Medicinal Treatment to Equine Gastrointestinal Dysfunctions

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This study was designed to investigate gastrointestinal dysfunctions, especially the effects of gastrointestinal prokinetic agents on digestive disorders involving lowered motility. The effects of α_2-adrenergic agonists for treating acute abdominal disorders involving intestinal torsion in horses were also investigated. The results are as follows: (1) It appeared that the functions of migrating contractions (MC) in horses were to transfer the contents of the digestive tract as soon as possible to the cecum and colon, in addition to maintaining homeostatis in the digestive tract. (2) Motilin was seen to be involved in the regulation mechanism of intestinal motility in the horse as well as in humans and dogs, and brought about MC. (3) The intravenous injection of cisapride brought about MC in the small intestine. With administration of a higher dose of 0.75 or 1.0 mg/kg, a significant increase (P<0.05) in MC frequency was observed. (4) It was clear that the inhibitory effects of the α_2-adrenergic agonists persisted for a longer time with a more remarkable reduction of contractions in the cecum and colon than in the jejunum. When α_2-adrenergic agonists are used for relieving intestinal tension, it is recommended that medetomidine is more effective than xylazine.

Key words: α_2-adrenergic agonist, equine, gastrointestinal dysfunction, motility, serotonin receptor agonist

In horses, digestive system diseases include a lot of acute abdominal problems which originate chiefly due to gastrointestinal dysfunction, including gastric ulcers, colic (hyperphagia colic, constipation colic, convulsion colic, flatulence colic, displacement colic, thrombus colic, and parasitic colic), and enteritis. Because the functions of digestive organs are feeding, digestion, and absorption, intestinal motility plays an important role in managing these functions smoothly. Intestinal motility is a crucial function in mechanical digestion for the intake of nutrients, for crushing these nutrients, and for their mixing, transportation, and excretion. These functions normally closely cooperate not only with the gastrointestinal system, but with all organs. Therefore, gastrointestinal motility disorders can become the main factor behind anorexia, grinding emaciation, colicky pain, constipation, diarrhea, and acute abdomens in horses.

The first report concerning the gastrointestinal motility in the horse is a measurement of the potential of digestive tract smooth muscle in mammals including the pony, and was conducted by Ruckebusch [53] in 1971. In the research that has been conducted so far on gastrointestinal motility, ponies or foals have been used [26, 33, 44, 45, 54]. There have been few studies [19] which use adult horses. Ross [47] reported that the movement of the cecum and the right ventral colon can be measured by the measurement of pressure inside the digestive tract in the pony, and stated in 1986 that a movement pattern exists. In the pony, the influence of feeding on the myogenic potential of the colon [49] and the influence of the prostaglandin E1 on the cecum myogenic potential [19] have been reported. Most of these reports concern the myogenic potential of the cecum and the colon [28, 46, 48, 49, 64]. However, in the 1983 research on the motility of the small intestines of the horse by Lamar [28], the
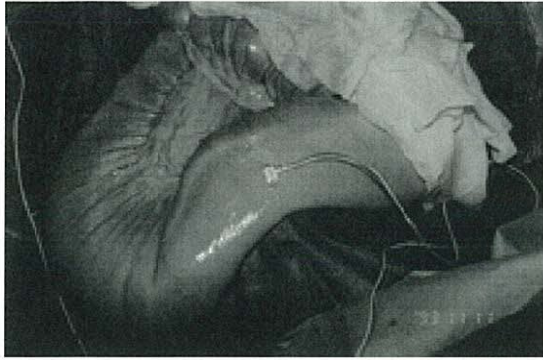
Fig. 1. Installation state for Force Transducer. The Force Transducer Method is intended to keep quantitative and chronic recording of contractions of the digestive tract in consious horses in an unrestrained state using a force transducer attached by laparotomy to the serous surface of the digestive tract.

Fig. 2. Recording method of Force Transducer. Records were continuously obtained using a thermal array recorder via a strain pressure amplifier with the lead cable from the Force Transducer connected to a resistance box. In addition, data of intestinal motility recorded in DAT data recorder and waveform analyzed by Bimutus. A: Resistance box (FB-01; Star Medical, Japan). B: Strain pressure amplifier (AP-100F; Nihon Kohden Kogyo, Japan). C: Thermal array recorder (RTA-1200; Nihon Kohden Kogyo, Japan). D: DAT data recorder (PC216Ax; NEC, Japan). E: Waveform analytical software BIMUTUS (TM;Kissei,Japan).

myogenic potential of the pony's jejunum and the motility were measured at the same time, and a correlation was seen between both. It was later discovered that the myogenic potential in the proximal part increases in more than the torsion parts in jejunum torsion [30], and the fact that the myogenic potential decreases irregularly when endotoxin is administered was clarified [27]. However, research on the prokinetic agents produced during medicinal treatment to the acute abdomen has not yet been conducted. In addition, an effective treatment for cases which present gastrointestinal dysfunction anomalous has not yet been established. In this study, therefore, the pharmacological and basic data concerning the regulation mechanism of intestinal motility was analyzed and evaluated on conscious horses. In addition, the bioactivity of the medicine needed to treat various digestive system diseases is discussed.

