The Effect of Lidocaine on Postoperative Jejunal Motility in Normal Horses

MELISSA MILLIGAN, DVM, MS, WARREN BEARD, DVM, MS, Diplomate ACVS,
BUTCH KUKANICH, DVM, PhD, Diplomate ACVCP, TIM SOBERING, MS, and SARAH WAXMAN, BS

Objective—To measure the effect of lidocaine on the duration of the migrating myoelectric complex (MMC) and Phases I, II, and III of the MMC, spiking activity of the jejunum, and number of Phase III events when administered postoperatively to normal horses.
Study Design—Nonrandomized cross-over design.
Methods—Horses were anesthetized and via flank laparotomy 4 silver–silver chloride bipolar electrodes were sutured to the proximal jejunum. Electrical activity was recorded for 6 hours during 3 recording sessions beginning 24, 48, and 72 hours postoperatively. Saline (0.9% NaCl) solution was administered for 3 hours followed by lidocaine administration for 3 hours (1.3 mg/kg bolus intravenously [IV], 0.05 mg/kg/min IV constant rate infusion).
Results—Duration of MMC was unchanged during lidocaine administration (77 minutes—saline versus 105 minutes—lidocaine, $P = .16$). Durations of Phase I and II were unchanged during lidocaine administration ($P = .19$ and $.056$, respectively). Phase III was shorter during lidocaine administration ($P = .002$). Spiking activity was unchanged at all time periods during lidocaine administration (24 hours—$P = .10$; 48 hours—$P = .95$; and 72 hours—$P = .12$). The number of Phase III events was unchanged over all time periods during lidocaine administration ($P = .053$).
Conclusions—Duration of MMC, spiking activity, and number of Phase III events was unchanged during lidocaine administration.
Clinical Relevance—Use of lidocaine as a prokinetic agent cannot be supported by this study in normal horses; however, results may differ in clinically affected horses.
© Copyright 2007 by The American College of Veterinary Surgeons

INTRODUCTION

POSTOPERATIVE ILEUS (POI) is an absence of progressive intestinal motility that can result in mortality rates up to 86% in affected horses.[1] Although survival rates for horses suffering from postoperative ileus have improved in recent years, POI remains an important clinical problem and is cited as the leading fatal complication in horses with colic.[1] Horses with POI are often euthanatized because of financial constraints, so death may not be directly related to POI. POI has many causes and treatment includes gastric decompression, fluid re-

placement, and analgesic therapy. Potassium and calcium are also frequently supplemented to promote smooth muscle contractility. When treatment designed to alleviate clinical signs fails, pharmacologic enhancement of intestinal motility is often attempted.

Peristalsis of the small intestine is directly correlated to the electrical activity of the muscularis.[2] Electrical activity of the small intestine can be divided into 2 patterns: slow waves and spike bursts. Slow waves of electrical activity spontaneously occur resulting from transient depolarization of the resting membrane potential. Slow waves do not result in muscular contractions, and occur at a rate of

12–14/minute. Spike bursts are action potentials that occur when a slow wave reaches threshold and are electro-mechanically coupled to muscular contractions.[2] Each spike burst is accompanied by a muscular contraction. This coupling allows assessment of intestinal motility by quantification of the number of spike bursts that occur during a given time period (spiking activity).[3]

In the jejunum, the pattern of spike bursts superimposed on slow waves forms a repeating, measurable cycle termed the migrating myoelectric complex (MMC).[2] The MMC has 3 distinct phases. Phase I is comprised almost completely of slow waves and very few spike bursts. Phase II consists of intermittently occurring spike bursts and spike bursts occur with every slow wave during Phase III.[4,5] Propulsive motility occurs during Phases II and III and the terminal Phase III propels any remaining ingesta aborally. The cycle then repeats, beginning with Phase I. Duration of the MMC is the most frequently cited measure of intestinal electrical activity in horses, cattle, and humans, and it is an accepted method for assessing the effects of drugs on intestinal motility in horses.[6–12] Atropine, butorphanol, pentazocine, and meperidine have all been assessed in this manner and are known to lengthen the MMC and inhibit electrical activity.[8,12]

