Influence of sildenafil on gastric sensorimotor function in humans

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Sarnelli, Giovanni, Daniel Sifrim, Jozef Janssens, and Jan Tack. Influence of sildenafil on gastric sensorimotor function in humans. Am J Physiol Gastrointest Liver Physiol 287: G988–G992, 2004; doi:10.1152/ajpgi.00419.2003.—After a meal, the proximal stomach relaxes probably through the activation of nitrergic neurons in the gastric wall. Nitric oxide-induced smooth muscle relaxation involves activation of soluble guanylate cyclase, with cGMP production, which is then degraded by phosphodiesterase-5 (PDE-5). The aim of this study was to investigate the effect of sildenafil, a selective PDE-5 inhibitor, on fasting and postprandial proximal gastric volume and on gastric emptying rates in humans. A gastric barostat was used to study gastric compliance and perception to isobaric distension in healthy subjects before and after placebo (n = 13) or sildenafil, 50 mg (n = 15). In 10 healthy subjects, two gastric barostat studies were performed in randomized order to study the effect of placebo or sildenafil on postprandial gastric relaxation. Similarly, solid and liquid gastric emptying rates were studied in 12 healthy subjects. Sildenafil significantly increased fasting intragastric volume (141 ± 15 vs. 163 ± 15 ml, P < 0.05) and volumes of first perception. Sildenafil induced a higher and prolonged gastric relaxation either at 30 min (357 ± 38 vs. 253 ± 42 ml, P < 0.05) or 60 min (348 ± 49 vs. 247 ± 38 ml, P < 0.05) after the meal. Sildenafil did not alter solid half-emptying time but significantly delayed liquid emptying (43 ± 4 vs. 56 ± 4 min, P < 0.01). In conclusion, sildenafil significantly increases postprandial gastric volume and slows liquid emptying rate, confirming that meal-induced accommodation in humans involves the activation of a nitrergic pathway. The effect of sildenafil on gastric fundus suggests a therapeutic potential for phosphodiesterase inhibitors in patients with impaired gastric accommodation.

nitric oxide; gastric accommodation; gastric sensitivity; gastric emptying

DURING FASTING, muscle fibers of the proximal stomach maintain a tonic contractile activity, which is dependent on vagally mediated cholinergic input (1, 2). During and after ingestion of a meal, a relaxation of the proximal stomach occurs, which provides the food and liquids with a reservoir and enables a volume increase without a rise in pressure. Previous studies, both in animals and in humans, have established that this accommodation reflex involves the activation of inhibitory nitrergic neurons in the gastric wall (3, 4, 13, 16, 21, 26, 37). Recent studies have established that impaired accommodation to a meal is a major pathophysiological mechanism in functional dyspepsia (14, 31, 42), and restoration of accommodation is considered a valid therapeutic target (12, 38). One way to achieve this goal would be to enhance the effect of activation of gastric nitrergic neurons.

Nitric oxide–induced smooth muscle relaxation involves the activation of soluble guanylate cyclase, leading to cGMP production (9). Sildenafil is an inhibitor of the cGMP–specific phosphodiesterase-5 (PDE-5), which breaks down cGMP. In the presence of sildenafil, nitric oxide–induced cGMP accumulates, without a concomitant increase in the concentration of nitric oxide (10, 28). Originally used in the treatment of male erectile dysfunction, recent observations demonstrate that this drug is also able to affect nitrergic control of esophageal and gastroduodenal motility in humans (5, 7, 15).

Hypersensitivity to gastric distension and delayed gastric emptying are two other pathophysiological mechanisms in functional dyspepsia (32, 33, 36). Studies using a nitric oxide synthase (NOS) inhibitor in humans did not reveal a major role of nitric oxide in the control of sensitivity to gastric distension (21, 37). In neuronal NOS-deficient mice, gastric emptying is strongly delayed, but the role of nitric oxide in the control of gastric emptying in humans has largely remained unexplored (18, 20, 34, 43).

