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Original Article

Ultrasonographic Evaluation of Duodenal and Cecal Motility after Administration of Different Doses of Domperidone in Donkeys (Equus Asinus).

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Abstract

The objective of the present study was to evaluate the effect of different doses of domperidone on duodenal and cecal motility in donkeys. Six adult donkeys (n = 6) were used in a crossover study. Domperidone was administered orally via nasogastric tube at a dose rate of 0.5, 1 and 2 mg kg^{-1}. Duodenal and cecal contractions were evaluated by ultrasonography using a 5 MHz curved-linear transducer. Examinations were performed before administration and at 15, 30, 60, 120 and 180 minutes post-administration. There was a significant ($p< 0.05$) increase of duodenal contractions after 15 minutes of domperidone administration at 1 mg kg^{-1} and lasted until 60 minutes. The cecal contractions were also significantly increased after 15 minutes and lasted until 60 minutes at a dose rate of 1 and 2 mg kg^{-1} (MANOVA fit, $p< 0.01$; Wilks, Lambda for dose × time interaction, $p < 0.05$). The results of the present study indicate that 1 mg kg^{-1} domperidone is the most effective prokinetic dose on duodenal and cecal contraction. Domperidone may be an alternative prokinetic drug for intestinal and cecal disorders in equines.

Key words: Domperidone, Duodenum, Caecum, Ultrasonography, Donkeys.

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Introduction

Abdominal pain in equines is produced by gas and fluid accumulation from the alteration in gastro-intestinal tract motility (Koenig and Cote, 2006). Paralytic ileus is a functional inhibition of propulsive intestinal motility. Ileus can occur either from local diseases involving digestive system or a consequence of systemic illness (Adams 1988, Lester 2002).

Large colon impaction is more common and constitutes the most cause of simple obstruction in horses especially in left ventral colon, pelvic flexure and right dorsal colon (Grosche 2000). The exact causes and pathogenesis of impactions are not fully understood until now. Parasitic infestation or migration, motility disorders, dental abnormalities, dietary or management factors, and reduced water intake are often implicated (Sullins 1990). Prokinetic agents are those drugs, which promote gastrointestinal motility either by increasing the frequency or strength of contraction, but without changing their rhythm (Hardman et al., 2001). They are useful in treatment of motility disorders in humans and animals and used to relieve gastrointestinal symptoms such as abdominal discomfort, bloat and constipation (Hardman et al., 2001).

Domperidone is a selective peripheral dopamine antagonist (DA2 receptor) and a novel gastroprokinetic lacking central side-effect. Due to its blocking activity on peripheral dopamine receptors, domperidone can enhance effectively esophageal peristalsis, lower esophageal pressure, gastric motility, and gastro-duodenal coordination and consequently improve gastric emptying and decrease small bowel transit time (Lester 2002).

Studies in animals and man have shown that domperidone enhances the peristaltic contractions of the esophageal body, increase the muscle tone of the lower esophageal sphincter, and stimulate gastric motor activity (Kilbinger and Weihrauch 1982). So, it has been found to be beneficial in the treatment of gastric motor failure and of reflux esophagitis secondary to lower esophageal sphincter incompetence (Kilbinger and Weihrauch 1982).

The prokinetic effect of domperidone in equines have not been described sufficiently. Consequently, the purpose of the present study was to evaluate the effect of different doses of domperidone on the motility of the small intestine and caecum in donkeys using transcutaneous ultrasonography.

Materials and Methods

Study Overview and Animals

Six adult healthy donkeys (Equus asinus) were used in a crossover study. The age of donkeys ranged from 9 to 17 years and body weight (B.W.) ranged from 100 to 220 kg. None of those donkeys had gastrointestinal disorders or evidence of systemic diseases based on thorough clinical examination (Kelly, 1984). Two weeks before starting the study, each donkey was stabled on straw-bedded boxes and fed twice a day with 1 kg chopped hay/100 kg B.W. and 0.5 kg concentrate with unlimited access to water. This study was carried out at Department of Animal Medicine, Faculty of Veterinary Medicine, Kafr Elsheikh University, Egypt. These trials were approved by Animal welfare and Ethics Committee, Faculty of Veterinary Medicine, Kafr-Elsheikh University.

