

Full Paper

Dual Role of Mosapride Citrate Hydrate on the Gastric Emptying Evaluated by the Breath Test in Conscious Rats

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Abstract. Mosapride citrate hydrate (mosapride) has been known to act as a 5-HT₄ agonist and to enhance gastric emptying. However, its mode of action, such as time course and dosage effect, on gastric emptying has not been clarified. This study aimed to clarify these points by the breath test using [1-¹³C]acetic acid in conscious rats. Mosapride significantly and dose-dependently enhanced the gastric emptying increased C_{max} and AUC_{120 min} at doses between 0.1 and 3 mg/kg. Pre-treatment with GR113808 (5-HT₄ antagonist) significantly attenuated the enhancement of gastric emptying by mosapride. On the contrary, at a dose of 30 mg/kg, mosapride significantly inhibited the gastric emptying. The major metabolite (M1: 5-HT₃ receptor antagonist) significantly inhibited gastric emptying at doses of 19.2 and 64.1 mg/kg (equimolar to 30 and 100 mg/kg of mosapride, respectively), suggesting that the inhibitory effect by mosapride may be caused at least in part by the 5-HT₃ receptor antagonistic effect of M1. These findings show that mosapride has dual role on the gastric emptying and may support the usefulness of mosapride for the therapy of postprandial distress syndrome such as early satiation and postprandial fullness.

Keywords: gastric emptying in rat, Gasmotin, mosapride citrate hydrate, metabolite (M1), GR113808

Introduction

5-Hydroxytryptamine (serotonin; 5-HT) has been known to be a neurotransmitter in the brain and the gut. The presence of 5-HT in the gastrointestinal tract has been demonstrated by immunohistochemical studies in enterochromaffin cells and in enteric neurons (1–3). Several 5-HT receptor subtypes have been identified in the gastrointestinal tract. These are located in nerves or on smooth muscle cells where they mediate a number of different actions (4, 5).

Mosapride citrate hydrate (mosapride) has been known to act as a 5-HT₄ agonist and has been known to enhance gastric motility (6). Seto et al. (7) reported that mosapride inhibited the gastric distension-induced visceromotor response in conscious rats, and this inhibitory effect of

mosapride was mediated via activation of 5-HT₄ receptors and blockage of 5-HT₃ receptors by a major metabolite of mosapride (M1). Yoshida et al. (8) also reported that M1 possessed a potent 5-HT₃ receptor-antagonistic property. Therefore, M1 would inhibit the gastric emptying. However, there were no detailed reports about the mode of action of mosapride and M1 on gastric emptying, including their effects on the time course of gastric emptying and dosage effect.

On the other hand, ¹³C-breath tests have been developed recently as a nonradioactive alternative in clinical study. The ¹³C-labeled urea breath test, in particular, has been widely employed clinically to monitor *Helicobacter pylori* infections. In addition, the [1-¹³C]octanoic acid breath test has been applied frequently in the clinical diagnosis of gastric-emptying disorder since it was first reported by Ghos et al. in 1993 (9). We recently reported a simple and non-invasive breath test for evaluating gastric emptying using [1-¹³C]acetic acid (10) and used it to evaluate the effects of drugs, such as metoclopramide,

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atropine sulfate, loperamide, morphine, and itopride (10–13).

Then, in this study we investigated the dosage effect of mosapride (5-HT₄ receptor agonist) and time course of the gastric emptying using the breath test with [1-¹³C] acetic acid. Moreover, the effect of M1 (5-HT₃ receptor antagonist) on the gastric emptying was also investigated.

Materials and Methods

The following animal studies were performed according to Guiding Principles for the Care and Use of Laboratory Animals approved by The Japanese Pharmacological Society.

Animals

Male Sprague-Dawley rats (200–250 g) was purchased from SLC (Shizuoka) and kept for 1 week before the experiments in a room whose temperature and humidity were kept at 21°C ± 2°C and 55% ± 5%, respectively. The light and dark cycle was 12 h, and the light period was from 7:00 to 19:00.

Breath test

The breath test was performed according to the method reported by us (10). In brief, the breath test system is composed of an animal chamber (desiccator, 2000 ml), pump (Masterflex L/S; Cole-Palmer Inst. Co., Court Vernon Hills, IL, USA) and breath sampling bag (Ohtsuka Pharmaceutical Co., Ltd., Tokyo). Collected ¹³CO₂ air was measured with UBiT IR-300 and UBiT-AS10 (Ohtsuka Electronics Co., Ltd., Osaka).