The individual components of the MMC (duration of each phase and spiking activity) have also been used as an additional determinant of electrical activity.[3,10,11] Scott et al[11] completed a meta-analysis of the human literature (1977–2006) and many publications use the duration of phase and spiking activity as an assessment of jejunal motility. Phase duration can be used to indirectly measure the duration of the MMC when complete MMCs are unavailable. Spiking activity is an index of motility using the number of spike bursts occurring per unit of time, and has been used to quantify small intestinal motility in horses, cattle, and humans.[3,10,11] These spike bursts are directly correlated to muscular contractions and presumably propulsive motility.[2] Therefore, more frequent spike bursts result in increases in motility.

Lidocaine hydrochloride is an amino-amide local anesthetic that is proposed to be an analgesic and to shorten the duration of POI in horses.[13,14] Clinical trials in humans suggest that lidocaine administration shortens the duration of POI by blocking inhibitory reflexes.[15,16] However, the results of human studies must be extrapolated to the horse with caution because POI in humans is a problem of the large intestine, and in horses, clinically recognized POI is confined to the small intestine. It is possible that large-bowel POI occurs in horses but is not widely recognized as a clinical entity.[17]

In vitro studies of equine smooth muscle extracts indicate that lidocaine increases the amplitude of duodenal smooth muscle contraction; however, these results are not easily translated to clinical patients.[18] A clinical trial in 32 horses with POI found that lidocaine decreased duration of POI in postoperative colic patients[14]; however, there are no in vivo studies in horses that assess the effect of lidocaine on the electrical activity of the small intestine.

Our purpose was to assess the effect of a lidocaine constant rate infusion on postoperative jejunal motility in normal horses by measuring the electrical activity of the jejunum using surgically implanted electrodes.

MATERIALS AND METHODS

Horses

We used 6 horses (2 geldings, 4 mares; aged 3–21 years; weighing, 378–580 kg) donated for reasons unrelated to the gastrointestinal tract. Horses had normal physical examination findings, complete blood counts, and serum biochemical profiles.

Horses were allowed water but not food for 8 hours before surgery and were premedicated with flunixin meglumine (1.1 mg/kg, intravenously [IV]) and administered tetanus toxoid. An IV catheter was placed in each jugular vein, 1 for drug administration and 1 for blood sample collection. Horses were sedated with xylazine (1.1 mg/kg IV), anesthetized with ketamine (2.2 mg/kg IV), and anesthesia was maintained by IV infusion of guaifenesin, xylazine, and ketamine. Horses were positioned in right lateral recumbency and the left flank was aseptically prepared for a 20 cm modified grid flank laparotomy.

Four ethylene-oxide sterilized silver–silver chloride bipolar electrodes were sutured to the antimesenteric border of the jejunum, ensuring penetration into the muscularis.[6] Electrodes were located 10 cm apart beginning 100–150 cm aboral to the pylorus. Approximately 60 cm of wire remained in the abdomen. The wires exited through the top of the incision and were secured to the skin. The incision was closed in routine fashion. The wires were secured to the horse with a reusable abdominal support bandage for anesthetic recovery. The wires interfaced with the data collection system and Labview 7.0 software (National Instruments, Austin, TX). Horses were administered flunixin meglumine (1.1 mg/kg IV once daily for 3 days) beginning 24 hours postoperatively.

Myoelectric Data Acquisition

The electronics used to measure and record the electrical signals from the intestine consisted of custom-made electrodes, a 4-channel preamplifier, and a commercial analog-to-digital converter (ADC) interfaced to a computer running a custom LabVIEW program (Fig 1).

