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A double-blind, randomized, placebo-controlled trial of itopride (100 and 200 mg three times daily) on gastric motor and sensory function in healthy volunteers

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Abstract *Itopride, a dopamine D2 antagonist and acetylcholinesterase inhibitor, significantly improved symptoms in patients with functional dyspepsia in one phase II randomized trial. However, the mechanisms by which itopride may improve symptoms are unknown. We aimed to compare the effects of two doses of itopride and placebo on gastric volumes, gastric emptying, small bowel transit and satiation in female and male healthy volunteers. Randomized, double-blind, placebo-controlled study evaluated gastric function before and after 7 days of itopride 100 mg (n = 16) or 200 mg (n = 15) or placebo (n = 15) t.i.d. Validated methods were used to study gastric accommodation (single photon emission computed tomography), gastric emptying and orocecal transit and satiation postnutrient challenge. The three arms were comparable with regard to age, gender and body mass index. There were no statistically significant effects of itopride on gastric emptying, orocecal transit, fasting gastric volume, maximum tolerated volume or aggregate symptom score with nutrient drink challenge. Postprandial (PP) change in gastric volume differed in the three groups (P = 0.019): 625[±28 (SEM)], 555(±26) and 512(±33) in placebo, itopride 100 and 200 mg groups, respectively. In healthy subjects, itopride reduced total PP gastric volume without accelerating gastric emptying or significantly altering gastric motor and sensory function in healthy individuals.*

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INTRODUCTION

Dyspepsia is a common condition accounting for 2–5% of all primary care consults; the annual prevalence is 25%, and most have unexplained or functional dyspepsia.[1–3] Dyspepsia is a major cause of morbidity and economic loss in the community.[4] Despite the high prevalence of functional dyspepsia and its significant impact on social and health care costs, pharmacologic treatments of patients with functional dyspepsia remain unsatisfactory.

Itopride HCl is a benzamide derivative bearing a distant structural resemblance to prokinetics like cisapride, metoclopramide and domperidone. It appears to stimulate endogenous acetylcholine release by antagonizing the dopamine-2 receptor on the postsynaptic cholinergic neurons, and to have the anticholinesterase activity which may cause the released acetylcholine to accumulate at cholinergic receptor sites.[5,6] Thus, itopride is potentially capable of enhancing cholinergic activity in the gastrointestinal (GI) tract, which in turn may enhance GI motility. Itopride is available on prescription for patients with functional dyspepsia in eight countries.

In animal studies, itopride stimulated motility in the stomach, duodenum, proximal colon and distal colon.[5–7] The effect of itopride on gastric motility was dose-dependent. Judging by the minimum effective doses, the potency of itopride is about one-tenth that of cisapride and metoclopramide. Recently, Holtmann *et al.*[8] reported a multicentre, randomized phase II trial of itopride in patients with functional dyspepsia in Germany. They observed that itopride 100 mg three times daily was more effective in improving the symptoms of functional dyspepsia than placebo. However, little is known about the effects of itopride on gastric function

in healthy volunteers or patients with functional dyspepsia. Furthermore, while some prokinetics such as cisapride may enhance gastric accommodation in healthy individuals through fundic relaxation,[9,10] others such as erythromycin may increase proximal gastric tone and reduce gastric volume in the postprandial (PP) state.[11] Failure of gastric accommodation has been identified as a potentially important pathophysiological mechanism in functional dyspepsia.[12,13] The effects of itopride on gastric volumes and accommodation have not been evaluated.

We, therefore, compared the effects of two itopride doses and placebo on gastric accommodation, gastric emptying and small bowel transit, and PP symptoms during nutrient challenge testing, in healthy volunteers.

METHODS

A randomized, parallel group, double-blind study was undertaken to evaluate the effects of 100 or 200 mg of itopride or matching identical placebo three times daily.

