Effects of prucalopride on esophageal secondary

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Effects of prucalopride on esophageal secondary peristalsis in humans

Chih-Hsun Yi, MD[1], Wei-Yi Lei, MD[1], Jui-Sheng Hung, MD[1], Tso-Tsai Liu, MD[1] and Chien-Lin Chen, MD, PhD[1]

OBJECTIVES: Prucalopride, a high-affinity 5-hydroxytrypatamine 4 ($5\text{-}HT_4$) receptors agonist, has been shown to improve colon motility in adults. Secondary peristalsis helps the clearance of retained food bolus and refluxate from the esophagus, but the effects of prucalopride on esophageal secondary peristalsis are unknown. We aimed to assess the effects of prucalopride on distension-induced secondary peristalsis in healthy adults.
METHODS: Two separate sessions with prucalopride and placebo were performed in 11 healthy adults to test the effects on secondary peristalsis. Secondary peristalsis was performed with slow and rapid mid-esophageal injections of air after a baseline recording of esophageal motility.
RESULTS: Prucalopride significantly decreased the threshold volume to generate secondary peristalsis during slow air injection (9.8 ± 1.4 vs. 14.4 ± 0.9 ml, $P = 0.005$) and rapid air injection (3.9 ± 0.3 vs. 5.2 ± 0.4 ml, $P = 0.008$). Secondary peristalsis was generated more frequently after application of prucalopride (80% (70–100%) vs. 70% (60–73%), $P = 0.01$). Prucalopride increased the wave amplitude of distal esophagus during slow air injection (147.9 ± 28.5 vs. 104.2 ± 16.8 mm Hg, $P = 0.048$) and rapid air injection (128.0 ± 13.3 vs. 105.7 ± 12.3 mm Hg, $P = 0.016$). Primary peristaltic amplitudes were also significantly increased by the application of prucalopride.
CONCLUSIONS: Acute administration of prucalopride enhances mechanosensitivity of distension-induced secondary peristalsis and promotes esophageal contractility in healthy adults. Whether prucalopride could be a therapeutic option for the treatment of subjects with esophageal hypomotility needs further study.
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INTRODUCTION

Primary peristalsis acts to help esophageal bolus clearance during swallowing, while secondary peristalsis facilitates the clearance of refluxed gastric contents[1] after swallowing. Secondary peristalsis is physiologically triggered by intra-esophageal stimuli such as injection with air or water, and balloon distension.[2] Initiation of secondary peristalsis is physiologically involved in a reflex arc mediated by a vagal afferent pathway in that rapidly adapting mucosal and slowly adapting muscular mechanoreceptors are both required in such responses.[3,4] The neural pathway of secondary peristalsis in the striated muscle is controlled by central mechanisms via vagal afferents, which then activate sequential vagal efferent discharge to the striated musculature of the proximal esophagus,[5] while that of the smooth muscle part of the esophagus is largely modulated by an intrinsic neuromuscular reflex inside enteric nervous system.[6]

Prucalopride, a novel enterokinetic agent, is a selective, high-affinity 5-hydroxytrypatamine 4 ($5\text{-}HT_4$) receptors agonist, which is thought to exert its action by facilitating the release of acetylcholine from neurons of the myenteric plexus via a high affinity and specificity for $5\text{-}HT_4$ receptors.[7] It differs from other $5\text{-}HT_4$ receptor agonists in that its cardiac side

effects are pharmacologically negligible.[8] It has been ademonstrated to be useful in the treatment of severe chronic constipation without significant side effects.[9,10] Prucalopride also reduces esophageal acid exposure and accelerates gastric emptying in healthy adults,[11] indicating its potential utility in the management of gastro-esophageal reflux disease. Although esophageal motility was not affected by prucalopride,[11] other *in vivo* work showed potential effect on esophageal motility by enhancing neuoromuscular response in muscle strips of isolated human esophageal body.[12]

The effect of prucalopride on upper gastrointestinal motility has been demonstrated in healthy adults.[11] However, it remains to be established whether such influence also occurs in human esophagus by its activation on $5\text{-}HT_4$ receptors. Our study, therefore, was designed to investigate the effects of prucalopride on physiological characteristics of secondary peristalsis in human esophagus. It was hypothesized that acute administration of prucalopride would promote distension-induced secondary peristalsis as generated by intraesophageal air injections. This work also investigated whether primary peristalsis could be affected by prucalopride as well.

