THE DISPOSITION OF LIDOCAINE DURING A 6-HOUR INTRAVENOUS INFUSION TO YOUNG FOALS

by

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Abstract

Differences in pharmacokinetics and drug disposition exist between young and adult animals which become especially important for drugs with a narrow therapeutic index. While the pharmacokinetics and plasma concentrations of intravenous lidocaine have been studied in adult horses, determination of the disposition in foals is necessary before appropriate clinical use can be determined. This study examined the disposition of intravenous lidocaine in healthy (phase I) and hospitalized (phase II) foals. Phase I consisted of 6 healthy 4-10 week old foals administered a 6-hour intravenous lidocaine infusion. Phase II consisted of 8 hospitalized foals (2-136 days old) administered intravenous lidocaine. A bolus (1.3 mg/kg) of lidocaine was administered intravenously to all foals followed by a 50 µg/kg/min infusion. Plasma lidocaine and monoethylglycinexylidide (MEGX) concentrations were determined. In phase I, plasma lidocaine concentrations remained below the suggested adult target range of 1-2 µg/mL with MEGX concentrations approximately half that of the parent drug. Total body clearance of lidocaine was 72.2 ± 7.8 mL/min/kg, elimination half-life ($t_{1/2}$) was 26.3 ± 3.7 min, peak concentration (C_{max}) was 0.79 ± 0.07 µg/mL, and the volume of distribution (V_d) was 1.8 ± 0.4 L/kg. The C_{max} for MEGX was 0.36 ± 0.11 µg/mL, $t_{1/2}$ was 60 ± 6 min and time to peak concentration (T_{max}) was 279.6 ± 90.3 min. In phase II, the severely compromised foals that were eventually euthanized had the largest fluctuations in plasma lidocaine and MEGX concentrations; foals that were discharged from the hospital had plasma concentrations below the target adult range similar to foals in phase I. In conclusion, despite low plasma lidocaine concentrations, the clinical benefits observed in foals may be due to the presence of metabolites. Further research in a larger population of unhealthy foals is required before comprehensive dosing recommendations can be made.

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Chapter 1 - Introduction

Lidocaine is an aminoamide local anesthetic with effects mediated through sodium channel blockade thereby inhibiting the action potential and stabilizing excitable membranes (Riviere and Papich 2009). Lidocaine is used intravenously in human and veterinary medicine as a treatment for ventricular arrhythmias and for its potential benefits as an analgesic, prokinetic, and anti-inflammatory as well as for its anesthetic sparing effects. While controversy exists over the proposed applications in human and veterinary medicine, its frequent use in foals makes it imperative to gain a complete understanding of the pharmacokinetics and plasma concentrations using the currently accepted adult dosage.

Evidence supports the use of intravenous lidocaine for analgesia in human medicine after abdominal surgery (Marret *et al.* 2008; Yardeni *et al.* 2009; Swenson *et al.* 2010). Similarly, intravenous lidocaine is currently used, many times in combination with other analgesics, to manage a number of painful conditions in foals including colitis, enteritis, meconium impactions, and for post-operative abdominal surgical pain. Intravenous lidocaine may also be used as a diagnostic tool to help differentiate certain painful conditions in foals. The authors' clinical impression is that non-surgical pain (due to colitis or enteritis) is often times controlled with administration of a continuous rate infusion (CRI) of lidocaine in combination with a non-steroidal anti-inflammatory (NSAID), but foals requiring surgical intervention remain painful with the same treatment.

The literature review to follow (chapter 2) focuses on the clinical applications of intravenous lidocaine, the pharmacology and pharmacokinetics of intravenous lidocaine in adult horses and other species, and comparative pharmacokinetics between adult horses and foals. While it seems plausible to extrapolate what we know about lidocaine from adult horses or

neonates of other species to young foals, it is never recommended to extrapolate drugs with a narrow therapeutic index as differences between age groups and species do exist. For example, differences in drug clearance, volumes of distribution, protein binding, concurrent hepatic or renal disease and the effects of other treatments administered may affect the pharmacokinetics and plasma concentrations of lidocaine.