The aim of the present study was to investigate the effect of sildenafil on proximal gastric sensory and motor function, using an electronic barostat in healthy subjects. In addition, to gain further insight into the involvement of nitric oxide in the control of gastric emptying, we also studied the effect on solid and liquid gastric emptying rate.

MATERIALS AND METHODS

Subjects

Forty-two healthy volunteers (27 men and 17 women, aged 19–29 yr, body mass index 19.7 ± 0.7) participated in the study. None of the subjects had symptoms or a history of gastrointestinal disease or drug allergies, nor were they taking any medication. Written informed consent was obtained from each participant. The protocol was approved by the Ethics Committee of the University Hospital.

Barostat Recording Technique

After an overnight fast of at least 12 h, a double-lumen polyvinyl tube (Salem sump tube 14 Charriere Sherwood Medical, Petit Rechain, Belgium) with an adherent plastic bag (1,200 ml capacity; 17-cm maximal diameter) finely folded was introduced through the mouth and secured to the subject’s chin with adhesive tape. The position of the bag in the gastric fundus was checked fluoroscopically.

The polyvinyl tube was then connected to a computer-driven programmable volume-displacement barostat device (Synectics Visceral Stimulator, Stockholm, Sweden). The barostat device can deliver volume ramps or pressure steps at different rates, while simultaneously monitoring pressure and volume at a sampling rate of 8 s⁻¹. Pressure is monitored within the inflation device. To unfold the intragastric bag, it was inflated with a fixed volume of 500 ml of air for 2 min with the study subject in a recumbent position and again deflated completely. After a 10-min equilibration period, the subjects

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were positioned in a comfortable sitting position, with the knees slightly bent (80°), in a bed specifically designed for that purpose.

**Specific Procedure and Design**

**Measurement of compliance and sensitivity to gastric distension.** Twenty-eight healthy subjects (15 men, age 19–29 yr) underwent a gastric barostat study to evaluate the influence on gastric compliance and on sensitivity to gastric distension of placebo or sildenafil. Sildenafil was administered in a single-blind fashion by a nurse who was otherwise not involved in the protocol. Data analysis was done in a blinded fashion.

After a 30-min adaptation period, minimal distending pressure (MDP) was determined by increasing intrabag pressure by 1 mmHg every 3 min until a volume of ≥30 ml was reached (29). This pressure level equilibrates the intra-abdominal pressure. Subsequently, a first series of isobaric distensions was performed in stepwise increments of 2 mmHg starting from MDP, each lasting for 2 min, while the corresponding intragastric volume was recorded. Subjects were instructed to score their perception of upper abdominal sensations induced by each distending stimulus at the end of every distending step, using a graphic rating scale that combined verbal descriptors on a scale graded from 0 to 6 (29). The type of sensation was not evaluated. The end point of each sequence of distensions was established at an intrabag volume of 1,000 ml or when the subjects reported discomfort or pain (score 5 or 6).

After another 30-min adaptation period, the pressure level was set at MDP + 2 mmHg. We recorded intrabag volume 30 min before and 45 min after the oral administration of placebo or sildenafil (50 mg). Afterward, intrabag pressure was set again at MDP and a second series of stepwise isobaric distensions was performed to score perception again.

**Measurement of postprandial gastric volume.** Ten healthy subjects (5 men, aged 21–29 yr) underwent two gastric barostat studies, 7–20 days apart. After introduction of the bag and an adaptation period, MDP was determined as described above. Isobaric tone measurements at MDP + 2 mmHg were performed 45 min before and 60 min after a liquid meal (200 ml, 300 kcal, 13% proteins, 48% carbohydrates, 39% lipids, Nutridrink, Nutricia, Bornem, Belgium). Twenty minutes before the meal, placebo or sildenafil (50 mg) was administered in a randomized double-blind fashion.

**Gastric emptying studies.** In 12 healthy subjects (7 men, aged 19–29 yr), gastric emptying rate for solids and liquids was assessed twice using the previously validated 

\[ ^{13}C\text{-octanoic acid }/^{13}C\text{-glycin} \]

breath tests (25, 32). The test meal consisted of 60 g of white bread and one egg, the yolk of which was dosed with 74 kBq of \n
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by averaging the recording. Perception threshold was defined as the first level of pressure and the corresponding volume that evoked a perception score of 1 or more. Discomfort threshold was defined as the first level of pressure and the corresponding volume that provoked a score of 5 or more. Pressure thresholds were expressed as pressures relative to MDP.