Methods of measuring gastrointestinal motility

In humans, intestinal motility has been measured and evaluated using the pressure measurement method [59, 60], the electromyogram method, the excretion method [20], and other methods. It is difficult to measure the tension degree of the shrinkage movement though the electromyogram method, which is a technique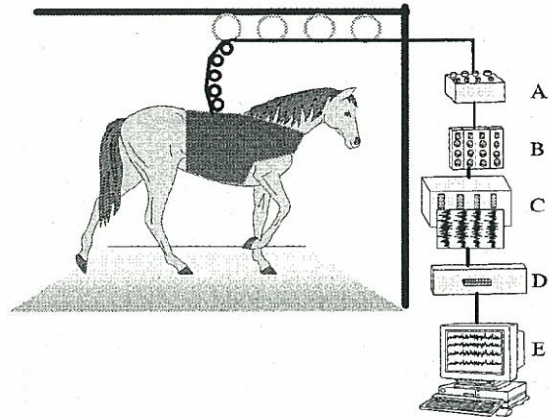 which uses electrodes to measure the potential changes in the smooth muscle of the digestive tract. The excretion method is a non-invasive technique which chiefly uses radioisotope or acetaminophen [20, 68]. However, the disadvantage of this method is that handling the radioisotope is complex. The disadvantage of the acetaminophen is that it takes a long time to measure the function using this method. The pressure measurement method [59, 60] is a technique to measure pressure by chiefly using the balloon catheter in the digestive tract of the gullet, stomach, small intestines, and large intestines. Recently, pressure in the pylorus pressure and the pluck ductus pancreaticus [66] has been measured by inserting a balloon catheter through an endoscope. However, it is necessary to keep the catheter in place. Therefore, the disadvantage of this method is that it influences the movement of the intestinal contents, and that it is not possible to apply this method to the measurement for a long time. The Force Transducer method is known as a method of evaluating an animal's gastrointestinal motility [13, 22, 37, 38]. This method continuously measures the contractile force of the digestive tract using a sewn Force Transducer for the digestive tract. Therefore, it is a technique with high
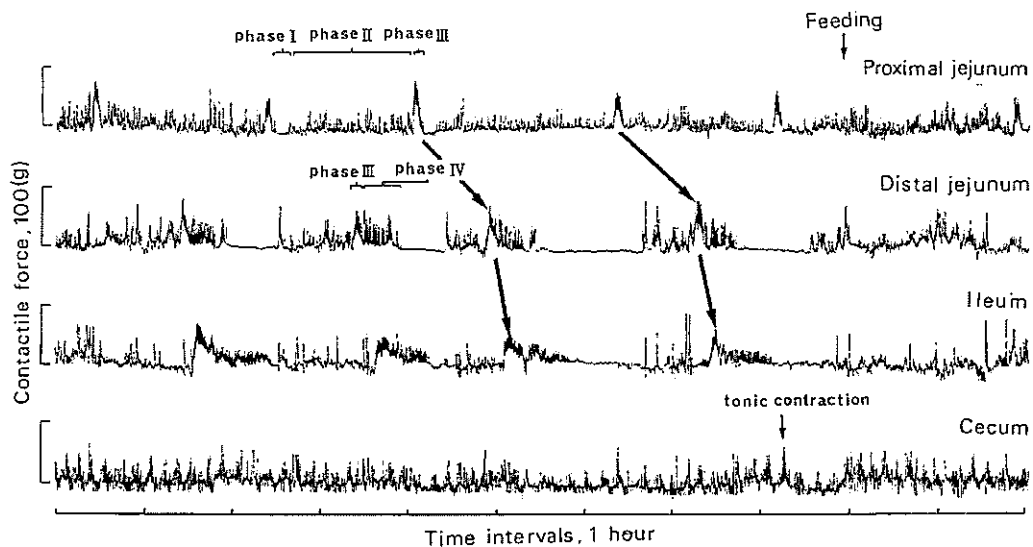
Fig. 3. Intestinal motility in horses. Phase I: Rest period during which few contractions occur. Phase II: Contraction period during which irregular contractions occur. Phase III: Period of strong contractions. Phase IV: Period of shift from Phase III to Phase I. Phase III which appeared in the proximal jejunum spread to lower small intestines (↓: migrating contractions, MC). References: Sasaki Naoki and Yoshihara Toyohiko 1999. The effect of motilin on the regulation mechanism of intestinal motility in conscious horses. J.Vet.Med.Sci. 61(2)167–170.

resolution which can measure the strain caused by the pressure on the digestive tract walls during gastrointestinal motility (Fig. 1). In general, it is known that the circular muscle and longitudinal muscle exist in digestive tract smooth muscle. The reason why the Force Transducer is sewn in the direction of circular muscle is that it is necessary to measure the contraction of the circular muscle in order to observe the strong contraction (phase III), which decreases the digestive tract lumen. The change in the contraction of the longitudinal muscle is smaller than the change in the contraction of the circular muscle [24]. In addition, it is possible to measure gastrointestinal motility under non-anesthetizing conditions accurately for six months [24] (Fig. 2). In 1963, Jacoby [25] succeeded in measuring the gastrointestinal motility by this method. Jacoby used the report by Walton [72], who measured the contraction motility of the heart in 1950. Afterwards, improvement [24] of the silicon processing on the surface of the Strain Gauge and other instruments used occurred, and the Force Transducer method became the main method of measuring gastrointestinal motility.

