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The effect of sildenafil on gastric motility and satiation in healthy controls

F Carbone and J Tack

Abstract

Sildenafil induces relaxation of smooth muscle cells by blocking PDE5. Dyspepsia is one of sildenafil's most frequently reported adverse events, suggesting its effect on gastric motility. Our aim was to study the effect of sildenafil on gastric accommodation (GA) and gastric emptying (GE) in healthy volunteers (HVs).

Methods: Sildenafil (50 mg) or placebo was randomly administered to 16 blinded HVs. After a manometry probe and an infusion catheter were positioned in the proximal stomach, the intragastric pressure (IGP) was measured before and during nutrient drink infusion (ND, 60 ml/min). HVs were asked to score their hunger, satiation and six epigastric symptoms at five-minute intervals. The experiment ended when the HVs scored maximal satiation during ND infusion at one-minute intervals. To assess GE, breath samples were collected every 15 minutes for six hours after the meal (244 kcal).

Results: ND infusion induced a drop in proximal stomach IGP, which was suppressed by sildenafil (average area under the curve for sildenafil: -33.6 ± 8.8 mmHg; placebo: -60.8 ± 11.3 mmHg, $p = 0.005$). Sildenafil-treated volunteers reached earlier maximal satiation compared to placebo (678 ± 70 ml vs. 836 ± 82.6 ml, $p = 0.019$). Finally, GE was significantly slower after sildenafil (90.6 ± 5.9 min vs. 76.6 ± 7.1 min, $p = 0.04$).

Conclusion: Sildenafil inhibits GA, leading to significantly decreased nutrient tolerance, and slightly delays the GE rate in humans.

Keywords

Gastric accommodation, intragastric pressure, gastric emptying, sildenafil

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Key summary

Previously, it was shown that dyspepsia is one of sildenafil's most frequently reported adverse events. Paradoxically, a previous gastric barostat study showed enhanced postprandial gastric volumes in response to sildenafil administration, suggestive of enhanced gastric accommodation, but was unable explain the origin of these dyspeptic symptoms. Interestingly, in this study we observed that sildenafil seems to supress the intragastric pressure drop, decreases nutrient tolerance and delays half emptying time in healthy individuals.

Introduction

Upon food intake, gastric distension activates mechanosensitive receptors in the gastric wall that send signals through a vago-vagal reflex pathway to induce relaxation of the proximal stomach.[1,2] This pathway, called the accommodation reflex, facilitates temporary storage of ingested food without a rise in intragastric pressure (IGP). Relaxation of smooth muscle in the proximal stomach is mediated through release of nitric oxide (NO) from non-adrenergic non-cholinergic inhibitory neurons in the gastric wall.[1,3] NO diffuses through the cell membrane of the smooth muscle cells where it increases the concentration of cyclic guanylyl monophosphate (cGMP) and this initiates a process that ends in hyperpolarisation. As a result, the smooth

TARGID and Department of Gastroenterology, Neurogastroenterology & Motility, University of Leuven, Leuven, Belgium

Corresponding author:
J Tack, TARGID and Department of Gastroenterology, University of Leuven, Neurogastroenterology & Motility, Herestraat 49, Box 701, 3000 Leuven, Belgium.
Email: jan.tack@med.kuleuven.be

muscles of the proximal stomach relax to keep IGP low while the intragastric volume increases.[4] Progressive filling of the proximal stomach induces a rise in IGP, accompanied by the feeling of satiation and followed by redistribution of gastric content from the proximal stomach to the antrum, allowing the initiation of gastric emptying (GE). The tissue levels of cGMP are determined and balanced by guanylyl cyclase (GC) and cGMP-specific phosphodiesterase-5 (PDE5). The former catalyses cGMP formation, while the latter induces its degradation by hydrolysation.[4]

Sildenafil citrate is a potent specific PDE5 inhibitor which is used in the treatment of erectile dysfunction.[5,6] Moreover, during sildenafil clinical trials and post-clinical studies, it has been reported that sildenafil induces dyspeptic symptoms as the most frequent adverse event besides headache and flushing.[5–7] Therefore, it is conceivable that sildenafil might have an effect on gastric motility.

Earlier studies in healthy volunteers (HVs) reported that sildenafil enhances meal-induced accommodation as measured by a gastric barostat, and does not alter solid emptying but significantly delays liquid GE.[8] However, the presence of a balloon in the stomach could disrupt the normal physiologic responses to food intake and therefore it might exaggerate the natural responses of gastric accommodation (GA) and GE.[2,9]

More recently, IGP measurement during nutrient intake was developed as a more physiological method to measure GA.[2] Our aim was to evaluate the effect of sildenafil on meal-induced satiation and GA during nutrient drink ingestion, measured with this minimally invasive and potentially more accurate alternative for the barostat. In addition, we used the C^{13}-breath test to quantify GE.