Pressure-volume and pressure-perception curves were obtained from the stepwise distensions and fitted with a linear regression model as previously described (35, 36, 38). Gastric compliance was calculated as the slope and the intercept of the pressure-volume curve obtained during at least the first three steps of isobaric distensions.

The mean intragastric volume was measured at 5-min intervals. The effect of sildenafil or placebo was quantified as the difference between the average volumes 30 min before and 45 min after administration of the drug.

Changes in intraballoon volume before and after administration of the meal were measured by calculation of the mean balloon volume for consecutive 5-min intervals. The meal-induced gastric relaxation was quantified as the difference between the average volumes during 30 min before and, respectively, 30 and 60 min after the administration of the meal. In addition, the maximum 5-min volume recorded after the meal was compared with the average volume before the meal.

Gastric half-emptying time (t_{1/2}) for liquids and solids was determined as previously described (25, 32).

**Statistical Analysis**

The sample size for the measurement of postprandial volume and gastric emptying (10 and 12 subjects, respectively) was based on one-sample t-test for a two-sided \( \alpha = 0.05 \) and \( \beta = 0.20 \) (80% power). Because we aimed to assess whether sildenafil has potential clinical effects, the studies were powered to demonstrate an effect size of meal-induced relaxation of 40% and of gastric emptying rate of 30%. For the study of compliance and sensitivity to gastric distension, the sample size was calculated by a two-sample t-test (\( \alpha = 0.05, \beta = 0.20, 80\% \) power) to have clinically meaningful effects of 45% for sensitivity thresholds and gastric compliance, respectively, and of 55% for gastric volume.

The meal-induced accommodation and the gastric half-emptying times after sildenafil or placebo were compared by Student’s t-test.

Gastric compliance, sensitivity to distension, and fasting intragastric volume, before and after administration of placebo or sildenafil, were analyzed by ANOVA for repeated measures. The Student’s t-test was used to compare the effect of placebo and sildenafil. All statistical analysis was performed with SPSS 10.0 for Microsoft Windows. Differences were considered to be significant at the 5% level. All data are given as means ± SE.

**RESULTS**

**Fasting Intragastric Volume and Perception of Gastric Distension**

Twenty-eight volunteers were administered sildenafil (\( n = 15 \), MDP = 7.9 ± 0.4 mmHg) or placebo (\( n = 13 \), MDP = 7.8 ± 0.2 mmHg) to evaluate the effect on fasting fundic tone in a single-blind manner. The average intragastric volume at MDP + 2 mmHg, as measured by the barostat, remained unchanged before and after administration of placebo (206 ± 18 vs. 182 ± 22 ml, not significant [NS]). In the subjects receiving sildenafil, the average intragastric volume at MDP + 2 mmHg significantly increased from 140.7 ± 15 to 162.6 ± 15 ml after the drug (\( P = 0.03 \)).

Both before and after the administration of placebo or sildenafil, distensions of the stomach with progressively higher set pressures produced progressively larger intragastric volumes. Placebo did not alter the intragastric volumes for the same distending pressure. Administration of placebo did not alter the slope (54 ± 7 vs. 57 ± 12 ml/mmHg, NS) and the y-intercept (128.6 ± 23 vs. 85 ± 49 ml, NS) of the pressure-volume curve obtained after linear model fitting. At the same distending pressures, intragastric volumes after sildenafil were significantly larger than the corresponding volumes before
drug administration (Fig. 1). The slope of the pressure-volume curves, obtained after linear model fitting, was not altered by sildenafil (61.6 ± 8.4 vs. 61.5 ± 6 ml/mmHg, NS), whereas the y-intercept of the pressure-volume curves was significantly increased after sildenafil (17 ± 22 vs. 122 ± 42 ml, P = 0.01). This shift of the pressure-volume curve toward higher volumes probably reflects a sildenafil-induced relaxation of the gastric fundus.

