Gastric motility disorders are induced by various pathological conditions and may be associated with upper gastrointestinal clinical symptoms, such as anorexia, nausea, or vomiting [2, 12]. A prokinetic agent promotes gastrointestinal motor activity and is used for symptomatic treatment of gastrointestinal motility disorders. Several prokinetic agents have been developed in humans and some of them are utilized in dogs [7, 12].

Mosapride citrate (mosapride), a selective 5-hydroxytryptamine-4 receptor (5-HT₄R) agonist, promotes the release of acetylcholine from enteric nerves by activating 5-HT₄R, thereby enhancing gastrointestinal motility [5]. This drug is widely used in humans as a prokinetic agent for the control of dyspeptic symptoms of gastrointestinal disorders, including chronic gastritis, functional dyspepsia, irritable bowel syndrome (IBS), and gastroesophageal reflux disease (GERD) [5]. Mosapride is also registered as a prokinetic agent in dogs (Pronamid; DS Pharma Animal Health Co., Ltd.) with a 7.5-MHz ultrasound (Aplio 80 SSA-770A; Toshiba Medical Systems Corporation, Co., Ltd., Tochigi, Japan) [13]. After the single administration of mosapride at each dose was compared with that of the control (9.37 ± 0.51). Mosapride administration (2.0 mg/kg, BID) for 1 week had no adverse effects on blood tests or health of the animals. In conclusion, 0.75 to 2 mg/kg of mosapride produces gastric prokinetic actions without adverse effects.

**NOTE**

Internal Medicine

**Prokinetic Effect of the 5-HT₄R Agonist Mosapride on Canine Gastric Motility**

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**ABSTRACT.** We assessed prokinetic action of gastroprokinetic agent, mosapride in dogs. Open-label cross-over study. Six healthy beagles were administered single oral mosapride at doses of 0.5, 0.75, 1, and 2 mg/kg 30 min prior to feeding, followed by 1-week interval. The motility index (MI) of gastric contraction was ultrasonographically evaluated by change rate of antral area and contraction number. Significant increases in MI were observed at doses of 0.75 mg/kg (mean ± SEM, 11.11 ± 0.19), 1 mg/kg (11.65 ± 0.34), and 2 mg/kg (12.04 ± 0.34), compared with that of the control (9.37 ± 0.51). Mosapride administration (2.0 mg/kg, BID) for 1 week had no adverse effects.

**KEY WORDS:** canine, gastrointestinal clinical symptoms, prokinetic agent.

body weight ranged from 10.5 to 15.0 kg (median, 12.5 kg). Three dogs were male and 3 were female. None of the dogs displayed any clinical symptoms prior to the experiments. Food was offered twice daily. Experiments and animal care complied with the policies outlined in the Guide to Animal Use and Care of the University of Tokyo. This study was performed with open-label cross-over study design. The dogs received mosapride at doses of 0.5, 0.75, 1, and 2 mg/kg (Pronamid; DS Pharma Animal Health Co., Ltd.) followed by 1-week washout period. The gastric antral motility was ultrasonographically assessed after single administration of mosapride according to a previous report in dogs [11]. The tablet drug was ground into powder and dissolved in 15 ml of distilled water. Administration of distilled water (15 ml) was used as control. Gastric motility after the single administration of mosapride at each dose was compared with that of control. The order of the assessment in the 6 dogs was randomly assigned and a washout period of at least 1 week was set between each experiment. Thirty minutes after mosapride was administered, 10 g/kg of commercial wet food (CIW; Intervet Schering-Plough Animal Health, Tokyo, Japan) was offered. Gastric antral motility was evaluated 30 min after feeding by using an ultrasound (Apio 80 SSA-770A; Toshiba Medical Systems Corporation, Co., Ltd., Tochigi, Japan) with a 7.5-MHZ phased array sector transducer. Dogs were restrained in the right recumbent position, and the probe was adjusted for maximum visualization of the transverse image of the gastric antrum close to the left lobe of the liver. The cross section of the antral area was measured by tracing the serosal margin of the antrum by using the built-in caliper. The antral area was measured 3 times in both the contracted and relaxed phases, and amplitude was calculated with the following formula: (mean area relaxed – mean area contracted)/mean area relaxed. Next, frequency was determined by counting the number of antral contractions in
Motility index (MI), an indicator of gastric motility, was determined by the multiplication of amplitude and frequency. The same investigator performed all ultrasonographic examinations.