Protocol of the Study

Each donkey underwent four trials. The first trial was carried out by counting the intestinal contractions at descending duodenum and cecal body before and after oral administration of 1000 ml of clean water via a nasogastric tube (control group). The second, third and fourth trials included the counting of intestinal contractions at the same regions of the intestine before and after oral administration of Dompridone (Motilium®, Miapharm, under licence of Janssen Pharmaceutica, Janssen-cilag, Belgium), at a dose rate of 0.5, 1 and 2 mg kg^{-1}, respectively (treated groups). The dose rate was selected based on that reported by the Merck veterinary manual. Domperidone was dissolved in 1000 ml of clean water and administered via nasogastric tube. The washout period between the experiments was one week. Intestinal contractions were counted in a control and treated groups one hour after feeding. They were counted over a period of 3 minutes before treatment and at 15, 30, 60, 120 and 180 minutes post-treatment. During the monitoring periods, there was no access to food or water. In addition, any evidence of adverse effects was observed during the monitoring period following the administration of dompridone.

Ultrasonographic Examination

Transcutaneous ultrasonographic examinations were performed for counting the intestinal contractions at the descending duodenum and the body of cecum (Kirberger et al., 1995, Freeman 2002, Mitchell et al. 2005, Gomaa et al., 2011). The donkeys were restrained in stocks without any sedation during the ultrasonographic examinations. The position of the descending duodenum and cecal body in each donkey was identified before the beginning of ultrasonographic examinations. The descending duodenum was located at the right thoracic area extending from the 8th to the 18th rib along the line joining the olecranon and tuber coxae. The cecal body was identified in the upper part of the right para-lumbar region. The abdomen was clipped at those identified regions, cleaned with alcohol and then coupling gel was applied to enhance the contact with the probe. Abdominal ultrasonographic examination was performed with a 5 MHz curved-linear transducer (CHISON Digital Color Doppler Ultrasound system, iVis 60 EXPERT VET, CHISON Medical Imaging Co., Ltd). The transducer was oriented in a longitudinal direction for better visualizing the sacculations of cecum and left ventral colon. In contrast to the gas-filled cecal base and movable cecal apex, the cecal body wall is easy to identify based on the cecal body fluid content. The transducer was positioned in a cross-sectional direction for the best visualization of the descending duodenum. Once the optimal imaging plane had been determined, the intestinal contractions were counted during a 3-minute period and assessed by the movement of intestinal wall and luminal contents. In the descending duodenum, the numbers of duodenal distensions or circular contractions were counted. The contractions of the cecal body were associated with deviation of cecal wall from the transducer of more than 2 cm. Nevertheless, the contractions of left ventral colon were assessed by changes in its sacculations.

In all trials, the intestinal contractions counting were done after one hour of feeding at 9:00 AM and were carried out by the same person and revised again by two persons to avoid any individual variations.

Statistical Analysis

Data analyses were performed using a statistical software program (GMP for windows Version 5.1; SAS Institute, Cary, NC, USA). Data were tested for normal distribution using D'Agostino and Pearson omnibus normality test. The data were normally distributed; therefore, mean and standard deviation for each assessed treatment at each time point was calculated. Repeated measures MANOVA (repeated measures on dose and time) were used to determine the main effect of dose and time. Wilks' Lambda test was selected to evaluate within group interactions and evidence of time x group interactions. Where Wilks' Lambda test indicated a statistically significant difference between groups, one way ANOVA with Tukey-Kramer HSD *post-hoc* multiple comparison tests was used to identify which group was statistically different. Differences between means at $p < 0.05$ were considered significant.

