学 位 論 文 の 要 旨

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学 位 論 文 名	A Comparative Study of Intragastric Acidity During Post- breakfast and Pre-dinner Administration of Low-dose Proton Pump Inhibitors: A Randomized Three-way Crossover Study
発 表 雑 誌 名 （巻，初頁～終頁，年）	Alimentary Pharmacology and Therapeutics 24,1445-1451, 2006
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論 文 内 容 の 要 旨

INTRODUCTION

The efficacy of anti-secretory drugs for healing peptic ulcers and gastroesophageal reflux disease depends on the degree of their acid-suppressive effect. Proton pump inhibitors (PPIs) are potent and widely used therapeutic agents for the treatment of acid-related diseases. PPIs inhibit the function of the proton pump responsible for the terminal step of gastric acid secretion, and are the most effective medical treatment for patients with acid-related diseases. PPIs bind to the active proton pump of parietal cells that secrete gastric acid. In addition, the peak PPI plasma concentration is observed at 1–2 h after oral administration of the drug, and the absorption and bioavailability of PPIs are known to be markedly affected by food intake. Thus, the best timing of PPI dosing may be 1–2 h before dinner, as gastric acid secretion is considered to be maximally stimulated after food intake, and the largest meal volume is usually taken at dinner. However, it has not been fully clarified whether the efficacy of PPIs differs between post-breakfast and pre-dinner dosing. Therefore, in the present study, we compared the efficacy of low-dose PPIs between pre-dinner and post-breakfast administration.

MATERIALS AND METHODS

The study subjects were 20 healthy male Japanese volunteers (mean age 38.9 years, range: 26–58). Written informed consent was obtained from all subjects before starting the study, which was carried out in accordance with the Declaration of Helsinki, and with approval from the Ethics Committee of Shimane University. The study participants were divided randomly into two groups of 10, who were administered 15 mg of lansoprazole and 10 mg of rabeprazole, respectively. All participants were examined using the urea breath test to confirm the presence or absence of *Helicobacter pylori* infection. All subjects underwent ambulatory intragastric 24-h pH monitoring under three conditions: (i) without medication, (ii) on the seventh day of administration of 15 mg lansoprazole or 10 mg of rabeprazole, 30 min after breakfast, and (iii) on the eighth day of administration of 15 mg lansoprazole or 10 mg of rabeprazole, 60 min before dinner. The three pH-monitoring sessions were performed in a randomized order, and an interval of at least 2 weeks was allowed to wash out the effect of the previous PPI administration. All ambulatory pH monitoring was undertaken with the subjects on a standard diet. The percentage time during which the intragastric pH was more than 4.0 was calculated for the total 24-h period, and for the daytime (06:30– 22:30 hours) and night-time periods. 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 for comparison of non-paired data.

RESULTS AND DISCUSSION

Intragastric pH was elevated during PPI administration using both of the two dosing regimens. The percentage time during which intragastric pH was ≥4.0 was significantly higher during both the post-breakfast and the pre-dinner dosing regimens for each PPI than during no drug medication. There was no significant difference in the percentage time during which pH was ≥4.0 during 24 h between the post-breakfast and the pre-dinner administrations (56.6% vs.

55.8%; p=0.557), although the percentage time during which intragastric pH was ≥4.0 tended to be longer during the daytime for post-breakfast dosing than for pre-dinner dosing, and the percentage time during which intragastric pH was ≥4.0 at night tended to be longer for pre-dinner dosing than for post-breakfast dosing. In addition, there was no significant difference in the percentage time during which pH was ≥4.0 between post-breakfast and pre-dinner administration in both subjects with and without *H. pylori* infection. When the percentage time during which intragastric pH was ≥4.0 was compared between the subjects with and without *H. pylori* infection, the value was significantly higher in the former than in the latter subjects, not only during PPI administration but also without drug administration.

We hypothesized that pre-dinner administration of PPI might be more effective than post-breakfast dosing for control of gastric acid secretion. Pre-dinner administration of PPIs has two benefits: first, the timing of the highest plasma concentration is synchronized with the highest activation of the proton pump resulting from the meal, and secondly, as dinner is usually the largest meal of the day, stimulation of the proton pump and activation of PPIs are maximal. However, our results failed to demonstrate any superiority of pre-dinner PPI administration over post-breakfast administration for inhibition of gastric acid secretion after 1 week of continuous administration. Therefore, the timing of PPI administration relative to meals did not influence the efficacy of the drugs for control of gastric acid secretion after repeated dosing.

CONCLUSION

The timing of drug administration does not significantly influence the efficacy of low-dose PPIs.