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Original Article

Effects of Histamine-2 Receptor Antagonists and Proton Pump Inhibitors on the Rate of Gastric Emptying: A Crossover Study Using a Continuous Real-Time ^{13}C Breath Test (BreathID System)

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Background/Aims
The effects of Histamine-2 receptor antagonists and proton pump inhibitors on the gastrointestinal motility have not yet been sufficiently investigated. The aim of this study was to determine the effects of intravenous bolus administration of famotidine and omeprazole on the rate of gastric emptying using the continuous ^{13}C breath test (BreathID system, Exalenz Bioscience Ltd, Israel).

Methods
Twelve healthy male volunteers participated in this randomized, 3-way crossover study. After fasting overnight, the subjects were randomly assigned to receive 20 mg of famotidine, 20 mg of omeprazole or 20 mL of saline alone by intravenous bolus injection before a test meal (200 kcal per 200 mL, containing 100 mg of ^{13}C-acetate). Gastric emptying was monitored for 4 hours after the ingestion of test meal by the ^{13}C-acetic acid breath test performed using the BreathID system.

Results
No significant differences in the calculated parameters, namely, the $T_{1/2}$, T_{lag}, GEC, β and κ, were observed among the 3 test conditions.

Conclusions
The study revealed that intravenous administration of gastric acid suppressant drugs had no significant influence on the rate of gastric emptying in comparison with that of saline alone as a placebo. Our results indicating the absence of any effect of either famotidine or omeprazole on accelerating the rate of gastric emptying suggest that both medications can be administered safely to patients suffering from hemorrhagic peptic ulcers who need to be kept nil by mouth from the viewpoint of possible acceleration of gastrointestinal motility in the clinical setting.
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Key Words
Breath tests; Gastric emptying; Histamine-2 antagonists; Proton pump inhibitors

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Introduction

Control of acid secretion is essential in the treatment of peptic ulcer disease, gastroesophageal reflux disease, and other acid-related diseases. Dramatic success in pharmacological acid suppression has been achieved with the discovery of histamine-2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs), and these gastric acid suppressants have been used widely as agents of first choice in the treatment of acid-related disorders. Intravenous bolus administration of such gastric acid suppressants is especially selected for patients suffering from hemorrhagic peptic ulcers who need to be kept nil by mouth.

However, the pharmacological effects of gastric acid suppressants on the rate of gastric emptying have not yet been sufficiently investigated, and previous studies have reported conflicting results (Table 1).[1-12] In most of these studies, the rate of gastric emptying was measured after oral administration of gastric acid suppressants, and few studies have described the effect of single intravenous injection of H_2RA or PPI.

In the present study, the physiological effects of intravenously administered gastric acid suppressants (famotidine and omeprazole), on the rate of gastric emptying were examined in healthy volunteers using a novel non-invasive technique for measuring the rate of gastric emptying, namely, the continuous real-time ^{13}C breath test (BreathID system).[13-18]

Materials and Methods

Subjects

Twelve healthy asymptomatic male volunteers (mean age 27.4 years, median age 24.0 years, range 20-40 years) participated in this randomized, 3-way crossover study. The height and weight of the subjects were as follows: mean height, 171.7 cm; median height, 172.0 cm; height range, 164-178 cm; mean weight, 68.1 kg; median weight, 66.5 kg; weight range, 53-84 kg. None of the subjects were habitual drinkers. All were non-smokers, and none had a history of gastrointestinal disease or abdominal surgery. None of the subjects were on any routine medication at the time of the study. All subjects were negative for anti-*Helicobacter pylori* immunoglobulin G antibodies (SRL Inc, Tokyo, Japan).

^{13}C-Acetic Acid Breath Test

Twelve subjects participated in this randomized, 3-way crossover study. The subjects were assigned in random sequence to receive an intravenous bolus injection of 20 mg of famotidine dissolved in 20 mL of saline, 20 mg of omeprazole dissolved in 20 ml of saline, or 20 mL of saline alone, as a placebo, just before ingestion of the test meal. The 3 test conditions were separated by a washout period of at least 7 days. The breath test was performed under each of the test conditions while the subjects were seated

Table 1. The Effects of Gastric Acid Suppressants on the Rate of Gastric Emptying: Previous Studies

