**Effect of citalopram on esophageal motility in healthy subjects - Implications for reflux
episodes, dysphagia and globus**

Running title: Effect of citalopram on esophageal function

Anastassios C Manolakis^{1, 2}, Charlotte Broers¹, Hannelore Geysen¹, Nick Goelen¹, Brecht Van Houtte¹, Nathalie Rommel³, Tim Vanuytsel^{1,4}, Jan Tack^{1,4}, Ans Pauwels¹

¹ Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Chronic diseases, Metabolism and Ageing, KU Leuven, Belgium

² Department of Gastroenterology, University Hospital of Larissa, Greece

³ Experimental Oto-Rhino-Laryngology, Department of Neurosciences, Deglutology, KU Leuven, Belgium

⁴ Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium

Correspondence: Jan Tack, MD, PhD
Division of Gastroenterology
University Hospital Leuven
Herestraat 49
B-3000 Leuven, Belgium
Tel.: +32 16 34 42 25
Fax: +32 16 34 44 19
E-mail: jan.tack@kuleuven.be

ABSTRACT

Background Drugs such as citalopram, “targeting” the serotonin pathway, can alter esophageal mechano-chemical sensitivity and gastrointestinal motility. The aim of this study is to clarify the effect of citalopram on esophageal motility and sphincter function, transient lower esophageal relaxations (TLESRs) and reflux events.

Methods Sixteen healthy volunteers (HV) receiving 20mg citalopram or placebo intravenously, in a randomized cross-over fashion, underwent two high-resolution impedance manometry studies involving liquid swallows and a high-fat, high-caloric meal. Manometric, reflux and symptom-related parameters were studied.

Key Results A lower distal contractile integral was recorded under citalopram, compared to placebo ($P=0.026$). Upper esophageal sphincter (UES) resting pressure was significantly higher after citalopram administration throughout the study ($P<0.05$, all periods). Similarly, the UES post-swallow mean and maximum pressures were higher in the citalopram condition ($P<0.0001$, in both cases) and this was also the case for the 0.2s integrated relaxation pressure ($P=0.04$). Esophago-gastric junction resting pressures in the citalopram visit were significantly higher during swallow protocol, pre-prandial period and the first post-prandial hour ($P<0.05$, in all cases). TLESRs and total reflux events were both reduced after citalopram infusion ($P=0.01$, in both cases). During treatment with citalopram, 5 participants complained about globus sensation ($P=0.06$). This citalopram-induced globus was associated with higher UES post-swallow mean and maximum pressure values ($P=0.01$ and $P=0.04$, respectively).

Conclusions and Inferences Acute administration of citalopram exerts a diversified response on esophageal motility and sphincter function, linked to clinically relevant phenomena: a reduction in postprandial TLESRs and the induction of drug-induced globus.

KEYWORDS

Citalopram, transient lower esophageal sphincter relaxations, esophageal motility, upper esophageal sphincter, lower esophageal sphincter

Key Points

- Serotonergic drugs altering lower esophageal sphincter (LES) function have been used in gastroesophageal reflux disease (GERD) management. The effect of citalopram, a selective serotonin reuptake inhibitor, on esophageal motility and LES as well as its anti-reflux potency, remain obscure.
- Citalopram alters esophageal motility and sphincters' function, and induces favorable (reflux reduction) or unfavorable (induction of globus) outcomes.
- The citalopram-induced esophageal motility and sphincter changes suggest possible implications for GERD management and offer insight into the pathogenesis of globus.

INTRODUCTION

Occupying a fair amount of gastroenterologists' every day practice worldwide, gastro-esophageal reflux disease (GERD) remains a challenge due to a high prevalence and a rather demanding management.¹ Although reflux of gastric contents into the esophagus is, to a certain degree, physiological, GERD represents a pathological condition accompanied by various symptoms (e.g. heartburn, regurgitation, chronic cough, hoarseness), mucosal damage (esophagitis, strictures) and potential evolution to metaplasia and malignancy.^{2, 3} The mainstream therapy for GERD, proton pump inhibitor (PPI) use, meant to reduce gastric acid secretion and overall quantity of the acidic refluxate, although largely effective,⁴ fails to control symptoms in 10-40% of patients.^{5, 6} For these refractory GERD patients, other strategies have been utilized, varying from pharmacotherapy to anti-reflux surgery.^{5, 6} In the pharmaco-therapeutic field, research has focused on the reduction of transient lower esophageal sphincter relaxations (TLESRs), the main mechanism underlying reflux.⁶ TLESRs are not triggered by swallowing and occur mainly postprandially allowing reflux of ingested air and gas during belching.⁷ They seem to be induced by gastric distension through mechanoreceptor activation in the proximal stomach and vago-vagal pathway involvement, resulting in release of nitric oxide at the level of lower esophageal spincter (LES).⁸⁻¹⁰ Although TLESR frequency is similar in GERD and health, the selectivity of TLESRs to gas reflux is lost in patients and liquid reflux is more likely to occur.^{11, 12}

Based on these observations, several studies evaluated the effect of pharmacologic agents on TLESRs and, consequently, on GERD. For example, γ -aminobutyric acid-B (GABA-B) receptor agonists and metabotropic glutamate receptor type 5 (mGLUR5) antagonists can increase postprandial LES pressure, inhibit TLESRs and reduce reflux events.^{13, 14} The effect on reflux symptoms, however, was variable and limited.¹⁴⁻²² It seems that, although these drugs inhibit

neurotransmission in the vago-vagal reflex pathways controlling TLESRs, parallel pathways using multiple neurotransmitters also exist.