Methods

Study participants

All study procedures were approved by the Ethics Committee of Leuven University Hospital, Belgium (reference S-number study: S53584; date: 2012), and the study was performed in accordance with the 1975 Declaration of Helsinki. Twenty HVs participated in this single-blind, cross-over study. The exclusion criteria included the presence of symptoms or a history of gastrointestinal diseases, any other significant disease or psychological disorder and pregnancy, or the use of any medication that may affect gastric sensorimotor function. HVs were asked to come to the clinic after fasting overnight. They were asked to refrain from alcohol, tea and coffee for at least 12 hours before participation; moreover, they were asked to refrain from smoking cigarettes at least one hour before the start of the experiments. Written informed consent was obtained from each participant.

IGP measurement

IGP was measured by means of a high-resolution manometry (HRM) catheter, as previously described.[2,10–12] A manometry probe (ManoScan 360, Sierra Scientific Instruments, Los Angeles, CA, USA), a small, flexible tube, was passed through the nose into the stomach. The probe contains 36 channels that measure pressure. The manometry probe was positioned in the stomach of the volunteer. For accurate data acquisition of the IGP it is important that the probe is properly placed from fundus to antrum following the larger curvature of the stomach without any curl or coil of the catheter. To correctly and confidently measure the IGP in the stomach, it is necessary to place at least one sensor at the oesophagus and at least once sensor at the site of the lower oesophageal sphincter (LOS). To infuse the nutrient drink directly into the stomach, a second infusion catheter (Nutricia Flocare line, Bornem, Belgium) was positioned through the mouth of the volunteers and advanced until the tip of this infusion catheter was located in the proximal stomach.

The catheters were fixed to the participants' chin and the volunteers were asked to sit in bed in a comfortable position with the trunk upright. After a stabilisation period, an oral dose of sildenafil (50 mg, Viagra®, Pfizer, UK) in an opaque gel capsule or a placebo was administered to the volunteers in a randomized fashion. The gel capsule was used to hide the colour and shape of the Viagra® pill from the volunteers. Forty-five minutes thereafter, a nutrient drink (Nutridrink®, Nutricia, 150 kcal per 100 ml with 6 g proteins, 18.4 g carbohydrates and 5.8 g lipids, Netherlands) was infused directly into the stomach of the volunteers at a constant speed of 60 ml/minute.

By positioning the probe in the distal stomach, additional information on the frequency and amplitude of antral contractions of the migrating motor complex (MMC) can be observed. Phase III of the MMC can be identified by the abrupt onset of repetitive (three per minute in the stomach), strong (>40 mmHg) peristaltic contractions sweeping through the stomach and proximal intestine for at least three minutes. Phase I MMC is defined as a short period of quiescence immediately after phase III with no discernible contractile activity. Phase II follows phase I and is characterised by progressively increasing phasic contractile activity of irregular frequency, constituting the longest MMC phase. Therefore, to properly assess the baseline IGP and to improve evaluation of GA we standardised the timing of intragastric nutrient infusion during either phase II of the MMC.

During the study, volunteers were asked to fill out visual analogue scales (VAS) for hunger, satiation and six epigastric symptoms (fullness, nausea, belching of air, cramps in the abdomen, bloating and pain) at five-minute intervals. In addition, during nutrient drink infusion they also had to score their satiation at one-minute intervals by using a graphic rating scale that combines verbal descriptors on a scale graded from 0 to 5 (1, threshold; 5, maximum satiation).

Intragastric infusion was stopped as soon as the volunteers reached the maximum score of 5 on their satiation scale or when they scored maximally on one of the epigastric symptoms. Five minutes thereafter the catheters were disconnected and removed and the volunteers could leave the hospital (Figure 1a).

GE measurement

The C^{13}-breath test was used to measure GE rate. After an overnight fast, volunteers ingested a standardised solid meal consisting of one non-radioactive ^{13}C-octanoic acid-labelled pancake (244 kcal) within 15 minutes. Sildenafil (50 mg, Viagra®) or placebo was administered to the HVs in a randomised fashion and two control breath samples were given. Thirty minutes thereafter the pancake was ingested. For consumption of the pancake, 5 g sugar was added as a sweetener and water was given as a drink. After eating, volunteers gave a breath sample and scored their satiation every 15 minutes until six hours postprandial. The breath samples were collected in sample tubes and GE rate was analysed by determining the exhaled $^{13}CO_2/^{12}CO_2$ ratio (Figure 1b).

Data analysis IGP measurements

The original IGP data were imported from the recorder software ManoAcquisition® into Excel. The data were calculated as previously described by Janssen et al. The IGP was measured as the average pressure of the first five pressure channels that were clearly positioned below the lower oesophageal sphincter or the pressure area influenced by the LOS.

To avoid influence from movements such as swallowing or moving, a moving median was calculated from the original data (median value over one minute of the original data). Per channel, a baseline value was calculated from the moving median data corresponding to the minimum pressure in the last five minutes of the stabilisation period before nutrient drink infusion. The paired *T* test was used to compare the mean area under the curve (AUC) between the IGP curve of the sildenafil and placebo groups.

