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Effects of mosapride citrate, metoclopramide hydrochloride, lidocaine hydrochloride, and cisapride citrate on equine gastric emptying, small intestinal and caecal motility

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ABSTRACT

Objective: Although extensive work has been done to elucidate the beneficial and unfavorable effects of gastrointestinal prokinetic agents in humans, little is known on the effects of these agents in horses. In this study, we compared the effects of mosapride, metoclopramide, cisapride, and lidocaine on equine gastric emptying, jejunal and caecal motility and evaluated these agents' adverse drug reactions (ADRs).
Animals: Seven healthy adult Thoroughbreds.
Procedure: Mosapride 1.0 mg/kg and 2.0 mg/kg, metoclopramide 0.2 mg/kg, and cisapride 1.0 mg/kg were dissolved in 100 mL distilled water for oral administration. Lidocaine 1.3 mg/kg was mixed with 500 mL saline for a 30-min intravenous infusion. Oral administration of 100 mL distilled water was used as control. Gastric emptying was evaluated using $^{13}CO_2$ breath test, and jejunal and caecal motility was assessed by electrointestinography.
Results: The present study demonstrates that mosapride at doses of 1.0 mg/kg and 2.0 mg/kg facilitates gastric emptying in horses. Improved jejunal motility was observed following administration of mosapride (1.0 mg/kg and 2.0 mg/kg), metoclopramide (0.2 mg/kg), and cisapride (1.0 mg/kg). Similarly, improved caecal motility was observed following administration of mosapride (2.0 mg/kg).
Conclusions and clinical relevance: This study shows that among the prokinetic agents studied here, only mosapride (2.0 mg/kg) promotes jejunal and caecal motility in horses. Considering mosapride ADRs profile, it is believed that this compound is useful in the treatment of diseases associated with decreased GI motility, including postoperative ileus.

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1. Introduction

Gastrointestinal (GI) prokinetic agents are used to treat equine diseases caused by decreased GI motility, including postoperative ileus. Conventional GI prokinetic agents, including cisapride citrate (cisapride), metoclopramide hydrochloride (metoclopramide), and lidocaine hydrochloride (lidocaine), are reported to have favorable (Dart et al., 1996; Malone et al., 2006; Nieto et al., 2000) and unfavorable (Milligan et al., 2007; Toga et al., 2007; Tonini et al., 2004) effects. For instance, cisapride, a 5-hydroxitriptophan 4 (5-HT_4) receptor agonist and a 5-hydroxitriptophan 3 receptor antagonist, is known to promote GI motility, mainly by acting on the 5-HT_4 receptor in the myenteric plexus of the digestive tract and to increase acetylcholine release from nerve endings (Fink et al., 2006; Koenig and Cote, 2006; Sasaki and Yoshihara, 2000; Taniyama et al., 1991; Weiss et al., 2002). However, cisapride has also been reported to cause adverse drug reactions (ADRs) in humans, including prolonged QT interval and ventricular tachyarrhythmia, both of which are associated with cisapride's inhibitory effect on ERG K+ channels (ERG channels) in the heart (Cubeddu, 2003; Finley et al., 2002; Lillich et al., 2003; Sekkarie, 1997). Metoclopramide, on the other hand, is a dopamine D_2 (D_2) receptor antagonist that suppresses vagal ganglias, leading to increased acetylcholine release in nerve endings and promotion of GI motility (Albibi and McCallum, 1983; DiPalma, 1990; Hay and Man, 1979). As metoclopramide also suppresses the central D_2 receptor, its ADRs have been reported to include extrapyramidal symptoms, such as tremor and agitation (Tonini et al., 2004). Unlike cisapride and metoclopramide, lidocaine promotes GI motility by directly suppressing sympathetic nerves in the GI tract. Lidocaine does not increase the number of emerging migrating motor complexes on the anal side, and the mechanism of its GI prokinetic effect is still mostly unknown (Malone et al., 2006; Milligan et al., 2007). ADRs associated with lidocaine include fasciculations (Malone et al., 2006) and possibly falling incidents.

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The recently developed GI prokinetic agent mosapride citrate (mosapride) is known to promote GI motility by selectively acting on the 5-HT_4 receptor in the myenteric plexus and increasing acetylcholine release from nerve endings (Kim and Choi, 2007; Yoshida, 1991; Yoshida et al., 1993). Mosapride has also been demonstrated to promote jejunal and caecal motility in horses (Sasaki et al., 2005a). Unlike conventional GI prokinetic agents in clinical use, mosapride has been shown to have minimal effects on the D_2 receptor and ERG channels, and to consequently cause fewer ADRs (Toga et al., 2007; Yoshida, 1991). Therefore, the clinical use of mosapride as a substitute for cisapride, metoclopramide, and lidocaine appears promising.

Although extensive work has been done to elucidate the beneficial and unfavorable effects of GI prokinetic agents in humans, little is known on the effects of these agents in horses. Our aim in this study is to compare the effects of mosapride, cisapride, metoclopramide, and lidocaine on gastric emptying, jejunal and caecal motility in adult Thoroughbred horses and to evaluate these agents' adverse drug reactions (ADRs). Gastric emptying, jejunal and caecal motility were evaluated by ^{13}C breath test and electrointestimography, respectively. As for ADRs, animals were observed for clinical signs throughout the study.

2. Materials and methods

2.1. Study animals

Seven adult Thoroughbred horses (three stallions and four mares aged 4.1 ± 1.8 years and weighing 490.0 ± 43.0 kg) were used in this study. The horses were fasted for 12 h before initiation of the study tests (^{13}C breath test and electrointestimography). General feed was provided 14 h before the tests and water was given ad libitum. This study was approved by the Animal Experimental Committee of Obihiro University of Agriculture and Veterinary Medicine.