The electrodes were fabricated as described by Merritt.[6] Briefly, each electrode consisted of a pair of silver wires soldered to individual Teflon™ (Alpha Wire Company, Elizabeth, NJ) jacketed copper wires and embedded in dental acrylic. The wire pairs from each electrode were twisted together over a length of 8 feet and bundled together with the other electrodes. In addition, a single reference electrode was attached to a shaved portion of the horse's withers (an area free of
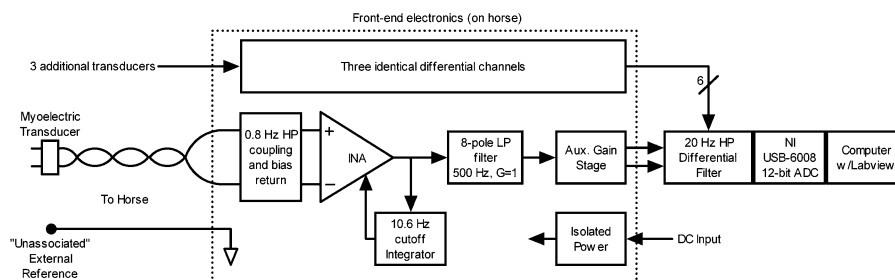
Fig 1. Simplified data acquisition front-end diagram.

muscle mass) using an alligator clip to eliminate environmental electronic noise that would otherwise mask the electrical signals from the intestine.

A custom graphical user interface was created with Lab-VIEW 7.0 software and was used to acquire, store, and display data. Data was displayed on a strip chart of voltage versus time and stored in binary to a file with a timestamp for the duration of the recording session. The data could be recalled to the strip chart at any time after capture was complete. Data could be compressed or extended to determine the exact electrical activity occurring at each time point during the recording session (Table 1).

Recording Sessions

Horses were allowed water but no hay or grain for 12 hours before recording sessions and were cross-tied during recording sessions. Recordings were obtained at the same time each day. Electrical activity was continuously recorded for 6 hours beginning at 24, 48, and 72 hours postoperatively. During the 6-hour recording sessions, saline (0.9% NaCl) solution control was administered as a constant rate infusion (CRI; 0.05 mg/kg/min) for 3 hours followed by 2% lidocaine hydrochloride administration (1.3 mg/kg IV bolus continued with a 0.05 mg/kg/min CRI) for 3 hours. Both solutions were administered at the same volume/minute rate. Blood samples were collected at T = 0, 1, 2, and 3 hours of lidocaine administration and analyzed using high-performance liquid chromatography with ultraviolet detection to measure serum concentrations of lidocaine. The lower level of quantification was determined to be 0.05 μg/mL.

Table 1. Specifications for Data Recording Variables

Variable	Specification	Comment
Input impedance	~ 80 M	Differential w/reference connection
Low-frequency cutoffs	20, 10.6, 0.8 Hz	Eliminates motion influence
High-frequency cutoff	500 Hz	8th order Butterworth LP filter
Gain	501 V/V	Typical maximum signal ± 5 mV
Sampling rate	2 kSPS	On 2 of 4 channels
ADC resolution	12 bits	± 2.5 V full scale

Analysis of Electrical Recordings

We used previously published definitions of intestinal electrical activity.[8] Spike bursts were identified as action potentials occurring when slow waves reached maximal depolarization. Each minute of each 6-hour recording session was categorized into Phase I, II, or III according to the following definitions. Phase I was defined as <10% of slow waves associated with spike bursts; Phase II was 11–99% of the slow waves associated with spike bursts, and 100% of the slow waves were associated with spike bursts during Phase III (Fig 2).[8] A complete MMC was defined as the electrical activity occurring from the beginning of Phase I to the end of Phase III.

Mean duration of the MMC during saline and lidocaine administration was compared using a Student's t-test applied to pooled data from 24, 48, and 72 hours. Only MMCs that began and ended entirely within each treatment period were considered for analysis. The duration of Phases I, II, and III occurring during saline and lidocaine administration was compared using the t-test applied to pooled data for 24, 48, and 72 hours. Only the phases that began and ended entirely within each treatment period were considered for analysis.