Therefore, the purpose of this investigation was to determine the pharmacokinetics and plasma concentrations of intravenous lidocaine and its primary metabolite, monoethylglycinexylidide (MEGX), in healthy young foals as well as the plasma concentrations in hospitalized, unhealthy foals using the recommended adult horse dosage (1.3 mg/kg followed by 50 µg/kg/min). In phase I, healthy foals were used to determine the pharmacokinetics and plasma concentrations of lidocaine and MEGX during a CRI of lidocaine administered for 6 hours. In phase II, the plasma concentrations of intravenous lidocaine and MEGX in unhealthy foals admitted to a referral hospital were determined. We hypothesized that foals would have lower plasma concentrations than adult horses administered the same dose due to an increased clearance from a higher basal metabolic rate (Taira *et al.* 1992). For unhealthy foals, we hypothesized that higher plasma concentrations would be evident, compared to healthy foals, due to variations in hepatic function and perfusion and the effects of other treatments administered on drug clearance. From this information, we determined that foals do have lower lidocaine plasma concentrations compared to adult horses however further work is needed in a larger population of unhealthy foals (the target population) to determine if a dosage adjustment is necessary.

Chapter 2 - Literature Review

Clinical applications of intravenous lidocaine

Lidocaine has become the most widely used local anesthetic agent in medical and veterinary practice (Riviere and Papich 2009). Besides its well-known use as a local anesthetic and treatment for ventricular arrhythmias acting as a class IB antiarrhythmic (Riviere and Papich 2009) the pharmacokinetics and clinical applications of CRIs of lidocaine in adult horses have been studied extensively for a number of other applications. Investigators have explored the anti-inflammatory (Cook *et al.* 2008; Cook *et al.* 2009a; Peiro *et al.* 2010; Williams *et al.* 2010; Wilson *et al.* 2012), prokinetic (Nieto *et al.* 2000; Brianceau *et al.* 2002; Malone *et al.* 2006; Milligan *et al.* 2007; Guschlbauer *et al.* 2011; Tappenbeck *et al.* 2013a; Tappenbeck *et al.* 2013b; Tappenbeck *et al.* 2014a; Tappenbeck *et al.* 2014b), and analgesic (Murrell *et al.* 2005; Robertson *et al.* 2005) properties as well as its use during general anesthesia (Doherty and Frazier 1998; Dzikiti *et al.* 2003; Valverde *et al.* 2005; Enderle *et al.* 2008; Rezende *et al.* 2011; Wagner *et al.* 2011; Nannarone *et al.* 2014).

Anti-inflammatory properties

The anti-inflammatory properties of intravenous lidocaine in horses have shown the most promise in cases of endotoxemia. Intravenous lidocaine has been shown to have beneficial effects on the severity of clinical signs and cytokine expression in horses exposed to lipopolysaccharide (LPS) and appears to have beneficial effects on transepithelial electrical resistance (TER) in horses concurrently administered flunixin meglumine (Cook *et al.* 2008; Cook *et al.* 2009a; Peiro *et al.* 2010). Lipopolysacharide signals through a toll like receptor (TLR-4) thereby activating the genes responsible for production of inflammatory mediators.

When LPS was injected intraperitoneally in horses and a CRI of lidocaine initiated 20 minutes later, horses treated with lidocaine had significantly lower clinical scores (comprised of fever, restlessness, muscle fasciculations, lethargy, yawning, hyperemic mucous membranes, respiratory and heart rate and behavioral evidence of abdominal pain or discomfort) at 180, 240 and 300 minutes as well as lower post-infusion serum and peritoneal fluid tumor necrosis factor-α activity compared to control horses. However, lidocaine did not attenuate the increase in microvascular permeability or leukocyte migration into the abdominal cavity. One limitation of this study was that a low dose of endotoxin was used in order to evaluate the inflammatory response without causing severe clinical disease or death, therefore the classic neutropenia and severity of clinical signs and hematologic variables (RBC count, HCT, and hemoglobin) were not appreciated (Peiro *et al.* 2010).