Such a candidate pathway is that of serotonin (5-hydroxytryptamine, 5HT) regulating sensory and motor functions both centrally and peripherally.²³ Cisapride, a 5HT₄ receptor agonist, originally used for GERD and gastroparesis, enhances LES pressure. Lintopride, a 5HT₃/5HT₄ receptor agonist, can increase LES basal tone and amplify esophageal peristalsis.²⁴⁻²⁶ Furthermore, buspirone, a 5HT_{1A} receptor agonist, can increase LES pressure and esophageal peristaltic vigor.²⁷ On the other hand, sumatriptan, a 5HT_{1B}/5HT_{1D} receptor agonist, increases the frequency of postprandial TLESRs and reflux, despite an increase in postprandial LES pressure.^{28, 29}

Other serotonergic pharmacologic agents, such as citalopram, a selective serotonin reuptake inhibitor (SSRI) enhancing the availability of physiologically released 5HT,^{30, 31} have been shown to reduce esophageal hypersensitivity.^{32, 33} Acute administration of citalopram modified human esophageal mechano-chemical sensitivity,³² induced gastric relaxation, altered gastric emptying and triggered gastroduodenal phase 2 contractions.^{34, 35} Interestingly, although the therapeutic effects of SSRIs become evident on a long-term basis, side effects such as dysphagia and globus sensation appear more acutely.^{36, 37} SSRIs, a.o. citalopram, are often the last resort in patients with refractory GERD, however, the only available studies are based on the symptom pattern. The acute effects of citalopram on LES function have not been elucidated. Bearing these in mind, the aim of the current study was to evaluate the effect of acute citalopram administration on esophageal motility, LES function and, subsequently, on TLESRs and reflux events in healthy subjects.

MATERIALS AND METHODS

Study Population

For the present study 16 healthy volunteers (HV) were recruited: 8 males and 8 females. Exclusion criteria were: history of upper gastro-intestinal (GI) symptoms or GI surgery, psychological disorders, history of drug use, any medication use, smoking and pregnant or nursing women. Mean ($\pm$ SEM) age, BMI and waist-to-hip ratio (WHR) of study participants were 23.9 ± 0.36 years, 23.9 ± 0.73 kg/m² and 0.86 ± 0.01 , respectively.

Study Description

All subjects underwent two study days, at least one week apart, with administration of citalopram or placebo in a double-blind cross-over fashion. The volunteers were fasted for at least 12 h before the study and refrained from alcohol and caffeine for the same period. A high-resolution impedance manometry (HRiM) catheter (Unisensor AG, Attikon, Switzerland) incorporating 36 pressure sensors, spaced either at 2 cm -stomach and esophagus- or 1 cm -LES and upper esophageal sphincter (UES)- and 16 impedance channels throughout the esophagus, was placed transnasally, after topical anesthesia with lidocaine gel (Xylocaine 2%, Astra Zeneca, Brussels, Belgium). High resolution manometry (HRM) was used to record pressure variations in the UES, esophagus, LES and stomach. The impedance channels were used to measure bolus movement, as well as to detect and characterize reflux episodes. Throughout the study, all subjects maintained a semi-recumbent position. Following a 10 min stabilization period after the placement of the catheter, 20 mg of citalopram (0.5 mL) (Cipramil, Lundbeck, Belgium) or placebo (0.5 ml saline) were administered i.v. over 30 min, using 100 mL saline 0.9% NaCl as vector, in a double-blind randomized controlled fashion (see Figure 1). The therapeutic dose range of citalopram is between 10 and 60 mg/day. For the present study, a dose of 20 mg was selected, so that any observed effects would be exerted through enhanced release of serotonin, with subsequent 5HT-receptor activation, and not via

non-serotoninergetic mechanisms.³⁴ Upon i.v. infusion, peak plasma levels are reached after 30 min and stable concentrations are maintained for at least 2h.^{35, 38} A randomization scheme was developed by an experienced researcher of our lab using internet based software (www.randomization.com) and this same person prepared citalopram or placebo solutions during the study. In this way, the investigator performing the study was blinded until the entire study had ended. Because citalopram can cause prolongation of the QTc interval, resulting in arrhythmia,³⁹ HV were screened during first visit by means of an electrocardiogram. Fifteen minutes after the infusion, subjects were given 10 wet swallows of 5 ml saline and one multiple rapid swallow sequence (MRS) of 5 x 2 ml saline, to study esophageal peristalsis. Thereafter, a thirty-minute recording took place followed by ingestion of a high-carbohydrate and high-fat meal of 1000 kcal (mashed potatoes, meatloaf and apple sauce), followed by a 2-hour postprandial recording.

