

The Prokinetic Effect of Mosapride Citrate on Horse Gastric Emptying Rates

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ABSTRACT. The prokinetic effect of the 5-HT₄ receptor agonist mosapride was evaluated in seven healthy thoroughbreds. Mosapride was orally administered at doses of 0.5, 1.0 or 1.5 mg/kg. The breath ¹³CO₂/¹²CO₂ rate ($\Delta^{13}\text{CO}_2$), an indirect indicator for the rate of gastric emptying, was measured at appropriate points for 4 hr after drug administration. There was a significant increase compared with the control value at 15, 20 and 165 min for 0.5 mg/kg, 30 min at 1.0 mg/kg and 165 min for 1.5 mg/kg. The results suggest that mosapride may facilitate the gastric emptying in horses.

KEY WORDS: equine, gastric emptying rate, mosapride citrate.

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Gastric emptying is delayed in horses with various gastrointestinal disorders including chronic or recurrent colic [2, 6–8] as well as postoperative ileus [1]. Delayed gastric emptying may not be only a consequence of these disorders but also may cause them. It actually dose cause anorexia and abdominal discomfort/pain, aggravating gastrointestinal disorders. A variety of prokinetic agents, including metoclopramide and cisapride, have been administered to horses in order to coordinate gastrointestinal motility [4, 9], although they may produce unfavorable side effects on both the central nervous and cardiovascular systems [14]. Evidence has suggested that mosapride citrate (mosapride), a 5-HT₄ receptor-preferring agonist, is a more promising prokinetic [30, 15]. This agent does not interact with central dopamine receptors and hardly has any extrapyramidal side effects. It also has little activity in blocking cardiac K⁺ channels and produces no significant ventricular arrhythmia with prolonged QT intervals [3, 10]. However, the effect of mosapride on gastric emptying in horses has yet to be investigated.

To do this, we used seven healthy thoroughbreds to examine the effect of orally-administrated mosapride on the rate of solid-phase gastric emptying using the ¹³C-octanoate breath test.

The animals used (1 mare and 6 geldings) had an average age of 5.6 ± 2.6 years (mean \pm SD: n=7) and a mean body weight of 485.7 ± 46.9 kg (n=7). They were fed an ordinary diet (0.9 kg oats, 0.3 kg bran and 3.5 kg hay) twice daily and were allowed *ad libitum* access to water. The individual horses were each subjected to the breath test repeatedly at intervals of 7 to 9 days. Housing and care of the horses and the present study were in accordance with the protocol approved by the institutional animal care and use committee of Obihiro University.

Breath samples were collected via a silicon tube inserted

into the ventral nasal meatus, as described previously [12], and into zoo or 1,300 ml UBit[®]-specialized breath sampling bags (Otsuka Pharmaceutical, Japan). The test meal consisted of 150 g oats, 100 g bran (200 mL in volume) and 500 mg ¹³C-octanoate (1-¹³C sodium octanoate, 99%; Wako Pure Chemical Industries, Japan) in 2 baked egg yolks. The test meal was ingested voluntarily.

Mosapride (GASMOTIN[®] Powder 1%) was purchased from Dainippon Sumitomo Pharma Co., Ltd. (Osaka, Japan). Following overnight fasting (12 hr), the drug was dissolved in 1,000 mL distilled water and administered at a dose of 0.5 to 1.5 mg/kg through a nasogastric tube. As a control, 1,000 mL distilled water alone was administered in a similar manner. Thirty minutes after drug administration, the test meal was given. Breath samples were collected into four 1,300 mL bags before administration and then into 200 mL bags at different times (5 to 240 min) after the test meal (see Fig. 1). The samples collected were analyzed using a

