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ORIGINAL ARTICLE

Effects of nizatidine and itopride hydrochloride on esophageal motor function

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Abstract
Background and Aim Nizatidine and itopride hydrochloride inhibit cholinesterase activity and increase acetylcholine in the cholinergic nervous systems. The effect of nizatidine and itopride hydrochloride on esophageal motor function has not been determined, although these drugs are reported to increase gastric motility. Esophageal peristalsis between the upper esophageal sphincter and lower esophageal sphincter (LES) has been shown to be composed of three segments (segments 1–3) using high-resolution manometry. The aim of this study was to clarify the effects of nizatidine and itopride on esophageal motor function using high-resolution manometry.
Methods Seven healthy male volunteers (mean age 37.8 years) were examined three times: without medication, treated with 150 mg of nizatidine, or treated with 50 mg of itopride. LES pressure (LESP) and peak peristaltic pressures in the three esophageal segments upon swallowing 5 ml of water were examined using high-resolution manometry 1 h after drug administration.
Results The mean LESP after administration of nizatidine or itopride hydrochloride tended to be higher than that without medication. There was no significant difference between the peak contraction pressure in the first (uppermost) esophageal segment with drug administration and that without. On the other hand, both nizatidine and itopride hydrochloride significantly augmented the peak contraction pressure in the second and third segments.
Conclusion Administration of nizatidine and itopride hydrochloride is suggested to augment peristaltic contraction in the second and third segments of the esophageal body.

Keywords High-resolution manometry · LES · Esophageal peristalsis

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Introduction

Gastroesophageal reflux disease (GERD) is caused by chronic exposure of the esophageal mucosa to refluxed gastric contents [1]. Therefore, impaired esophageal motor function is a well known and important factor involved in the occurrence of GERD, and drugs that can increase the lower esophageal sphincter pressure (LESP) or peristaltic contraction of the esophageal body may be effective for the treatment of GERD patients [1–3]. Gastrointestinal motor function is regulated mainly by acetylcholine, and several drugs that augment acetylcholine in nerve endings are reported to increase gastrointestinal motor function [4, 5]. Nizatidine, a histamine H_2 receptor antagonist, has been demonstrated to inhibit acetylcholine esterase, with a resulting increment of acetylcholine in the cholinergic nervous systems [6–8]. Itopride hydrochloride is a prokinetic agent acting both as a dopamine D2 receptor antagonist and acetylcholine esterase inhibitor [9, 10]. Administration of nizatidine and itopride hydrochloride has been reported to augment gastric motor function [7, 9, 11]. However, the

effect of nizatidine and itopride hydrochloride on esophageal motor function has not been fully determined.

Recently, it has been demonstrated that esophageal body contraction between the upper esophageal sphincter (UES) and LES can be divided into three segments (segments 1–3) with two troughs using high-resolution manometry (Fig. 1) [12, 13]. The first (uppermost) segment is considered to consist of predominantly striated muscle, whereas the second and third segments consist of predominantly smooth muscle [12, 13]. Thus, stimulation of the cholinergic nerves might have different effects on each of the three segments. However, the effects of nizatidine and itopride hydrochloride on the peristaltic contraction of these segments have not been investigated. Therefore, we performed this study to clarify the effect of nizatidine and itopride hydrochloride on contraction of the esophageal segments using high-resolution manometry.

Subjects and methods

The study subjects were seven healthy male Japanese volunteers (mean age 37.8 years, range 22–48 years). None of the subjects had upper gastrointestinal symptoms, a history of upper gastrointestinal surgery, or were taking regular medications known to influence esophageal motor function. Written informed consent was obtained from all subjects before starting the study, which was carried out in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Shimane University.