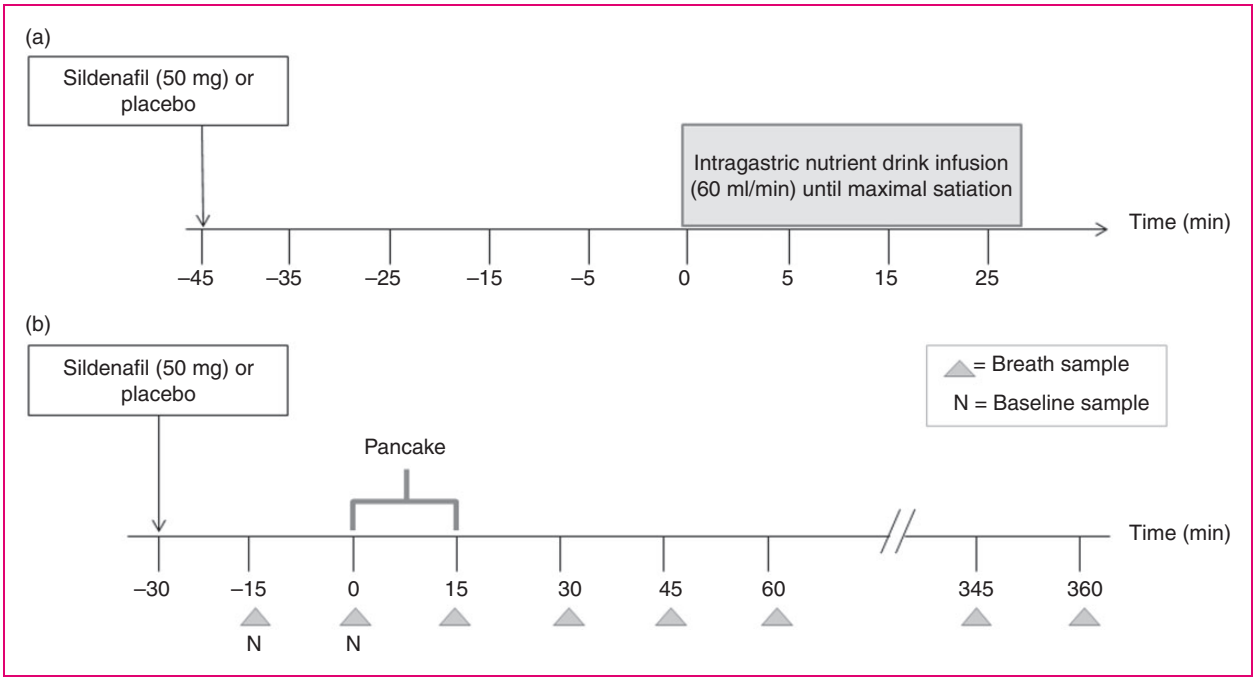

Figure 1. (a) Representation of the intragastric pressure protocol on a time scheme in minutes. Sildenafil or placebo was administered 45 minutes before nutrient drink infusion. Intragastric infusion was stopped when the volunteers reached the maximum score on their satiation scale. (b) Representation of the breath test protocol on a time scheme in minutes. Between ingestion of the drug and the pancakes, volunteers had to give two neutral (N) breath samples. After the pancakes were ingested, breath samples were given every 15 minutes until six hours postprandial.

The nadir IGP was defined as the minimal IGP or the lowest relaxation point during nutrient drink infusion. Mean AUC satiation scores curves and the mean volume and time to reach maximal satiation were compared with the paired T test. The slope of the satiety score curve was calculated by linear interpolation and compared between groups with the paired T test.

The VAS for epigastric symptoms (fullness, nausea, belching of air, cramps in the abdomen, bloating and pain) at five-minute intervals for the sildenafil group and placebo group were measured and the mean AUC was compared with the paired T test. In all analyses $p < 0.05$ was considered significant. All data are presented as mean ± SEM.

Data analysis GE measurements

Isotope ratio mass spectrometry measured the abundance profile of ^{13}C and compared it to the abundance of ^{12}C in the sample tubes. Then, the ratio of $^{13}C/^{12}C$ was calculated and compared to a conventional reference of ^{12}C abundance. Data were then imported into Excel where the time when 50% of the meal had emptied from the stomach ($T_{1/2}$) was automatically calculated. In this calculation, the molar mass of the substrate and its dose were taken into account. Student's paired T test was used to compare the means of $T_{1/2}$ between placebo and sildenafil groups. In all analyses $p < 0.05$ was considered significant. All data are presented as mean ± SEM.

