

Early effect on intragastric pH of oral administration of rabeprazole with mosapride compared with rabeprazole alone

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Abstract

Background An ideal medication for acid-related diseases would offer prompt stopping of blood flow as well as efficient symptom resolution. The aim of this study was to investigate the gastric acid suppression potency of a single oral dose of rabeprazole alone, compared with administration of rabeprazole plus mosapride.

Methods Twelve male volunteers, *Helicobacter pylori* (*H. pylori*)-negative, participated in this randomized, three-way crossover study. After a single oral administration of rabeprazole, rabeprazole with mosapride, or rabeprazole administered 1 h after mosapride, we monitored their intragastric pH constantly for 6 h. A 7-day washout period was allowed between each administration.

Results The median 6-h intragastric pH after the administration of rabeprazole 1 h after mosapride was 4.41 ± 1.22 (mean \pm s.d.), significantly higher than after rabeprazole alone 3.45 ± 1.33 , $P=0.0376$). There was no significant difference between the median 6-h pH after the administration of rabeprazole plus mosapride and that after rabeprazole alone (3.81 ± 0.98 vs. 3.45 ± 1.33 , respectively; $P=0.0927$).

Conclusion An oral dose of rabeprazole administered 1 h after mosapride increased the intragastric pH more rapidly than rabeprazole alone, in healthy, male, *H. pylori*-negative volunteers.

Keywords Intragastric acidity, rabeprazole, mosapride

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Introduction

Recently, the number of Japanese patients with gastroesophageal reflux disease (GERD) has been increasing, because of changes in eating habits and a decrease in infections with *Helicobacter pylori* (*H. pylori*). Heartburn is a common problem in Japan and it interferes with daily life. Proton pump

inhibitors (PPIs) are usually used globally for the treatment of acid related diseases such as gastric and duodenal ulcers, and GERD, and as a component of eradication therapy for *H. pylori* [1-4]. Most GERD patients are controlled with standard PPIs, but about 10-40% of patients continue to have heartburn [5].

On-demand therapy for GERD patients is cost-effective and safe, in the form of one-dose PPIs taken when symptoms occurs [6,7]. An ideal medication for GERD patients should have the ability to act rapidly and achieve efficient symptom resolution. Multiple medicines, including antacids, PPIs, histamine 2 receptor antagonists (H2RAs), and mosapride citrate (mosapride) are currently used for GERD patients [8]. We showed previously that the oral administration of H2RA with mosapride increased the intragastric pH more rapidly than H2RA alone [9]. In addition, our previous study showed that omeprazole orally administered 1 h after mosapride increased the intragastric pH more rapidly than omeprazole alone [10]. However, no crossover comparisons have been reported of the acid-suppressive effect of oral PPI with mosapride versus PPI alone. We chose rabeprazole and mosapride, because we usually use these drugs for GERD patients in Japan. The dosage in this study was within the usual range in Japan. We designed this

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Conflict of Interest: None

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three-way crossover study to compare the acute efficacies of rabeprazole alone, rabeprazole with mosapride, and rabeprazole administered 1 h after mosapride on intragastric pH.

Patients and methods

Subjects

Twelve male, *H. pylori*-negative volunteers participated in this randomized, three-way crossover study. Their mean age was 23.2 years (range 20-35 years) and they were not using acid suppressive medications, PPIs, and/or H2RAs, and/or mosapride. All volunteers were negative for anti-*H. pylori* immunoglobulin G antibodies according to an E plate EIKEN *H. pylori* antibody test (Eikenkagaku Inc., Tochigi, Japan).

Study protocol and pH-metry

All volunteers followed three oral medication protocols, as follows: rabeprazole (20 mg; Pariet®, Eisai Co. Ltd., Tokyo, Japan), rabeprazole with mosapride (5 mg; Gasmotin®, Dainippon Sumitomo Pharmaceutical Co. Ltd., Osaka, Japan), or rabeprazole administered 1 h after mosapride. After each administration, we monitored their intragastric pH constantly for 6 h. A washout period of at least 7 days was allowed between successive administrations. The volunteers fasted overnight (at least 8 h) before the administration of medicine or medicines, and for 6 h after their administration; each protocol was performed in the morning.