Cook and colleagues further evaluated the effects of lidocaine administration prior to an ischemic event in horses also administered flunixin meglumine (Cook *et al.* 2008; Cook *et al.* 2009a). Flunixin meglumine is commonly used in post-operative colic patients for its analgesic and anti-inflammatory properties. However, by inhibiting beneficial prostaglandins essential for repair of ischemic injured mucosa, flunixin meglumine impairs recovery of barrier function, decreases TER and increase permeability to LPS (Tomlinson *et al.* 2004; Tomlinson and Blikslager 2005). While Peiro et al (2010) did not observe a significant benefit of lidocaine administration alone on TER, when lidocaine was administered in combination with flunixin meglumine and prior to an ischemic event, the deleterious effects on TER, permeability to LPS, and the increase in mucosal neutrophil counts caused by flunixin meglumine administration were ameliorated. Cook et al also observed beneficial effects of lidocaine on cyclooxygenase-2 (COX-2) expression, further supporting its anti-inflammatory properties (Cook *et al.* 2009a).

Immediately after an ischemic event, lidocaine administration led to a significant decrease in western blot COX-2 expression compared to saline or flunixin meglumine administration; the combination of lidocaine and flunixin meglumine also decreased COX-2 expression, although the decrease was not significant. Further support for COX-2 inhibition was evidenced by lidocaine inhibiting the increase in prostaglandin E_2 (PGE_2) that occurs after an ischemic event and the combination of lidocaine with flunixin meglumine actually decreasing PGE_2. Lidocaine however, does not appear to affect COX-1 expression as lidocaine alone had no effect on thromboxane B_2 expression, a specific indicator of COX-1 expression, and only flunixin meglumine alone or with lidocaine inhibited the increase in plasma thromboxane B_2 as would be expected with a non-selective COX inhibitor (Cook *et al.* 2009a).

Contrary to the purported beneficial findings in cases of endotoxemia, especially when co-administered with flunixin meglumine, lidocaine was not found to have anti-inflammatory effects in a black walnut model of laminitis or during episodes of recurrent airway obstruction (RAO), and evidence may in fact suggest a pro-inflammatory effect (Williams *et al.* 2010; Wilson *et al.* 2012). Similar to the findings by Peiro et al who found that intravenous lidocaine did not decrease neutrophil migration into the peritoneal cavity in horses after intraperitoneally injected LPS, lidocaine did not inhibit neutrophil migration into the laminar interstitium in experimentally induced laminitis or in bronchoalvelolar lavage fluid in horses with RAO (Peiro *et al.* 2010; Williams *et al.* 2010; Wilson *et al.* 2012). This is in contrast to findings by Cook et al who found that lidocaine appeared to inhibit the mucosal neutrophil influx that occurs after flunixin meglumine administration in cases of ischemia (Cook *et al.* 2009a). Williams et al treated horses with lidocaine (1.3 mg/kg bolus followed by 50 µg/kg/min) or saline for 10 hours after inducing laminitis and found no differences between groups with regard to mRNA

concentrations of IL-1β, IL-6, IL-8, COX-2 or white blood cell counts within the laminar interstitium or skin dermis. In contrast, they found an inflammatory/activating effect of lidocaine on the endothelium evidenced by an increased expression of laminar E-selectin responsible for the initial attachment/rolling of neutrophils and other leukocytes (Williams *et al.* 2010). These findings are in agreement with in vitro data evaluating lidocaine exposure to neutrophils in which neither neutrophil migration nor adhesion were inhibited at therapeutic lidocaine concentrations and higher dosages, consistent with toxicity, actually led to increased transendothelial migration and adhesion (Cook *et al.* 2009b). Similarly, horses with acute exacerbation of RAO treated with a CRI of lidocaine, starting 4 hours before challenge and lasting during the entire 68 hour challenge period, had significantly increased total number of white blood cells in bronchoalveolar lavage fluid due to an increased neutrophil and macrophage cell count compared to horses treated with saline (Wilson *et al.* 2012). Taken together, these results suggest that lidocaine administration does have beneficial effects when administered concurrently with flunixin meglumine, however there appear to be anti-inflammatory and pro-inflammatory properties suggesting its use may be beneficial in cases of endotoxemia but further research should be done before it can be recommended in other inflammatory disorders.