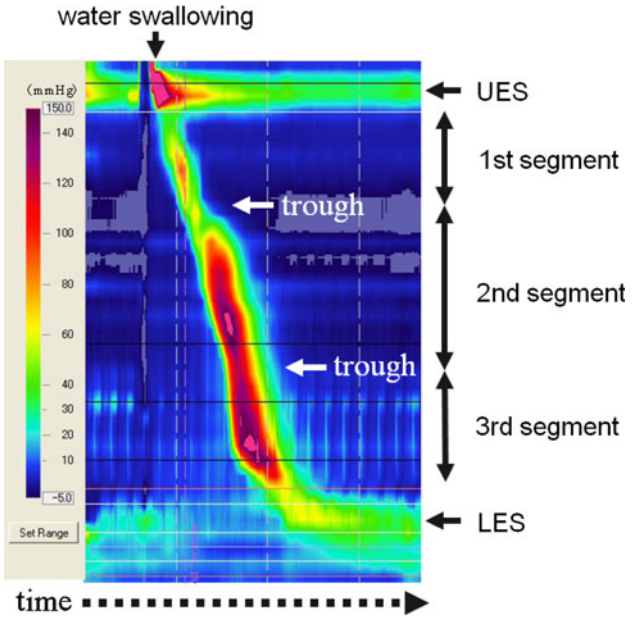

Fig. 1 Typical features of the segmental peristaltic architecture revealed using high-resolution manometry. High-resolution manometry used in this study has 36 solid-state circumferentially sensitive sensors spaced at 1-cm intervals. The sensor catheter was inserted transnasally and positioned to record from the hypopharynx to stomach with about five intragastric sensors. The changes of pressures of the lower esophageal sphincter (LES) and esophageal body during peristalsis can be indicated as color alterations in this system. Esophageal body contraction between the upper esophageal sphincter (UES) and lower esophageal sphincter (LES) was divided into three segments (segments 1–3) according to the presence of two troughs

Esophageal motor function in all the subjects was examined three times: without medication, with 150 mg of nizatidine, or with 50 mg of itopride hydrochloride in a cross-over manner. These three tests were conducted in random order and were performed at almost the same time in each of the subjects at least 1 week apart. The doses of nizatidine and itopride hydrochloride employed were standard ones in clinical usage in Japan. After more than a 4-h fast, 150 mg of nizatidine or 50 mg of itopride hydrochloride was administrated with 100 ml of tap water. Esophageal motor function tests were done at 1 h after drug administration, since the T_{max} of nizatidine and itopride hydrochloride is reported to be 1.3 ± 0.6 h and 1.0 ± 0.5 h, respectively [14, 15]. At the examination without medication, the subjects were instructed to drink 100 ml of tap water 1 h before the esophageal motor function test.

In this study, we used a high-resolution manometry system (ManoScan^{360TM}; Sierra Scientific Instruments, Los Angeles, CA) to examine esophageal motor function. The manometric catheter of this system is 4.2 mm in diameter and has 36 intraluminal pressure transducers spaced at 1-cm intervals. These transducers can measure the intra-esophageal pressure from the UES to the LES simultaneously and continuously (Fig. 1) [12, 13]. Before performing the esophageal motor tests, the transducers were calibrated at 0 and 100 mmHg using externally applied pressure in accordance with the manufacturer's instructions. The manometric catheter was inserted transnasally by using 2% lidocaine jelly (Xylocaine jelly; AstraZeneka Co., Osaka, Japan). LESP in the sitting position was firstly measured during a 5-min rest period. Then, intra-esophageal pressures of esophageal peristalsis in the sitting position were examined by swallowing 5 ml of water of room temperature. Swallowing of water was repeated at 2-min intervals until five recordings of complete esophageal peristalsis had been obtained. After the esophageal motor function tests in the sitting position, LESP and the pressures of esophageal peristalsis at swallowing of water were measured in the supine position (Fig. 2). LESP and peak peristaltic pressures in the three segments of the esophageal body were analyzed using ManoView™ analysis software (Sierra Scientific Instruments, Los Angeles, CA). To determine the peak pressures of esophageal body contraction at each measurement, we calculated the mean values of three measurements after excluding the highest and lowest values of five

