Difference in the Motile Reactivity of Jejunum, Cecum, and Right Ventral Colon to Xylazine and Medetomidine in Conscious Horses

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We investigated effects of xylazine and medetomidine on contractive motility in different regions of the intestine in conscious horses, to provide some insight into elucidation of the regional difference in the painrelieving effect of $\alpha_2$-adrenergic agonists. We used 6 healthy adult male thoroughbread horses. Horses were intravenously given one of two calmatine-anodines, xylazine (1.0 mg/kg) and medetomidine (0.0075 mg/kg). The jejunum, cecum, and right ventral colon were examined for contractive motility. Both xylazine and medetomidine inhibited contractive motility for relatively similar durations, the effect of medetomidine was more potent than that of xylazine. After the horses were treated with both drugs, the contractive motility of the cecum and colon was inhibited for a longer duration and the inhibition was more intense than the corresponding duration and intensity of inhibition of the jejunum. These results suggest that the cecum and colon of the horse is more sensitive than the jejunum to $\alpha_2$-adrenergic agonists.

Key words: equine, intestinal motility, medetomidine, xylazine

Xylazine and medetomidine, $\alpha_2$-adrenergic agonists, have been used as calmatine-anodines for preanesthetic treatment in horses [2, 5, 10, 21]. These drugs are also used to treat acute abdominal disorders of horses such as flatulent colic and intestinal torsion [4, 22, 23], because they have been shown to relieve intestinal tension and its concomitant organic pains in the equine [20]. However, clinical observations have indicated that effects of the $\alpha_2$-adrenergic agonists in relieving the organic pains are relatively weak in cases of torsion of the small intestine, compared with that of the large intestine [4, 8]. Such regional difference has been serious for treatment of equine abdominal disorders, but the explanation for it is at present unclear.

In the gastrointestinal tract, acetylcholine functions as the major excitatory neurotransmitter to control gut movement, and its neuronal release is regulated by $\alpha_2$-adrenoreceptor-mediated inhibitory mechanisms [6, 7, 12, 13]. It has been shown that $\alpha_2$-adrenergic agonists can reduce intestinal tension and contractive motility by activating the inhibitory mechanisms [6, 7, 9, 19]. If such effects vary from one region to another of the intestine, the drugs would be expected to also exhibit regional differences in their effect on the intestinal torsion-associated pain.

Therefore, we investigated effects of xylazine and medetomidine on contractive motility in different regions of the intestine in conscious horses, to provide some insight into elucidation of the regional difference in the painrelieving effect of $\alpha_2$-adrenergic agonists.

Materials and Methods

Six healthy adult male thoroughbred horses were fed routinely three times a day, and water was freely given. The mean age and weight were 4.0 ± 0.0 years and 457.5 ± 9.2 kg, respectively.

After tranquilizing the horses with xylazine (1.0 mg/kg, IV), 10% guaiacal-glycerol-ether (GGE) (400 ml) containing thiopental sodium (2.0 g) was rapidly...
injected intravenously to anesthetize the animals. The animals were then moved to an operating table, and laid and fixed on their backs. Anesthesia was maintained by forced inhalation of isoflurane-O₂. Laparotomy was conventionally conducted at the medial line [16, 17] and the digestive tract was exposed. To monitor contractive motility of the circular muscle of the intestine, force transducers (F-121S: Star Medical, Japan) were each sewed with a 4–0 nylon string on the serosae of the following regions of the intestine; the jejunum (50 cm distal from the duodenocolonal folding), cecum (50 cm distant from the apex), and the right ventral colon. A coaxial lead cable from the force transducers were passed through the thoracic subcutis and extracted at and fixed on the withers.

Contractive motility in the individual regions of the intestine was recorded using a thermal array recorder (Nihon Kohden Kogyo, Japan) connected with the lead cable to a resistance box (FB-01, Star Medical, Japan), and a strain pressure amplifier (AP-100F; Nihon Kohden Kogyo, Japan). Recordings were started shortly after the animals became conscious following finish of surgery, and then continued for 2 months.

Experiments were begun after the elapse of 2 weeks from surgery. This period was considered long enough for the animals to recover from the laparotomy. Recordings made without drug administration showed that all three regions of the intestine had a sustained activity that repetitively generated transient contractions (Fig. 1 and also see Fig. 2). However, in jejunal regions, the contractile activity was periodically interrupted by a longer, strong contraction which lasted 7.9 ± 1.7 min (n=6). The strong contraction

**Fig. 1.** Recording of physiological intestinal motility and the effect of saline on intestinal motility. The jejunum motility displayed repetition of three phases, i.e., Phase I, Phase II and Phase III (*). The entire cycle lasted for an average of 130.1 ± 76.0 min (n=6). No effect on intestinal motility was identified after saline treatment.

**Fig. 2.** Effect of xylazine on intestinal motility. *=Indicates strong contractions (Phase III). After xylazine treatment, contractive motility was inhibited in the intestine.
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Occurred at an interval of $130 \pm 76$ min (n=6) in the jejunum. Previous studies [17] termed the active state with the transient contractions Phase II and that with the strong contraction (Phase III), and thus, in the present study, the respective contractions will be referred to as Phase II contraction and Phase III contraction.