Results

The descending duodenum was constantly observed at 12th -13th intercostal space. It was visualized between the liver and the right dorsal colon as an oval to round shape (Figure 1 and 2). During ultrasonographic examination, segmental contractions were noticed.

The cecal body wall appeared as a mobile hypoechoic line overlying a hyperechoic gas shadow adjacent to the right abdominal wall (Figure 3). The normal cecal motility comprised either localized segmental contractions (mixing) or propagating (propulsive) contractions in both forward and backward directions. The segmental contraction of cecum was measured by moving the cecal body wall away from abdominal wall about 2 cm (Figure 4). Only the segmental contractions were counted during ultrasonographic examination of descending duodenum and body of cecum.

In control group, mean and standard deviation of the recorded pre-administration intestinal contractions at the descending duodenum and cecal body were 6.7 ± 1.0 and 4.0 ± 0.9 contractions / 3 minutes, respectively. There was non-significant difference of duodenal or cecal contractions during a three-hours monitoring period after clean water administration.

The duodenal contractions were increased significantly (MANOVA fit, $p < 0.01$; Wilks,

Lambda test for dose × time interaction, $p<0.05$) at 15 minutes post-administration at a dose rate of 1 mg kg-1 and lasted until 60 minutes post administration. Meanwhile, the duodenal contractions started to increase significantly after 30 minutes post-administration of 0.5 mg kg-1 domperidone. However, the dose rate at 2 mg kg-1 produced non-significant increase of duodenal contractions at different time points (Figure 5).

In addition, the cecal contractions were significantly increased (MANOVA fit, $P< 0.01$; Wilks, Lambda test for dose × time interaction, $p<0.05$) after 15 minutes of administration of 1 and 2 mg kg -1 of dompridone and persisted till 60 minutes. However, 0.5mg kg-1 produced non-significant increase of cecal contractions at different time points (Figure 6).

Regarding adverse effects, no apparent behavioral abnormalities were recorded in treated donkeys at different dose rates.

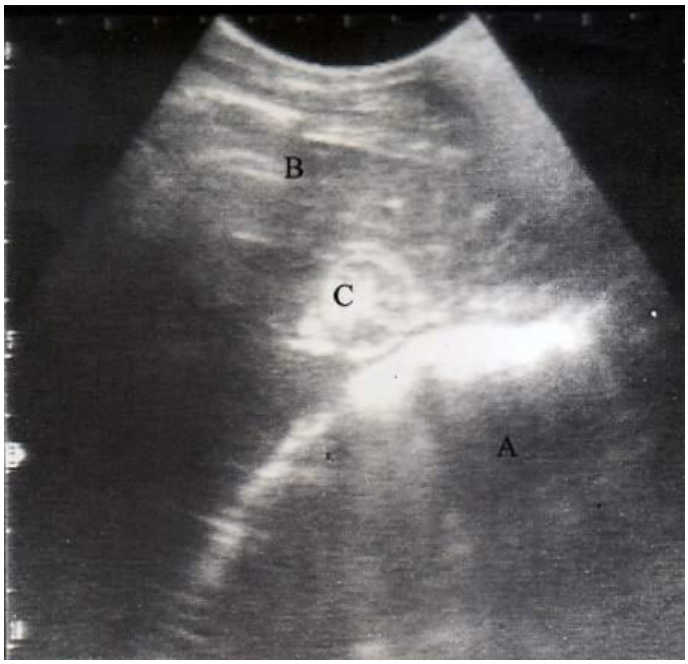

Fig.1. Ultrasound scan of descening duedenum during relaxation phase. (A) right dorsal colon; (B) liver; (C) duodenum which appears an oval shape.