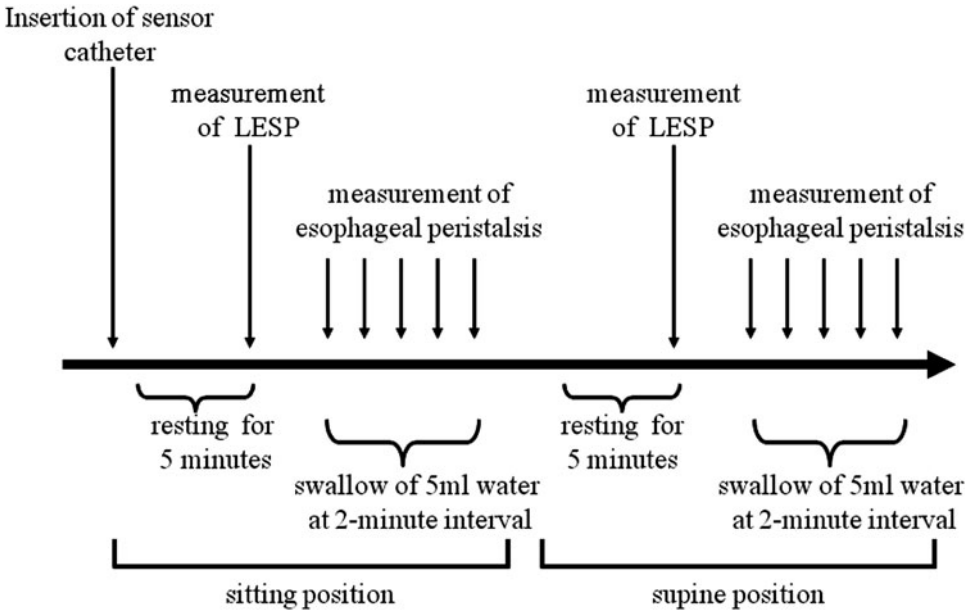

Fig. 2 Protocol of the esophageal motor function test

measurements. We did not examine the ratio of incomplete peristalsis, since the aim of this study was to clarify the effect of nizatidine and itopride on LESP and peak peristaltic pressures in healthy subjects.

Statistical analysis to compare the values without medication was performed by using the Wilcoxon signed rank test. Differences at $p < 0.05$ were considered to be statistically significant.

Results

All seven subjects completed the study protocol without any adverse events. LESP and peak pressures of esophageal body contraction in the supine position were significantly higher than those in the sitting position, not only with administration of drugs but also without medication. The administration of nizatidine and itopride hydrochloride tended to augment the LESP, although the difference from the value without medication did not reach statistical significance (Fig. 3a). The peak peristaltic pressure in the first segment of esophageal body contraction was not augmented by administration of nizatidine or itopride hydrochloride (Fig. 3b). On the other hand, the peak peristaltic pressures in the second and third segments were increased by nizatidine or itopride hydrochloride in both the sitting and supine positions (Fig. 3c, d).

Discussion

GERD is defined as chronic symptoms or mucosal damage produced by gastroesophageal reflux [1]. Esophageal body motor function and LESP have been repeatedly reported to be the most important mechanisms for preventing the occurrence of GERD [1–3]. LESP has an important function in the prevention of gastroesophageal reflux, and peristaltic contraction of the esophageal body plays a major role in pushing the refluxate out to the stomach. Indeed, low LESP and impaired esophageal peristalsis were reported to be frequently observed in patients with GERD [16, 17]. Therefore, drugs that can increase the LESP or peristaltic contraction of the esophageal body may be effective for the treatment of GERD patients.

Esophageal body contraction from the UES to the LES is known to be divided into three segments (segments 1–3) using high-resolution manometry [12, 13]. The present results showed that the administration of nizatidine or itopride hydrochloride, which can increase acetylcholine in the terminals of cholinergic nerves, augmented the peak peristaltic pressures in the second and third segments of the esophageal body, but did not increase the peak peristaltic pressure in the first (uppermost) segment. This observation is similar to the results already reported by Staiano and Clouse, who demonstrated that administration of cisapride augmented the peak pressures in the second and third segments of esophageal body contraction [18]. The part of first segment was reported to consist of predominantly striated muscle, and those of second and third segments were reported to consist of predominantly smooth muscle [12, 13]. Thus, stimulation of the cholinergic nervous system may augment esophageal peristaltic contraction in the second and third esophageal segments.

Stimulation of the cholinergic system has also been reported to augment LESP [19–21]. In this study, LESP