Study subjects

Forty-six healthy subjects were enrolled. These subjects were either healthy males ($n = 14$) or non-pregnant, non-breast feeding healthy female volunteers ($n = 32$) recruited by advertisement. They were required to have a body mass index between 20 and 32 kg m^{-2}, and have no alarm indicators suggesting disease or GI symptoms by valid self-report GI symptom questionnaire.[14] Appropriate birth control for female participants was required during this study. Excluded were subjects with a history of abdominal surgery other than appendectomy, cholecystectomy, caesarian section or tubal ligation. Subjects were not allowed to be on any medications except birth control, hormone replacement therapy and stable thyroid replacement. Medications that may alter GI motility including metoclopramide, domperidone and other similar drugs were prohibited. Over the counter drugs were also prohibited. The study was approved by the Mayo Foundation's Institutional Review Board. Eligible subjects freely gave their written consent prior to starting the study in all cases.

Randomization and concealed allocation

Each subject was assigned a unique patient number to ensure concealed allocation. Randomization was performed by the Axcan Pharma quality assurance packaging development group using a validated system that automated the random assignment of randomization numbers to treatments groups. Treatment allocation was 1 : 1 : 1. Subjects entering the study were all given the next available medication with the lowest randomization number.

Study medications

Following the usual screening, subjects were randomized to receive itopride 100 or 200 mg three times daily or identical placebo. Itopride is rapidly absorbed after oral administration with peak plasma concentrations being reached about 1-h after dosing.[15]

Study procedures

The study was performed over a week. On the first day, the subjects underwent the nutrient drink test. Baseline symptoms and PP symptoms were recorded every 15 min. Subjects were then started on study medication from days 2 through 7, taking a tablet 30 min before meals three times daily. On the last three days, the morning dose of the medication was taken under the supervision of staff in the General Clinical Research Center (GCRC) 30 min prior to testing. On day 6, each subject presented fasting and underwent scintigraphic gastric and small bowel transit measurement as described below. On day 7, participants again presented fasting to the GCRC and completed a second nutrient drink test. Postprandial symptoms were measured every 15 min. On the eighth day of the study, subjects returned again fasting and underwent single photon emission computed tomography (SPECT) imaging to obtain fasting gastric volumes starting 30 min after ingestion of study medication.

Scintigraphic transit measurement

A ^{99m}Tc-Sulphur-colloid labelled egg meal was used to assess gastric emptying and small bowel transit via scintigraphic imaging.[16] Anterior and posterior gamma camera images were obtained at 0, 1, 2, 3, 4 and 6 h after the test meal ingestion to assess solid gastric emptying. The proportion of ^{99m}Tc reaching the colon at 6 h was used as a surrogate marker for small bowel transit.

Nutrient drink test

Subjects ingested 30 mL of a nutrient (Ensure®; ~1 kcal mL^{-1}; 11% fat, 73% carbohydrate, and 16% protein) per minute.[12] Thus, the participants were asked to drink 120 mL of Ensure every 4 min until maximal fullness was reached. They scored satiety at 5-min intervals using a rating scale that combined

verbal descriptors on a scale of 0–5 (0 = no symptoms, 5 = maximum or unbearable fullness). Participants stopped the meal when a score of five was reached. At 30 min after reaching maximum satiation, the study subjects scored their symptoms of bloating, fullness, nausea and pain using a 100-mm visual analogue scale (VAS) anchored with the words unnoticeable and unbearable at the left and right ends. The aggregate symptom score was defined as the sum of VAS scores for each symptom (i.e. maximum 400). The method has been thoroughly characterized and used extensively in our laboratory.[17]

Gastric volumes by single photon emission computed tomography

Tomographic images were acquired using a dual-head gamma camera system (SMV SPECT System™).[18] The gastric mucosa takes up and excretes ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$) from the circulating blood pool. Ten minutes after the intravenous injection of 10 mCi $^{99m}TcO_4^-$, dynamic tomographic acquisition was performed and transaxial images of the stomach constructed. Images were performed fasting and for a total of 32 min after ingestion of 300 mL Ensure®. Two PP periods (1–16 min and 17–32 min) following the meal were assessed. The average of these two volumes was considered to constitute the primary end point for estimating PP responses. Volume changes and ratios between fasting and PP periods were calculated. The proximal stomach volumes were also calculated using the vertical axis to identify the proximal two-thirds of the stomach.

