Alimentary Pharmacology & Therapeutics

# The effects of tegaserod on oesophageal function and bolus transport in healthy volunteers: studies using concurrent high-resolution manometry and videofluoroscopy

M. FOX*, D. MENNE†, B. STUTZ*, M. FRIED* & W. SCHWIZER*

*Department of Gastroenterology and Hepatology, University Hospital of Zürich, Zürich, Switzerland; †Menne Biomed, Tübingen, Germany

Correspondence to:
Dr M. Fox, Department of Gastroenterology and Hepatology, University Hospital of Zürich, Rämistrasse 100, CH-8091 Zürich, Switzerland.
E-mail: markfox_2@hotmail.co.uk

*Publication data*
Submitted 31 May 2006
First decision 28 June 2006
Resubmitted 11 July 2006
Accepted 12 July 2006

## SUMMARY

### Background
Tegaserod is a partial 5-hydroxytryptamine 4 receptor agonist with prokinetic effects on the gastrointestinal tract, its effects on oesophageal function are unknown.

### Aim
A randomized, placebo controlled, double-blind trial assessed the effect of tegaserod on the oesophagus in healthy, asymptomatic subjects.

### Method
A 7-day course of tegaserod 6 mg b.d. vs. placebo was prescribed ($n$ = 17/21 completed both phases of study). High-resolution manometry and pH measurements were performed before and after a test meal. Bolus transport of liquids and solids was studied by high-resolution manometry and videofluoroscopy.

### Results
Tegaserod had no effect on lower oesophageal sphincter pressure compared with placebo, peristaltic velocity increased ($P < 0.001$) and distal contractile pressure decreased slightly ($P < 0.05$). Transient lower oesophageal sphincter relaxations and reflux were infrequent regardless of treatment. During the studies of bolus transport, high-resolution manometry revealed that tegaserod promoted mid-oesophageal contractility ($P < 0.02$) and shortened the 'proximal transition zone' ($P < 0.05$), the level where bolus escape occurred most frequently. These effects had no effect on liquid bolus transport; however a non-significant trend to improved solid bolus transport was observed (66% vs. 31%;$P = 0.07$).

### Conclusion
Tegaserod did not alter lower oesophageal sphincter pressure, but had significant effects on peristaltic function. High-resolution manometry promoted mid-oesophageal contractility during bolus transport. This effect was associated with a non-significant trend to improved solid bolus transit.

*Aliment Pharmacol Ther* **24**, 1017–1027


doi:10.1111/j.1365-2036.2006.03090.x

## INTRODUCTION

Tegaserod is a potent 5-hydroxytryptamine 4 (5-HT4) receptor agonist with prokinetic effects on the gastrointestinal tract, and clinical efficacy in disorders associated with the reduced gastrointestinal motility.[1, 2] Tegaserod accelerates gastric emptying, small bowel and colonic transit;[2–4] however, its effects on oesophageal motor function and bolus transport are unknown.

The primary functions of the oesophagus are the transport of food and fluid from the mouth to the stomach and the prevention of gastro-oesophageal reflux. The pathogenesis of upper gastrointestinal symptoms is multi-factorial, but the importance of oesophageal and gastric motor dysfunction is accepted. Correcting this dysfunction is a rational therapeutic objective. In the past, cisapride, another prokinetic with 5-HT4 agonist activity, was successfully used in disorders of oesophageal and gastric function.[5, 6] In patients with gastro-oesophageal reflux disease (GERD), cisapride reduced the oesophageal acid exposure, healed low-grade oesophagitis and reduced the reflux symptoms.[6] More recently, cisapride was found to increase the risk of serious cardiac arrhythmias and is no longer widely prescribed.[7] Tegaserod belongs to a different class of 5-HT4 agonists, which do not have adverse effects on the heart.[8] A dose-finding study of tegaserod in patients with mild-to-moderate GERD documented a significant decrease in postprandial acid reflux;[9] however, conventional manometry could not establish the physiological basis of this effect.

For a prokinetic medication to provide clinical benefits, it must not only have effects on oesophageal motor activity, but these effects must also improve oesophageal bolus transport. An adequate description of the effects of tegaserod on oesophageal physiology must address both these aspects. High-resolution manometry (HRM) provides important advantages over conventional manometry for this purpose. Firstly, the technique provides stable measurements over prolonged periods of time because shifts of catheter position do not alter the data collection. Secondly, HRM displays the segmental neuro-functional anatomy of the oesophagus and identifies focal abnormalities of oesophageal peristalsis that have been shown to disturb function.[10–12] Thirdly, high-resolution pressure measurement provides an assessment of intra-bolus pressure and the propulsive force that drives bolus transport (pressure gradient).[13, 14] As a result, HRM improves the ability of investigators to describe the physiological basis for the success or failure of bolus transport;[15] an important advantage because oesophageal symptoms and mucosal damage are more closely related to bolus transport and reflux clearance than abnormal motor function as assessed by conventional manometry.[16, 17]

This randomized, placebo controlled, double-blind trial studied the effect of tegaserod on the oesophagus in healthy, asymptomatic subjects. Concurrent HRM and pH measurement was performed before and after a test meal to assess the effect of tegaserod on the lower oesophageal sphincter (LOS), gastro-oesophageal reflux and oesophageal clearance. Concurrent HRM and videofluoroscopy were used to investigate the effects of tegaserod on oesophageal peristalsis and bolus transport. Solid and liquid bolus transports were studied because the mechanism and efficacy of their transit is different.[18] It was considered that resistance to solid bolus transit would provide a greater challenge to oesophageal function, increasing sensitivity of investigations to any prokinetic effect in healthy volunteers.[16, 19]

## MATERIALS AND METHODS

### Subjects

Healthy asymptomatic subjects were recruited by advertisement April–October 2003. Subjects with a history of gastrointestinal disease or symptoms, psychological problems or abnormalities on electrocardiogram or laboratory testing were excluded. No subject on regular medication (except contraception) was included. All participants signed an informed consent to participate in these studies, which were approved by the ethical committee of the University Hospital of Zürich.

