Effect of itopride on gastric emptying in longstanding diabetes mellitus

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Abstract *Delayed gastric emptying (GE) occurs in 30–50% of patients with longstanding type 1 or 2 diabetes, and represents a major cause of morbidity. Current therapeutic options are limited. We aimed at evaluating the effects of itopride on GE in patients with longstanding diabetes. Twenty-five patients (20 type 1, 5 type 2; 10 males, 15 females; mean age 45.2 ± 2.7 years; body mass index 27.5 ± 0.9 kg m^{-2}; duration of diabetes 20.2 ± 2.4 years) were enrolled in a double-blind, placebo-controlled, randomized, crossover trial. Subjects received both itopride (200 mg) and placebo t.i.d. for 7 days, with a washout of 7–14 days. GE (scintigraphy), blood glucose (glucometer) and upper gastrointestinal (GI) symptoms (questionnaire) were measured following each treatment period. The test meal comprised 100 g ground beef (^{99m}Tc-sulphur colloid) and 150 mL of 10% dextrose [^{67}Ga-ethylenediaminetetraacetic acid (EDTA)]. There was a slight trend for itopride to accelerate both solid (P = 0.09) and liquid (P = 0.09) GE. With itopride treatment, the emptying of both solids and liquids tended to be more accelerated, as the emptying with placebo was slower (solids: r = 0.39, P = 0.057; liquids: r = 0.44, P < 0.03). Twelve (48%) patients had delayed solid and/or liquid GE on placebo and in this group, itopride modestly acceler-ated liquid (P < 0.05), but not solid (P = 0.39), empty-ing. Itopride had no effect on mean blood glucose during the GE measurement (placebo: 9.8 ± 0.6 mmol L^{-1} vs itopride: 9.6 ±0.6 mmol L^{-1}), or GI symptoms (placebo: 1.4 ± 0.4 vs itopride: 1.8 ± 0.5). Itopride, in a dose of 200 mg t.i.d. for 7 days, tends to accelerate GE of liquids and solids in longstanding diabetes. The magnitude of this effect appears to be modest and possibly dependent on the rate of GE without itopride.*

Keywords *diabetes, gastric emptying, itopride.*

INTRODUCTION

Delayed gastric emptying (GE) occurs in 30–50% of patients with longstanding type 1 or type 2 diabetes and may be associated with upper gastrointestinal (GI) symptoms, impaired nutrient and drug absorption, and poor glycaemic control.[1–4] Treatment with prokinetic drugs, including metoclopramide, domperidone, cisapride and erythromycin, forms the mainstay of symptomatic diabetic gastroparesis therapy.[5] While short-term administration of all of these drugs has been shown to accelerate GE and improve symptoms, both the magnitude of symptomatic improvement and the change in GE are variable.[5] Moreover, all of the currently available drugs have significant limitations. The use of metoclopramide is associated with a high incidence of adverse central nervous system effects.[6] There is evidence that the prokinetic effects of erythromycin, metoclopramide and domperidone are not sustained during chronic administration;[7,8] in the case of erythromycin, tachyphylaxis probably reflects downregulation of motilin receptors.[5] Cisapride was

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arguably the first-choice therapy [8] but its use has been greatly curtailed because of its tendency to prolong the Q–T interval and induce potentially fatal cardiac arrhythmias.[9] The prokinetic effect of some drugs, including erythromycin and cisapride, is also attenuated during hyperglycaemia.[10–14] Hence, current pharmacological therapy is suboptimal and there is a need for new options.

