Alimentary Pharmacology & Therapeutics

The effect of sildenafil on segmental oesophageal motility and gastro-oesophageal reflux

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Publication data
Submitted 14 June 2006
First decision 17 June 2006
Resubmitted 13 July 2006
Accepted 13 July 2006

SUMMARY

Background
Sildenafil is an inhibitor of type 5 phosphodiesterase. It relaxes or inhibits contraction of smooth muscle by increasing cellular concentrations of cyclic guanosine monophosphate. Multichannel intraluminal impedance manometry/pH allow the precise evaluation of oesophageal bolus transit and acid/non-acid reflux.

Aim
To investigate the effect of sildenafil on segmental oesophageal motor function and gastro-oesophageal reflux.

Methods
Eight healthy volunteers underwent multichannel intraluminal impedance manometry baseline, and 15, 30 and 45 min before and after a 50-mg dose of sildenafil successively. The subjects underwent 2-h multichannel intraluminal impedance/pH studies on two separate days after either water or sildenafil ingestion.

Results
Sildenafil decreased the resting lower oesophageal sphincter pressure and prolonged the duration of lower oesophageal sphincter relaxation for the 45 min following its ingestion. At 15 min, distal onset velocity, total bolus transit time, bolus presence time and segmental transit time were delayed in the mid to distal oesophagus. At 30 min, distal onset velocity was restored but bolus presence time and bolus presence time were still delayed in distal smooth muscle segment. At 45 min, total bolus transit time and distal onset velocity were restored but bolus presence time and segmental transit time were delayed more in the transition zone. Sildenafil did not alter the reflux.

Conclusion
Sildenafil alters lower oesophageal sphincter function and oesophageal bolus transit, but not induce gastro-oesophageal reflux.

Aliment Pharmacol Ther **24**, 1029–1036

doi:10.1111/j.1365-2036.2006.03091.x

INTRODUCTION

Nitric oxide (NO) is a major inhibitory neurotransmitter in the enteric nervous system. It is abundantly produced in myenteric neurons that supply the terminal motor innervation to most gastrointestinal smooth muscles.[1] It stimulates soluble guanylyl cyclase to raise the intracellular guanosine 3′, 5′-cyclic monophosphate (cGMP). Cyclic GMP then activates a signalling cascade that relaxes smooth muscle or inhibits its contraction.[2] The biological actions of cGMP are terminated by phosphodiesterase (PDE) type 5. Sildenafil (Viagra, Pfizer Australia Pty Ltd, West Ryde, New South Wales, Australia) antagonizes the activity of this PDE, allowing the cellular accumulation of cGMP and smooth muscle relaxation. Its use as a treatment for impotence is based upon its ability to relax the vascular smooth muscle.[3]

Several reports describe the effects of sildenafil on the human oesophageal motor function. They generally agree that it decreases lower oesophageal sphincter (LES) pressure and the amplitude of peristaltic pressure waves.[4–7] These observations led to the idea that sildenafil might be used to treat the spastic oesophageal motor disorders. As yet, this has not proven to be the case. Because it decreases LES pressure, there is the theoretical risk of its allowing pathological gastro-oesophageal reflux.

Recently, multichannel intraluminal impedance and oesophageal manometry (MII–EM) was introduced as a way to simultaneously evaluate the oesophageal contractile activity and bolus transit.[8] Combined MII and pH recording allows the detection of reflux episodes whether they are acid, non-acid or gas.[8] We aimed to test the hypotheses that sildenafil alters segmental oesophageal bolus transit and increases the gastro-oesophageal reflux.

