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Effects of Tegaserod and Erythromycin on Upper Gut Motility- A Comparative Study

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Abstract

Objectives—Tegaserod enhances upper gut transit in healthy subjects. However, its prokinetic effects on antral/small bowel motility and how this compares with erythromycin is unknown. We prospectively assessed and compared the effects of tegaserod and erythromycin on upper gut motility.

Methods—22 patients (M/F = 4/18; mean age = 37) with upper gut dysmotility underwent 24 hour ambulatory antroduodenjejunal manometry with a 6 sensor solid state probe. The effects of 12 mg oral tegaserod were compared with 125 mg intravenous erythromycin by quantifying pressure wave activity and assessing motor patterns.

Results—Motor activity increased ($p < 0.05$) in antrum, duodenum and jejunum with both drugs when compared to baseline period. The motor response with tegaserod was higher ($p < 0.05$) in jejunum and occurred during the 2nd/3rd hours, whereas with erythromycin, it was higher ($p < 0.05$) in antrum and occurred within 30 min. After tegaserod, a 'fed-response' like pattern was seen whereas after erythromycin, large amplitude (> 100 mmHg) antral contractions at 3 cycles/min were seen. Following tegaserod and erythromycin, phase III MMCs occurred in 12 (55%) and 8 (36%) patients respectively ($p > 0.05$).

Conclusions—Both drugs increase upper gut motility and induce MMC's, but exert a differential response. Tegaserod produces a more sustained prokinetic effect in the duodenum/jejunum, whereas erythromycin predominantly increases antral motor activity.

Keywords

Tegaserod; Erythromycin; Antroduodenal Motility; Dysmotility; Dyspepsia

INTRODUCTION

Functional GI symptoms are common in the general population, with a reported prevalence of 25–40% [1]. They are responsible for up to 33% of gastroenterology office consultations in Great Britain and 40% in the United States [2]. These patients present with a variety of symptoms that include fullness, bloating, nausea, vomiting, abdominal pain, diarrhea, constipation or weight loss. These symptoms suggest an upper or lower gastrointestinal dysfunction that may be caused by a sensory or mixed sensori-motor disorder.

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Physiological studies of patients with functional dyspepsia (non ulcer) have demonstrated delayed gastric emptying, abnormal small bowel motility, and visceral hypersensitivity [3, 4]. Because there is no approved treatment, and the pathophysiology continues to evolve, current therapies largely consist of empirical trials of anti-secretory agents, anti-*Helicobacter pylori* therapies, antidepressants, anti-nausea and prokinetic agents [4].

Recently, 5-Hydroxytryptamine (5-HT), acting through 5-HT₁, 5-HT₃ and 5-HT₄ receptors has been shown to play a significant role in gastrointestinal motility, sensation and secretion [5–9]. Stimulation of 5-HT₄ receptors has been shown to trigger the peristaltic reflex in animals [10, 11]. Tegaserod, a selective 5-hydroxytryptamine-4 (5-HT₄) receptor partial agonist has been shown to stimulate motility throughout the gastrointestinal tract [10, 11]. In healthy subjects, tegaserod had no effect on gastric emptying, but accelerated orocecal and colonic transit [12]. Another clinical study demonstrated that tegaserod enhanced fasting gastric compliance and significantly accelerated gastric emptying and gut transit in healthy subjects [13]. Large controlled trials have shown that it improves abdominal pain, bloating, stool frequency and consistency in female patients with constipation-predominant irritable bowel syndrome [12], and in chronic constipation [14]. However, very little is known regarding the effects of tegaserod on antral and small bowel motor activity in humans.

Erythromycin, a macrolide antibiotic and a motilin agonist, is widely used as a promotility agent [15, 16]. Clinical trials have demonstrated that erythromycin improves gastric emptying in diabetic gastroparesis [17–19]. However, a recent randomized controlled trial showed that erythromycin was not effective as a prokinetic agent when compared to placebo in the treatment of post operative ileus after urological surgery [20]. Furthermore, its prokinetic effects on the upper gut have not been compared with another promotility agent such as tegaserod.