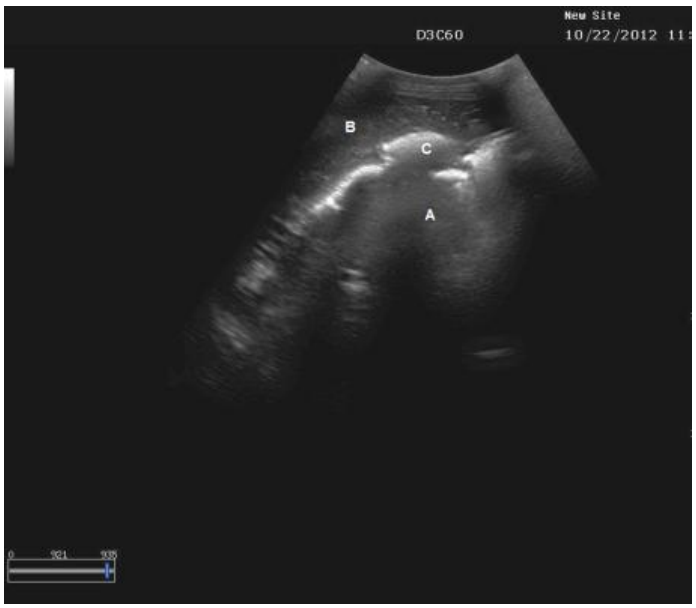

Fig.2. Ultrasound scan of descending duedenum during segemental contraction phase. (A) right dorsal colon; (B) liver; (C) duodenum which appears a round shape.

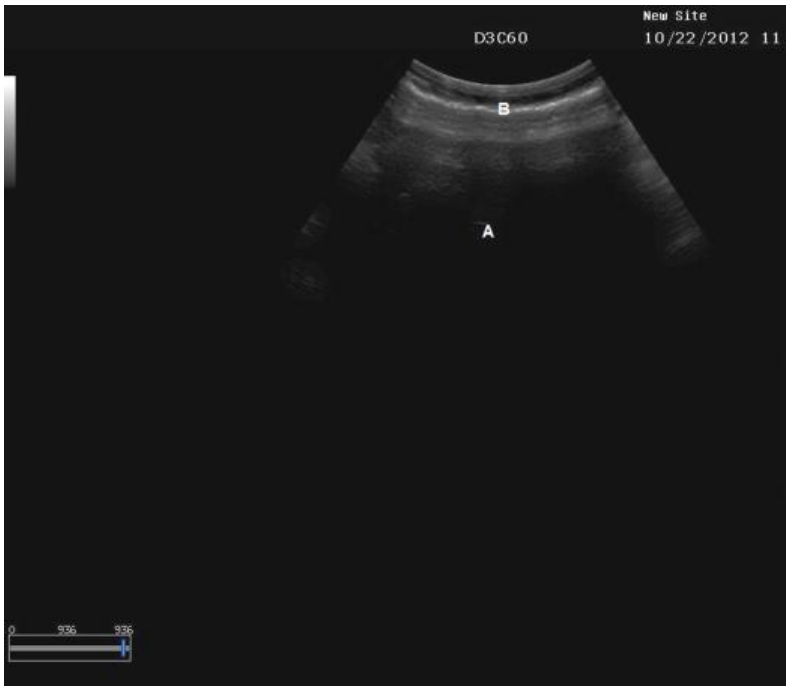

Fig.3. Ultrasound scan of cecum. It appears adjacent to body wall at the most upper part of picture. The cecal body wall (B) appears as hypoechoic line over lining a hyperechoic line of mucosa with multi-hyperechoic lines (reverberation artifact) and hypoechoic area at the distal part of picture (A) representing the food and fluid in cecum.