Statistical analysis

The primary analysis was focused on total gastric volumes, specifically the fasting gastric volume, PP gastric volume and the difference (PP – fasting). An analysis of covariance (ANCOVA) was used to test for overall treatment effects (differences between the two groups) incorporating gender as a covariate. Secondary endpoints (e.g. transit summaries such as gastric emptying $T1/2$ values and proximal gastric volumes) were analysed using a similar ANCOVA, while for the nutrient drink test symptom scores and maximum tolerated volume from the day 7 satiety test, the corresponding predrug (day 1) values were also included as a covariate along with gender.

In order to undertake an intention-to-treat (ITT) analysis, missing data values for quantitative endpoints were imputed using the corresponding overall mean (from subjects with non-missing data) and the degrees of freedom for the residual error variance in the ANCOVA reduced by one for each missing value imputed. A per protocol analysis was also performed, but yielded results very comparable to the ITT analysis. Unless otherwise noted, the data are summarized as mean (±SE), and an alpha level of 0.05 was used for assessing statistical significance.

Sample size assessment

The primary endpoint was the change in gastric volume [(post-drug fasting) – (pre-drug fasting)], which has a coefficient of variation of 18% based on previous studies in healthy volunteers.[11,19] There was 80% power to detect a difference between the three groups of approximately 16% using a two-sample comparison ($\alpha = 0.05$). This effect size [100 × (difference in group means divided by overall mean of the two groups)] corresponds to a difference between groups that would be considered clinically relevant in healthy volunteers. The ANCOVA analysis was expected to provide somewhat better power to detect similar size differences between the three groups with 15 subjects per group.

RESULTS

Participant characteristics

A total of 46 subjects were enrolled into the study after screening 52 volunteers. One subject on itopride 100 mg dropped out because of poor compliance and had missing data for gastric volumes. The demographics of the subjects are shown in Table 1. There were no clinically important differences in age, gender, height, weight or body mass index among the three groups.

Table 1 Demographic and baseline satiety test results (symptom scores at 30 min post-maximum tolerated volume)

	Placebo ($n = 15$)	Itopride 100 mg ($n = 16$)	Itopride 200 mg ($n = 15$)
Age*	32 (±2)	32 (±2)	30 (±2)
Female gender (%)	10 (67)	10 (62)	12 (80)
BMI (kg m^{-2}) *	25.1 (±0.9)	24.3 (±0.7)	25.3 (±1.1)
Maximum tolerated volume* (minimum, maximum)	1096 (±58) (840, 1560)	1213 (±101) (600, 1800)	1069 (±90) (650, 1800)
Nausea*	34 (±8)	15 (±5)	36 (±8)
Fullness*	69 (±5)	52 (±6)	67 (±7)
Bloating*	49 (±8)	25 (±6)	50 (±8)
Abdominal pain*	14 (±7)	8 (±4)	26 (±7)
Aggregate score*	166 (±23)	101 (±14)	179 (±25)

*Mean (±SE), BMI = body mass index.

Gastric volumes measured while fasting and postprandially

The total and proximal gastric volumes and the deltas between fasting and the PP state during placebo and drug treatment are shown in Table 2. Fig. 1 summarizes the proximal fasting gastric volumes in the total population. No significant differences in fasting gastric volumes were observed.

Figs 2 and 3 show the PP (minus fasting) gastric volumes (a surrogate of the volume of accommodation). Postprandial change in gastric volume for the whole stomach differed significantly among the three treatment groups ($P = 0.019$), with mean (±SE) volumes of 625(±28), 555(±26), and 512(±33) among placebo, 100, and 200 mg groups, respectively ($P = 0.006$ *vs* placebo, unadjusted). Differences in proximal gastric volume of accommodation were similar, although only borderline statistically significant ($P = 0.087$, Table 2).