Xylazine and medetomidine were intravenously injected at the respective doses of 1 mg/kg and 0.0075 mg/kg. Drug injection was conducted at 40 min after a Phase III contraction occurred in the jejunal region. To evaluate effects of the drugs on contractile motility, the amplitudes of Phase II contractions elicited for 5 min were averaged at various times over a period of 150 min after drug injection, and the averaged amplitude at each time was expressed as percentage of the corresponding value obtained in the same way before drug injection. In each individual horse, drug injection was performed at intervals of 1 week or more.

When there was heterogeneity of variance and the standard deviations were proportional to the means, logarithmic transformation was carried out before analysis of variance. Repeated measures analysis of variance (ANOVA) with post hoc comparison using the Newman-Keuls test was used to test for significant differences from pretreatment concentrations. The Mann-Whitney U test was used to compare the evaluations of percentage amplitude between the xylazine and medetomidine. All differences with values of p<0.05 were considered significant.

Results

Injection of physiologic saline (10 ml, IV) almost unaffected contractive motility in the jejunum, cecum and right ventral colon (n=6), as shown in Fig. 1.

Injection of xylazine (1 mg/kg, IV) immediately inhibited contractive motility in all the three intestinal regions, and the inhibition reached a maximum level in 20–30 min (Fig. 2). In the jejunal region, Phase III contractions did not occur for such a period that its generation was expected from the periodicity seen before drug injection ($130 \pm 76$ min in the jejunum); In other words, xylazine injection prevented the generation of Phase III contractions for a while (Fig. 2).

Figure 3 shows plots of the percentage amplitude of Phase II contractions against the time after xylazine injection. The percent amplitudes at 30 min were 52.8 $\pm$ 10.2, 7.1 $\pm$ 0.7 and 11.0 $\pm$ 6.8% (n=6), respectively, in the jejunal, cecal and colonic regions (Table 1). The mean value for the jejunum was significantly greater (p<0.05) than that for any other region. After its marked inhibition sustained for several ten minutes, contractive motility gradually restored at different rates depending on the intestinal regions. When the period of the significant inhibition was estimated from the graphs in Fig. 3, it was about 80, 100, and 120 min, respectively, in the jejunal, cecal and colonic regions.
Injection of medetomidine (0.0075 mg/kg, IV) also immediately inhibited contractive motility (Fig. 4). The percent amplitudes of Phase II contractions at 30 min after its injection were 49.5 ± 14.4, 5.3 ± 1.2, and 7.3 ± 3.3% (n=6), respectively, in the jejunal, cecal, and colonic regions. The mean value for the jejunal region was significantly greater (p<0.05) than that for any other region (Table 1). In addition, the mean values for the cecal region was significantly smaller (p<0.05) than the respective corresponding values obtained with xylazine (Table 1). In the jejunal regions, Phase III contractions did not occur for an expected period after drug injection, as described for the case of xylazine. From the graphs in Fig. 4, the periods of significant inhibition of Phase II contractions were estimated to be 80, 100, and 110 min, in the jejunal, cecal, and colonic regions respectively.

**Discussion**

The present experiments have shown that contractive motility in the jejunum, cecum, and right ventral colon of the equine are inhibited by xylazine (1 mg/kg, IV) or medetomidine (0.0075 mg/kg, IV). Comparisons of the reduction of Phase II contractions among the intestine regions suggest that the inhibitory effect of both drugs is relatively weak in the jejunal region, compared with the other regions. This may also be supported by the observation that the period during which Phase II contractions were significantly reduced tended to be relatively short in the jejunum. Such regional difference in the effect of these α₂-adrenergic agonists may account at least in part for the clinical observation in equine acute abdominal disorders that they were less effective in relieving symptoms including pains caused by torsion of the small intestine than by that of the large intestine [4, 8]. The present experiments found that the effects of xylazine and medetomidine in the jejunum region were stronger than those in the cecum and colon. Based on these findings, both drugs might be as effective in treating jejunal torsion as in doing cecal and colonic torsion.

The reason the regional difference in the effect on contractive motility of the α₂-adrenergic agonists is exactly unknown [14, 15]. A possible explanation might come from the suggestion by Malone et al. [11]. That nervous control of contractive motility differs in the small and the large intestine, and especially in the

![Fig. 4. Change in contractive motility of the jejunum (□), cecum (□), and right ventral colon (□) after the administration of medetomidine (0.0075 mg/kg, IV). Each contraction amplitude is represented by the percentage amplitude. *=Significantly different from pre-contraction amplitude (P<0.05).](image-url)
jejunal region, the exogenous sympathetic and parasympathetic nerves both have only poor connections to the intramural nerve plexuses. To test the possibility, further studies need such as pharmacological analyses of mechanical responses of the various intestines to stimulation of the exo- and endogenous nerves.

Phase III contractions in equine small intestine are known to serve for food residues and desquamated epithelial cells to descend and for prevention of bacterial overgrowth [3, 18]. The present study indicated that intravenous injection of xylazine interfered with generation of Phase III contraction for a period of time, as reported by Adams et al. [1]. During the interference of Phase III contractions, however, Phase II contractions were still allowed to occur with reduced amplitudes. These findings may imply that Phase III and Phase II contractions differ in mechanisms for their generation, and suggest that the mechanism for the former contraction involves α2-adrenoceptor-mediated processes to a more serious extent.

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References