### Experimental protocol and patient assignment

This was a Phase II single centre study with a double-blind, placebo controlled, cross-over design consisting of two 7-day treatment periods interspersed with a 5–14-day washout period. The treatment dose of tegaserod 6 mg b.d. was based on the preliminary studies of the acute effects of tegaserod on LOS pressure (unpubl. observations) and advice from the manufacturers (Zelmac; Novartis, Basel, Switzerland, data on file). The hospital pharmacy dispensed placebo or tegaserod according to a computer-generated randomization list.

Investigations were performed at the end of each treatment period after a minimum of 6 h fast.

## Physiological investigation

As described previously, 32 channel HRM was performed using a water perfused, micromanometric catheter assembly (Dentsleeve, Wayville, South Australia).[15, 20] The HRM catheter was passed transnasally such that highest resolution section (1 sensor/cm) traversed the LOS. A single use dual-sensor antimony pH catheter (Oakfield Instruments, Oxford, UK) connected to a portable digital data recorder (Flexilog 2000; Oakfield Instruments, Oxford, UK) was then placed such that the proximal pH electrode was 5 cm above the upper border of the LOS and the distal pH electrode 15-cm distal to this position in the stomach. The pH data were recorded at 1 Hz and displayed in real time on a separate computer (Flexisoft, Oakfield Instruments, Oxford, UK). Recordings of HRM and pH data were synchronized by an on-line clock.

The experimental protocol is presented in Figure 1. Baseline recordings were acquired for 1 h in the supine and upright, seated positions with 10 swallows of 10-mL room temperature water acquired in both positions. A liquid test meal was consumed, comprising 200-mL Ensure (450 kcal, 47% fat) titrated to pH4 with vitamin C (10% ascorbic acid, prepared in-house) and diluted to 300 mL. Following the meal, recordings continued in the seated position for 2 h. In addition, concurrent videofluoroscopy and HRM were performed.[15, 20] With the patients in the supine position 10 mL swallows of a barium suspension [Micropaque, Guerbet, Zürich (100cPois, consistency of light syrup)] and 10-mm cubed solid bolus (marshmallow swallowed with 5 mL barium suspension) were recorded. The oesophagus was imaged by digital videofluoroscopy, digitized *in situ* in 8-bit gray scale and stored at 4 Hz by an imaging card (IMAQ; National Instruments, Austin, TX, USA). Standard measures kept the effective radiation dose to a minimum.

## Data analysis

Analogue pressure recordings from the HRM channels are digitized and displayed (Figure 2) by custom-made software (TRACE!; Advanced Manometry Systems, Melbourne, Australia).[15, 20] HRM and pH data were transferred to patient-specific spreadsheets. To facilitate analysis, the pH data were expanded to match HRM-recording frequency.

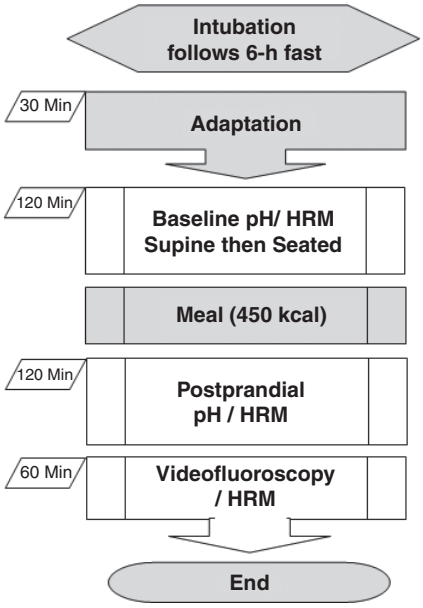


**Figure 1.** Timeline of physiological measurements. The final 6-mg dose of tegaserod was taken on arrival in the department before intubation. Water swallows were obtained during the last 10 min of each measurement period.

The primary outcome variable was baseline LOS pressure assessed by 6-cm 'virtual sleeve' LOS sensor derived from the HRM data.[15] Stable measurements of median LOS and distal peristaltic contractile pressures and peristaltic velocity were acquired during the prolonged baseline recordings and repeated water swallows by semi-automatic analysis. Transient lower oesophageal sphincter relaxations (TLOSR) and reflux events were identified according to the published criteria.[21]

Data acquired during the study of bolus transport were analysed initially without reference to the manometric record to determine the oesophageal bolus transport time and the position of bolus escape (if present). Then HRM was analysed in detail to assess the proximal-, mid- and distal-oesophageal segmental contractions, as defined by Clouse and Staiano by (i) the characteristic rise and fall of contractile pressure, (ii) velocity and (iii) duration as the peristaltic contraction passes from the pharynx to the stomach.[22] HRM measurements of oesophageal peristalsis included onset velocity (i.e. upstroke of the peristaltic wave), median contractile pressure and contractile integral [HRM plot 'contraction volume' with *x*, *y* and *z* axes

