

Intravenous Continuous Infusion of Lidocaine for Treatment of Equine Ileus

ERIN MALONE, DVM PhD Diplomate ACVS, JOS ENSINK, DVM PhD Diplomate ECVS, TRACY TURNER, DVM MS Diplomate ACVS, JULIE WILSON, DVM Diplomate ACVIM, FRANK ANDREWS, DVM MS Diplomate ACVIM, KEVIN KEEGAN, DVM Diplomate ACVS, and JONATHAN LUMSDEN, BVSc MS Diplomate ACVS

Objective—To determine if intravenous lidocaine is useful and safe as a treatment for equine ileus.

Study Design—Prospective double-blinded placebo-controlled trial.

Study Population—Horses ($n = 32$) with a diagnosis of postoperative ileus (POI) or enteritis and that had refluxed > 20 L or had been refluxing for > 24 hours.

Methods—Refluxing horses were administered lidocaine (1.3 mg/kg intravenously [IV] as a bolus followed by a 0.05 mg/kg/min infusion) or saline (0.9% NaCl) solution placebo for 24 hours. Variables evaluated included volume and duration of reflux, time to 1st fecal passage, signs of pain, analgesic use, heart rate and arrhythmias, respiratory rate, temperature, days of hospitalization, outcome (survival to discharge), and complications.

Results—Of the lidocaine-treated horses, 65% (11/17) stopped refluxing within 30 hours (mean \pm SD, 15.2 ± 2.4 hours) whereas 27% (4/15) of the saline-treated horses stopped within 30 hours. Fecal passage was significantly correlated with response to treatment; horses that responded to lidocaine passed feces within 16 hours of starting the infusion. Compared with placebo treatment, lidocaine treatment resulted in shorter hospitalization time for survivors, equivalent survival to discharge, no clinically significant changes in physical or laboratory variables, and no difference in the rate of incisional infections, jugular thrombosis, laminitis, or diarrhea. Muscle fasciculations occurred in 3 lidocaine-treated horses (18%).

Conclusion—IV lidocaine significantly improved the clinical course in refluxing horses with minimal side effects.

Clinical Relevance—At the infusion rate studied, IV lidocaine is safe and should be considered for the treatment of equine ileus.

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INTRODUCTION

POSTOPERATIVE ILEUS (POI) has remained an important cause of increased morbidity and mortal-

ity in the early postsurgical period for horses, particularly after small intestinal surgery.¹ Similarly, clinical ileus is a primary component of the syndrome of proximal duodenitis–jejunitis (PDJ). PDJ is associated with a relatively

From the Department of Veterinary Population Medicine, University of Minnesota, Minneapolis, MN; the Department of Equine Sciences, Utrecht University, Utrecht, the Netherlands; the Department of Large Animal Clinical Sciences, University of Tennessee, Knoxville, TN; the Department of Veterinary Medicine and Surgery, University of Missouri, Columbia, MO; Anoka Equine Veterinary Services, Anoka, MN; and Randwick Equine Centre, Sydney, Australia.

This was a multicenter study with the reported cases submitted from the University of Minnesota, Utrecht University, University of Tennessee, University of Missouri, and Michigan State University.

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Address reprint requests to: Erin Malone, DVM PhD Diplomate ACVS, Department of Veterinary Population Medicine, 225K VMC, 1365 Gortner Ave, St Paul, MN 55108. E-mail: malon001@tc.umn.edu

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high complication rate, including gastric rupture, laminitis, renal dysfunction, and death.² Various motility modifiers have been used clinically and experimentally for treatment of these syndromes, but none has gained widespread favor in the horse, either because of lack of proven efficacy or potentially severe side effects.^{3,4}

Intravenous (IV) lidocaine is a reemerging treatment that has been successful in decreasing POI in humans.^{5,6} Lidocaine improved propulsive motility, provided pain relief, and shortened hospital stays.⁵⁻⁷ Preliminary studies have indicated IV lidocaine might also be a useful motility modifier in the horse.^{1,8-10} We hypothesized that lidocaine would decrease reflux duration, analgesic use, and duration of hospital stay for horses with signs of ileus. To test the safety and efficacy of IV lidocaine for treatment of equine POI and PDJ, we undertook a multicenter double-blinded prospective study.

