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Effects of mosapride on motility of the small intestine and caecum in normal horses after jejunocaecostomy

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The purpose of the present study was to evaluate the prokinetic effects of mosapride with non-invasive assessment of myoelectrical activity in the small intestine and caecum of healthy horses after jejunocaecostomy. Six horses underwent celiotomy and jejunocaecostomy, and were treated with mosapride (treated group) at 1.5 mg/kg per osos once daily for 5 days after surgery. The other six horses did not receive treatment and were used as controls (non-treated group). The electrointestinography (EIG) maximum amplitude was used to measure intestinal motility. Motility significantly decreased following surgery. In the treated group, the EIG maximum amplitude of the small intestine was significantly higher than in the controls from day 6～31 after treatment. These findings clearly indicate that mosapride could overcome the decline of intestinal motility after jejunocaecostomy in normal horses.

Keywords: horse, ileus, mosapride, small intestine

Introduction

Jejunocaecostomy is performed in horses if the distal ileum requires resection due to strangulating obstruction and/or stenosis or bypass [6-8]. However, after jejunocaecostomy, the horses experienced reduced intestinal motility with postoperative ileus, resulting in death [2,5,12]. From rodent studies, it is apparent that at least three major mechanisms are involved in manipulation-induced postoperative ileus (neurogenic, inflammatory, and pharmacologic) [1]. Medical treatment with prokinetic agents is known to be effective for gastrointestinal motility dysfunctions, such as postoperative ileus [3,14,15].

Mosapride selectively acts on the 5-hydroxytryptamine 4 ($5HT_4$) receptor, thereby increasing neuronal release of acetylcholine in the digestive tract and promoting gastrointestinal motility in dogs [17,18]. Although it has been reported that mosapride promotes motility in the small intestine and caecum of horses [13], no study has investigated the effects of mosapride on reduced motility of the small intestine and caecum using electrointestonography (EIG) in horses after celiotomy and jejunocaecostomy. Therefore, the purpose of the present study was to evaluate the effects of mosapride on motility of the small intestine and caecum in horses after jejunocaecostomy using EIG.

Materials and Methods

Experimental animals

Twelve healthy thoroughbred horses (5 stallions, 4 mares, and 3 geldings) were used in the present study. Six horses (5.0 ± 3.2 years old; 484 ± 32 kg) were treated with mosapride (treated group) after jejunocaecostomy, and the other six horses (6.8 ± 4.0 years old; 504 ± 41 kg) were used as controls (non-treated group). The horses were fed an ordinary two-meal diet per day (0.9 kg oats, 0.3 kg bran, and 3.5 kg dried grass per meal) with unrestricted water intake. Housing and care of the horses and conduct of the study were in accordance with a protocol approved by the Obihiro University Institutional Animal Care and Use Committee.

Surgical procedure

All foods and water were withheld for 12 h before the surgery. All horses were intravenously pre-medicated with 4 μg/kg of medetomidine (Domitor; Orion, Japan), and anesthesia was intravenously induced 5 min later with 0.03 mg/kg of diazepam (10 mg, Horizon; Yamanouchi

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Pharmaceutical, Japan) and 2.2 mg/kg of ketamine (Veterinary Ketalar 50; Sankyo Yell Yakuhin, Japan). Guaifenesin (25～50 mg/kg; Kyoto Pharmaceutical Industries, Japan) was infused rapidly until the horse became ataxic. The trachea was then intubated and the horse was held on a surgical table. Anesthesia was maintained by inhalation of halothane and oxygen. At the beginning of surgery, 20 mg/kg of cefalotin sodium (Coaxin; Tobishi Pharmaceutical Industries, Japan) and 1.1 mg/kg of flunixin meglumine (Banamine; Dainippon Sumitomo Pharmaceutical, Japan) were administered to each horse intravenously.

The surgical area was routinely prepared for aseptic surgery in dorsal recumbency and a ventral midline celiotomy was performed. The caecum was exteriorized and the apex was pulled caudally to expose the dorsal taenital band. The surgical method of jejunocaecostomy used in the present study was essentially the same as performing hand suturing as used by Donawick *et al.* [4]. The ileum and jejunum were resected approximately 50 and 200 cm proximal to the ileocaecal junction, respectively.