Study parameters

The parameters studied and included for analysis were: UES resting pressure before, during and after swallowing protocol, UES pressure immediately after swallowing/UES re-closure (UES post-swallow mean and maximum pressure), as higher post-swallow residual pressures have been associated with globus in a previous study,⁴⁰ UES postprandial pressure, UES integrated relaxation pressure (IRP) 0.2s, distal contractile integral (DCI), distal latency (DL), contractile front velocity (CFV), esophago-gastric junction (EGJ) IRP4s, EGJ resting pressure before, during and after swallowing protocol, EGJ resting pressure during first and second post-prandial hour (all referenced to intragastric pressure (IGP)), postprandial IGP, number of TLESRs and reflux episodes. Throughout the study, the sensations of fullness, nausea, belching, satiety, hunger and heartburn were measured every 15 min using validated 100-mm visual analogue scales (VAS). During swallows and immediately after meal ingestion, HV were

asked to describe deglutition as being normal, painful, slow, stepwise, obstructed, as well as to note and report additional irregular sensations e.g. xerostomia, globus sensation. Globus sensation (the sensation of an irritating foreign body in the throat) was evaluated throughout both studies (citalopram or placebo) and was coded in a binary manner.

Data analysis tools

All HRiM recordings were analyzed by one of the researchers (ACM) in a blinded fashion, using dedicated software (Medical Measurement System, Enschede, Netherlands). For assessment of esophageal motility, the Chicago 3.0 classification was used.⁴¹ Mean UES and EGJ resting pressures for the swallowing protocol were measured utilizing QUICKVIEW, the MMS ambulatory measurement and analysis software 9.3d. As the values for UES and EGJ resting pressures before and after swallowing protocol (all preprandial values) were almost identical ($P=0.89$ for UES resting pressures between before the swallowing protocol and the preprandial period and 0.9 , respectively), they were averaged to generate a single preprandial mean. This was also the case for the EGJ resting pressures ($P=0.9$ for EGJ resting pressures between before the swallowing protocol and the preprandial period) before and after the swallowing protocol, so values here were also averaged. Post-swallow UES mean and maximum pressure were measured manually by “pinpointing” and averaging values within the area of interest (UES,) at the 1s interval adjacent to UES relaxation margin re-closure. Pre- and post-prandial EGJ resting pressures were calculated by averaging values measured relative to IGP, at end-expiration every minute, provided that the measurement was stable and no TLESR or swallow occurred. TLESRs were identified using established criteria: 1) absence of pharyngeal swallowing for 4 s before to 2 s after the onset of EGJ relaxation; 2) relaxation rate of ≥ 1 mmHg/s; 3) time from the onset of relaxation to complete relaxation of ≤ 10 s; and 4) nadir pressure of ≤ 2 mmHg. EGJ relaxations lasting longer than 10s were also classified as

TLESR, irrespective of the timing of swallowing onset.⁴² Gastro-esophageal liquid reflux was identified as an orally progressing drop in impedance to at least 50% of baseline values, starting at the most distal segment and propagating to at least 5 cm proximal of the EGJ. Gas reflux was identified as an increase in impedance over 5000 Ω .⁴³ Reflux episodes with combined gas-liquid component were classified as mixed.

For the determination of IGP, a previously described methodology was used.^{44, 45} In brief, pressure values from the first five pressure channels that were clearly positioned below the EGJ or the pressure area influenced by the EGJ (approximately 3–8 cm under the EGJ) were used to create means corresponding to different time points. Mean IGP-values were plotted over time. The parameter of interest, i.e. postprandial IGP, was calculated using the area under the plotted curve for the relevant period.

Statistical analysis

Values are expressed as mean $\pm$ SEM or median (interquartile range) depending on whether they passed or not the Shapiro-Wilk Normality test. The paired t-test was used for the comparison of IRP4s, DCI, CFV, DL, IRP0.2s, UES post-swallow metrics and postprandial IGP, between the drug and placebo studies. TLESRs and symptom scores were compared with a Wilcoxon matched pairs signed-rank test. TLESR occurrence during first and second postprandial hour was compared between citalopram and placebo studies using McNemar's test. Symptom score variations over time were assessed by a Friedman test with Dunn's post-hoc tests. Changes regarding UES, LES pressure between different periods (swallow, pre-prandial, post-prandial during first and second hour after meal) were evaluated using one or two-way analysis of variance (ANOVA) for repeated measures and Bonferroni correction. For reflux parameters comparison, McNemar's and an SAS General Linear Model procedure with binary outcomes were used. A P-value <0.05 was considered to be statistically significant.