MATERIALS AND METHODS

Criteria for Case Selection

Horses were included if they had a presumptive diagnosis of PJD or POI concomitant with gastric reflux for ≥ 24 hours (>2 L/h) or had a cumulative reflux volume >20 L in <24 hours. Cases were admitted to the University of Minnesota, University of Tennessee, University of Missouri and Michigan State University between April 1993 and April 1996 and to Utrecht University between September 2000 and April 2002. Cases were later excluded from analysis if the diagnosis was altered by additional testing, surgery, or necropsy, or if surgery was performed after initiation of the trial. Horses that had nearly simultaneous discontinuation of reflux with the onset of therapy were also eliminated from the study ($n=19$ total exclusions).

Drug Administration Protocol

The study was performed in a randomized, double-blinded format. Light-protected bottles, filled with 100 mL of either saline (0.9% NaCl) solution or 2% lidocaine (Phoenix Pharmaceutical, Inc., St Joseph, MO) and labeled with only an identification number, were distributed to participating centers in North America. At Utrecht University, distribution was performed in a blinded manner by the pharmacist at that location. For each horse, the selection of saline or lidocaine was determined using a random number generator. After obtaining owner permission, horses were treated with a slow IV lidocaine bolus (1.3 mg/kg) followed by an infusion (gravity flow) at 0.05 mg/kg/min for 24 hours or an equivalent volume of saline placebo. Dosage was based upon preliminary studies to produce blood concentrations of 1–2 mg/L without evidence of toxicity. This range was selected based upon human analgesic response and preliminary positive response in refluxing horses.^{10,11} This dose rate has subsequently been demonstrated to have jejunal effects and to remain below the toxic level in most cases.⁸ No other motility agents could be used for 24 hours

before treatment or for 36 hours after initiation of lidocaine infusion. Clinicians were asked to correct serum electrolyte deficiencies before the start of the trial and electrolytes were rechecked at the end of the infusion. Because of ethical considerations, the code was broken at clinician request after the 24-hour posttreatment period to allow treatment with lidocaine if the horse was initially treated to placebo and/or to allow treatment with other agents in a timely manner.

Data Collection

Monitored variables included amount and duration of reflux, time to 1st fecal passage, signs of pain as recorded in the record (pawing, looking at flank, rolling), analgesic use, heart rate and arrhythmias, respiratory rate, temperature, days of hospitalization, outcome (survival to discharge), and complications. Reflux (net volume of fluid obtained) was measured every 1–2 hours, depending upon reflux rates. In 14 cases (6 saline, 8 lidocaine), nasogastric tubes were maintained for several hours at a time while in 18 cases (9 in each group), tubes were passed intermittently on a scheduled basis. If necessary to prevent spontaneous reflux losses, tubes were plugged between reflux attempts. Physical examination variables and volume of reflux were recorded for 24 hours (or until start of the trial) before drug infusion and continued until 24 hours after the infusion was discontinued. Data was also collected on surgical lesions, other treatments, laboratory and necropsy results. Cases were considered to respond to the lidocaine if they stopped refluxing (<0.3 L/h for ≥ 6 hours) by 6 hours after discontinuation of the lidocaine infusion and did not reflux again for at least 6 additional hours.

Data Analysis

Comparisons were made between lidocaine and placebo cases for differences between groups using a Wilcoxon' rank sum test for response to treatment and χ^2 tests for categorical data (anastomotic rates, complication rates). Complete blood count results and serum electrolyte concentrations were compared before and after lidocaine infusion using Student's paired t- tests. Comparisons between lidocaine and placebo groups in terms of measured continuous variables were made using Student's t-test. Physical variables and reflux volumes were compared before, during, and after lidocaine infusion using a repeated measures ANOVA and a Bonferroni's multiple comparison procedure when significant differences were detected. Hourly reflux volumes were compared similarly, both in terms of the average rate over each treatment period and comparing the reflux rate for the last 6 hours of each treatment period with the rate for the first 6 hours of the next treatment period. If a horse was admitted with significant reflux (>10 L), the total volume was divided over a 6-hour period to obtain an hourly rate.