First author	Subjects	Drug	Method	Test meal	Result
Houghton and Read[1]	HV	CIM and RAN	RI	Liquid	NS[b]
Sanaka et al[2]	HV	LPZ	Drug	Water	Accelerate
Chang et al[3]	HV	OPZ	RI	Water	Accelerate
Anjiki et al[4]	HV	RPZ	BT	Solid	Delay[c]
Corinaldesi et al[5]	HV and DU	RAN and CIM	RI	Solid	NS[d]
Parkman et al[6]	HV	RAN, FAM and OPZ	RI	Solid	Delay
Rasmussen et al[7]	HV	OPZ	RI	Solid	Delay
Sanaka et al[8]	HV	RPZ	BT	Liquid	Delay
Horowitz et al[9]	DU	OPZ	RI	Solid	NS
Chremos[10]	HV	FAM	RI	Solid	NS
Takahashi et al[11]	HV	RAN, FAM and RPZ	BT	Liquid	NS
Madsen and Graff[12]	HV	RAN	RI	Liquid	NS
Nonaka T[a]	HV	OPZ and FAM	BT	Liquid	NS

[a]Our study, [b]Only high level of ranitidine showed accelerated gastric emptying, [c]Rabeprazole showed initial accelerated and overall delayed gastric emptying, [d]Only high level of ranitidine showed delayed gastric emptying.
HV, healthy volunteers; DU, duodenal ulcer patients; CIM, cimetidine; RAN, ranitidine; LPZ, lansoprazole; OPZ, omeprazole; RPZ, rabeprazole; FAM, famotidine; RI, radioisotope method; BT, breath test; NS, not significant.

after overnight fasting (at least 8 hours).

The test meal was a 200 kcal per 200 mL liquid meal (Racol with milk flavor, Otsuka Pharmaceutical, Co, Ltd, Tokyo, Japan) containing 100 mg of ^{13}C-acetic acid (Cambridge Isotope Laboratories, Inc, USA), and the subjects were requested to consume the meal within 5 minutes. Breath samples were collected via a nasal tube using the BreathID system (Exalenz Bioscience Ltd, Israel) at the baseline before the test meal ingestion, and continuously for up to 4 hours after completion of the test meal ingestion (time 0) (Fig. 1).[13-18]

Data Analysis of the ^{13}C-Acetic Acid Breath Test

The data were analyzed using the Oridion Research Software, β version (Oridion Medical Ltd, Israel). The time versus $^{13}CO_2$ excretion rate curve was fitted to the conventional formula of $z(t) = m(1\text{-}e^{-kt})^{\beta}$, and the regression-estimated constants of β and κ were determined.[13,14] After the mathematical analyses, the time required for emptying 50% of the labeled meal ($T_{1/2}$), 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.[4,19,20]

CYP2C19 Genotyping

DNA samples were obtained from the white blood cells separated from whole blood samples obtained from the 12 subjects.[21] Their S-mephenytoin 4'-hydroxylase (CYP2C19) genotype was determined by polymerase chain reaction-restriction fragment length polymorphism analysis. There are 2 reported point-mutations of CYP2C19: the wild-type allele has G at position 636 in exon 4 and G at position 689 in exon 5; one of the mutated alleles (m1 allele) has A at position 689 in exon 5 and the other (m2 allele) has A at position 636 in exon 4.[22,23] The CYP2C19 genotyping was done by SRL Inc (Tokyo, Japan).