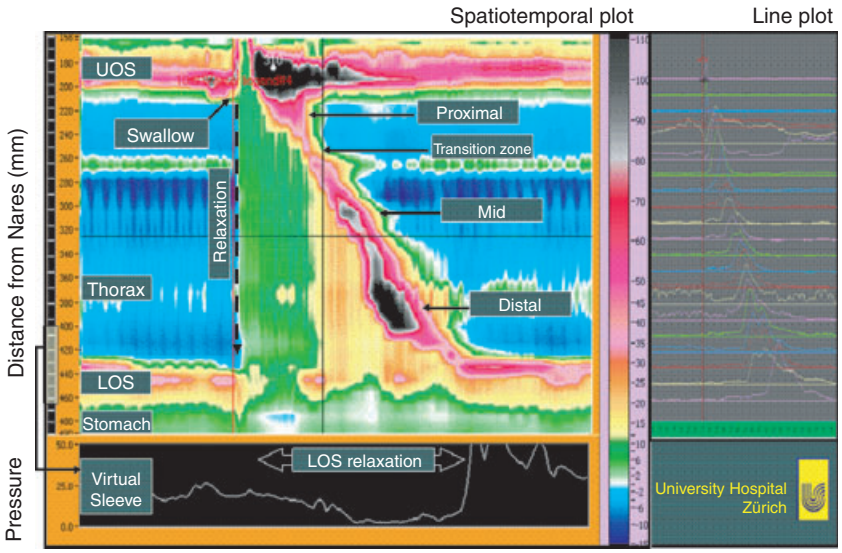


**Figure 2.** High-resolution manometry depicts oesophageal pressure activity from the pharynx to the stomach. The spatio-temporal plot presents the same information as presented in the line plots; however, the large volume of data is easier to appreciate in a single image than multiple line plots. Time is on the *x*-axis and distance from the nares is on the *y*-axis. Each pressure is assigned a colour (legend adjacent). The synchronous relaxation of the upper oesophageal sphincter (UOS) and lower oesophageal sphincter (LOS) is seen, as is the increasing pressure and duration of the peristaltic wave as it passes distally. Other functionally important pressure events include the proximal transition zone (pressure trough) between the proximal and mid-oesophagus and the changes in velocity, contractile pressure and width in the proximal-, mid- and distal- segmental contractions. The intra-bolus pressure (common cavity pressure 'beneath' the peristaltic wave) and pressure gradient across the gastro-oesophageal junction are clearly visualized. These factors rather than conventional manometric measurements describe the forces that drive the bolus transport.[13 14]

represented by the length (cm), width (s) and pressure (mmHg)].[24]

The proximal 'transition zone' was defined by the presence of a pressure trough between the proximal and mid-oesophageal peristaltic contractions. The co-ordination (temporal and spatial separation) between these contractions and nadir pressure were quantified as described previously.[a] In the absence of a clear pressure trough at this level, a position 2/3 down the length of the oesophagus was used for measurement.[22]

## STATISTICS

A sample size of 17 subjects allows the detection of an 8-mmHg difference in LOS pressure at a level of alpha = 0.05, and beta = 0.8. This assumes a 6-mmHg within the subject variation of LOS pressure and an s.d. of 12 mmHg (based on in-house measurements of LOS pressure).[15] A mixed model ANOVA was used to assess the effects of position, prandial state, test medication and treatment sequence on oesophageal function, oesophageal acid exposure and bolus transport. Treatment sequence was never significant and is not reported further. Pairwise comparisons were reported only in the presence of significant group effects. Student's *t*-test or chi-squared analysis was used as appropriate.

The summary results for position, prandial state and treatment are derived from the mixed model ANOVA. Detailed results from pairwise analysis of bolus transport are presented as mean (±s.d.) or median (±interquartile range) as appropriate. Data were significant at alpha <0.05.

## RESULTS

### Patient progression

Twenty-one subjects were screened and 17 subjects [eight male:nine female, median age 30 (22–40 years), BMI 23 (18–25 kg/m$^2$)] successfully completed both treatment phases and physiological testing. There were

[a]The biomechanics of the transition zone have been described by Ghosh *et al.*[20] The measurements are simple to derive from the high-resolution manometry plot: $\Delta X_A$, spatial and $\Delta X_t$, temporal separation (jump) between proximal and mid-oesophageal contractions and nadir pressure ($P_{TZ}$).

no clinically relevant changes in haematological, biochemical or electrocardiographc parameters between screening and either phase of the study. Tegaserod was not associated with any severe side-effects. Loose stool was reported by 13 subjects on active treatment and none on placebo ($P < 0.001$). One subject withdrew because of loose stool, two because of failure to tolerate the naso-oesophageal intubation, and another because of family problems.

## Effect of position and prandial state on oesophageal peristalsis and sphincter function

The results are summarized in Figures 3–5. Moving from the supine to the seated position had no effect on LOS pressure [22 (15–29) vs. 22 (14–29) mmHg, $P$ = N.S.]. Compared with the supine position, in the seated position, peristaltic velocity for 10 mL water swallows was faster [14.1 (±5.9)% faster, $P < 0.002$] and median peak contractile pressure was lower [69 (48–87) vs. 63 (40–80) mmHg, $P < 0.01$]. Compared with the preprandial seated position, after the test meal LOS pressure fell [22 (14–29) mmHg vs. 14 (12–17) mmHg, $P < 0.001$], median peristaltic velocity for water swallows increased [8.8 (±1.9)% faster, $P < 0.001$] and median peak contractile pressure for water swallows decreased [63 (40–80) vs. 60 (46–72) mmHg, $P < 0.05$]. Compared with water swallows, peristalsis following 'dry swallows' during the baseline recordings was more rapid [13.5 (±2.0)% faster, $P < 0.002$] and less powerful [69 (48–87) vs. 58 (54–63) mmHg, $P < 0.0001$].

In this study of healthy volunteers, TLOSRs and reflux events were very infrequent (median <1/subject) and formal comparisons were not possible. Moreover, the percentage of time with very low LOS pressure was very small (median <1% below 5 mmHg). In addition to gastro-oesophageal reflux during TLOSRs, brief drops in pH < 4 (<10 s) were occasionally observed. These events represent movement of the pH electrode relative to the LOS during the oesophageal shortening (longitudinal muscle contraction on swallowing) such that the electrode enters the 'acid pocket' at the gastro-oesophageal junction (GOJ).[23]

## Effect of tegaserod on oesophageal peristalsis and sphincter function

Results from the mixed model ANOVA revealed that tegaserod had no effect on median LOS pressure compared with placebo [23 (18–29) vs. 23 (18–28) mmHg, $P$ = N.S.], increased peristaltic velocity [8.6 (±2.0)% faster, $P < 0.001$] and had a small, *negative* effect on

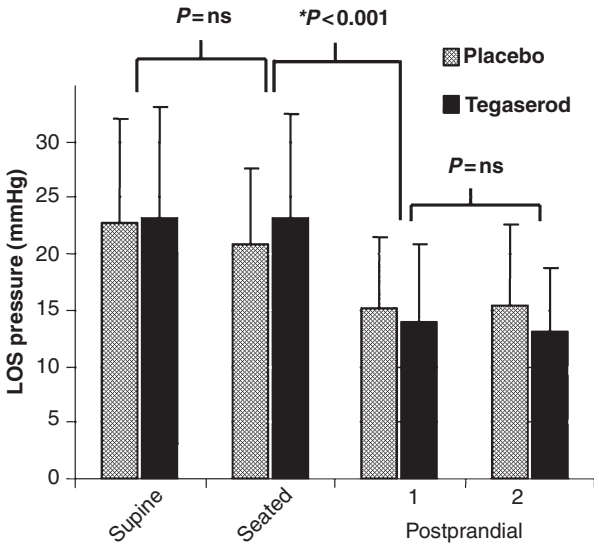


**Figure 3.** Lower oesophageal sphincter (LOS) pressure was not affected by position. The LOS pressure fell after the test meal and did not recover in the postprandial period. Tegaserod had no effect on LOS pressure and there was no interaction between the test medication, position or prandial phase.