Spike bursts occurring during Phases I and II were counted and this number was divided by time (in hours) to obtain a value of spike bursts occurring per hour; this value was defined as spiking activity. Spiking activity during saline and lidocaine administration was compared using the paired t-test. Data from 24, 48, and 72 hour recording sessions were analyzed individually.

The number of Phase III events occurring during saline and lidocaine administration was compared using the Sign test with pooled data from 24, 48, and 72 hours. Phase III events beginning during saline administration and ending during lidocaine administration were considered part of the saline-treatment group. A level of significance of $P < .05$ was selected for all analyses.

RESULTS

Electrodes functioned correctly in all horses throughout the study. Recordings were obtained at all time periods for all horses except Horse 3 at 24 hours. Loss of data was because of a technical error. Horse 6 was removed from analysis at the 72-hour time period because of development of an incisional infection and signs of
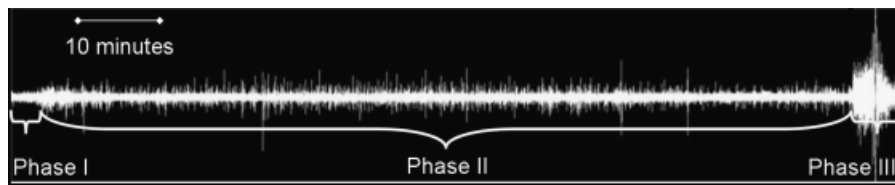
Fig 2.   Phases I, II, and III of the migrating myoelectric complex (MMC).

systemic illness. Phases were easily distinguishable using criteria developed by Adams et al.[8] Serum lidocaine concentrations in all horses ranged between 1.21–1.94 μg/mL. Lidocaine residues were not detected in any of the pretrial samples indicating complete drug clearance between each trial.

Duration of MMC and Phases I, II, and III at 24, 48, and 72 hours was analyzed separately using 2-way ANOVA for repeated measures, and no differences were identified. Therefore, data from all 3 recording periods were pooled for analysis of duration of MMC and duration of Phases I, II, and III. Mean duration of MMC was not different during saline (77 minutes) and lidocaine administration (105 minutes; $P = .16$). Mean duration of Phase I was not different between saline (6.28 minutes) and lidocaine administration (4.75 minutes; $P = .19$). Mean duration of Phase II was not different between saline (67.05 minutes) and lidocaine administration (97.4 minutes; $P = .056$). Mean duration of Phase III during lidocaine administration was shorter (saline 8.65 minutes, lidocaine 5.88 minutes; $P = .002$). Spiking activity was not different during saline and lidocaine administration. Mean spiking activity was 103 versus 125 at 24 hours ($P = .10$), 90 versus 91 at 48 hours ($P = .95$), and 106

versus 124 at 72 hours ($P = .12$), during saline and lidocaine administration, respectively.

Data from all 3 time periods were pooled for analysis. The number of Phase III events occurring during saline and lidocaine administration was not different ($P = .053$). Total numbers of Phase III events at 24, 48, and 72 hours during saline and lidocaine administration were 7 versus 4, 11 versus 6, and 8 versus 5, respectively (Figs 3–5).

DISCUSSION

Evidence of a prokinetic effect for lidocaine is provided by an in vitro study using isolated strips of jejunal smooth muscle and from a clinical trial of 32 horses with POI.[14,18] Our study assessed the effect of lidocaine on the electrical activity of the small intestine in normal horses and our results do not support the clinical use of lidocaine as a prokinetic agent.

