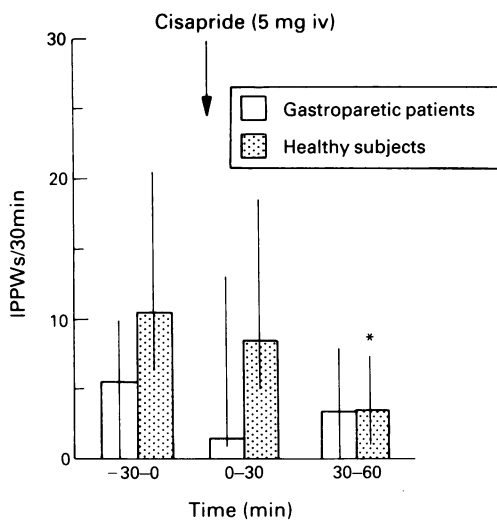


Figure 2: Group data for isolated pyloric pressure waves (IPPWs) for gastroparetic patients and volunteers (medians and interquartile range) before and after intravenous cisapride. (* $p < 0.05$ compared with values before cisapride.)

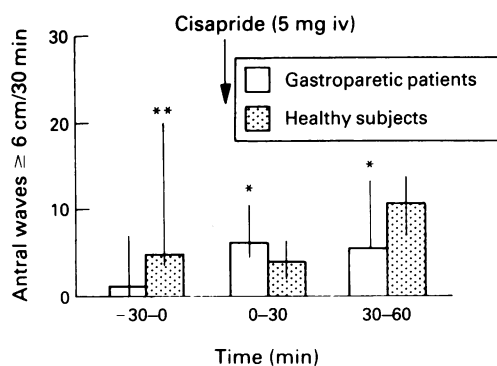


Figure 3: Group data for antral pressure waves of extent ≥ 6 cm for gastroparetic patients and volunteers (medians and interquartile range) before and after intravenous cisapride. (* $p < 0.05$ compared with values before treatment; ** $p < 0.05$ control v gastroparetic patients.)

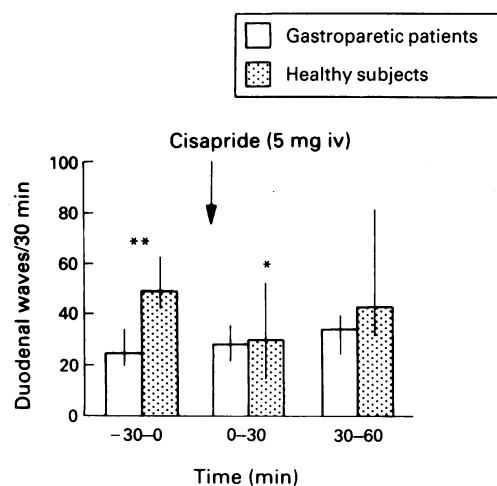


Figure 4: Group data for duodenal pressure waves for gastroparetic patients and volunteers (medians and interquartile range) before and after intravenous cisapride. (* $p < 0.05$ compared with values before cisapride; ** $p < 0.05$ control v gastroparetic patients.)

($p < 0.05$, Fig 3), and the number of duodenal pressure waves was also less ($p < 0.05$, Fig 4). An example of a manometric trace from a patient is shown in Figure 5. There was no significant difference in antropyloroduodenal pressures in gastroparetic patients with or without evidence of autonomic neuropathy. There was also no significant relationship between the score for gastrointestinal symptoms and antropyloroduodenal motility.

In the control subjects there was a decrease in both antral ($p < 0.05$) and duodenal pressure waves ($p < 0.05$) in the 30 minutes immediately after cisapride. The subsequent 30 minute values were not significantly different from those before cisapride ($p > 0.2$, Figs 1 and 3). The number of IPPWs was reduced ($p < 0.05$) in the second 30 minute interval after cisapride (Fig 2). Cisapride had no effect on basal pyloric pressure (Table II). The median increased number of antral waves of extent ≥ 6 cm in the second 30 minutes after cisapride did not approach statistical significance ($p < 0.3$) (Fig 4).