Although the paired, randomized, cross-over design of the study confers to the robustness of results exceeding the threshold of statistical significance, multivariate testing considering carry-over effects -despite the presence of only two major groups (citalopram and placebo) and an adequate wash-out period- was performed using an SAS mixed procedure model. For postprandial IGP comparisons the area under the curve (AUC) was used. Statistical analysis was performed using GraphPad 5, MedCalc 11.2.0.0 and SAS 9.3 software packages.

Ethical considerations

The study was approved by the UZ Leuven ethics committee (S59148). All study participants signed a detailed informed consent form, prior to study initiation (NCT03746691).

RESULTS

Effect of citalopram on UES function

UES resting pressure values in HV when treated with citalopram were 65.6 ± 6.2 mmHg during the swallowing protocol, 40.8 ± 4.4 mmHg for the preprandial and 40.2 ± 4.4 mmHg for the postprandial period. For the placebo visit the UES metrics were 42.9 ± 3.9 mmHg during swallowing sequence, 32.9 ± 4.8 mmHg during pre- and 32.8 ± 5.0 during post-prandial period. UES resting pressure was significantly higher after citalopram administration throughout the study period ($P < 0.05$ in all study periods). Both UES post-swallow mean pressure and UES post-swallow maximum pressure were higher in the citalopram compared to the placebo condition: 165.2 ± 10.8 mmHg vs 111.4 ± 10.15 mmHg and 252.5 ± 19.1 mmHg vs 159.3 ± 16.2 mmHg, respectively (both $P < 0.0001$, Figure 2A). As for the relaxation of UES, the median IRP0.2s was 3.4 mmHg (2-4.4) for the citalopram and 1 mmHg (0.4-3.6) for the placebo visit ($P = 0.04$, Figure 2B). Figure 3 gives an example of a HRiM swallow in placebo and citalopram.

Effect of citalopram on esophageal motility parameters

A significantly lower DCI was recorded under citalopram condition (506 ± 117 mmHg*s*cm) compared to placebo (644 ± 138 mmHg*s*cm) ($P=0.026$). DL was comparable between the two groups: 7.1 ± 0.3 s and 7.3 ± 0.3 s for the drug and placebo visit, respectively ($P=0.18$).

Effect of citalopram on EGJ function

EGJ resting pressures under citalopram were 27.9 ± 3.6 mmHg during swallowing protocol, 20.3 ± 1.9 mmHg preprandially, 14.1 ± 1.6 mmHg during first postprandial hour and 13.6 ± 1.6 mmHg during the second postprandial hour ($P<0.01$ between swallowing vs. postprandial periods and preprandial vs. postprandial periods). EGJ resting pressure during treatment with placebo was 21.7 ± 3.16 mmHg for the swallowing sequence, 15.9 ± 1.62 mmHg preprandially, 11.8 ± 1.2 mmHg during first postprandial and 13.0 ± 1.7 mmHg during second postprandial hour, with only the difference between swallowing and first or second postprandial periods reaching statistical significance ($P<0.01$). EGJ resting pressures in the citalopram visit were significantly higher in the swallowing, preprandial and first postprandial hour periods ($P<0.04$, in all cases) but not in the second postprandial hour ($P=0.6$), compared to the placebo visit (Figure 3 and 4). IRP4s was similar between citalopram (9.4 ± 1.4 mmHg) and placebo (8.5 ± 1 mmHg) studies ($P=0.4$).

Effect of citalopram on TLESRs and reflux parameters

The median number of TLESRs was 5 (4-7.6) vs 7.5 (6.6-10.7) in the citalopram and placebo conditions respectively ($P=0.01$, Figure 5). TLESRs occurred more frequently during the first compared to the second postprandial hour both for citalopram and placebo studies: 3.5 (2-5.5) vs 2 (1-3) and 5 (4-6.8) vs 2.5 (1-5), respectively ($P<0.01$, in both cases; but no difference between the treatment groups ($P=0.28$)). A decreased number of postprandial reflux episodes was recorded after citalopram compared to placebo: 4.6 (3.8-7.3) vs 7.2 (6.1-10.3) ($P=0.01$). No difference in proximal extent of reflux was found between citalopram and placebo studies:

70.8% vs 68.2% for proximal and 29.2% vs 31.8% for distal extent ($P>0.1$). Similarly, no differences were recorded between citalopram and placebo visits when the type of refluxate was taken into account: 66.6% vs 48.5% for mixed, 4% vs 9.1% for pure gas and 29.2% vs 42.4% for pure liquid reflux, respectively ($P>0.1$).

Effect of citalopram on postprandial IGP

Postprandial IGP, reported as AUC, was 304.6 ± 41.3 in the citalopram condition and 340.2 ± 49.7 after placebo infusion ($P=0.46$).