Intragastric pH was measured using a portable pH meter connected to an antimony pH electrode (Chemical Instrument Co. Ltd., Tokyo, Japan). Under local anesthesia, the pH electrode was inserted transnasally and positioned in the upper part of the gastric body. Measurements were made at 10-sec intervals. Before each protocol, we calibrated the pH electrode using standard buffer solutions at pH 4.01 and 6.86. We analyzed the pH data using commercially available software (Chemical Instrument Co. Ltd., Tokyo, Japan). During the 6 h after the administration of each medicine, we measured the intragastric median pH, as well as the percentages of time with intragastric pH above 2, 3, 3.5, 4, 5, 6, and 7.

CYP2C19 genotyping and status

DNA was obtained from each volunteer's white blood cells. Genotyping, using the polymerase chain reaction-restriction fragment length polymorphism method, was performed at the laboratories of SRL Inc. (Tokyo, Japan) to identify the wild-type *CYP2C19* and two point-mutated alleles; the wild-type allele has a G at position 636 in exon 4 and a G at position 689 in exon 5 [11]. One of the mutated alleles (m1 allele) has an A at position 689 in exon 5, and the other mutated allele (m2 allele) has an A at position 636 in exon 4 [12,13].

The prevalence of the *CYP2C19* genotype varies among different races. The prevalence of *CYP2C19* EM is 27-35% in Japanese, 56-69% in Caucasians, 81% in African-Americans, 38% in Chinese and 13% in Koreans [11].

Statistical analysis

Wilcoxon's signed-rank test was used as appropriate for statistical analysis. All P-values were two-sided; $P < 0.05$ was taken to indicate statistical significance. We performed all statistical analyses using StatView (SAS Institute, Cary, NC, USA).

Ethics

Approval for this study was given in advance by the Ethics Committee of Yokohama City University School of Medicine. This study was conducted in accordance with the Declaration of Helsinki. Written informed consent to participation was obtained from all volunteers before the start of this study. We registered this study protocol at the UMIN Clinical Trials Registry (UMIN-CTR; ID=UMIN000002082).

Results

All volunteers completed this study and there were no adverse events.

Intragastric pH and holding times (%) of various pH levels

The median 6-h intragastric pH following the administration of rabeprazole 1 h after mosapride was 4.41 ± 1.22 (mean \pm s.d.), significantly higher than that after rabeprazole alone (3.45 ± 1.33 , $P = 0.0376$). However, there was no significant difference in the median 6-h pH for rabeprazole plus mosapride 3.81 ± 0.98 versus rabeprazole alone ($P = 0.0927$), or versus rabeprazole administered 1 h after mosapride ($P = 0.116$) (Fig. 1).

The intragastric median pH following the administration of rabeprazole 1 h after mosapride was higher than that following rabeprazole alone during the 0- to 4-, 0- to 5- and 0- to 6-h intervals (4.35 ± 0.83 vs. 3.30 ± 0.78 , $P = 0.0284$; 4.37 ± 1.07 vs. 3.47 ± 0.89 , $P = 0.0393$; 4.41 ± 1.22 vs. 3.45 ± 1.33 , $P = 0.0376$, respectively). There was no significant difference for the 0- to 1-, 0- to 2-, and 0- to 3-h intervals. No significant differences were observed between the average pH following the administration of rabeprazole plus mosapride and the administration of rabeprazole alone during the 0- to 1-, 0- to 2-, 0- to 3-, 0- to 4-, 0- to 5- and 0- to 6-h study periods. Nor were any significant differences observed between the average pH following the administration of rabeprazole plus mosapride and rabeprazole 1 h after mosapride during the 0- to 1-, 0- to 2-, 0- to 3-, 0- to 4-, 0- to 5- and 0- to 6-h intervals (Fig. 2).