Results

Conducting of the study

All 16 HVs (mean age: 30.1 ± 3.2 years old, mean body mass index: 23.2 ± 0.5 kg/m^2, female: 68%) completed the study as planned. All procedures were well tolerated and no adverse events occurred. Four volunteers were excluded from the study because the timing of the intragastric infusion of the nutrient drink took place during phase III of the MMC, when the high amplitude contractions interfered with baseline measurements.[13]

IGP during nutrient infusion

GA was initiated when the nutrient drink infusion started. In an initial phase, IGP progressively decreased from baseline pressure, followed by a phase during which IGP stabilised and recovered until maximal satiation (Figure 2). After placebo treatment, the infusion of nutrient drink caused an IGP drop to a nadir of −6.7 ± 0.9 mmHg. After sildenafil treatment, the IGP dropped from baseline to a nadir of −4.3 ± 0.9 mmHg ($p = 0.06$ compared to placebo). Thereafter, IGP gradually increased until the end of the experiment (Figure 3).

The average AUC of the IGP curve during nutrient drink infusion until maximal satiation was significantly lower after sildenafil treatment compared to placebo (−33.6 ± 8.8 vs. −60.8 ± 11.3 mmHg.minute; $p = 0.005$) (Figure 4).

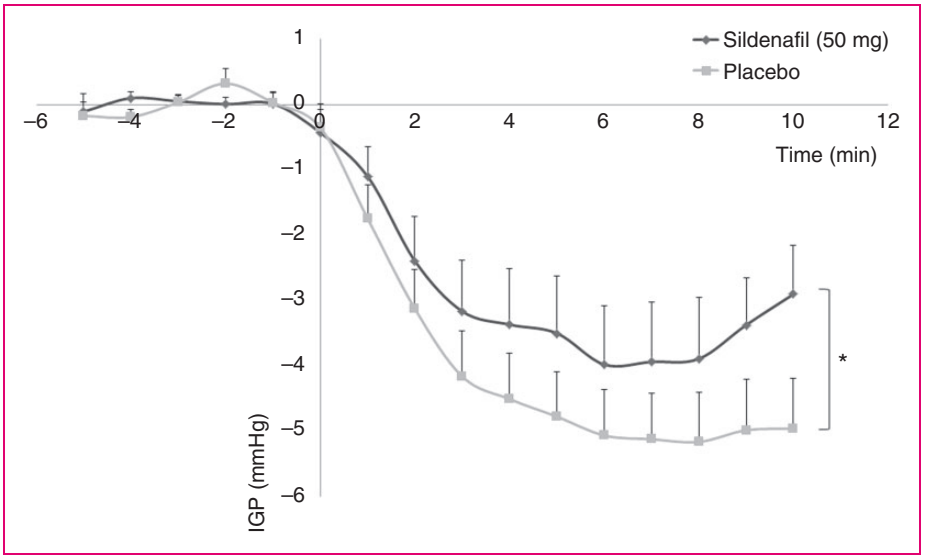

Figure 2. Intragastric pressure (IGP) change over time. During both treatments the IGP progressively decreased from baseline pressure when nutrient drink infusion was started. During the control study the IGP stabilised after five minutes. However, during the sildenafil study, the first IGP drop was less than during placebo and then it gradually increased until the end of the experiment. The results are presented as mean ± SEM.

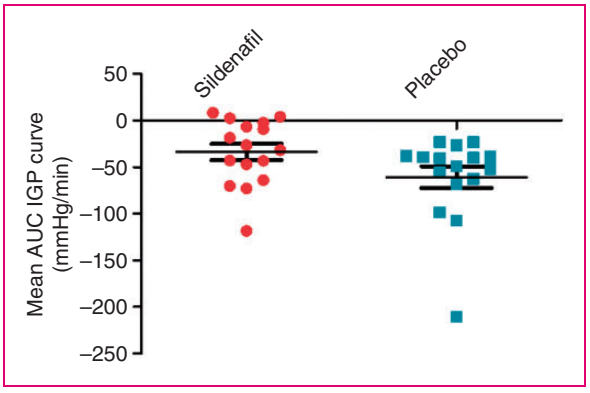

Figure 3. Mean area under the curve (AUC) values of intragastric pressure (IGP) curves. The mean AUC value of the IGP curve during nutrient drink infusion until maximal satiation after sildenafil treatment was higher than after placebo ($p = 0.005$). The values were compared with the student's *T* test. The results are presented as mean ± SEM.

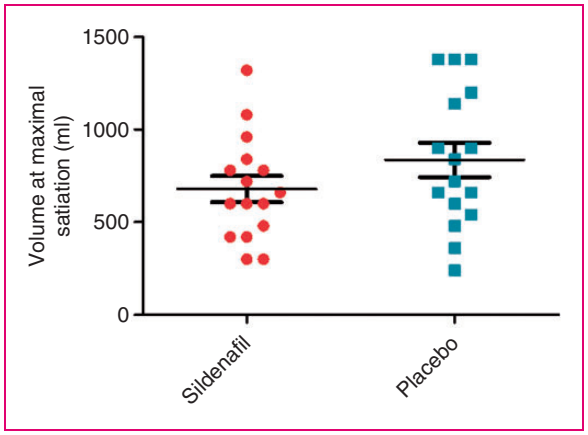

Figure 4. Nutrient challenge test. Left, healthy volunteers (HVs) ($n = 16$) drank significantly less after oral sildenafil treatment (50 mg) compared to placebo ($p = 0.019$). HVs drank 836 ± 82.6 ml after placebo and 678 ± 70 ml after sildenafil. Average values were compared with the student's *T* test. The results are presented as mean ± SEM.

