

Effect of Rabeprazole (E3810), a Novel Proton Pump Inhibitor, on Intra-gastric pH in Healthy Volunteers

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HONGO, M., KIMPARA, T., MORIYAMA, S., OHARA, S., SONE, S., TAMURA, T., ASAKI, S. and TOYOTA, T. *Effect of Rabeprazole (E3810), a Novel Proton Pump Inhibitor, on Intra-gastric pH in Healthy Volunteers.* Tohoku J. Exp. Med., 1998, 186 (1), 43-50 — In this study, we examined the effect of rabeprazole (E3810), a novel proton pump inhibitor, on gastric acidity under physiological conditions in healthy volunteers using 24-hour intra-gastric pH monitoring. Twenty-four-hour intra-gastric pH monitoring was performed three times to seven subjects randomly assigned in a cross over fashion to one of the following groups; without drug administration (basal), and with 10 mg or 20 mg of rabeprazole for four days. The median pH for 24 hours was 2.15 in the basal study, while the corresponding median pH were 5.05 and 5.90 after treatment with 10 mg and 20 mg of rabeprazole, respectively. Significant differences in the median pH were observed between the basal study and that after administration of the 10 mg and 20 mg doses of rabeprazole. The cumulative percentage of pH readings above the threshold pH 4 value, was 34.1% in the basal study, and 72.6% and 78.3% after treatment with 10 mg and 20 mg doses of rabeprazole, respectively. This result indicates that the efficacy of rabeprazole allows for substantial control of gastric acidity with once-daily dosing, and that both the 10 mg and 20 mg doses result in potent inhibition of gastric acid secretion. — proton pump inhibitor; rabeprazole; antisecretory effect; intra-gastric pH; pH monitoring © 1998 Tohoku University Medical Press

Investigators have recently attached more importance to *Helicobacter pylori* with regard to the recurrence of peptic ulcers. However, the suppression of gastric acid is still important in the treatment of peptic ulcers irrespective of the presence of *H. pylori* infection. It is particularly important in the treatment of

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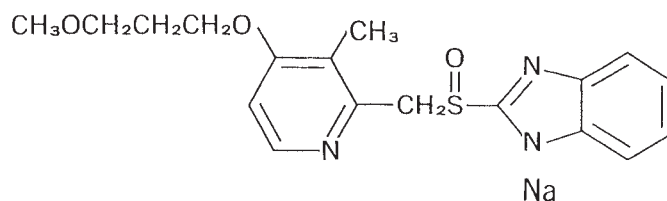


Fig. 1. Chemical structure of rabeprazole.

duodenal ulcers, which are accompanied by excessive gastric acid secretion.

Previous studies have shown that the enzyme H^+ , K^+ -ATPase, a proton pump, is involved in the final stage of gastric acid secretion by gastric parietal cells (Ganser and Forte 1973). This discovery resulted in the development of proton pump inhibitors that block gastric acid secretion by direct suppression of the enzyme activity. The proton pump inhibitors available in Japan include omeprazole and lansoprazole, both of which have been reported to potently inhibit gastric acid secretion and to have a higher therapeutic efficacy in the treatment of peptic ulcers than histamine H_2 -receptor antagonists (Clissold and Campoli-Richards 1986; Barradell et al. 1992).

Rabeprazole (E3810) is a novel proton pump inhibitor, the chemical structure of which differs from those of omeprazole and lansoprazole due to substituents on the pyridine and benzimidazole rings (Fig. 1) (Morii et al. 1990). In this study, we examined the effect of rabeprazole on gastric acidity under physiological conditions in healthy volunteers using 24-hour intragastric pH monitoring.

MATERIALS AND METHODS

Subjects

Seven healthy volunteers participated in this study. Their mean age was 20 years (range 19–22). Physical examinations and laboratory screening tests revealed no abnormalities. Prior to enrollment in the study, written informed consent was obtained from each subject.

Drug

Enteric-coated tablets each containing 10 mg of rabeprazole (Eisai Co., Ltd., Tokyo) were used.