Statistical Methods

Statistical evaluation was carried out using Wilcoxon's sign-

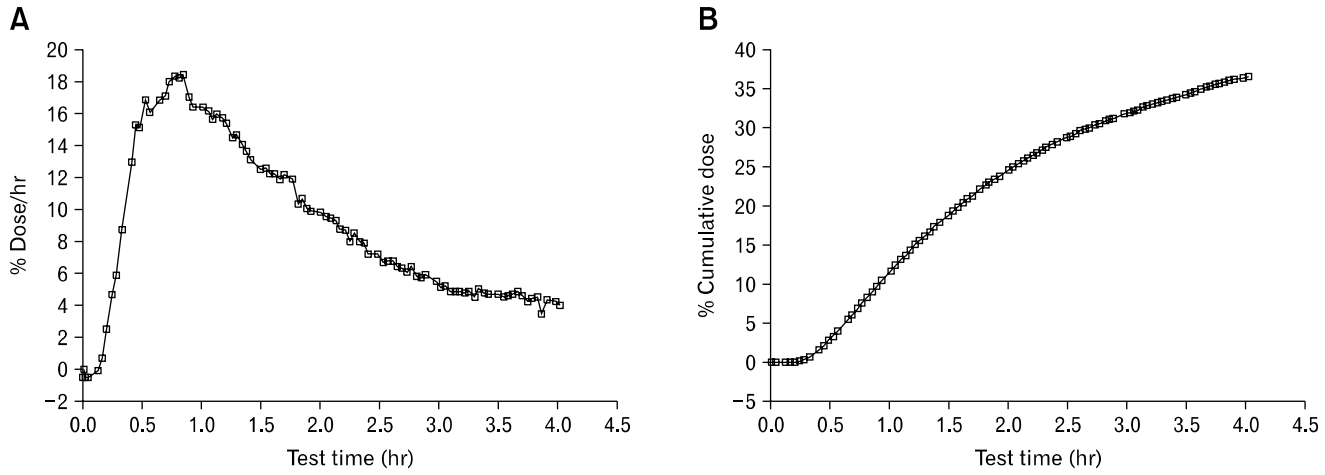

Figure 1. $^{13}CO_2$ concentrations in the breath are showed in the different time period. It shows 1 percentage dose ratio graph as sample (A) and 1 cumulative percentage dose ratio graph as sample (B).

Table 2. Comparison of the Breath Test Parameters Among the Famotidine, Omeprazole and Control Groups

Parameter	Famotidine	Omeprazole	Control	*P*-value
$T_{1/2}$	101.1 (83.7-169.4)	111.2 (81.2-143.3)	110.4 (84.9-134.0)	0.339
T_{lag}	55.0 (35.2-109.7)	60.5 (4,439-92.6)	53.9 (49.8-77.8)	0.174
GEC	3.62 (3.08-3.90)	3.63 (3.12-3.93)	3.50 (3.11-3.81)	0.076
β	1.76 (1.52-2.51)	1.97 (1.55-2.50)	1.83 (1.60-2.17)	0.339
κ	0.681 (0.504-0.775)	0.638 (0.542-0.922)	0.612 (0.543-0.899)	0.714

$T_{1/2}$, 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, gastric emptying coefficient; β and κ, the regression-estimated constants.
All values represent median values (range).

ed-rank test and Friedman's test. The level of significance was set at $P < 0.05$. All the statistical analyses were performed using the StatView 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

All 12 subjects completed this study, and no adverse events occurred during the study.

