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.

論文審査及び最終試験又は学力の確認の結果の要旨

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論文審査の結果の要旨

胃食道逆流症（GERD）診療ガイドラインでは、プロトンポンプ阻害剤を用いた治療に抵抗するGERDに対して消化管運動機能改善薬を投薬することが推奨されている。ところが消化管運動機能改善薬の有効性に関する十分な臨床的エビデンスも食道の生理機能に対する影響についての検討もない。モサプリドはセロトニン受容体刺激作用を有する消化管運動機能改善薬であり、食道の運動能に影響を及ぼす可能性がある。申請者は消化管の運動能の評価に用いられてきた収縮力を評価するための内圧モニタリング検査に加え、食道壁のコンプライアンスを評価できる新しい手法を用いて、高用量のモサプリドが食道運動機能にどのような効果を有するかを、健常人ボランティア９名を対象に検討した。その結果、モサプリドの投薬は食道体部の蠕動運動の収縮力を高め、特に下部食道においてその効果が大きかった。さらにモサプリドは食道胃移行部の下部食道括約筋静止収縮圧を上昇させた。食道胃移行部のコンプライアンスはモサプリドの投薬後に低下し、伸展性が低下することが明らかとなった。本研究は、消化管運動機能改善薬であるモサプリドが食道体部の蠕動運動を亢進させ、食道胃移行部の収縮能を高め、さらにその伸展性を低下させることで、胃食道逆流の防止と逆流胃液のクリアランスに有用な作用を有することを明らかにした。

以上より、本研究の成果は臨床応用への可能性を示すもので、学位授与に値すると判断した。

最終試験又は学力の確認の結果の要旨

申請者は、健常人ボランティアにセロトニン受容体刺激作用を有するモサプリドを高用量投与すると下部食道の蠕動運動亢進、下部食道括約筋静止収縮圧の上昇、食道胃移行部のコンプライアンスの低下をきたすことを明らかにした。この結果は、モサプリドがGERDの治療薬になる新たな可能性を示唆するものである。質疑応答も的確で、関連分野の知識も豊富であり、学位授与に値すると判断した。

（主査：田島義証）

申請者は、セロトニン受容体作動薬であるモサプリドの高用量を健常者ボランティアに投与することにより、食道蠕動運動の亢進、そして食道胃移行部の収縮能の上昇と伸展性の低下が起こることを示した。本研究結果は治療抵抗性のGERDの治療戦略を考える上で貴重であり、関連知識も豊富で、学位授与に値すると判断した。

（副査：杉本利嗣）

申請者は、高用量のセロトニン受容体作用薬による食道ならびに食道胃移行部の運動機能評価を行いその薬理効果を明確にした。特に食道胃移行部の機能評価には新たな検査手技を用いて貴重な知見が示されている。これらの結果はGERDの薬物療法においてセロトニン受容体作用薬を用いた新たな治療法の可能性を示唆するものであり臨床的にも非常に有用で興味深い結果と考える。またGERD関連分野における知識も豊富であり、学位授与に値すると判断した。

（副査：藤代浩史）

（備考）要旨は、それぞれ４００字程度とする。