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BRIEF ARTICLE

Effect of sumatriptan on gastric emptying: A crossover study using the BreathID system

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Abstract

AIM: To determine the effect of oral sumatriptan on gastric emptying using a continuous ^{13}C breath test (BreathID system).

METHODS: Ten healthy male volunteers participated in this randomized, 2-way crossover study. The subjects fasted overnight and were randomly assigned to receive a test meal (200 kcal/200 mL) 30 min after pre-medication with sumatriptan 50 mg (sumatriptan condition), or the test meal alone (control condition). Gastric emptying was monitored for 4 h after administration of the test meal by the ^{13}C-acetic acid breath test performed continually using the BreathID system. Then, using Oridion Research Software (β version), the time taken for emptying of 50% of the labeled meal ($T_{1/2}$) similar 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. The statistical significance of any differences in the parameters were analyzed using Wilcoxon's signed-rank test.

RESULTS: In the sumatriptan condition, significant differences compared with the control condition were found in $T_{1/2}$ [median 131.84 min (range, 103.13-168.70) *vs* 120.27 min (89.61-138.25); $P = 0.0016$], T_{lag} [median 80.085 min (59.23-125.89) *vs* 61.11 min (39.86-87.05); $P = 0.0125$], and β [median 2.3374 (1.6407-3.8209) *vs* 2.0847 (1.4755-2.9269); $P = 0.0284$]. There were no significant differences in the GEC or κ between the 2 conditions.

CONCLUSION: This study showed that oral sumatriptan significantly delayed gastric emptying of a liquid meal.

Key words: Sumatriptan; Gastric emptying; Breath test; Liquid meal; BreathID system

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INTRODUCTION

Sumatriptan, a selective 5-HT$_1$ receptor agonist, was launched in the market in 1991, representing the single most remarkable advance to date in the treatment of migraine[1]. It was suspected that the drug might delay gastric emptying of liquids in healthy subjects by prolonging the lag phase of gastric emptying[2,3]. Several studies have reported that sumatriptan restores gastric accommodation in patients with functional dyspepsia[4-9].

A recent study showed that the accelerated gastric emptying of nutrient liquids can be a surrogate marker of impaired distension-induced accommodation[10]. After aggressive filling of the stomach with a nutrient liquid, the resultant increase in intragastric pressure determines the rate of gastric emptying; higher luminal pressure caused by defective accommodation accelerates gastric emptying[10,11]. Conversely, it would be logical to consider that the gastric emptying of a nutrient liquid would be delayed when distension-induced accommodation is enhanced. Compared with second-generation 5HT$_{1B/1D}$ receptor agonist antimigraine drugs, sumatriptan shows poor oral bioavailability and a relatively short elimination half-life[6]. According to a previous report, the T_{max} of sumatriptan is 2-3 h, the $T_{1/2}$ is 2 h, and the oral bioavailability is 14%[6]. The aim of this preliminary study was to test our hypothesis that oral sumatriptan intake would cause a delay in the gastric emptying of nutrient liquids. If the hypothesis were proven to be true, it would lend indirect support to the suggestion that sumatriptan enhances distension-induced gastric accommodation[11].

In this study, we investigated the physiologic effect of sumatriptan on the rate of gastric emptying using a continuous real-time ^{13}C breath test (BreathID system: Exalenz Bioscience Ltd., Israel).

MATERIALS AND METHODS

Ethics

The study was conducted in accordance with the principles laid down in the Declaration of Helsinki. The study protocol using the BreathID system was approved by the Ethics Committee of Yokohama City University School of Medicine (No. A110929010).

Subjects

The subjects were 10 asymptomatic male volunteers, all of whom were students of Yokohama City University, non-smokers, none were habitual drinkers, and none had a history of gastrointestinal disease or abdominal surgery. None of the subjects were on any routine medications at the time of the study.

^{13}C-acetic acid breath test

Ten subjects participated in this randomized, 2-way crossover study. The 2 tests were conducted as follows: (1) The subjects were assigned to receive a test meal 30 min after intake of a 50 mg tablet of sumatriptan; and (2) The subjects only received the test meal. The two test protocols were administered in crossover fashion separated by a washout period of at least 7 d. In both experiments, the protocols were started after the patients had fasted overnight (for at least 8 h), and the breath test was performed for 4 h while the subjects were seated.

