FULL PAPER *Pharmacology*

Pharmacokinetics of the Gastroprokinetic Agent Mosapride Citrate after Single Oral Administration in Horses

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ABSTRACT. The purpose of this study was to determine the pharmacokinetics and dose proportionality of mosapride citrate, a selective 5-HT_4 agonist, after oral administration in horses. Seven healthy Thoroughbreds were dosed with distilled water and 0.5, 1.0, or 1.5 mg/kg mosapride citrate through a nasogastric tube. Serum mosapride concentrations were measured by a liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. Mosapride showed the C_{max}s of 31, 60, and 104 *n*g/g and AUCs of 178, 357, and 566 *n*g·hr/g at doses of 0.5, 1.0, 1.5 mg/kg, respectively. The C_{max}s and AUCs increased in proportion to the dose, indicating linear pharmacokinetics of mosapride up to 1.5 mg/kg. The pharmacokinetic profiles of mosapride in horses are quite different from that in humans. The average $t_{1/2}$ in horses was almost 2 fold longer than that reported in healthy adult humans. Therefore, it is thought that it is suitable to reduce the number of doses a day in horses compared to humans.

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

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Mosapride citrate, a selective 5-HT_4 receptor agonist, is a gastroprokinetic agent used clinically in the treatment of human with gastrointestinal motility dysfunctions in Japan [3]. In horses, it has been reported that oral administration of mosapride citrate can promote motility in the small intestine and cecum [4, 9]. However, the pharmacokinetics of mosapride citrate in horses has not been cleared. In order to provide a basis for the clinical use of mosapride citarate in horses, we performed the pharmacokinetic study. In this study, we report mosapride citrate pharmacokinetic data obtained following after single oral dosing.

MATERIALS AND METHODS

Horses: Seven healthy Thoroughbred horses (6 geldings and 1 mare aged 5.6 ± 2.6 years and weighing 485.7 ± 46.9 kg) were used in this study. Horses were housed in individual box stalls, fed an ordinary diet (0.9 kg oats, 0.3 kg bran and 3.5 kg hay) twice daily, and allowed free access to water during the study. Housing and care of the horses and this study ware in accordance with the protocol approved by the institutional animal care and use committee of Obihiro University (No. 16–43).

Dosing and experimental design: All animals were fasted for 12 hr before dosing. Horses were dosed with distilled water and 0.5, 1.0, or 1.5 mg/kg mosapride citrate (Gasmotin® Dainippon Sumitomo Pharma, Co., Ltd., Osaka, Japan). For dosing, the powder were suspended in 500 m*l* water and administered by nasogastric tube. An additional 500 m*l* water was flushed through the tube to ensure complete delivery of the test dose. The study was conducted as a Latin-square design; thus, each horse received each dosage. There was a 1-week washout period between subsequent treatments.

Jugular venous blood was collected just before mosapride administration and at 0.25, 0.5, 1, 2, 3, 6, and 8 hr after dosing. After isolating the serum from the blood samples, the harvested serum samples were stored at –20°C pending mosapride analysis.

Analytical methods: Serum mosapride and M-1 (its metabolite) concentrations were measured by the liquid chromatography/tandem mass spectrometry (LC/MS/MS) method [1]. Mosapride, M-1 (des-*p*-fluorobenzyl mosapride; (±)-4-amino-5-chloro-2-ethoxy-*N*-[(2-morpholinyl)methyl]benzamide), and I.S. {(±)-4-amino-5-chloro-2-ethoxy-*N*-[[4-(2-chlorobenzyl)morpholinyl]methyl]benzamide} for concentrations measurement were obtained from Dainippon Sumitomo Pharmaceutical Co., Ltd. (Osaka, Japan). The quantification limits of mosapride and M-1 were 4 *n*g/g, and calibrations were linear (r>0.999) from 1 to 200 *n*g/m*l* in this study.