Rats were placed in the chamber just after the oral administration of Racol (2.5 ml/kg, Nutrient formula; Ohtsuka Pharmaceutical Co., Ltd.) containing [1-¹³C] acetic acid (16 mg/kg). Expired ¹³CO₂ air was collected and measured at 5-min intervals until 70 min, followed by collection and measurement at 90 and 120 min after Racol administration. Expired ¹³CO₂ air was collected for 1.5 min at each measured point. Ventilation volume was 150 ml/min.

Analysis of the gastric emptying

The measured values were presented as the $\Delta^{13}\text{CO}_2$ (‰). The maximum concentration (C_{max} , ‰), the time taken to reach the maximum concentration (T_{max} , min), and the area under the curve ($\text{AUC}_{120 \text{ min}}$, ‰·min) were calculated using the $\Delta^{13}\text{CO}_2$ values.

Effect of mosapride on the gastric emptying

Mosapride was dissolved in the distilled water and administered orally (0.1 to 3 mg/kg, 5 ml/kg). The breath test was performed 30 min after mosapride administra-

tion. In the control rats distilled water was administered instead of mosapride (5 ml/kg).

In another experiment, mosapride at a dose of 30 mg/kg (5 ml/kg) was orally administered and the breath test was performed 30 min after its administration. In the control rats, distilled water was administered instead of mosapride (5 ml/kg).

Effect of GR113808 on the enhancement of the gastric emptying by mosapride

GR113808 suspended in distilled water was administered at a dose of 10 mg/kg (1 ml/kg, i.p.) 30 min before oral administration of mosapride at a dose of 3 mg/kg (5 ml/kg). The breath test was performed 30 min after mosapride treatment. In the control rats, distilled water was administered instead of GR113808 and mosapride.

Effect of M1 on the gastric emptying

M1 (19.2 and 64.1 mg/kg, 5 ml/kg) was dissolved in distilled water and orally administered. The breath test was performed 30 min after the administration. In the control rats, distilled water was administered instead of M1 (5 ml/kg). M1 of 19.2 and 64.1 mg/kg was equimolar to 30 and 100 mg/kg mosapride, respectively.

Agents

Mosapride citrate hydrate and M1 were kindly given to us by Dainippon Sumitomo Pharmaceutical Co., Ltd. [1-¹³C] acetic acid and Racol were purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA) and Ohtsuka Pharmaceutical Co., Ltd., respectively. GR113808 was purchased from Sigma-Aldrich (St. Louis, MO, USA).

Statistical analysis

Results were represented as the mean ± S.E.M. Statistical analyses were performed by Student's *t*-test or Dunnett's multiple comparison method, and values of $P < 0.05$ were regarded as significant.

Results

Effect of mosapride on the gastric emptying

In the control rats, expired ¹³CO₂ increased with time until 32.5 min when it peaked and decreased thereafter (Fig. 1). C_{max} and $\text{AUC}_{120 \text{ min}}$ values were 271.2‰ ± 7.5‰, 18627‰ ± 736‰·min, respectively (Table 1). By the pre-treatment with mosapride, gastric emptying was dose-dependently enhanced (Fig. 1). C_{max} and $\text{AUC}_{120 \text{ min}}$ values were significantly increased at 1 mg/kg or over, but T_{max} was not affected (Table 1).

In another experiment to evaluate the effect of 30 mg/kg of mosapride, expired ¹³CO₂ increased in with time until

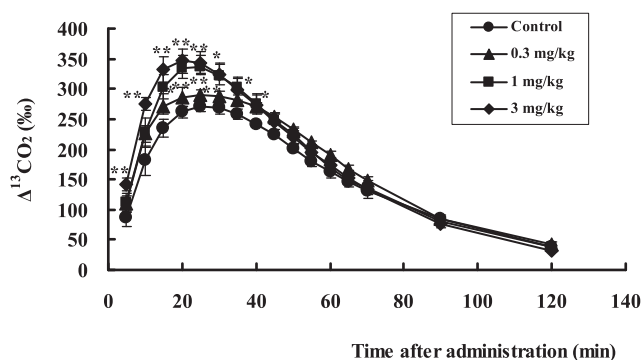


Fig. 1. Effect of mosapride citrate hydrate (0.3–3 mg/kg) on the time course of $^{13}\text{CO}_2$ in the expired air from rats after administration of Racol containing $[1-^{13}\text{C}]$ acetic acid. Values represent the mean \pm S.E.M. of 4 rats. * $P < 0.05$, ** $P < 0.01$: significant difference from the control.