For anesthesia, after sedative administration with 1.0 mg/kg of xylazine, 400 ml of 10% guaiacol-glycerin ether mixed with 2 g of thiopental sodium was given to

the subjects by rapid intravenous administration to render them unconscious. They were held on the surgical table in the supine position and anesthetized by inhalation of isoflurane and oxygen. The surgical method used was basically the same as the one employed by Hunrt [19]. That is, the abdomen was opened by median section to expose the digestive tract, and one Force Transducer unit was fixed on the serous membrane of the bottom of the digestive tract with a 4-0 nylon suture to detect the contractions of the circular muscle. The animal was handled and cared for in accordance with the principles and procedures outlined by the Equine Research Institutes Animal Care and Use Committee.

Physiological gastrointestinal motility in horses

In humans [74], dogs [11, 65], and other mammals, gastrointestinal motilities are cyclic, and are divided roughly into a digestive state, which appears concurrent with meal intake, and an interdigestive state, which appears concurrent with gastric emptying [24, 39]. The interdigestive state has been divided into a motility pattern of three or four phases. They are

Phase I

Phase II

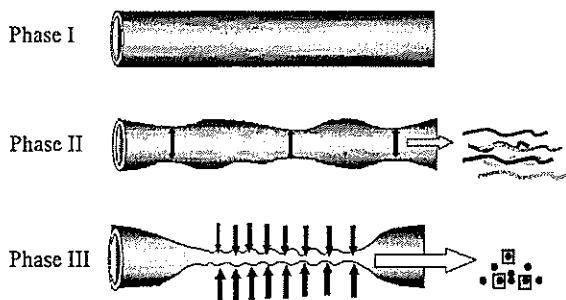Phase III

Fig. 4.   Relation between Phase and contraction of each small
          intestines. Contents are transported at the latter half of
          Phase II, but contents are not transported at the time of
          Phase I. The transportation of contents of Phase III is a
          little. The remainder of digestive tract internal diet and
          the flaking off cuticle are chiefly transported in Phase III.
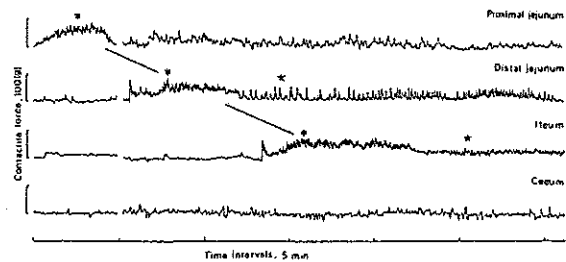

Fig. 5.   High-speed waveform analysis. *: Phase III. ★: Phase IV.
          ↓: Migrating contractions (MC). It can be said that
          intestinal motility is caused by the lumen narrowing in
          phase III, because intestinal motility is observed
          continuously as a large amplitude wave type
          accompanied by the rise of the radial line by wavy
          analysis of the high speed. Because the contraction wave
          type of phase IV presented like phase II, it was clear that
          the lumen opens each contraction in phase IV. That is,
          the contents might be transported in phase IV.

Table 1.   The data of duration (N=7) and the cycle of each Phase in each digestive tract were shown by mean ± standard deviation (N=7)

	Proximal jejunum	Distal jejunum	Ileum	Cecum	Right ventral colon
phase I	—	31.6 ± 17.0	22.3 ± 14.4	—	—
phase II	122.2 ± 26.3	110.8 ± 67.0	95.3 ± 63.5	—	—
phase III · IV	7.9 ± 1.7	29.0 ± 6.1*	44.6 ± 9.0*	—	—
cycle	130.1 ± 26.0	183.9 ± 72.2	160.8 ± 56.3	10.0 ± 1.8	13.0 ± 2.5

The duration of Phase III · IV in the distal jejunum and the ileum has significantly extended compared with the proximal jejunum
($P<0.05$). References: Sasaki Naoki and Yoshihara Toyohiko 1999. The effect of motilin on the regulation mechanism of intestinal motility
in conscious horses. J.Vet.Med.Sci. 61(2)167–170.

classified into phase I (the rest period, during which
few contractions occur), phase II (the contraction
period, during which irregular contractions occur),
phase III (the period of strong contractions), and
phase IV (the period of shift from phase III to phase I)
[24, 56, 39]. Phase III appears in the proximal jejunum
and spreads to the distal jejunum and the ileum (Fig.
3). The spread of phase III is called migrating
contractions (MC) [65], and this result is in accordance
with that reported by Gerring [16], who had measured
this phase in the pony using an electromyogram. After
Szurszewski [65] reported in 1969 that phase III
appeared periodically in the interdigestive state in the
small intestines of dogs, phase III has been reported in
many other mammals [4, 11, 33, 51]. It is assumed that
the physiologic meaning of this phase is that it prepares
the animal for feeding, controls excessive proliferation
of the bacillus, acts as a cleaning motility in the
digestive tract, and maintains the homeostasis of the
digestive tract [69]. Generally, it can be said that
intestinal motility is caused by the lumen narrowing in