Itopride is a benzamide derivative bearing a distinct structural resemblance to prokinetic drugs including cisapride, metoclopramide and domperidone.[15–20] Itopride blocks dopamine (D_2) receptors on cholinergic motor neurones and inhibits acetylcholinesterase (AChE) to increase the acetylcholine level and thereby, stimulate GI motility.[16,20,21] Itopride is highly polar and, therefore, does not cross the blood–brain barrier readily so that the risk of extrapyramidal effects is low. Itopride also does not affect the Q–T interval and is metabolized by flavine-dependent monooxygenases (FMO3), rather than cytochromes P450, so the potential for drug–drug interactions is low.[22]

A recent study reported that itopride was effective in the treatment of functional dyspepsia with a low risk of adverse effects.[19] In dogs, itopride has been shown to dose-dependently stimulate motility in the antrum, duodenum and colon.[20] In a Japanese study, itopride, when administered as a single dose of 50 mg, was reported to accelerate GE, as assessed by the relatively insensitive acetaminophen method, in 15 'chronic gastritis' patients, of whom 11 apparently had delayed GE.[23] There is only limited evidence that itopride is an effective prokinetic agent in patients with diabetes, and there have hitherto been no randomized, placebo-controlled trials. In a study reported in abstract form, oral administration of itopride (150 mg day^{-1} for 2 weeks) improved both GE and gastric myoelectrical activity in 12 type 2 diabetic patients with peripheral neuropathy.[24] However, the study was not randomized and GE was quantified by the acetaminophen [25] and radiopaque marker [26] methods, rather than scintigraphy, which is considered to be the 'gold standard'.[26]

The purpose of this study was to evaluate the effect of itopride on GE of solids and liquids measured by scintigraphy in an unselected cohort of patients with longstanding diabetes mellitus, using a randomized, placebo-controlled design.

MATERIALS AND METHODS

Subjects

Twenty-five Caucasian patients with diabetes (20 type 1, 5 type 2; 10 male, 15 female; age 45.2 ± 2.7 years; body mass index 27.5 ± 0.9 kg m^{-2}; duration of known diabetes 20.2 ± 2.4 years; and glycated haemoglobin 8.7 ± 0.4%) were enrolled in the study. Patients were randomly selected from those attending outpatient clinics at the Royal Adelaide Hospital and through advertisements posted in local community newspapers. Patients were not selected on the basis of the presence or absence of GI symptoms or known gastroparesis. None had a history of liver, cardiac or respiratory disease or GI surgery, apart from uncomplicated appendicectomy. All patients had normal renal function (serum creatinine 0.05–0.12 mmol L^{-1}; calculated creatinine clearance >60 mL min^{-1}). One of the five patients with type 2 diabetes was using insulin. The oral hypoglycaemic agents used to treat patients with type 2 diabetes included metformin, gliclazide, glimepiride, rosiglitazone, pioglitazone and acarbose. Patients taking medication known to influence GI motility were excluded and smoking was prohibited for 24 h prior to, and during, each GE measurement. Written, informed consent was obtained from each subject prior to their enrolment in the study. The protocol and advertisements were approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and all studies were performed in accordance with the Declaration of Helsinki.

Protocol

Subjects were enrolled in a randomized, double-blind, placebo-controlled, crossover trial consisting of a screening visit (V1) (performed within 14 days from start of treatment), followed by two 7-day treatment periods, during which each subject received both itopride (200 mg) and placebo three times daily before meals. The two treatment periods were randomized and separated by 7–14 days. Autonomic nerve function was assessed during the screening visit (V1). Immediately following each treatment period (i.e. V2 and V3), subjects attended the Department of Nuclear Medicine, PET and Bone Densitometry at 09.30 hours after an overnight fast (14 h for solids, 12 h for liquids) and an intravenous cannula was inserted into an antecubital vein for subsequent blood sampling. The venous blood glucose concentration was then measured. If the blood glucose concentration was <12 mmol L^{-1}, the subjects were asked to administer their usual morning dose of insulin 15 min before the test meal; if the blood glucose concentration was ≥12 mmol L^{-1}, the subjects were instructed to administer their usual dose of insulin immediately and the GE measurement was not commenced until the blood glucose concentration was <12 mmol L^{-1}. Subjects on oral hypoglycaemic

agents took their usual morning dose approximately 15 min before the test meal. Subjects took their last dose of trial medication 60 min before commencement of the GE measurement. Compliance was assessed by a count of returned tablets.