METHODS

Subjects

Ten healthy volunteers were recruited. The exclusion criteria were a history of hypertension, cardiovascular disease, retinitis pigmentosa, liver failure, renal failure, active peptic ulcer or an idiosyncratic reaction to sildenafil. Those who used medications that might alter normal oesophageal motility or anti-ulcer medications within 7 days were also excluded. Volunteers also had no subjective oesophageal symptoms such as dysphagia, globus, regurgitation or chest pain. After baseline oesophageal manometry, two subjects were diagnosed with nutcracker oesophagus and excluded. Two males and six females were ultimately enrolled. The mean age was 38.5 ± 6.4 years and mean body mass index was 24.9 ± 2.1 kg/m^2. An informed written consent was obtained from each volunteer.

Study schedule

All subjects visited us three times. On the first visit, a physical examination was performed. Particular attention was paid to the cardiovascular exam including the blood pressure and heart rate. An electrocardiogram and oesophagogastroduodenoscopy were done as baseline studies. They all underwent combined MII–EM study before and after ingesting a 50-mg dose of sildenafil. On the other 2 days, combined MII-pH study was done for 2 h each day: baseline combined MII-pH study on the second day and after a 50-mg dose of sildenafil on the third day.

Combined MII–EM

We used the combined MII–EM with a Koenigsberg 9-channel solid-state probe (Sandhill EFT catheter; Sandhill Scientific Inc., Highlands Ranch, CO, USA). The catheter has five pressure sensors: two circumferential pressure sensors located at 5 and 10 cm from the tip and three unidirectional pressure sensors at 15, 20, and 25 cm from the tip. Impedance measuring segments are 2 cm length and centred at 10, 15, 20, and 25 cm from the tip, straddling the four proximal pressure sensors. All subjects were studied in the supine position after an overnight fast. The EFT catheter was inserted *trans*-nasally and passed into the stomach. It was then withdrawn slowly until LES was identified. The catheter was positioned so that the proximal four oesophageal pressure sensors and impedance segments were located at 5, 10, 15, 20 cm above the LES. The volunteers were allowed to accommodate to the catheter for 30 min. They swallowed 20 cc of water. Then, they performed three wet swallows of 5 cc saline at 30-s intervals. Next, the subjects were asked to swallow the sildenafil 50 mg dissolved in 20 cc of water. We repeated the combined MII–EM study in the same manner 15, 30, and 45 min after ingestion of sildenafil (Figure 1). The subjects performed this successively without knowledge when they took the sildenafil.

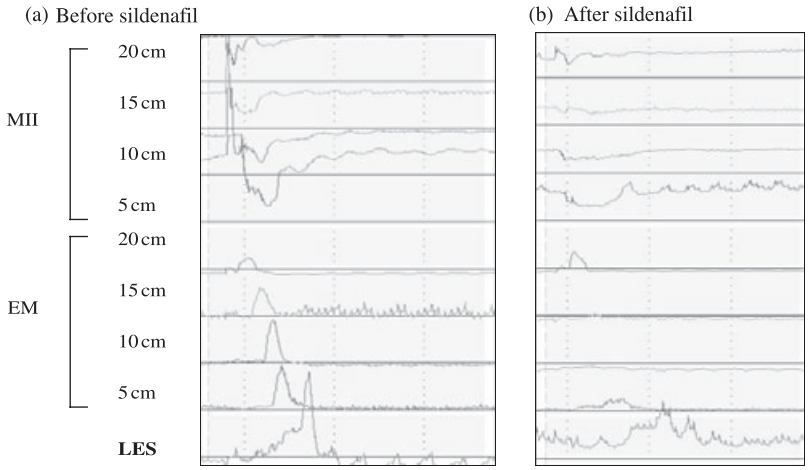

Figure 1. Combined multichannel intraluminal impedance and oesophageal manometry of the oesophagus before and after 50-mg sildenafil. This is one example of bolus transit (top four traces in each panel) and peristaltic pressure waves (bottom four traces in each panel) (a) before and (b) after sildenafil infusion. Impedance scale 0–3000 Ohm, pressure scale 0–100 mmHg.