Study design

Twenty-four-hour intragastric pH monitoring for four days was performed three times on the subjects assigned in a cross over fashion to one of the following groups; without drug administration (basal), and with 10 mg or 20 mg of rabeprazole. Drugs were administered once a day after breakfast. Each monitoring session performed on the 4th day of rabeprazole administration when it is given starting at 0700 hour. Each session was separated five days or more of interval to washout the previous medication. Meals were provided at 0800, 1200 and 1900

hour. Extra snacks, beverages and smoking were prohibited during 24-hour intra-gastric pH monitoring.

Intra-gastric pH monitoring

Intra-gastric pH was monitored using miniature glass electrodes (CM151B, Chemical Kiki Co., Tokyo) connected to a portable pH recorder (CR5501, Chemical Kiki Co.). This device records pH data every 10 seconds and stores it in a built-in solid-state memory (Hongo et al. 1988). Data were then transferred to floppy disks and analyzed by a computer. The electrode was calibrated at 25°C with commercially available buffers (pH 1.68 and 6.86, Wako Pure Chemical Industries, Ltd., Osaka) at the start and at the end of each period of 24-hour intra-gastric pH monitoring and the readings were adjusted for a temperature at 37°C. Recording was repeated if the pH electrode drift was more than 1 pH unit. Electrodes were intranasally inserted into the stomach, and the tips of the electrodes were positioned at the middle of the gastric corpus under fluoroscopic control. A reference electrode was placed on the right anterior chest wall.

Safety evaluation

Routine laboratory tests were performed on the morning of each intra-gastric pH monitoring day. The tests performed included plasma urea and creatinine, blood cell counts, hepatic enzymes, and urinalysis. If any adverse signs or symptoms occurred during drug administration, a follow-up evaluation was performed until the symptoms disappeared and the laboratory values had returned within the normal range.

Analysis

The mean 5-minute pH values for each subject for the 24-hour pH recording period were used for evaluation, and a nonparametric method was used for statistical analysis. Based on the raw data, the individual median 24-hour pH values for each of the three recording periods in the seven subjects were calculated. The median pH for 24 hours of the basal study and those with medications were compared. To support these data, pH 4 holding times (time with pH above 4 in 24 hours) of the basal study and those with medications were compared, and pH holding time curves (the cumulative percentage of pH readings at pH values from 1 to 6) were also constructed (Fimmel et al. 1985). Statistical analysis was made using Wilcoxon's signed rank test (Walt 1986; Emde et al. 1987), and the correction for multiplicity was made using Bonferroni's method, and *p* values less than 0.0167 were considered to be statistically significant.

RESULTS

Median 24-hour pH values

The median pH for 24 hours was 2.15 in the basal study, while the correspond-

TABLE 1. Median 24-hour pH values in the basal study and after treatment with 10 mg and 20 mg of rabeprazole

| Subject number | Basal | Rabeprazole 10 mg | Rabeprazole 20 mg |
|-----------------------------|-------|-------------------------------------|-------------------------------------|
| 1 | 4.60 | 6.10 | 6.40 |
| 2 | 1.80 | 4.20 | 5.30 |
| 3 | 5.05 | 6.80 | 5.90 |
| 4 | 1.50 | 5.00 | 6.10 |
| 5 | 2.15 | 3.20 | 7.00 |
| 6 | 2.30 | 5.05 | 4.00 |
| 7 | 1.50 | 6.10 | 5.90 |
| Median | 2.15 | 5.05 | 5.90 |
| Wilcoxon's signed rank test | | $p = 0.0156^a$ (Basal vs. 10 mg) | $p = 0.0156^a$ (Basal vs. 20 mg) |
| | | $p = 0.3438$ (10 mg vs. 20 mg) | |

Wilcoxon's signed rank test: The correction for multiplicity was made by Bonferroni's method. a: p values less than 0.0167 were considered to be statistically significant.