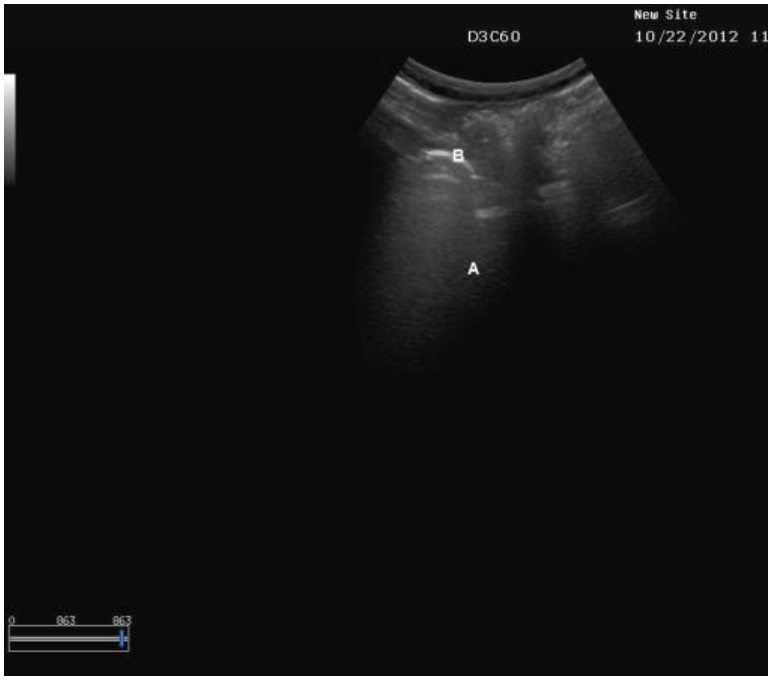

Fig.4. Ultrasound scan of cecum during mixing contraction. The cecal body wall (B) moves away the abdominal wall about 2 cm which representing the mixing contraction. A hypoechoic area at the distal part of picture (A) representing the food and fluid in cecum.