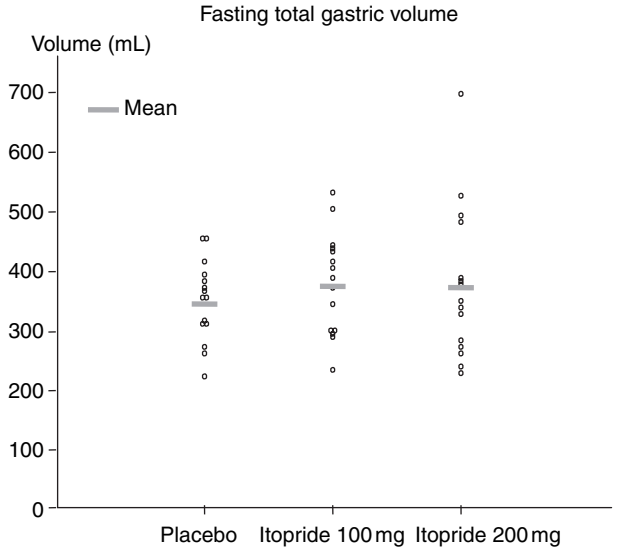

Figure 1 Fasting total gastric volumes in subjects on placebo, itopride 100 or 200 mg three times daily for 6 days.

Maximum tolerated volume and postprandial symptoms with nutrient drink test

After 6 days of therapy, the mean (±SE) maximum tolerated volume and (Table 3) from the nutrient drink challenge on placebo were 1006 mL (±51) *vs* 1050 mL (±85) on itopride 100 mg, and 1069 mL (±75) on itopride 200 mg (overall $P = 0.49$). A significant linear correlation ($r = 0.63$) between the satiety test maximum tolerated volume on day 7 *vs* day 1 over all subjects was observed ($P < 0.001$).

The baseline PP symptom scores 30 min postsatiety for nausea, fullness, bloating, abdominal pain and the corresponding aggregate score were somewhat lower in the itopride 100 mg group *vs* the itopride 200 mg or placebo group (Table 1), but the postdrug (day 7) symptom scores were analysed after adjusting for the corresponding baseline symptom score. The bloating symptom score post-treatment was lower in the itopride 100 mg group at 32 (±8), *vs* 48 (±8) on itopride 200 mg and 49 (±8) on placebo, but this was not significant ($P > 0.05$, Table 2). The aggregate symptom score post-treatment was lower in the itopride 100 mg group at 140 (±17), *vs* 180 (±24) on itopride 200 mg and 163 (±21) on placebo, but this was also not significant ($P = 0.65$, Table 2).

Gastric emptying of solids and orocecal transit

The mean (±SE) solid gastric emptying $T1/2$ on placebo was 109 min (±6), compared with 108 min (±8) and

Table 2 Gastric volumes during fasting and after 300 mL of ensure

	Placebo ($n = 15$)	Itopride 100 mg ($n = 16$)	Itopride 200 mg ($n = 15$)
Fasting total gastric volume†	338 (±26)	375 (±25)	348 (±31)
Postprandial total gastric volume†	963 (±34)	930 (±32)	861 (±41)
Difference on total gastric volume (*postprandial fasting*)†*	625 (±28)	555 (±26)	512 (±33)
Fasting proximal gastric volume†	239 (±23)	268 (±22)	228 (±27)
Postprandial proximal gastric volume†	754 (±32)	735 (±30)	677 (±37)
Difference on proximal gastric volume (*postprandial fasting*)†**	516 (±25)	467 (±23)	449 (±29)

*$P = 0.019$, **$P = 0.087$.
†Least squares adjusted mean (±SE) values from ANCOVA adjusting for gender.

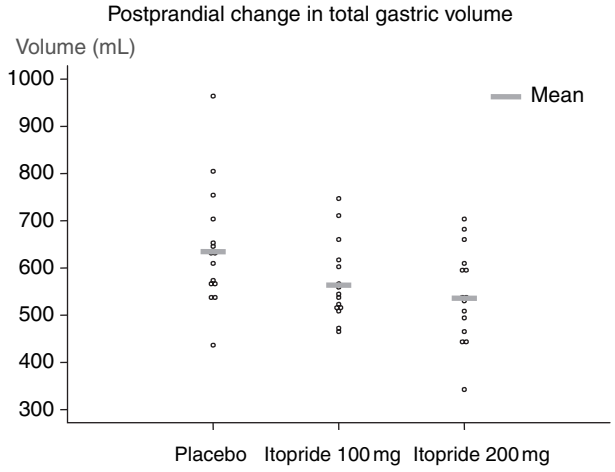

Figure 2 Postprandial change (accommodation) in total gastric volume for subjects on placebo, itopride 100 or 200 mg three times daily for 6 days.