The maximum serum concentration (C_{max}) and the time to C_{max} (t_{max}) were obtained from individual profile by inspection. The apparent serum elimination half-life ($t_{1/2}$) was determined as $0.693/K_{el}$, where K_{el} is the elimination rate constant calculated by the least-squares method using the log-linear portion serum concentration-time curve. The area under the plasma concentration-time curve (AUC) was determined according to the trapezoidal rule, and area to infinity was added as calculated C_t/K_{el}, where C_t is the serum concentration at the terminal data point. The mean residence time (MRT) as area under the first moment of serum concentration-time curve/AUC.

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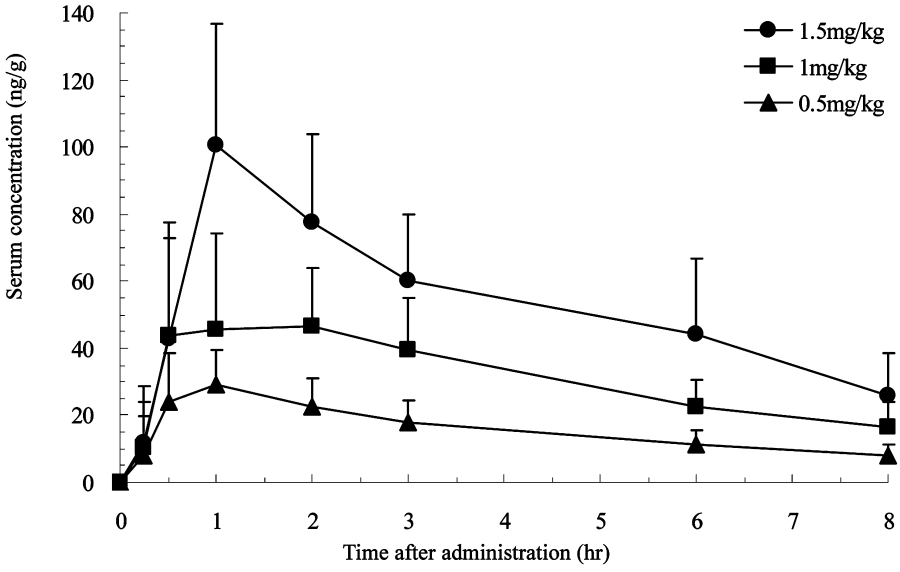

Fig. 1. Mean serum concentration of mosapride vs. time in horses after single oral administration at doses of 0.5 mg/kg (▲), 1.0 mg/kg (■), and 1.5 mg/kg (●). Results are expressed as the mean ± SD of 7 subjects.

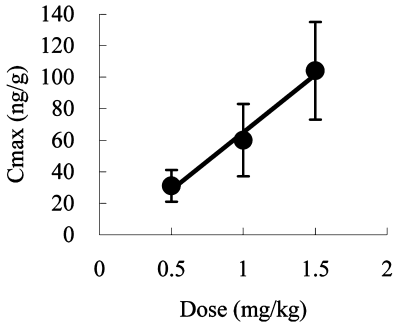

Fig. 2. Correlation of C_{max} of mosapride with dose in horses. The C_{max} increased in a dose-dependent manner (r=0.993, *P*=0.075). Results are expressed as the mean ± SD of 7 subjects.

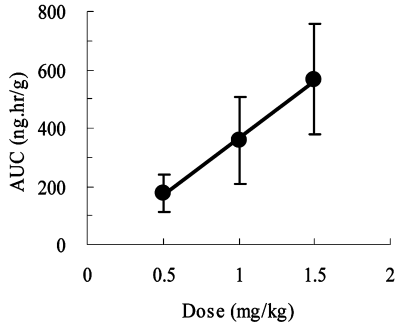

Fig. 3. Correlation of $AUC_{0-\infty}$ of mosapride with dose in horses. The $AUC_{0-\infty}$ increased in a dose-dependent manner (r=0.999, *P*=0.028). Results are expressed as the mean ± SD of 7 subjects.