The resting LES pressure, residual LES pressure and duration of LES relaxation were determined. The resting LES pressure was defined as the pressure in the high-pressure zone measured relative to intra-gastric pressure at the end of expiration. The parameters of oesophageal motor function derived from oesophageal manometry were the amplitude of peristaltic pressure waves and distal onset velocity. The distal onset velocity was calculated from the time it took the peristaltic pressure wave to travel from the most proximal to the most distal pressure-recording site. Several parameters of oesophageal motor function were derived from impedance measurements. Bolus entry is defined as the 50% point between the baseline impedance for 3 s before a swallow and the nadir in impedance during presence of the bolus. Bolus exit is defined as the point on the impedance recovery curve when the impedance rose to 50% of its preswallow baseline. Total bolus transit time (TBTT) is the time elapsed between bolus entry at the impedance-sensing site 20 cm above the LES and bolus exit at the impedance-sensing site 5 cm above the LES. Bolus head advance time is the time between bolus entry 20 cm above the LES and bolus entry 15, 10 and 5 cm above the LES. Bolus presence time (BPT) is the time between bolus entry and exit at each impedance-measuring site – 5, 10, 15 and 20 cm above the LES. Segmental transit time (STT) is the time between bolus entry at any particular level above the LES and its exit from the next lower level. These definitions of the impedance parameters were introduced in the report by Tutuian *et al.*[8] Incomplete bolus transit is defined as failure of bolus exit at any one of the three distal impedance-measuring sites.

Combined MII-pH

We used the MII-pH probe (Sandhill Scientific, Inc.). It has four distal and two proximal impedance-measuring ring electrodes and a single pH sensor at the same level as the centre of the second distal impedance-measuring segment. On the second visit, the MII-pH catheter was inserted *trans*-nasally and positioned so that the pH sensor was located 5 cm above the LES. The impedance-measuring segments were located 3, 5, 7, 9, 15 and 17 cm above the LES. After insertion, the subject swallowed 20 cc of water and then lay in the supine position. To correlate the symptoms with reflux events, the subject was asked to press the buttons of the recorder (Sleuth; Sandhill Scientific Inc.) as follows; (i) heartburn, (ii) regurgitation and (iii) acid taste. We recorded for 2 h and determined the total number of reflux episode, number of acid (pH < 4.0) reflux events, non-acid episodes (pH remained above 4.0 with a drop of no more than 1 pH U), minor acid reflux events (pH remains above 4.0, with a drop of more than 1 U) refluxes, and acid re-reflux (acid reflux while pH is already <4). We also categorized the reflux events as gas, liquid or mixed. We determined the reflux symptom index (SI, Reflux-related symptom events/Total symptom events *100%) and symptom sensitivity index (SSI, Reflux-related symptom events/Total reflux episodes *100%).[9] Transient LES relaxation (TLESR) was also monitored. On the third visit, the subject was asked to swallow sildenafil 50 mg dissolved in 20 cc of water and we repeated combined MII-pH study in the same manner. We followed the method of 2 h recording from the reports by Vela *et al.*[9, 10] with modification.

Statistical analysis

Combined MII–EM parameters measured after the administration of either sildenafil or placebo were compared with baseline measurements using one-way analysis of variance (ANOVA). Measurements evaluated after the administration of sildenafil or placebo were also compared using the Mann–Whitney *U*-test. The Wilcoxon's signed rank test was used to compare the parameters of combined MII-pH study between sildenafil and placebo. All values were expressed as mean ± S.E.M. and statistical significance was considered when *P*-value was <0.05.

RESULTS

Combined MII–EM Lower oesophageal sphincter

After ingesting the sildenafil, resting LES pressure decreased by nearly 50% (Figure 2). This drop in LES pressure was statistically different from the baseline for the entire study ($P < 0.05$). Sildenafil did not change residual LES pressure, but it lengthened the duration of LES relaxation during the entire experiment. Prolongation of LES relaxation was statistically different from the baseline and placebo at all times after the ingestion of sildenafil ($P < 0.05$) (Figure 3).