phase III (Fig. 4), because intestinal motility is observed
continuously as a large amplitude wave type
accompanied by the rise of the radical line by wavy
analysis of the high speed (Fig. 5). In other words, it is
known that the transportation of contents occurs in a
small amount at this time, and that the internal diet
refuse is transported in the digestive tract [13]. Phase
IV, however, during which the shift from phase III to
phase I occurs, was observed in the proximal jejunum
and the ileum in this research. Because the contraction
wave type of phase IV presented like phase II in the
analysis of BIMUTUS (TM: Kissei; Japan), it was clear
that the lumen opens each contraction. That is, we
therefore showed that the contraction wave occurs in
horses, and that the contents might be transported in
phase IV. Moreover, the duration of phases III and IV
are 29.0 ± 6.1 min in the distal jejunum on average, and
44.6 ± 9.0 min in the ileum on average. Both of these
phases are extended significantly compared with 7.9 ±
1.7 min of the proximal jejunum on average (Table 1).
The continuation of phase III · IV extending over such

a long time has not been reported in other mammals [4, 7, 38, 51]. We guessed that phase III · IV plays a role in maintaining the homeostasis of the digestive tract, and that it quickly transports the contents of the digestive tract to the cecum and the colon in horses.

In the large intestines of humans and dogs, gastrointestinal motility is not distinguishable from the interdigestive state and the digestive state seen in the stomach and small intestines [55]. It is known that the interdigestive state and the digestive state of dogs have two different styles of contraction, a tense contraction with a small contraction wave group, which is called Colonic motor complexes (CMCs), and a spread contraction, which is called Giant migrating contractions (GMCs) [21]. CMCs are thought to be a mixing of the contents by a clause motility in the large intestines. In addition, it is thought that GMCs appear several times a day, and play a role in determining which contents of the large intestines are transported to the anus at a stretch [37]. In this research, tense contractile motility, which was accompanied by the basic pressure change of the period dividing frequency of 10.0 ± 1.8 min on the average in the cecum, and 13.0 ± 2.5 on the average in the right ventral colon, was regularly observed, and the resting stage did not exist. These contractile motilities were shown to be cyclic by electromyogram, and have been reported to be cyclic as well by Ross [48, 49], who measured cecum motility in the pony. However, because the rise of a periodic based line was accompanied by the contractile motilities, these motilities were thought to be equivalent to the CMCs of the above-mentioned dog. As for the contractile style of the cecum and the colon, tense contraction, which is contraction with a large degree of tension, was found to occur throughout the entire digestive tract wall in the horse. In general, when you auscultate the cecum located in the vicinity of the right abdomen of the horse, you will be able to continuously listen to the peristaltic sounds of the intestines, by which this contraction is repeated. It was clear that the contraction motility of a healthy cecum is continuously observed, and never ceases, in horses. However, it was thought to be unlikely that the peristaltic sounds of the small intestines in the vicinity of the left abdomen could be heard, because a rest period (phase I) of about 30 min was observed in the small intestines from the distal jejunum to the ileum.
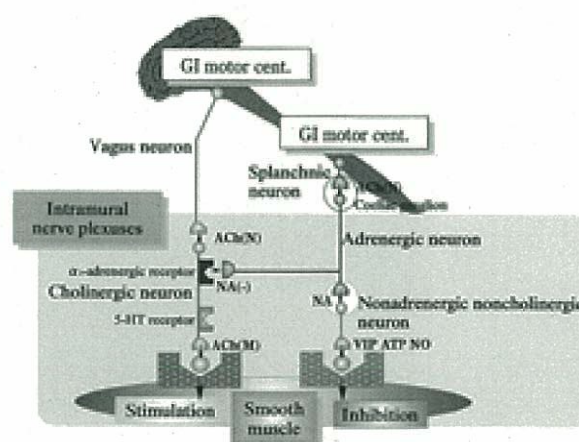

Fig. 6. Innervation to gastrointestinal motility

Regulation mechanism of intestinal motility

The regulation of intestinal motility has been divided into neural and hormonal mechanisms (Fig. 6). The neural adjustment is done in the center and the periphery of the nerves. As the gastrointestinal motility center are given though the vertebra and the medulla oblongata, it is thought that the adjustment mechanism also exists in a high-ranking center (mesencephalon and telencephalon), because a emotional upset influences on the gastrointestinal motility [74]. It is known that there is both a cholinergic nerve which promotes the gastrointestinal motility in a parasympathetic nerve (vagus and pelvis nerve), and an adrenergic nerve which inhibits in the sympathetic nerve (splanchinic nerve), in the centrifugal nerves of a periphery adjustment [74]. The presynaptic fiber in the vagus goes out of the dorsal motor nucleus of the vagus nerve of the medulla oblongata, and forms the postganglionic nerve and synapse with the plexus myentericus (Auerbach nerve plexus). Acetylcholine (Ach) releases after electrical excitement transmits to the postganglionic nerve. The gastrointestinal motility is promoted by the contraction of smooth muscle to unit Ach with the muscarinic receptor of smooth muscle [74]. However, the presynaptic fiber (cholinergic) in the sympathetic nerve passes the radix ventralis through the nucleus intermediolateralis of the chest and the lumbar spinal cord, and then forms a synapse with the postganglionic fiber (adrenaline agonist) in the gangliaca celiaca, the ganglion mesentercum craniale, and the ganglion mesentricum caudale. The majority of this fibre is distributed in the

