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The effects of itopride on oesophageal motility and lower oesophageal sphincter function in man

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SUMMARY

Background
Itopride is a new prokinetic agent that combines antidopaminergic and cholinesterase inhibitory actions. Previous studies suggested that itopride improves heartburn in functional dyspepsia, and decreases oesophageal acid exposure in gastro-oesophageal reflux disease. It remains unclear whether this effect is due to effects of itopride on the lower oesophageal sphincter (LES).

Aims
To study the effects of itopride on fasting and postprandial LES function in healthy subjects.

Methods
Twelve healthy volunteers (five men; 32.6 ± 2.0 years) underwent three oesophageal sleeve manometry studies after 3 days premedication with itopride 50 mg, itopride 100 mg or placebo t.d.s. Drug was administered after 30 min and a standardized meal was administered after 90 min, with measurements continuing to 120 min postprandially. Throughout the study, 10 wet swallows were administered at 30-min intervals, and gastrointestinal symptoms were scored on 100 mm visual analogue scales at 15-min intervals.

Results
Lower oesophageal sphincter resting pressures, swallow-induced relaxations and the amplitude or duration of peristaltic contractions were not altered by both doses of itopride, at all time points. Itopride pre-treatment inhibited the meal-induced rise of transient LES relaxations (TLESRs).

Conclusions
Itopride inhibits TLESRs without significantly affecting oesophageal peristaltic function or LES pressure. These observations support further studies with itopride in gastro-oesophageal reflux disease.

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INTRODUCTION

Itopride is a novel prokinetic agent acting both as a dopamine D2 receptor antagonist and as an acetylcholine esterase inhibitor. Both animal[1–3] and human studies[4–6] have shown the ability of the drug to accelerate delayed gastric emptying, associated with antiemetic properties. In a phase 2 controlled trial, itopride was superior to placebo in relieving symptoms of functional dyspepsia (FD).[6] In a phase 3 programme, this superiority was not confirmed, and comparison of both studies suggested that the presence of heartburn, which was excluded in the phase 3 programme, was a predictor of response in the phase 2 studies.[7] Heartburn is a typical symptom of gastro-oesophageal reflux disease (GERD),[8] and a pilot study in GERD patients confirmed the ability of itopride to decrease oesophageal acid exposure.[9] The mechanisms underlying a potential beneficial effect of itopride in GERD remain to be elucidated.

The pathophysiology of GERD is multifactorial and involves several well-known mechanisms such as failure of the antireflux barrier, impaired oesophageal clearance, the presence of caustic factors in the refluxate (acid and/or non-acid) and defective oesophageal mucosal resistance.[10] The influence of itopride on the antireflux barrier has not been studied. Among the dysfunctions of the antireflux barrier, transient lower oesophageal sphincter (LES) relaxations (TLESRs) comprise the major mechanism underlying gastro-oesophageal reflux events in normal subjects, and in a majority of GERD patients.[10, 11] TLESRs are controlled by a vago–vagal reflex pathway, triggered by activation of stretch receptors of the proximal stomach and organized in the brain stem, leading to transient relaxation of the LES.[12] Pharmacological inhibition of TLESRs is considered a relevant target for the control of GERD.[10] Several pharmacological agents, including atropine, morphine, GABA-B agonists, cholecystokinin 1 receptor antagonists and nitric oxide synthase inhibitors, have been shown to inhibit the occurrence of transient LES relaxations.[12, 13]

The aim of this study was to investigate the effect of itopride on oesophageal and LES function in healthy subjects, with a focus on the occurrence of TLESRs.

MATERIALS AND METHODS

Subjects

Studies were performed in 12 healthy volunteers (five men and seven women; mean age, 32.6 ± 2.0 years; range, 23–41 years) with a mean body mass index of 22.2 ± 0.9 kg/m^2. None of the subjects had symptoms or a history of gastrointestinal disease or upper gastrointestinal surgery, nor were they taking any medication. Written informed consent was obtained from each subject and the study protocol had been approved previously by the Ethics Committee of the University Hospital.