After the surgical intervention, 20 mg/kg of cefalotin sodium and 1.1 mg/kg of flunixin meglumine were intravenously administered twice a day at 9:00 and 18:00 for 5 days, and 10,000 ml of lactated Ringer's solution (Solulact; Terumo, Japan) was intravenously administered twice a day for 4 days. Incisions were treated as necessary. Water was offered *ad libitum* starting 13 h after the surgery, and the horses were fed 0.7 kg of alfalfa softened by hot water 47 h after operation. The quantity of feed was then gradually increased over a period of 5 days until the amount of their meal diet reached its former level.

Treatment with mosapride

Mosapride (Gasmotin; Dainippon Sumitomo Pharmaceutical, Japan) at a dose of 1.5 mg/kg was administered in 1,000 ml distilled water via a nasogastric tubation once daily at 9:00 am for 5 consecutive days.

Evaluation of intestinal motility

EIGs of the small intestine and caecum were performed on conscious horses at rest in a stall. After clipping the hair over the paralumbar fossa on the left and right sides of the abdomen, the skin was washed and EIG electrodes were installed via surface electrodes (Vitrode M-150 Disposable Electrodes; Nihon Kohden, Japan) at three sites: the front edge of the tuber coxae (EIG mini-amplifier), the intersection of the horizontal line extending from the tuber coxae and the rear edge of the last rib (noninductive electrodes), and the apex of an inverted regular triangle formed by placing the other two electrodes on the other apexes (EIG mini-amplifier; Fig. 1). At a sampling rate of 1 Hz, the frequency was measured within the range of 1.6～12 cycles per min. An electrogastrographic (EGG) recorder (Nipro EG; A&D, Japan) and a digitrapper EGG system were used to measure the percutaneous potential of the small intestine and caecum

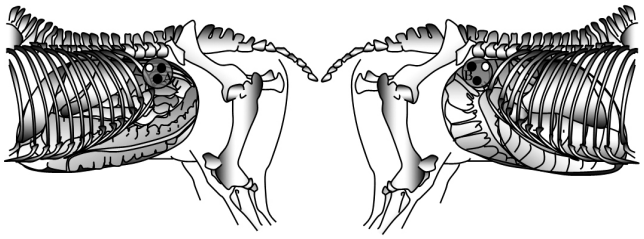

Fig. 1. Electrointestinography (EIG) electrode position. A: Small intestine, B: Ceacum, ●: EIG mini-amplifier, ○: EIG in different electrodes.

[10]. The system was attached to the trunk by means of a saddle, a girth, and a saddlecloth.

Preoperative EIGs were recorded for 24 h before the surgical operation after horses were fed an ordinary diet. Postoperative EIG data were collected immediately following recovery from general anesthesia, continued to be recorded for 10 consecutive days, and were thereafter collected on days 17, 24, and 31 for 24 h each day.

For EIG analysis, a running spectrum method with fast Fourier transform was used. The waveform was divided into 1-min intervals. The relative value of maximum amplitude (μv) of the wave form at 10 min per h was calculated. Preoperative data were regarded as 100% of relative values.

Statistical analysis

Data were indicated as the mean ± SD. Two-way repeated measure ANOVA was used to determine significant differences between the treated group and the control. Significant differences were evaluated by a *post-hoc* test (Fisher's PLSD). The significance level was set at $p < 0.05$.

Results

In the control group, the EIG maximum amplitudes of the small intestine and caecum on postoperative day 1 were significantly lower than those recorded before the surgical operation (44.2 ± 19.1% *vs*. 100.0 ± 0.0% for the small intestine and 45.7 ± 19.3% *vs*. 100.0 ± 0.0% for the caecum, Figs. 2A and B). The EIG maximum amplitudes of the small intestine and caecum tended to increase from postoperative days 2～10; however, they stayed significantly lower than those before the surgical operation ($p < 0.05$). EIG maximum amplitudes from postoperative days 10～31 continued to increase reaching preoperative levels.