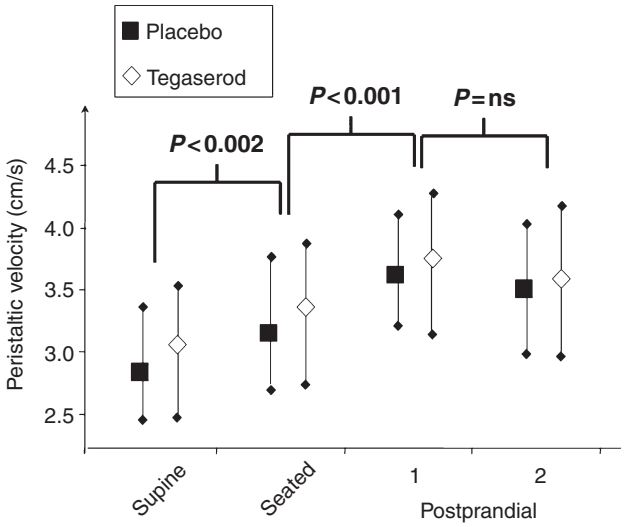


**Figure 4.** Peristaltic velocity increased from the supine to the upright, seated position and increased again after the test meal. Tegaserod had a significant positive effect on peristaltic velocity in both positions and prandial phase ($P < 0.01$).

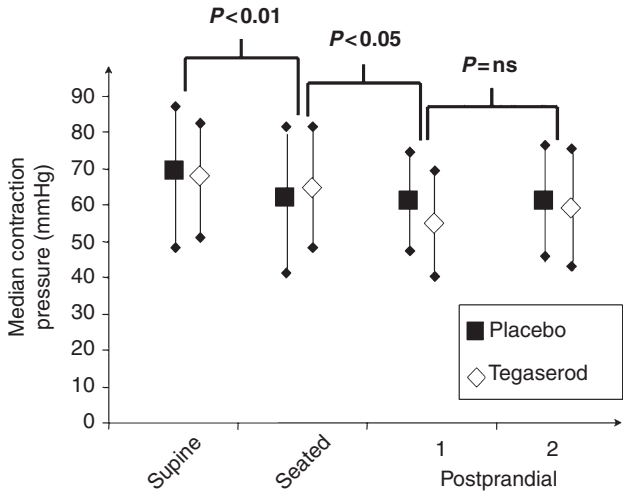


**Figure 5.** The effect of position and prandial-state on median distal peristaltic contractile pressure. Oesophageal contractile pressure decreased from the supine to the upright, seated position and decreased further after the test meal. Tegaserod had a small but significant *negative* effect on contractile pressure ($P < 0.05$).

median peak contractile pressure [69 (48–87) vs. 66 (50–80) mmHg, $P < 0.05$]. The effects of tegaserod were consistent in both positions and prandial states (i.e. no interaction between measurement conditions and medication effects in ANOVA). The small number of TLOSRs and reflux events prevented meaningful comparisons between placebo and tegaserod treatment.

## Effect of bolus characteristics on oesophageal peristalsis and bolus transport

The mechanism of liquid and solid bolus transport was different. Liquid bolus entered and filled the oesophagus rapidly through the action of the 'pharyngeal pump', an event that was always associated with a small, 'common cavity' pressure rise (<10 mmHg) through the fluid filled portion of the oesophagus. The onset of occlusive contraction and progressive clearance of the oesophagus corresponding to the appearance and progress of peristaltic contraction in the mid- to distal-oesophagus. The tail of the bolus was always at the upstroke of the peristaltic contraction. The head of the liquid bolus did not pass into the stomach until the peristaltic contraction approached the GOJ and intra-bolus pressure was sufficient to overcome the resistance to flow and the negative oesophago-gastric pressure gradient (Figure 2). Solid bolus also entered the oesophagus by the action of the 'pharyngeal pump' and passed through the oesophagus in the head of the bolus (with 5-mL liquid barium taken at the same time). In some individuals, solid bolus escape occurred frequently at the level of the aortic arch. This was most common in the presence of a relatively wide proximal 'transition zone' between the proximal- and mid-oeosphageal segmental contractions (see below). Less frequently solid bolus escape was observed at the retrocardiac level, the distal 'transition zone' between the mid- and distal-oeosphageal segmental contractions.

Quantifying the observations from 75 swallows by the 17 subjects (median 4/subject) summarized in Table 1. Oesophageal solid bolus transit was significantly less effective than liquid clearance after a single swallow [88% liquid vs. 55% solid bolus swallows ($P < 0.01$)]. For successful swallows, peristalsis and bolus transport from pharynx to stomach was slower for solid than liquid bolus (8.7 s vs. 8.2 s; $P < 0.05$). The contractile integral, a variable that summarizes the vigour of oesophageal contractility,[20] was higher in the smooth muscle oesophagus during solid than liquid bolus transport (Table 1) and the pressure gradient across the gastro-oesophageal junction was greater ($P < 0.01$).

Oesophageal function and bolus transport were highly reproducible in a given individual and bolus escape occurred more frequently in some subjects than others (>80% in eight of 17 patients). Failure of solid bolus transport occurred most commonly (85% of events) at the level of the aortic arch. Bolus escape was more common in subjects with a relatively long than a short 'proximal transition zone', 13/16 events in subjects with mean PTZ > 3 cm vs. 3/16 events in those with mean PTZ < 3 cm ($P < 0.01$, chi-squared contingency analysis). The small number of events at the retrocardiac position/distal transition zone events precluded formal analysis; however, bolus escape at this level appeared to occur if the peristaltic contraction was relatively weak (below ~50 mmHg) or rapid (above ~4 cm/s).

