

# Early effects of acotiamide or mosapride intake on gastric emptying: a randomized 3-way crossover study using the $^{13}\text{C}$ breath test

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The effects of acotiamide on gastrointestinal motility have not been sufficiently investigated. The aim of this study was to determine whether single preprandial acotiamide or mosapride intake might affect the gastric emptying rate using the  $^{13}\text{C}$  breath test. Here, 11 healthy volunteers participated in a randomized three-way crossover study. The subjects received acotiamide (100 mg) or mosapride (5 mg) or placebo before liquid test meal ingestion. Gastric emptying was estimated by determining following parameters: the time required for 50% emptying of the labeled meal (T1/2), lag time for 10% emptying of the labeled meal (Tlag), gastric emptying coefficient (GEC) and regression-estimated constants ( $\beta$  and  $\kappa$ ). These parameters were calculated from a  $^{13}\text{CO}_2$  breath excretion curve using conventional formulas. The acotiamide, mosapride and placebo conditions were compared, revealing that for gastric emptying rates (values expressed as median), T1/2 (87.83571 min vs 79.95057 min vs 88.74378 min,  $p = 0.1496$ ), Tlag (46.36449 min vs 42.2897 min vs 47.08094 min,  $p = 0.4966$ ), GEC (4.382027 vs 4.211441 vs 4.248495,  $p = 0.8858$ ),  $\beta$  (1.917728 vs 1.757062 vs 1.869141,  $p = 0.4066$ ) and  $\kappa$  (0.834051 vs 0.819820 vs 0.789523,  $p = 0.1225$ ) did not significantly differ. In this study, acotiamide (100 mg) or mosapride (5 mg) had no effect on gastric emptying.

**Key Words:** acotiamide, mosapride, breath test, gastric emptying

Although functional dyspepsia (FD) is not a serious disease associated with life prognosis, it is known that symptoms may persist chronically or intermittently, significantly reducing patients' quality of life (QOL). In Japan, acotiamide, which is only indicated for FD, has been reported to improve the symptoms of patients.<sup>(1-3)</sup>

Acotiamide has acetylcholinesterase and M1/M2 muscarinic receptor inhibitory activities and is thought to improve dyspepsia symptoms and QOL by improving gastric dysfunction. Phase II and III trials have been conducted in Europe and Japan and have been shown acotiamide to be effective in postprandial distress syndrome (PDS).<sup>(1-3)</sup> Only acotiamide has been shown to be stable and effective in placebo-controlled double-blind studies in patients with FD. For other drugs, clinical trial results with high evidence levels showing effectiveness in patients with FD have not been obtained.<sup>(4)</sup>

However, little is known about how acotiamide improves gastric dysfunction. The effect of acotiamide on gastric emptying varies from report to report, as there are reports that there is no

effect on gastric emptying and reports that it promotes gastric emptying.<sup>(5-7)</sup>

The gastrointestinal motility effects of acotiamide have not yet been sufficiently investigated. The aim of this study was to determine whether single preprandial acotiamide intake might have an effect on the rate of liquid gastric emptying using the  $^{13}\text{C}$  breath test.

## Materials and Methods

**Subjects.** In this study, the subjects included 11 asymptomatic male and female volunteers (F/M 3/8; age 20–42 years). All were nonsmokers, and no subjects had a previous history of gastrointestinal disease or abdominal surgery. None of the subjects were taking any routine medication at the time of the study.

**$^{13}\text{C}$  breath test.** In the liquid meal experiments, the 11 subjects participated in a randomized, three-way crossover study. After they had fasted overnight (at least 8 h), the subjects received 100 mg of acotiamide or 5 mg of mosapride or placebo before ingesting a liquid test meal in a random sequence.

The test meal consisted of 200 kcal per 200 ml liquid meal (Racol with milk flavor, Otsuka Pharmaceutical, Co., Ltd., Tokyo, Japan) containing 100 mg of  $^{13}\text{C}$ -acetic acid (Cambridge Isotope Laboratories, Inc., Andover, MA),<sup>(8-10)</sup> and the subjects were asked to consume the meal within 5 min.

Gastric emptying was measured using the  $^{13}\text{C}$ -acetic acid breath test while the subjects were seated. Breath samples were collected in air bags at baseline (before the test meal) and at 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, 120, 135, and 150 min after the test meal was ingested.<sup>(11,12)</sup> The  $^{13}\text{CO}_2/^{12}\text{CO}_2$  ratio in the collected breath samples was determined to compare to the baseline sample using nondispersive infrared spectrophotometry (POCone, Otsuka Electronics Co., Ltd., Osaka, Japan).