In patients, cisapride had no significant effect on the number of antral, or duodenal pressure waves, or basal pyloric pressure (Table II, Figs 1-3). The median decrease in the number of IPPWs after cisapride was not statistically significant ($p < 0.2$). Cisapride administration was associated with an increase in the number of antral pressure waves of extent ≥ 6 cm ($p < 0.05$) in both of the 30 minute periods after cisapride (Fig 4). This effect is illustrated in Figure 5. In the first 30 minutes after cisapride the number of antral pressure waves was less in the controls than in the gastroparetic patients ($p < 0.05$, Fig 1). After cisapride there was no significant difference between the two groups in the number of antral waves of extent ≥ 6 cm.

GASTRIC EMPTYING

The duration of the lag phase did not differ between the healthy volunteers and the patients (median 48 min v 49 min, $p < 0.3$). Emptying of the meal in the 30 minutes before cisapride was slower ($p < 0.05$) in the patients with gastroparesis (Fig 6). In the healthy volunteers there was a non-significant trend for slower emptying in the first 30 minutes after cisapride ($p < 0.08$) and an increase in the amount emptied in the second 30 minutes ($p < 0.05$). In the patients with gastroparesis, emptying was increased in both 30 minute periods after cisapride ($p < 0.01$). After cisapride administration there was no significant difference in the rate of gastric emptying between the two groups.

RELATIONSHIP BETWEEN GASTRIC EMPTYING AND PRESSURE WAVES

There was a significant correlation between the number of antral waves of extent ≥ 6 cm and the rate of gastric emptying in both the healthy subjects ($r = 0.50$, $p < 0.01$) and the patients with gastroparesis ($r = 0.38$, $p < 0.05$) (Fig 7). There was also a significant correlation between the number of duodenal pressure waves and the rate of gastric emptying in the healthy subjects ($r = 0.48$, $p < 0.01$), but not in the patients ($r = 0.31$,

