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Low-dose ramosetron accelerates gastric emptying in the early phase: A crossover study in healthy volunteers using a continuous real-time 13C breath test (BreathID System)

STOMACH

Sho Inoue[1], Yasunari Sakamoto[2], Yusuke Sekino[2], Takashi Nonaka[2], Hiroshi Iida[2], Hiroki Endo[2], Tomoko Koide[2], Hirokazu Takahashi[2], Shin Maeda[2], Atsushi Nakajima[2], Eiji Gotoh[1], Masahiko Inamori[2,3]

[1]Department of Medical Education, Yokohama City University Faculty of Medicine, Yokohama, Japan
[2]Gastroenterology Division, Yokohama City University Hospital, Yokohama, Japan
[3]Office of Postgraduate Medical Education, Yokohama City University Hospital, Yokohama, Japan

Original Article

ABSTRACT

Background/Aims: The aim of this study was to determine the correlation between low-dose ramosetron pre-treatment and gastric emptying using a novel, non-invasive technique for measuring gastric emptying, namely, the continuous real-time 13C breath test (BreathID system: Exalenz Bioscience Ltd., Israel).

Materials and Methods: Twelve healthy male volunteers participated in this randomized two-way crossover study. The subjects fasted overnight and were randomly assigned to receive the test meal (200 kcal per 200 mL) after an hour pre-treatment with 5 μg ramosetron or the test meal alone. Gastric emptying was monitored for 4 hours after administration of the test meal with the 13C-acetic acid breath test performed continuously using the BreathID system. Using Oridion Research Software (β version), T 1/2, T lag, GEC and the regression-estimated constants (β and κ) were calculated. The differences in the parameters measured at two time-points were analyzed using Wilcoxon's signed-rank test.

Results: There was a significant difference in the calculated parameter β. No significant differences in the calculated parameters T 1/2, T lag, GEC or κ were observed between the test meal with ramosetron group and the test meal alone group.

Conclusion: This study showed that ramosetron pre-treatment enhances the early gastric emptying of liquid nutrients.

Keywords: Ramosetron, gastric emptying, breath test

INTRODUCTION

5-Hydroxytryptamine (5-HT) is present in the gastrointestinal tract, and it is mainly localized in the enterochromaffin (EC) cells of the mucosa (1). 5-HT mediates various physiological and pharmacological actions of the gastrointestinal system through the activation of four types of 5-HT receptors (2-4). Among them, 5-HT3 receptors are widely distributed in the enteric nervous system (5) and play important roles in the regulation of gastrointestinal motility (2,6-8). In fact, the potent and highly selective 5-HT3 receptor antagonist ondansetron accelerates gastric emptying (9,10) and inhibits cisplatin-induced emesis in animals and humans (10-14).

Some studies (15,16) have revealed an association between a stressful experience and disturbances in bowel function, indicating that gut function is affected by various stresses. In humans, stress commonly results in gastrointestinal disorders, such as irritable bowel syndrome (IBS) (17,18), in association with changes in gastrointestinal motility (15) and digestive transit (16). Recently, it was reported (19) that the selective 5-HT receptor antagonists ramosetron and granisetron inhibit restraint stress-induced defecation in rats, suggesting that endogenous 5-HT mediates stress-induced changes in bowel function through 5-HT3 receptor.

If ramosetron intake affects human gastric emptying, we would expect an antiemetic effect by oral intake. Therefore, we studied the effect of ramosetron on gastric emptying.

Address for Correspondence: Masahiko Inamori, Yokohama City University Hospital, Office of Postgraduate Medical Education, Yokohama, Japan
E-mail: inamorim@med.yokohama-cu.ac.jp
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MATERIALS AND METHODS

Subjects

The subjects included twelve asymptomatic male volunteers. None of the volunteers had a history of gastrointestinal disease or abdominal surgery, none were habitual drinkers and all of them were non-smokers. None of the subjects were on any routine medication at the time of the study.

