学 位 論 文 の 要 旨

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学 位 論 文 名	Tolerance to H2 Receptor Antagonist Correlates Well With the Decline in Efficacy Against Gastroesophageal Reflux in Patients With Gastroesophageal Reflux Disease
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論 文 内 容 の 要 旨

INTRODUCTION

H2 receptor antagonists (H2RAs) are well known to have a rapid acid-suppressing effect, providing early symptom relief in patients with gastroesophageal reflux disease (GERD). However, the anti-secretory activity of H2RAs is reported to decrease during continuous administration. This attenuation of the anti-secretory activity of H2RAs has been described as tolerance. Recently, we have clarified that presence or absence of *Helicobacter pylori* (*H. pylori*) infection influences the occurrence of the tolerance phenomenon during 2-week administration of H2RAs. However, it was not fully investigated whether oral administration of H2RA effectively controls gastro-esophageal acid reflux of patients with GERD on the 1st day of administration. In addition, it was not clarified whether the efficacy of H2RA for the control of gastro-esophageal acid reflux is attenuated during continuous administration. We performed the present study to clarify whether H2RA effectively controls gastroesophageal reflux on the 1st day of administration and whether tolerance to H2RA is correlated with attenuation of its inhibitory effect against gastro-esophageal acid reflux in patients with GERD.

MATERIALS AND METHOD

Male Japanese patients who had GERD symptoms were recruited for this study. GERD symptoms were assessed by the Japanese version of the Carlsson-Dent self-administered questionnaire (QUEST). For the purpose of this study, we defined subjects whose QUEST scores were over 6 as positive for GERD symptoms. Written informed consent was obtained from all the subjects before starting the study, which was

on day 15.

The intraesophageal acidity was significantly decreased on both days 1 and 15 of famotidine administration. When intraesophageal acidity was analyzed after dividing the patients into *H. pylori*-negative and positive groups, the percentage time for which the intraesophageal pH was <4.0 tended to increase after 2-week continuous administration of famotidine in the *H. pylori*-negative patients. This trend was not observed in *H. pylori*-positive patients, and the efficacy of famotidine for inhibition of intraesophageal acidity was maintained even after 2 weeks of continuous administration.

Seven of the 10 subjects stated that their GERD symptoms were improved on the 1st day of famotidine administration, and one subject stated that the symptoms had disappeared entirely. However, the number of patients whose GERD symptoms were improved or disappeared tended to decrease after 15 days of continuous famotidine administration. This tendency was observed in subjects without *H. pylori* infection, but not in subjects with *H. pylori* infection.

The results of this study clearly demonstrated that famotidine effectively controlled gastro-esophageal acid reflux on the 1st day of administration, and the occurrence of tolerance to H2RA in patients without *H. pylori* infection was accompanied by increased gastro-esophageal acid reflux during the 2-week administration period. The lack of tolerance to H2RAs in subjects with *H. pylori* infection may explain the long-term efficacy of H2RAs as maintenance therapy for peptic ulcer patients with *H. pylori* infection. Since approximately half of all patients with low-grade reflux esophagitis are infected with *H. pylori*, H2RA may be useful as maintenance therapy in GERD patients with *H. pylori* infection. A future large-scale prospective study is warranted to clarify the efficacy of H2RA as maintenance therapy for GERD patients with *H. pylori* infection.

CONCLUSION

We have clarified that famotidine effectively controls gastro-esophageal acid reflux in patients with GERD on the 1st day of administration. The occurrence of tolerance to H2RA in patients without *H. pylori* infection was accompanied by attenuated inhibition of gastro-esophageal acid reflux after 2 weeks of famotidine administration. Long-term effective control of gastro-esophageal acid reflux was possible in patients with *H. pylori* infection, who did not show tolerance phenomenon to H2RA.

carried out in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Shimane University.

All participants were examined by ambulatory 24-hour intraesophageal and intragastric pH monitoring without medication. In this study, we recruited participants until the number of subjects in whom the percentage time of the intraesophageal pH was below 4.0 was abnormal (over 4.2) during the 24-hour monitoring period, reached ten. The ten subjects (mean age 37.5 y, range 24~52 y) whose intraesophageal pH during 24 hours was abnormal were then investigated by further pH monitoring during a 15-day course administration of famotidine (20 mg twice daily; Yamanouchi Pharmaceutical Co. Ltd., Tokyo, Japan). pH monitoring during famotidine administration was performed on days 1 and 15. All ambulatory pH monitoring was undertaken with the subjects on a standard diet. The percentage of the time for which the intragastric and intraesophageal pH values were below 4.0 was calculated for the total 24 h, daytime (06:30–22:30) and night-time periods. The presence or absence of *H. pylori* infection was examined using the urea breath test (UBT). Subjects whose $\delta\ ^{13}C$ values were lower than 5.0‰ were regarded as having a negative UBT result.

The changes in GERD symptoms after famotidine medication were assessed using a four-point scale (disappeared, improved, no change, worsened) after 1 day (at the end of the pH monitoring study on the 1st day) and 15 days (at the end the pH monitoring study on the 15th day) of famotidine administration.

Statistical analysis of paired data was performed using the Wilcoxon signed rank test if the Friedman test showed a significant difference. The Mann-Whitney *U* test was also applied to compare non-paired data, and the chi-squared test was used for comparison of categorical data.

RESULTS AND DICUSSION

The intragastric acidity of the 10 subjects was significantly suppressed on both day 1 and day 15 of famotidine administration, especially during the night. When intragastric acidity was analyzed after dividing the patients into 7 *H. pylori*-negative and 3 positive cases, the anti-secretory effect of famotidine was found to be significantly decreased after 2-week continuous administration in the *H. pylori*-negative patients. However, no such trend was observed in *H. pylori*-positive patients, and the intragastric acidity of the *H. pylori*-positive patients was significantly lower than that of the *H. pylori*-negative patients