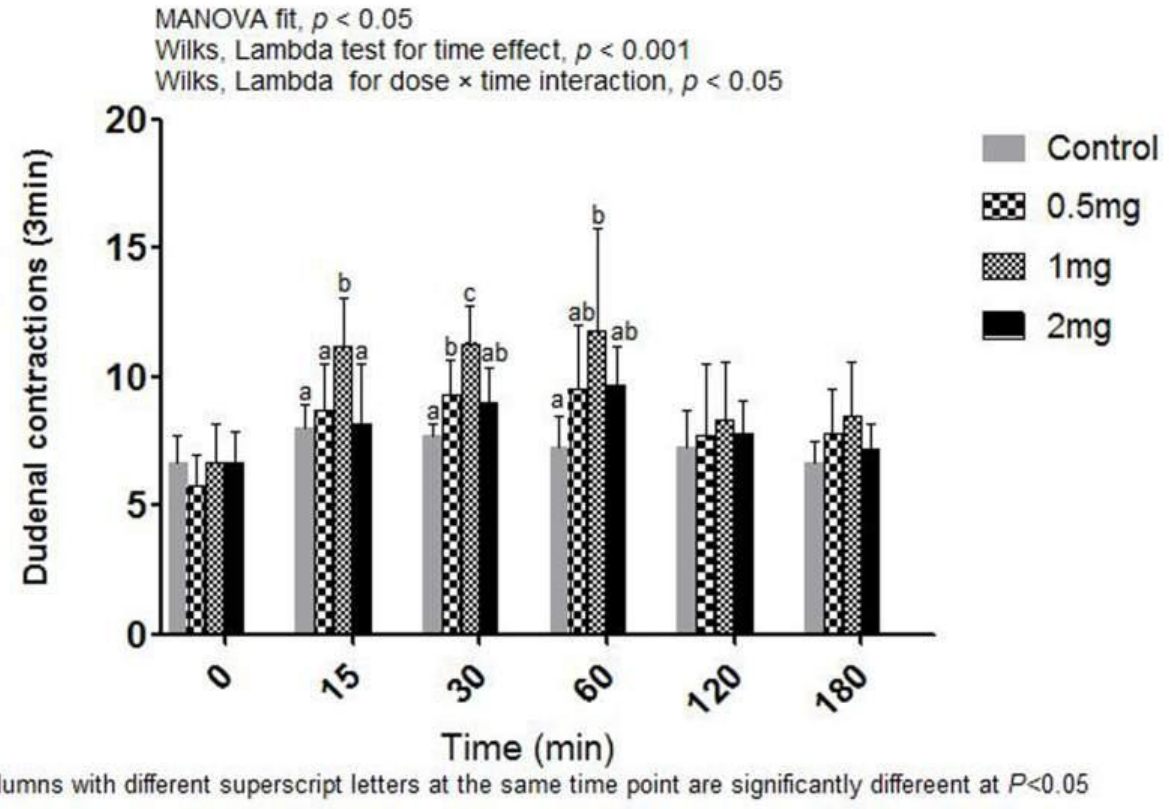

Fig.5. Duodenal contractions (number/3minutes) after administration of different doses of domperidone in donkeys.

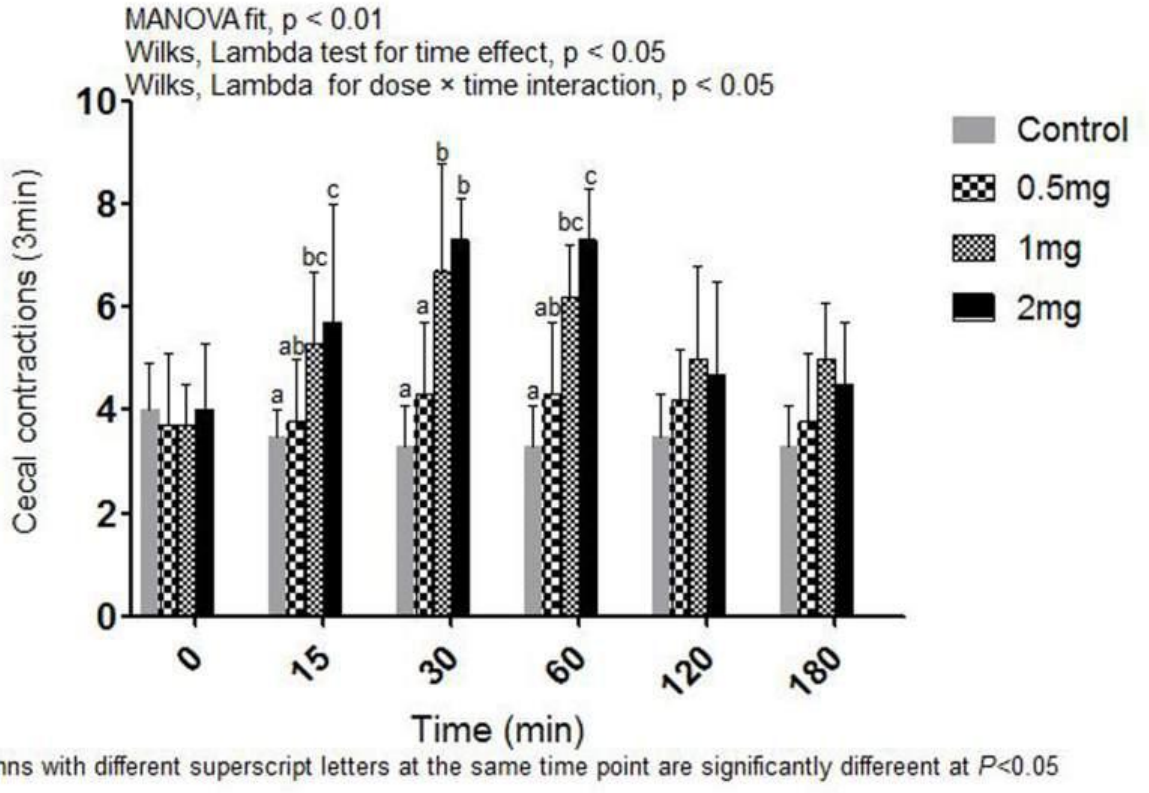

Fig.6. Cecal contractions (number/3minutes) after administration of different doses of domperidone in donkeys.