plexus myentericus, and Noradrenaline (NA) releases when getting excited. After the separating NA unites with the α₂-adrenergic agonist which exists in the cholinergic nerve end, the gastrointestinal motility is controlled by the inhibition of the release of ACh from this nerve [74]. Recently, the existence of a non-cholinergic non-adrenergic has been clarified, and nitric oxide (NO), which is a slack factor (endothelium derived relaxing factor: EDRF) of capillary endothelium origin, is known as one of the nerve transmitter substances of the digestive tract adjustment [74].

The hormonal adjustment is done with the intestinal tract peptide gastrin, cholecystokinin (CCK), motilin, substance P, the 5-hydroxytryptamine, and gastrin releasing peptide (bombesin), are known as gastrointestinal motility enhancers. Secretin, glucagon, vasoactive intestinal polypeptide(VIP), enkephalin, and somatotropin release inhibiting hormone, along with other hormones, are known as a motility inhibitor [23, 50]. Moreover, the dopamine 2 (D2) receptor, 5-hydroxytryptamine (5-HT) receptor, and opioids (type and type) receptors as well as other receptors are found in the plexus myentericus [43]. It is thought that the gastrointestinal motility is regulated by the above-mentioned hormonal controlling agent (nerve transmitter substance) acting on these receptors [74]. In the research that has been conducted on medicine which acts as a regulation mechanism of gastrointestinal motility in horses, it has been reported that the neostigmine has an inhibitive action in ponies [1]. The effectiveness of metoclopramide for intestinal obstruction after surgery, [16, 61], and the stimulative action to the colon myogenic potential and gastric emptying of the bethanecol have been shown [46]. Moreover, it has been clarified that hydroxytyramine causes the blood flow of the cecal artery to increase, and that the action potential of the cecum wall is raised in horses [6]. Thus, the neural regulation mechanism, which centers on the autonomic drug, has been examined in research on gastrointestinal motility in horses. However, there has not been enough research conducted on the gastrointestinal hormone and its effect on the regulation mechanism of intestinal motility.

Gastrointestinal motility regulation hormone

Motilin is a peptide which was discovered by Brown [2] in Canada in 1973. It is composed of 22 amino acids. After Brown, its chemical structure was clarified in the dog, cat, and rabbit [22]. However, the necessity of the N-end structure of the amino acid sequences is known to the appearance of the physiology revitalization [22]. Motilin is produced and discharged in the motilin cell, which belongs to the open type basal granulated cell, and lies in the mucosal epithelium of the duodenum [10]. It is known that motilin causes phase III, which consists of a peculiar strong contraction in the stomach of humans and dogs [73], and that the periodic change of motilin in a plasma concentration regulates the regular appearance of phase III. That is, when a physiological dose of motilin is intravenously administered in the interdigestive state, a physiological phase III is generated [73]. Moreover, it is known that the plasma concentration of the endogenous motilin indicate the highest value when phase III appears in the stomach or the duodenum [22]. In addition, when the action of the endogenous motilin is neutralized with the antiserum of motilin, it becomes clear that phase III in the stomach or the duodenum does not appear [23]. Thus, the mechanism of the appearance of the phase III of motilin has not been clarified yet in the horse, though the active mechanism of motilin is being elucidated in the human and the dog. Finally, the action of motilin is vagus dependent, and is known to use the 5-hydroxytryptamine (5-HT₃) receptor of the cholinergic nerve [22]. Because the peculiar phase III in the interdigestive state spreads from the small intestines to the anus side one contraction at a time, it is called interdigestive migrating contractions (IMC) in single stomach animals like the human and the dog [22, 23]. However, the group of strong contractions are known as migrating contractions (MC), because the distinction at the period and the after the meal interdigestiveness does not exist in the horse and the cattle [50]. IMC and MC are observed in many mammals, and it is assumed that they function to transport the stagnant saburra and the exfoliative cuticle to the large intestines at a stretch [13]. Moreover, cell kinetics, in which various cells of the small intestine mucous membrane change places within six days, are known [22], and the significance of IMC and MC are known to maintain the normal physiological function of the digestive tract mucous membrane. In addition, bacterial overgrowth is observed in the digestive tract when IMC and MC disappear [36, 41]. It is thought that IMC and MC function in gastrointestinal motility not only to clean
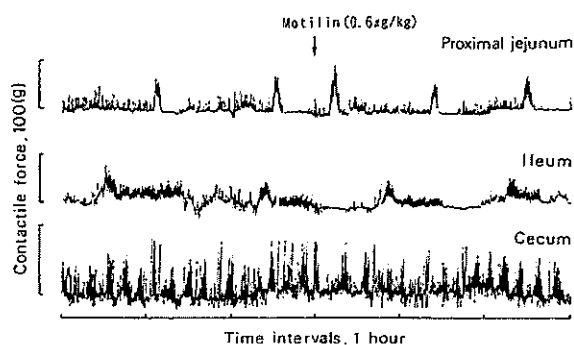
Fig.7. Effect of motilin on intestinal motility. Phase III appeared by administering in the vein of motilin (0.6 g/kg) in the proximal jejunum. References: Sasaki Naoki and Yoshihara Toyohiko 1999. The effect of motilin on the regulation mechanism of intestinal motility in conscious horses. J.Vet.Med.Sci. 61(2)167–170.

