学 位 論 文 の 要 旨

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学 位 論 文 名　Effects of Metoclopramide and Acotiamide on Esophageal Motor Activity and Esophagogastric Junction Compliance.

発 表 雑 誌 名
（巻，初頁～終頁，年）　} 別紙参照
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論 文 内 容 の 要 旨

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a gastrointestinal disorder induced by reflux of gastric acidic contents. Proton pump inhibitors (PPIs) are widely used as first-line therapy, because of their excellent suppression of gastric acid secretion. However, approximately 30% of treated patients complain about reflux symptoms with PPI use alone and require additional treatment. Prokinetic drugs such as mosapride, metoclopramide, and acotiamide are anticipated to be shown effective for GERD, because they improve esophageal motor activity and facilitate gastric emptying, and previous reports have suggested that addition of a prokinetic drug to PPI therapy can improve GERD symptoms. However, the beneficial effects of prokinetic drug treatment for esophageal motility are controversial. It was recently reported that esophageal motor activities and compliance of the esophagogastric junction (EGJ) are important for prevention of gastroesophageal reflux, with the latter considered to cause greater volume reflux of gastric contents into the esophagus. Therefore, drugs that reduce EGJ compliance and decrease the cross-sectional area (CSA) of the EGJ are expected to inhibit pathological gastroesophageal reflux. An endo-luminal functional lumen imaging probe (EndoFLIP) is a novel device used to measure CSA and distensibility at the EGJ. Using this probe and high-resolution manometry, we previously found that high-dose mosapride augmented peristaltic contractions and mean resting lower esophageal sphincter (LES) pressure, and also significantly reduced EGJ compliance. On other hand, no related studies of other prokinetic agents have been presented. Using an EndoFLIP system and high-resolution manometry (HRM), the effects of

metoclopramide and acotiamide, prokinetic agents, on EGJ compliance and esophageal motor function were investigated in healthy volunteers, while those of acotiamide were also examined in GERD patients.

MATERIALS AND METHODS

To investigate the effects of metoclopramide, 9 healthy males (mean age 25.4 years) were enrolled. Esophageal motor activity function was evaluated using HRM, while EGJ compliance was examined with the EndoFLIP system. After obtaining baseline measurements of esophageal motor activities and EGJ compliance, metoclopramide (10 mg) was intravenously administered, then all measurements were repeated 15 minutes later in each subject.

To investigate the effects of acotiamide, 9 healthy individuals (6 males, 3 females; mean age 51.2 years) as well as 3 GERD patients (1 male, 2 females; mean age 66.7 years) were enrolled. Each of the patients with GERD were receiving treatment with a PPI and that was continued during the study. Esophageal motor activities were determined by HRM and those data were evaluated using parameters based on the Chicago classification, version 3.0. EGJ compliance was examined with the EndoFLIP system. After obtaining baseline measurements of esophageal motor activities and EGJ compliance, acotiamide was administered with 100 ml of water 3 times a day for 3 days, the standard dose for adult patients with FD. On the final day of acotiamide administration, all measurements were repeated in the same manner. The period of administration was decided based on drug information provided by the manufacturer.

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

RESULTS AND DISCUSSION

In the present investigation of metoclopramide, all 9 subjects completed the study protocol without any adverse events. EndoFLIP data for 1 subject were not appropriately recorded due to technical problems, thus those obtained for 8 subjects were analyzed. In HRM measurements, mean resting LES pressure was significantly increased following administration of metoclopramide as compared with the baseline (13.7±9.2 vs. 26.7±8.8 mmHg, $P<0.05$). In addition, metoclopramide significantly augmented peak peristaltic contractions, especially in the distal esophageal segment (109.8±45.4 vs. 140±51.7 mmHg, $P<0.05$). On the other hand, EndoFLIP measurements showed that EGJ compliance was not changed after intravenous administration of metoclopramide. Furthermore, the distensibility index was also not changed after that administration (4.5±0.5 vs. 4.1±0.5 mm2/mmHg, distention volume 40 ml), suggesting no significant effect of metoclopramide on EGJ compliance.

In our investigation of acotiamide, all 12 subjects completed the study protocol without any adverse events. However, EndoFLIP data for 1 of the 9 healthy subjects were not

appropriately recorded due to technical problems, thus those obtained for 8 were analyzed. In HRM measurements, acotiamide administration did not significantly augment mean resting LES pressure as compared with the baseline (19.2±2.5 vs. 19.9±2.8 mmHg, P=0.58). Moreover, acotiamide did not change esophageal motor activity parameters, as defined by the Chicago criteria (IRP: 15.4±1.2 vs. 14.2±1.1 mmHg, P=0.31; DCI: 3921.8±535.3 vs. 4030.0±722.8 mmHg/cm/second, P=0.95; CFV: 5.1±0.9 vs. 4.5±0.5 cm/second, P=0.37; DL: 7.1±0.2 vs. 7.5±0.3 seconds, P=0.34). In EndoFLIP measurements of the healthy subjects, there were no statistically significant differences between baseline and after administration of acotiamide in regard to the values for CSA (150.3±12.2 vs. 133.7±15.5 mm^2, distention volume 40 ml, P=0.24) or distensibility index (3.5±0.4 vs. 3.3±0.5 mm^2/mmHg, distention volume 40 ml, P=0.67). In the GERD patients, EGJ distensibility index was higher than the control value of the normal volunteers (distensibility index in 40-ml distension: 3.5±0.4 vs. 6.2±0.5 mm^2/mmHg). Also, following the administration of acotiamide, there was no change in EGJ compliance (distensibility index in 40-ml distension: 6.2±0.5 vs. 6.5±1.1 mm^2/mmHg).

In our previous study we found that a high dose of mosapride augmented esophageal body peristaltic contractions and resting LES pressure, which suggested that mosapride facilitates the esophageal clearance mechanism and provides efficient protection against gastroesophageal reflux. Metoclopramide and acotiamide are used as prokinetic drugs, and have been shown to have pharmacological actions similar to mosapride. In the present study, metoclopramide was found to augment LES pressure to the same degree as mosapride. However, in contrast to the effects of mosapride, metoclopramide did not decrease EGJ distensibility and acotiamide did not have effects on either of those in the present examinations. These results are important for understanding the different pharmacological characteristics of mosapride, metoclopramide, and acotiamide. Although each is administrated for gastrointestinal motility disorders and are similar prokinetic agents, mosapride mainly stimulates 5-HT4 serotonin receptors, while metoclopramide primarily inhibits dopamine D2 receptors in the peripheral autonomic motor nervous system, and acotiamide functions as a selective AchE inhibitor in the peripheral autonomic motor nervous system. The pharmacological differences shown by these 3 drugs are likely related to their different effects on esophageal motor activity and EGJ compliance.

CONCLUSION

In healthy adults, metoclopramide augmented esophageal contractions without changing EGJ compliance. On the other hand, acotiamide at a standard dose did not have significant effects on esophageal motor activities or EGJ compliance in both healthy individuals and GERD patients.

別紙

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論文名

1. Effects of metoclopramide on esophageal motor activity and esophagogastric junction compliance in healthy volunteers.

2. Acotiamide has no effects on esophageal motor activity or esophagogastric junction compliance.

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1. Journal of Neurogastroenterology and Motility (22(1), 112-117, 2016)

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