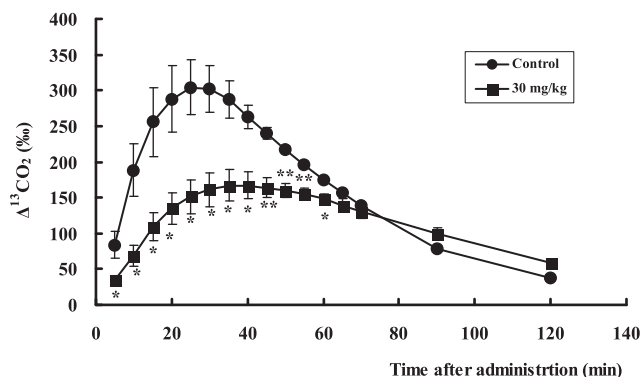


Fig. 2. Effect of mosapride citrate hydrate (30 mg/kg) on the time course of $^{13}\text{CO}_2$ in the expired air from rats after administration of Racol containing $[1-^{13}\text{C}]$ acetic acid. Values represent the mean \pm S.E.M. of 3 or 4 rats. * $P < 0.05$, ** $P < 0.01$: significant difference from the control.

Table 1. Effects of mosapride citrate hydrate (0.3–3 mg/kg) on the pharmacokinetic parameters of the expired $^{13}\text{CO}_2$ levels from $[1-^{13}\text{C}]$ acetic acid in conscious rats

	Control	Mosapride citrate hydrate (mg/kg)		
		0.3	1	3
C_{\max} (‰)	271.2 ± 7.5	189.9 ± 15.2	$339.3 \pm 12.5^{**}$	$395.2 \pm 18.3^{**}$
T_{\max} (min)	30.0 ± 2.1	27.5 ± 1.4	23.3 ± 1.7	21.3 ± 1.3
$\text{AUC}_{120 \text{ min}}$ (‰·min)	18627 ± 736	19992 ± 416	20254 ± 269	20662 ± 7918

Values represent the mean \pm S.E.M. (n = 4). ** $P < 0.01$: significant difference from the control.

Table 2. Effects of mosapride citrate hydrate (30 mg/kg) on the pharmacokinetic parameters of the expired $^{13}\text{CO}_2$ levels from $[1-^{13}\text{C}]$ acetic acid in conscious rats

	Control	Mosapride citrate hydrate (30 mg/kg)
C_{\max} (‰)	309.1 ± 34.7	$178.9 \pm 15.3^*$
T_{\max} (min)	25.0 ± 2.9	41.3 ± 5.5
$\text{AUC}_{120 \text{ min}}$ (‰·min)	19051 ± 1444	$13822 \pm 1290^*$

Values represent the mean \pm S.E.M. (n = 3 or 4). * $P < 0.05$: significant difference from the control.

it peaked at 25.0 min and decreased thereafter in the control rats (Fig. 2). C_{\max} and $\text{AUC}_{120 \text{ min}}$ values were $309.1\% \pm 34.7\%$, $19051\% \pm 1444\% \cdot \text{min}$, respectively (Table 2). Mosapride significantly inhibited the gastric emptying (Fig. 2). C_{\max} and $\text{AUC}_{120 \text{ min}}$ values were also significantly decreased, but T_{\max} was not affected (Table 2).

Effect of GR113808 on the enhancement of the gastric emptying by mosapride

In the control rats, expired $^{13}\text{CO}_2$ increased with time until it peaked at about 30 min and decreased thereafter (Fig. 3). C_{\max} and $\text{AUC}_{120 \text{ min}}$ values were $299.2\% \pm 16.6\%$, $22400\% \pm 356\% \cdot \text{min}$, respectively (Table 3). Mosapride at a dose of 3 mg/kg (5 ml/kg, p.o.), significantly enhanced

the gastric emptying and C_{\max} value significantly increased as compared with the control (Table 3). Pre-treatment with GR113808 significantly attenuated the mosapride-induced increase of expired $^{13}\text{CO}_2$ (Fig. 3) and C_{\max} value showed a tendency to decrease as compared with mosapride-administered rats ($P < 0.10$) (Table 3).