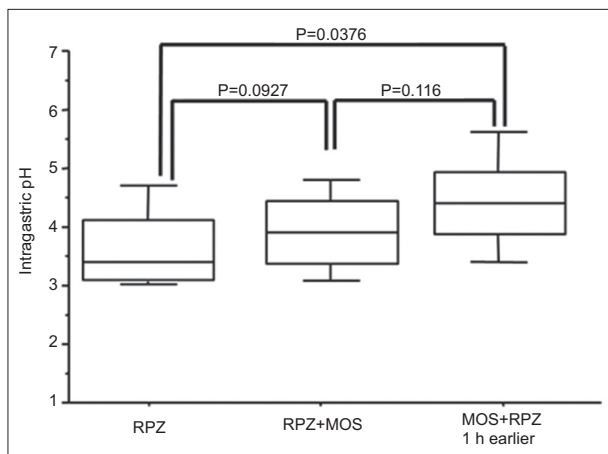


Figure 1 The average pH during the first 6 h was higher following the administration of 20 mg rabeprazole 1 h after the administration of 5 mg mosapride than following 20 mg rabeprazole alone

* $P=0.0376$ by the Wilcoxon signed-rank test

RPZ, Rabeprazole; MOS, Mosapride

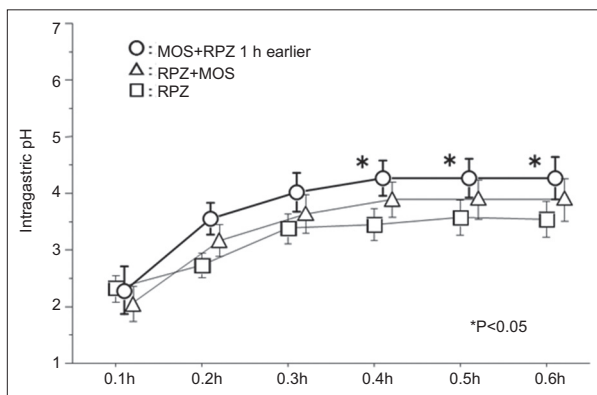


Figure 2 Administration of 20 mg rabeprazole 1 h after 5 mg mosapride resulted in a higher average pH compared to 20 mg rabeprazole alone in the 0- to 4-, 0- to 5- and 0- to 6-h study periods following administration. Squares (20 mg rabeprazole administered 1 h after 5 mg mosapride), triangles (20 mg rabeprazole with 5 mg mosapride) and circles (20 mg rabeprazole), mean values; vertical lines, standard deviations (SD); horizontal lines, \pm SD

* $P=0.0284$, 0.0393 and 0.0343 by the Wilcoxon signed-rank

RPZ, Rabeprazole; MOS, Mosapride

During the 6-h study, the administration of rabeprazole 1 h after mosapride provided longer durations of pH >3.5, 4, 5 and 6 compared with rabeprazole alone (median: $56.4 \pm 8.64\%$ vs. $36.8 \pm 9.98\%$, $P=0.0461$; $51.6 \pm 8.64\%$ vs. $29.9 \pm 6.74\%$, $P=0.0412$; $42.5 \pm 6.85\%$ vs. $19.6 \pm 3.11\%$, $P=0.0347$; $38.6 \pm 5.36\%$ vs. $12.8 \pm 2.89\%$, $P=0.0449$, respectively). No such significant differences were observed between the pH durations after the administration of rabeprazole plus mosapride and those after the administration of rabeprazole alone. Nor was any such significant difference seen between the pH durations following the administration of rabeprazole with mosapride and rabeprazole 1 h after mosapride (Fig. 3).

CYP2C19 genotype

CYP2C19 has the following alleles: wild-type, CYP2C19*1, CYP2C19*2 (G681A in exon 5), and CYP2C19*3 (G636A in exon 4). The volunteers were classified into three genotype groups by the presence of m1 and m2: extensive metabolizer (EM: CYP2C19*1/*1), intermediate metabolizer (IM: CYP2C19*1/*2 and *1/*3), and poor metabolizer (PM: CYP2C19*2/*2, *2/*3, *3/*3).

CYP2C19 is a major enzyme related to the metabolism of PPIs. Therefore, differences in the plasma concentration of PPI are observed among CYP2C19 genotypes and the degree of inhibition of acid secretion is influenced by these differences. In this study, 4 subjects were genotyped as EM, 5 subjects were IM and the other 3 subjects were PM (Table 1). No significant differences among EM, IM, and PM were observed with regard to pH or pH holding time.