Oesophageal body

Sildenafil decreased the amplitude of peristaltic pressure waves at 5, 10 and 15 cm above the LES (Figure 4). This decrease was statistically different from baseline and placebo at all time points ($P < 0.05$). The distal onset velocity was slowed compared with placebo only at 15 min after sildenafil ingestion ($P < 0.05$) (Figure 5).

Total bolus transit time was prolonged by sildenafil, but the difference did not reach the statistical significance at any time point. There was, however, a trend towards the statistical significance at 15 and 30 min when compared with placebo ($P = 0.054$ at 15 min, $P = 0.072$ at 30 min) (Figure 6). Bolus presence time was lengthened at all but the most cephalad-recording site 15 min after ingesting the sildenafil ($P < 0.05$ at 5 cm and 15 cm, $P = 0.072$ at 10 cm) (Figure 7). Prolongation of the BPT was also statistically significant 10 cm above LES at 45 min ($P < 0.05$ at 10 cm, $P = 0.054$ at 15 cm). Segmental transit time was prolonged at 15 → 10 cm and 10 → 5 cm above LES 15 min after taking the sildenafil ($P < 0.05$). While not statistically significant,

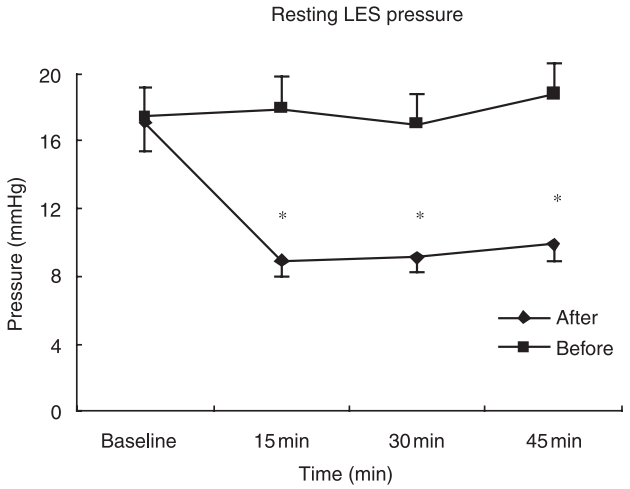

Figure 2. Effect of 50-mg sildenafil on resting lower oesophageal sphincter (LES) pressure. Sildenafil decreased the resting LES pressure significantly compared with that of basal value at 15, 30, 45 min (* $P < 0.05$). All values are in mean ± S.E.M.

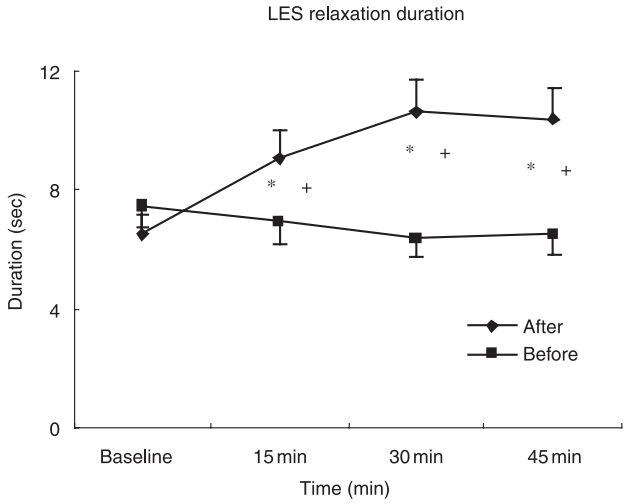

Figure 3. Effect of 50-mg sildenafil on the duration of lower oesophageal sphincter (LES) relaxation. Sildenafil prolonged the duration of LES relaxation during wet swallows significantly compared with basal values at 15, 30, and 45 min (* $P < 0.05$), and compared with corresponding placebo values at 15, 30, and 45 min († $P < 0.05$). All values are in mean ± S.E.M.