Measurements

Gastric emptying Gastric emptying was measured using a standardized, dual-isotope scintigraphic test.[27] The test meal comprised 100 g lean ground beef, labelled with 20 MBq ^{99m}Tc-sulphur colloid chicken liver, followed immediately by 150 mL of 10% dextrose, labelled with 6 MBq ^{67}Ga-ethylenediaminetetraacetic acid (EDTA). The solid component of the meal was consumed within 5 min, followed by the liquid within 1 min. Radioisotopic data were acquired, with the subjects seated with their back against a gamma camera (GEnie; GE Healthcare Technologies, Milwaukee, WI, USA) at 1-min intervals for the first hour and at 3-min intervals thereafter. Time zero was defined as the time of meal completion and GE was monitored for 120 min. Data were corrected for subject movement, radionuclide decay and gamma-ray attenuation, the latter by using correction factors derived from a lateral image of the stomach.[27] The lag phase was determined visually as the time between meal completion and the appearance of radioactivity in the proximal small intestine.[27] From the GE curves (expressed as the percentage retention over time), the intragastric retention at t = 0, 15, 30, 45, 60, 75, 90, 105 and 120 min was derived.[27] The amount (%) of solid remaining in the stomach at 100 min (T100 min) and the time taken for 50% of the liquid to empty (T50%) were also quantified;[1] GE was considered to be delayed when the solid T100 min was ≥61% and/or the liquid T50% was ≥31 min, based on an established normal range.[1,8]

Glycaemic control During each GE measurement, venous blood samples (5 mL) were obtained at t = −2, 30, 60, 90 and 120 min. Blood glucose concentrations were determined immediately using a portable blood glucose meter (Medisense Companion 2 meter; Medisense Inc., Waltham, MA, USA). The mean of these blood glucose measurements was calculated.

Gastrointestinal symptoms Upper GI symptoms were assessed by questionnaire on the morning of both study days, prior to consumption of the test meal. 'Gastric' (anorexia, nausea, early satiation, abdominal bloating/fullness, vomiting, abdominal pain) and 'oesophageal' (dysphagia, heartburn and acid regurgitation) symp-

toms were graded as 0 = none, 1 = mild (the symptom could be ignored), 2 = moderate (the symptom could not be ignored, but did not influence daily activities) and 3 = severe (the symptom influenced daily activities). As there were nine symptoms, the maximum possible total score was 27.[28]

Autonomic nerve function Cardiovascular autonomic nerve function was assessed on V1 using standardized cardiovascular reflex tests.[29] Parasympathetic function was calculated by the variation (R–R interval) of the heart rate during deep breathing (E/I) and the immediate heart rate response to standing (30 : 15). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. Each of the tests was scored 0 = normal, 1 = borderline, 2 = abnormal, for a maximum total score of 6. A score of ≥3 was considered to be indicative of autonomic neuropathy.[1,28]

Statistical analysis The sample size of 25 patients was based on the number of subjects included in our previous studies, which demonstrated beneficial effects on GE after oral prokinetic therapy (domperidone and cisapride) in patients with diabetes,[7,8] in order to provide a statistical power of 80% with $P < 0.05$. Data (GE and blood glucose concentration) were evaluated using repeated-measures analysis of variance (ANOVA) with 'treatment' and 'time' as factors and are presented as mean ± SEM. Student's *t*-test (two-tailed) for paired comparisons was used to compare sample mean values (T100 min and T50%). Relationships between variables were analysed using linear regression analysis. For the rejection of the null hypothesis, an error probability of $P < 0.05$ was considered as significant. Treatment order effect was assessed by repeated-measures ANOVA, with treatment order as a between-subject factor. A carryover effect of the drug was deemed evident if there was significance for the treatment order main effect or any of its interactions.

RESULTS

No serious adverse events were reported. The total score for autonomic neuropathy was 3.0 ± 0.2 (median score 3, range 0–4). Fifteen of the 25 patients had evidence of autonomic neuropathy (i.e. total score ≥3) and in the remaining 10, the result was 'borderline' (i.e. total score ≥1 and <3). Assessment of tablet counts revealed adequate patient compliance with respect to medication; 3 patients missed 1 of the 22 doses and 1 patient missed 3 doses. There was no evidence of a treatment order effect in any of the analyses.