Study design

All subjects underwent the studies after 3 days premedication with itopride 50 mg, itopride 100 mg or matching placebo t.d.s. in a double-blind randomized crossover design. Treatment periods occurred at least 1 week apart. On each day of measurements, subjects were studied after an overnight fast of at least 12 h. A summary of the protocol is shown in Figure 1. Together with a stationary manometry probe, a pH assembly was passed through the nose under topical anaesthesia and positioned with the pH electrode at 5 cm above the LES. After placement of the assembly, the subjects remained in a sitting position for a habituation period of 20 min. This period allowed baseline assessment of oesophageal peristalsis and LES function. Ten wet swallows of 5 mL of water were administered at 1-min interval and followed by ingestion of itoprode or placebo according to the double-blind, randomized crossover design. During the 30 min after administration of the drug, oesophageal and LES pressure and oesophageal pH were continuously monitored. Sixty minutes after drug administration, the

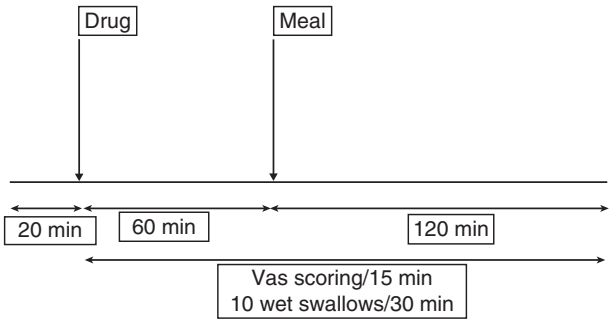

Figure 1 | Study protocol. Healthy volunteers underwent oesophageal sleeve manometry and pH measurement studies after 3 days premedication with itopride 50 mg, itopride 100 mg or placebo. After placement of the assembly 10 wet swallows of 5 mL of water were administered, followed by ingestion of the medication. After 60 min a standardized meal was administered and measurements continued for another 120 min. At 30-min intervals, 10 wet swallows were administered. Throughout the study, at 15-min intervals the intensity of eight epigastric symptoms was scored on visual analogue scales.

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subjects ingested a mixed liquid meal (400 mL, 600 kcal, 13% proteins, 48% carbohydrates, 39% lipids; Nutridrink, Nutricia, Bornem, Belgium), and recordings continued for 2 h after the meal. Throughout the study, 10 wet swallows of 5 mL of water were administered at 30-min intervals. Throughout the study, the sensations of fullness, nausea, heartburn, belching, satiety, hunger, anxiety, dizziness, sleepiness and fatigue were measured every 15 min using validated 100-mm visual analogue scales.

Recording methods

Following an overnight fast, an oesophageal manometric catheter fitted with a 6-cm Dent Sleeve was introduced through the mouth. Subsequently, the oesophageal catheter was positioned so that pressures could be recorded from the gastric fundus (side hole 2 cm below the sleeve), the LES (sleeve), oesophageal body (side holes 4, 7 and 10 cm proximal to the sleeve) and pharynx (side hole 28 cm proximal to the sleeve, to detect swallows). The oesophageal catheter was infused at a flow rate of 0.5 mL/min with distilled water using a low-compliance pneumo-hydraulic capillary infusion system (Arndorfer Medical Specialties, Milwaukee, WI, USA). The infusion system was connected to external pressure transducers, and signals were recorded on a polygraph (Synectics Medical, Stockholm, Sweden).

The oesophageal pH was measured with an antimony pH electrode (Synectics Medical) positioned 5 cm above the proximal margin of the sleeve. The pH electrode was calibrated in buffers of pH 1 and pH 7 before and after each study. During the study period, the oesophageal pH was recorded continuously using an ambulatory data-logger (MicroDigitrapper, Synectics Medical).