the digestive tract, but also to help control bacterial overgrowth and to prepare for the next feeding [24]. Therefore it has been presumed that generating of IMC and MC are an effective treatment for enhancing gastrointestinal motility. Administering a medicine with a prokinetic agent like motilin and generating MC would be effective in treating motility disorders involving lowered motility. Phase III appeared in the proximal jejunum by intravenous administering motilin (0.6 g/kg) (Fig. 7). The appearance cycle of the strong contraction group significantly decreased for 41.3 ± 8.5 min after administration, compared with 126.6 ± 34.5 (mean ± S.D., n=7) before administration [56]. From these results, it was suggested that a gastrointestinal prokinetic agent which includes motilin was useful as a treatment for digestive system diseases in the horse which cause lowered motility. However, motilin is a chemically unstable nervous peptide. Also, it has a short activation time and loses activation when applied as a therapuetic agent orally [22].

The gastrointestinal prokinetic agent (serotonin receptor agonist)

The effect on the digestive tract of the serotonin receptor (5-HT$_4$) agonist, that it is known to have generating MC as motilin [5, 32], is discussed next in application to medical practices. Bethanechol chloride, which is of the cholinergic drugs and neostigmine, which is the cholinolytic agent thing, have

been used as a medicine with the stimulation action of the gastrointestinal motility function for medical practices in horses so far [40, 44]. However, the action of these medicines is limited only by some part of the digestive tract. The side effects of these medicines are stimulation of the extrapyramidal tract system, pain caused by overstimulation of the parasympathetic nerve, and weaknesses such as the supersecretions of prolactin [15, 50]. Therefore, these medicines have been known to cause a great deal of pain when administered to thoroughbreds with hypersensitive sensory nerves [9]. Recently, cisapride was developed as a motility enhancing drug for the entire digestive tract, and as a medicine without a 5-HT$_4$ antagonist [12]. Moreover, it is known that cisapride has a regulatory action on gastrointestinal motility to promote the release of acetylcholine, and to promote as effectively as motilin, through the serotonin receptor (5-HT$_4$), which exists in the digestive tract's myenteric plexus [12, 62, 67]. In horses, cisapride has been mainly given orally [9] to treat flatulence or constipation colic or to prevent postoperative ileus [15, 34, 70]. The response to the intestinal motility after oral administration remains unclear, although reactions to the drug have been observed after intramuscular and intravenous administration [17, 70]. However, researchers who have studied the effect on gastrointestinal motility after oral administration have not thoroughly evaluated the effective dosage. They have evaluated the index of the recovery rate from disease, and the ausculation of the peristaltic sounds [34, 63]. However the effect the dose change in oral administration exerts on the regulation mechanism of intestinal motility has not yet been clarified.

Phase III appeared in the proximal jejunum upon intravenous administration of cisapride (0.1 mg/kg), and the phase III occurrence in the jejunum significantly increased with oral administration of cisapride (0.75 mg/kg and 1.0 mg/kg) (Figs. 8 and 9) [58]. Milne [34] reported that an oral dose of 0.8 mg/kg cisapride was clinically effective for chronic gas sickness in horses. King [26] observed an increased electric potential at the left dorsal and the small colon in ponies after intravenous treatment with 0.1 mg/kg cisapride, indicating that the drug might have an effect on the regulation of motilities not only of the small intestine, but also of the colon. And yet, no effect of cisapride has been reported on the equine cecum [26, 34]. Such differences in the effectiveness of cisapride between the intestinal parts might be ascribed to the
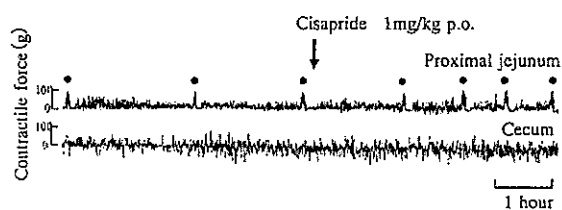
Fig. 8. Effect of cisapride oral administration on intestinal
         motility. ●: Phase III. The Phase III occurrence count
         of the jejunum has increased by oral administration of
         the cisapride (1 mg/kg). References: Sasaki Naoki and
         Yoshihara Toyohiko 2000. The effect of orally
         administered cisapride on international motility in
         conscious horses. J.Vet.Med.Sci. 62(2)211–213.