## Effect of tegaserod on liquid and solid bolus transport

Tegaserod had no effect on bolus transport for liquids, but there was a trend to more successful solid bolus transport compared with placebo (66% vs. 31%; $P = 0.07$). Consistent with significant findings from the

**Table 1.** Detailed high-resolution manometry (HRM) analysis of oesophageal peristalsis acquired during the concurrent HRM videofluoroscopy study of liquid and solid bolus transport (combined data from both treatment periods)

| | | Liquid bolus | | Solid bolus | | |
|---|---|---|---|---|---|---|
| | | Median | IQR | Median | IQR | significance |
| Overall function | Bolus transport | 88% | | 55% | | $P < 0.01$ |
| | duration (s) | 8.2± | 7.0–9.0 | 8.7± | 7.6–10.5 | $P < 0.05$ |
| Proximal-oesophagus | Length (cm) | 4.9± | 4.0–5.0 | 5.5± | 4.0–6.3 | $P =$ N.S. |
| | Pressure (mmHg) | 67± | 58–72 | 75± | 63–84 | $P =$ N.S. |
| | Contraction integral (mmHg/cm/5) | 690± | 480–848 | 736± | 460–1075 | $P = 0.06$ |
| | Velocity (cm/s) | 2.9± | 2.0–3.5 | 3.3± | 2.7–4.0 | $P =$ N.S. |
| Proximal transition zone | Spatial separation, $\Delta X_A$ (cm) | 1.8± | 0.5–3.0 | 1.5± | 0.5–2.0 | $P =$ N.S. |
| | Temporal separation, $\Delta X_t$ (s) | 1.3± | 1.0–2.0 | 2.0± | 1.4–2.0 | $P = 0.07$ |
| | Nadir pressure $P_{TZ}$ (mmHg) | 24.5± | 18–34 | 26.0± | 17–33 | $P =$ N.S. |
| Mid-oesophagus | Length (cm) | 8.8± | 8.0–10.0 | 8.9± | 8.0–11.0 | $P =$ N.S. |
| | Pressure (mmHg) | 70± | 54–86 | 90± | 66–99 | $P < 0.04$ |
| | Contraction integral (mmHg/cm/s) | 1119± | 900–1300 | 1742± | 1050–2370 | $P < 0.02$ |
| | Velocity (cm/s) | 4.7± | 3.0–5.0 | 4.8± | 2.7–5.5 | $P =$ N.S. |
| Distal oesophagus | Length (cm) | 6.8± | 6.0–8.0 | 6.7± | 6.0–7.5 | $P =$ N.S. |
| | Pressure (mmHg) | 102± | 89–117 | 119± | 97–131 | $P = 0.11$ |
| | Contraction integral (mmHg/cm/s) | 1813± | 1400–2226 | 2286± | 1459–3108 | $P < 0.03$ |
| | Velocity (cm/s) | 2.7± | 1.8–3.6 | 2.8± | 2.0–4.1 | $P =$ N.S. |

The normal ranges for HRM measurements of oesophageal peristalsis are very similar to those reported by Ghosh *et al.*[14] in a study of 75 asymptomatic volunteers.

4-h HRM and pH measurement data set, tegaserod decreased the duration of peristalsis and bolus transport (7.7 s vs. 8.5 s). As detailed in Table 2 and Figure 6, proximal peristaltic contractile length and pressure were not affected by tegaserod; however, the mid-oesophageal contractile integral increased ($P < 0.02$). The proximal transition zone (separation between the proximal and mid-oesopaheageal contractions) was shorter on tegaserod than placebo ($P < 0.05$) and temporal separation tended to be less ($P = 0.06$).

## DISCUSSION

This double-blind, placebo controlled, cross-over study is the first to describe the effects of tegaserod on oesophageal function in healthy volunteers. Prolonged measurements of LOS pressure and peristaltic function were made during HRM and pH recordings in the supine and upright (seated) positions, before and after a test meal (based on the 4-h recording). In addition, measurements from concurrent HRM and videofluoroscopy were analysed to assess the effect of tegaserod on bolus transport (based on the 75 individual swallows).

Tegaserod 6 mg b.d. had no effect on LOS pressure in healthy subjects in the pre- or postprandial period. This finding is similar to that reported for patients with mild-to-moderate GERD,[9] in whom tegaserod tended to reduce the number of TLOSRs, reflux events and acid exposure after a test meal.[9] The small number of these events during this study precluded meaningful analysis. It is unlikely that our experimental method failed to detect the TLOSRs[23] or was confounded by non-acid reflux (test meal was titrated to pH4); however, the use of 24-h ambulatory studies or increasing the volume and caloric density of the test meal may have improved the sensitivity of the investigation.

Baseline LOS pressure was not affected by posture, but fell after the test meal. Oesophageal peristalsis was affected by both position change and the test meal. Moving from the supine to the upright position increased oesophageal velocity and decreased contractile pressure, changes that likely reflect a reduction in workload required for bolus transport in the upright

**Table 2.** Detailed high-resolution manometry (HRM) analysis of oesophageal peristalsis during tegaserod and placebo treatment phases. Data acquired during the concurrent HRM videofluoroscopy study of bolus transport. Statistical analysis is by Student's *t*-test with correction for multiple comparisons