Association of citalopram with VAS scores and swallow-related sensations

Different symptoms were examined by comparing VAS scores between citalopram and placebo infusion studies. No significant differences or statistical trends were recorded between citalopram and placebo visits ($P>0.1$ in all cases) for the VAS-scored symptoms (Table 1). VAS scores for postprandial fullness and satiety decreased over time ($P<0.001$) while a gradual increase was recorded for hunger ($P=0.06$). Similarly, no significant differences were recorded between citalopram and placebo studies while evaluating deglutition sensations ($P>0.1$), with the exception of globus. During treatment with citalopram, 5 HVs reported a globus sensation compared to none of the HV during placebo visit ($P=0.06$). HVs with citalopram-induced globus had UES post-swallow mean values within the two higher quartiles ($P=0.01$) and UES post-swallow maximum pressure in the highest quartile ($P=0.04$). No correlation was detected between globus sensation and UES resting pressures (swallow-related, pre- and post-prandial or the IRP0.2s ($P=0.8$, $P=0.2$, $P=0.18$ and $P=0.6$, respectively)

Overall model assessment and adjustment

Despite the presence of only two major groups (citalopram and placebo) and the presence of an adequate wash-out period, the study was examined for potential carryover/order effects by evaluating each HV, at each period while co-factoring outcome, treatment, patient code

and sequence, in an SAS mixed procedure or general model for binary outcomes. During this re-evaluation, no order effects were detected ($P>0.2$ in all cases).

DISCUSSION

Based on the present study, acute administration of citalopram exerts a multifarious response on esophageal motility and sphincter function. A decrease in peristaltic vigor of the esophagus was induced by citalopram infusion. At the same time, an increased muscular tone in UES and LES was recorded, also accompanied by reduction of UES relaxation during swallowing, as well as a more pronounced post-swallow after-contraction. The recorded changes in sphincter metrics led to onset of globus sensation in some subjects, on one hand, and a decrease in postprandially occurring TLESRs, on the other. These changes were unrelated to any other subjective sensations.

The increase in LES tone after administration of the SSRI citalopram did not come as a surprise, as earlier studies have linked drugs acting on 5HT-receptors with higher LES pressure values.²⁴⁻

²⁷ In our study, although the ability of the LES to relax was maintained, citalopram infusion led to higher LES resting pressures extending from the preprandial period until the first postprandial hour. In that concept, it would be reasonable to assume that the TLESRs should mostly occur during the second instead of the first postprandial hour since this is when LES pressures between citalopram and placebo were not different. That, however, would be an oversimplified approach, as gastric content volume –a high fat, high caloric meal in this study– is maximal after meal ingestion and gradually decreases due to gastric emptying,⁴⁶ a fact also depicted in VAS scores concerning fullness and satiety, which decrease over time.

Another parameter that could be involved in postprandial TLESR decrease is gastric accommodation. An enhanced gastric accommodation, determined through barostat or IGP-

based studies has been associated with fewer TLESRs⁴⁷ and could be induced by neuromodulating pharmacologic substances such as buspirone, a 5-HT_{1A} receptor agonist.⁴⁸ Citalopram has previously been associated with decreased gastric accommodation,³⁴ a finding that was not replicated by the IGP profiles in the present study as postprandial IGP measurements were not different between citalopram and placebo visits. This discrepancy may reflect differences in methodology e.g. 1000kcal meal and HRiM instead of a 300kcal nutrient drink and IGP measurement instead of barostat,³⁴ between the two studies.

Apart from its effect on the esophago-gastric junction, citalopram seems to alter esophageal motility: citalopram infusion led to a decrease in DCI or in other words to a weaker esophageal contractility. This is in contradiction to an older study utilizing classic water perfused manometry, where no significant changes in motility metrics were recorded.³² The use of HRiM and DCI, a parameter incorporating and integrating three variables (pressure, length and time) into one, have probably optimized detection of such alterations in the present study. When combining this finding to the increased LES pressure, it is not surprising that dysphagia-related symptoms also manifest as side effects in patients under serotonergic compounds such as SSRIs.^{36,49,50} This observation also highlights the complexity behind the diverse and often contradictory effects of 5HT-receptor agonists, probably through binding to different receptors.²³⁻³⁹ Dysphagia, however, may not solely arise from the esophagus or the LES but from a more proximal site, as well.

The myotonic effect of citalopram is not confined to the LES, with similar changes being observed in UES-related metrics. Indeed, an increase in UES resting pressure occurs, after citalopram administration, also accompanied by a compromise in UES relaxation depicted in the higher IRP0.2s values recorded in this study. Following the impaired resting and relaxation period, an enhanced after-contraction occurs and is recorded as increased post-swallow mean

and maximum pressure amplitudes. This amplified post-swallowing phase was well associated with the manifestation of pharmacogenic globus sensation in HV. This finding is in accordance with the study of Peng et al,⁴⁰ as well as with preliminary unpublished data from our study group, showing that an intense UES after-contraction following swallows may be a key feature in globus patients.

