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Effects of Orally Administrated Mosapride, a 5-HT_4 Receptor Agonist on the Digestive Tract of Horses

Naoki SASAKI, Inhyung LEE, Yu AYUKAWA and Haruo YAMADA

Department of Veterinary Surgery, Obihiro University of Agriculture & Veterinary Medicine, Inada-town, Obihiro-city, Hokkaido 080-8555, Japan

The effects of mosapride, a 5-hydroxytryptamine 4 (5-HT_4) receptor agonist, on the motility of horse small intestine were examined by means of electrointestinography (EIG). Six adult healthy thoroughbreds were used, in which EIG signals from the small intestine were measured by a Degetorappar EGG system. Mosapride, dissolved in 200 ml water, was orally administered at a dose of 2 mg/kg. The total power of EIG signals at a frequency band of 3 cpm was 419.1 ± 122.0 $(\mu V)^2 \times$ cpm (n=6) before, and 2,093.6 ± 850.0 $(\mu V)^2 \times$ cpm (n=6) after the drug administration, the latter mean value being significantly greater than the former. This result suggests that mosapride has a prokinetic action on the motility of horse small intestine.

Key words: *equine, gastrokinetic agent, mosapride, oral adoministration, 5-HT_4 receptor agonist*

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A high incidence of digestive disorders has been reported in horses with abnormal function of the digestive tract [19], and regulation of the tract motility was of importance in its treatment [20]. Recently, mosapride, a benzamide derivative [9, 15], was developed as a gastroprokinetic agent[13, 25, 27, 28]. This agent causes neither dopamine D_2 receptor blockade action nor QT prolongation[2, 3, 16], but it is found to selectively stimulate 5-HT_4 receptors, increase neuronal release of acetylcholine, and promote gastrointestinal motility [10, 11, 28]. In human clinical work mosapride is used for treatment of reflux esophagitis [17], chronic gastritis, and postoperative ileus [7, 8].

Little known is about how mosapride affects the gastrointestinal function of horses. Therefore, we have investigated the effects of orally administrated mosapride on the motility of horse small intestine by means of electrointestinography(EIG).

Animals: Six healthy male thoroughbreds (all female, mean age 4.0 ± 0.0 years of age (n=6), mean weight 457.0 ± 9.7 kg (n=6)) were used. These horses were fed an ordinary three-meal ration (dried grass 5 kg, oats 3 kg, wheat bran 2 kg, and soybean cake 0.5 kg) with unrestricted water intake.

Procedure for measurement of electrointestinography (EIG): Changes in the electrical activity of the small intestine were monitored by EIG with a Degetorappar EGG system (Synectics Company, Sweden). EIG surface electrodes were installed at three sites: the front edge of the tuber coxae (with another EIG mini-amplifier), the intersection of the horizontal line extending from the tuber coxae and the rear edge of the last rib (with an uninductive electrode), and the apex of an inverted regular triangle formed by placing the other two electrodes on the other apexes (by means of another EIG mini-amplifier). At a sampling rate of 1 Hz, the frequency of electrical activity was measured within the range of 1.8 to 12 cycles per minute (cpm).

EIG analytical method: EIG signals from the small intestine were analysed with a running spectrum method involving fast fourier transform (FFT) analysis [18]. That is, power was analyzed through the EIG waves for 256 seconds by FFT and displayed at one minute interval as a FFT line. The frequency band was classified into 3 cpm (1.8 to 4.5 cpm), 6 cpm (4.5 to 7.5 cpm), 9 cpm (7.5 to 10.5 cpm), and 12 cpm (10.5 to

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*Corresponding author. E-mail: naoki@obihiro.ac.jp

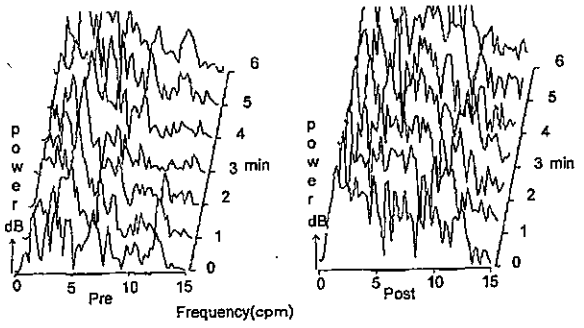

Fig. 1. Electrointestinography (EIG) of the small intestine at 120 min before and 120 min after mosapride administration. The FFT line on the side of the graph shows the results of the FFT analysis of the EIG waves for 256 sec. C.P.M.: cycles per minute.