Inhalant sparing and anesthetic effects

Horses are especially sensitive to the cardiovascular and respiratory depressant effects of inhalation anesthetics (Wagner 1995) and it is presumed that lidocaine may be of benefit in not only decreasing the dose-dependent cardiovascular depressant effects by lowering the minimum alveolar concentration (MAC) but also by effecting the metabolic profile and recovery from anesthesia. The dosage commonly used in conscious horses (1.3 mg/kg followed by 50 µg/kg/min) appears to be a starting place for anesthesia for many clinicians, however dosages as

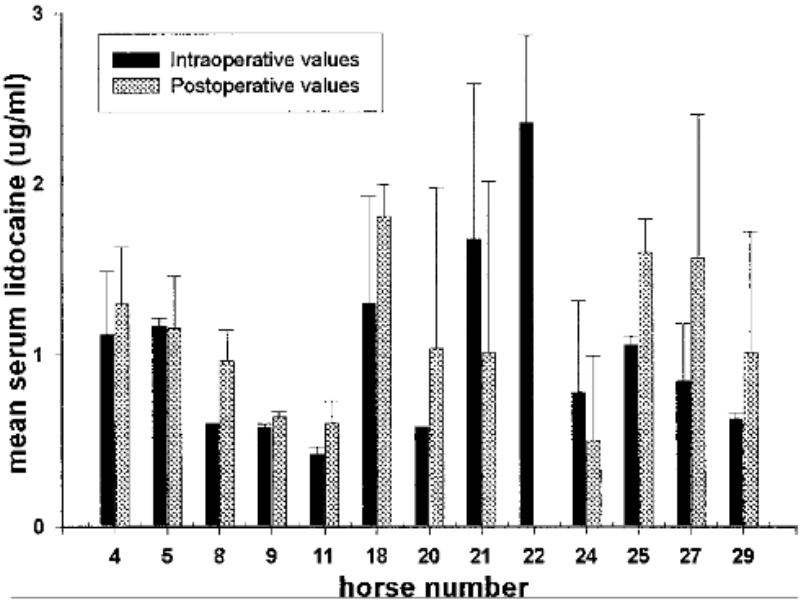
high as 100 µg/kg/min have been used, resulting in serum concentrations up to 7 µg/mL (Doherty and Frazier 1998). While recommendations have been made to decrease the dosage in anesthetized horses, there is not a general consensus as to the appropriate dose of lidocaine to be administered during anesthesia and each patient should be evaluated individually.

The hemodynamic status of each patient must be evaluated before establishing a dose as the clearance of lidocaine is dependent on hepatic blood flow and extraction of lidocaine from the plasma by hepatocytes (Brianceau *et al.* 2002). When cardiac output decreases, potentially during anesthesia or hypovolemia, hepatic blood flow decreases thereby decreasing lidocaine clearance and potentially leading to toxic drug concentrations (Brianceau *et al.* 2002). When cardiac output increases, for instance in painful conditions or during painful procedures, drug clearance may increase resulting in lower lidocaine plasma concentrations.