Gastric emptying

On both days, solid emptying approximated an overall linear pattern after an initial lag phase (itopride: 17.6 ± 2.5 min vs placebo: 20.6 ± 3.1 min; $P = 0.31$), and liquid GE an overall monoexponential pattern, after a short lag phase (itopride: 1.3 ± 0.2 min vs placebo: 1.4 ± 0.2 min; $P = 0.65$). There was a slight trend for an acceleration of GE by itopride for both solids ($P = 0.09$, $F = 3.05$, d.f. $= 24$) and liquids ($P = 0.09$, $F = 3.15$, d.f. $= 24$) (Fig. 1). However, there was no significant difference in either the solid T100 min (itopride: $47.7 \pm 4.3\%$ vs placebo: $52.2 \pm 4.1\%$; $P = 0.23$, d.f. $= 24$) or liquid T50% (itopride: 25.5 ± 2.4 min vs placebo: 27.4 ± 2.2 min; $P = 0.43$, d.f. $= 24$) between treatments. In all 25 patients, the emptying of both solids and liquids tended to be more accelerated, as the emptying with

Figure 2 Relationship between the magnitude of the change in gastric emptying (placebo–itopride) for (A) solid (retention at 100 min) and (B) liquid (T50) with gastric emptying on placebo ($n = 25$, data are mean ± SEM).

placebo was slower (solids: $r = 0.39$, $P = 0.057$; liquids: $r = 0.44$, $P < 0.03$) (Fig. 2). Of the 25 patients, about one-third emptied solids and liquids more rapidly on placebo compared with itopride (Fig. 2).