**Data analysis.** The results were converted to percent  $^{13}\text{C}$  recovered in the expired air per hour (percent dose per hour) and to the cumulative percent of  $^{13}\text{CO}_2$  recovered based on the subject's default production of 300 mmol  $\text{CO}_2$  per  $\text{m}^2$  body surface per hour.

Using the method reported by Ghooos *et al.*,<sup>(13)</sup> the percent  $^{13}\text{CO}_2$  recovery in the expired air per hour (percent dose per hour) against time was fit with the formula  $y(t) = at^{b-e^{-ct}}$  by nonlinear

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regression analysis, where  $y$  is the percent  $^{13}\text{C}$  excretion in the expired air per hour,  $t$  is the time in hours, and  $a$ ,  $b$ , and  $c$  are constants. The time course of cumulative  $^{13}\text{CO}_2$  recovery in the expired air was fit with another formula,  $z(t) = m(1 - e^{-kt})^\beta$ , where  $z$  is the cumulative percent  $^{13}\text{C}$  excretion in the expired air and an integral of  $y(t)$ ,  $m$  is the cumulative  $^{13}\text{CO}_2$  recovery at an infinite time, and  $\beta$  and  $\kappa$  are regression-estimated constants.  $\beta$  and  $\kappa$  were determined using the mathematical curve-fitting technique. A larger  $\beta$  indicates slower emptying in the early phase, a larger  $\kappa$  indicates faster emptying in the late phase, and *vice versa*. The time required for 50% emptying of the labeled meal (T1/2), the analog to the scintigraphy lag time for 10% emptying of the labeled meal (Tlag) and the gastric emptying coefficient (GEC) were calculated as overall measures of gastric emptying:  $T1/2 = -[\ln(1 - 2^{-1/\beta})]/\kappa$ ,  $Tlag = (\ln\beta)/\kappa$ , and  $GEC = \ln(a)$ .<sup>(4-6)</sup> These parameters were calculated using the Solver procedure in Excel 2010 (Microsoft Corp., Tokyo, Japan).

**Statistical analysis.** In the liquid meal study, statistical evaluation was performed using the Friedman test and Wilcoxon's signed-rank test. The level of significance was set at a  $p$  value  $<0.05$ . All the statistical analyses were performed with EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions that are frequently used in biostatistics.<sup>(14)</sup>

**Ethics.** The study was conducted in accordance with the principles of the Declaration of Helsinki. Prior to study initiation, written informed consent was obtained from all participants. The study protocol using the  $^{13}\text{C}$ -acetic acid breath test was approved

by the Ethics Committee of the Yokohama City University School of Medicine (A130725009). This study was conducted as part of a clinical trial enrolled as UMIN000010966.

## Results

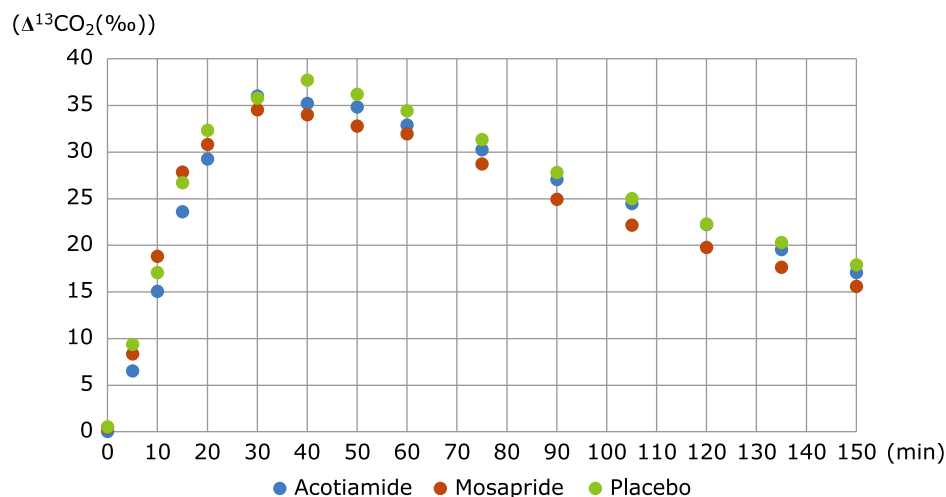
The liquid meal study was completed in all 11 subjects, and no adverse events occurred during the study. The results obtained for the three conditions regarding the breath test parameters are summarized in Table 1. All data are expressed as medians and ranges. No significant differences were observed for T1/2 [(87.83571: 70.69122–103.9367 min) vs (79.95057: 74.07966–99.05346 min) vs (88.74378: 78.13759–104.9147 min),  $p = 0.1496$ ; median: range, acotiamide vs mosapride vs placebo], Tlag [(46.36449: 35.47682–63.0211 min) vs (42.2897: 30.7577–67.03682 min), vs (47.08094: 40.86219–60.12731 min),  $p = 0.4966$ ; median: range, acotiamide vs mosapride vs placebo], GEC [(4.382027: 3.912023–4.499810) vs (4.211441: 3.942050–4.489715), vs (4.248495: 4.094345–4.442651),  $p = 0.8858$ ; median: range, acotiamide vs mosapride vs placebo],  $\beta$  [(1.917728: 1.572550–2.240398) vs (1.757062: 1.515265–3.064374), vs (1.869141: 1.676357–2.184435),  $p = 0.4066$ ; median: range, acotiamide vs mosapride vs placebo] or  $\kappa$  [(0.834051: 0.690610–0.960832) vs (0.819820: 0.630320–1.002294), vs (0.789523: 0.712032–0.887127),  $p = 0.1225$ ; median: range, acotiamide vs mosapride vs placebo] among the acotiamide group, the mosapride group and the placebo group.