We tested the hypothesis that tegaserod increases pressure activity in the stomach and small bowel, and that its motor effects are similar to those of erythromycin. The aim of our study was to examine and compare the effects of tegaserod and erythromycin on the motor activity of the antrum, duodenum and jejunum in subjects with upper gastrointestinal dysmotility and dyspeptic symptoms.

MATERIALS AND METHODS

Subjects

Consecutive patients with symptoms of functional dyspepsia (Rome II) and dysmotility-like symptoms participated in this study. For at least 12 weeks, during the previous year, all of these patients reported at least two of the following symptoms: abdominal pain, fullness, bloating, nausea, vomiting, diarrhea, indigestion, or weight loss. All patients underwent standard investigations that included esophagogastroduodenoscopy (EGD), right upper quadrant ultrasound or CAT scan, routine hematology, liver biochemistry, and *H. pylori* testing to exclude any luminal pathology or secondary causes for their symptoms. Additional exclusion criteria were pregnancy or breast-feeding; abdominal surgery other than appendectomy and cholecystectomy, and use of drugs that affected motility such as opiates and anticholinergics. Each participant completed a medical interview, received a full physical examination, and responded to a symptom survey. All subjects gave written informed consent for the study which was approved by the Human Investigation Review Board.

Questionnaire

A symptom questionnaire was administered to all subjects prior to the study. It enquired about the presence or absence of the following eight symptoms in the preceding two weeks:

fullness, bloating, nausea, vomiting, abdominal pain, diarrhea, indigestion and chest pain. If present, they were asked to rate its frequency, intensity, and duration on a 0–3 Likert-like scale; 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe symptoms. On this scale, the total score for each symptom could range from 0–9. A mean total score was calculated for each symptom. A comprehensive drug history, including dosage and duration of use of any prokinetic medications (metoclopramide, erythromycin, tegaserod, domperidone), and any unintentional weight loss in the preceding six months were also recorded.

Manometric Assembly

We used a 250 cm long elastic catheter that was custom built with 6 solid state pressure transducers (Konigsberg Instruments, Pasadena, California). The probe was connected to a six-channel portable solid-state digital data-logger (MicroDigitrapper 4 Mb, Medtronics; Minneapolis, MN) with a sampling frequency of 4 Hz, A-D conversion, temporary storage up to 4 Mb and event markers. Upon completion of the study, data were downloaded to an IBM-compatible personal computer for analysis (Gastrosoft version 6.3, Multigram, Synectics Medical Inc.).

Study Protocol

We performed antroduodenal jejunal manometry using the following protocol: (Figure 1). Following an overnight fast, a 6-sensor solid-state manometry probe was placed under endoscopic and fluoroscopic guidance such that 2 sensors that were located 5 cm apart were placed in the antrum, 2 sensors 15 cm apart were located in the duodenum, and 2 sensors 15 cm apart were located in the jejunum. The recorder was placed in a shoulder bag and the patients slept at home and were free to ambulate throughout the study. One and a half hour after probe placement, all patients, in the fasted state, received 125 mg of intravenous erythromycin lactobionate and thereafter they were discharged home. The following morning they were instructed to wake up at 6 am. At 8 am, they were asked to take 12 mg of oral tegaserod (Zelnorm, Novartis pharmaceuticals, New Jersey). The motility recording was continued until 11 am and thereafter the probe was removed. An event marker was attached to the recorder, and the patients were encouraged to use this and mark the time of events such as eating, walking, and sleeping or to indicate the occurrence of symptoms such as abdominal pain, passing flatus, etc. They were also provided with a diary, in which they described any event(s) or symptom(s), and recorded its time and duration.