A Kaplan–Meier method for estimation of survival function was used to check for differences in survival to discharge and duration of hospitalization in survivors. Pearson's correlation coefficients (r) were calculated to determine if there was a relationship between 1st fecal passage and success rate or

reflux duration. For the latter test, if cases did not stop refluxing and/or refluxed for >4 days, the total duration of reflux was recorded as 96 hours. In all statistical operations $P < .05$ was considered significant and parametric tests were used for numerical data after evaluation for normal distribution.

RESULTS

Seventeen horses were treated with lidocaine (4 PDJ, 13 POI) and 15 horses were treated with saline placebo (4 PDJ, 11 POI). Five other horses were excluded because of change in diagnosis or lack of continued nasogastric reflux whereas another 14 horses were excluded for other types of noncompliance with the study design (e.g., repeat laparotomy performed, lidocaine administered unblinded). The total dose of lidocaine was administered over a mean (\pm SD) of 28.5 ± 2.6 hours. Cases with a slow infusion rate were still included in analyses.

Horses undergoing surgery were induced with ketamine (\pm guaifenesin) and maintained on isoflurane (halothane was used in 3 horses) in oxygen. Two horses were not administered antibiotics (both treated for enteritis; both in the lidocaine treatment group), 20 were administered procaine penicillin and gentamicin, 8 potassium penicillin (7 gentamicin also), 1 ampicillin, and 1 ceftiofur. For horses with POI, lesions in the lidocaine-treated group were ileal impaction (4), small intestinal entrapment (3), small intestinal volvulus (2), small intestinal foreign body (1), ascending colon displacement (2), and ascending colon impaction (1). Side-to-side jejunocostomy was performed in 4 horses and jejunojunal anastomosis (type not recorded) performed in 1 horse. In the placebo-treated group, lesions were small intestinal entrapment (2), small intestinal volvulus (1), other small intestinal strangulating lesions (3), small intestinal mesenteric avulsion (1), chronic anastomotic stricture (1), and ascending colon displacement or torsion (4). Side-to-side jejunocostomy was performed in 4 horses and resection with jejunojunal anastomosis in 3 horses. The number of anastomoses was not significantly different between groups.

Of the lidocaine-treated horses, 11/17 (65%) stopped within 30 hours of starting lidocaine treatment (lidocaine responsive), including 8/13 with POI and 3/4 with PDJ. This was significantly better than the placebo treated horses, of which 4/15 (27%) stopped within the same time frame ($P = .04$; 4/11 with POI, 0/4 with proximal enteritis). In the lidocaine-treated group, nasogastric reflux stopped an average of 15.2 ± 2.4 hours after the start of lidocaine infusion, with a median of 12.5 hours (Fig 1).

Reflux rates did not differ between groups at any of the evaluated time points (hourly reflux/24 hour or hourly reflux/6 hours). However, when groups were evaluated

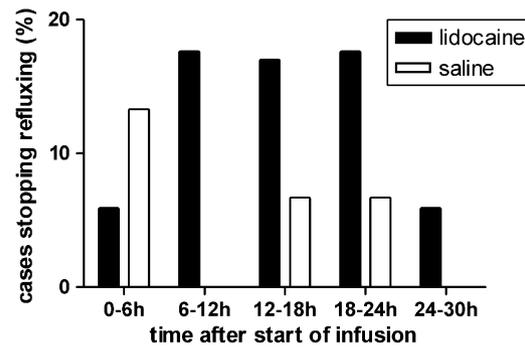


Fig 1. Graph of the percent of cases stopping reflux in each time period after start of lidocaine or saline infusion.

for within-group differences, significant temporal decreases in reflux rate were noted only in the lidocaine group. Mean hourly reflux rate was 2.4 ± 0.3 L/h in the pretreatment period and this significantly decreased to 0.9 ± 0.2 L/h during lidocaine infusion and to 0.6 ± 0.2 L/h after infusion ($P < .01$; postinfusion values not significantly different from the reflux rate during infusion). Reflux rate in the placebo group did not significantly decrease either during or after saline infusion ($P = .11$; pretreatment: 2.3 ± 0.2 L/h; during infusion: 1.5 ± 0.3 L/h; posttreatment 1.4 ± 0.5 L/h; Fig 2). Significant within-group decreases in reflux rate were also noted when the last 6 hours of the pretreatment period was compared with the first 6 hours of lidocaine treatment (3.0 ± 0.7 versus 1.3 ± 0.2 L/h; $P < .01$); no difference was noted between the reflux rate in the last 6 hours of lidocaine treatment and the first 6 hours posttreatment or in either of the corresponding placebo pairs ($P = .15$).