Two groups of investigators evaluated the effects of general anesthesia on serum lidocaine concentrations and both suggested a decreased dosage in anesthetized horses (Brianceau *et al.* 2002; Feary *et al.* 2005). After an initial pilot study showed that general anesthesia may have profound effects on the serum concentrations of lidocaine, Brianceau and colleagues sought to investigate the effects in clinical patients undergoing surgical intervention to correct an intestinal disorder (Brianceau *et al.* 2002). The authors confirmed that halving the dosage while under anesthesia (0.65 mg/kg followed by 25 µg/kg/min) led to the same mean serum lidocaine concentrations as conscious horses that received 1.3 mg/kg followed by 50 µg/kg/min **(Fig. 2-1)**. The authors concluded that this lower dosage should not be exceeded in anesthetized horses, even though concentrations >1 µg/mL were not achieved in all horses, as one horse had a serum concentration approaching the reported toxic range (2.27 µg/mL). Feary and colleagues compared conscious versus anesthetized healthy horse and found marked

pharmacokinetic differences attributed to changes in the volume of distribution (V_d) and clearance (Cl) due to a decreased hepatic blood flow secondary to decreased cardiac output. The smaller V_d and decreased Cl in anesthetized horses led to an increased peak concentration (C_{max}) and area under the curve (AUC). The authors concluded that a change in dosing during anesthesia should be considered (Feary *et al.* 2005). However, in a follow up study evaluating a population of anesthetized horses with gastrointestinal lesions undergoing an exploratory laparotomy, the same group concluded that a dose modification was not necessary; however the authors caution extrapolating the results to all horses requiring gastrointestinal tract surgery because the influence of severe disease on drug disposition remains unclear (Feary *et al.* 2006).

Figure 2-1 Mean ± SD serum lidocaine concentrations in horses administered lidocaine intraoperatively (0.65 mg/kg followed by 25 µg/kg/min) and postoperatively (1.3 mg/kg followed by 50 µg/kg/min) (Brianceau *et al.* 2002).



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Many clinicians administer a loading dose of lidocaine over 10-15 minutes prior to initiating a CRI as clinical observations and published data have both reported severe hypotension with rapid administration (Doherty and Frazier 1998). However, in conscious healthy adult horses administered 50 µg/kg/min, steady state without administration of a bolus was achieved in only 3 hours with a mean concentration of 0.934 (± 0.252) µg/mL (Dickey *et al.* 2008). A lidocaine bolus (1.5 mg/kg over 15 minutes) prior to a CRI (50 µg/kg/min) of lidocaine in anesthetized horses also did not lead to any advantages in isoflurane requirement, mean arterial pressure, end tidal CO_2, respiratory rate, blood gas data, ECG findings or recovery from anesthesia compared to horses not administered a bolus. The only significant finding was that the mean heart rate during the lidocaine bolus and during the infusion at 25, 35 and 95 minutes was lower than the group not administered lidocaine (Nannarone *et al.* 2014). These results question to use of a lidocaine bolus as part of an anesthetic protocol in horses undergoing colic surgery.

The most well-known advantage of using a lidocaine CRI during anesthesia is to decrease the MAC of inhalant anesthetics, namely halothane, isoflurane, and sevoflurane. Doherty and Frazier investigated the inhalant sparing effects of lidocaine (50 or 100 mg/kg followed by 50 or 100 µg/kg/min, respectively) in combination with halothane and found that lidocaine decreased halothane MAC in a linear fashion ($P<0.0003$, $r=0.86$) up to serum concentrations of 7 µg/mL (Doherty and Frazier 1998). Lidocaine concentrations less than 2 µg/mL decreased MAC by as much as 20%, between 2.1-3.5 µg/mL decreased MAC by 30-50% and between 5-7 µg/mL decreased MAC by 50-70%; the decrease in halothane MAC was dependent on the serum lidocaine concentration **(Fig. 2-2)** according to the equation $y= 1.94 + 0.0093x$ (y=percentage decrease in halothane MAC and x= serum lidocaine concentration). In contrast, the metabolites MEGX and GX were not correlated with a MAC reduction. Dzikiti et al evaluated lidocaine (2.5