Table 1. Mean pharmacokinetic parameters of unchanged mosapride calculated following single oral administration of mosapride to horses

Dose (mg/kg)	C_{max} (*n*g/g)	t_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (*n*g·hr/g)	$MPT_{0-\infty}$ (hr)
0.5	31 ± 10	0.9 ± 0.5	4.2 ± 0.6	178 ± 64	6.2 ± 1.0
1.0	60 ± 23	1.1 ± 0.6	4.2 ± 1.3	357 ± 149	6.5 ± 1.8
1.5	104 ± 31	1.1 ± 0.4	3.6 ± 1.5	566 ± 190	5.8 ± 1.9

Results are expressed as the mean ± SD of 7 subjects.
C_{max}: peak serum concentration, t_{max}: time to peak serum concentration, $t_{1/2}$: apparent serum elimination half-life, $AUC_{0-\infty}$: area under the serum concentration-time curve to infinity, MRT: mean residence time.

RESULTS

Serum concentration-time profiles of unchanged mosapride after single oral administration of 0.5, 1.0, 1.5 mg/kg are shown in Fig. 1, and pharmacokinetic parameters are listed in Table 1. Mean ± SD serum levels of the mosapride reached maximum 1–2 hr after administration, with levels of 29 ± 10, 47 ± 17, and 101 ± 36 *n*g/g at doses of 0.5, 1.0, and 1.5 mg/kg, respectively (Fig. 1). Thereafter, serum levels of mosapride decreased monoexponentially with $t_{1/2}$s of 3.6 to 4.2 hr.

Mosapride showed the C_{max}s of 31, 60, and 104 *n*g/g and AUCs of 178, 357, and 566 *n*g·hr/g at doses of 0.5, 1.0, and 1.5 mg/kg, respectively (Table 1). These two pharmacokinetic parameters increased in proportion to the dose (Figs. 2, and 3).

M-1 was measured in serum after administration of 0.5,

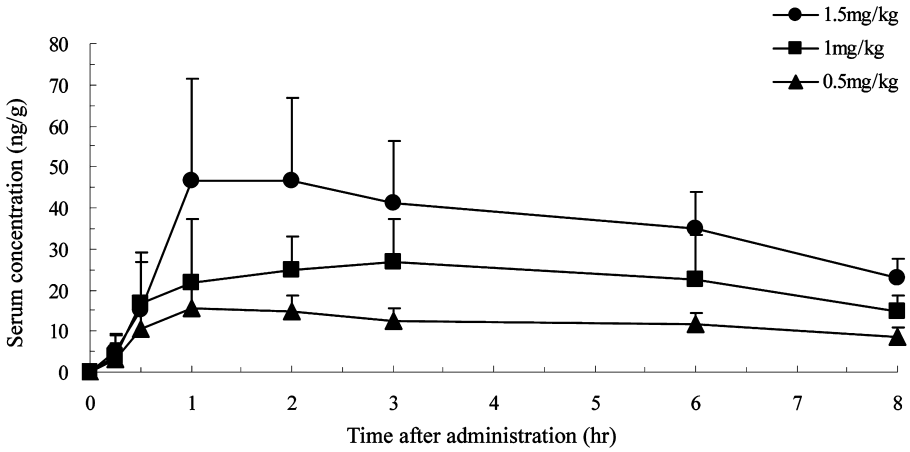

Fig. 4. Mean serum concentration of M-1 vs. time in horses after single oral administration at doses of 0.5 mg/kg (▲), 1.0 mg/kg (■), and 1.5 mg/kg (●). Results are expressed as the mean ± SD of 7 subjects.

1.0, 1.5 mg/kg. Mean ± SD concentrations of M-1 peaked 1–3 hr after dosing, with concentrations of 16 ± 5, 27 ± 10, 47 ± 20 *n*g/g (Fig. 4). The C_{max}s were 17, 32, and 53 *n*g/g and AUCs of 244, 292, and 458 *n*g·hr/g at doses of 0.5, 1.0, and 1.5 mg/kg, respectively (Table 2). The C_{max}s were approximately one-second of those of the unchanged mosapride. T1/2 of M-1 (11.7, 5.6, and 5.2 hr) were slower than those of the unchanged drug.