In experiment A, subjects were asked to take a 50 mg tablet of sumatriptan prior to the administration of a test meal. The test meal consisted of 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, United States)[12-23], which the patients were requested to consume within 5 min. In experiment B, subjects underwent the breath test after ingestion of the test meal alone. Breath samples were continuously collected *via* a nasal tube using the BreathID system (Exalenz Bioscience Ltd., Israel) from baseline, before administration of the test meal, until 4 h after completion of the test meal ingestion (time 0)[14-23].

Analysis of the ^{13}C-acetic acid breath test data

The data from the ^{13}C acetic acid breath test were analyzed using the Oridion Research Software, version β (Oridion Medical Ltd., Israel)[14-23]. The time *vs* $^{13}CO_2$ excretion rate curve was fitted to the conventional formula of $z(t) = m(1\text{-}e^{-\kappa t})^{\beta}$, and the regression-estimated constants κ and β were determined[24]. After the mathematical analysis, the time required for emptying of 50% of the labeled meal ($T_{1/2}$) similar 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 also calculated. A larger (smaller) value of β indicates slower (faster) emptying in the early phase, and a larger (smaller) value of κ indicates faster (slower) emptying in the later phase.

Statistical analysis

Statistical evaluation was carried out using the Wilcoxon's signed-rank test. The level of significance was set at $P < 0.05$. The statistical analysis were performed with the StatView software (SAS Institute, Cary, NC, United States).

RESULTS

The study was completed in 10 male subjects (mean age, 30.7 years; median age, 31 years; range, 24-38). No adverse events occurred during the study. The subjects'

Table 1 Comparison of breath test parameters

	Sumatriptan	Control	*P* value
$T_{1/2}$	131.84 (103.13-168.70)	120.27 (89.61-138.25)	0.0166
T_{lag}	80.085 (59.23-125.89)	61.11 (39.86-87.05)	0.0125
GEC	3.545 (3.20-3.97)	3.55 (3.19-4.03)	0.6460
β	2.3374 (1.6407-3.8209)	2.0847 (1.4755-2.9269)	0.0284
κ	0.5833 (0.3689-0.7836)	0.6180 (0.4661-0.8872)	0.3329

$T_{1/2}$: Time to emptying of 50% of the labeled meal (min); T_{lag}: Very similar to the percentage dose recovery peak time (min); GEC: Gastric emptying coefficient; β and κ: Regression-estimated constants. A larger (smaller) value of β indicates slower (faster) emptying in the early phase, and a larger (smaller) value of κ indicates faster (slower) emptying in the later phase.

mean height was 171.5 cm, their median height was 171 cm (range, 165-180 cm), their mean weight was 72.6 kg, and their median weight was 69.5 kg (range, 62-92 kg).

Table 1 summarizes the sumatriptan-induced changes in the breath test parameters. In the sumatriptan condition, significant differences compared with the control condition were found in $T_{1/2}$, [median, 131.84 min (range, 103.13-168.70) *vs* 120.27 min (89.61-138.25); $P = 0.0016$], T_{lag}, [median, 80.085 min (59.23-125.89) *vs* 61.11 min (39.86-87.05); $P = 0.0125$], and value of β [median 2.3374: 1.6407-3.8209) *vs* 2.0847 (1.4755-2.9269); $P = 0.0284$]. On the other hand, there were no significant differences in GEC [median, 3.545 (3.20-3.97) *vs* 3.55 (3.19-4.03); $P = 0.6460$] or κ [median, 0.5833 (0.3689-0.7836) *vs* 0.6180 (0.4661-0.8872); $P = 0.3329$] between sumatriptan and control conditions, respectively.

DISCUSSION

In this study, we examined the changes in the rate of gastric emptying during the first 4 h after oral administration of a 50 mg tablet of sumatriptan half an hour prior to a test meal in healthy subjects. The rate of gastric emptying was measured by the ^{13}C-acetic acid breath test.

The ^{13}C-acetic acid breath test is a non-invasive and well-established test for measuring the rate of gastric emptying of liquid meals, and the results of this test have been shown to be significantly correlated with those of scintigraphy[12-24]. The subject ingests ^{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 test thus enables gastric emptying to be measured in a non-invasive manner[12-24]. The BreathID system allows continuous evaluation of gastric emptying. In patients, it allows real-time breath analysis with a shortened examination time and minimal patient discomfort. Continuous analysis also provides quick, immediate results[14-23].