Data analysis

After completion of the recording, the data stored in the portable recorder was transferred to a personal computer for visual display and analysis. Tracings were analyzed by visual inspection for motility patterns such as phase III MMCs, and for quantitative assessment of pressure activity such as area under the curve (AUC) of the pressure waves. Pressure waves that occurred simultaneously in several channels with similar amplitude and duration of 3 seconds were identified as artifacts and excluded from the analysis. Phase III MMCs were defined as propagating cluster of repetitive contractions with a frequency of 3/minute in the antrum and 11–13/minute in the duodenum and with a duration of at least 3 minutes that was followed by a period of motor quiescence [21]. Their incidence, duration, propagation velocity and site of origin were calculated. The pressure activity data from each of the two sensors located in the antrum, duodenum, and jejunum were averaged and were used as an overall index of motility for each segment. Motor activity in the first half hour prior to ingestion of each drug was used as the baseline period. Data were analyzed for 90 minutes after erythromycin, and for 180 minutes following tegaserod.

Statistical analysis

The data was found to be non parametric and was therefore analyzed using the Mann-Whitney U test and ANOVA with Kruskal-Wallis analysis of rank, where appropriate, using a commercially available software package (Prism 3.0; GraphPad Software, Inc., San Diego, California, USA). A p-value < 0.05 was considered significant. The data are expressed as the mean $\pm$ 95% confidence interval (CI).

RESULTS

Demographics and Symptom Patterns

Twenty two subjects (four males and eighteen females) with symptoms of dyspepsia and upper gut dysmotility and mean age $\pm$ SD of 37 ± 12 years were recruited for the study. The prevalence of dysmotility-like symptoms is shown in Figure 2A. Fullness and bloating were the most commonly reported symptoms, but over 50% of subjects reported other 5 symptoms that are commonly described by patients with dysmotility and dyspepsia. The mean total score reveals that most of the symptoms were not only frequent but also moderately severe in intensity and duration. Although chest pain was reported in 21% of patients, this symptom was quite severe and bothersome. Figure 2B summarizes the mean total score for each symptom in this group of patients. Nausea was reported after erythromycin and tegaserod administration in 5 and 6 patients respectively. However, all of these subjects reported frequent nausea over the preceding few weeks prior to the study.

Effects of tegaserod on antroduodenal and jejunal motility

Tegaserod increased ($p < 0.02$) motor activity in all 3 segments of the upper gut when compared to the baseline period (Table 1). The effect of tegaserod on upper gut motor activity extended into the 3rd hour of recording. This increased motor activity peaked between 120 – 150 minutes in ten patients, and between 150 – 180 minutes in twelve patients. In addition, the increased motor response was higher ($p < 0.05$) in jejunum when compared to the duodenum or antrum, and occurred mostly during the 2nd and 3rd hours (Figure 3).

The pattern of motor response was similar to a 'fed-response' with intermittent, phase II-like pressure waves that occurred at 2–3 cycles/min in the antrum and 10–14 cycle/min in the small bowel (Figure 4). A single phase III MMC was observed in 12 subjects, two phase III MMCs were seen in 4 subjects and 3 phase III MMCs in 1 subject. Seven of the 17 MMCs originated in the antrum, and 10 in the duodenum. Most of the phase III MMCs occurred in the first 2 hours (6 in the 1st and 9 in the 2nd hour), and only 2 were observed in the 3rd hour. The average duration of MMCs in the antrum, duodenum and jejunum were 5.1 (SD 2.3), 6 (SD 2.7) and 7 (SD 2.7) minutes, and the propagation velocities were 7.5, 5.2 and 4.4 cm/min respectively.

Effects of erythromycin on antroduodenal and jejunal motility

Erythromycin also increased ($p < 0.01$) motor activity in the antrum, duodenum and jejunum when compared to the baseline period (Table 1). The increase in motor activity was short lived, and typically lasted up to one hour after infusion. It was significantly higher ($p < 0.05$) in the antrum during the first 30 minutes and in the duodenum and jejunum during the next 30 minutes (Figure 5).