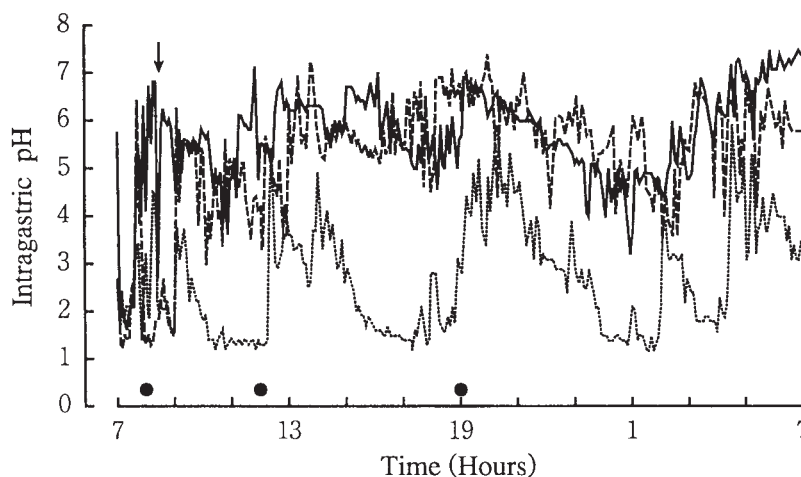


Fig. 2. 24-Hour median intragastric pH profiles.

The intragastric pH monitoring was performed without drug administration (basal) and with 10 mg or 20 mg of rabeprazole for four days. -----, basal; - -, rabeprazole 10 mg; —, rabeprazole 20 mg; ↓, drug administration; ●, meal.

ing median pH were 5.05 and 5.90 after treatment with 10 mg and 20 mg of rabeprazole, respectively (Table 1). The median pH for 24 hours after administration of both 10 mg and 20 mg rabeprazole markedly elevated compared with the basal study, and significant differences were observed between the basal study and that after drug administration. However, no significant difference was observed between the 10 mg and 20 mg dose of rabeprazole.

The 24-hour median intragastric pH profiles of the basal study, and the 10 mg

TABLE 2. *pH 4 Holding times in the basal study and after treatment with 10 mg and 20 mg of rabeprazole*

| Subject number | Basal | Rabeprazole 10 mg | Rabeprazole 20 mg |
|-----------------------------|-------|-------------------------------------|-------------------------------------|
| 1 | 830 | 1170 | 1005 |
| 2 | 310 | 805 | 1005 |
| 3 | 1185 | 1410 | 1425 |
| 4 | 155 | 945 | 1115 |
| 5 | 505 | 615 | 1375 |
| 6 | 315 | 1105 | 735 |
| 7 | 135 | 1265 | 1235 |
| Mean | 491 | 1045 | 1128 |
| Wilcoxon's signed rank test | | $p = 0.0156^a$ (Basal vs. 10 mg) | $p = 0.0156^a$ (Basal vs. 20 mg) |
| | | $p = 0.6875$ (10 mg vs. 20 mg) | |

Wilcoxon's signed rank test: The correction for multiplicity was made by Bonferroni's method. a: p values less than 0.0167 were considered to be statistically significant.

and 20 mg dose of rabeprazole are shown in Fig. 2, respectively. Both doses of rabeprazole resulted in a constant increase in the median intra-gastric pH compared to the basal study throughout the monitoring period. The increase in the median pH with rabeprazole was small during the period of 0700–1300, both with 10 mg and 20 mg doses.

pH 4 Holding time

The mean pH 4 holding time was 491 minutes in the basal study, and the corresponding times for the 10 mg and 20 mg dose were 1045 minutes and 1128 minutes, respectively (Table 2). Significant differences were observed between the basal study and that after drug administration. However, no significant difference was observed between the 10 mg and 20 mg dose of rabeprazole.

pH Holding time curves

The pH holding time curves, based on the cumulative percentage of pH readings above each pH value, was shifted to the right by the administration of both the 10 mg and 20 mg doses of rabeprazole (Fig. 3).

The percentage of readings above pH 4 in 24 hours was 34.1% in the basal study, and 72.6% and 78.3% after treatment with 10 mg and 20 mg of rabeprazole, respectively. And the percentage of readings above pH 3 were 45.5%, 79.7% and 83.3% for the basal study, and the 10 mg and 20 mg doses, respectively.

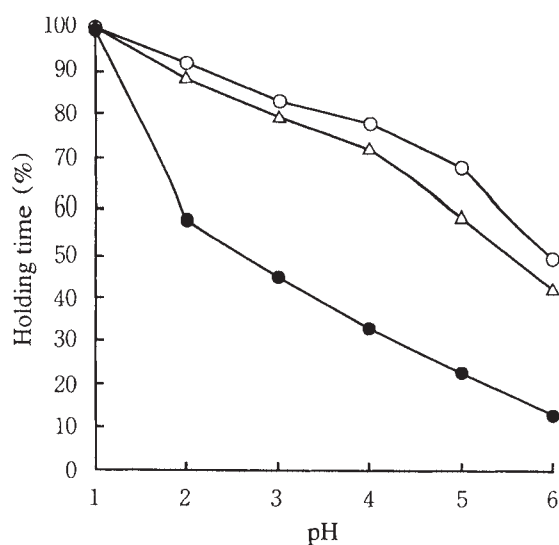


Fig. 3. pH Holding time curves in the basal study and after treatment with 10 mg and 20 mg of rabeprazole.