mg/kg bolus followed 50 µg/kg/min) in combination with isoflurane administered to horses (American Society of Anesthesiologists class I or II) anesthetized for elective procedures (Dzikiti *et al.* 2003). The results showed that lidocaine decreased the end-tidal isoflurane concentration (mean ± SD) by 25% compared to controls (0.96 ± 0.06 vs. 1.28 ± 0.06%; $P < 0.05$) with plasma lidocaine concentrations ranging from 0.03 to 4.23 µg/mL **(Fig. 2-3)**. Lastly, the inhalant sparing effects of lidocaine (1.3 mg/kg followed by 50 µg/kg/min) in combination with sevoflurane were investigated in healthy horses and revealed a mean MAC reduction of 26.7 ± 12% with mean plasma lidocaine concentrations ranging from 2.6 ± 8.1 to 2.1 ± 4.4 µg/mL (Rezende *et al.* 2011).

Figure 2-2 Correlation between serum lidocaine concentration and percent decrease in halothane MAC (r=0.86, P<0.0003) (Doherty and Frazier 1998).

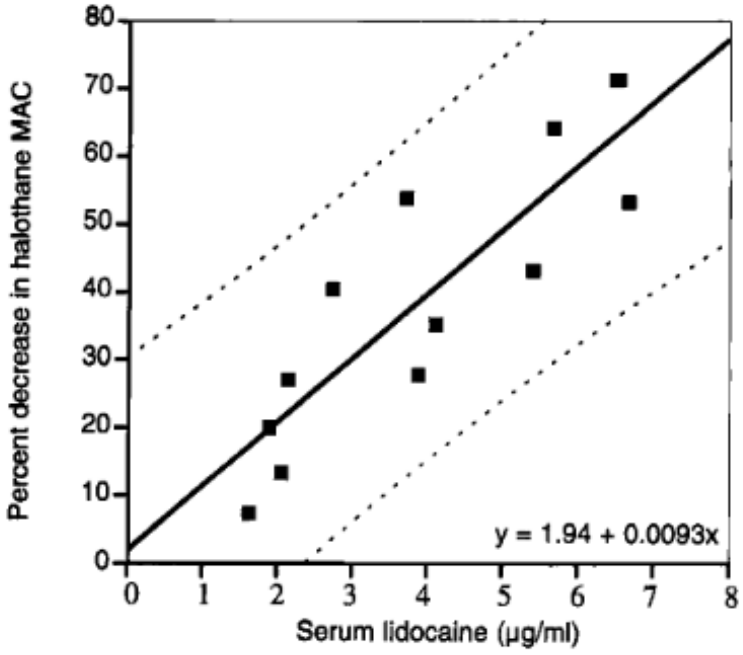

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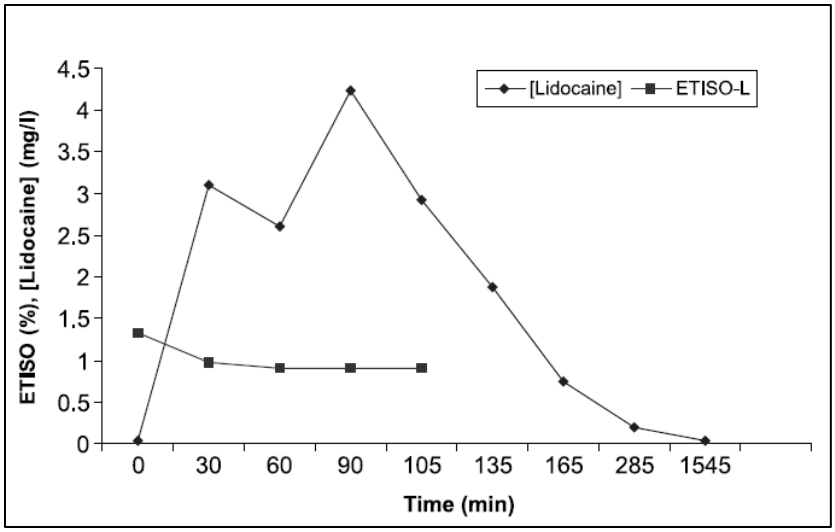
Figure 2-3 End-tidal isoflurane concentration (ETISO-L) and plasma lidocaine concentration trend in 6 horses administered a loading dose (2.5 mg/kg over 10 minutes) followed by a 75 minute CRI (50 µg/kg/min) during general anesthesia for an elective procedure (Dzikiti *et al.* 2003).