Of the 25 patients, 12 (48%) had delayed solid and/or liquid GE on placebo. In this group, there was no difference in solid ($P = 0.39$, $F = 0.81$, d.f. $= 11$) emptying, however, there was a treatment-by-time interaction for liquid ($P = 0.02$, $F = 3.03$, d.f. $= 11$); itopride accelerated liquid GE in this group (Fig. 3). There was no significant difference in either the solid T100 min
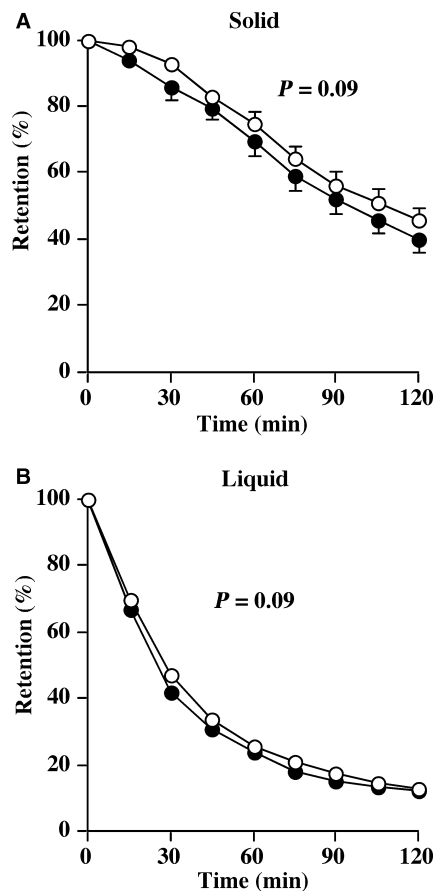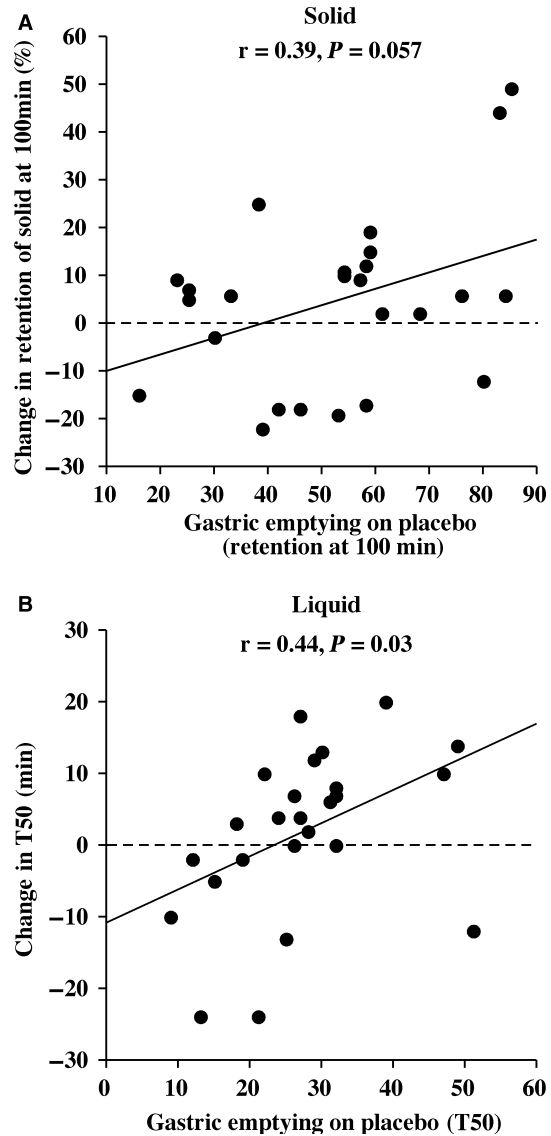
Figure 1 Gastric emptying of (A) solid and (B) liquid meal components following treatment with itopride (200 mg p.o. t.i.d.) and placebo (black circles, itopride; white circles, placebo; $n = 25$, data are mean ± SEM, P-values generated by ANOVA).
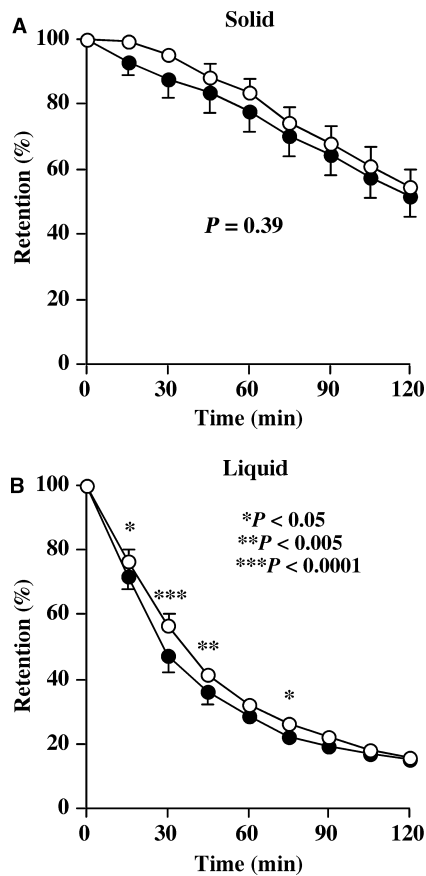
Figure 3 Gastric emptying of (A) solid and (B) liquid meal components following treatment with itopride (200 mg p.o. t.i.d.) and placebo in patients with delayed gastric emptying of solids and/or liquids on placebo (black circles, itopride; white circles, placebo; *n* = 12, data are mean ± SEM; *P*-values generated by ANOVA, *$P < 0.05$, **$P < 0.005$, ***$P < 0.0001$).

(itopride: 60.2 ± 6.1% *vs* placebo: 62.7 ± 5.9%; $P = 0.72$, d.f. = 11) or liquid T50% (itopride: 30.3 ± 3.9 min *vs* placebo: 34.1 ± 3.0 min; $P = 0.29$, d.f. = 11) between treatments. Seven of the 12 patients with delayed solid and/or liquid GE on placebo had evidence of autonomic neuropathy (i.e. total score ≥3).