Table 2. Mean pharmacokinetic parameters of M-1 calculated following single oral administration of mosapride to horses

Dose (mg/kg)	C_{max} (*n*g/g)	t_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (*n*g·hr/g)	$MPT_{0-\infty}$ (hr)
0.5	17 ± 4	1.3 ± 0.7	11.7 ± 4.5	244 ± 90	16.8 ± 6.0
1.0	32 ± 9	2.4 ± 1.8	5.6 ± 1.7	292 ± 101	9.0 ± 2.0
1.5	53 ± 22	3.3 ± 2.6	5.2 ± 2.3	458 ± 129	8.5 ± 3.0

Results are expressed as the mean ± SD of 7 subjects.
C_{max}: peak serum concentration, t_{max}: time to peak serum concentration, $t_{1/2}$: apparent serum elimination half-life, $AUC_{0-\infty}$: area under the serum concentration-time curve to infinity, MRT: mean residence time.

DISCUSSION

Cisapride and tegaserod have been shown to have prokinetic effects in horses [2, 9]. Their pharmacokinetic information also have been reported [2, 10]. Although mosapride citrate has been reported that has gastroprokinetic effects in horses, pharmacokinetic data is not available. So we performed the pharmacokinetic study of mosapride in horses.

After oral administration to horses, mosapride was rapidly absorbed from gastrointestinal tract, and serum concentrations of unchanged drug peaked 1 hr. In this study, C_{max} and AUC of mosapride increased in a dose-dependent manner after single administration at doses from 0.5 to1.5 mg/kg. On the other hand, the t_{max}, $t_{1/2}$ and MRT were independent and remained constant on the administered dose. Therefore, these results indicate the linear pharmacokinetics of mosapride under doses of this study.

M-1 was found in horse serum together with the unchanged drug, as similar to experimental animals, dogs, and human [5–7]. Mosapride was shown to receive first-pass effect in experimental animals [5, 6]. The bioavailability (F) value was 0.47 in female rats, 0.14 in monkeys, 0.08 in dogs and 0.07 in male rats. The extent of first-pass effect could be approximately estimated from M-1 to mosapride concentration (C_{max}) ratio after single oral administration: 0.2 in female rats, 1.1 in monkeys, 1.0 in dogs and 6.3 in male rats [7]. The sequence of these ratio is consitent with those of first-pass effect. In addition, in human subjects, this ratio was 0.2 [7], and in horses, that was 0.5. These results suggest that mosapride undergoes less first-pass effect in horses than dogs, not less than man. So it is reasonable that optimal dosage in horses is much higher than that of man [4, 11]. Meanwhile, orally-administered M-1 enhanced gastric emptying of a semisolid meal and of a resin pellet meal in rats, and the potency was equal to or slightly less than that of the unchanged drug [12]. Therefore, M-1 may contribute in part to the pharmacological effects exerted by mosapride in horses.

The pharmacokinetic profiles of mosapride in horses are quite different from that in humans [7]. The $t_{1/2}$ in this study was almost 2 fold longer than in healthy adult humans. As described above, mosapride undergoes greater first-pass effect in horses than human. So it means the extended $t_{1/2}$ in horses is due to lower metabolism in horses compared to in human. Actually, the t_{max} of M-1 increased dose-dependently even though the t_{max} of unchanged drug was stable against dosage. Therefore, it is thought that it is suitable to reduce the number of doses a day in horses to half. On the other hand, the C_{max} obtained after single oral administration

of 5 mg mosapride in man is equall to that following after single oral dosing of 0.5 mg/kg mosapraide in horses [7]. Considering about this, it is reasonable that the administration of 0.5 mg/kg mosapride showed the prokinetic effect on horse gastric emptying rates [4].

The therapeutic dosage regimen of mosapride citrate in man is 5 mg, three times a day. Meanwhile, it has been reported that the optimal orally administered dosage of mosapride citrate in horse cecum is 1.5 to 2 mg/kg [8]. Although further studies are needed to establish the dosage regimen, it seems to be that the predicted therapeutic dosage regimen of mosapride citrate in horse gastric is 0.5 mg/kg, and in horse cecum is 1.5 to 2 mg/kg, once or twice a day.

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