In general, administration of sumatriptan, a $5HT_1$ receptor agonist, has been reported to delay gastric emptying of calorie-containing liquids, and to restore gastric accommodation. In other words, sumatriptan allows both increased gastric relaxation after ingestion of a meal and an increased caloric intake at maximum satiety[9,25,26]. However, several studies have reported these effects of sumatriptan after subcutaneous sumatriptan injection[3,9,26-28]. As previously mentioned, sumatriptan shows poor oral bioavailability and a relatively short elimination half-life profile. To the best of our knowledge, no researchers have reported the aforementioned effects following administration of sumtriptan *via* the oral route. Therefore, we studied the effect of oral sumatriptan on the rate of gastric emptying.

Sumatriptan has been reported to be effective in relieving nausea associated with a migraine attack[7], although specific antiemetic agents are often required to control the symptoms and to restore normal gastrointestinal motor patterns[7,9].

In the present study, the amount of sumatriptan administered was not adjusted to the body weight of each individual, with the drug being administered *via* the oral route. T_{lag} of sumatriptan has been reported to be 2 or 3 h. In a recent study, the BreathID examination was started half an hour after the subjects took sumatriptan orally, and was continued for 4 h. Therefore, the T_{lag} of sumatriptan would have been reached while the BreathID examination was still ongoing.

In the present study, an increase in T_{lag} and $T_{1/2}$, and also in the value of β, was observed in the subjects administered sumatriptan prior to the test meal. Thus, sumatriptan delayed gastric emptying. In addition, the increase in the value of β indicated that sumatriptan in particular delayed the early phase of gastric emptying. We think that these findings were attributable to restoration of distention-induced gastric accommodation by sumatriptan. Several studies have shown that in patients with functional dyspepsia, who showed impaired accommodation of the proximal stomach, subcutaneously administered sumatriptan restored gastric accommodation, thereby significantly improving meal-induced satiety[9,26,27]. In healthy volunteers, accommodation of the proximal stomach may be thought to increase after administration of sumatriptan. A previous study using real-time ultrasonography and computed tomography demonstrated that subcutaneous administration of sumatriptan, after distention of the stomach with liquids, produced a reduction in the proximal and distal transverse area and an increase in the sagittal axis of the proximal stomach[28]. Another study using duplex sonography showed that subcutaneous administration of sumatriptan 10 min postprandially caused a significant widening of both the gastric antrum and the proximal stomach. Therefore, the authors concluded that the time to commencement of peristalsis-related emptying is delayed following administration of sumatriptan[26].

The effect of 5-HT on gastric fundus tone has not been studied. However, Tack *et al*[29] recently showed that sumatriptan, which is a $5\text{-}HT_1$ receptor agonist, is an agonist at $5\text{-}HT_{1P}$ receptors on nitrergic myenteric neurons in the stomach. We consider this action was induced through $5\text{-}HT_{1P}$ receptors as one of the side effects of

sumatriptan.

In the present study, we found that despite its low bioavailability, oral administration of even one tablet of sumatriptan consistently affected the rate of gastric emptying. Delayed gastric emptying may represent an increase in gastric accommodation.

In conclusion, this study suggests that sumatriptan, which can restore gastric accommodation, may be of benefit to many patients suffering from the distress of early satiety.

COMMENTS

Background

The incidence of functional gastrointestinal disorders is currently increasing worldwide though the cause of this disease is largely unknown. Rome Ⅲ criteria included postprandial distress syndrome, which might come from impaired gastric accommodation and gastric emptying.

Research frontiers

It is accepted that both gastric emptying and gastric accommodation are important in functional gastrointestinal disorders. However, how gastric accommodation affects gastric emptying in a breath test has not been researched. In this study, the authors demonstrated that oral sumatriptan significantly delayed gastric emptying and suggest that delayed gastric emptying may represent an increase in gastric accommodation.

Innovations and breakthroughs

This is the first study to report that oral administration of sumatriptan affected the rate of gastric emptying. Furthermore, the studies would suggest that delayed gastric emptying may represent an increase in gastric accommodation.

Applications

By understanding both gastric emptying and gastric accommodation, this study may represent a future strategy for therapeutic intervention in the treatment of patients with functional dyspepsia.

Terminology

The BreathID system allows measurement of gastric emptying by a breath test. This allows continuous and real-time evaluation of gastric emptying. Continuous analysis also provides quick, immediate results.

Peer review

This paper demonstrated a new way to identify the gastric emptying in human subjects; this is the main merit of this study.

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