| | | Tegaserod | | Placebo | | |
|---|---|---|---|---|---|---|
| | | Median | IQR | Median | IQR | significance |
| Overall function | Liquid bolus transport | 85% | | 87% | | $P$ = N.S. |
| | Solid bolus transport | 66% | | 31% | | $P = 0.07$ |
| | Duration (s) | 6.9± | 6.2–8.6 | 8.5± | 7.0–10.8 | $P = 0.11$ |
| Proximal oesophagus | Length (cm) | 5.0± | 4.0–5.6 | 4.7± | 4.3–5.3 | $P$ = N.S. |
| | Pressure (mmHg) | 69.0± | 64–77 | 66.5± | 63–80 | $P$ = N.S. |
| | Contraction integral (mmHg/cm/s) | 653± | 567–829 | 668± | 539–969 | $P$ = N.S. |
| | Velocity (cm/s) | 2.7± | 2.3–3.4 | 3.0± | 2.4–3.4 | $P$ = N.S. |
| Proximal transition zone | Spatial separation, $\Delta X_A$ | 1.4± | 0.3–1.8 | 2.1± | 1.5–4.0 | $P = 0.05$ |
| | Temporal seperation, $\Delta X_t$ | 1.0± | 0.7–1.4 | 1.7± | 1.2–2.0 | $P = 0.06$ |
| | Nadir pressure, $P_{TZ}$ (mmHg) | 26.8± | 16–35 | 23.6± | 17–35 | $P$ = N.S. |
| Mid-oesophagus | Length (cm) | 9.1± | 8.0–10.1 | 8.6± | 7.4–9.2 | $P$ = N.S. |
| | Pressure (mmHg) | 86.2± | 65–105 | 74.5± | 54–82 | $P = 0.08$ |
| | Contraction integral (mmHg/cm/s) | 1407± | 942–2029 | 1117± | 685–1507 | $P < 0.02$ |
| | Velocity (cm/s) | 4.6± | 3.7–6.1 | 6.6± | 3.7–5.2 | $P$ = N.S. |
| Distal oesophagus | Length (cm) | 6.7± | 6.0–7.0 | 4.7± | 5.9–7.0 | $P$ = N.S. |
| | Pressure (mmHg) | 100.0± | 80–121 | 101.9± | 92–120 | $P$ = N.S. |
| | Contraction integral (mmHg/cm/s) | 1518± | 1115–2263 | 1674± | 1394–2006 | $P$ = N.S. |
| | Velocity (cm/s) | 2.8± | 2.3–3.5 | 2.7± | 1.8–3.4 | $P$ = N.S. |

position.[24–27] There was a further increase in oesophageal velocity and decrease in contractile pressure after the meal. This may also reflect the reduced resistance to bolus transport following the fall in LOS pressure and length after a meal.[27] Further support for the idea that peristaltic velocity and contractile pressure vary with oesophageal workload is provided by the response to different physical characteristics of the bolus (properties that affect the resistance to bolus transport). Consistent with previous work,[18, 25 26] peristaltic velocity was faster and contractile pressure less powerful for dry (i.e. no bolus) vs. liquid, and liquid vs. solid swallows. Together these findings demonstrate that oesophageal function is not stereotyped but adapts in response to the workload required to drive the bolus transport from the pharynx to the stomach.

Tegaserod had significant effects on oesophageal motor activity. Compared with placebo, active treatment increased the peristaltic velocity and had a small, but significant *negative* effect on contractile pressure. The magnitude of these effects was similar to those seen with position change and prandial state (i.e. physiologically relevant). As discussed above, these effects may reflect a reduction in the workload required for bolus transport. Observations during concurrent HRM and videofluoroscopy provide preliminary evidence that supports the presence of a prokinetic effect for tegaserod and describes the mechanism by which this appears to occur.

For healthy subjects in the supine position, liquid bolus transport was usually successful after a single swallow, whereas solid bolus transport was less reliable. Solid bolus escape was most frequent in the 'proximal transition zone' between the proximal and mid-oesophageal contractions described by Clouse and Staiano.[22] Previous studies have reported solid bolus escape at the aortic arch level,[18] but could not explain why this occurs because conventional manometry lacks the spatial resolution required to 'visualize' the segmental anatomy of the oesophagus. This study shows that solid bolus escape occurs more frequently in subjects with a wide 'proximal transition zone' (>3 cm) than in those with closely opposed, well-coordinated proximal- and mid-oesophageal contractions. Solid bolus escape occasionally occurred at 'distal transition zone' between the mid- and distal-oesophageal contractions (the retrocardiac level) if mid-oesophageal peristalsis was rapid or weak,