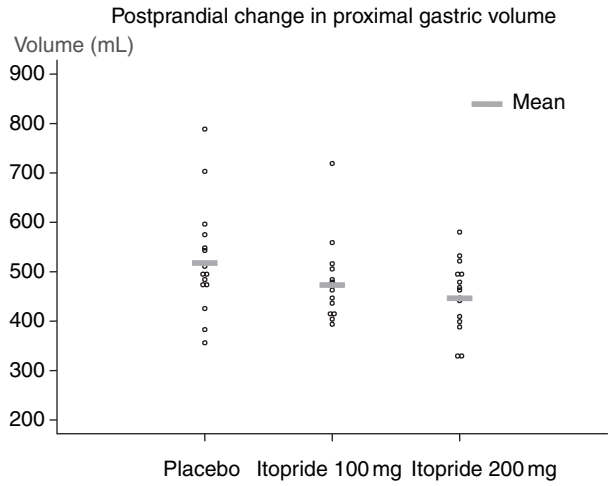

Figure 3 Postprandial change (accommodation) in proximal gastric volume for subjects on placebo, itopride 100 or 200 mg three times daily for 6 days.

103 min (±7) on itopride 100 and 200 mg, respectively ($P = 0.82$).

The mean (±SE) colonic filling at 6 h on placebo was 51% (±9), *vs* 44% (±8) on itopride 100 mg, and 21% (±10) on itopride 200 mg. The overall treatment differences in colonic filling among the three groups adjusting for gender was not significant ($P = 0.51$).

However, there was a borderline significant interaction of gender and treatment for colonic filling ($P = 0.065$), but with just three males in 200 mg group this may not be very robust. The pairwise treatment group differences in females were not significant ($P = 0.70$ for 100 mg *vs* placebo, and $P = 0.98$ for 200 mg *vs* placebo, unadjusted for multiple comparisons). In males, these were $P = 0.67$ for 100 mg *vs* placebo, and $P = 0.014$ for 200 mg *vs* placebo (unadjusted for multiple comparisons), although this should be interpreted cautiously given the small number of males in the 200 mg group.

Safety and tolerability

Two subjects developed mild headache on itopride or placebo, but this did not lead to discontinuation. Otherwise, study drug and placebo were well tolerated.

DISCUSSION

If itopride is efficacious in relieving dyspepsia, this may occur through effects on gastric function or central effects, such as through dopamine D2 antagonist activity. However, our study suggests that itopride impairs gastric volume responses after a meal, a surrogate of accommodation in healthy subjects. In contrast, other gastric motor and sensory functions, including symptoms induced by the nutrient drink challenge to the point of full satiation, gastric emptying and small bowel transit, were not altered.

Itopride is a benzamide derivative and acts through both dopamine D2-receptor antagonism and

Table 3 Post-treatment nutrient drink test maximum tolerated volumes and symptom scores (30 min post-maximum tolerated volume) on placebo, itopride 100 mg and itopride 200 mg

Mean (±SE)*	Placebo ($n = 15$)	Itopride 100 mg ($n = 16$)	Itopride 200 mg ($n = 15$)
Maximum tolerated volume (minimum, maximum)	1006 (±51) (720, 1440)	1050 (±85) (360, 1560)	1069 (±75) (600, 1560)
Nausea	27 (±8)	26 (±6)	34 (±7)
Fullness	71 (±6)	65 (±5)	73 (±5)
Bloating	49 (±8)	32 (±8)	48 (±8)
Abdominal pain	17 (±7)	18 (±6)	25 (±8)
Aggregate score	163 (±21)	140 (±17)	180 (±24)

*Least square adjusted means from ANCOVA adjusting for gender and corresponding baseline nutrient drink test results.