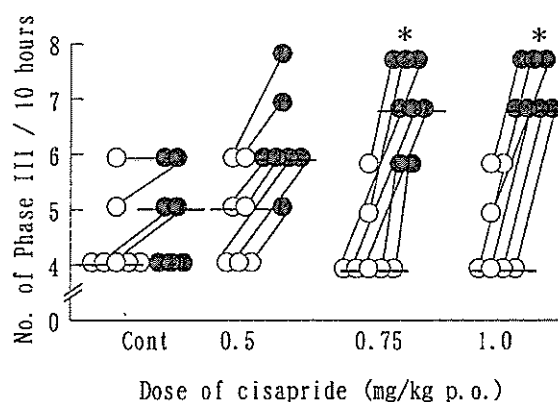Dose of cisapride (mg/kg p. o.)

Fig. 9. Dose dependency of the frequencies of phase III at the
         proximal jejunum in cisapride-treated horses (N=7).
         ○:10 hr before treating. ●:10 hr after treating.
         *:P<0.05. The Phase III occurrence count significantly
         increased after oral administration of the cisapride (0.75
         mg/kg and 1.0 mg/kg). References: Sasaki Naoki and
         Yoshihara Toyohiko 2000. The effect of orally
         administered cisapride on international motility in
         conscious horses. J.Vet.Med.Sci. 62(2)211–213.

difference in the distribution of the serotonin (5-HT) receptor, that is, the targets of cisapride [42]. Steinebach [63] reported that clinical signs improved in horses with costipation colic after nine oral dosings of cisapride (0.1mg/kg) at 8 hr-intervals. Cisapride might have been the cause of the gastrointestinal motility with cooperation on the entire small intestine, though there are differences among the various intestinal parts in the effectiveness of cisapride. It was revealed that motilin is involved in the regulation mechanism of intestinal motility in horses as well as in humans and dogs, and that gastrointestinal motility was enhanced after oral administration of 0.75 mg/kg and 1.0 mg/kg cisapride in horses [58]. Recently, Mosapride [35], Alosetron [3], and Tegaserod [39] along with other researchers examined the serotonin receptor agonists in humans. It is known that Mosapride shows gastrointestinal motility enhancing action through the serotonin receptor (5-HT$_4$) [76, 77]. Moreover, it was confirmed that Mosapride had neither the D2 receptor action nor the QT extension action. Mosapride is expected to have an effect similar to cisapride in the horse.

α$_2$-adrenergic agonist

In horse, the gastrointestinal motility disorders are divided into two types as follows [57]. One is an example of lowered motility, such as the constipation colic and intestinal obstructions that occur after surgery. The other is an example of intestinal tension, for example, convulsion colic, diarrhea, flatulence, and twisting of the bowel. It is thought that the application of the serotonin receptor agonist as the gastrointestinal

prokinetic agent is effective for lowered motility. However, the tension should be removed or eased when the animal has intestinal tension. The pain is caused by the tension of the digestive tract smooth muscle according to the expansion of the digestive tract contents, and by flatulence and acute abdomenal pain caused by the twisting of the bowels. This splanchnodynia tension in the digestive tract smooth muscle makes gastrointestinal motility decrease. In addition, harmful conditions such as ischaemia disorders and endotoxicemia are caused in the digestive tract by the vagal reflex [8]. Therefore, the α$_2$-adrenergic agonist is applied to ease turgescence in the digestive tract, and to reduce splanchnic pain [9, 14, 72]. However, it has been discussed that if used to treat different disorders, the level of the pain control of the α$_2$-adrenergic agonist might differ depending on each acute abdomen. It is known that it is difficult to control torsion or pain of the small intestines, though the α$_2$-adrenergic agonist is comparatively effective for pneumatosis intestinalis, displacement, and the torsion of the cecum and the colon over a long term [9, 18]. It is thought that it is extremely important to clarify the action characteristic of the α$_2$-adrenergic agonist for each part of the digestive tract, in order to diagnose and treat the surgical abdomen. With regards to the effects on the digestive tract of the α$_2$-adrenergic agonist in ponies, it is known that a decrease in the
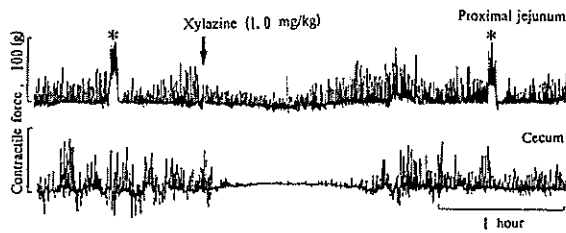
Fig. 10. Effect of xylazine on intestinal motility. *: Phase III. Soon after xylaxine treatment, the contractive motility was inhibited in the proximal jejunum and cecum.
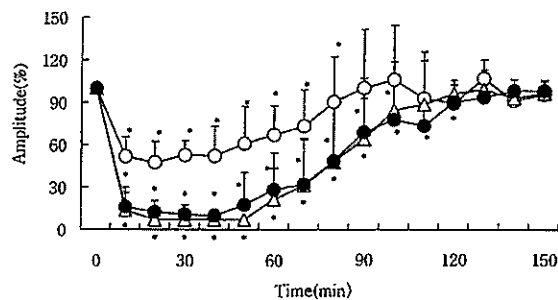

Fig. 11. Change in contractive motility of the proximal jejunum(○), cecum(●) and right ventral colon (△) after administration of xylazine (1.0 mg/kg, i.v.) (N=7). Each contraction amplitude is represented by % of maximum pre-contraction. Data were shown by mean ± standard deviation. After statistical analyses were done with two-way analysis of variance (ANOVA), the multiple comparison test (Dunnett's test) was executed between before and after administration. *: Significantly different from before administration (P<0.05).