Data analysis

Lower oesophageal motility. The basal LES pressure was measured at end-expiration relative to the end-expiratory intra-gastric pressure. The basal LES pressure was visually determined every 3 min and averaged over 30-min intervals. The influence of drug administration on the basal LES pressure was assessed by comparing the value of the first with the value of the third preprandial 30-min interval. Transient LES relaxations were defined according to published criteria:[14] (i) absence of a swallowing signal for 4 s before to 2 s after the onset of LES relaxation; (ii) relaxation rate of ≥1 mmHg/s; (iii) time from onset to complete relaxation of ≤10 s; and (iv) nadir pressure of ≤2 mmHg. Excluding multiple swallows, LES pressure falls that fulfil the last three criteria, but have a duration of >10 s, can also be classified as TLESRs irrespective of the timing of LES relaxation relative to swallowing.

Oesophageal pH. The percentage of time with an oesophageal pH < 4 and the number of acid reflux episodes were calculated. Acid reflux episodes were defined as a decrease in oesophageal pH to a value below pH 4 for at least 4 s or as a rapid drop of at least 1 pH unit if the pH was already below 4.

Statistical analysis

Based on previous studies, the study had 85% power to detect 30% difference in TLESR rate at 5% significance level. The changes in the basal LES pressure were evaluated using analysis of variance for repeated measures. The changes in TLESRs were analysed using analysis of variance for repeated measures and Tukey-Kamer multiple comparisons post-test correction.

$P < 0.05$ was considered to be statistically significant. Data are presented as the mean ± standard error of the mean (S.E.M.).

RESULTS

Conduct of the study

The positioning of oesophageal manometry catheter and pH probe were all well tolerated, and all subjects completed the three sessions of studies as planned.

Lower oesophageal sphincter pressure

Prior to drug administration, LES resting pressure and swallow-induced relaxations were similar for all three conditions (Table 1). However, both doses of itopride significantly decreased intra-gastric pressures compared with placebo (respectively 16.0 ± 1.3 and 17.3 ± 1.5 vs. 20.4 ± 1.7 mmHg, both $P < 0.05$). After drug administration, no significant changes in LES pressure occurred, although there was a tendency towards decreased resting pressure after itopride 50 mg (15.8 ± 2.8 to 11.8 ± 1.8 mmHg, $P = 0.07$). In the placebo condition and after itopride 100 mg, ingestion of the meal was associated with a significant drop in LES pressure, which was already present during the first postprandial hour and persisted during the second postprandial hour. After itopride 50 mg, LES pressure was significantly decreased during the first postprandial hour, but LES pressure had recovered to values that did not differ significantly from preprandial values during the second postprandial hour (Table 1).

Table 1 | Oesophageal motility parameters for the three treatment conditions, before and after drug intake, and before and after the meal. No significant differences between groups occurred

		Placebo	Itopride 50 mg	Itopride 100 mg
LES pressure (mmHg)	Basal	19.7 ± 2.5	15.8 ± 2.8	20.2 ± 3.0
	Postdrug	17.3 ± 3.0	11.8 ± 1.6	19.8 ± 3.7
	Postprandial 1st hour	10.3 ± 1.5*	8.3 ± 1.5*	11.1 ± 1.8*
	Postprandial 2nd hour	8.6 ± 3.0*	10.0 ± 2.0	8.8 ± 4.8*
Distal contraction amplitude (mmHg)	Basal	76.0 ± 3.4	78.4 ± 4.3	76.9 ± 3.7
	Postdrug	83.0 ± 4.8	80.2 ± 4.2	86.2 ± 2.9
	Postprandial 1st hour	78.6 ± 3.6	76.8 ± 3.1	79.5 ± 3.9
	Postprandial 2nd hour	73.9 ± 4.3	73.3 ± 2.9	76.9 ± 4.1
Distal contraction duration (s)	Basal	4.6 ± 0.3	5.2 ± 0.4	4.8 ± 0.3
	Postdrug	5.0 ± 0.3	5.3 ± 0.4	4.7 ± 0.2
	Postprandial 1st hour	5.1 ± 0.3	5.4 ± 0.3	4.7 ± 0.2
	Postprandial 2nd hour	4.9 ± 0.3	5.2 ± 0.3	4.6 ± 0.2

* $P < 0.05$ compared with basal.