^{13}C-acetic acid breath test

Twelve subjects participated in this randomized two-way crossover study. The two tests were conducted as follows: A, the subjects were assigned to receive a test meal one hour after taking a ramosetron 5μg tablet; B: the subjects only took a test meal. The two test were separated by a washout period of at least 7 days. In both of the experiments, the tests were started after the patients had fasted overnight (at least 8 hours), and the breath test was performed while the subjects were seated for 4 hours (20-29).

The subjects participating in experiment A were asked to intake ramosetron 5 μg tablet before the meal intake. The test meal was a 200 kcal/200 mL liquid meal (Racol with milk flavor, Otsuka Pharmaceutical, Tokyo, Japan) containing 100 mg of ^{13}C-acetic acid (Cambridge Isotope Laboratories, Boston, MA, USA), which the patients were requested to consume within 5 min. Subjects participating in experiment B took the breath test after meal intake. Breath samples were continuously collected via a nasal tube using the BreathID system (Exalenz Bioscience Ltd., Israel) at baseline before the test meal and following the completion of test meal ingestion (time 0) for up to 4 hours (20-29).

Data analysis of the ^{13}C-acetic acid breath test

The data from the ^{13}C breath test were analyzed using Oridion Research Software, β version (Oridion Medical Ltd., Israel). The time versus $^{13}CO_2$ excretion rate curve was fitted to the conventional formula $z(t)=m(1-e^{-kt})^{\beta}$, and the regression-estimated constants κ and β were determined. After mathematical analysis, the time required for the emptying of 50% of the labeled meals (T 1/2), the analog to the scintigraphy lag time for 10% emptying of the labeled meal (T lag), the gastric emptying coefficient (GEC), and the regression-estimated constants (β and κ) were calculated. A larger (smaller) β indicates slower (faster) emptying in the early phase, and a larger (smaller) κ indicates faster (slower) emptying in the later phase.

Statistical analysis

Statistical evaluation was carried out using Wilcoxon's signed-rank test. The level of significance was $p<0.05$. Statistical analyses were performed with Stat View software (SAS Institute, Cary, NC, USA).

Ethics

The study was conducted in accordance with the Declaration of Helsinki. The study protocol using the BreathID system was approved by the Ethics Committee of Yokohama City University School of Medicine.

RESULTS

^{13}C-acetic acid breath test

Twelve male subjects (mean age, 31 years; median age, 31 years; range, 24-38 years) completed this study. No adverse events occurred during the study. The subjects' mean height was 172.3 cm, their median height was 171 cm (range, 165-185 cm), their mean weight was 71.6 kg, and their median weight was 69.5 kg (range, 62-92 kg).

Table 1 summarizes the ramosetron-induced changes in the breath test parameters. Figures 1-5 show the details of each parameter. No significant differences were found between the two groups in the T 1/2, [(125.96: 81.67-184.68) vs. (116.18: 84.53-138.25) (p=0.4328)] (median: range, ramosetron versus control, min) (Figure 1a), T lag, [(56.905: 39.46-87.05) vs. (59.785: 39.46-87.05) (p=0.0712)] (Figure 1b), GEC, [(3.605: 3.14-4.19) vs. (3.59: 3.19-4.03) (p=0.4328)] (Figure 1c) or κ, [(0.5975: 0.2638-0.9265) vs. (0.6487: 0.4661-0.8872) (p=0.0844)] (Figure 4e). There was a significant difference between the two conditions in β [(1.7506: 1.1812-2.1595) vs. (1.9508: 1.4755-2.9269) (p=0.0229)] (Figure 1d).

DISCUSSION

This study examined changes in the rate of gastric emptying during the first 4 hours after pre-treatment with 5 μg ramosetron for an hour in healthy subjects. Gastric emptying was measured by the ^{13}C-acetic breath test.

Ramosetron has the following pharmacokinetic data in a healthy man: T max 1.7±0.8 hours, C max 18.5±5.9 pg/mL, T 1/2 5.7±1.9 hours, and AUC 125.3±45.1 pg h/mL (30). Therefore, in all of the subjects, the drug concentration would be close to the maximum level while they were undergoing the breath test.