Fig. 12. Change in contractive motility of the proximal jejunum(○), cecum(●) and right ventral colon (△) after administration of medetomidine (0.0075 mg/kg, i.v.) (N=7). Each contraction amplitude is represented by % of maximum pre-contraction.

Table 2. Contraction amplitudes (% of maximum pre-contraction; n=6, mean ± S.D.) of each part of the digestive tract at 30 min after administration (N=7)

	Jejunum	Cecum	Right ventral colon
Xylazine	52.8 ± 10.2	7.1 ± 0.7[a]	11.0 ± 6.6[a]
Medetomidine	49.5 ± 14.4	5.3 ± 1.2[a,b]	7.3 ± 3.3[a]
Saline	97.1 ± 10.9	103.8 ± 8.9	104.7 ± 14.1

a) Significantly different from the proximal jejunum (P<0.05). b) Significantly different between xylazine and medetomidine (P<0.05). Data were shown by mean ± standard deviation. The drug was significantly less effective in the proximal jejunum than in other part of the tract(a). As compared to xylazine, medetomidine had more remarkable inhibitory effect on the contractive motility, and difference between the drugs was significant in the cecum(b). Statistical analysis were done with Mann-Whitney's test.

intraluminal pressure of the pelvic flexure by administering xylazine [29] occurs, and that a decrease [54] on the myoelectic activity of the cecum and the right ventral colon [54] occurs. Moreover, it was reported that detomidine, which is a α_2-adrenergic agonist, had the same inhibitive action on the myoelectric activity of the colon as xylazine [45].

It was recently reported that both the arterial blood flow and motility on the cecum decreased at the same time after xylazine administration [52]. Thus, the regional difference in the effect on contractive motility of the α_2-adrenergic agonists is unknown. Therefore, we investigated the effects of xylazine and medetomidine on the contractive motility in different regions of the intestine in conscious horses, in order to help elucideate the regional difference in the pain relieving effect of xylazine (1.0 mg/kg) and
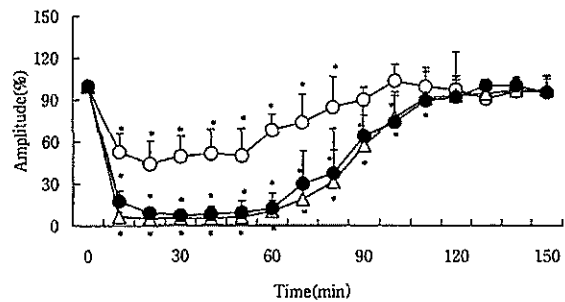
medetomidine (0.0075 mg/kg). The injection of xylazine (1 mg/kg, IV) immediately inhibited contractive motility in the proximal jejunum, the cecum, and the right ventral colon (Fig.10). When the period of significant inhibition was estimated from the graphs in Fig.11, it was found to be about 80, 100, and 120 min, respectively, in the jejunal, cecal, and colonic regions. The periods of significant inhibition of contractions were estimated to be 80, 100, and 110 min, in the jejunul, cecal, and colonic, respectively (Fig.12) [57]. The present experiments found that the effects of xylazine and medetomidine in the cecum and colon were stronger than those in the jejunum region. Based on these findings, both drugs might be as effective in treating jejunal torsion as in treating cecal and colonic torsion. The reason the regional difference in the effect on contractive motility of the α_2-adrenergic

agonists is exactly unknown [52, 54]. A possible explanation might come from the suggestion by Malone *et al.* [31] that nervous control of contractive motility differs in the small and the large intestine, and especially in the 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.

The percent amplitudes at 30 min after xylazine injection were 52.8 ± 10.2, 7.1 ± 0.7, and 11.0 ± 6.6 %, respectively, in the proximal jejunum, cecum, and right ventral colon. The percent amplitudes at 30 min after medetomidine injection were 49.5 ± 14.4, 5.3 ± 1.2, and 7.3 ± 3.3%, respectively, in the proximal jejunum, cecum, and right ventral colon (Table 2). The mean values of both xylazine and medetomidine for the jejunum were significantly greater ($P<0.05$) than that for any other regions ($p<0.05$). Moreover, the duration of the inhibitory effect of xylazine and medetomidine were similar, but the inhibitory effect with medetomidine was significantly greater than with xylazine. When using α_2-adrenergic agonists for relieving intestinal tension, medetomidine is recommended over xylazine.

Summary

In this research, the effects of medicines on the regulation mechanism of intestinal motility in the horse were clarified, and valuable findings on the safety of using the medicine were obtained. In the future, we expect these findings on the medicinal treatment of gastrointestinal dysfunctions to contribute to advancements in the diagnosis and treatment of digestive organ diseases.

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