Placebo did not affect the pressure inducing first perception (2.9 ± 0.4 vs. 3.3 ± 0.3 mmHg above MDP, NS) or discomfort pressure (10.7 ± 0.8 vs. 10 ± 0.6 mmHg above MDP, NS), and the corresponding intra-balloon volumes were not altered (first perception: 275 ± 29 vs. 287 ± 29 ml; discomfort: 652 ± 47 vs. 618 ± 50 ml) (all NS).

Sildenafil also had no significant influence on the pressure levels inducing first perception (3.3 ± 0.3 vs. 3.1 ± 0.3 mmHg above MDP, NS) or discomfort (10 ± 0.6 vs. 8.4 ± 0.6 mmHg above MDP, NS). However, the corresponding volume at the thresholds for first perception (234 ± 39 vs. 336 ± 41 ml, P = 0.02) and at the thresholds for discomfort (561 ± 39 vs. 633 ± 38 ml, P = 0.05) was significantly increased by sildenafil.

Postprandial Intragastric Volume

The effect of placebo or sildenafil on postprandial intraballoon volume was assessed in 10 volunteers. MDPs (7.5 ± 0.3 vs. 7.8 ± 0.2 mmHg, NS) and preprandial intragastric volumes (176 ± 20 vs. 154 ± 22 ml, NS) were similar in both groups.

Ingestion of the meal caused an immediate relaxation of the proximal stomach in all subjects, reflected by an increase in the balloon volume (Fig. 2). However, after administration of sildenafil, a higher gastric relaxation was observed during the first 30 min (357 ± 38 vs. 253 ± 42 ml, P < 0.05) and 60 min after the meal (348 ± 49 vs. 247 ± 38 ml, P < 0.05). In addition, sildenafil significantly increased the maximum postprandial volume (444 ± 51 vs. 338 ± 48 ml, P < 0.05), whereas the time to maximum postprandial volume was not significantly different (43.5 ± 3.0 vs. 52 ± 5.4 min, NS).

Gasctic Emptying

Sildenafil induced a significant delay of liquid gastric emptying (t1/2 43 ± 4 vs. 56 ± 4 min, P < 0.01, Fig. 3), whereas solid emptying was not significantly affected (t1/2 65 ± 6 vs. 66 ± 4 min, NS).

DISCUSSION

We used sildenafil, a selective PDE-5 inhibitor, to study the involvement of nitricergic neurons in the control of fasting and postprandial gastric tone, of gastric sensitivity to distension, and of gastric emptying in humans.

In the interdigestive state, administration of sildenafil causes a significant relaxation of the gastric fundus: at the same intragastric pressure, larger intragastric volumes are present and consequently larger volumes are needed before thresholds for perception or discomfort are reached. In the postprandial state, pretreatment with sildenafil significantly enhanced gastric accommodation to a meal and delayed liquid gastric emptying.

Nitric oxide is the principal inhibitory transmitter at the neuromuscular junction in the gastrointestinal tract, and its mechanism of action involves cGMP production by soluble guanylate cyclase in smooth muscle cells. Sildenafil inhibits the PDE-5, thereby allowing the accumulation of the nitric oxide-induced cGMP and enhancing the physiological effects of nitric oxide (10). During fasting, the proximal stomach is in a continuous state of tonic contraction that is maintained by a vagally mediated cholinergic input (3, 23). In the cat, administration of the nitric oxide synthase inhibitor Nw-nitro-L-arginine methyl ester results in an increase of the resting fundus tone, an effect that is reversed by L-arginine, suggesting that resting fundus tone in this species is maintained by the balance of a cholinergic and a nitricergic drive (11). Fasting gastric tone in humans is susceptible to nitric oxide, because the administration of a nitric oxide donor induces a proximal gastric relaxation (40). Here we provide further evidence of the contribution of a nitricergic drive to resting fundus tone in humans. Sildenafil significantly increased interdigestive intra-gastric volumes and shifted the pressure-volume curve toward higher volumes. In keeping with this observation, it can be hypothesized that the inhibition of cGMP degradation enhances the effects of the nitric oxide physiologically released at
the level of nitrergic neurons of the gastric wall, which would in turn result in the sildenafil-induced gastric relaxation.