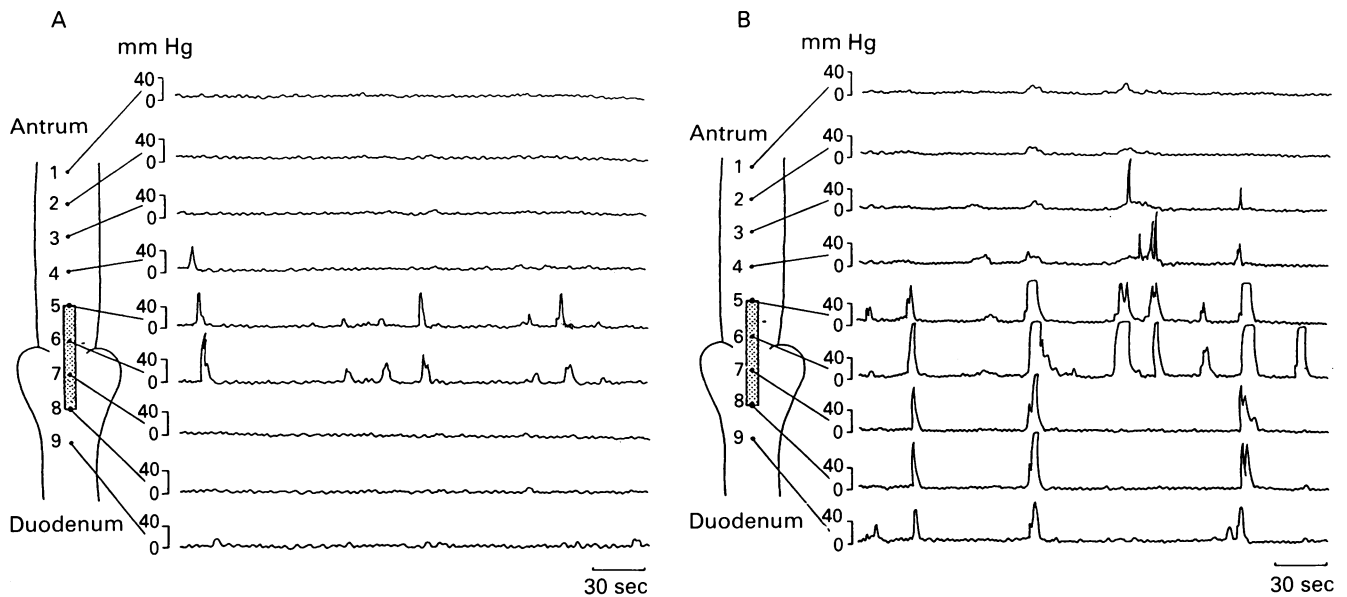


Figure 5: Representative manometric tracing during emptying in a patient with gastroparesis before (A) and after (B) cisapride administration. Schema shows the approximate position of manometric channels. Port 1 is located in the antrum and port 9 in the proximal duodenum. The position of the sleeve sensor is indicated by the stippled area. The predominant pattern before cisapride consists of pressure waves confined to the distal antrum and pylorus, and few duodenal pressure waves. Thirty minutes after cisapride administration an antral pressure wave of extent ≥ 6 cm is recorded.

$p < 0.1$). There was no significant correlation between gastric emptying and the number of antral pressure waves ($r = 0.06$, NS; $r = 0.25$, NS), or IPPWs ($r = -0.29$, NS; $r = -0.21$, NS) in either group.

Discussion

A clear understanding of the motor dysfunctions responsible for delayed gastric emptying is of fundamental importance for the rational use and further development of pharmacological treatments. The results from this study suggest that

disturbance of the relationship between antral, pyloric, and duodenal pressure waves is a major abnormality of postprandial gastric motor function in patients with gastroparesis. Our data also indicate that the improvement in gastric emptying in patients with gastroparesis after intravenous cisapride (5 mg) is related to stimulation of antral pressure waves of extent ≥ 6 cm, rather than to an overall increase in the number of antral pressure waves.

The observation that the slow rate of gastric emptying in patients with gastroparesis is related to a decreased number of associated antral pressure waves of extent ≥ 6 cm, rather than to the absolute number of antral pressure waves is not unexpected, although this has not been evaluated previously to our knowledge. In normal subjects, it is recognised that antral contractions have markedly different effects on the movement of gastric contents, ranging from powerful expulsion into the duodenum that is not selective for particle size, to a totally retroulsive and, presumably, triturative pattern.¹² The rate of gastric emptying of a solid meal has been reported to relate to the number of temporally associated antropyloroduodenal pressure waves.²⁷ Studies which have reported reduced fasting^{4,6,10} and postprandial^{3,7,8} antral motility in symptomatic patients with severe gastroparesis have employed a motility index, which takes into account both the frequency and amplitude of antral pressure waves, but provides no indication as to the organisation of these waves, nor indeed a clear indication of the number of antral pressure waves. It should be recognised that our technique was designed to record basal pyloric pressure and the peak amplitude of all antral pressure waves could not be measured. Our findings may therefore not be at variance with the reduced postprandial antral motility reported in other studies of patients with gastroparesis,^{3,7} as it is likely that antral pressure waves that occur over a greater extent are of higher amplitude than those which are more localised. Our observations are also consistent with Stacher *et al*,¹⁹ who reported a reduction in the amplitude but not the frequency of antral contractions