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There also appears to be beneficial cardiopulmonary effects in anesthetized horses administered intravenous lidocaine. Similar to conscious horses administered lidocaine at dosages approaching toxicity with no significant changes in heart rate, electrocardiogram, blood pressure or respiratory rate (Meyer *et al.* 2001), anesthetized horses administered clinical dosages of lidocaine do not appear to have changes in cardiovascular parameters different from what is generally expected to occur during anesthesia (Doherty and Frazier 1998; Feary *et al.* 2005). In fact, lidocaine appears to have a stabilizing effect on heart rate. Healthy horses undergoing isoflurane anesthesia for elective procedures administered lidocaine (2.5 mg/kg followed by 50 µg/kg/min) had consistent, stable heart rates over time compared to control horses that developed an increase in heart rate throughout the anesthetic period (Dzikiti *et al.*

2003). However, contrary to most other reports, Dzikiti et al reported an increase in blood pressure in the lidocaine treated horses compared to baseline which was attributed to an increase in systemic vascular resistance (Dzikiti *et al.* 2003).

While lidocaine appears to decrease the MAC of inhalant anesthetics and may have beneficial cardiopulmonary effects, it has not been confirmed that the decreased MAC will negate the hypotension that occurs from general anesthesia. Similar to other investigators, Wagner and colleagues found that lidocaine did not significantly alter heart rate, cardiac output, blood pressure, or blood gas parameters in healthy anesthetized horses compared to horses not treated with lidocaine (Wagner *et al.* 2011). However, lidocaine administration resulting in a decreased MAC was not associated with a significant improvement in blood pressure. The authors therefore concluded that at 1.5 MAC sevoflurane, lidocaine should be used for its other purported benefits as clinically important hypotension is likely to develop with or without the use of lidocaine. To obtain the benefits of decreasing MAC and stabilizing heart rate while at the same time having a positive effects on blood pressure, lidocaine may have to be combined with other cardiostimulating drugs, such as ketamine. Healthy horses undergoing elective surgery with isoflurane anesthesia and a CRI of lidocaine (1.5 mg/kg followed by 40 µg/kg/min) and ketamine (60 µg/kg/min) had significantly lower heart rates and end-tidal concentrations of isoflurane with fewer horses requiring dobutamine and lower dobutamine infusion rates (Enderle *et al.* 2008).

Other areas investigated in horses undergoing anesthesia with intravenous lidocaine administration include evaluation of physiologic and metabolic parameters, the effects on stress hormones and recovery from anesthesia. Dzikiti and colleagues evaluated pH, PaO_2, $PaCO_2$, concentrations of lidocaine, cortisol, lactate dehydrogenase, creatine kinase, aspartate

aminotransferase, and non-esterified fatty acids in horses undergoing surgery for an elective procedure. Anesthesia with isoflurane and lidocaine (2.5 mg/kg bolus followed by 50 µg/kg/min) revealed no significant differences compared to the control group in any parameter evaluated with the exception of insulin, which was significantly different between groups at baseline. The authors therefore concluded that the use of lidocaine during general anesthesia does not have subsequent effects on physiological and metabolic parameters or stress-related hormones (Dzikiti *et al.* 2003).