The ^{13}C-acetic acid breath test is a noninvasive and well-established test for measuring the rate of gastric emptying of liquid meals and has been shown to be significantly correlated with the results of scintigraphy (31-36). The subjects ingested ^{13}C-labeled acetic acid, which passes through the stomach and is absorbed in the duodenum and upper small bowel. The ^{13}C-labeled acetic acid is then metabolized in the liver and excreted from the lung as $^{13}CO_2$. This pathway enables gastric emptying to be measured in a noninvasive manner. The BreathID system allows continuous evaluation of gastric emptying. For patients, it can serve as real-time breath analysis. It also decreases the examination time and alleviates patient discomfort. Continuous analysis also provides quick, immediate results (20-29).

In rats, it has been demonstrated that the inhibition of gastric emptying induced by glucose in the intestine is mediated by

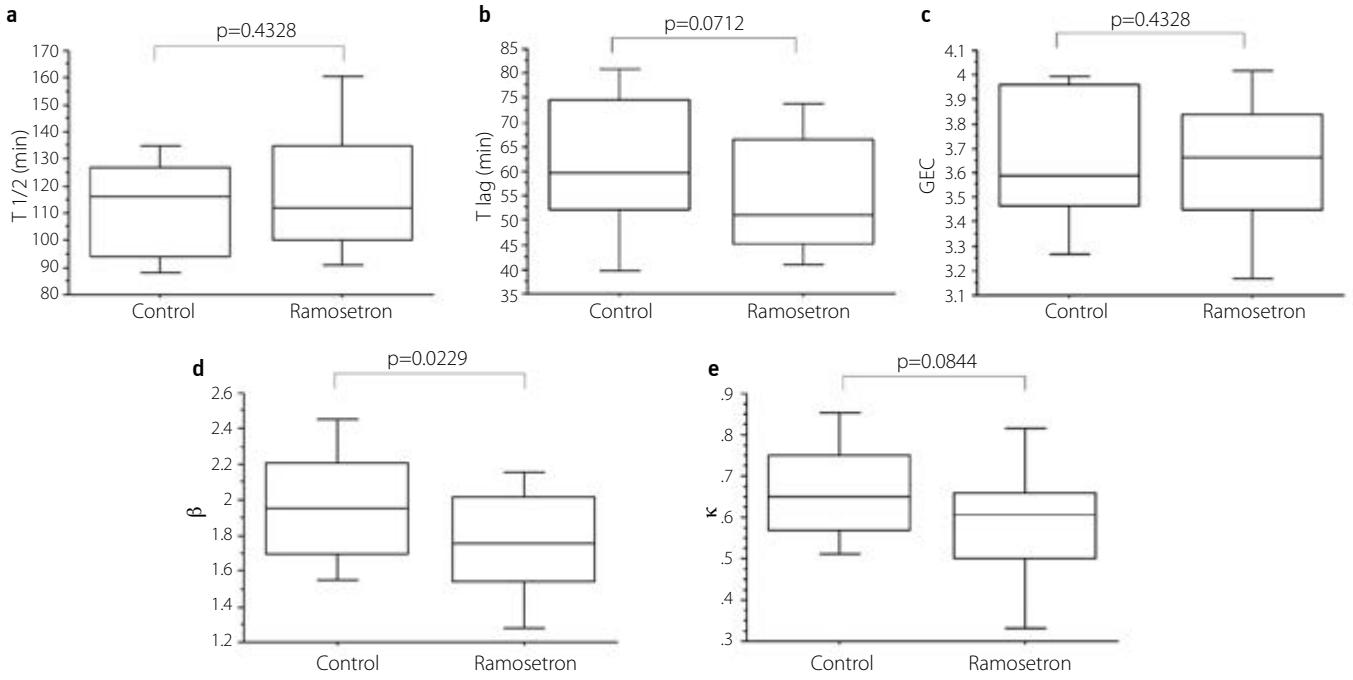

Figure 1 a-e. No significant differences were found in the T 1/2 **(a)**, T lag **(b)**, GEC **(c)** or κ **(e)** between the 2 study conditions. The β constant was higher after the administration of a test meal plus Low-dose ramosetron than after the test meal alone (p=0.0229, Wilcoxon signed-rank test) **(d)**. T 1/2, the time required for emptying 50% of the labeled meal (min); T lag, the analog to the scintigraphy lag time for 10% emptying of the labeled meal (min); GEC, the gastric emptying coefficient; β and κ, the regression-estimated constants.