The holding time was based on the cumulative percentage of pH readings above each pH value. ●, basal; △, rabeprazole 10 mg; ○, rabeprazole 20 mg.

Drug safety

Rabeprazole administration produced no detectable alterations in the laboratory tests, and no subjective symptoms were observed during the course of the study.

DISCUSSION

The use of intragastric pH monitoring provides long-term information on the intragastric environment under physiological conditions without aspirating gastric juice, although the pH information obtained is limited to the site of the monitor. The collection of gastric juice is also useful in analyzing the dynamics of gastric acid secretion. However, this method forces uncomfortableness to subjects and therefore does not allow long-term monitoring of intragastric acidity. It also has the potential disadvantage of the removal of all the gastric juice.

We monitored intragastric pH using a portable pH recorder with a miniature glass electrode (Hongo et al. 1988, 1992; Ohara et al. 1988). The results of our studies indicate the importance of 24 hours of monitoring under physiological conditions, because it may change with food and brain activity such as sleep, also it reflects not only secretory state but also motility state of the stomach. In our previous report on the effects of famotidine, a histamine H₂-receptor antagonist, and omeprazole (after 4 days of medication) on intragastric acidity in healthy subjects (Ohara et al. 1988), the 2 drugs had different effects on gastric acidity: Famotidine (20 mg twice a day) selectively increased the nocturnal pH, while the diurnal pH slightly increased, and omeprazole (20 mg once a day) markedly increased both the nocturnal and diurnal pH.

In this study, we monitored the effect of rabeprazole, a novel proton pump

inhibitor, on gastric acidity under physiological conditions in healthy volunteers using 24-hour pH monitoring. Ten milligram and 20 mg doses were selected as administration dosages of rabeprazole, because both dosages of the drug have been used in the treatment of peptic ulcers. Rabeprazole was administered after breakfast, as a previous pharmacokinetic study in healthy volunteers had shown that this was the optimal dosing time (Yasuda et al. 1994). Twenty-four-hour intra-gastric pH monitoring was performed at the 4th day of administration of rabeprazole, following to our previous study (Ohara et al. 1988). Each monitoring session was separated five days or more of interval to washout the previous medication, as the suppression of gastric acid secretion by rabeprazole has been shown to last for 48 hours (Fujisaki et al. 1991).

The median pH for 24 hours after administration of rabeprazole were significantly increased compared with the basal study (Table 1). In the 24-hour median intra-gastric pH profiles (Fig. 2), the administration of rabeprazole resulted in a constant increase in the median intra-gastric pH when compared with the basal study throughout the monitoring period. The increase in the median intra-gastric pH with rabeprazole was small during the period of 0700–1300, despite the agents were given in the morning. In previous experiments in rats and dogs, recovery of gastric acid secretion was observed 24 hours after the administration of rabeprazole (Fujisaki et al. 1991; Tomiyama et al. 1994). The peak plasma concentration of rabeprazole when administered after meals occurs at 3.8 hours to 5.1 hours after administration (Yasuda et al. 1994), which may refuse parietal cells to bind the agent blocking the activity of a proton pump with some time of delay to show its most potent effect.

To support the results obtained for the median 24-hour pH values, the pH 4 holding times were calculated (Table 2), the pH value of 4 was selected as peptic activity is markedly decreased at this pH (Piper and Fenton 1965). The mean pH 4 holding times after administration of rabeprazole were significantly longer than in the basal holding time.

In this study, the administration of both 10 mg and 20 mg doses of rabeprazole resulted in a constant increase in intra-gastric pH. This result indicates that the efficacy of rabeprazole substantial by control gastric acidity with once-daily dosing, and that both the 10 mg and 20 mg doses result in potent inhibition of gastric acid secretion.

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