Changes in the electrical activity (the MMC) of the small intestine are directly correlated with changes in muscular activity. This relationship was confirmed by Davies et al[2] using implanted electrodes and strain gauges, documenting that each muscular contraction was
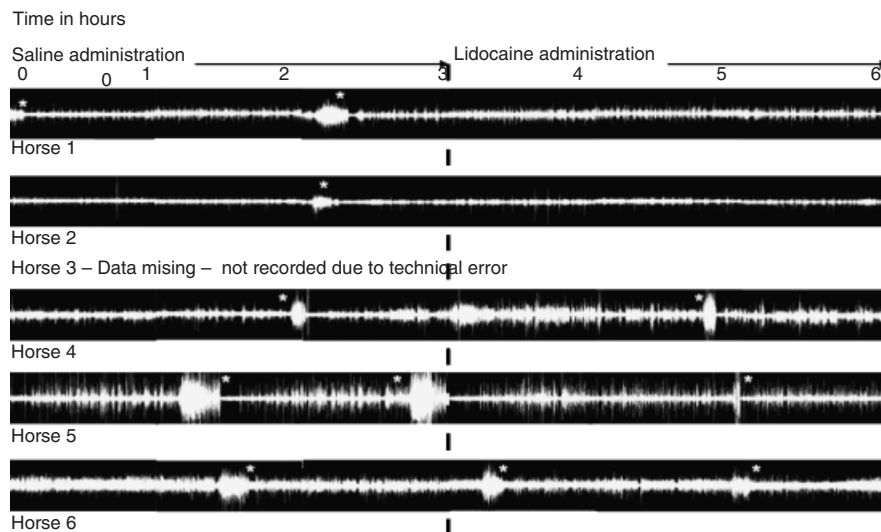

Fig 3.   Recording sessions from 5 horses 24 hours postoperatively. Dotted line indicates beginning of lidocaine administration. *Phase III event.
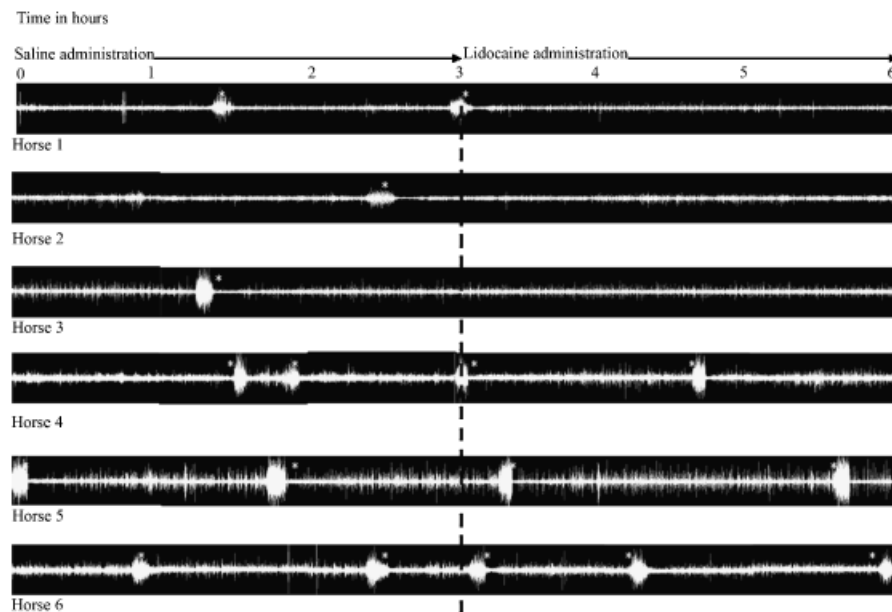
**Fig 4.   Recording sessions for all horses 48 hours postoperatively. Dotted line indicates beginning of lidocaine administration.
*Phase III event.**

associated with a spike burst. Duration of the MMC is the most common method for measuring small intestine motility.