Effect of M1 on the gastric emptying

In the control rats, expired $^{13}\text{CO}_2$ increased with time, peaking at about 30 min (Fig. 4). C_{\max} and $\text{AUC}_{120 \text{ min}}$ values were $274.3\% \pm 13.4\%$ and $18491\% \pm 715\% \cdot \text{min}$, respectively (Table 4). Treatment with M1 significantly inhibited the gastric emptying at both doses of 19.2 and 64.1 mg/kg (Fig. 4). C_{\max} value was significantly decreased at doses of 19.2 and 64.1 mg/kg and $\text{AUC}_{120 \text{ min}}$

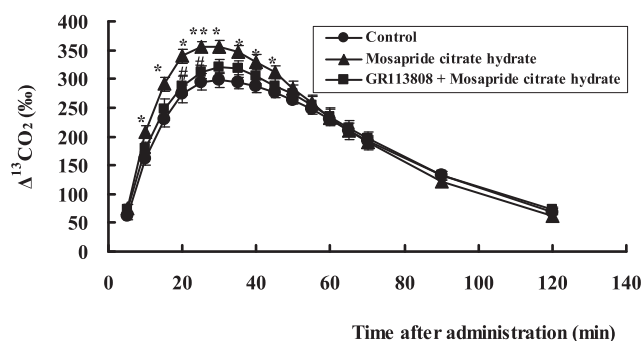


Fig. 3. Effect of GR113808 on the enhancement of gastric emptying by mosapride citrate hydrate (3 mg/kg) in rats after administration of Racol containing [1-¹³C]acetic acid. * $P < 0.05$, ** $P < 0.01$: significant difference from the control. # $P < 0.05$: significant difference from mosapride citrate hydrate.

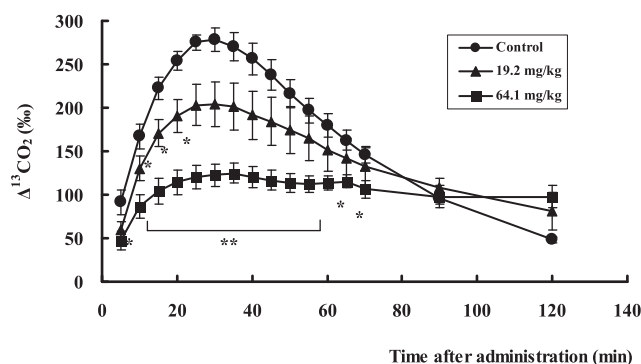


Fig. 4. Effect of M1 on the time course of ¹³CO₂ in the expired air from rats after administration of Racol containing [1-¹³C]acetic acid. Values represent the mean \pm S.E.M. of 4 rats. * $P < 0.05$, ** $P < 0.01$: significant difference from the control.

Table 3. Effects of GR113808 on the enhancement of gastric emptying by mosapride citrate hydrate: Pharmacokinetic parameters of the expired ¹³CO₂ levels from [1-¹³C]acetic acid in conscious rats

	Control	Mosapride citrate hydrate (3 mg/kg)	
		Control	GR113808 (10 mg/kg)
C _{max} (‰)	299.2 \pm 16.6	363.0 \pm 10.0**	318.8 \pm 15.5 ⁺
T _{max} (min)	28.8 \pm 2.4	27.5 \pm 2.5	30.1 \pm 2.00
AUC _{120 min} (‰·min)	22400 \pm 356	24334 \pm 862	23369 \pm 824

Values represent the mean \pm S.E.M. (n = 4). ** $P < 0.01$: significant difference from the control. ⁺ $P < 0.10$: tendency to decrease as compared with mosapride citrate hydrate.

Table 4. Effects of M1 (major metabolite of mosapride citrate hydrate) on the pharmacokinetic parameters of the expired ¹³CO₂ levels from [1-¹³C]acetic acid in conscious rats

	Control	M1 (mg/kg)	
		19.2	64.1
C _{max} (‰)	274.3 \pm 13.4	206.4 \pm 24.9	127.4 \pm 11.1**
T _{max} (min)	27.5 \pm 1.4	28.8 \pm 2.4	36.3 \pm 4.3
AUC _{120 min} (‰·min)	18491 \pm 715	16433 \pm 1427	12647 \pm 937**

Values represent the mean \pm S.E.M. (n = 4). ** $P < 0.01$: significant difference from the control.

value at a dose of 64.1 mg/kg (Table 4). T_{max} value was not affected (Table 4).

Discussion

5-HT is contained in serotonergic neurons in the enteric nervous system. 5-HT interacts with seven different receptor subtypes, five of which are found in the gastrointestinal tract, namely 5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄, and 5-HT₇ receptors (14, 15). Serotonergic modulation of upper gut sensitivity appears to be promis-

ing for the development of novel approaches to the treatment of functional disorders of the upper gastrointestinal tract (16). 5-HT₃ and 5-HT₄ receptors have been investigated as a major therapeutic target for management of gastrointestinal motility disorders, and 5-HT₄ receptor agonists have been shown to have potent prokinetic effects in the gastrointestinal tract (17).

