学 位 論 文 の 要 旨

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学 位 論 文 名　Effects of Mosapride on Esophageal Motor Activity and Esophagogastric Junction Compliance in Healthy Volunteers

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論 文 内 容 の 要 旨

INTRODUCTION

Gastroesophageal reflux disease (GERD) is caused by the pathological reflux of gastric contents. Proton pump inhibitors (PPIs) is widely used as first-line therapy. However, approximately 30% of treated patients complain about reflux symptoms with PPI use and require additional treatment. As a second-line therapy, mosapride, a prokinetic agent activating the serotonin 5-HT 4 receptor, has been used in clinical practice, though reports concerning its beneficial effects for GERD are conflicting. These conflicting results may be derived from different dosages, with higher doses possibly necessary to gain beneficial therapeutic effects.

The esophago-gastric junction (EGJ) is an important structure to prevent gastro-esophageal reflux. Patients with GERD show high compliance of this area and the cross-sectional area (CSA) of EGJ during pressure distension is known to be larger than that in normal individuals. The increased EGJ compliance is considered to increase the CSA of EGJ and to diminish air/fluid discrimination during transient lower esophageal sphincter relaxation-associated reflux with increasing volume of gastro-esophageal fluid reflux.

Therefore, drugs that reduce EGJ compliance and decrease the CSA of EGJ are expected to inhibit pathological gastroesophageal reflux. Recently, endoluminal functional lumen-imaging probe (FLIP; EndoFLIP®, Crospon Ltd, Galway, Ireland) has been demonstrated to be useful to evaluate the compliance of upper and lower esophageal sphincter. In this study, the effect of

high-dose mosapride on EGJ compliance and esophageal motor function was investigated by using EndoFLIP system and high-resolution 36-channel manometry in healthy volunteers.

MATERIALS AND METHODS

Nine normal healthy male volunteers (age 21-52 years old, mean 35.2 years) without any abdominal symptoms were enrolled in the study. Peristaltic esophageal contraction and lower esophageal sphincter pressures before and after administration of 40 mg mosapride were examined by high resolution esophageal manometry. Esophageal compliance was also investigated by intra-esophageal impedance planimetry (EndoFLIP®). The dose of mosapride used in this study is the standard approved dose widely used for bowels preparation for colonoscopy in daily clinical practice in Japan.

The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

RESULTS AND DISCUSSION

In the lower segment, high-dose mosapride given twice resulted in a statistically significant increase in mean maximum contraction pressure. In addition, mean LES resting pressure in a supine position increased. Therefore, high-dose mosapride at was considered to augment esophageal contractions, especially in the distal segments and EGJ areas.

The hiatal diameter (D min) and CSA progressively increased with distending volume, as did the intra-bag pressure. During the mosapride administration period, intra-bag pressure was higher and the hiatal CSA was lower with the 40- and 50-ml intra-bag volumes ($P < 0.05$). At all distensible pressures, the extent of the EGJ opening during the mosapride treated period was smaller than that during the non-treated period. Using intra-bag pressure and hiatal CSA, an EGJ distensibility index (DI) was calculated for each distension volume. This index was significantly and consistently lower during administration of mosapride at each distention volume, suggesting a reducing effect of mosapride on EGJ compliance.

In the present study, high-dose (40 mg) mosapride was found to not only augment peristaltic esophageal body contractions and LES pressure but also reduce EGJ compliance. The anti-reflux mechanism of the esophagus is composed of 3 different factors. First, the high pressure zone at the LES prevents reflux of gastric contents. Indeed, free and stress-induced gastroesophageal refluxes are known to frequently occur in GERD patients with lowered LES pressure. Next, the limited range of EGJ compliance reduces high volume fluid reflux from the stomach, whereas patients with GERD have been reported to have a higher amount of EGJ compliance in studies using a FLIP or similar method. Finally, efficient esophageal body

peristaltic contractions are important to clear refluxed gastric contents from esophagus. These 3 factors composing the anti-reflux mechanism were investigated in the present study using 2 different techniques; high resolution manometry of the esophagus and a FLIP method.

We enrolled 9 normal volunteers without GERD to assess the feasibility of mosapride as a possible drug to treat PPI-resistant GERD patients. Mosapride stimulates gastrointestinal contractions by activating the serotonin 5-HT 4 receptor and releasing acetylcholine from vagal efficient neurons. With its administration, gastric emptying has been reported to be accelerated. Although lower doses of mosapride failed to augment esophageal motor functions, higher doses were reported to enhance esophageal contractions. In the present study, a high dose of 40 mg was shown to augment esophageal body peristaltic contractions and suggested to facilitate the esophageal clearance mechanism. In addition, we found that mosapride elevated resting LES pressure with possible efficient protection against stress-induced gastroesophageal reflux. In the present study, esophageal high-resolution manometry revealed the potential anti-GERD action of mosapride in normal individuals.

In addition to augmented esophageal contractions, mosapride was found to reduce EGJ compliance. When a FLIP bag was serially inflated at the EGJ, the narrowest part of the hiatus gradually widened both before and during mosapride administration. The intra-bag pressure was higher with the same intra-bag volume during mosapride treatment, while the CSA of the narrowest hiatal locus was smaller. These changes in minimal diameter at the hiatal locus also showed a similar trend with those of the hiatal CSA. Together, our results indicated that intraluminal pressure-induced distension of the EGJ was reduced by mosapride administration, suggesting its effect to produce a stronger EGJ barrier against high volume fluid reflux.

The diminishing effect of mosapride on EGJ compliance was firstly found in this study. During mosapride administration, EGJ opening during pressure distension is limited. This is expected to decrease the volume of refluxate and limit the upper esophageal reflux. The effect of mosapride on EGJ compliance found in this study will be an important information for understanding the mechanism of these gastro-esophageal reflux-related diseases.

CONCLUSION

Mosapride, a prokinetic drug featuring 5-HT4 stimulation, at a dose of 40 mg reduced EGJ compliance, and also augmented esophageal body peristalsis and LES pressure.