Most propulsive motility occurs during Phase II, the longest phase of the MMC. Additional small intestine propulsive motility occurs during Phase III of the MMC, which propels any food remaining in the small intestine aborally. Thus, duration of the MMC is likely the most useful index of intestinal motility and this was unchanged by lidocaine in our study. Counting the number of Phase III events is an indirect assessment of MMC duration that we used because our recording duration was insufficient to capture complete MMCs during saline and lidocaine administration for each horse. Analysis of the number of Phase III events has not been individually documented in previous studies of equine small intestine electrical activity; however, several studies of drug administration or intestinal obstruction report data in
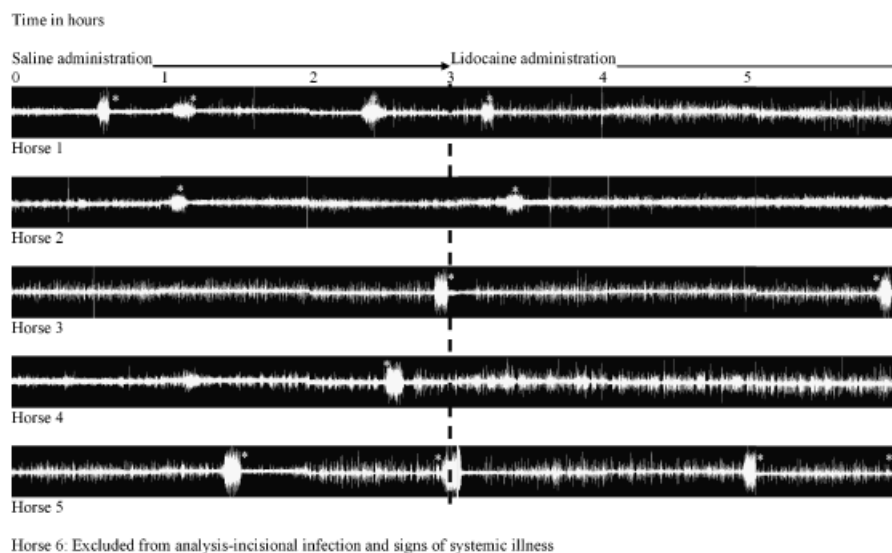

**Fig 5.   Recording sessions for all horses 72 hours postoperatively. Dotted line indicates beginning of lidocaine administration.
*Phase III event.**

graphical format that identifies Phase III events. From these studies it is easy to determine the number of Phase III events and the change that occurs during drug administration.[8,19] Careful review of our results show that although we did not achieve statistical significance there was a trend for lidocaine to lengthen MMC duration and decrease the number of Phase III events. Both of these findings would be interpreted as detrimental to motility.

A drug with prokinetic properties could shorten the MMC, reset the MMC completely, or increase the spiking activity. Lidocaine did not shorten or reset the MMC, which would cause the cycle to immediately begin repeating after lidocaine administration. Spiking activity has previously been shown to be directly coupled to muscular contractions.[2] Lidocaine did not change the spiking activity of the jejunum, therefore, the rate of muscular contractions during lidocaine administration did not change. The MMCs we recorded were of longer duration than those reported by Adams, who waited a minimum of 14 days after electrode implantation to record.[8] Our MMCs were of similar or shorter length to those reported by Merritt et al[6] who recorded a minimum of 7 days after electrode implantation. We chose a recording session length of 6 hours based on the results of these 2 studies; however, longer recording sessions would have allowed analysis of a greater number of complete MMCs. We conducted our recordings immediately postoperatively which may account for differences in MMC duration between our study and previous reports. Future studies should consider that MMCs may be longer than previously identified in the immediate postoperative period. The advantage of recording immediately is its relevance to the clinical situation where POI appears in the first 24–72 hours postoperatively. It is likely that the inflammation created by intestinal manipulation is an additional source of variability for our results. However, we believe our model mimics conditions occurring within the abdomen immediately after exploratory abdominal surgery.