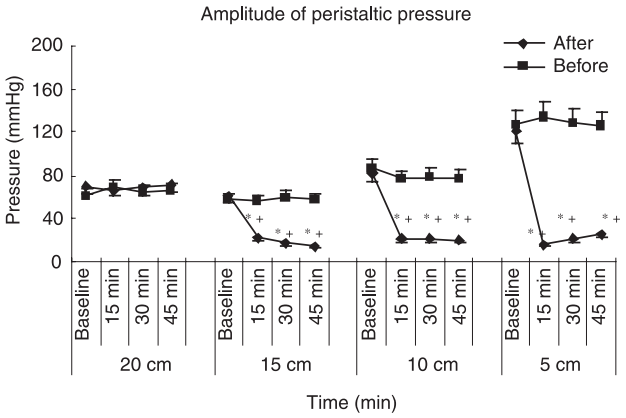

Figure 4. Effect of 50-mg sildenafil on the amplitude of peristaltic pressure waves. Sildenafil significantly decreased the amplitude of peristaltic pressure waves at 5, 10, 15 cm above lower oesophageal sphincter compared with both the basal value (* $P < 0.05$) and corresponding placebo values († $P < 0.05$). All values are in mean ± S.E.M.

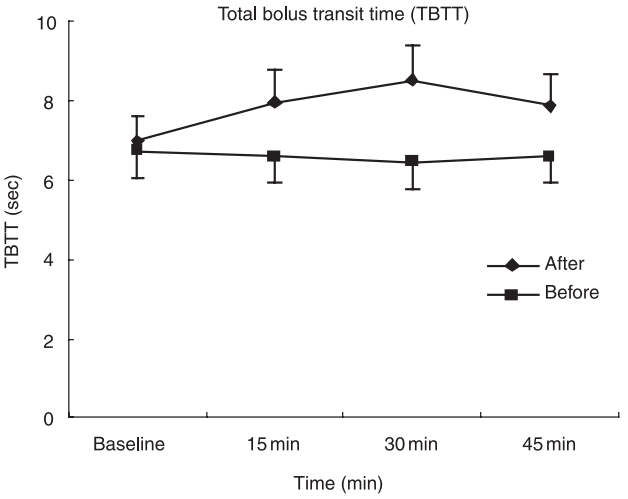

Figure 6. Effect of 50-mg sildenafil on the total bolus transit time (TBTT). Sildenafil delayed TBTT, but this delay was not statistically significant. There was a trend towards the statistical significance at 15 and 30 min after its ingestion ($P = 0.054$ at 15 min, $P = 0.072$ at 30 min). All values are in mean ± S.E.M.

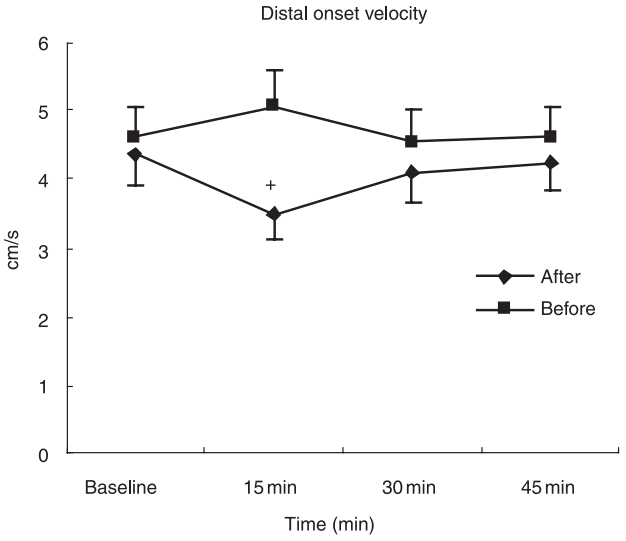

Figure 5. Effect of 50-mg sildenafil on the distal onset velocity of peristalsis. Sildenafil significantly prolonged the distal onset velocity 15 min after its ingestion compared with placebo († $P < 0.05$). All values are in mean ± S.E.M.