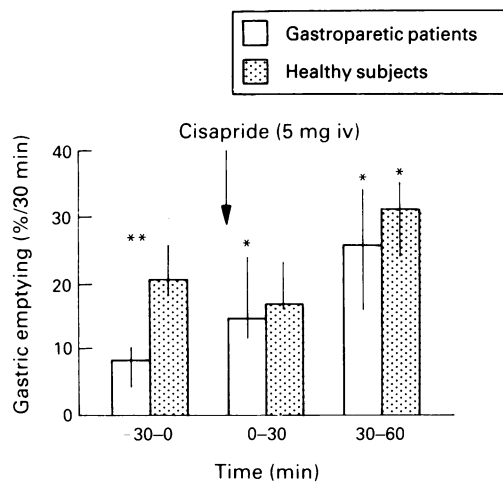


Figure 6: Group data for gastric emptying of a solid meal in patients with gastroparesis and volunteers (medians and interquartile range) before and after intravenous cisapride. (* $p < 0.05$ compared with values before treatment; ** $p < 0.05$ controls v gastroparetic patients.)

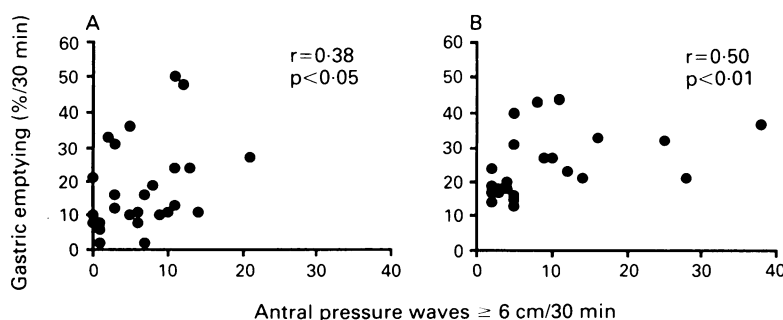


Figure 7: Relationship between gastric emptying and the number of antral pressure waves ≥ 6 cm in extent in patients (A) with gastroparesis ($r = 0.38$, $p < 0.05$) and healthy controls (B) ($r = 0.50$, $p < 0.01$). Values for each subject are shown as three 30 minute intervals (one before and two after intravenous cisapride.)

evaluated scintigraphically in patients with delayed gastric emptying because of primary anorexia nervosa.

In normal subjects, the pylorus seems to be important in the regulation of gastric emptying.^{25,26} A previous study suggested that an increased number of localised pyloric contractions may contribute to delayed gastric emptying in patients with diabetes mellitus.⁹ In this latter study pyloric pressures were evaluated by a sidehole judged on manometric grounds to be positioned in the pylorus. Using a sleeve sensor in the present study we did not detect any evidence of abnormal phasic or tonic pyloric motility in patients with gastroparesis, of whom three had diabetes mellitus, as a group. The zone of the pylorus that generates IPPWs and tone is narrow (<6 mm length) and mobile.³² We therefore believe that the use of sideholes at 1 cm intervals is inadequate for pyloric manometry. Consequently, even though we evaluated a heterogeneous group of patients with gastroparesis, the discrepancy between our results and those of Mearin *et al*⁹ is likely to primarily reflect methodological differences, rather than the patient groups that were studied. It should also be recognised that hyperglycaemia slows gastric emptying in normal subjects³³ and patients with diabetes mellitus.³⁴ Hyperglycaemia stimulates IPPWs in healthy subjects,³⁵ but there are no data in patients with gastroparesis. The increased pyloric motility reported in the study by Mearin *et al*⁹ may have been due to hyperglycaemia, as blood glucose concentrations were apparently not monitored.