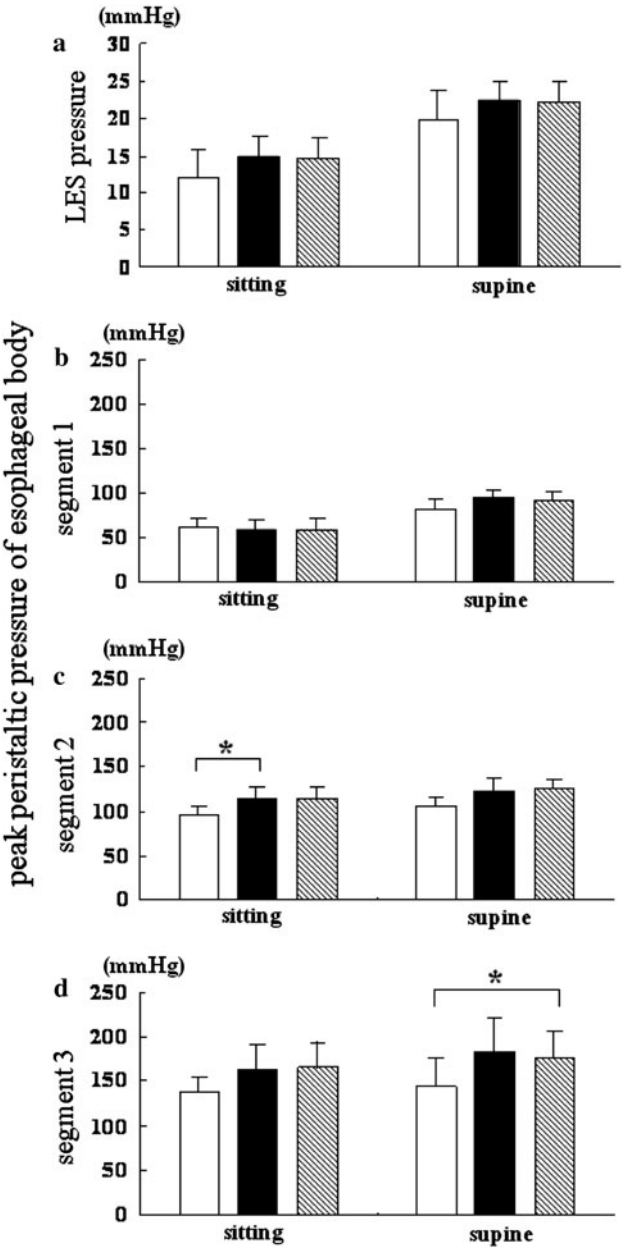

Fig. 3 Lower esophageal sphincter pressure (**a**) and peak peristaltic pressures in three segments of the esophageal body (**b** segment 1, **c** segment 2, and **d** segment 3) after administration of nizatidine or itopride hydrochloride. *White bar* no medication, *black bar* with administration of nizatidine, *shaded bar* with administration of itopride hydrochloride. Data are expressed as mean ± SE. $*p < 0.05$

tended to increase after the administration of nizatidine or itopride hydrochloride, although the increments of LESP after the administration of these drugs were not significant. The augmenting function of nizatidine and itopride hydrochloride on esophageal body peristalsis and LESP may be favorable for treatment of patients with GERD. Indeed, several authors have demonstrated the usefulness of nizatidine and itopride hydrochloride for the treatment of patients with reflux esophagitis and reflux symptoms [22–25]. Scarpellini et al. [26] recently reported that administration of itopride hydrochloride inhibited the meal-induced rise of transient LES relaxation in healthy subjects. The increment of LESP and esophageal peristaltic pressure, however, was not observed by the administration of itopride hydrochloride in their study. Thus, the results of their study do not fit well with those of our present study. The numbers of study subjects in both our and Scarpellini's studies, however, were relatively small. Therefore, further large-scale study is needed to clarify the effect of itopride hydrochloride on the LESP and esophageal peristaltic pressure in not only healthy subjects but also patients with GERD.

LESP was previously demonstrated to be significantly higher in the supine position than when sitting in both healthy subjects and patients with reflux esophagitis [27–29]. The present study using high-resolution manometry also showed that the peak peristaltic pressures in all the three segments of the esophageal body were significantly higher when the subjects were supine than when sitting. The reason for the increment of LESP and the peak peristaltic pressure in the esophageal body in the supine position is unclear. These increments might have an important role in preventing gastroesophageal reflux and promoting the return of refluxate to the stomach. Gastroesophageal reflux occurs mainly in the daytime in patients with nonerosive gastroesophageal reflux disease or lower grade esophagitis, whereas it occurs predominantly at night in the supine position in patients with higher grade esophagitis [30, 31]. Therefore, further study is needed to verify whether the function in the supine position to augment LESP and esophageal body peristaltic activity is impaired in patients with higher grade esophagitis or not.

There are some limitations to this study. The number of study subjects was relatively small. In addition, esophageal motor function tests were performed after a single oral dosage of nizatidine and itopride hydrochloride in this study, and the study subjects were healthy volunteers who had no reflux symptoms. The dose of itopride hydrochloride fitted to the standard dose in Japan in this study, and it was smaller than that used in Western countries. Therefore, a further large-scale study should be performed in patients with GERD, whose esophageal motor function is impaired, in order to confirm the efficacy of nizatidine and itopride hydrochloride for augmenting esophageal motor function.

In conclusion, administration of nizatidine or itopride hydrochloride is suggested to augment the peristaltic contraction of the second and third segments of the esophageal body.

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