2.2. Study drugs

Mosapride[1] 1.0 mg/kg and 2.0 mg/kg, metoclopramide[2] 0.2 mg/kg, cisapride[3] 1.0 mg/kg were dissolved in 100 mL of distilled water for oral administration. Lidocaine[4] 1.3 mg/kg was mixed with 500 mL of saline for 30-min intravenous infusion. Oral administration of 100 mL of distilled water was used as control.

Drugs were evaluated over a period of 3–5 months with at least one week cross over period. Each of the study tests ($^{13}CO_2$ breath test and electrointestinography) was performed seven times and ADRs were monitored at 14 occasions.

2.3. Rationale for dose selection

The doses of metoclopramide and lidocaine (0.2 mg/kg, p.o. and 1.3 mg/kg, i.v., respectively) were selected based the dosages used to treat equine postoperative ileus and colon impaction (Malone et al., 2006; Milligan et al., 2007; Cubeddu, 2003). The dose of cisapride (1.0 mg/kg, p.o.) was selected based on the results of a previous study where cisapride at 1.0 mg/kg improved caecal motility (Spiller, 2002). Similarly, the doses of mosapride (1.0 mg/kg and 2.0 mg/kg, p.o.) were selected based on the results of a previous study showing that mosapride at these doses promotes intestinal and caecal motility (Sasaki et al., 2005a).

2.4 ^{13}C breath test

Breath samples were collected into UBit®-specialized breath sampling bags[5] (200–1300 mL) via a silicon tube inserted into the ventral nasal meatus, as described previously (Sasaki et al., 2005b). The test meal consisted of 150 g oats, 100 g bran (200 mL in volume), and 500 mg ^{13C}-octanoate[6] in two baked egg yolks. The test meal was ingested voluntarily 30 min after drug administration.

Breath samples were collected into four 1300 mL breath sampling bags before drug administration, and then collected in duplicate into 200 mL breath sampling bags at different times (5–240 min) after drug administration. The samples collected were analyzed by a $^{13}CO_2$-infrared spectrophotometry analyzer.[7] Excretion of ^{13}C was expressed as the difference ($\Delta^{13}CO_2$, ‰) in $^{13}CO_2/^{12}CO_2$ ratio before and after drug administration. Data collected from the assay system used were valid only when CO_2 concentration in a breath sample was more than 0.5%. The time at which $\Delta^{13}CO_2$ reached a maximum was regarded as the time of peak excretion (t_{max}). When multiple $\Delta^{13}CO_2$ peaks occurred, the time of the earliest peak was taken as t_{max}.[8,9]

2.5. Analysis of ^{13}C breath test results

^{13}C (% dose/h) excretion rate was determined using a program that incorporates Ghoos' theory (Ghoos et al., 1993; Kim and Choi, 2007), and $^{13}CO_2$ production rate was considered constant at 0.1561/m^2 body surface area/min. Body surface area was calculated using the following formula: body surface area (m^2) = 10.5 × body weight (g)$^{2/3}$/10,000 (Orr et al., 1975).

^{13}C (% dose/h) excretion rate was obtained using the X^2 probability density function model as follows: % dose/h = $at^b e^{-ct}$ (t = time; a, b, c = regression constants). Gastric empting coefficient (GEC = ln(a)) and t_{lag} ($t_{lag} = b/c$) were also calculated. The time corresponding to maximum $^{13}CO_2$ concentration in the exhaled breath was taken as t_{max}, and cumulative ^{13}C recovery rates (C%D, % dose) were determined from the cumulative time of the % dose/h value using the following formula: C%D = $m(1 - e^{-kt})^{\beta}$ (k, m, β = regression constants). Half-empty time ($t_{1/2}$) was calculated using the following formula: $t_{1/2} = (-1/k) \times \ln(1 - 2^{-1/\beta})$.

2.6. Electrointestinography

Analysis of electrical activity – Electrointestonography – was used to measure percutaneous potential of the small intestine and caecum in each horse. Surface electrodes were attached at three sites, i.e., cranial edge of the right tuber coxae (using a mini-amplifier), caudal edge of the caudal rib at a point horizontal to the first electrode (using a noninductive electrode), and at the apex of an inverted equilateral triangle in which the first two electrodes formed the triangle base (using another mini-amplifier). Frequency of electrical activity was measured at a sampling rate of 1 Hz within a range of 1.7–12 cycle/min (Sasaki et al., 2005a).

Electrical activity of the small intestine and caecum in each horse was recorded for a period of 1 h before drug administration, and for another period of 1 h beginning 6 h after drug administration. Data were analyzed using fast Fourier transform (FFT) as reported elsewhere. Mean amplitude of electrical activity for a 30-min period 2 h after drug administration was expressed as percentage of mean amplitude of electrical activity for a 30-min period before drug administration.

[1] Gasmotin® Powder, Dainippon Pharmaceutical Co., Ltd., Japan.
[2] Telperane®, Teikokuzouki Co., Ltd., Japan.
[3] Acenalin®, fine granules, Kyowa Hakko Kogyo Co., Ltd., Japan.
[4] Xylocaine®, Injection, AstraZeneca Co., Ltd., Japan.
[5] Otsuka Pharmaceutical Co., Ltd., Japan.
[6] 1-^{13}C sodium octanoate, 99%; Wako Pure Chemical Industries Co., Ltd., Japan.
[7] POC One®, Otsuka Pharmaceutical Co., Ltd., Japan.
[8] Life Scope®, Nihon Kohden Co., Ltd., Japan.
[9] PowerLab®, ADinstruments Pty Ltd., USA.