Other sensations and phenomena were also assessed throughout the study such as hunger, satiety, fullness, reflux and nausea. Apart from the already described decrease in hunger and the increase in satiety and fullness scores over time, no other significant differences were found, either during the same or between citalopram and placebo visits. This was also the case, when the recorded changes in esophageal motility and sphincter function, recorded in the present study, were evaluated while considering the same set of symptoms.

Based on the results presented and discussed above, a question arises: can citalopram be used for favorable control of TLESRs, gastro-esophageal, laryngo-pharyngeal reflux or perhaps even rumination syndrome? Before answering, certain limitations have to be taken into account. First, the present study was performed in HV, not in patients with GERD or laryngo-pharyngeal reflux, so both the results, as well as the effectiveness of citalopram as potential therapy for these conditions, have to be validated directly in these patient populations. Moreover, the exposure of study participants to citalopram was acute, reflecting enhanced 5HT availability, whereas therapeutic effects of this SSRI in other GI disorders e.g. esophageal hypersensitivity are thought to be exerted through receptor desensitization, resulting from prolonged treatment.³³ It is therefore not possible at this point, to know whether the phenomena induced acutely by citalopram wear off after longer treatment periods or not.

In all, the present study sets a basis for further reflection, discussion and experimentation on the potential of citalopram as an anti-reflux treatment while at the same time shedding light

into mechanisms and defects that could either mediate drug related side-effects or be involved in the pathogenesis of other conditions, such as globus. As for the emerging and pending questions regarding therapeutic application in specific patient groups and long term efficacy, these are issues that need to be addressed, evaluated and validated through future, carefully designed and well-powered studies.

ACKNOWLEDGEMENTS

The authors would like to thank the GI-motility nurses and in particular Lien Timmermans for the logistical and practical help.

FUNDING INFORMATION

The study was supported by a Methusalem grant from KU Leuven to Prof Tack. TV is a senior clinical investigator of the Research Foundation Flanders (FWO). AP is funded as a post-doctoral researcher by the Research Foundation Flanders (FWO). ACM is a Hellenic Society of Gastroenterology grant holder.

DISCLOSURES

None

AUTHOR CONTRIBUTIONS

JT, TV, AP, BVH, CB and NR were involved in study conception and design. ACM, CB and AP performed HRiM protocols. ACM performed analysis of HRiM recordings. ACM, AP and NG participated in data acquisition and analysis. ACM, AP, TV, NR and JT performed interpretation of results. All authors were involved in manuscript drafting.

REFERENCES

1. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*. 2005;54(5):710-717.
2. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Group GC. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006;101(8):1900-1920.
3. Malfertheiner P, Hallerbäck B. Clinical manifestations and complications of gastroesophageal reflux disease (GERD). *Int J Clin Pract*. 2005;59(3):346-355.
4. Holloway RH, Dent J, Narielvala F, Mackinnon AM. Relation between oesophageal acid exposure and healing of oesophagitis with omeprazole in patients with severe reflux oesophagitis. *Gut*. 1996;38(5):649-654.
5. Fass R. Therapeutic options for refractory gastroesophageal reflux disease. *J Gastroenterol Hepatol*. 2012;27 Suppl 3:3-7.
6. Richter JE. Gastroesophageal reflux disease treatment: side effects and complications of fundoplication. *Clin Gastroenterol Hepatol*. 2013;11(5):465-471.
7. Mittal RK, Holloway RH, Penagini R, Blackshaw LA, Dent J. Transient lower esophageal sphincter relaxation. *Gastroenterology*. 1995(2);109:601-610.
8. Bredenoord AJ, Weusten BL, Timmer R, Akkermans LM, Smout AJ. Relationships between air swallowing, intragastric air, belching and gastro-oesophageal reflux. *Neurogastroenterol Motil*. 2005;17(3):341-347.
9. Holloway RH, Kocyan P, Dent J. Provocation of transient lower esophageal sphincter relaxations by meals in patients with symptomatic gastroesophageal reflux. *Dig Dis Sci*. 1991;36(8):1034-1039.