Sildenafil significantly affected the gastric sensitivity to isobaric distensions and caused a significant increase in the volumes needed to reach the thresholds for discomfort. Because the drug did not alter the pressure-expressed sensory thresholds, it seems likely that the decrease in tone is the principal effect of sildenafil and that the higher volume thresholds are most likely occurring secondary to the sildenafil-induced relaxation.

Postprandial intragastric volumes were significantly enhanced by pretreatment with sildenafil, suggesting that meal-induced accommodation in humans involves the activation of a nitrergic pathway (16, 38). Gastric relaxation is mediated through a vagovagally driven nonadrenergic noncholinergic (NANC) mechanism (2). Both in vivo and in vitro studies suggest that the principal candidate neurotransmitters released by NANC neurons during gastric accommodation are nitric oxide and vasoactive intestinal polypeptide (4, 6, 7, 13, 22, 26, 41). Depending on the species studied, both inhibitory neurotransmitters can act concurrently in mediating NANC relaxations of the fundus (6, 22, 39, 41), or nitric oxide can be the only mediator of the NANC relaxation (13, 26, 27). Enhancement of meal-induced gastric relaxation by sildenafil suggests involvement of nitric oxide in the gastric accommodation reflex in humans, and this observation is in agreement with our previous observation that nitric oxide synthase inhibition significantly inhibits gastric accommodation in humans (37).

After sildenafil, higher intragastric volumes were recorded up to 60 min after the meal, suggesting that sildenafil also prolongs meal-induced fundus relaxation. Several studies have shown involvement of recovery in proximal gastric tone as a drive for gastric emptying, especially of liquids (8, 17, 30). The delay in liquid emptying observed after pretreatment with sildenafil probably reflects this postponed recovery of postprandial proximal gastric driving force. Sildenafil did not seem to affect solid gastric emptying. Although a limiting factor for solid emptying may be solid grinding, which may not have been affected by nitrogem modulation, enhanced pyloric sphincter relaxation with a diminished outflow resistance, compensating for the decreased driving force of the proximal or distal stomach, is an alternative explanation (19, 24). Using the dual-emptying breath test, emptying rates for liquids are relatively slow. This may be attributed both to the glycogen content of the liquid meal and to the simultaneous administration with a solid meal (25, 32).

Previous studies have suggested a therapeutic potential for phosphodiesterase inhibitors in gastrointestinal disorders such as achalasia or diabetic gastroparesis (5, 43). The current study also indicates a therapeutic potential of phosphodiesterase inhibitors in patients with impaired accommodation of the proximal stomach to a meal (14, 38). Studies investigating its potential in these patients seem warranted.

In conclusion, we showed that sildenafil affects proximal stomach motility in normal subjects. The drug increases proximal gastric compliance during the fasting state and enhances gastric accommodation to a meal. Furthermore, administration of sildenafil causes a delay in the emptying of liquids. Our results suggest the presence of a nitrergic tonic inhibitory influence on proximal gastric tone during fasting. They also confirm that meal-induced accommodation in humans involves

Fig. 2. Mean intragastric volume at 5-min intervals as measured by gastric barostat in 10 healthy volunteers before and after administration of a liquid meal (time = 0). Twenty minutes before the meal, placebo or sildenafil (50 mg) was administered in a randomized double-blind fashion (time = −20). Ingestion of the meal induces a rapid and marked fundus relaxation that is significantly larger after sildenafil than placebo.

Fig. 3. Effect of sildenafil or placebo on the half-emptying time (t_{1/2}) of the solid and liquid phases of the meal (n = 12 subjects); t_{1/2} for liquid emptying was significantly delayed after sildenafil compared with placebo (*P < 0.01).
the activation of a nitricg pathway and suggest a therapeutic potential for phosphodiesterase inhibitors in patients with impaired gastric accommodation.

REFERENCES