Effect of sildenafil on satiation

Sildenafil-treated volunteers scored maximal satiation at a significantly lower volume compared to placebo-treated participants (678.8 ± 70.1 ml vs. 836.3 ± 82.6 ml, $p = 0.02$) (Figure 4). The satiation score curve increased in a quasi-linear fashion during nutrient infusion. After sildenafil, compared to placebo the average AUC of the satiation curve was significantly higher (28.6 ± 2.3 vs. 34.2 ± 2.9 minute.satiation units, $p = 0.04$). Moreover, the linear slopes of the satiety scores curves were significantly different between the groups (0.4 ± 0.02 and 0.3 ± 0.03 minute^{-1}, sildenafil and placebo, respectively, $p = 0.04$) (Figure 5). Dyspeptic symptom intensity assessed by VAS scores did not differ significantly between both groups (Figure 6).

GE rate

After sildenafil, the half GE time ($T_{1/2}$) was significantly slower compared to placebo ($T_{1/2}$: 76.6 ± 7.1 minutes for placebo vs. 90.6 ± 5.9 minutes for sildenafil; $p = 0.04$) (Figure 7).

Discussion

Sildenafil citrate is a potent specific PDE5 inhibitor which is used in the treatment of erectile dysfunction.[5–7] During sildenafil clinical trials and post-clinical studies, it has been reported that sildenafil is generally well tolerated, although it may induce some side effects such as headache, flushing and especially dyspeptic symptoms.[5–8] The mechanism of action through which sildenafil induces dyspeptic symptoms is unknown. Therefore, in this study we focused on the effects of sildenafil on gastric motor function.

It has previously been reported by barostat and HRM experiments that IGP decreases during stomach distention triggered by a meal; therefore IGP could be used to assess gastric accommodation.[2] Moreover, the use of HRM IGP measurements during nutrient drink infusion in the stomach allows the observation of the association between IGP and satiation during meal ingestion.[2,10–12] Several studies have used IGP measurement to describe gastric motility and control of satiation in HVs, supporting the concept that IGP drop reflects GA.[2,10–12] Moreover, in these studies it was observed that the HRM was less invasive and easier to perform than the gastric barostat measurement in HVs.[2,10–12]

In the present study, the IGP was measured by the HRM to estimate changes in gastric muscle tone after oral administration of 50 mg sildenafil in HVs. It was observed that oral administration of sildenafil significantly supressed the drop in IGP during nutrient infusion, suggesting an inhibitory effect of sildenafil on GA. In addition, we observed that the healthy individuals reached earlier maximal satiation after sildenafil treatment and consequently ingested significantly less nutrient volume. These nutrient tolerance effects are in agreement with a possible underlying decreased GA.

Furthermore, the GE rate for solids was delayed by the same sildenafil dose. Literature reports on the effect of sildenafil on GE rate show divergent outcomes, and both absence of a significant effect on GE and delay in emptying after sildenafil treatment have been reported.[8,14,15] The pylorus plays an important role as regulator of GE. No literature specific to the effect of sildenafil on the pylorus was found. Nevertheless,

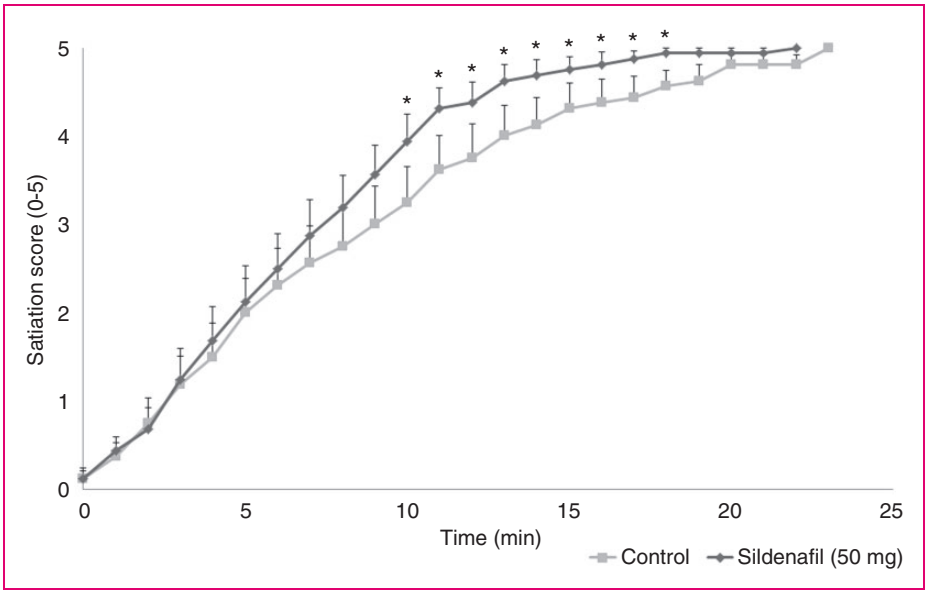

Figure 5. Satiety score over time. The area under the curve (AUC) was higher with oral sildenafil treatment (50 mg) than during placebo. This difference was significant ($p = 0.036$). Participants scored faster maximal satiation after sildenafil (slope sildenafil: 0.4 ± 0.02 and slope placebo 0.3 ± 0.03, $p = 0.04$). Average values were compared with the student's *T* test. * < 0.05 and results are presented as mean $\pm$ SEM.