STT was prolonged at 30 min in segment 10 → 5 cm ($P = 0.054$) and at 45 min in segment 15 → 10 cm above LES ($P = 0.072$).

Combined MII-pH

Sildenafil did not affect any of the parameters determined with combined MII-pH. Transient LES relaxa-

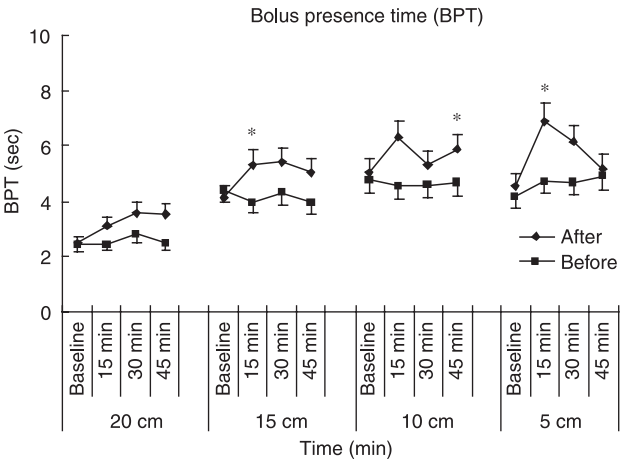

Figure 7. Effect of 50-mg sildenafil on the bolus presence time (BPT). Sildenafil significantly prolonged BPT at 5, 10, 15 cm above lower oesophageal sphincter 15 min after its ingestion, compared with basal values. It was also delayed statistically at the 10-cm site 45 min after its ingestion. All values are in mean ± S.E.M. (* $P < 0.05$).

tion was detected only one time in one subject after sildenafil ingestion.

DISCUSSION

In this study, we investigated the effect of the cGMP PDE inhibitor sildenafil on oesophageal motor function and bolus movement using the combined MII–EM equipment. We used MII-pH to determine if sildenafil causes gastro-oesophageal reflux.

It is now well established that the NO/cGMP signalling system is key to the control of oesophageal motor function in humans and other mammalian species. Nitric oxide produced by myenteric motor neurons increases the cGMP concentrations in oesophageal smooth muscle. Activation of this signalling system controls LES relaxation and the timing of peristalsis in the smooth muscle oesophagus. Diminishing the activity of the NO/cGMP signalling system reduces an LES relaxation and accelerates peristalsis in the smooth muscle oesophagus. Nitric oxide donors that activate the cGMP signalling cascade decrease the LES tone, but do little to oesophageal peristalsis. Zaprinast, a type 5 (cGMP) PDE inhibitor, decreases the resting LES tone and the amplitude of off-responses of opossum oesophageal smooth muscle. These data suggest that type 5 PDE inhibitors, like sildenafil, should alter oesophageal motor function in humans.

The manometric data we obtained are similar to what we and others described previously.[4–7] Sildenafil diminished the resting LES pressure and prolonged LES relaxation. The amplitude of peristaltic pressure waves decreased to levels defined clinically as ineffective peristalsis. The velocity peristalsis in the smooth muscle oesophagus was slowed, but by a relatively small amount. Sildenafil had little effect on peristalsis in the most proximal oesophagus. This portion of the oesophagus is constituted by striated muscle that is not controlled by the NO signalling system, and is therefore not likely to be affected by a cyclic GMP PDE inhibitor. The effect of sildenafil on the propagation of oesophageal pressure waves remains somewhat controversial. There are reports that say it slows propagation and others saying it does not. Resolution of this disparity may come from a study by Zhang *et al.*[11] These authors described a slowing of peristalsis, which occurred because the onset of peristalsis was delayed in the smooth muscle segment of the oesophagus. This slowing gives the appearance of a delay across the transition zone and a fixed delay along the smooth muscle oesophagus. Thus, observing the slowing of propagation is likely to depend upon where in the oesophagus it is measured.