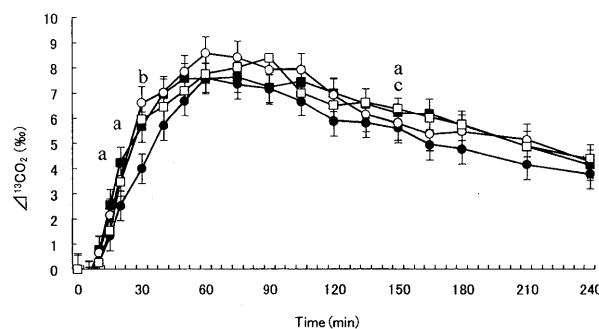


Fig. 1. Mean values of $\Delta^{13}\text{CO}_2$ (‰) \pm SD of breaths collected over the 4-hr test period, following solid test food intake and mosapride administration at doses of 0.5 mg/kg (■, n=7), 1.0 mg/kg (○, n=7) and 1.5 mg/kg (□, n=6). ●: control (without drug administration, n=7). One-way repeated measures ANOVA and Fisher's PLSD was used to determine significant differences between values. a: Significantly ($p < 0.05$) different between 0 mg and 0.5 mg, b: Significantly ($p < 0.05$) different between 0 mg and 1.0 mg, c: Significantly ($p < 0.05$) different between 0 mg and 1.5 mg.

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$^{13}\text{CO}_2$ -infrared spectrophotometry analyzer (POC One[®], Otsuka Pharmaceutical, Japan). The excretion of ^{13}C was expressed as the difference ($\Delta^{13}\text{CO}_2$, ‰) between the $^{13}\text{CO}_2$ / $^{12}\text{CO}_2$ ratios before and after test meal administration. The assay system used was valid only when the CO_2 concentration in the breath sample was above 0.5%. The time when $\Delta^{13}\text{CO}_2$ reached the maximum was regarded as the time of peak excretion (t_{max}). If there were multiple peaks for $\Delta^{13}\text{CO}_2$, the earliest one was taken as the t_{max} .

The results are presented as means \pm SD. One-way repeated measures ANOVA was used to determine significant differences between values. When a significant difference was found, a post-hoc test (Fisher's PLSD) was performed for further evaluation. Differences were considered significant when $P < 0.05$.

During the ^{13}C -octanoated breath tests, none of the horses had any abnormal clinical signs, such as colic, sweating and agitation. Figure 1 shows plots of the rate of breath $\Delta^{13}\text{CO}_2$ (‰) against the time after administration of mosapride at 0.5, 1.0 or 1.5 mg/kg. The breath $\Delta^{13}\text{CO}_2$ of the drug-treated groups increased more rapidly and decreased more slowly, compared with that for the control group. Significantly higher rates ($p < 0.05$) than the control value were observed at 15, 20, and 165 min with 0.5 mg/kg mosapride, at 30 min with 1.0 mg/kg mosapride, and at 165 min with 1.5 mg/kg mosapride.

The breath $\Delta^{13}\text{CO}_2$ was determined by measuring the ^{13}C levels of breath samples hourly. It has previously been described as fluctuating depending on changes in the rate of duodenum absorption, liver metabolism, lung excretion or gastric emptying [5]. It is possible that the breath $\Delta^{13}\text{CO}_2$ may preferentially reflect changes in the rate of gastric emptying [5]. Thus, the increases in breath $\Delta^{13}\text{CO}_2$ observed with oral administration of mosapride may suggest that this drug has a facilitating effect on gastric emptying in horses. In addition, it is generally considered that the t_{max} measured for the breath $\Delta^{13}\text{CO}_2$ is reached before the ^{13}C gastric emptying rate increases [11], and thus it is possible that the facilitating effect of mosapride lasts longer than expected from the t_{max} for the breath $\Delta^{13}\text{CO}_2$.

However, there was no eminent dose-dependence for the mosapride effect. Furthermore, significant increases in the breath $\Delta^{13}\text{CO}_2$ by mosapride only occurred at limited time

points after oral administration. Further studies are needed to establish the facilitating effect of mosapride on gastric emptying. Mosapride is a selective 5-HT₄ receptor agonist, but no evidence has been provided for the distribution of 5-HT₄ receptors in the horse stomach. Further studies are needed again to elucidate the mechanism underlying the mosapride effect found in the present study.

The present results indicate the possibility that oral administration of mosapride facilitates gastric emptying of solid food in healthy horses and that it might be promising as a prokinetic agent for horses with delayed gastric emptying.

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