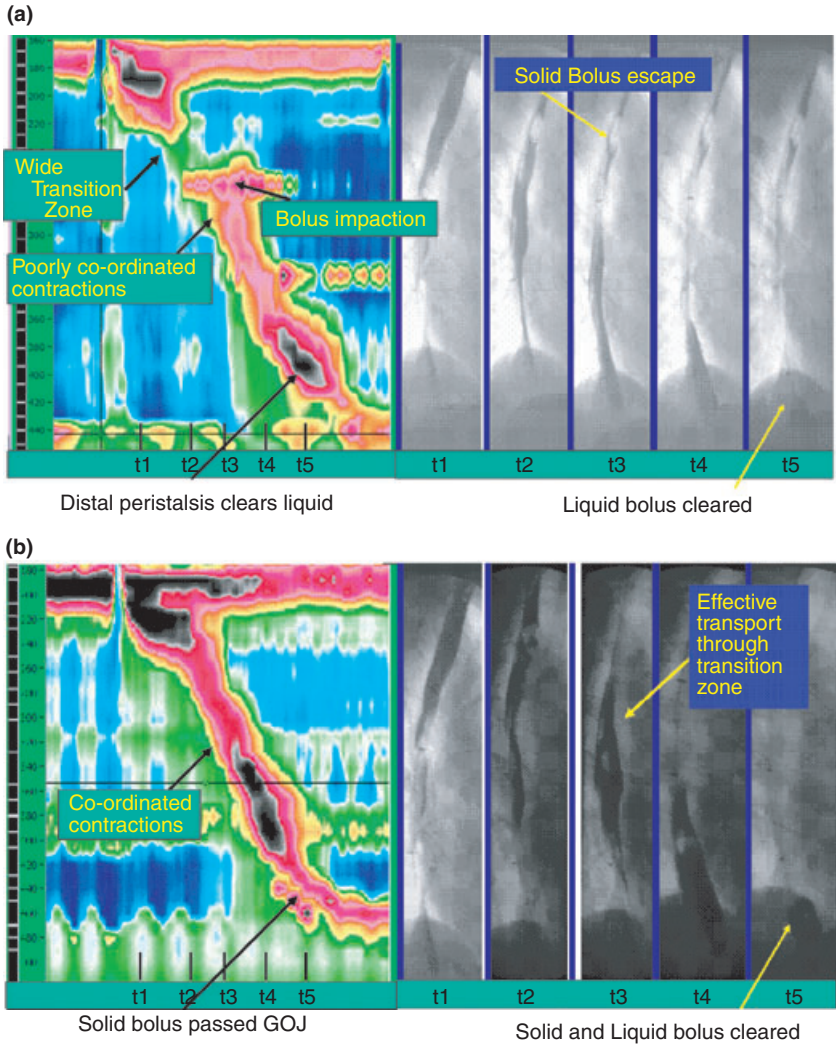


**Figure 6.** High-resolution manometry (HRM) findings were highly reproducible for a given individual and treatment phase and most episodes of bolus escape occurred in subjects with a long (>3 cm) than a short 'proximal transition zone'. Consistent with previous case series[15] and the hypothesis of Ghosh *et al.*,[20] co-ordination of the proximal and mid-oesophageal contractions appears to be required to develop and maintain a pressure gradient within the oesophagus and drive bolus transport. In these terms, a wide 'proximal transition zone' represents a local failure of peristaltic contraction to occlude the lumen allowing the propulsive force (pressure gradient) to dissipate and bolus escape to occur. (a) A Placebo concurrent HRM and videofluoroscopy of solid bolus transport in patient #6: placebo treatment. A wide proximal transition zone (>3 cm) is seen on the HRM spatiotemporal plot, the peristaltic contraction is otherwise preserved. Concurrent videofluoroscopy reveals solid bolus escape at the level of the transition zone (note the corresponding pressure rise at the level of bolus impaction). In contrast, the liquid barium ingested with the marshmallow was propelled into the distal oesophagus and most was transported into the stomach. (b) Tegaserod concurrent HRM and videofluoroscopy of solid bolus transport in patient #6: tegaserod treatment. The pressure trough at the proximal transition zone is less pronounced on the HRM plot, the peristaltic contraction in the proximal oesophagus is well co-ordinated with the mid- and distal-oesophagus. Concurrent videofluoroscopy reveals effective solid and liquid bolus transport (note the pressure rise as the bolus passes through the gastro-oesophageal junction into the stomach).

probably because the propulsive force was not sufficient to overcome the relatively high resistance to the passage of the solid bolus.

Tegaserod tended to improve the solid bolus transport in healthy volunteers. Although it is emphasized that the effect did not reach statistical significance,

this may represent a type I error because several subjects had effective solid bolus transport on placebo as well as active treatment (a positive effect can only be demonstrated if an improvement can be achieved). An increase in peristaltic contractile pressure was not observed. Instead, tegaserod reduced the width of the 'proximal transition zone' by promoting the mid-oesophageal contractility (increased contractile integral).[20] It is interesting to note that Staiano and Clouse demonstrated similar effects of cisapride on the mid-oesophagus,[28] suggesting a shared, prokinetic mechanism of action for 5-HT4 agonists. The mechanism by which tegaserod could facilitate bolus transport without a rise in contractile pressure requires explanation. Activation of 5-HT4 receptors facilitates the release of neurotransmitters from the enteric cholinergic nerves, increasing the gastrointestinal reactivity and lowering the threshold needed to trigger the peristaltic reflex.[29] Facilitation of the peristaltic reflex also enhances the descending relaxation, reducing the oesophageal workload and contractile pressure (see above). On swallowing, the 'pharyngeal pump' delivers the bolus into the oesophagus. For bolus transport to continue, a peristaltic contraction in the smooth muscle of the mid-oesophagus must be triggered. When contractions of the proximal- and mid-oesophagus are not coordinated, the 'proximal transition zone' is wide and bolus escape is likely to occur.[15 20] This study provides initial evidence that the action of 5-HT4 agonists including tegaserod may be to facilitate prompt and effective peristalsis of the mid-oesophagus in response to the delivery of a bolus. It must be noted that preliminary data from Tutuian *et al.*[30] did not identify a prokinetic effect of tegaserod using the impedance and conventional manometry. This discrepancy may be because of the consistency of viscous fluid used in this work is more similar to the liquid barium in the current study than the solid marshmallow bolus.

In healthy volunteers, bolus escape was rarely associated with symptoms and further research is required firstly to confirm the prokinetic effect of tegaserod, and secondly to establish their clinical relevance (if any). Case reports have identified individuals with endoscopy-negative dysphagia in whom a wide 'proximal transition zone' is associated with recurrent, symptomatic solid bolus escape.[15] Similar findings are common in patients with reflux oesophagitis and may impair oesophageal clearance.[31] Early reports from trials of tegaserod in GERD show promise.[9 32]

This study provides an example of how HRM identifies the functionally important aspects of oesophageal motor activity that affect the success or failure of bolus transport and that are not detected by conventional manometry.[15] As new and more effective prokinetic medications with specific effects on oesophageal motor activity are developed, HRM may identify the patients that will benefit from these new treatments.

In conclusion, the 5-HT4 agonist tegaserod had no effect on LOS function in healthy, asymptomatic subjects, but had effects on oesophageal motor activity that tended to improve the success of oesophageal solid bolus transit. If confirmed, studies in patients with endoscopy-negative, 'functional' dysphagia and GERD will be required to assess the clinical benefits of tegaserod.

## ACKNOWLEDGEMENTS

The authors are grateful for the support and advice of Prof. Geoff Hebbard who developed the HRM equipment used in these studies, and for the insight into the biomechanics of oesophageal function provided by Prof. Jim Brasseur and Sudip Ghosh. Mark Fox was supported by a grant from the Swiss National Fund for Medicine. This study was supported by Novartis the makers of Tegaserod (Zelmac).

## REFERENCES

1 Camilleri M. Review article: tegaserod. *Aliment Pharmacol Ther* 2001; **15**: 277–89.
2 Muller-Lissner SA, Fumagalli I, Bardhan KD, *et al*. Tegaserod, a 5-HT4 receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther* 2001; **15**: 1655–66.
3 Prather CM, Camilleri M, Zinsmeister AR, McKinzie S, Thomforde G. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. *Gastroenterology* 2000; **118**: 463–8.
4 Degen L, Matzinger D, Merz M, *et al*. Tegaserod, a 5-HT4 receptor partial agonist, accelerates gastric emptying and gastrointestinal transit in healthy male subjects. *Aliment Pharmacol Ther* 2001; **15**: 1745–51.
5 Horowitz M, Maddox A, Harding PE, *et al*. Effect of cisapride on gastric and esophageal emptying in insulin-dependent diabetes mellitus. *Gastroenterology* 1987; **92**: 1899–907.