Blood glucose concentrations

There was no significant difference in baseline blood glucose concentrations between treatments (itopride: 8.3 ± 0.6 mmol L^{-1} *vs* placebo: 8.4 ± 0.7 mmol L^{-1}). On both days, there was a rise ($P = 0.0001$ for both) in blood glucose after the meal (Fig. 4), without any significant difference between itopride and placebo. There was also no difference in mean blood glucose concentrations (itopride: 9.6 ± 0.6 mmol L^{-1} *vs* placebo: 9.8 ± 0.6 mmol L^{-1}) during the studies. The
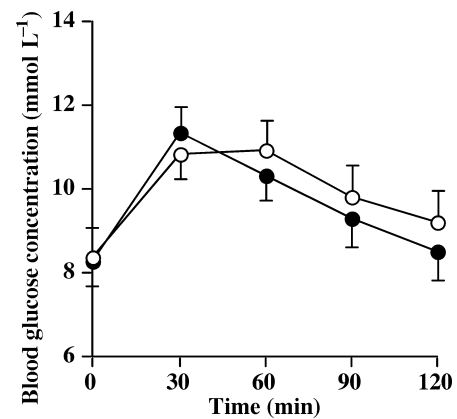

Figure 4 Blood glucose concentrations during gastric emptying measurements following treatment with itopride (200 mg p.o. t.i.d.) and placebo (black circles, itopride; white circles, placebo; *n* = 25, data are mean ± SEM).

blood glucose concentration–time profile did not differ significantly between treatments in the 12 patients with delayed solid and/or liquid GE on placebo (data not shown). The effect of itopride on GE was not significantly related to the blood glucose concentration (data not shown).

In the eight patients in whom GE of solids was faster on placebo than itopride, there was a relationship with the change in blood glucose concentration ($r = 0.83$, $P = 0.01$), i.e. GE was slower when the blood glucose concentration at baseline was relatively higher.

Upper gastrointestinal symptoms

Fourteen patients had GI symptoms on placebo: two of these rated at least one symptom as 'severe'. There was no difference in the total score for upper GI symptoms between treatments (itopride: 1.8 ± 0.5 *vs* placebo: 1.4 ± 0.4), nor was there any difference in either 'gastric' (itopride: 1.6 ± 0.4 *vs* placebo: 1.3 ± 0.4) or 'oesophageal' (itopride: 0.2 ± 0.1 *vs* placebo: 0.1 ± 0.1) symptoms.

DISCUSSION

Our observations indicate that itopride hydrochloride, when administered as a dose of 200 mg t.i.d. for 7 days, has little effect on GE of solid and/or liquid meal components in patients with longstanding diabetes mellitus. This is perhaps unexpected in view of previous reports relating to the effects of itopride on gastric motility/GE.[23,24]

Itopride has been reported to have beneficial effects on GE and gastroduodenal motility in both animals[15–17,20] and humans.[23,24] In conscious dogs, intravenous

itopride (3 mg kg^{-1}) increased antral and duodenal contractility and antagonized dopamine-induced inhibition of gastric contractions.[15] When administered orally, itopride (30 mg kg^{-1}) accelerated GE in dogs and antagonized dopamine-induced delay in GE in rats.[16] At higher doses (10 mg kg^{-1} i.v.), itopride enhanced contractile activity in all regions of the GI tract from the stomach to the colon in the dog.[20] In 15 Japanese 'chronic gastritis' patients, in whom itopride (50 mg p.o.), or placebo, was administered 30 min prior to ingestion of a drink containing 1.5 g acetaminophen, itopride was reported to accelerate GE in all of them, as reflected by an increase in the serum acetaminophen concentration 45 min after the test meal.[23] While it was suggested that of these 15 patients, 11 had delayed GE, this diagnosis was made on the basis of serum acetaminophen levels. In another Japanese study, itopride (150 mg p.o. daily) was administered for 2 weeks in 12 patients with type 2 diabetes who had peripheral neuropathy and been 'diagnosed with gastroparesis'. Itopride was reported to accelerate GE of a meal containing radiopaque capsules and acetaminophen, however, the study was not placebo-controlled or randomized.[24] In a more recent study performed in the US, itopride in doses of 100 and 200 mg t.i.d. reduced total gastric volume without accelerating GE in healthy volunteers.[30] Thus, although both a single dose of 50 mg p.o.[23] and 150 mg p.o., administered for 2 weeks,[24] were reported to accelerate GE in Japanese patients with gastroparesis, doses of 100 mg and 200 mg t.i.d. proved ineffective in healthy volunteers.[30] The absence of an effect of itopride on GE in healthy subjects[30] does not argue strongly against an effect in patients with gastroparesis, as it is well recognized that the effect of prokinetic drugs is usually more marked when GE is delayed.[5] It should also be noted that in Caucasians, the AUC and C_{max} for itopride are some 30–50% less than that in Japanese subjects for the identical dose, so that 50 mg itopride in Japanese subjects resulted in a C_{max} comparable with that achieved with a 100 mg dose in Caucasians.[31]