Discussion

Domperidone is a unique gastroprokinetic drug because of its safety profile in human; it appears to be alternative to metoclopramide (Barone 1999). In a preliminary study using an experimental model of post-operative ileus in ponies; domperidone was effective in restoring transit time, electromechanical activity, and coordination of gastric and intestinal cycles at a dose rate of 0.2 mg kg-1 intravenously (Gerring and King 1989). No further information about domperidone as a gastroprokinetic agent in equines; therefore, the present study was constructed to evaluate the effect of domperidone on both the duodenal and cecal contractions in donkeys via ultrasonography.

In the present study, oral administration of domperidone at a dose rate 1 mg kg -1 produced a rapid significant increase in duodenal motility after 15 minutes post-administration. This could be attributed to the fact that the absorption of domperidone solution was very rapid, with mean peak plasma concentration attained at 0.6 hour (ten minutes) after its oral administration (Huang et al., 1986).

The increase of duodenal contractions was attributed to the stimulatory effect of domperidone on gastrointestinal muscle itself as well as on the cholinergic neurons/receptors in the gastrointestinal wall (Nakayama et al., 1979, Li et al., 2009).

The prokinetic effect of domperidone is likely a result of block of D2 inhibitory receptors. It has been shown to increase lower esophageal sphincter pressure, improve antro-duodenal co-ordination and gastric emptying and normalize gastric dysrhythmias (Koch et al., 1989, Prakash and Wagstaff 1998). Consequently, domperidone may improve antral and duodenal contraction by dopaminergic antagonism in the myenteric plexus similar to metoclopramide but it does not possess the serotonin effect of metoclopramide and cisapride (Barone 1999).

In a study conducted on dogs, domperidone was found to enhance the gastric body and antrum motility (Shuto et al., 1980). The enhancement pattern of gastric body motility did not last so long and showed an increase in tone of contraction. The authors reported that the augmentation of the gastric motility by domperidone was observed even after vagotomy and splanchnicotomy, but it was weaker and shorter than that in the intact state. Therefore, it was reported that domperidone activates the gastric motility not only by central mechanism, but also by stimulation of intramural neurons.

Domperidone improves gastric emptying of liquids and solids by an inhibition of adaptive fundic relaxation, an increase in antral contractility and improvement of antro-duodenal coordination (Johnson 1992). The prokinetic effect of domperidone on the cecal contraction began after 15 minutes of administration of 1 mg kg-1 and had the same effect of 2 mg kg-1, while, 0.5 mg kg-1 did not have any significant effect during monitoring period. This could be attributed to the effect of domperidone as D2 receptor antagonists such as metoclopramide which has shown to increase gastric emptying, and mouth-to-cecum transit time in human (Kirby et al., 1989). On the contrary, high doses of metoclopramide (D2 receptor antagonist) had weak and unspecific stimulatory motor effects at the equines ileo-caeco-colonic junction (Ruckebusch and Roger 1988). Generally, limited studies on D2 receptor antagonists on cecal contractions in equine are available and mechanism of action is not explained. The present study in the first report provides a preliminary result about the effect of domperidone on the cecal motility in donkeys.

Conclusion

Domperidone at a dose rate of 1 mg kg-1 promotes duodenal and cecal contractions in conscious donkeys without any adverse effects. Consequently, domperidone may be an alternative safe prokinetic in equines. However, the findings of the present study in healthy donkeys may not be extrapalatable to findings in donkeys and horses with GIT dysfunction. Therefore, further studies need to be done on diseased cases related to the clinical practice.

Conflict of interest statement

The authors have indicated that they have no financial involvement with any organization or entity with a financial interest in, or in financial competition with, the subject matter or materials discussed in this article.

References

Adams SB (1988). Recognition and management of ileus. Veterinary Clinic North American Equine Practice 4, 91-104.

Barone JA (1999). Domperidone: a peripherally acting dopamine2-receptor antagonist. The Annals of Pharmcotherap., 33, 429-440.

Freeman LS (2002). Ultrasonography of the equine abdomen: Techniques and normal findings. In Practice 24, 204-211.