[1]Department of Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, Hualien, Taiwan
Correspondence: C-L Chen, MD, PhD, Department of Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, 707, Section 3, Chung-Yang Road, Hualien 970, Taiwan. E-mail: harry.clchen@msa.hinet.net
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METHODS

Subjects. Studies were performed in 11 healthy subjects (6 female, mean age 23, range 21–25 years) enrolled from the university by the advertisement. None of the subjects had previous history of esophageal disorders or any evidence of acute or chronic illness. Before the study, all subjects did not take any medications known to affect esophageal motility. The study was approved by the Human Ethics Committee of Hualien Tzu Chi Hospital, Hualien, Taiwan. All subjects provided written informed consents before the study.

Esophageal manometry. Intraluminal pressures were recorded by a Koenigsberg 4-channel manometric catheter (Sandhill EFT catheter; Sandhill Scientific, Inc., Highlands Ranch, CO). The design of 4.5 mm-diameter solid-state catheter includes three unidirectional pressure sensors located at 10, 20, and 25 cm, and one circumferential pressure sensor at 5 cm from the tip, whereas the infusion port was located between 15 and 20 cm from the tip with approximately in the mid esophagus. The catheter was inserted through nose into the esophagus up to a depth of 60 cm. After detecting lower esophageal sphincter (LES) by stationary pull-through method, we placed the most distal sensor of the high-pressure zone of the LES. The pressure data were then continuously recorded on the computer throughout the entire study period. Swallowing was identified from the most proximal sensor of the assembly located in the pharynx, thus allowing differentiating primary and secondary peristaltic activities.

Study protocol. The subjects fasted overnight and reported to the motility laboratory in the morning. Oral prucalopride (4 mg) and placebo were studied on 2 separate occasions at least 1 week apart in randomized order. Two hours after the drug administration,[13] we performed esophageal manometry. Each subject was asked to be positioned in sitting position and was allowed to accommodate the assembly for 10–15 min. Primary peristalsis was performed with 5-ml boluses of normal saline. Ten swallows were performed with each of the swallows separated by at least a 20-second (s) interval.

For generating secondary peristalsis, we performed slow air injection into the esophagus first by a slow air infusion (0.25 ml s^{-1}) via an infusion pump attached to the assembly of the manometry. The amount of volume tested was automatically determined by a pump machine based on the rate and time for infusion of air. For rapid air injection, we started at 1-mL volume with continuous increase of the volume by 1-mL increments until the occurrence of secondary peristalsis was seen or the volume of the injection reached 20 ml. The threshold volume of air injected was then determined as the lowest injected volume that could activate a successful peristaltic pressure wave.[14] Finally, ten 20-ml boluses of air within 0.5 s were injected to determine effectiveness of secondary peristaltic response (%) and relevant manometric parameters. Each stimulus allowed an interval of 20 s to see any response to occur, during which subjects were asked not to swallow. All subjects were asked to have a dry swallow at the end of 20 s for ensuring no residual

air before the next stimulus and reducing the desire to swallow during the stimulation. The average duration for completing secondary peristalsis protocol took about 30 min for each subject.

Data analysis. Complete or normal primary peristalsis was recognized if the pressure wave of ≥ 12 mm Hg was found in the proximal esophagus and ≥ 25 mm Hg in distal part of the esophagus associated with normal propagation.[2] The minimal latency of wave onset between two recording channels was 0.5 s. Secondary peristalsis in response to air injection (rapid and slow) was analyzed in the same manner as primary peristalsis.[2] For assessing primary peristaltic wave amplitude (mmHg), duration (s), proximal recording sensors were located 5, 15, and 20 cm above the LES. Data for secondary peristaltic wave amplitude and duration of contraction were determined and compared for middle and distal esophagus.

Statistical analysis. All data were expressed as mean $\pm$ s.e.m. The effects on LES, threshold volumes and esophageal peristaltic parameters between prucalopride and the placebo were compared by a paired t-test. The data for the success rate (%) of secondary peristalsis which were shown as median with interquartile ranges were evaluated by the Wilcoxon signed-rank test. Two-tailed P value of less than 0.05 was accepted as statistical significance. Statistical analyses were performed with SPSS 19 for Windows (SPSS Inc., IL, USA).

Sample size calculation. Based on our previous data regarding between-group differences in the threshold volumes and relevant esophageal peristaltic amplitudes of secondary peristalsis,[15] we determined at least 10 normal subjects would be necessary to detect statistically significant differences with a power of 80% and $P < 0.05$.