acetylcholinesterase inhibition. Holtmann *et al.*[8] reported that itopride was associated with improvement in pain and fullness in functional dyspepsia, although these results remain to be confirmed. Impaired gastric accommodation has been considered to be a major pathophysiological mechanism in the development of dyspeptic symptoms.[12,13,20] We speculated that itopride would probably increase gastric accommodation, just as cisapride increase gastric accommodation through fundus-relaxing effects.[9] An adequate gastric accommodation response probably reduces meal-induced increases in gastric pressure. However, this study showed that itopride significantly decreased PP gastric volumes. Validation studies have shown correlations between volume responses to a meal and distension and gastric tone measured by means of an intragastric barostat.[21] Our current study suggests but does not prove that itopride worsened gastric accommodation, although this needs to be confirmed by the measurement of gastric tone with a barostat. Fundic relaxation occurs via nitrergic pathways, with inhibition of cholinergic and serotonergic pathways.[22–24] As itopride may stimulate endogenous acetylcholine release and promote accumulation of acetylcholine at cholinergic receptor sites, this may explain the decrease in gastric volume after the meal,[25] and conceivably itopride might have an effect of increasing the contractility of both proximal and distal stomach after a meal. Other prokinetic drugs such as motilin agonists (e.g. erythromycin) may also exacerbate gastric accommodation and reduce gastric volumes.[11,23]

We also observed that itopride did not alter fasting proximal gastric volumes when compared with placebo; higher fasting volumes may be associated with less dyspepsia. Delgado-Aros *et al.*[26] have shown, in 39 patients with functional dyspepsia, that lower fasting gastric volumes were a significant determinant of PP symptoms, and suggested that there is a relationship between fasting gastric volume and symptoms in functional dyspepsia. The lack of a reduction in fasting gastric volumes may similarly explain the lack of a deleterious effect on symptoms postchallenge with a fully satiating meal.

We did not show any significant effects of itopride on gastric emptying. Our results are different to the findings of Harasawa *et al.*[27] who reported accelerated gastric emptying in Japanese patients with dyspepsia. However, they assessed gastric emptying by the acetaminophen method and studied patients with delayed gastric emptying; the different findings may be related in part to the different methods used. Thus, the acetaminophen test evaluates liquid emptying while we studied the emptying of a solid meal containing fat. We chose a high-fat meal in the present study, which could conceivably have slowed gastric emptying and may have reduced the ability to detect the effect of any prokinetic.[28] In health, intact reflex mechanisms such as duodenal feedback loops may minimize the opportunity for a prokinetic to accelerate gastric emptying; the most convincing evidence for acceleration of transit by drugs has been detected in patients with delayed gastric emptying, not in healthy volunteers with normal gastric emptying.[29–31] We therefore cannot exclude the possibility that this study was underpowered for detecting a modest effect of itopride on gastric emptying. In addition, because of short-term treatment period of itopride, an effect of itopride in healthy subjects may also require more than 1 week to detect a change of the gastric physiology.

We did observe that small bowel transit was faster in the itopride 200 mg group than placebo or the itopride 100 mg group, especially in males. However, the overall treatment effect was not significant adjusting for gender, and further large studies in males are needed to evaluate the effects of itopride on orocecal transit time.

The nutrient drink test is a potent dyspeptic stimulus in health, and provides a human model of functional dyspepsia. We did not observe a significant benefit of itopride on nutrient drink test-induced symptoms, although symptoms were slightly lower in the 100 mg itopride arm on therapy, particularly bloating. Notably, although baseline satiety symptom scores were different in the itopride 100 mg group from the placebo or itopride 200 mg groups, we adjusted for the difference in our analyses. Hypersensitivity is also an important pathophysiological mechanism in functional dyspepsia,[32,33] but our study could not evaluate whether itopride alters perception of gastric distension. Recently, Katagiri *et al.*[34] reported that itopride significantly decreased plasma cholecystokinin-like immunoreactive substances (IS), and suppressed adrenocorticotropic hormone-IS when compared with placebo. They suggested that itopride might have a modulatory effect on the hypothalamo-pituitary-adrenal axis and autonomic nervous system. Thus, it is conceivable that central effects not evaluated in our study may underpin the beneficial symptom effects reported by Holtmann *et al.*[8]

In conclusion, this study has shown that while itopride at a dose of 100 or 200 mg three times daily for seven consecutive days in health decreased total (and to lesser extent, proximal) gastric volume change after a meal, it does not appear to have significant effects on other gastric motor and sensory functions in healthy individuals. The effect on orocecal transit

with 200-mg itopride deserves further study. Additional studies are also needed to evaluate the effects of itopride on gastric physiology in patients with functional dyspepsia.

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