Mosapride, selective 5-HT₄ receptor agonist, stimulates gastric motility and gastric emptying in animals and human (6, 18) and has been shown to enhance colonic motility and rectorectal and rectoanal reflexes in guinea

pigs (19, 20). In a clinical study, Ruth et al. (21) reported the efficacy of mosapride in the patients with gastroesophageal reflux disease from the finding that mosapride significantly improved total acid clearance time by enhancing gastric emptying.

In the present study, mosapride dose-dependently and significantly enhanced the gastric emptying at doses of 0.3 to 3 mg/kg. This action would be mediated through the 5-HT₄ receptor–agonistic action as reported by other researchers (6, 18, 21). Sakamoto et al. (22) also reported that mosapride accelerated the delayed gastric emptying of high-viscosity liquids in a crossover study using the continuous real-time C breath test (BreathID System). This finding supports the present results using the same breath test system, although the precise methods were different from each other. In the present study, the pre-treatment with GR113808 significantly attenuated the enhancement of gastric emptying by mosapride. This finding strongly suggests the involvement of 5-HT₄ receptors in the enhancement of gastric emptying by mosapride.

Wang et al. (23) reported that 5-HT₁ and 5-HT₄ receptors may mediate the contraction of the 5-HT–induced response and 5-HT₂ and 5-HT₃ receptors may mediate 5-HT–induced relaxation in feline ileal longitudinal smooth muscles. Tsukamoto et al. (24) reported that the use of mosapride in combination with prednisolone is effective for attenuating prednisolone-induced gastrointestinal adverse events. Kato et al. (25) reported that endogenous 5-HT exerts a dual role in the pathogenesis of indomethacin-induced intestinal lesions: pro-ulcerogenic action via 5-HT₃ receptors and anti-ulcerogenic action via 5-HT₄ receptors. As mentioned above, 5-HT₃ and 5-HT₄ receptors are closely related to each other in their gastrointestinal function.

In the present study, a significant inhibition of gastric emptying was observed by mosapride at a dose of 30 mg/kg. If the 5-HT₄ receptor–agonistic action had a major effect on gastric emptying, gastric emptying at 30 mg/kg would be enhanced more than at a dose of 3 mg/kg, but the gastric emptying was significantly inhibited. The LD₅₀ value of mosapride was > 3000 mg/kg (cited from the Interview Form of Gasmotin). Therefore, the dose of 30 mg/kg seems not to be toxic. Indeed, no toxic symptom was observed in this study. In the clinic, 5 mg is administered orally three times a day. In the case of a barium enema, 20 mg is administered orally at once. Therefore, 30 mg/kg seems not to be a toxic dosage. Mosapride has been known to be metabolized to the M1. Yoshida et al. (26) reported that M1 possessed a potent 5-HT₃ receptor antagonist property. Indeed, M1 dose-dependently inhibited gastric emptying. Mosapride at 30 mg/kg is equimolar to M1 at 19.2 mg/kg, suggesting

that the inhibitory effect by mosapride may be caused at least in part by the 5-HT₃ receptor–antagonistic effect of M1. However, to clarify the inhibitory mechanism of gastric emptying by mosapride at 30 mg/kg, further study is needed.

In Rome III, functional dyspepsia is categorized into postprandial distress syndrome and epigastric pain. Postprandial distress syndrome is further divided into early satiation and postprandial fullness, which are closely related to gastric motility. Seto et al. (6) reported that mosapride was useful in alleviating functional dyspepsia-associated gastrointestinal symptoms via increase in pain threshold using the balloon gastric distension method to enable measurements of abdominal muscle contractions in conscious rats and that M1 also inhibited the gastric distension-induced visceromotor response. This finding shows the enhancement of adaptive relaxation (accommodation) by mosapride and suggests its usefulness for early satiation following the delay of gastric emptying. However, mosapride is also used in the therapy for postprandial fullness following the enhancement of gastric emptying. Therefore, the dual role of mosapride on gastric emptying observed in the present study may explain its clinical usefulness for the therapy of postprandial distress syndrome mentioned above.

In conclusion, mosapride showed dual roles on gastric emptying through a 5-HT₄ receptor–agonistic effect and a 5-HT₃ receptor–antagonistic effect. This dual role may explain the utility of mosapride for the therapy of postprandial distress syndrome.

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