10. Holloway RH, Hongo M, Berger K, McCallum RW. Gastric distention: a mechanism for postprandial gastroesophageal reflux. *Gastroenterology*. 1985;89(4):779-784.
11. Sifrim D, Holloway R. Transient lower esophageal sphincter relaxations: how many or how harmful? *Am J Gastroenterol*. 2001;96(9):2529-2532.
12. Sifrim D, Holloway R, Silny J, Tack J, Lerut A, Janssens J. Composition of the postprandial refluxate in patients with gastroesophageal reflux disease. *Am J Gastroenterol*. 2001;96(3):647-655.
13. Vela MF, Tutuian R, Katz PO, Castell DO. Baclofen decreases acid and non-acid postprandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. *Aliment Pharmacol Ther*. 2003;17(2):243-251.
14. Zerbib F. Medical treatment of GORD. Emerging therapeutic targets and concepts. *Best Pract Res Clin Gastroenterol*. 2010;24(6):937-946.
15. Shaheen NJ, Denison H, Björck K, Karlsson M, Silberg DG. Efficacy and safety of lesogabran in gastro-oesophageal reflux disease: a randomised controlled trial. *Gut*. 2013;62(9):1248-1255.
16. Boeckstaens GE, Beaumont H, Hatlebakk JG et al. A novel reflux inhibitor lesogabran (AZD3355) as add-on treatment in patients with GORD with persistent reflux symptoms despite proton pump inhibitor therapy: a randomised placebo-controlled trial. *Gut*. 2011;60(9):1182-1188.
17. Vakil NB, Huff FJ, Bian A, Jones DS, Stamler D. Arbaclofen placarbil in GERD: a randomized, double-blind, placebo-controlled study. *Am J Gastroenterol*. 2011;106(8):1427-1438.
18. Vakil NB, Huff FJ, Cundy KC. Randomised clinical trial: arbaclofen placarbil in gastrooesophageal reflux disease--insights into study design for transient lower sphincter relaxation inhibitors. *Aliment Pharmacol Ther*. 2013;38(2):107-117.

19. Keywood C, Wakefield M, Tack J. A proof-of-concept study evaluating the effect of ADX10059, a metabotropic glutamate receptor-5 negative allosteric modulator, on acid exposure and symptoms in gastro-oesophageal reflux disease. *Gut*. 2009;58(9):1192-1199.
20. Zerbib F, Bruley des Varannes S, Roman S et al. Randomised clinical trial: effects of monotherapy with ADX10059, a mGluR5 inhibitor, on symptoms and reflux events in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2011;33(8):911-921.
21. Kahrilas PJ, Boeckxstaens G. Failure of reflux inhibitors in clinical trials: bad drugs or wrong patients? *Gut*. 2012;61(10):1501-1509.
22. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. *Gut*. 2012;61(9):1340-1354.
23. Gershon MD, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. *Gastroenterology*. 2007;132(1):397-414.
24. Tack J, Coremans G, Janssens J. A risk-benefit assessment of cisapride in the treatment of gastrointestinal disorders. *Drug Saf*. 1995;12(6):384-392.
25. Staiano A, Clouse RE. The effects of cisapride on the topography of oesophageal peristalsis. *Aliment Pharmacol Ther*. 1996;10(6):875-882.
26. Delvaux M, Maisin JM, Arany Y et al. The effects of lintopride, a 5HT-4 antagonist, on oesophageal motility. *Aliment Pharmacol Ther*. 1995;9(5):563-569.
27. Di Stefano M, Papathanasopoulos A, Blondeau K et al. Effect of buspirone, a 5-HT_{1A} receptor agonist, on esophageal motility in healthy volunteers. *Dis Esophagus*. 2012;25(5):470-476.
28. Foster JM, Houghton LA, Whorwell PJ, Morris J. Altered oesophageal motility following the administration of the 5-HT₁ agonist, sumatriptan. *Aliment Pharmacol Ther*. 1999;13(7):927-936.

29. Sifrim D, Holloway RH, Tack J et al. Effect of sumatriptan, a 5HT₁ agonist, on the frequency of transient lower esophageal sphincter relaxations and gastroesophageal reflux in healthy subjects. *Am J Gastroenterol*. 1999;94(11):3158-3164.
30. Milne RJ, Goa KL. Citalopram. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. *Drugs*. 1991;41(3):450-477.
31. Baumann P, Nil R, Souche A et al. A double-blind, placebocontrolled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. *J Clin Psychopharmacol*. 1996;16(4):307-314.
32. Broekaert D, Fischler B, Sifrim D, Janssens J, Tack J. Influence of citalopram, a selective serotonin reuptake inhibitor, on oesophageal hypersensitivity: a double-blind, placebo-controlled study. *Aliment Pharmacol Ther*. 2006;23(3):365-370.
33. Viazis N, Keyoglou A, Kanellopoulos AK et al. Selective serotonin reuptake inhibitors for the treatment of hypersensitive esophagus: a randomized, double-blind, placebo-controlled study. *Am J Gastroenterol*. 2012;107(11):1662-1667.
34. Janssen P, Van Oudenhove L, Casteels C, Vos R, Verbeke K, Tack J. The effects of acute citalopram dosing on gastric motor function and nutrient tolerance in healthy volunteers. *Aliment Pharmacol Ther*. 2011;33(3):395-402.
35. Janssen P, Vos R, Tack J. The influence of citalopram on interdigestive gastrointestinal motility in man. *Aliment Pharmacol Ther*. 2010;32(2):289-295.
36. Navarro V. Improving medication compliance in patients with depression: Use of orodispersible tablets. *Adv Ther*. 2010;27(11):785-795.