Our model did not allow for randomization of the order for lidocaine and saline administration. Saline was always administered first to prevent residual effects of lidocaine during the saline administration period; however, 3 trials were completed on each horse and lidocaine failed to demonstrate a positive effect on jejunal electrical activity at any time. We believe that the ability to replicate our results at 3 different periods strengthens our conclusion that lidocaine is ineffective as a prokinetic in normal horses.

It is improbable that our anesthetic protocol affected our results. Xylazine has been shown to decrease motility for 30–45 minutes.[9] Lester showed that guaifenesin and ketamine decrease motility but that the effect lasts for only 9 hours.[20] By recording at 24, 48, and 72 hours, we were beyond the time frame in which motility would be affected by the anesthetic agents used. Flunixin meglu-

mine does not affect small intestine motility as shown in a similarly conducted study by Adams et al.[8]

The dose of lidocaine we chose is the one used most frequently by equine veterinary surgeons and has been shown to achieve serum levels in the therapeutic range.[21,22] Serum lidocaine concentrations of $\geq 0.9\,\mu g/$ mL have been considered therapeutic.[21] We exceeded this concentration in all horses and an increase in jejunal electrical activity was not observed. It is unknown if larger doses of lidocaine are required to exert prokinetic effects. Increasing the dose may increase side effects such as collapse, muscle tremors, or seizures. It is also possible that a longer duration of administration is required for lidocaine to exert a prokinetic effect.

A drug can act as a prokinetic indirectly by anti-inflammatory and analgesic mechanisms. Neither the cause of POI nor all mechanisms of action of lidocaine is known. Previous studies have indicated that lidocaine exerts anti-inflammatory effects in experimental colitis.[23] Lidocaine may indirectly promote intestinal motility by secondarily decreasing inflammation in the bowel wall. Suppression of sympathetic inhibitory reflexes within the intestinal wall may provide another mechanism of action for lidocaine to indirectly stimulate intestinal motility. Our study did not address mechanisms of action. Lidocaine did not improve motility in these normal horses but it remains a possibility that lidocaine could be effective in clinical cases through a mechanism not present in normal horses.

Gastrointestinal motility may be indirectly increased during lidocaine infusion because of analgesic effects of lidocaine. Robertson et al[13] identified a small somatic analgesic effect of lidocaine but did not show a visceral analgesic effect. Decreases in minimum alveolar concentrations of inhalant anesthetic have also been demonstrated in horses during lidocaine adminsitration.[24,25] However, we used healthy horses and flunixin meglumine was administered at regular intervals throughout the study to control postoperative pain.

Lidocaine failed to produce prokinetic effects in the jejunum of postoperative normal horses. Other effects such as anti-inflammatory and antinociceptive effects may occur during lidocaine administration, but were not investigated. Lidocaine was well tolerated during the 3-hour infusion period with no adverse effects observed.