RESULTS

Effects on esophageal distension thresholds by slow and rapid air injections. Prucalopride significantly decreased the threshold volume to trigger secondary peristalsis in response to slow air injections (prucalopride, 9.8 ± 1.4 vs. placebo, 14.4 ± 0.9 ml, $P = 0.005$) and rapid air injections (prucalopride, 3.9 ± 0.3 vs. placebo, 5.2 ± 0.4 ml, $P = 0.008$) (Figure 1). Similarly, the frequency of secondary peristalsis during rapid air injections was greater after prucalopride as compared with the placebo (80% (70–100%) vs. 70% (62–73%), $P = 0.01$) (Figure 2).

Effects on esophageal motility characteristics. Table 1 shows the results of primary peristalsis. Prucalopride significantly increased the pressure wave amplitude when compared with the placebo in proximal ($P = 0.036$), middle ($P = 0.017$), and distal esophagus ($P = 0.043$). Prucalopride did not affect pressure wave duration (Table 1). Basal and residual LES pressure was significantly higher after prucalopride as compared with the placebo (basal LES pressure, 27.8 ± 4.2 vs. 19.5 ± 2.8 mm Hg, $P = 0.045$; residual LES
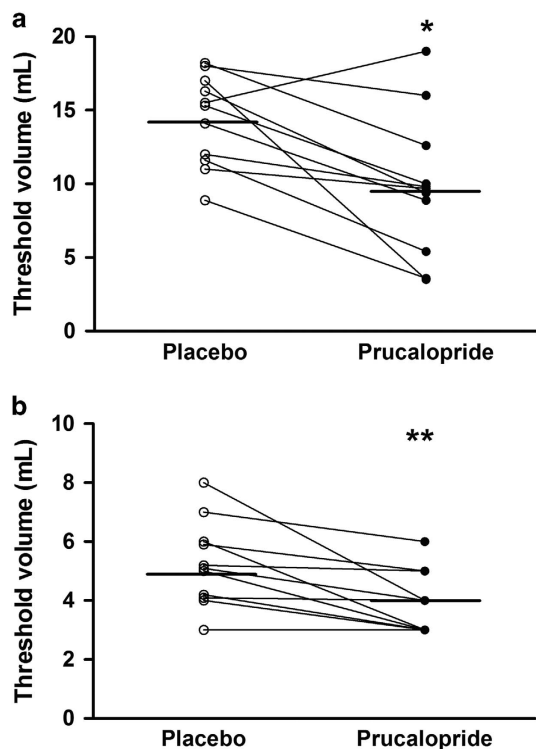
Figure 1 Effects of prucalopride on distension thresholds of secondary peristalsis. The threshold volume to induce secondary peristalsis was significantly reduced by prucalopride during slow air injection (*$P = 0.005$) (**a**), and was significantly decreased during rapid air injection (**$P = 0.008$) (**b**). Values are expressed as mean ± s.e.m. Line represents the mean value.
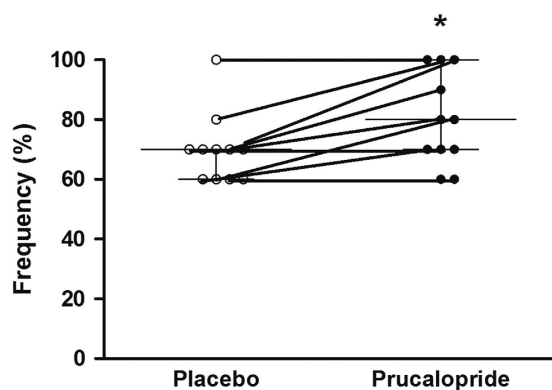

Figure 2 Effects of prucalopride on the frequency of secondary peristalsis in response to rapid air injections. The frequency of secondary peristalsis was significantly greater after prucalopride as compared with the placebo (*$P = 0.01$). Values are expressed as median with interquartile range.

pressure, 1.3 ± 1.0 vs. 0.1 ± 0.9 mm Hg, $P = 0.038$). Prucalopride had no effect on the frequency of complete primary peristalsis compared with the placebo ($P = 0.53$) (Table 1).