Fecal passage was significantly correlated with reflux response to lidocaine ($P = .02$; $r = 0.43$). Mean time to 1st

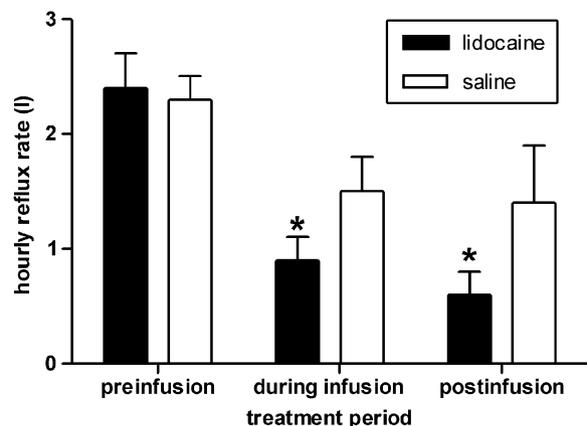


Fig 2. Graph of hourly reflux rates (mean \pm SEM) before, during, and after treatment with either lidocaine or saline. *Significantly different from preinfusion rate for lidocaine-treated group.

fecal passage for lidocaine responsive cases was 15.8 ± 4.1 hours (95% confidence interval (CI) 7.0–16.0 hours) whereas mean time to 1st fecal passage for cases deemed unresponsive to lidocaine (did not stop refluxing within 30 hours of initiating treatment) was significantly longer at 43.9 ± 9.3 hours (95% CI 24.2–63.4 hours; $P < .01$). There was no significant correlation between 1st fecal passage and duration of reflux ($P = .66$).

Surviving lidocaine-treated horses spent significantly fewer days in hospital compared with placebo-treated horses (12.2 ± 1.4 versus 17.4 ± 2.1 days; $P = .05$). There was no difference in hospital stay between POI and PDJ survivors. There was no difference between the lidocaine and placebo groups in survival to discharge. Ten of 17 (59%) horses in the lidocaine group were discharged while 10/15 (67%) of the placebo group were discharged. Seven of the placebo group also received lidocaine after concluding placebo treatment; 4 were discharged. Of the horses in the lidocaine group, 2 were euthanized for nongastrointestinal lesions (laminitis, renal failure), 1 because of colitis, 1 because of continued colic and adhesions, and 3 because of continued reflux (no causative agents found at necropsy). In the saline group, 2 were euthanized because of laminitis and 3 for continued reflux (peritonitis and paralytic ileus in 1, no necropsy performed in 2). No significant differences were noted between groups in the rate of jugular thrombosis (0/15 placebo; 2/17 lidocaine), laminitis (3/15 saline, 2/17 lidocaine), diarrhea (3/15 saline, 1/17 lidocaine), or incisional infections (3/15 saline, 2/17 lidocaine). No horses developed detectable arrhythmias. Three lidocaine-treated horses (18%) developed muscle fasciculations (1 during bolus administration and 2 during infusion; blood concentration in one of the latter was 2.4 mg/dL). One horse had delayed detection of laminitis.

No differences in heart rate, respiratory rate, or temperature were noted before, during or after treatment either within or between groups. Pain notations and medications decreased over time with no difference between groups. No significant differences were noted between groups in terms of complete blood count or electrolyte concentrations. Few horses had complete blood cell counts taken before, during and after treatment. Of those with samples taken before and after treatment, there were no differences in total nucleated cell counts, neutrophil counts, bands, or fibrinogen levels in either group. Of those with samples taken before and during treatment, the placebo group had significantly fewer bands during treatment than before treatment (0.33 ± 0.28 versus $0.05 \pm 0.05 \times 10^3/\mu\text{L}$; $n = 4$); no other significant differences were detected.