Oesophageal motility

Both the amplitude and duration of peristaltic contractions were not significantly altered by both doses of itopride in the preprandial and postprandial periods (Table 1). Swallow-induced relaxations were not altered by either dose of itopride at any time point (Table 2).

Table 2 | Characteristics of swallow-induced relaxations for the three conditions, before and after drug intake, and before and after the meal. No significant differences occurred between groups or over time

	Placebo	Itopride 50 mg	Itopride 100 mg
Relaxation (%)			
Basal	97.7 ± 0.8	97.8 ± 0.7	96.4 ± 0.7
Postdrug	94.4 ± 1.6	92.4 ± 2.3	96.4 ± 1.2
Postprandial 1st hour	92.2 ± 3.9	95.5 ± 1.1	96.8 ± 0.6
Postprandial 2nd hour	95.9 ± 1.2	93.3 ± 1.7	93.0 ± 3.0
Duration (s)			
Basal	11.9 ± 0.4	13.9 ± 0.8	12.8 ± 0.8
Postdrug	11.3 ± 0.7	13.0 ± 0.5	11.7 ± 0.5
Postprandial 1st hour	11.6 ± 0.6	13.4 ± 0.7	11.7 ± 0.7
Postprandial 2nd hour	11.7 ± 0.5	13.0 ± 0.5	12.9 ± 0.6

Swallowing rate

Both before and after the meal, the swallowing rate was significantly altered by itopride 100 mg. However, the 50-mg dose was associated with a significant rise in swallowing rate compared with placebo, both before and after the meal (Table 3).

Transient lower oesophageal sphincter relaxations

The numbers of transient LES relaxations after the administration of placebo and itopride are summarized in Figure 2 and Table 4. After placebo, ingestion of the meal was associated with a significant increase in the rate of transient LES relaxations during the first and the second postprandial hour (ANOVA, $P < 0.001$). After itopride 50 mg, no significant rise of TLESR rate was observed during the first postprandial hour (ANOVA, $P > 0.05$), and in a paired comparison, the rate of TLESRs was significantly lower than after placebo during the first hour (*t*-test, $P < 0.05$). After itopride 100 mg, no significant rise of TLESR rate was seen during the first and the second postprandial hour (ANOVA, $P > 0.05$), and the rate of TLESRs was significantly lower than after placebo during the second hour (*t*-test, $P < 0.05$). The duration of TLESRs did not differ significantly between the treatment conditions (Table 3).

Oesophageal pH monitoring

The percentage of time pH < 4 in the oesophagus did not differ between the itopride and placebo studies in

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Table 3 | Number of swallows for the three treatment conditions, before and after the meal

Pre-treatment	Preprandial	First postprandial hour	Second postprandial hour	Total
Placebo	25.2 ± 2.8	19.0 ± 1.1	20.5 ± 2.2	63.8 ± 5.1
Itopride 50 mg	27.3 ± 2.3	24.6 ± 2.1*	23.8 ± 1.7	75.8 ± 5.5*
Itopride 100 mg	25.3 ± 2.7	21.4 ± 2.5	21.9 ± 2.6	63.1 ± 8.4

* $P < 0.05$ compared with placebo.

the preprandial (0.3 ± 0.1%; 0.3 ± 0.2% and 0.8 ± 0.5%, for placebo, itopride 50 mg and itopride 100 mg respectively; N.S.) and postprandial periods (0.3 ± 0.1%; 0.4 ± 0.1% and 0.3 ± 0.2%, for placebo, itopride 50 mg and itopride 100 mg respectively; N.S.).