The results of secondary peristalsis are summarized in Table 2. Prucalopride significantly increased the pressure wave amplitude of secondary peristalsis in response to slow air (147.9 ± 28.5 vs. 104.2 ± 16.8 mm Hg, $P = 0.048$) and rapid air injections (128.0 ± 13.3 vs. 105.7 ± 12.3 mm Hg, $P = 0.016$)

Table 1 Effects of prucalopride on peristaltic characteristics of primary peristalsis

	Placebo	Prucalopride	*P* value
Amplitude of contractions (*mmHg*)			
Proximal	34.6 (5.4)	40.6 (3.7)	0.036
Middle	50.5 (5.1)	70.1 (8.6)	0.017
Distal	67.2 (9.4)	81.8 (12.3)	0.043
Duration of contractions (*s*)			
Proximal	2.3 (0.2)	2.5 (0.2)	0.27
Middle	2.0 (0.1)	2.5 (0.2)	0.06
Distal	2.8 (0.2)	3.1 (0.2)	0.28
LES pressure (*mmHg*)			
Basal	19.5 (2.8)	27.8 (4.2)	0.045
Residual	0.1 (0.9)	1.3 (1.0)	0.038
Complete peristalsis (*%*)	90	100	0.58

compared with the placebo. Prucalopride significantly increased the pressure wave duration of secondary peristalsis in response to slow air injection in middle (3.3 ± 0.5 vs. 2.5 ± 0.2 s, $P = 0.004$) and distal esophagus (4.5 ± 0.5 vs. 2.8 ± 0.2 s, $P = 0.005$) compared with the placebo. Prucalopride did not affect the pressure wave duration of secondary peristalsis in response to rapid air injection.

DISCUSSION

Our work has demonstrated that the 5-HT$_4$ receptors agonist, prucalopride, enhanced esophageal mechanosensitivity in triggering second peristalsis and consequently increased the effectiveness of secondary peristaltic responses to abrupt esophageal distension in healthy adults. The principal findings of motor effects were that prucalopride significantly increased pressure wave amplitudes of secondary peristalsis as triggered by both slow and rapid air injections into the esophagus. Similarly, prucalopride significantly increased primary peristaltic wave amplitude, as well as basal and residual LES pressure.

We have previously used 5-HT$_4$ agonist mosapride and demonstrated in healthy volunteers that it significantly enhanced esophageal mechanosensitivity of distension-induced secondary peristalsis and subsequently increased the effectiveness of secondary peristaltic response to abrupt esophageal distension.[15] In addition, we observed that mosapride significantly increased pressure wave amplitudes of secondary peristalsis.[15] Notably, the activation of secondary peristalsis by slow air injection was not affected by mosapride. Although current findings are in line with our prior investigation with mosapride;[15] nevertheless, the new evidence is that prucalopride significantly enhanced distension-induced thresholds of secondary peristalsis regardless the types of the stimuli inside the esophagus. Our results indicate that the highly selective 5-HT$_4$ agonist prucalopride appears to be more potent than mosapride in sensory modulation of esophageal secondary peristalsis via different types of mechanoreceptors in human esophagus.

In the present study, we found that prucalopride significantly increased primary peristaltic activity and LES pressure. Our data were in contrast with an earlier work investigating the

Table 2 Effects of prucaloride on manometric parameters of secondary peristalsis

	Slow distension		P value	Rapid distension		P value
	Placebo	Prucalopride		Placebo	Prucalopride	
Pressure waves (mm Hg)						
Middle	69.3 (10.5)	93.4 (14.9)	0.11	70.2 (8.7)	92.1 (9.3)	0.07
Distal	104.2 (16.8)	147.9 (28.5)	0.048	105.7 (12.3)	128.0 (13.3)	0.016
Duration (s)						
Middle	2.5 (0.2)	3.3 (0.5)	0.04	2.9 (0.6)	2.8 (0.3)	0.93
Distal	2.8 (0.2)	4.5 (0.5)	0.005	3.3 (0.4)	3.8 (0.5)	0.33

effect of prucalopride 4 mg daily on esophageal motility, Kessing *et al.* did not observe any effect of prucalopride on esophageal peristaltic activities or LES function using high-resolution manometry.[11] Although the cause of this discrepancy is not fully clear, it may be due to different methodology, study design, or dosage and timing of the medication used. However, in agreement with an earlier work[12] studying on the prokinetic activity of prucalopride on human isolated esophageal body, prucalopride was shown to increase the amplitude of circular muscle contractions. This *in vivo* study has demonstrated better intrinsic activity of prucalopride on the modulation of neuromuscular functions in human esophagus.