Next, we evaluated the safety of repeated administration of mosapride in these dogs according to the result of blood tests and clinical assessments. Dogs were administered mosapride at a dose of 2 mg/kg twice daily for 1 week. Blood testing was performed before and after 1-week administration of mosapride. Venous blood samples were collected into EDTA tubes for the measurement of red blood cell (RBC) counts, white blood cell (WBC) counts, differential WBC counts, hematoctrit, hemoglobin concentration and platelet counts. Additional blood samples were collected into heparin tubes for analysis of blood chemistry (blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, glucose, total cholesterol, triglyceride, calcium, phosphate, sodium, chloride, potassium, albumin, and total protein levels). During the medication period, the dogs were assessed for clinical symptoms 3 times a day, and physical examination was also performed. The clinical assessments were performed by a veterinarian.

The difference in MI for each treatment was analyzed by one-way repeated measures of ANOVA. When significant, multiple comparisons were adjusted using Dunnett’s t test. Results were expressed as mean ± SEM. P<0.05 was considered as a significant difference.

None of the dogs had any blood test abnormalities before or after the 1-week administration of mosapride (data not shown). Clinical adverse events were not observed in any of the dogs, and there were no abnormalities on the physical examinations.

Our study demonstrated that oral administration of mosapride increases canine postprandial gastric motility in a dose-dependent fashion within the dose of 2 mg/kg. However, a significant increase in gastric motility was not observed when 0.5 mg/kg of mosapride was orally administered to the dogs. This result is consistent with that of a previous report that evaluated the intravenous administration of mosapride (AS-4370) in dogs. In that report, more than 1 mg/kg, but not 0.5 mg/kg, of mosapride enhanced the motility of the gastric antrum and duodenum in conscious dogs [15]. In humans, mosapride is usually prescribed at 5 mg TID for the treatment of gastrointestinal discomfort [5]. The dose of mosapride appears to be higher in dogs than that in humans. This dose difference may be associated with dissimilar bioavailability or metabolism. A previous report indicated that the bioavailability of mosapride in dogs was lower than that in other species, such as monkeys [10]. Considering the present results and previous reports [8, 15], the recommended dose of mosapride in dogs is 0.75 to 2 mg/kg. Doses of up to 2 mg/kg may be required in low-response patients or cases of severe gastric motility disorders, such as gastroparesis. Further studies are required to evaluate the prokinetic action of mosapride in gastric motility disorders in dogs and the effect of oral mosapride administration on canine intestinal motility.

We evaluated the prokinetic action of mosapride by assessing the postprandial gastric antral motility in dogs. Postprandial gastric motility function could be assessed either by gastric emptying assessment or gastric antral motility evaluation. Gastric antral motility is regarded as one of the major regulator of the gastric transit [4]. The ultrasonographic method we used in the present study had already confirmed the correlation with gastric emptying time determined by 13C-octanoic acid breath test in advance [11]. Following our studies, further studies may be required to investigate whether mosapride enhance the gastric emptying rate as well.

We confirmed that repeated administration of mosapride in dogs for 1 week did not cause any adverse clinical effects or blood test abnormalities. The advantage of mosapride over several prokinetic agents in humans is its safety. Some gastroprokinetic agents, like metoclopramide, may cause sedation through dopamine receptors in the central nervous system [1, 6]. Mosapride has a high affinity for the 5-HT4R in the gastrointestinal tract and does not have affinity for the 5-hydroxytryptamine-1 (5-HT1), 5-hydroxytryptamine-2 (5-HT2), or Dopamine-2 (D2) receptors in the central nervous system [16]. Further to this study, longer safety assessments should be conducted in cases of canine gastric motility disorder receiving mosapride. The pharmacological action of mosapride is similar to that of cisapride. Both agents enhance gastrointestinal motility by triggering acetylcholine release from enteric nerves subsequent to 5-HT4R stimulation. Cisapride had been used for the treatment of gastrointestinal motility disorders in humans and dogs [3, 12]. However, cisapride has potent action on cardiac tissue,
which may inhibit the K⁺ channel, leading to cardiac adverse effects such as QT prolongation [9, 13]. Due to the cardiac adverse effects in human, cisapride was withdrawn from market and only available in experimental use [7, 13]. In contrast, it has been confirmed that mosapride has no effect on cardiac K⁺ channel and do not cause any cardiac adverse effects in both humans and dogs [5, 9, 14]. Mosapride can be an alternative prokinetic agent to cisapride for the treatment of gastrointestinal discomfort associated with upper gastrointestinal motility disorders in dogs.

In summary, oral mosapride administration dose-dependently increased canine postprandial gastric motility without causing any adverse effects within the dose of 2 mg/kg. We hope that this study will facilitate appropriate prescription of mosapride for the treatment of upper gastrointestinal clinical signs in dogs.

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