6 Wiseman LR, Faulds D. Cisapride. An updated review of its pharmacology and therapeutic efficacy as a prokinetic agent in gastrointestinal motility disorders. *Drugs* 1994; **47**: 116–52.

7 Griffin JP. Prepulsid withdrawn from UK & US markets. *Adverse Drug React Toxicol Rev* 2000; **19**: 177.

8 Morganroth J, Ruegg PC, Dunger-Baldauf C, *et al*. Tegaserod, a 5-hydroxytryptamine type 4 receptor partial agonist, is devoid of electrocardiographic effects. *Am J Gastroenterol* 2002; **97**: 2321–7.

9 Kahrilas PJ, Quigley EM, Castell DO, Spechler SJ. The effects of tegaserod (HTF 919) on oesophageal acid exposure in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2000; **14**: 1503–9.

10 Freidin N, Mittal RK, Traube M, McCallum RW. Segmental high amplitude peristaltic contractions in the distal esophagus. *Am J Gastroenterol* 1989; **84**: 619–23.

11 Traube M, Peterson J, Siskind BN, McCallum RW. ''Segmental aperistalsis'' of the esophagus: a cause of chest pain and dysphagia. *Am J Gastroenterol* 1988; **83**: 1381–5.

12 Massey BT, Dodds WJ, Hogan WJ, Brasseur JG, Helm JF. Abnormal esophageal motility. An analysis of concurrent radiographic and manometric findings. *Gastroenterology* 1991; **101**: 344–54.

13 Brasseur JG, Dodds WJ. Interpretation of intraluminal manometric measurements in terms of swallowing mechanics. *Dysphagia* 1991; **6**: 100–19.

14 Ghosh SK, Pandolfino JE, Zhang Q, JaroszA, Shah N, Kahrilas PJ. Quantifying Esophageal Peristalsis with High-Resolution Manometry: a study of 75 asymptomatic volunteers. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G988–97.

15 Fox M, Hebbard G, Janiak P, *et al*. High-resolution manometry predicts the success of oesophageal bolus transport and identifies clinically important abnormalities not detected by conventional manometry. *Neurogastroenterol Motil* 2004; **16**: 533–42.

16 Tutuian R, Castell DO. Combined multichannel intraluminal impedance and manometry clarifies esophageal function abnormalities: study in 350 patients. *Am J Gastroenterol* 2004; **99**: 1011–9.

17 Bredenoord AJ, Weusten BL, Curvers WL, Timmer R, Smout AJ. Determinants of perception of heartburn and regurgitation. *Gut* 2006; **55**: 313–8.

18 Pouderoux P, Shi G, Tatum RP, Kahrilas PJ. Esophageal solid bolus transit: studies using concurrent videofluoroscopy and manometry. *Am J Gastroenterol* 1999; **94**: 1457–63.

19 Meshkinpour H, Eckerling G. Unexplained dysphagia: viscous swallow-induced esophageal dysmotility. *Dysphagia* 1996; **11**: 125–8.

20 Ghosh SK, Janiak P, Schwizer W, Hebbard GS, Brasseur JG. Physiology of the esophageal pressure transition zone: separate contraction waves above and below. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G568–76.

21 Holloway RH, Penagini R, Ireland AC. Criteria for objective definition of transient lower esophageal sphincter relaxation. *Am J Physiol* 1995; **268**: G128–33.

22 Clouse R, Staiano A. Topography of the esophageal peristaltic pressure wave. *Am J Physiol Gastroint Liver Physiol* 1991; **261**: G677–84.

23 Fox M. Bravo vs. catheter pH monitoring. *Gut* 2006; **55**: 434–5.

24 Trudgill NJ, Hussain FN, Moustafa M, Ajjan R, D'Amato M, Riley SA. The effect of cholecystokinin antagonism on postprandial lower oesophageal sphincter function in asymptomatic volunteers and patients with reflux disease. *Aliment Pharmacol Ther* 2001; **15**: 1357–64.

25 Dooley CP, Schlossmacher B, Valenzuela JE. Modulation of esophageal peristalsis by alterations of body position. Effect of bolus viscosity. *Dig Dis Sci* 1989; **34**: 1662–7.

26 Tutuian R, Elton JP, Castell DO, Gideon RM, Castell JA, Katz PO. Effects of position on oesophageal function: studies using combined manometry and multichannel intraluminal impedance. *Neurogastroenterol Motil* 2003; **15**: 63–7.

27 Pandolfino JE, Shi G, Curry J, Joehl RJ, Brasseur JG, Kahrilas PJ. Esophagogastric junction distensibility: a factor contributing to sphincter incompetence. *Am J Physiol Gastrointest Liver Physiol* 2002; **282**: G1052–8.

28 Staiano A, Clouse RE. The effects of cisapride on the topography of oesophageal peristalsis. *Aliment Pharmacol Ther* 1996; **10**: 875–82.

29 Grider JR, Foxx-Orenstein AE, Jin JG. 5-Hydroxytryptamine4 receptor agonists initiate the peristaltic reflex in human, rat, and guinea pig intestine. *Gastroenterology* 1998; **115**: 370–80.

30 Tutuian R, Castell DO. Effects of tegaserod on oesophageal bolus transport. *Gut* 2005 (Suppl VII): A52 [abstract].

31 Janiak P, Ghosh S, Hebbard G, *et al*. Changes in upper esophageal motor function in reflux esophagitis defined by high resolution manometry. *Gastroenterology* 2001; **120**: A922 [abstract].

32 Rodriguez-Stanley S, Wolff M, Proskin H. An exploratory open label trial of tegaserod in non-erosive GERD patients with incomplete response to PPIs. *Am J Gastroenterol* 2005; **100**: S–38 [abstract].