Multichannel intraluminal impedance is a technique that tracks bolus movement in the oesophagus. The impedance sensors are metallic pairs of ring electrodes between which an alternating current voltage is passed. When a bolus of swallowed ionic material like saline passes a pair of electrodes, impedance falls and current flows between the electrodes increases. The measured impedance is inversely proportional to current flow. As the MII/manometry catheter has several sets of impedance electrodes along its length, bolus movement can be inferred from changes in impedance as the swallowed material moves along the oesophagus.[8, 12] In this and our previous study, sildenafil lowered the amplitude of peristaltic pressure waves so much that bolus transit may be affected. The MII allowed us to study the effects of sildenafil on liquid bolus movement in the oesophagus. We observed that the characteristics of bolus movement are altered by sildenafil and that they are time-dependent. Total bolus transit time, BPT and STT were all prolonged in all but the most proximal oesophagus. Thus, as oesophageal peristalsis deteriorates, the bolus dwells longer in the smooth muscle segment of the oesophagus. These changes were, in general, most pronounced 15 min after taking sildenafil; the time at which it is known to have its greatest effect.[5]

There is some risk that sildenafil will predispose to gastro-oesophageal reflux because it decreases LES pressure and the strength of peristalsis. In many clinical trials, dyspepsia, a symptom often ascribed to reflux, is one of the major side effects of sildenafil.[13] In our study, dyspepsia was not observed.

Ours is the first attempt to determine whether sildenafil induces gastro-oesophageal reflux. Conventional pH-metry detects only acid reflux. Combined MII-pH is able to detect the retrograde movement (reflux) of boluses with low impedance (i.e. liquid, food) or high impedance (i.e. air).[8] This means that MII-pH can detect all reflux events whether acid, non-acid, minor acid reflux, acid re-reflux, gas or mixed gas and liquid. Vela *et al.* used MII-pH to evaluate the effects of the GABA B agonist, baclofen,[10] or omeprazole on gastro-oesophageal reflux.[9] They assessed the occurrence of postprandial acid and non-acid reflux with 2-h MII-ph studies before and after treatment. Subjects

were given a refluxogenic meal and were placed in the right lateral decubitus position during recording to maximize the reflux events as they were testing the therapeutic effects of these agents. We did not use these refluxogenic conditions because we already knew that sildenafil decreases LES pressure and were interested in isolating this refluxogenic effect.

Sildenafil did not affect any of the MII-pH parameters in our study. This suggests that the drop in LES pressure we saw with sildenafil – on average to about 8 mmHg – did not predispose to gastro-oesophageal reflux. A number of other factors are thought to predispose to gastro-oesophageal disease: immunological responses of the oesophageal mucosa to injury,[14] TLESR,[15] hiatus hernia,[16] and defects of acid clearing[17] are all candidates. We recorded TLESR only one time in one subject after sildenafil and none of our subjects had a hiatus hernia.

We must say several limitations of this study. Firstly, we selected the supine position appropriate to study the oesophageal function, but not proper to assess the reflux and TLESRs. In this study, decreased LES pressure by sildenafil itself did not contribute to GER. But this must be evaluated further under refluxogenic condition including the recumbent position. Next, this is neither double blinded nor randomized study. We recruited volunteers and determined MII–EM and MII-pH parameters before and after the ingestion of sildenafil with only single-blinded manner.

But, along with the publication by Simren *et al.*[18] in which only severe ineffective oesophageal motility induced by sildenafil is associated with prolonged oesophageal clearance, at least we can conclude that gastro-oesophageal reflux may not be a major side effect of sildenafil.