Discussion

In this study, we examined intra-gastric pH transition during the early post-administration phase after a single oral administration of rabeprazole alone, rabeprazole plus mosapride, and rabeprazole administered 1 h after mosapride in *H. pylori*-negative volunteers. The intra-gastric pH in *H. pylori*-positive subjects is higher than that in *H. pylori*-negative volunteers, because gastric acid decreases in *H. pylori*-positive subjects. Hence, we chose *H. pylori*-negative volunteers for this study.

Mosapride is a novel gastrokinetic agent that enhances gastrointestinal motility by stimulating the serotonin receptor. In conscious dogs, mosapride enhances upper gastrointestinal motor activity in the postprandial state [14]. After oral administration in rats, mosapride is absorbed in the small intestine [15].

In healthy adults, mosapride accelerates gastric emptying [16]. This study suggests that mosapride might accelerate rabeprazole absorption in the small intestine by accelerating gastric emptying. For example, capsule endoscopy has demonstrated that mosapride speeds up gastric emptying and increases the completion rates of a small bowel examination in patients [17]. In the mosapride group, the gastric emptying time was decreased, suggesting that mosapride shortens the gastric emptying time. We often use mosapride with oral intestinal lavage solution, polyethylene glycol-electrolyte lavage solution (PEG-ELS) as preparation for a barium enema examination. PEG-ELS with mosapride is more effective than PEG-ELS alone (the modified Brown's method), commonly used in Japan [18]. Moreover, mosapride reduces gastric emptying time and gastroesophageal reflux by improving gastrointestinal motility [19]. Mosapride influences the pharmacokinetics of rabeprazole. The use of mosapride resulted in significant increases in the mean C(max) and mean area under the curve of rabeprazole [20].

There are multiple factors related to the exacerbation of GERD. Acid reflux from the stomach to the esophagus is understood as the major reason for GERD. PPIs have a potent, long-term ability to suppress gastric acid, so PPIs are essential medicine for GERD [21] management. In contrast, the short-term, temporary gastric acid reflux is mainly attributed to the mild GERD transient heartburn. Water and H2RAs increase the intragastric pH immediately, whereas PPIs increase it slowly [22]. However, PPIs have a more prolonged effect than H2RAs [3]. Consequently, for the resolution of heartburn symptoms, the rapid suppression of gastric acid secretion is one of the most important factors [23]. Because omeprazole with mosapride increases the intragastric pH immediately [10], it was naturally recognized as a useful on-demand therapy for

patients with mild GERD. Rabeprazole with mosapride might accelerate the onset of action; it might be more suitable for on-demand therapy than rabeprazole alone. Moreover, fixed rabeprazole plus mosapride combination therapy might be more useful than rabeprazole alone.

If mosapride accelerates the absorption of rabeprazole that raises the question why was the gastric pH not higher during the 0- to 1-, 0- to 2-, or 0- to 3-h periods (Fig. 2)? We suspect that mosapride has a less strong and less rapid effect during the earlier phases, otherwise we might have observed an accelerated gastric emptying during the above-mentioned early periods. The T_{max} is 0.8 ± 0.1 (h), the C_{max} is 30.7 ± 2.7 ng/mL, and the $T_{1/2}$ is 2.0 ± 0.2 h after oral administration of 5 mg mosapride.

Intragastric pH did not increase during the 0- to 4- and 0- to 5-h study periods (Fig. 2). What was the reason for this transient lack of increase in intragastric pH while using a PPI? Because PPIs can block only activated proton pumps, the blood concentration of rabeprazole does not directly reflect intragastric pH. Our previous report showed that, after administration of a PPI, the increase in intragastric pH value exhibited some up and down fluctuations, whereas after the administration of H2RA, the intragastric pH value consistently increased [23-25]. This is because, after repeated intravenous or

Table 1 Patient characteristics of CYP2C19 genotype

No	Age	Height	Weight	CYP2C19	<i>H. pylori</i>
1	35	179	70	EM	Negative
2	27	170	80	IM	Negative
3	20	175	60	IM	Negative
4	21	173	58	EM	Negative
5	22	180	75	PM	Negative
6	20	168	63	PM	Negative
7	22	175	73	EM	Negative
8	24	175	69	EM	Negative
9	20	169	59	IM	Negative
10	21	175	88	IM	Negative
11	26	182	73	PM	Negative
12	20	174	68	IM	Negative