The data of mean time course changes in  $^{13}\text{CO}_2$  in the three groups are shown in Fig. 1. Figure 1 shows that no significant differences were visually apparent among the three groups.

**Table 1.** Comparison of breath test parameters among the acotiamide group, the mosapride group and the placebo group for the liquid meal test

Parameter	Acotiamide	Mosapride	Placebo	$p$ value
Tlag (min)	46.36449 (35.47682–63.0211)	42.2897 (30.7577–67.03682)	47.08094 (40.86219–60.12731)	0.4966
T1/2 (min)	87.83571 (70.69122–103.9367)	79.95057 (74.07966–99.05346)	88.74378 (78.13759–104.9147)	0.1496
GEC	4.382027 (3.912023–4.499810)	4.211441 (3.942050–4.489715)	4.248495 (4.094345–4.442651)	0.8858
$\beta$	1.917728 (1.572550–2.240398)	1.757062 (1.515265–3.064374)	1.869141 (1.676357–2.184435)	0.4066
$\kappa$	0.834051 (0.690610–0.960832)	0.819820 (0.630320–1.002294)	0.789523 (0.712032–0.887127)	0.1225

All values represent the median value (range). T1/2, time required for emptying of 50% of the labeled meal (min); Tlag, the analog to the scintigraphy lag time for 10% emptying of the labeled meal; GEC, gastric emptying coefficient;  $\beta$  and  $\kappa$ , regression-estimated constants.



**Fig. 1.** Time course of  $\Delta^{13}\text{CO}_2$  (%o). Mean time course changes in  $^{13}\text{CO}_2$  in the acotiamide (blue), mosapride (red) and placebo (green). This figure reveals that no significant differences were detectable among the 3 groups. See color figure in the on-line version.

**Table 2.** Effect of various drugs on gastric emptying

	Acotiamide	Mosapride	Rikkunshito	Itopride	PPI
Zai <i>et al.</i> <sup>(5)</sup>	→ (HV)				
Masuy <i>et al.</i> <sup>(7)</sup>	→ (HV)				
Nakamura <i>et al.</i> <sup>(6)</sup>	↑ (FD)				
Kusunoki <i>et al.</i> <sup>(21)</sup>		↑ (HV)			
Sakamoto <i>et al.</i> <sup>(15)</sup>		↑ (HV)			
Kusunoki <i>et al.</i> <sup>(16)</sup>			↑ (FD)		
Nonaka <i>et al.</i> <sup>(17)</sup>				→ (HV/FD)	
Abid <i>et al.</i> <sup>(18)</sup>				→ (FD)	
Tougas <i>et al.</i> <sup>(19)</sup>					↓ (HV)
Nonaka <i>et al.</i> <sup>(20)</sup>					→ (HV)

→: No change. ↑: Acceleration. HV, healthy volunteer; FD, functional dyspepsia; PPI, proton pump inhibitor.