The number of acid reflux episodes during the postprandial period after itopride was not significantly different from that after placebo (Figure 3). The number of acid reflux episodes was significantly increased postprandially in the placebo and itopride 100 mg groups, but not in the 50 mg group. Individual data showed a decrease in reflux episodes in all subjects after 100 mg, except for one subject who had a very high rate of reflux episodes under this dose.

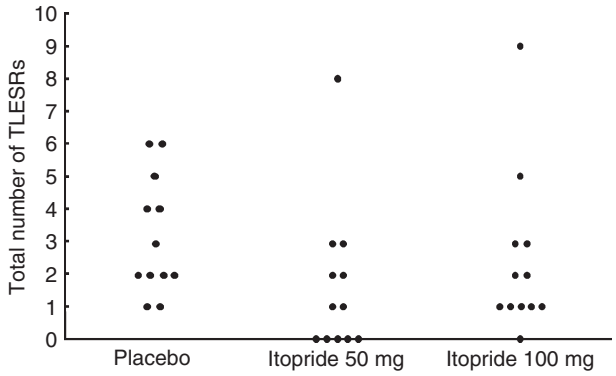

Figure 2 | Individual numbers of total transient LES relaxations for the three treatment conditions.

Symptoms and side effects

No significant difference in symptom scores (calculated as area under the curve, *AUC*) during both the preprandial and postprandial periods was found between the itopride and placebo studies (details not shown).

DISCUSSION

The analysis of phase 2 and phase 3 clinical trials with itopride in FD, as well as a small pH monitoring study in patients with heartburn suggested a beneficial effect of itopride in GERD.[6, 7, 9] To elucidate the underlying mechanism, we studied the influence of two doses of

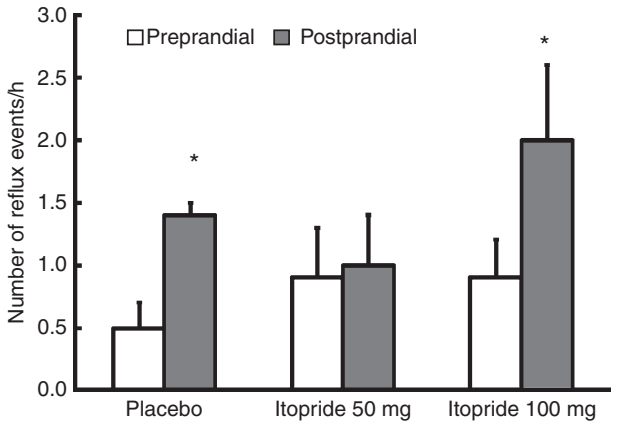

Figure 3 | Acid reflux episodes for the three treatment conditions, before and after the meal. *$P < 0.05$ compared with preprandial.

Table 4 | Number of transient lower oesophageal sphincter relaxations for the three treatment conditions, before and after the meal

Pre-treatment	Preprandial	First postprandial hour	Second postprandial hour	Total
Placebo	0.3 ± 0.1	1.3 ± 0.2*	1.7 ± 0.3*	3.0 ± 0.5*
Itopride 50 mg	0.4 ± 0.3	0.5 ± 0.3†	1.2 ± 0.4*	1.7 ± 0.7*
Itopride 100 mg	0.7 ± 0.2	1.0 ± 0.3	0.4 ± 0.2†	1.7 ± 0.4*

* $P < 0.05$ compared with preprandial.

† $P < 0.05$ compared with placebo.

itopride in a double-blind placebo-controlled crossover study on pre- and postprandial oesophageal motility in healthy volunteers. Our main finding was that itopride inhibited the postprandial increase in the rate of TLESRs without significantly affecting postprandial LES pressure. Oesophageal body peristalsis was also not altered by itopride.

Inhibition of TLESRs is a now well-established therapeutic target in GERD, and this effect may help to explain clinical effects of itopride on heartburn and on oesophageal acid exposure.[6, 7, 9] On the other hand, itopride did not affect oesophageal acid exposure in the present study, and the rise in postprandial acid reflux events was only significantly inhibited in the 50 mg group, with some evidence of large inter-individual variability in the 100 mg group. The lack of major effects on these reflux parameters is probably attributable to the fact that this study recruited healthy volunteers, and not GERD patients, and the relatively low sample size. Confirmation of these effects in a larger group of GERD patients seems warranted.