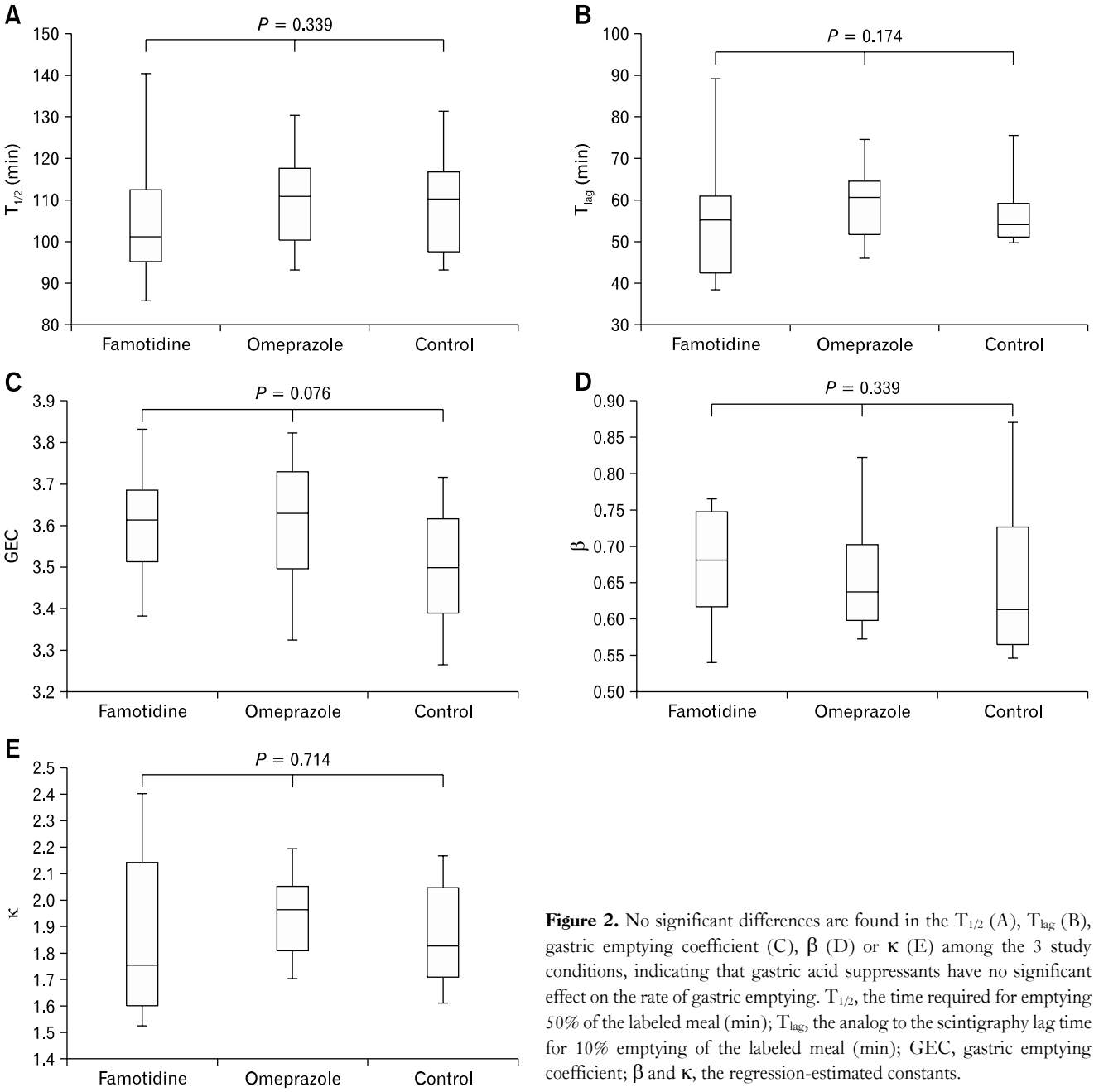

Figure 2. No significant differences are found in the $T_{1/2}$ (A), T_{lag} (B), gastric emptying coefficient (C), β (D) or κ (E) among the 3 study conditions, indicating that gastric acid suppressants have no significant effect on the rate of gastric emptying. $T_{1/2}$, the time required for emptying 50% of the labeled meal (min); T_{lag}, the analog to the scintigraphy lag time for 10% emptying of the labeled meal (min); GEC, gastric emptying coefficient; β and κ, the regression-estimated constants.

Table 2 summarizes the famotidine- and omeprazole-induced changes in the breath test parameters. No significant differences were observed in the median (range) of $T_{1/2}$ ([101.1: 83.7-169.4], [111.2: 81.2-143.3] and [110.4: 84.9-134.0] in the famotidine, omeprazole and saline alone groups; $P = 0.339$, respectively); T_{lag} ([55.0: 35.2-109.7], [60.5: 44.4-92.6] and [53.9: 49.8-77.8]; $P = 0.174$, respectively), GEC ([3.62: 3.08-3.90], [3.63: 3.12-3.93] and [3.50: 3.11-3.81]; $P = 0.076$, respectively), β ([1.76: 1.52-2.51], [1.97: 1.55-2.50] and [1.83: 1.60-2.17]; $P = 0.339$, respectively), or κ ([0.681: 0.504-0.775], [0.638: 0.542-0.922] and [0.612: 0.543-0.899]; $P = 0.714$, respectively) values among the 3 study conditions (Fig. 2). These results indicate that intravenous bolus administration of neither famotidine nor omeprazole had any significant effect on the rate of gastric emptying.

CYP2C19 Genotype

On the basis of the genotyping, 9 subjects were classified as extensive metabolizers, including 3 homozygous extensive metabolizers with 2 wild-type alleles each, and 6 heterozygous extensive metabolizers with 1 wild-type allele and 1 mutated allele each; the remaining 3 subjects were classified as poor metabolizers with 2 mutated alleles. There were no significant differences in the breath test parameters among the groups with the 3 genotypes of CYP2C19: $T_{1/2}$ ([110.2: 81.2-143.3] and [113.3: 110.8-120.7] in the extensive metabolizer and poor metabolizer in omeprazole administration; $P = 0.405$, respectively), T_{lag} ([59.3: 44.9-92.6] and [63.7: 57.5-66.9]; $P = 0.309$, respectively), GEC ([3.64: 3.12-3.93] and [3.62: 3.49-3.74]; $P = 0.926$, respectively), β ([1.981: 1.552-2.501] and [1.953: 1.814-1.988]; $P = 0.782$, respectively) or κ ([0.658: 0.542-0.922] and [0.621: 0.600-0.647]; $P = 0.518$, respectively).

Discussion

The present study was conducted to examine the changes in the rate of gastric emptying after single intravenous administration of famotidine 20 mg or omeprazole 20 mg during the first 4 hours after ingestion of a liquid meal in healthy volunteers. In our observation, these medications did not influence the rate of gastric emptying.