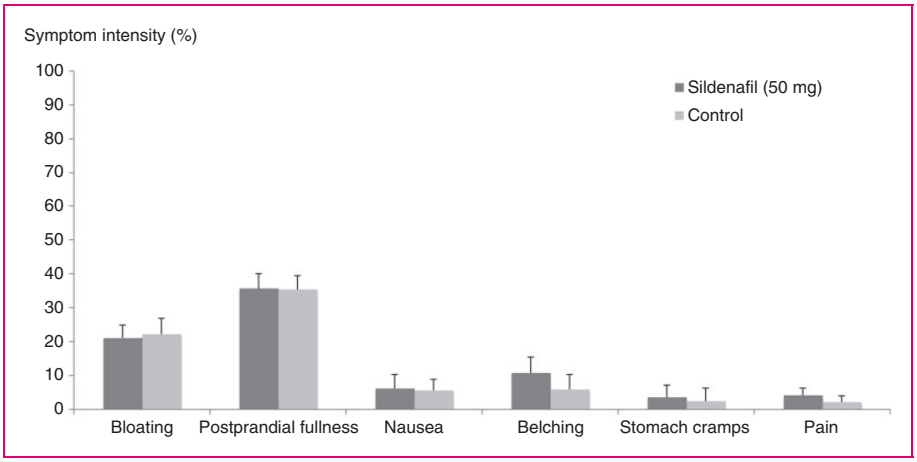

Figure 6. Intensity of gastric symptoms during nutrient drink infusion. The intensity of symptoms did not differ between the sildenafil (50 mg) and placebo. The values were compared with the student's *T* test. The results are presented as mean $\pm$ SEM.

studies in dogs using the NO synthase inhibitor L-NAME and L-arginine (the substrate of NO synthase) showed that compared to a saline control group, both L-arginine and L-NAME significantly delayed GE, but the effect of L-NAME was much more pronounced.[16,17] Furthermore, when combining the compounds, L-arginine significantly shortened the GE delay caused by L-NAME. It was observed that L-NAME changed pyloric motor patterns to a dominant contraction state leading to significant attenuation of postprandial antropyloric coordination and of the solid GE.[17] However, L-arginine showed only the suppression of gastric contractions[16] suggesting that, in this case, NO enhancement has an effect at the level of gastric motility rather than pyloric motility. These studies conclude that NO can function as a neurotransmitter of nonadrenergic noncholinergic neurons in the stomach, pylorus and the duodenum, therefore affecting GE rate.

It is conceivable that our observations explain the occurrence of dyspeptic symptoms after sildenafil intake: Both impaired GA and delayed GE are well-established pathophysiological mechanisms in

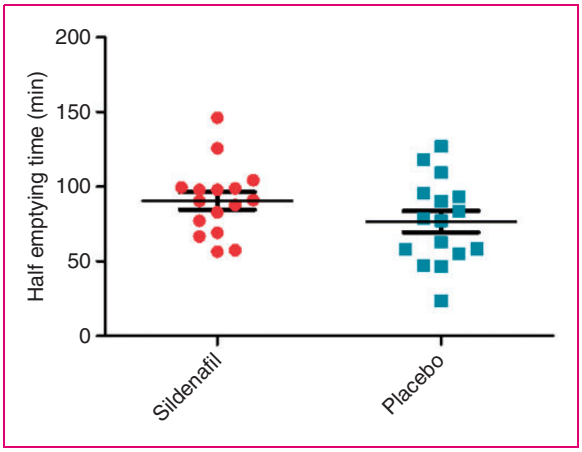

Figure 7. Gastric emptying test. The $T_{1/2}$ (half emptying time) was slightly decreased after sildenafil treatment ($p = 0.04$). The values were compared with the student's *T* test. The results are presented as mean ± SEM.

functional dyspepsia and are associated with postprandial fullness, nausea, vomiting, decreased nutrient tolerance, early satiation and, over time, weight loss.[18–20]

The finding of an inhibitory effect of sildenafil on GA was unexpected: Sildenafil would be anticipated to enhance the relaxatory effect of NO, considering its mechanism of action described in earlier animal and human studies.[2,3,21–23] However, studies in recent years have established that the GA reflex is not mediated by a single mediator such as NO, but is a complex phenomenon in which a range of neurotransmitters are involved such as serotonin, galanin, endogenous opioids and endocannabinoids.[24–27] Moreover, factors determining the size of GA are not only the arrival of nutrients in the stomach, but also feedback from the duodenum and intragastric antro-fundic reflex pathways.[28–30]