Anion gap values were above normal ranges in both groups (lidocaine group: 12.7 ± 0.9 ; placebo group: 15.7 ± 2.1) and had returned to normal ranges (and were

not significantly different) after treatment. No changes in calcium, chloride, sodium, or potassium concentrations were noted after treatment in either group. Calcium concentrations were slightly below the normal range in the placebo group (9.9 ± 0.6 mg/dL) but were not significantly different from the lidocaine group (10.7 ± 0.4 mg/dL) or from posttreatment values (10.7 ± 0.5 mg/dL). All other values were within normal ranges for our laboratory.

DISCUSSION

Our results suggest that IV lidocaine is useful for the treatment of gastric reflux in horses and is safe at the infusion rate studied. IV lidocaine, administered after the start of reflux, significantly decreased the amount of gastric reflux and shortened hospital stay by a mean of 6 ± 2.6 days compared with placebo-treated horses. Lidocaine treatment completely eliminated gastric reflux in 65% of the cases treated.

Lidocaine has been hypothesized to alter sympathetic tone to the bowel by suppressing transmission through afferent sensory pathways.⁵ Peritonitis, enteritis, serosal damage, intestinal distension, endotoxemia, and surgical manipulation have all been associated with increased sympathetic stimulation experimentally.^{12–14} Lidocaine may act to prevent the reflexive inhibition because of one or more of these factors by blocking transmission through afferent nerves.¹⁵ Many of these factors have also been documented to increase the release of non-adrenergic–noncholinergic neurotransmitters with a concomitant alteration in motility in rats and dogs.^{12,16,17} Lidocaine may be preventing the effects of these neuro-hormonal agents rather than or in addition to altering sympathetic neurotransmission. Potentially, lidocaine may inhibit abnormal motility patterns in many cases allowing the gut to “restart” in a more normal and coordinated pattern of activity, similar to other anesthetic agents.¹⁸ Alternately, lidocaine may prevent motility alterations primarily through its anti-inflammatory, anti-endotoxic, or analgesic actions^{19–21} and may have direct effects on fluid accumulation.⁸ Lidocaine also had direct effects on the proximal duodenum *in vitro*.²²

In our study, lidocaine-treated horses had decreased reflux rates and were more likely to stop refluxing within 30 hours of starting treatment than were placebo-treated horses. Reflux rates do tend to slow naturally but our results were consistent even when evaluated over a shorter time frame (i.e., the 6-hour period on either side of the 24-hour blocks) and we could not detect a significant temporal differences in reflux volumes in saline-treated horses. We did not find any significant differences between groups that would indicate more severe electrolyte

abnormalities or more severe disease in placebo-treated horses. Calcium concentration was below our normal ranges in the placebo group but was normalized within 24 hours and did not correlate with improvement in reflux status. Ionized calcium was not measured frequently enough to be evaluated statistically and may still have played a role in continuing reflux.² Individual variability in lidocaine serum concentrations has also been reported to be high, likely influenced by cardiac output.⁸

Survival rates were not different between groups but only 3/17 horses in the lidocaine-treated group were euthanatized because of continued reflux, and complications were similar to previous reports of horses with these lesions. No significant alterations in physical examination variables were detected. Muscle fasciculations and ataxia have been reported with IV lidocaine at this dose but were rare in our study. Fasciculations were evident in 2 horses, 1 of which was receiving the initial bolus and the other during infusion. The corresponding blood concentration in the latter horse was higher than the target range of 1–2 mg/dL (2.4 mg/dL). Both horses had low serum protein concentrations (5–6 mg/dL) at the time of infusion. Lidocaine is extensively protein bound and increased active drug may have been present in these horses. However, 7 other lidocaine-treated horses had similar protein concentrations without fasciculations. Additionally, in a few cases, the drip rate was slower than recommended. Side effects may have been observed in these horses under a faster rate of infusion. After approximately 8 minutes, lidocaine is redistributed from the plasma, meaning any side effects of the drug resolve within minutes if the drug is discontinued.²³ Corresponding, fasciculations and ataxia in horses respond rapidly to discontinuation or slowing of the infusion rate and no horses required cessation of the infusion because of persistent side effects. There is no evidence of structural damage to nerve fibers or cells after lidocaine toxicity in other species¹⁵; however, because of the potential for injury associated with ataxia in larger animals, careful monitoring is required and the rate of administration should be slowed or stopped with any signs of toxicity. Horses do appear to be more sensitive to the effects of lidocaine, with toxicity noted at much lower levels than in most other species.^{21,24}