37. Barth M, Kriston L, Klostermann S, Barbui C, Cipriani A, Linde K. Efficacy of selective serotonin reuptake inhibitors and adverse events: meta-regression and mediation analysis of placebo-controlled trials. *Br J Psychiatry*. 2016;208(2):114-119.
38. Lotrich FE, Bies R, Muldoon MF, Manuck SB, Smith GS, Pollock BG. Neuroendocrine response to intravenous citalopram in healthy control subjects: pharmacokinetic influences. *Psychopharmacology (Berl)*. 2005;178(2-3):268-275.
39. Tampi RR, Balderas M, Carter KV et al. Citalopram, QTc Prolongation, and Torsades de Pointes. *Psychosomatics*. 2015;56(1):36-43.
40. Peng L, Patel A, Kushnir V, Gyawali CP. Assessment of Upper Esophageal Sphincter Function on High-resolution Manometry: Identification of Predictors of Globus Symptoms. *J Clin Gastroenterol*. 2015;49(2):95-100.
41. Kahrilas PJ, Bredenoord AJ, Fox M et al. The Chicago Classification of esophageal motility disorders, v3.0. *Neurogastroenterol Motil*. 2015;27(2):160-174.
42. Roman S, Holloway R, Keller J et al. Validation of criteria for the definition of transient lower esophageal sphincter relaxations using high-resolution manometry. *Neurogastroenterol Motil*. 2017;29(2):e12920.
43. Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut*. 2004;53(7):1024-1031.
44. Janssen P, Verschuere S, Ly HG, et al. Intragastric pressure during food intake: a physiological and minimally invasive method to assess gastric accommodation. *Neurogastroenterol Motil*. 2011;23(4):316–322.

45. Carbone F, Tack J, Hoffman I. The Intra-gastric Pressure Measurement: A Novel Method to Assess Gastric Accommodation in Functional Dyspepsia Children. *J Pediatr Gastroenterol Nutr.* 2017;64(6):918-924.
46. Rao SS, Camilleri M, Hasler WL et al. Evaluation of gastrointestinal transit in clinical practice: position paper of the American and European Neurogastroenterology and Motility Societies. *Neurogastroenterol Motil.* 2011;23(1):8-23.
47. Pauwels A, Altan E, Tack J. The gastric accommodation response to meal intake determines the occurrence of transient lower esophageal sphincter relaxations and reflux events in patients with gastro-esophageal reflux disease. *Neurogastroenterol Motil.* 2014;26(4):581-588.
48. Tack J, Janssen P, Masaoka T, Farré R, Van Oudenhove L. Efficacy of buspirone, a fundus-relaxing drug, in patients with functional dyspepsia. *Clin Gastroenterol Hepatol.* 2012;10(11):1239-1245.
49. Passmore MJ, Devarajan S, Ghatavi K, Gardner DM, Kutcher SP. Serotonin syndrome with prolonged dysphagia. *Can J Psychiatry.* 2004;49(1):79-80.
50. Liu Y, Gao ZS. Case report of dysphagia caused by sertraline. *Shanghai Arch Psychiatry.* 2011;23:246-247.

TABLES

Table 1. Visual Analogue Scale (VAS) scores for different symptoms between the citalopram visit and the placebo visit. Values are expressed as median (IQR).

	Citalopram	Placebo	p-value
Fullness	6.7 (4.7-8.4)	6.6 (2.8-8.4)	NS
Satiety	6.8 (5.6-7.7)	7.1 (5.6-8.5)	NS
Heartburn	0 (0.1-0.7)	0 (0.2-0.8)	NS
Belching	0.4 (0.3-2.2)	0.7 (0.5-2.4)	NS
Hunger	0.7 (0.5-2.9)	1.2 (0.8-2.9)	NS
Nausea	0.9 (0.2-2.9)	0 (0-1)	NS

FIGURES AND FIGURE LEGENDS

Figure 1 Schematic representation of study protocol

Figure 2 Upper esophageal sphincter (UES) pressure fluctuations between citalopram and placebo visits: **A.** UES mean (citalopram 165.2 ± 10.8 vs. placebo 111.4 ± 10.15 mmHg, $P < 0.0001$) and maximum (max) (citalopram 252.5 ± 19.1 vs. placebo 159.3 ± 16.2 mmHg, $P < 0.0001$) pressure values adjacent to UES re-closure after swallow (postswallow) **B.** Difference in integrated relaxation pressure 0.2s (IRP0.2) values (citalopram 3.4 ($2 - 4.4$) vs. placebo 1 ($0.4 - 3.6$) mmHg, $P = 0.04$).

Figure 3 Example of a swallow in **A.** placebo condition and **B.** citalopram condition.

Figure 4 Comparative graphic representation of lower esophageal sphincter (LES) pressure within and between visits. $*P < 0.05$

Figure 5 Median number of TLESRs was significantly lower in the citalopram condition compared to the placebo condition. $*P = 0.01$