Paradoxically, a previous gastric barostat study in fact showed enhanced postprandial gastric volumes in response to sildenafil administration, suggestive of enhanced GA.[8] In contrast, the current study, using IGP monitoring, suggested inhibition of GA by sildenafil. The results of the satiation test, which showed a significant decrease in nutrient tolerance, are in line with an inhibition of gastric volume capacity by sildenafil, and thus support the concept of impaired GA.[31] Two factors may play a role in these differences. First of all, the gastric barostat exerts a positive distending force on the proximal stomach, and this may artificially increase the proximal stomach volume as a consequence of reflex-driven changes in gastric tone.[9,32] It is conceivable that sildenafil alters some of the reflex pathways that are driven by the distending force of the balloon in the proximal stomach. Second, while IGP measurement provides information on pressure events in different regions of the stomach (36 measurement points), the barostat balloon extends from the proximal stomach into the distal stomach and may be influenced by events in the antrum.[9,32] In humans, proximal and distal gastric motor activity are closely correlated, and both the proximal and distal stomach relax during nutrient drink infusion.[33,34] Previously, Bortolotti reported that sildenafil inhibited phasic contractions in the antrum as well as the duodenum,[35] and Cho et al. found evidence for rapid redistribution of radiopaque markers from the proximal stomach to the distal stomach.[14] Hence, it is conceivable that sildenafil primarily inhibits antral tone and contractility, leading to redistribution of the gastric content from the proximal to the distal stomach, therefore resulting in a more restricted gastric relaxation, and consequently a smaller IGP drop, at the level of the fundus. Antral hypocontractility and distention are also likely to result in delayed GE, and this is consistent with the effects we found with the GE breath test in the current study. Furthermore, as the distal stomach is less compliant, antral distention is more likely to induce dyspeptic symptoms, and this may contribute significantly to the induction of dyspeptic symptoms after sildenafil.[33,34] Providing solid proof for redistribution of the meal to the antrum after sildenafil would require additional imaging studies and is beyond the scope of the current protocol.

In conclusion, in humans 50 mg sildenafil inhibits the IGP drop of the proximal stomach upon nutrient ingestion, suggestive of impaired GA. This was associated with significantly decreased nutrient tolerance and delayed solid GE in HVs. These observations may underlie occurrence of dyspeptic symptoms induced by sildenafil.

Acknowledgement

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Declaration of conflicting interests

None declared.

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Ethics approval

All study procedures were approved by the Ethics Committee of Leuven University Hospital, Belgium (reference S-number study: S53584; date: 2012), and the study was performed in accordance with the 1975 Declaration of Helsinki.

Informed consent

Written informed consent was obtained from each participant.