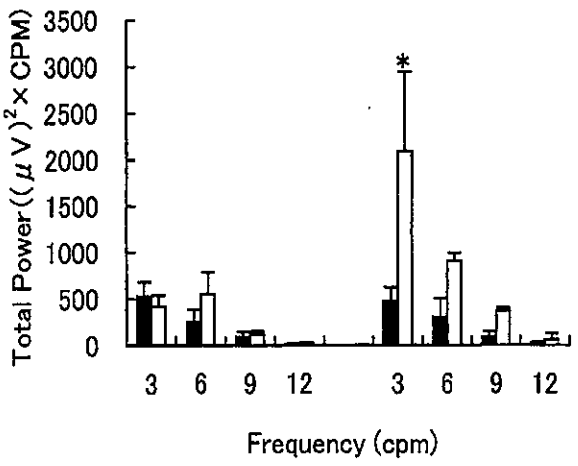

Fig. 2. Total power value of each frequency band of the small intestine at 120 min before and 120 min after mosapride administration. As seen from the data on the left half, which the closed and open columns indicate before and after oral administration of water respectively , this administration caused no significant change in the total power for any frequency band. On the other hand, the administration of mosapride caused a significant increase in the total power, especially for a frequency band of 3 cpm, where it was increased from 419.1 ± 122.0($(\mu V)^2$ × cpm, closed column) to 2093.6 ± 850.0 ($(\mu V)^2$ × cpm, open column) (n=6 for each). And the total power for the other frequency bands (6 to 12 cpm) was somewhat increased, but there was no statistical significance. The values are the mean ± S.D. *: P<0.05.

12.0 cpm), and for each frequency band the total power ($(\mu V)^2$ × cpm) was calculated.

Mosapride administration method and assessment procedure: As a control, water (200 m*l*) was orally administered. The total EIG power was calculated for 10 min, 120 min before and after the oral administration of either mosapride or water alone, and analyzed for the different frequency bands.

Statistical Method: To determine significant differences, Wilcoxon test was employed. All differences with values of P≤0.05 were considered significant.

Figure 1 shows EIG signals from the small intestine before and after administration of mosapride (2 mg/kg). The frequency and power of the signals were increased after its administration. An increase in power was observed in low frequency bands of 3 cpm and 6 cpm.

Figure 2 shows the total powers for the different frequency bands obtained from the control group (200 m*l* water) and the mosapride group. As seen from the data in the left half, of which the closed and open columns indicate before and after oral administration of water respectively, this administration caused no significant change in the total power for any frequency band. On the other hand, the administration of mosapride caused a significant increase in the total power, especially for a frequency band of 3 cpm, where it was increased from 419.1 ± 122.0($(\mu V)^2$ × cpm, closed column) to 2093.6 ± 850.0 ($(\mu V)^2$ × cpm, open column) (n=6 for each). And total power for the other frequency bands (6 to 12 cpm) was somewhat increased, but there was no statistical significance.

EIG is a non-invasive method with which changes in smooth muscle electrical activity of the digestive tract can be detected from the body surface via the abdominal wall [4, 6]. EIG is applied to human, for diagnosis and treatment of conditions such as reflux oesophagitis [1, 5] and non-ulcer dyspepsia (NUD) [22]. Sasaki *et al.* [18] have demonstrated its usefulness for monitoring cecum motility in the horse. In the present study, we used this method to examine the effect of mosapride on the motility of horse small intestine.

The multiple 5-HT receptor subtypes (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7) are distinguished [21]. 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4 [21] are concerned with regulation of gastrointestinal motility. In the horse, both 5-HT_3 and 5-HT_4 receptors exist on the ileum and cecum [24]. Mosapride activates 5-HT_4

receptors to promote acetylcholine release, and because it promotes gastrointestinal motility [12], so that it is expected to improve gastrointestinal tract dysfunction. The present results showing that the frequency and power of the EIG in horse small intestine was increased by oral administration of mosapride may indicate a prokinetic action of the agent on the gut movement in this species.

Neither intravenous injection[26] nor oral administration of mosapride at 1 mg/kg[14] has any effect on colonic motility in dogs, suggesting that mosapride is not very effective in a lower region of the gastrointestinal tract. The regional distribution of 5-HT_4 receptors in the digestive tract is known to decrease in order of the duodenum, jejunum, ileum, colon, and rectum. Yoshida *et al* [26] have reported that rat colonic motility was promoted by administration of mosapride at 3 mg/kg, although its influence was not observed in dog ileum on colon when administered at 1 mg/kg intravenously. Therefore, it was necessary to examine the effect of an increased dose on lower region intestinal motility.

Because mosapride increased contraction amplitude without an increase in contraction frequency of the duodenum and gastric antrum [26], it is thought that mosapride improves the contractile forces more than the contraction frequency. The amplitude and frequency of EIG signals may reflect the amplitude and frequency of the contractile motility [18]. The present study demonstrated a significant increase in the total power at a low frequency band of 3 cpm after the oral administration of mosapride to horses, which suggesting that it may increase the contractile motility accompanied by a little contractive frequency.

A total power increase in the EIG in the small intestine was observed after oral administration of mosapride at 2 mg/kg, suggesting its potential for prokinetic action on small intestine motility in the horse. Therefore, it may be useful for treatment of gastrointestinal dysfunction in the horse.

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