In mosapride-treated horses, the EIG maximum amplitudes of the small intestine were significantly higher than those in the control group from postoperative days 6～31 (Fig. 2A). Although the EIG maximum amplitudes of the caecum in mosapride-treated horses tended to be higher than those in the control group, the difference was not

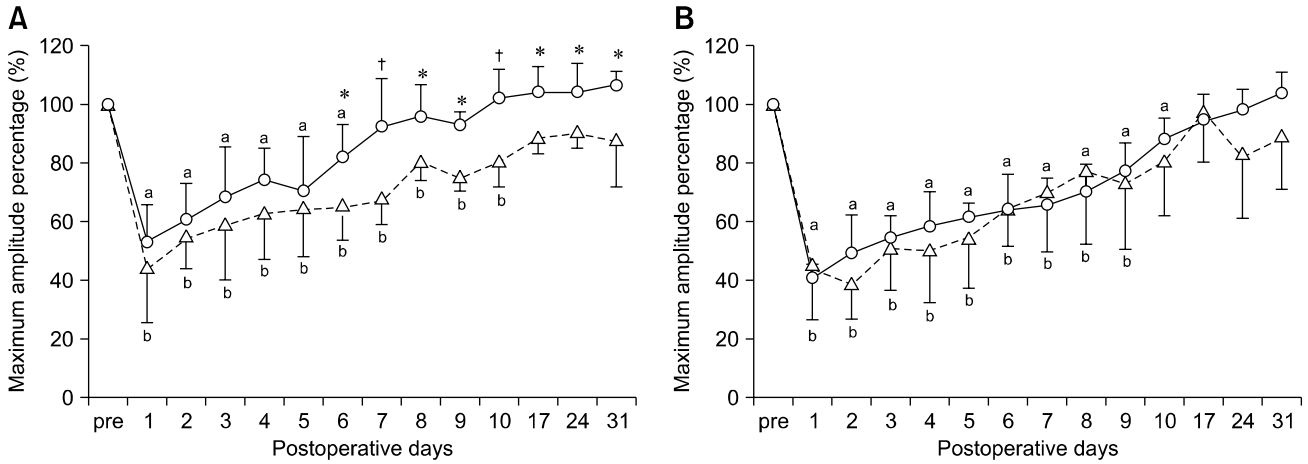

Fig. 2. Electrointestinography maximum amplitude of the small intestine (A) and caecum (B). Preoperative value was taken as 100% and each value was shown as mean ± SD, [○: treated group (N = 6), △: control (N = 6)]. [a,b]Significant differences ($p < 0.05$) compared with each preoperative value of the treated group (A) and the control group (B). [*, †] Significant differences ($p < 0.05, p < 0.01$) compared between the treated group and the control group on the same day.

statistically significant (Fig. 2B).

Discussion

Mosapride selectively acts on 5-HT_4 receptors and increases the level of acetylcholine released from cholinergic nerve endings in the digestive tract [17,18]. Acetylcholine binds to muscarinic receptors on the smooth muscle and induces contractions. Generally, mosapride is administrated three times a day in humans. However, it has been reported that administration of 1.5 mg/kg once a day significantly enhances small intestinal and caecal motility in horses [13]. Therefore, in the present study, mosapride was administered at 1.5 mg/kg once a day for 5 consecutive days.

In mosapride-treated horses, the parameters measured returned to their preoperative levels earlier compared to the control group. These findings indicate that mosapride effectively improves a decline in intestinal motility by increasing both peristalsis and the number of intestinal contractions [11]. In addition, the EIG maximum amplitudes from days 2～31 were significantly higher in mosapride-treated horses than in the control group. It is considered that the EIG maximum amplitude reflects contractility of smooth muscle [9]. Therefore, it is believed that mosapride enhances contractile motility and thus alleviates decline in intestinal motility.

In the caecum, no significant difference between the two groups was observed in the EIG maximum amplitude. Therefore, we conclude that mosapride acts more effectively on the small intestine than on the caecum in healthy horses. It has been reported that the distribution of $5HT_4$ receptor differs depending on gastrointestinal sites and species. In horses, it is known that $5HT_4$ receptors are widely distributed in the ileum and pelvic flexure [16]. Therefore, it is suggested that the difference in the distribution of the $5HT_4$ receptor is at the base of different effects of mosapride in the small intestine and caecum.

In this study, we demonstrated that administration of mosapride is an effective treatment for the decline of intestinal motility in the period following jejunocaecostomy in healthy horses. Mosapride appeared to have more of an effect on motility in the small intestine than in the caecum. It is therefore concluded that administration of mosapride may improve the decline of intestinal motility after surgery, but further studies are needed to understand the mechanism by which this drug may act as a prokinetic and to determine whether the potential beneficial effects on intestinal motility occur in clinical colic cases.

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