Inconsistent effects of gastric acid suppressants, both H_2RAs and PPIs, on the gastric emptying rate have been reported.[1-12] However, Table 1 showed controversial results of previous studies using various methods (radioisotope method or breath test), test meals (solid or liquid) and subjects (healthy volunteers or patients).[1-12]

Several possible mechanisms by which gastric acid suppressants may influence the gastric emptying rate have been proposed, as follows. Reduction of gastric acid secretion might accelerate the gastric emptying rate by removing the normal breaking action of acid in the duodenum.[24,25] In contrast, acid-pepsin maldigestion due to gastric hypoacidity might prolong the time for hydrolyzing a meal, resulting in a deceleration of gastric emptying.[26,27] In addition, acid suppression might increase the serum levels of gastrin, a peptide known to decelerate gastric emptying.[28,29] Furthermore, as gastric acid suppression is known to decrease the volume of the secreted gastric juice,[6,11] a decrease in the volume and viscosity of the intragastric contents might facilitate the transfer of a liquid meal from the stomach to the small gut.[2,30,31] Conversely, high caloric density and hyperosmolarity caused by reduced gastric juice secretion might delay gastric emptying by triggering the physicochemical receptors in the duodenum.[32-35] Apart from the effect exerted via gastric acid suppression, since histamine-2 receptors are present in the gastric muscular layer,[24] some H_2RAs, but not PPIs, may also have a direct effect on the gastric motility.[36-40] Ranitidine and nizatidine have also been reported to have anti-cholinesterase activity and to thereby increase the gastrointestinal motility,[38] whereas famotidine, as shown in our study, is considered to have minimal anti-cholinesterase activity.[6,10]

Based on our finding of the absence of any significant effect of gastric acid suppressants on gastric emptying rate, we speculate that the aforementioned hypothetical mechanisms might counterbalance the effects in an unpredictable manner, explaining the conflicting results reported by previous studies.

Several other factors may also contribute to the discrepant results, for example, the differences in the methodologies used for assessing gastric emptying, test meal contents and pretreatment regimens. In our study design, we did not try to measure the changes of intragastric pH before and after administration of gastric acid suppressants, but we have previously reported that adequate acid suppression and elevation of the intragastric pH is achieved in the early post-administration phase after a single intravenous administration of gastric acid suppressants.[41,42] Although intravenous famotidine had a more rapid onset of action and exerted stronger inhibition of intragastric acid secretion than intravenous omeprazole or lansoprazole in our previous study, there were no significant differences in the gastric emptying rate between the famotidine and omeprazole administration groups in

the present study.

Gastric acid suppressants can be administered intravenously as an infusion to patients with hemorrhagic ulcers with the risk of rebleeding or necessity of being kept nil by mouth. Drugs such as domperidone and metoclopramide, which accelerate gastric motility do not predispose to gastrointestinal hemorrhage, in general. Accordingly, it was considered very important to clearly elucidate whether gastric acid suppressants might influence the rate of gastric emptying, especially following intravenous administration. Our results suggest that both famotidine and omeprazole can be administered safely by intravenous injection from the viewpoint of any adverse effect on the gastrointestinal motility.

One of the weak points in this study was lack of information about intragastric pH. However, our previous report showed that intravenous injection of famotidine (20 mg) and omeprazole (20 mg) decreased gastrin acid secretion within 4 hours.[42]

The evaluation of gastric emptying using the ^{13}C-acetic acid breath test is a noninvasive method. We measured gastric emptying using the BreathID system, which collects continuous breaths. The subject ingests ^{13}C-labeled acetic acid, which passes through the stomach and is absorbed in the duodenum and superior small bowel. The ^{13}C-labeled acetic acid is then metabolized in the liver and excreted from the lungs as $^{13}CO_2$. This pathway enables gastric emptying to be measured in a noninvasive manner.[13] Value of breath test parameters is influenced by method (for example, radioisotope method or breath test), test meal (solid or liquid), label (acetate or octanete) and subjects (healthy volunteers or patients). Our studies using breathID with 200 kcal per 200 mL liquid meal containing 100 mg of ^{13}C-acetic acid usually showed $T_{1/2}$ of about 100 minutes.[14-18,43]

In conclusion, the present study revealed that single intravenous administration of neither famotidine nor omeprazole had any influence on the rate of gastric emptying in healthy subjects. The clinical implications of our results remain unclear, and further investigation on the effects of gastric acid suppressants on the gastrointestinal motility should be conducted.

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