Erythromycin also induced large amplitude (> 100 mmHg) antral contractions usually at 3 cycles/min (Figure 6). Following erythromycin infusion, a phase III MMC-like response was seen immediately in 8 subjects (36%). All phase III MMC-like responses originated in the antrum with average response duration in the antrum of 15.25 min (SD 9.7), duodenum of

5.5 min (SD 2.0) and jejunum of 6.6 min (SD 2.9). The propagation velocity of the MMC response was 3.3 cm/min in the antrum, 4.2 cm/min in the duodenum and 7cm/min in the jejunum.

Comparison of effects of erythromycin and tegaserod on antroduodenal and jejunal motility

The pressure activity in the antrum, duodenum, and jejunum during the baseline period (half an hour prior to drug administration) were similar for erythromycin and tegaserod (Table 1). After tegaserod, the maximum increase in motor activity (peak) was observed in the 3rd hour whereas after erythromycin it was observed in the first hour. When we compared the peak motility effects that were induced by each drug, we found that the effects of tegaserod on duodenal and jejunal motor activity were higher ($p<0.05$) than that induced by erythromycin (Table 1). Also, in the 3rd hour, the tegaserod induced increase in antral motor activity was similar to that of erythromycin ($p = 0.3$) (Table 1).

DISCUSSION

In this prospective, case-controlled study, we evaluated and compared the prokinetic responses of erythromycin and tegaserod in patients with suspected gastrointestinal dysmotility and functional dyspepsia. To our knowledge, this is the first study that has examined the prokinetic effects of tegaserod on upper gut motility in humans, particularly in patients with dysmotility.

We found that tegaserod increased motor activity in all 3 segments by inducing a 'fed-response' like pattern that was most pronounced in the jejunum and it lasted for at least three hours. Because the recording was discontinued after three hours, we were unable to fully quantify the motor effect of this drug. This increase in motor activity together with the occasional induction of MMCs in several subjects most likely represented a prokinetic effect with improved peristaltic activity in the upper gut. This observation was consistent with previous reports that showed an acceleration of gastric emptying and small bowel transit with tegaserod [14, 16].

Erythromycin also enhanced motor activity in the antrum, duodenum and jejunum when compared to the baseline period. During the first 30 minutes there was over 50% increase in the area under the curve (AUC) of pressure waves in the antrum. During the next 30 minutes there was a similar and approximately 33% increase in motor activity over baseline. However this effect was short lived and was significantly higher in the antrum than in the duodenum or jejunum. In addition, erythromycin induced a phase III MMC-like response in more than one third of subjects. These findings are in agreement with the known prokinetic effects of erythromycin that include accelerated gastric emptying, increased antral contractions and enhanced antroduodenal coordination [16, 19, 22].

Erythromycin is a potent gastric prokinetic [16, 17], but clinical studies of motilin receptor agonists such as erythromycin and ABT-229 have been disappointing in the treatment of dyspeptic symptoms [23]. This is partly due to the suppression of the gastric accommodation and presumed antral distension by motilides which may negate promotility benefits. Despite limited or negative impact on dyspeptic symptoms, intravenous erythromycin is widely used as a prokinetic agent particularly in patients with gastroparesis and as demonstrated by this study can be useful. Long-term use, however, is limited by its anti-bacterial action, development of tolerance to the drug and drug-drug interactions [22].

In contrast, tegaserod not only appears to increase gastric and small bowel motility, but has also been reported to improve gastric accommodation [24, 25]. Thus, in selected patients

with dyspepsia and dysmotility or gastroparesis, tegaserod by improving both upper gut motility and accommodation may be clinically useful. However, in a large randomized controlled trial, only a modest therapeutic effect was seen with tegaserod in patients with functional dyspepsia [26]. This inadequate therapeutic response may in part be due to the heterogenous population that was examined. In a more recent open label study, tegaserod was shown to be useful in improving dyspepsia and reflux symptoms in patients with chronic constipation [27].

The limitations of our study include the smaller sample size, and the acute nature of our assessment. Whether these acute prokinetic effects translate into long term clinical benefit, merits further appraisal. In addition, there was a lack of blinding to the drug administered. While erythromycin's half life is 1–2 hours [28], tegaserod's is estimated to be 11 hours [29]. This difference in pharmacokinetics together with the route of administration (intravenous vs. oral) may also explain some of the differences that were observed in the study with regards to the onset and duration of motor effects on the upper gut. We chose two different routes of administration for each drug to simulate their usage in routine practice.