H. pylori, *Helicobacter pylori*

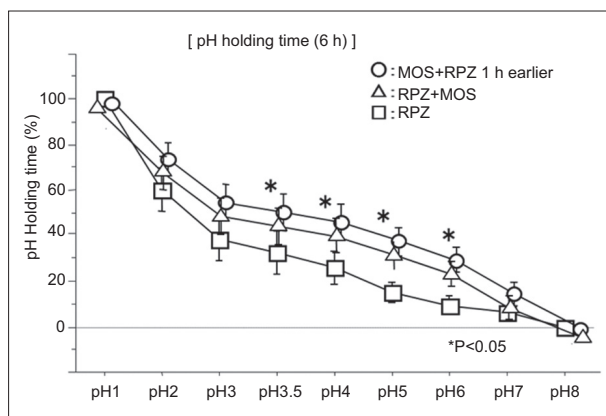


Figure 3 During the 6-h study period, 20 mg rabeprazole administered 1 h after 5 mg mosapride resulted in longer durations of pH >3.5, 4, 5 and 6 compared to 20 mg rabeprazole alone. Squares (20 mg rabeprazole administered 1 h after 5 mg mosapride), triangles (20 mg rabeprazole with 5 mg mosapride) and circles (20 mg rabeprazole), mean values; vertical lines, standard deviations (SD); horizontal lines, \pm SD

* $P=0.0461, 0.0412, 0.0347$ and 0.0449 by the Wilcoxon signed-rank test
RPZ, Rabeprazole; MOS, Mosapride

Summary Box

What is already known:

- Oral administration of histamine 2 receptor antagonists (H2RAs) plus mosapride citrate increases the intragastric pH more rapidly than H2RA alone
- Omeprazole administered 1 h after mosapride increases the intragastric pH more rapidly than omeprazole alone
- No study has yet examined whether administration of a proton pump inhibitor (PPI) plus mosapride might also produce a more rapid increase in intragastric pH than a PPI alone

What the new findings are:

- The average intragastric pH of healthy male subjects in the 6 h following the administration of 20 mg rabeprazole 1 h after the ingestion of 5 mg mosapride was significantly higher than that after the administration of 20 mg rabeprazole alone
- In contrast, no significant difference in the average pH was found when rabeprazole was administered simultaneously with mosapride and compared with rabeprazole alone
- Oral administration of 20 mg rabeprazole preceded by 5 mg mosapride tablets might be suitable for the on-demand treatment of patients with mild GERD

oral administration of PPIs, the antisecretory activity increases progressively and it takes about 5 days to achieve a steady state. Nakamura reported that H2RAs were bound uniformly to parietal cells in the stomach, whereas PPIs only accumulated on young activated parietal cells and other proton pumps were quickly activated. Thus, in the early period after the medicine, we found a slower onset of antisecretory action with PPIs than with H2RAs [26].

Our study has a number of limitations. First, the short (6-h) study term might be insufficient to determine the end effect of both rabeprazole and mosapride on intragastric pH. Second, the data were collected from healthy volunteers and not from GERD patients in whom on-demand therapy might be insufficient. Further studies might be necessary to overcome these limitations.

An ideal medication for acid-related diseases should offer both a rapid action to promote the stopping of blood flow and the efficient achievement of symptom resolution. According to our results, we conclude that rabeprazole administered 1 h after mosapride produced an increase in intragastric pH more rapidly than rabeprazole alone in healthy, male, *H. pylori*-negative volunteers. Although the clinical implications of our results are unclear, our findings suggest that oral administration of rabeprazole preceded by mosapride might be suitable for the on-demand treatment of mild GERD. To evaluate the effects on GERD patients, further studies might be necessary.

In conclusion, an oral dose of rabeprazole administered 1 h after mosapride increased the intragastric pH more rapidly than rabeprazole alone in healthy, male, *H. pylori*-negative volunteers.

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