Gerring EL, (King JN 1989). Cisapride in the prophylaxis of equine post operative ileus. Equine. Vet. J. Supplment 7, 52-55.

Gomaa N, Uhlig A, (Schusser GF 2011). Effect of Buscopan compositum on the motility of the duodenum, cecum and left ventral colon in healthy conscious horses. Berl. Munch Tierarztl Wochenschr., 124, 168-174.

Grosche A (2000). Kolik bei Pferden-Retrospektive Studie aus dem Patientengut der Medizinischen Tierklinik Leipzig 1994-1998 [Dissertation med.vet]. Leipzig 2000: Univ. Leipzig. (Article in German).

Hardman JG, Limbird LE, (Gilman AG 2001). Goodman & Gilman's. The Pharmacological Basis of Therapeutics. 10th ed. New York: McGraw-Hill.

Huang YC, Colaizzi JL, Bierman RH, Woestenborghs R, Heykants JJ (1986). Pharmacokinetics and dose proportionality of domperidone in healthy volunteers. J. Clinic. Pharm. cology, 26, 628-632.

Johnson AG (1992). Domperidone in the treatment of gastroesophageal reflux disease. Frontiers of gastrointestinal research 20, 45-53.

Kelly WR (1984). The thorax. Textbook of Veterinary Clinical Diagnosis, 3rd ed, 143- 185.

Kilbinger H, Weihrauch TR (1982). Drugs increasing gastrointestinal motility. Pharmacology 25, 61-72.

Kirberger MR, van den Berg JS, Gottschalk RD, Guthrie AJ (1995). Duodenal ultrasonography in the normal adult horse. Vet. Radio. Ultrasound., 36, 50-56.

Kirby MG, Dukes GE, Heizer WD, Bryson JC, (Powell JR 1989). Effect of metoclopramide, bethanechol, and loperamide on gastric residence time, gastric emptying, and mouth-to-cecum transit time. Pharm. cotherap., 9, 226-231.

Koch KL, Stern RM, Stewart WR, (Vesey MW 1989). Gastric emptying and gastric myoelectrical activity in patients with

diabetic gastroparesis: Effect of long-term domperidone treatment. Am. J. Gastroenter., 84, 1069-1075.

Koenig J, (Cote N 2006). Equine gastrointestinal motility-ileus and pharmacological modification. Canadian. Vet. J., 47, 551-555.

Lester G (2002). Gastrointestinal Ileus. In: Large Animal Internal Medicine, Smith, B. (Ed.). Mosby, St. Louis, p. 674-679.

Li F, Zou Y, (Huang T (2009). Effect of prokinetic agents on the electrical activity of stomach and duodenum in rats. Zhong Nan Da Xue Xue Bao Yi Xue Ban 34, 599-602.

Mitchell CF, Malone ED, Sage AM, (Niksich K 2005). Evaluation of gastrointestinal activity in healthy horses using B mode and Doppler ultrasonography. Canadian. Vet. J., 46, 134-140.

Nakayama S, Neya T, Yamasato T, Takaki M, (Mizutani M 1979). Effects of domperidone on gastrointestinal and gallbladder motility and gastric emptying (author's transl). Nihon Heikatsukin Gakkai Zasshi., 15, 327-335.

Prakash A, (Wagstaff AJ 1998). Domperidone. A review of its use in diabetic gastropathy. Drugs., 56, 429-445.

Ruckebusch Y, (Roger DT 1988). Prokinetic effects of cisapride, naloxone and parasympathetic stimulation at the equine ileo-caeco-colonic junction. J. Vet. Pharm. Ther., 11, 322-329.

Shuto K, Shiozaki S, Kojima T, (Tanaka M 1980). Effects of KW-5338 (domperidone) on gastric motility. J. Pharm. cobiodynamic., 3, 715-719.

Sullins KE (1990). Diseases of the Large Colon. In: The Equine Acute Abdomen, White, N.A. (Ed.). Lea and Febiger, Philadelphia, p. 375-391.