学 位 論 文 の 要 旨

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学 位 論 文 名	Adding Acotiamide to Gastric Acid inhibitors is Effective for Treating Refractory Symptoms in Patients with Non-Erosive Reflux Disease
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論 文 内 容 の 要 旨

INTRODUCTION

Although proton pump inhibitors (PPIs) are widely used for treatment of gastro-esophageal reflux disease (GERD), 20–30% of those patients experience persistent heartburn and/or regurgitation. Gastrointestinal motility plays an important role in generating reflux and GERD symptoms, thus it is considered that prokinetic drugs may improve reflux symptoms by augmenting gastric motility by reducing the number of reflux events. The effects of acotiamide, a new prokinetic agent shown to improve delayed gastric emptying and impaired gastric accommodation, have been scarcely examined in patients with PPI-refractory GERD. Here, we assessed symptomatic improvement, esophageal reflux parameters, and esophageal contraction characteristics as effects of acotiamide in patients with gastric acid inhibitor-refractory GERD.

MATERIALS AND METHODS

This randomized, prospective, double-blind, placebo-controlled trial was conducted from September 2015 to March 2018 (UMIN No. 000026364). The study protocol was approved by the Institutional Review Board of Saiseikai Nakatsu Hospital and the Ethics Committee of Shimane University, and written informed consent was obtained from all subjects. Seventy-one patients [15 reflux esophagitis (RE), 56 with non-erosive reflux disease (NERD)] were enrolled and given an upper endoscopy examination before starting therapy. Those with persistent reflux symptoms despite treatment with a PPI or vonoprazan at a standard dose for at least 8 weeks

were randomly administered 300 mg/day of acotiamide or a placebo for 2 weeks. The primary endpoint was overall treatment effect (OTE), graded using a 7-point Likert scale from 1 (extremely improved) to 7 (extremely aggravated), by which gastrointestinal symptoms were evaluated. Grades 1 and 2 indicated that the therapy was effective. We also calculated the sum of severity, rated from 0 for none to 3 for severe, and frequency, rated from 0 for none to 4 for daily, scores for gastrointestinal symptoms, with a responder defined as having a greater than 50% decrease in symptom score after 2 weeks of treatment as compared to the baseline. High-resolution manometry (HRM) and 24-hour multiple intraluminal impedance-pH (MII-pH) monitoring were conducted before and after treatment when possible.

RESULTS AND DISCUSSION

A total of 70 patients were randomized (35 each in acotiamide and placebo groups) before analysis, and 67 (35 acotiamide, 32 placebo) completed the study. Sixteen in the acotiamide group and 10 in the placebo group agreed to MII-pH and HRM after 2 weeks of treatment. There were no significant differences in regard to baseline characteristics between the groups.

The responder rate based on OTE grading after 2 weeks was 28.6% for patients in the acotiamide group and 14.3% for those in the placebo group, which was not a significant difference. (p = 0.145). Furthermore, in sub-group analysis findings of patients with RE (8 acotiamide, 7 placebo), there was no significant difference between those in the acotiamide (n=8) and placebo (n=7) groups (25.0% vs. 42.8%, p = 0.464). In contrast, for patients with NERD (27 acotiamde, 28 placebo), the OTE improvement rate was significantly higher in the acotiamide group (29.6% vs. 7.1%, p = 0.030).

For the rates of responder to all symptoms divided according to RE and NERD, there were no significant differences between the acotiamide and placebo groups for each symptom in patients with RE. In contrast, in patients with NERD, the response rates for regurgitation, epigastric pain, and epigastric burning were significantly higher in the acotiamide group (37.0% vs. 10.7%, p = 0.021; 37.0% vs. 10.7%, p = 0.032; 44.4% vs. 17.8%, p = 0.021, respectively).

Acotiamide did not have effects on lower esophageal sphincter pressure, distal esophageal contractile integral, or percentage of successful peristalsis, whereas peristaltic breaks after treatment with the drug were significantly shorter than at baseline (3.1 vs. 0.8 cm, p = 0.020). No significant differences were found in the placebo group for any parameters.

In MII-pH monitoring, acotiamide administration significantly reduced total reflux (39.5 vs. 29.0, p = 0.001), acid reflux (13.5 vs. 3.5, p = 0.020), and liquid reflux (19.0 vs. 12.0, p = 0.013) episodes, whereas he differences for weakly acidic reflux (20.5 vs. 16.0, p = 0.064) and mixed reflux (20.0 vs. 14.0, p = 0.057) episodes were not significant between the groups. Proximal reflux and distal reflux episodes were significantly reduced with acotiamide (17.5 vs.

13.0, $p = 0.007$; 21.0 vs. 14.5, $p = 0.047$, respectively). while no significant differences were found in the placebo group.

This is the first study to use a placebo-controlled double-blind protocol for assessment of the efficacy of adding acotiamide to a gastric acid inhibitor to treat patients with refractory GERD. We found a significant difference in OTE improvement in patients with NERD, but not in those with RE. It is well known that NERD patients have esophageal hypersensitivity to refluxate, thus addition of acotiamide to reduce gastric acid reflux may contribute to a better response. It has also been reported that regurgitation can be caused by not only acid reflux but also weak acidic reflux extending to the proximal esophagus. A reduction in proximal reflux episodes caused by acotiamide administration may be an important factor for improving regurgitation symptoms. Furthermore, our findings showed that peristaltic breaks, which can affect esophageal clearance, were shortened by acotiamide, which may prevent reflux extending to a more proximal region of the esophagus.

CONCLUSION

In conclusion, this placebo-controlled study of patients with refractory GERD revealed that OTE and regurgitation were significantly improved by adding acotiamide as compared to a placebo in patients with NERD, as total reflux episodes, particularly acid and proximal reflux episodes were, significantly reduced. Furthermore, no harsh side effects were noted in the acotiamide group. We concluded that addition of acotiamide in a complementary manner with a gastric acid inhibitor may be beneficial for patients with refractory NERD.