Although our prior work did not show any effect of 5-HT$_4$ agonist mosapride on basal LES pressure or residual LES pressure during swallowing,[15] prucalopride does significantly increase both basal and residual LES pressure. Data regarding the prokinetic effect of 5-HT$_4$ on LES functioning remain to be established;[16–18] however, the reason for the discrepancy between different 5-HT$_4$ agonists may reflect the notion that there are marked variations in the effects and potency of those agonists at the 5-HT$_4$ receptors with also interfering with other receptors,[19] and prucalopride may possess relatively higher intrinsic and selective activity for 5-HT$_4$ receptors.

The distension-induced secondary peristalsis can be classified according to the types of the stimuli.[4] In human esophagus, rapidly adapting mechanoreceptors in response to rapid esophageal distension are located in the mucosal layer, whereas slowly adapting esophageal mechanoreceptors in response to slow distension are found in the muscularis.[4,20–22] Our prior work in healthy adults has documented that both mucosal and muscular mechanoreceptors contribute to mediate esophageal reflexes (secondary peristalsis), which can be generated by *in vivo* slow and rapid air injections into the esophagus.[15,23] Given the known mechanisms of secondary peristalsis, the notion that distension thresholds of secondary peristalsis triggered by slow and rapid air injections were influenced by prucaloride suggests that esophageal distension-induced secondary peristalsis appears to be equally modulated by 5-HT$_4$ receptors in accordance with both slow and rapid adapting mechanoreceptors.

Some limitations need to be acknowledged in this study. Although complete peristaltic events were well observed with conventional manometry, the high resolution manometry may have the advantage by avoid missing some of the peristalsis.

The lack of high resolution manometry may limit comprehensive characterization of distension-induced secondary peristalsis due to the notion that secondary peristalsis may not run through the entire length of the esophagus.[4] Prior work using 4 mg prucalopride has well demonstrated its effects in reducing esophageal acid exposure and accelerating gastric emptying; however,[11] it is still unclear whether the dose we used is optimal to induce a series of physiological events related to secondary peristalsis. This has been overcome by the notion that the efficacy in promoting secondary peristalsis has been well observed in current work at the dose of 4 mg. Finally, the pattern and response to esophageal distension may depend on the type of the stimulation. The air boluses disperse rapidly along the esophagus and can be moved ahead of any peristaltic wave after injection. In contrast, the balloon distension provides a focal stimulus that can't be moved by any induced motor response.[2] However, balloon distension has lower response rate when compared with those of air and water in the normal subjects.

Our study merits some clinical implications. It suggests that prucalopride is capable of promoting secondary peristaltic activities that would further facilitate the efficiency of esophageal clearance relevant to defense mechanism when abrupt reflux or regurgitation of residual bolus occurs.[14] A recent work has demonstrated that prucalopride significantly reduces esophageal acid exposure and accelerates gastric emptying in healthy volunteers.[11] Together with our findings, it is suggested that prucalopride has its prokinetic effects in not only human stomach,[12] but also in the esophagus. Since secondary peristalsis appears to be important during sleep states when salivation and primary peristalsis are suppressed;[24] it is expected that prucalopride has potential clinical utility in improving nocturnal acid reflux because of its benefits on decreasing acid reflux[11] and promoting secondary peristalsis, as shown in this work. Moreover, since it has been demonstrated that impaired secondary peristalsis occurs in patients with gastro-esophageal reflux disease and was found more in those with severe esophagitis or concomitant ineffective motility,[25–27] current findings indicate that prucalopride is theoretically helpful in improving esophageal hypomotility in patients with complicated gastro-esophageal reflux disease. This notion needs to be further confirmed in gastro-esophageal reflux disease patients with significant esophageal hypomotility.

In summary, although prior work has revealed that the involvement of 5-HT$_4$ receptors in mediating the modulation of

distension-induced secondary peristalsis,[15] the present study has further demonstrated that prucalopride, a novel enterokinetic agent,[28] also promotes physiological characteristics of secondary peristalsis by enhancing distension thresholds and improving peristaltic activities in health adults. As secondary peristalsis can be influenced by prucalopride regardless type of the stimuli, this notion may support the evidence that both slowly adapting muscular and rapidly adapting mucosal mechanoreceptors can be both modulated via 5-HT$_4$ receptors in the generation of secondary peristalsis in human esophagus.

CONFLICT OF INTEREST

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