In summary, we investigated the effect of sildenafil on segmental oesophageal motility and gastro-oesophageal reflux using combined MII–EM and MII-pH devices. We found that sildenafil alters segmental bolus transit and does not induce gastro-oesophageal reflux.

ACKNOWLEDGEMENTS

No external funding was received for this study.

REFERENCES

1 Tomita R, Kurosu Y, Munakata K. Relationship between nitric oxide and non-adrenergic, non-cholinergic inhibitory nerves in human lower esophageal sphincter. *J Gastroenterol* 1997; **32**: 1–5.

2 Shahin W, Murray JA, Clark E, Conklin JL. Role of cGMP as a mediator of nerve-induced motor functions of the opossum esophagus. *Am J Physiol Gastrointest Liver Physiol* 2000; **279**: G567–74.

3 Moreland RB, Goldstein I, Traish A. Sildenafil, a novel inhibitor of phosphodiesterase type 5 in human corpus cavernosum muscle cells. *Life Sci* 1998; **62**: 309–18.

4 Rhee PL, Hyun JG, Lee JH, *et al*. The effect of sildenafil on lower esophageal sphincter and body motility in normal male adults. *Am J Gastroenterol* 2001; **96**: 3251–7.

5 Bortolotti M, Mari C, Giovannini M, Pinna S, Miglioli M, Pandolfo N. Effects of sildenafil on esophageal motility of normal subjects. *Dig Dis Sci* 2001; **46**: 2301–6.

6 Eherer AJ, Schwetz I, Hammer HF, *et al*. Effect of sildenafil on oesophageal motor function in healthy subjects and patients with oesophageal motor disorders. *Gut* 2002; **50**: 758–64.

7 Lee JI, Park H, Kim JH, Lee SI, Conklin JL. The effect of sildenafil on oesophageal motor function in healthy subjects and patients with nutcracker oesophagus. *Neurogastroenterol Motil* 2003; **15**: 617–23.

8 Tutuian R, Vela MF, Shay SS, Castell DO. Multichannel intraluminal impedance in esophageal function testing and gastroesophageal reflux monitoring. *J Clin Gastroenterol* 2003; **37**: 206–15.

9 Vela MF, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and non-acid gastroesophageal reflux: effect of omeprazole. *Gastroenterology* 2001; **120**: 1599–606.

10 Vela MF, Tutuian R, Katz PO, Castell DO. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. *Aliment Pharmacol Ther* 2003; **17**: 243–51.

11 Zhang X, Tack J, Janssens J, Sifrim DA. Effect of sildenafil, a phosphodiesterase-5 inhibitor, on oesophageal peristalsis and lower oesophageal sphincter function in cats. *Neurogastroenterol Motil* 2001; **13**: 325–31.

12 Silny J. Intraluminal multiple electric impedance procedure for measurement of gastrointestinal motility. *J Gastrointest Motil* 1991; **3**: 151–62.

13 Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil study group. *N Engl J Med* 1998; **338**: 1397–404.

14 Fitzgerald RC, Onwuegbusi BA, Bajaj-Elliott M, Saeed IT, Burnham WR, Farthing MJ. Diversity in the esophageal phenotypic response to gastro-esophageal reflux: immunological determinants. *Gut* 2002; **50**: 451–9.

15 Boeckxstaens GE, Tytgat GN. More pathophysiologically oriented treatment of GORD? *Lancet* 2002; **359**: 1267–8.

16 Pandolfino JE, Shi G, Curry J, Joehl RJ, Brasseur JG, Kahrilas PJ. Esophagogastric junction distensibility: a factor con-

tributing to sphincter incompetence *Am J Physiol Gastrointest Liver Physiol* 2002; **282**: G1052–1058.

17 Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Amdorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1986; **91**: 897–904.

18 Simren M, Silny J, Holloway R, Tack J, Janssens J, Sifrim D. Relevance of ineffective oesophageal motility during oesophageal acid clearance. *Gut* 2003; **52**: 784–90.