We intentionally selected a heterogeneous cohort of patients with longstanding type 1 or type 2 diabetes, the majority of whom had autonomic neuropathy and less-than-optimal chronic glycaemic control. While itopride did not accelerate GE of solids or liquids significantly, the observed relationship between the magnitude of the improvement of GE by itopride with GE on placebo suggests that an acceleration of GE may only be evident in patients with gastroparesis, particularly those with markedly delayed GE. As discussed above, this would not be surprising.[5] Twelve of the 25 patients we studied had delayed solid and/or liquid GE (as would be expected given the selection criteria)[1,4]

and in this group, itopride accelerated GE of liquids significantly, although the magnitude of this acceleration was modest. These data should also be regarded circumspectly as there was no significant difference in the T50% value (P = 0.29). Hence, particularly given the P-value (0.09), the use of a larger sample size may well have detected a difference in GE on itopride compared with placebo, although any effect would seem likely to be small. Previous studies have demonstrated substantial effects of short-term administration of other prokinetics (e.g. domperidone, erythromycin, metoclopramide) with comparable, or smaller, numbers of subjects.[7,8,32] It should also be recognized that the prokinetic effects of such agents may be dose-dependent, as is the case for erythromycin[33] and that higher doses may induce a motor pattern which slows GE.[33] Hence, further evaluation of the effects of different doses of itopride on GE in patients with diabetic gastroparesis, particularly those with markedly delayed GE, would be warranted.

It should also be recognized that acute changes in the blood glucose concentration have a substantial, and reversible, effect on GE in both healthy subjects and patients with diabetes. Marked hyperglycaemia (blood glucose 16–20 mmol L^{-1})[34] and even blood glucose concentrations that are within the normal postprandial range (4–8 mmol L^{-1}),[35] slow GE when compared with euglycaemia, while insulin-induced hypoglycaemia accelerates emptying.[36] Acute hyperglycaemia, including changes in the blood glucose concentration within the postprandial range, may also attenuate the response to prokinetic drugs.[10,12–14] Hence, while we ensured that the blood glucose concentration immediately prior to the GE measurement was <12 mmol L^{-1} and the mean blood glucose during the GE measurements were <10 mmol L^{-1}, we cannot discount the possibility that the effects of itopride on GE may be more marked during euglycaemia. This can only be resolved by the use of glucose clamps to stabilize blood glucose concentrations in the euglycaemic range. It is, however, relevant to note that while the effects of erythromycin on GE have been evaluated during euglycaemia,[32] blood glucose concentrations have not been stabilized (or in most cases even monitored) in essentially all studies relating to the effects of prokinetic drugs on GE in diabetes and despite this, beneficial effects have been demonstrable.[7,8]

Upper GI symptoms occur frequently in patients with diabetes and affect quality of life adversely.[1] The relationship between symptoms and disordered GE is, however, relatively weak.[28] Similarly, there is a poor correlation between the effects of prokinetic drugs on

symptoms and GE.[5] A beneficial effect on symptoms may also potentially be mediated by mechanisms unrelated to acceleration of GE.[5] In a recent study, itopride in a dose of 50 mg p.o. t.i.d. has been reported to improve GI symptoms in patients with functional dyspepsia, but GE was not measured.[19] The majority of our subjects did not have severe symptoms and our study was not designed to evaluate the effect of itopride on upper GI symptoms.

ACKNOWLEDGMENTS

CONFLICTS OF INTEREST

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