Most horses that were lidocaine responsive stopped refluxing during the infusion itself but response times were distributed throughout that period. We recommend a full 24-hour infusion and waiting 6 hours after infusion to determine lidocaine responsiveness. However, we also found a correlation between early fecal passage and response to lidocaine infusion, similar to that observed by Brianceau et al.⁸ It may be that fecal passage can be used as an early indicator of response to treatment with horses that do not pass fecal within 16 hours being unlikely to

respond to lidocaine. Whereas many factors can alter defecation, the ascending colon is the last segment of intestine to regain normal activity during POI in humans.²⁵ Potassium penicillin has also been shown to stimulate colonic and cecal activity in the horse and to stimulate defecation within 15 minutes of exposure or administration.²⁶ Potassium penicillin was administered to 4 horses in each of the groups; however, the significant correlation between early fecal passage and response to lidocaine infusion remained even when these cases were removed from analysis.

Analgesic effects have been documented in humans with lidocaine blood concentrations of 1.5 mg/dL.¹¹ No significant changes in pain notations or analgesic use were documented in our study. Lack of statistical significance may be related to low numbers of colics administered postoperative analgesics, low blood concentrations of lidocaine in some horses, and/or insufficient sample size. Analgesic effects have been observed by the some of the authors in laminitic horses (data not shown). Delayed detection of laminitis could therefore be of concern in lidocaine-treated horses. Close attention should be paid to increased heat and digital pulses despite lack of significant lameness. Similarly, although not observed in this study, lidocaine infusion has the potential to mask the pain associated with gastric expansion and regular evaluation for reflux is recommended. Lidocaine infusion does not have prolonged effects and the infusion can be stopped to allow better evaluation if necessary; repeat bolus is recommended each time the infusion is stopped for more than 8 minutes.

Lidocaine can be locally irritating and can cause temporary immune suppression. The latter effects are generally reversible and self-limiting. No consequences of the anti-inflammatory actions of lidocaine were documented in an emergency room study.¹⁹ However, chronic exposure to lidocaine can result in impaired lymphocyte function in mice.²⁷ We detected no changes in white blood cell counts or body temperatures. The rate of jugular vein thrombosis and incisional infections we observed were less than or similar to other reports.^{28–30} Survival rates and necropsy findings did not suggest fatal or other specific effects of the lidocaine. However, prolonged infusions of lidocaine are probably not necessary and should be avoided to minimize any risks associated with prolonged immunosuppression. Similarly, lidocaine cannot be recommended for cases of known septic peritonitis at least until the infection is under control.

Problems with the study included inconsistent rate of drug administration (likely to underestimate treatment efficacy and side effects), prior belief that lidocaine is effective in the treatment of ileus (led to problems with compliance to study guidelines and lack of inclusion of all possible cases), and natural resolution of ileus that may

have occurred in both groups. The placebo group underwent 2 more jejunojunal anastomotic procedures than did the lidocaine group, potentially affecting the success rates. Clinic-related differences in treatment of refluxing horses may have similarly affected success rates. Whereas we could detect minimal changes in the treatment of these horses between centers, subtle differences may play a more significant role than anticipated. Our survival rates may also be skewed by the later treatment of many placebo horses with lidocaine. Greater numbers would assist in correcting these deficiencies but collecting cases in a prospective manner was found to be very difficult in North American veterinary clinics.

Summarily, lidocaine can act as a motility modifier in refluxing horses. We recommend a slow bolus of 1.3 mg/kg IV followed by a 24-hour infusion at 0.05 mg/kg/min. At this rate we found side effects to be minimal and included muscle fasciculations, masking of pain, and potentially ataxia. The dose should be monitored carefully in horses with moderate-to-severe hypoproteinemia and/or decreased cardiac output. Lidocaine blood concentrations taken at 4–6 hours are recommended to allow for individual variation. Further work should be done to determine the prognostic value of fecal passage on horses with ileus. Based upon the results of this study, horses that do not stop refluxing within 17.6 hours and do not defecate within 16 hours of starting treatment have a poorer response rate and may require alternative therapy.

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