**Table 3.** Effects of acotiamide on gastrointestinal function

	Esophageal motor function	LES pressure	EGJ compliance	Gastric emptying	Gastric accommodation
Ishimura <i>et al.</i> <sup>(25)</sup>	→ (HV)				
Zai <i>et al.</i> <sup>(5)</sup>				→ (HV)	
Mikami <i>et al.</i> <sup>(26)</sup>	→ (HV) → (GERD)	→ (HV) → (GERD)	→ (HV) → (GERD)		
Nakamura <i>et al.</i> <sup>(6)</sup>				↑ (FD)	↑ (FD)
Masuy <i>et al.</i> <sup>(7)</sup>				→ (HV)	
Funaki <i>et al.</i> <sup>(27)</sup>	↑ (FD)				

→: No change. ↑: Acceleration. LES, lower esophageal sphincter; EGJ, esophagogastric junction; HV, healthy volunteer; GERD, gastroesophageal reflux disease; FD, functional dyspepsia; PPI, proton pump inhibitor.

## Discussion

The present study was conducted to examine changes in the rate of gastric emptying after a single dose of preprandial acotiamide or mosapride before ingesting a liquid meal in healthy volunteers. The results of the liquid meal studies showed that 100 mg of acotiamide or 5 mg of mosapride had no effect on gastric emptying. The finding that acotiamide had no effect on the gastric emptying rate is consistent with the results reported by Zai *et al.*<sup>(5)</sup> and Masuy *et al.*<sup>(7)</sup>

The effects of commonly used drugs on gastric emptying in patients with functional gastrointestinal disease are summarized in Table 2.<sup>(5–7,15–20)</sup> In clinical settings, various drugs are used to treat dyspepsia in patients with functional gastrointestinal disease, but few drugs improve gastric emptying. Proton pump inhibitors, which are frequently used to treat dyspepsia in patients with functional gastrointestinal disease, delay gastric emptying.<sup>(19)</sup> The difference between healthy volunteers and patients with functional gastrointestinal disease is noteworthy. This study was conducted on healthy volunteers, and the results may be different in patients with functional gastrointestinal disease.

Is there a delay in gastric emptying in patients with FD? Several reports suggest that gastric emptying is impaired in some patients with FD, and a meta-analysis indicates that gastric emptying is significantly delayed in almost 40% of patients with FD.<sup>(22)</sup> Most studies failed to find a convincing relationship between delayed gastric emptying and symptom patterns, and some studies reported rapid gastric emptying after meals in some patients with FD.<sup>(23,24)</sup>

There is overwhelming evidence that acotiamide reduces dyspepsia symptoms in patients with FD. However, it is difficult to explain the effect of acotiamide on patients with FD by

gastric emptying alone. The reported effects of acotiamide on gastrointestinal function are summarized in Table 3.<sup>(5–7,25–27)</sup> Many reports indicate that acotiamide has no effect on gastrointestinal function. Current trackable gastrointestinal function tests may not be able to detect changes in gastrointestinal function caused by acotiamide.

The gastric emptying rate, as measured by the breath test, is affected by gastric accommodation, as measured by the barostat method, and by the outflow of gastric contents into the duodenum due to contraction of the gastric antrum. Sekino *et al.*<sup>(28)</sup> reported that improved gastric accommodation may lead to a reduction in gastrointestinal symptoms in patients with FD but it may also lead to a delay in gastric emptying, as measured by the breath test. Even if acotiamide promotes gastric antrum contraction, this effect may be counterbalanced by improved gastric accommodation, and the gastric emptying rate may remain unchanged.

Mosapride is a drug derived from cisapride. Cisapride was effective in treating dyspepsia symptoms in patients with FD but is no longer available due to arrhythmia side effects.<sup>(18)</sup> Mosapride is available in limited areas, and there is little evidence of its use in patients with FD. In our study, we found no effect on gastric emptying. There are two reports that show that gastric emptying is promoted in healthy subjects, one by Kusunoki *et al.*<sup>(21)</sup> using an ultrasonic method and the other by Sakamoto *et al.*<sup>(15)</sup> using a highly viscous test food. Differences in methods and test meals may have affected the results.

The present study had some limitations. First, the number of subjects was small. Second, the subjects were healthy volunteers who did not have any symptoms. If possible, we would like to perform the same study in patients with functional gastrointestinal disease and compare the results with those from healthy volunteers.

Our study findings revealed that single-dose acotiamide or mosapride intake had no significant influence on the rate of gastric emptying. The effect of acotiamide on dyspepsia symptoms in patients with FD was considered to be caused by a mechanism other than promotion of gastric emptying, for example, the amount of gastric acid secretion and acylated ghrelin level.<sup>(29,30)</sup>

## Author Contributions

MK, MI, YI, and HI designed the study; MK, MI, MM, KF, AK, and AN performed the experiments, analyzed the data, and wrote the manuscript.

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## Abbreviations

GEC      gastric emptying coefficient

## Conflict of Interest

No potential conflicts of interest were disclosed.

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