The mechanism underlying the inhibition of TLESRs by itopride remains to be established. In the absence of effects on oesophageal peristalsis and LES resting pressure, oesophageal motility does not seem to be the target for itopride in TLESR inhibition. TLESRs are controlled by a vago–vagal reflex pathway, which is triggered by gastric distention, integrated in the brainstem and induces release of nitric oxide from intrinsic nerves at the LES.[11–13] The absence of an influence of itopride on swallow-induced LES relaxations, which are also mediated by intrinsic nitrergic nerves, argues against an effect of itopride at this level. Itopride does have the potential to affect the occurrence of TLESRs at the level of triggering through distention of the proximal stomach. Both positron emission tomography studies and gastric barostat studies showed a decreased postprandial volume of the proximal stomach in healthy volunteers after itopride pre-treatment.[15, 16] Finally, an effect of itopride, which is likely to cross the blood–brain barrier,[17] on integration of TLESRs in the brainstem cannot be excluded, but is difficult to study in man.

The effect of itopride on TLESRs seems to lack a clear dose dependency. This could in part be due to some increased variability with the 100-mg dose, as illustrated in Figure 3. However, itopride has a dual pharmacological action as it acts both as a dopamine-2 receptor antagonist and as an acetylcholine esterase inhibitor. It is unclear which one of these pharmacological properties underlies the observed effect on TLESRs. For domperidone, another dopamine-2 antagonist, conflicting data are found in the literature regarding its clinical efficacy in GERD,[18–20] but its effects on TLESRs have not been studied to date. In a preliminary study, decreased postprandial gastric volumes, measured with the barostat, were also reported in healthy volunteers treated with domperidone.[16] Besides D2 receptor antagonism, itopride also exerts cholinesterase inhibitory action. In a gastric barostat study in healthy volunteers, a cholinesterase inhibitor did not alter proximal stomach volume, but increased the number of phasic contractions.[21] It is less likely that this would result in decreased triggering of TLESRs, but the effect of cholinesterase inhibition on TLESRs has not been investigated so far. Conversely, acetylcholine receptor antagonism has been shown to inhibit the occurrence of TLESRs, probably via a central site of action.[22] It is conceivable, but unproven to date, that enhanced cholinergic activity, induced by a cholinesterase inhibitor, might thus lead to enhanced occurrence of TLESRs. If this is indeed the case, higher doses of itopride exerting higher cholinesterase inhibition levels might act to enhance rather than inhibit TLESRs, and this could have contributed to the lack of a dose-dependent effect of itopride in the present study. A decreased rate in swallowing has been implicated in the effects of baclofen on TLESRs and reflux events,[23] but we only observed a modest but significant increase in swallowing rate with the 50-mg dose of itopride.

The present study has a number of limitations. First, the number of reflux events and the number of TLESRs are generally low. This is probably attributable to the selection of asymptomatic healthy subjects with a normal body mass index, and the small size and caloric content of the meal. Second, the liquid meal may lead to more rapid buffering of intragastric acid, thereby under-estimating reflux events when pH monitoring is used. Taken together, it is conceivable that a larger therapeutic effect could be obtained in a population of GERD patients, using a larger meal. Furthermore, the study set-up used two independent systems to monitor manometry and reflux events. Hence, reliable analysis of the motor events underlying the reflux patterns is not possible.

In summary, we demonstrated that the dopamine D2 receptor antagonist and cholinesterase inhibitor, itopride, is able to inhibit the meal-induced increase in transient LES relaxations. The underlying mechanisms require further studies, but could be related to altered postprandial gastric volumes. Based on these observations, further studies of the impact of itopride in GERD seem warranted.

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