References

1. Vanden Berghe P, Janssen P, Kindt S, et al. Contribution of different triggers to the gastric accommodation reflex in humans. *Am J Physiol Gastrointest Liver Physiol* 2009; 297: G902–G906.
2. Janssen P, Verschueren S, Ly HG, et al. Intragastric pressure during food intake: A physiological and minimally invasive method to assess gastric accommodation. *Neurogastroenterol Motil* 2011; 23: 316–322, e153–e154.
3. Tack J, Demedts I, Meulemans A, et al. Role of nitric oxide in the gastric accommodation reflex and in meal induced satiety in humans. *Gut* 2002; 51: 219–224.
4. Surks HK. cGMP-dependent protein kinase I and smooth muscle relaxation: A tale of two isoforms. *Circ Res* 2007; 101: 1078–1080.
5. Morales A, Gingell C, Collins M, et al. Clinical safety of oral sildenafil citrate (VIAGRA) in the treatment of erectile dysfunction. *Int J Impot Res* 1998; 10: 69–73. discussion 73–74.
6. Fink HA, Mac Donald R, Rutks IR, et al. Sildenafil for male erectile dysfunction: A systematic review and meta-analysis. *Arch Intern Med* 2002; 162: 1349–1360.
7. Boyce EG and Umland EM. Sildenafil citrate: A therapeutic update. *Clin Ther* 2001; 23: 2–23.
8. Sarnelli G, Sifrim D, Janssens J, et al. Influence of sildenafil on gastric sensorimotor function in humans. *Am J Physiol Gastrointest Liver Physiol* 2004; 287: G988–G992.
9. de Zwart IM, Haans JJ, Verbeek P, et al. Gastric accommodation and motility are influenced by the barostat device: Assessment with magnetic resonance imaging. *Am J Physiol Gastrointest Liver Physiol* 2007; 292: G208–G214.
10. Janssen P, Verschueren S and Tack J. Intragastric pressure as a determinant of food intake. *Neurogastroenterol Motil* 2012; 24: 612–615, e267–e268.
11. Papathanasopoulos A, Rotondo A, Janssen P, et al. Effect of acute peppermint oil administration on gastric sensorimotor function and nutrient tolerance in health. *Neurogastroenterol Motil* 2013; 25: e263–e271.
12. Rotondo A, Janssen P, Mulè F, et al. Effect of the GLP-1 analog liraglutide on satiation and gastric sensorimotor function during nutrient-drink ingestion. *Int J Obes (Lond)* 2013; 37: 693–698.
13. Papathanasopoulos A, Rotondo A, Janssen P, et al. Tu1457 The effect of interdigestive motility on intragastric pressure and satiation during intragastric nutrient infusion. *Gastroenterology* 2012; 142(Suppl 1): S–838.
14. Cho SH, Park H, Kim JH, et al. Effect of sildenafil on gastric emptying in healthy adults. *J Gastroenterol Hepatol* 2006; 21(1 Pt 2): 222–226.
15. Madsen JL, Søndergaard SB, Fuglsang S, et al. Effect of sildenafil on gastric emptying and postprandial frequency of antral contractions in healthy humans. *Scand J Gastroenterol* 2004; 39: 629–633.
16. Ueno T, Uemura K, Harris MB, et al. Role of vagus nerve in postprandial antropyloric coordination in conscious dogs. *Am J Physiol Gastrointest Liver Physiol* 2005; 288: G487–G495.
17. Orihata M and Sarna SK. Inhibition of nitric oxide synthase delays gastric emptying of solid meals. *J Pharmacol Exp Ther* 1994; 271: 660–670.
18. Kindt S and Tack J. Impaired gastric accommodation and its role in dyspepsia. *Gut* 2006; 55: 1685–1691.
19. Tack J, Piessevaux H, Coulie B, et al. Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology* 1998; 115: 1346–1352.
20. Sarnelli G, Caenepeel P, Geypens B, et al. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. *Am J Gastroenterol* 2003; 98: 783–788.
21. Desai KM, Zembowicz A, Sessa WC, et al. Nitroxergic nerves mediate vagally induced relaxation in the isolated stomach of the guinea pig. *Proc Natl Acad Sci U S A* 1991; 88: 11490–11494.
22. Janssen P, Nielsen MA, Hirsch I, et al. A novel method to assess gastric accommodation and peristaltic motility in conscious rats. *Scand J Gastroenterol* 2008; 43: 34–43.
23. Boeckxstaens GE, Pelckmans PA, Bogers JJ, et al. Release of nitric oxide upon stimulation of nonadrenergic noncholinergic nerves in the rat gastric fundus. *J Pharmacol Exp Ther* 1991; 256: 441–447.
24. Ameloot K, Janssen P, Scarpellini E, et al. Endocannabinoid control of gastric sensorimotor function in man. *Aliment Pharmacol Ther* 2010; 31: 1123–1131.
25. Grover M and Camilleri M. Effects on gastrointestinal functions and symptoms of serotonergic psychoactive agents used in functional gastrointestinal diseases. *J Gastroenterol* 2013; 48: 177–181.
26. Janssen P, Pottel H, Vos R, et al. Endogenously released opioids mediate meal-induced gastric relaxation via peripheral mu-opioid receptors. *Aliment Pharmacol Ther* 2011; 33: 607–614.
27. Sarnelli G, Vanden Berghe P, Raeymaekers P, et al. Inhibitory effects of galanin on evoked [Ca2+]i responses in cultured myenteric neurons. *Am J Physiol Gastrointest Liver Physiol* 2004; 286: G1009–G1014.
28. Carrasco M, Azpiroz F and Malagelada JR. Modulation of gastric accommodation by duodenal nutrients. *World J Gastroenterol* 2005; 11: 4848–4851.
29. Janssen P, Vanden Berghe P, Verschueren S, et al. Review article: The role of gastric motility in the control of food intake. *Aliment Pharmacol Ther* 2011; 33: 880–894.
30. Caldarella MP, Azpiroz F and Malagelada JR. Antrofundic dysfunctions in functional dyspepsia. *Gastroenterology* 2003; 124: 1220–1229.

31. Tack J, Caenepeel P, Piessevaux H, et al. Assessment of meal induced gastric accommodation by a satiety drinking test in health and in severe functional dyspepsia. *Gut* 2003; 52: 1271–1277.
32. Mundt MW, Hausken T and Samsom M. Effect of intragastric barostat bag on proximal and distal gastric accommodation in response to liquid meal. *Am J Physiol Gastrointest Liver Physiol* 2002; 283: G681–G686.
33. Lee KJ, Vos R, Janssens J, et al. Differences in the sensorimotor response to distension between the proximal and distal stomach in humans. *Gut* 2004; 53: 938–943.
34. Jones KL, Doran SM, Hveem K, et al. Relation between postprandial satiation and antral area in normal subjects. *Am J Clin Nutr* 1997; 66: 127–132.
35. Bortolotti M, Mari C, Lopilato C, et al. Sildenafil inhibits gastroduodenal motility. *Aliment Pharmacol Ther* 2001; 15: 157–161.