In conclusion, we found that both drugs can increase upper gut motility, and induce MMC's, but exert a differential response. Erythromycin predominantly increases antral motor activity but its effect is short lived, either because of the pharmacokinetic effect of the drug or its intravenous route of administration or both. Tegaserod induces a more pronounced prokinetic effect in the jejunum as well as the antrum and duodenum and causes a more sustained increase in upper gut motor activity. These data suggest that tegaserod may be useful as a prokinetic agent for the treatment of gastric and small bowel dysmotility. The differential effects observed in this study may allow clinicians to better tailor the prokinetic drugs, based on the nature of upper gut dysfunction.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- Functional GI symptoms are common with a reported prevalence of 25–40%. However, its treatment remains unsatisfactory and there is no approved drug therapy.
- Although widely advocated, there is limited knowledge on the mechanistic role of prokinetic drugs in the management of symptoms related to functional dyspepsia (FD).
- Erythromycin, a motilin agonist, is a potent gastric prokinetic, but its effects on motility in patients with FD has not been systematically evaluated or compared with other agents.
- Likewise, tegaserod, a 5-HT₄ agonist, increases gastric compliance and accelerates gastric emptying and gut transit in healthy subjects but its effects on antral, duodenal and jejunal motility has not been investigated.

What Is New Here

- We examined the prokinetic effects of tegaserod and erythromycin on upper gut motility by performing prolonged antroduodenal and jejunal manometry recordings in patients with functional dyspepsia.
- This study provides direct comparative data for the effects of two prokinetic agents in the same subject.
- Although both drugs increase upper gut motility, and induce MMC's, they exert a differential response.
- Tegaserod induces a greater motor effect in both the duodenum and jejunum when compared to erythromycin and its effects persist longer.

Figure 1.
Schematic diagram of the study protocol

Figure 2. Prevalence of dyspeptic symptoms (panel A) and the mean total severity score of each symptom at baseline (panel B)

Figure 3.

Effects of tegaserod on antral, duodenal and jejunal motility (mean $\pm$ SEM) Data represent % change from control period

* = $p < 0.05$ vs. baseline; ¥ = $p < 0.05$ jejunum vs. antrum or duodenum

Figure 4.

Typical upper gut motility response to tegaserod

A1 and A2 represent the antral motility channels, D1 and D2 duodenal motility channels and J1 and J2 Jejunal motility channels. Arrow = time of tegaserod administration.

As can be seen, a fed-response like pattern is induced in the antrum, duodenum and jejunum, starting approximately 1 hour after ingestion of tegaserod. The response appears to last for at least 3 hours.

Figure 5.

Effects of erythromycin on antral, duodenal and jejunal motility (mean $\pm$ SEM) Data represent % change from control period

* = $p < 0.05$ vs. baseline; ¥ = $p < 0.05$ antrum vs. duodenum or jejunum

Figure 6.

Typical upper gut motility response to erythromycin

A1 and A2 represent the antral motility channels, D1 and D2 duodenal motility channels and J1 and J2 Jejunal motility channels.

Arrow = time of erythromycin administration.

Within 5 minutes after erythromycin infusion, strong, high amplitude (>100 mmHg) contractions can be seen in the antrum, and at 30 minutes some increase in the duodenal and jejunal motor activity.

Table 1

Comparison between baseline area under the curve of pressure wave (AUC) before every drug and peak AUC induced by that drug

	Erythromycin			Tegaserod		
	Baseline	Peak	p	Baseline	Peak	p
Antral AUC (mmHg. s)	21590	33036	0.001	24336	30297	0.02
Duodenal AUC (mmHg. s)	21179	28351	0.001	27360	34251 *	0.02
Jejunal AUC (mmHg. s)	17611	24492	0.001	17723	28788 *	0.001

* p < 0.05; tegaserod vs. erythromycin