The heterogeneous nature of the motor dysfunctions in patients with gastroparesis³⁻⁹ has important implications for pharmacotherapy.¹ The increased rate of gastric emptying caused by cisapride in the patients with gastroparesis and normal subjects was related to the stimulation of associated antral pressure waves of extent ≥ 6 cm. It is unlikely that the progressive reduction in the volume of gastric contents contributed to an enhanced detection of antral contractions, as the amount of a solid meal in the distal stomach remains relatively constant for most of the emptying phase.³¹ A double-blind controlled study design was not used because of ethical limitations in the radiation dose that could be used, the substantial technical challenges in performing transpyloric intubation with a sleeve-sidehole manometric assembly in patients with gastroparesis, and the previous finding that placebo (saline) injection given about 30 minutes after a solid meal has started to empty from the stomach has no effect on either gastric emptying or antropyloroduodenal pressures.³⁶ While previous studies in patients with gastroparesis reported that the increase in gastric emptying after intravenous cisapride is associated with increased antral motility, as evaluated by an index,^{5,19,37} the effects of cisapride on the organisation of antropylic contractions has not been examined. Our results are consistent with studies in dogs which showed that cisapride decreased the number of antral contractions, but increased the number of temporally associated antral and duodenal contractions.²³ The observation that the magnitude of the stimulatory effect

of cisapride on gastric emptying and antral waves of extent ≥ 6 cm was greater in the patients with delayed emptying, when compared with normal subjects, is consistent with previous studies indicating that the beneficial effects of cisapride on gastric emptying are most marked when the latter is delayed.^{14,17}

There have been no studies which have assessed the effects of cisapride on pyloric motility in patients with gastroparesis. The observation that there was a significant fall in the number of IPPWs in the healthy subjects and a trend for a decrease in the patients with gastroparesis after cisapride is consistent with the findings of Edelbroek *et al*,²¹ who reported that cisapride abolished the IPPW response to intraduodenal nutrient stimulation in the dog. More IPPWs are recorded after ingestion of nutrient liquids, and during small intestinal nutrient infusion than after solid meals.^{25,27} Therefore while further studies are required to determine the effect of cisapride on the pyloric motility after these stimuli, our results suggest that suppression of isolated pyloric motility may contribute to the beneficial effects of cisapride on gastric emptying.

The methods used in our study did not allow us to evaluate proximal stomach motility, which is likely to be important in the regulation of gastric emptying.³⁸ Further studies need to be performed to evaluate proximal stomach motility in patients with non-surgical gastroparesis and address the role of gastrokinetic agents on this region of the stomach as it is possible that effects of cisapride on fundic tone may contribute to acceleration of gastric emptying. The linkage between proximal and distal gastric motility in gastroparesis warrants further evaluation. Such studies will provide most information if pressure and flow can be measured simultaneously.

Although the plateau serum levels after 5 mg of intravenous cisapride are comparable with those from conventional oral dosage, peak serum levels may be higher.¹⁶ The transient suppression of antral contractions observed immediately after cisapride in the normal subjects is consistent with our previous study³⁶ and is likely to reflect higher plasma drug concentrations. It is unlikely that the initial suppressive effects are of relevance to clinical practice. The lack of suppression by cisapride in the gastroparetic patients may be a consequence of the relatively lower number of antral contractions in this group, but may also reflect differences in function of the enteric nervous system between the groups.

The lightheadedness and nausea reported by two of our patients and one of our volunteers are likely to be related to the cardiovascular effects of cisapride and may have become apparent because subjects were studied seated and in the postprandial state. Transient faintness and dizziness have been observed after parenteral administration of cisapride, (¹⁶, personal communication Dr M Verlinden). Bateman *et al*³⁹ reported that intravenous cisapride produced transient falls in blood pressure and an increase in heart rate of about 10 beats/min in healthy ambulant subjects, possibly as a result of vaso-

dilatation. Further circumstantial support for this concept of vasodilatation comes from a study by Horowitz *et al*¹⁵ in which some patients with progressive systemic sclerosis reported improvement in Raynaud's phenomenon while taking cisapride. It is of interest that in our study no side effects were reported in those patients with evidence of autonomic neuropathy. These cardiovascular effects may be due to interaction of cisapride with serotonin receptors.⁴⁰⁻⁴² At present there are no plans for the intravenous formulation of cisapride to be marketed (Dr M Verlinden personal communication) and there have been no reports of a similar adverse effect with oral cisapride in doses up to 40 mg/day.¹⁶ It is therefore unlikely that these apparent adverse effects are important during clinical practice.

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