REFERENCES

1. Roussel AJ Jr., Cohen ND, Hooper RN, et al: Risk factors associated with development of postoperative ileus in horses. J Am Vet Med Assoc 1:72–78, 2001
2. Davies JV, Gerring EL: Electromechanical activity of the equine small intestine and its correlation with transit of fluid through Thiry-Vella loops. Res Vet Sci 3:327–333, 1983
3. Roussel AJ Jr., Hooper RN, Cohen ND, et al: Prokinetic effects of erythromycin on the ileum, cecum, and pelvic flexure of horses during the postoperative period. Am J Vet Res 61:420–424, 2000
4. Argenzio R: Gastrointestinal motility, in Swenson MJ, Reece WO (eds): Dukes' Physiology of Domestic Animals (ed 11). Ithaca, NY, Cornell University Press, 1993, pp 336–348
5. Steiner A, Rakestraw PC: Motility modifiers, in Fubini SL, Ducharme NG (eds): Farm Animal Surgery. St. Louis, MO, Saunders, 2004, pp 118–123
6. Merritt AM, Campbell-Thompson ML, Lowrey hS: Effect of butorphanol on equine antroduodenal motility. Equine Vet J Suppl 7:21–23, 1989
7. Merritt AM: Normal equine gastroduodenal secretion and motility. Equine Vet J Suppl 29:7–13, 1999
8. Adams SB, Lamar CH, Masty J: Motility of the distal portion of the jejunum and pelvic flexure in ponies: effects of six drugs. Am J Vet Res 4:795–799, 1984
9. Merritt AM, Burrow JA, Hartless CS: Effect of xylazine, detomidine, and a combination of xylazine and butorphanol on equine duodenal motility. Am J Vet Res 5:619–623, 1998
10. Zanolari P, Steiner A, Meylan M: Effects of erythromycin on myoelectric activity of the spiral colon of dairy cows. J Vet Med A Physiol Pathol Clin Med 51:456–461, 2004
11. Scott SM, Knowles CH, Wang D, et al: The nocturnal jejunal migrating motor complex: defining normal ranges by study of 51 healthy adult volunteers and meta-analysis. Neurogastroenterol Motil 18:927–935, 2006
12. Sojka JE, Adams SB, Lamar CH, et al: Effect of butorphanol, pentazocine, meperidine, or metoclopramide on intestinal motility in female ponies. Am J Vet Res 49:527–529, 1988
13. Robertson SA, Sanchez LC, Merritt AM, et al: Effect of systemic lidocaine on visceral and somatic nociception in conscious horses. Equine Vet J 2:122–127, 2005
14. Malone E, Ensink J, Turner T, et al: Intravenous continuous infusion of lidocaine for treatment of equine ileus. Vet Surg 1:60–66, 2006
15. Rimback G, Cassuto J, Tollesson PO: Treatment of postoperative paralytic ileus by intravenous lidocaine infusion. Anesth Analg 4:414–419, 1990
16. Groudine SB, Fisher HA, Kaufman RP Jr., et al: Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. Anesth Analg 2:235–239, 1998
17. Little D, Redding WR, Blikslager AT: Risk factors for reduced postoperative fecal output in horses: 37 cases (1997–1997). J Am Vet Med Assoc 218:414–420, 2001
18. Nieto JE, Rakestraw PC, Snyder JR, et al: In vitro effects of erythromycin, lidocaine, and metoclopramide on smooth muscle from the pyloric antrum, proximal portion of the duodenum, and middle portion of the jejunum of horses. Am J Vet Res 4:413–419, 2000
19. MacHarg MA, Adams SB, Lamar CH, et al: Electromyographic, myomechanical, and intraluminal pressure changes associated with acute extraluminal obstruction of the jejunum in conscious ponies. Am J Vet Res 47:7–11, 1986
20. Lester GD, Bolton JR, Cullen LK, et al: Effects of general anesthesia on myoelectric activity of the intestine in horses. Am J Vet Res 9:1553–1557, 1992
21. Meyer GA, Lin HC, Hanson RR, et al: Effects of intravenous lidocaine overdose on cardiac electrical activity and blood pressure in the horse. Equine Vet J 5:434–437, 2001
22. van Hoogmoed LM, Nieto JE, Snyder JR, et al: Survey of prokinetic use in horses with gastrointestinal injury. Vet Surg 3:279–285, 2004
23. McCafferty DM, Sharkey KA, Wallace JL: Beneficial effects of local or systemic lidocaine in experimental colitis. Am J Physiol 4(Part 1): G560–G567, 1994
24. Doherty TJ, Frazier DL: Effect of intravenous lidocaine on halothane minimum alveolar concentration in ponies. Equine Vet J 4:300–303, 1998
25. Dzikiti TB, Hellebrekers LJ, van Dijk P: Effects of intravenous lidocaine on isoflurane concentration, physiological parameters, metabolic parameters and stress-related hormones in horses undergoing surgery. J Vet Med A Physiol Pathol Clin Med 4:190–195, 2003