学 位 論 文 の 要 旨

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学 位 論 文 名　*Helicobacter pylori* Infection Prevents the Occurrence of the Tolerance Phenomenon of Histamine H2 Receptor Antagonists

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論 文 内 容 の 要 旨

INTRODUCTION

Histamine H2 receptor antagonists (H2RAs) are widely used as potent therapeutic agents for peptic ulcer disease and gastroesophageal disease (GERD). However, the anti-secretory activity of H2RAs is reported to decrease during continuous administration, and this attenuation is referred to as tolerance. Several previous studies have demonstrated that the long-term therapeutic effect of H2RAs is low in patients with GERD. In contrast, H2RAs are reported to be fairly effective for the long-term prevention of recurrence in patients with peptic ulcer disease. The rate of infection with *Helicobacter pylori* differs markedly between patients with GERD and those with peptic ulcer disease. Therefore, it may be hypothesized that *H. pylori* infection prevents the occurrence of the tolerance phenomenon during long-term administration of H2RAs. This study was performed to clarify whether *H. pylori* infection affects the occurrence of the tolerance phenomenon during a 2-week period of H2RAs (famotidine and lafutidine) administration.

MATERIALS AND METHODS

The study subjects were 20 healthy male Japanese volunteers (mean age 38.1 years, range 31–52 years). Written informed consent was obtained from all the subjects before

starting the study, which was approved by the Ethics Committee of Shimane University.

All participants were examined using the urea breath test (UBT) to confirm the presence or absence of *H. pylori* infection. All subjects, placed on a standard diet, were examined five times by ambulatory 24-hour pH monitoring (from 08:00 hours on one day to the same time on the following day) before starting the study treatment, on the first and last days of a 15-day course of lafutidine (10 mg twice daily administration; UCB Japan Co. Ltd., Tokyo, Japan), and on the first and last days of a 15-day course of famotidine (20 mg twice daily administration; Yamanouchi Pharmaceutical Co. Ltd., Tokyo, Japan). The H2RAs were administered in a randomized order, and an interval of at least 2 weeks was allowed between the two treatment courses in order to make sure that there were no remaining effects from the previous H2RA.

The percentage of the time during which the intragastric pH was below 4.0, and the median pH values, were calculated for the daytime (06:30–22:30 hours) and nighttime periods. Plasma samples for the measurement of serum concentrations of lafutidine and famotidine were collected at 2 h after the morning dose on the first (the first pH-monitoring day), eighth and 15th (the final pH-monitoring day) drug administration days.

Statistical analysis of paired data was performed by using the Wilcoxon-signed rank test if the Friedman test showed a significant difference. The Mann–Whitney U test was also applied for comparison of non-paired data. Differences at $P < 0.05$ were considered to be statistically significant.

RESULTS AND DISCUSSION

Seven subjects were found to be infected by *H. pylori* and 13 subjects were not infected. There was no significant difference in age between the *H. pylori*-infected and non-infected subjects. Also, there was no statistically significant difference in plasma lafutidine and famotidine concentrations between *H. pylori*-negative and positive subjects at each measurement point.

In *H. pylori*-negative subjects, the percentages of intragastric pH<4.0 in the daytime without medication, on the 1st and 15th days of lafutidine administration, and on the 1st and 15th days of famotidine administration were 95.3%, 62.5% and 79.7% ($P<0.05$), and 72.0% and 80.4% (not significant: ns), respectively. The percentages of intragastric pH<4.0 at night without medication, on the 1st and 15th days of lafutidine administration, and on the 1st and 15th days of famotidine administration were 95.7%, 35.1% and 51.9% ($P<0.05$), and 41.4%

and 66.2% (P<0.05), respectively. After 2-week-long continuous administration, both H2RAs partially lost their acid-suppressing effect in the *H. pylori*-negative subjects and showed evidence of the tolerance phenomenon.

In *H. pylori*-positive subjects, the percentages of intragastric pH<4.0 in the daytime without medication, on the 1st and 15th days of lafutidine administration, and on the 1st and 15th days of famotidine administration were 70.2%, 27.9% and 18.2% (p<0.05), and 33.3% and 38.5% (ns), respectively. The percentages of intragastric pH<4.0 at night without medication, on the 1st and 15th days of lafutidine administration, and on the 1st and 15th days of famotidine administration were 27.7%, 7.9% and 8.9% (ns), and 11.6% and 12.0% (ns), respectively. No H2RAs tolerance phenomenon was observed during the 2 weeks of continuous administration in *H. pylori*-positive subjects.

In this study, we have clarified for the first time that *H. pylori* infection has a decisive effect on the occurrence of tolerance to the acid-suppressing effect of H2RAs. The precise mechanism whereby *H. pylori* infection prevents the occurrence of the tolerance phenomenon was not clarified. H2RAs suppress gastric acid secretion by competition with their specific receptors on gastric parietal cells. Therefore, the number of histamine H2 receptors on parietal cells is an important factor affecting the potency of H2RAs. An increased number of histamine H2 receptors on parietal cells leaves H2RA-unbound histamine H2 receptors on gastric parietal cells and increases the chance of secreted histamine stimulating acid secretion by binding to any remaining open H2 receptors. During long-term administration of H2RAs, the number of H2 receptors on parietal cells is reported to increase significantly. *H. pylori* infection is known to directly and indirectly influence the physiological functions of gastric parietal cells. Therefore, *H. pylori* may possibly affect the H2RAs-induced increase of histamine H2 receptors. *H. pylori*-induced gastric mucosal atrophy, which is demonstrated to reduce gastric acid secretion, may also correlate with the lack of tolerance to H2RAs in subjects with *H. pylori* infection. Further investigations need to focus on the temporal changes in the number of histamine H2 receptors on parietal cells of *H. pylori*-infected and uninfected individuals during long-term administration of H2RAs.

CONCLUSION

We have clarified for the first time that tolerance to the acid-suppressing effect of H2RAs is not observed in patients infected with *H. pylori* during 15-day administration of lafutidine and famotidine.