Table 1. Comparison of breath test parameters

	Ramosetron	Control	p value
T 1/2	125.96 (81.67-184.68)	116.18 (84.53-138.25)	0.4328
T lag	56.905 (39.46-87.05)	59.785 (39.46-87.05)	0.0712
GEC	3.605 (3.14-4.19)	3.59 (3.19-4.03)	0.4328
β	1.7506 (1.1812-2.1595)	1.9508 (1.4755-2.9269)	0.0229
κ	0.5975 (0.2638-0.9265)	0.6487 (0.4661-0.8872)	0.0844

Median (range). T 1/2: the time required for the emptying of 50% of the labeled meal (min); T lag: similar to the percentage dose recovery peak time (min); GEC: gastric emptying coefficient. β and κ: the regression-estimated constants. A larger (smaller) β indicates slower (faster) emptying in the early phase, and a larger (smaller) κ indicates faster (slower) emptying in the later phase.

5-HT3 receptor. Glucose-induced inhibition of proximal gastric motility, which is part of the gastroduodenal motility pattern predictive of decreased gastric emptying, was also inhibited by ondansetron, a 5-HT3 receptor antagonist. In addition, vagal and spinal afferents innervating the duodenum, which mediate the intestinal feedback inhibition of gastric emptying in response to the digestive products of dietary carbohydrates, express 5-HT3 receptor. Intraluminal glucose inhibits gastric emptying by releasing 5-HT from EC cells and activating 5-HT3 receptor on the peripheral terminals of vagal and spinal afferents in the duodenum (37,38). In the present study, ramosetron pre-treatment enhanced the early gastric emptying of liquid nutrients in healthy male volunteers. It is suggested that as a 5-HT3 receptor antagonist, ramosetron inhibits 5-HT3 activation; therefore, gastric emptying was not inhibited in the early phase despite stimulation by glucose within the liquid meal. We used 200 mL of Racol in this study, which contains 31.24 g of carbohydrate. We hypothesize the following mechanism: after the early acceleration of gastric emptying produced by ramosetron, the liquid meal, whose excretion from the stomach into the duodenum was accelerated, provided feedback to inhibit gastric emptying by releasing 5-HT from EC cells and activating 5-HT3 receptor on the peripheral terminals of vagal and spinal afferents in the duodenum.

Two effects of the ingested liquid meal are accelerated early gastric emptying and subsequent feedback from the duodenum. It was previously reported that postprandial water intake inhibits gastric antral motility along with an increase in cholecystokinin (CCK) in normal subjects. In that report, it was assumed that the rapid increase in CCK after water intake was initiated by a feedback mechanism related to the inflow of fatty chyme into the duodenum, which inhibits gastric antral activity. This duodeno-gastric interaction is known as the "duodenal break" (39). In a previous study, there were no significant differences between the test meal with ramosetron group and the test meal alone group in T 1/2, T lag, GEC, or κ. However, there was a significant difference in the calculated parameter β. We theorize that the acceleration of early gastric emptying and the duodenal break balanced each other out.

In Japan, ramosetron is only administered to male patients because it was demonstrated that ramosetron did not have significant effect for female patients Irritable Bowel Syndrome (IBS) (40). So we studied only male volunteer in this study.

Low dose Ramosetron effected early gastric emptying to accelerate, but looking at overall gastric emptying phase, there was no significant change as between with low dose ramosetron intake and without intake. We got a useful result that the male patients with IBS can take ramosetron orally without any anxieties about gastric emptying to bring neither excessive velocity nor too much delaying.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yokohama City University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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