Investigations into the recovery from general anesthesia after lidocaine use found that when lidocaine is discontinued prior to the end of anesthesia, there does not appear to be an effect on the quality or length of recovery. Dzikiti and colleagues determined that lidocaine (2.5 mg/kg followed by 50 µg/kg/min) could be administered during the entire anesthetic period without affecting the length or behavior of recovery. However, these horses required 25% less isoflurane than control horses which may have partially contributed to the differences (Dzikiti *et al.* 2003). Rezende et al also found that healthy horses administered lidocaine (1.3 mg/kg followed by 50 µg/kg/min) with sevoflurane anesthesia had a "good quality" recovery (mean ± SD, 3.5 ± 1.0; median 3.3/5) when the lidocaine was administered up until 15 minutes before the end of anesthesia (Rezende *et al.* 2011). Wagner et al evaluated the same dose of lidocaine discontinued 20 minutes before the end of surgery, also with sevoflurane anesthesia, and similarly found no difference in recovery time or quality; horses administered lidocaine tended to have longer times to standing (P= 0.056) which most likely led to better recoveries than had they stood at earlier times (Wagner *et al.* 2011). Valverde and colleagues evaluated horses undergoing general anesthesia with isoflurane or sevoflurane along with a placebo or CRI of lidocaine (2 mg/kg bolus followed by 50 µg/kg/min) discontinued at the end or 30 minutes before the end of

surgery. Similar to other investigations, discontinuing the infusion 30 minutes prior to the end of surgery led to similar recoveries compared to placebo horses. However, horses that received lidocaine until the end of surgery had a significantly higher degree of ataxia with a tendency towards significance for a lower quality of recovery. There was no correlation between lidocaine plasma concentrations at recovery and the quality of recovery and horses in both groups received similar dosages of inhalant anesthesia in contrast to the study performed by Dzikiti et al (Valverde *et al.* 2005). Lastly, when lidocaine and ketamine were administered together during isoflurane anesthesia and discontinued at least 15 minutes before the end of surgery, recovery times and quality were comparable to horses only administered isoflurane (Enderle *et al.* 2008). Taken together, the data suggests that lidocaine alone, or in combination with ketamine, should not have a negative effect on recovery especially if the CRI is discontinued at least 15 minutes prior to the end of anesthesia.

Prokinetic properties

The beneficial prokinetic properties of lidocaine reported in humans had many equine clinicians interested in its potential use in colic patients. The human investigations led to meta-analyses that further supported its use. One meta-analysis, of 8 randomized double blinded controlled trials in humans, showed a significant reduction in ileus ($P<0.001$) in patients treated with a CRI of lidocaine during or after abdominal surgery compared to controls (Marret *et al.* 2008). A second meta-analysis, of 29 randomized controlled trials, found that in patients receiving a CRI of lidocaine during general anesthesia for any type of surgery, the time to first flatus and first feces were reduced (Vigneault *et al.* 2011). The beneficial effects may be from directly stimulating the intestinal smooth muscle or indirectly by acting as an analgesic, anti-

inflammatory including inhibition of free radical formation, or reduction in circulating catecholamines (Rimback *et al.* 1990).

In horses, post-operative ileus (POI) is one of the most common complications resulting in death of surgical colic patients and accounts for upwards of 43% of postoperative fatalities (Hunt *et al.* 1986; Blikslager *et al.* 1994). Lidocaine has become the most commonly used drug as a potential prokinetic for postoperative management of horses with colic (Van Hoogmoed *et al.* 2004). In vitro data evaluating healthy equine muscle strips showed that lidocaine increased the contractile amplitude in tissues from the proximal portion of the duodenum but not the pyloric antrum or middle portion of the jejunum (Nieto *et al.* 2000). Further in vitro research revealed that lidocaine increased intrinsic smooth muscle contractility by directly affecting the smooth muscle cells or the interstitial cells of Cajal when tetrodotoxin was used to block participation of the enteric nervous system. However, extremely high concentrations of lidocaine ($\geq$100 mg/L) by itself decreased enteric nervous system activity which may lead to impaired intestinal motility in vivo (Tappenbeck *et al.* 2014a). A third study found that administration of lidocaine during anesthesia in horses in which artificial ischemia and reperfusion injury of jejunal segments was induced had beneficial effects on smooth muscle motility when evaluated in vitro; specifically, lidocaine infusion significantly improved the frequency of contractions in muscle samples compared to samples without lidocaine treatment, ameliorating the negative contractility effects of ischemia and reperfusion injury. These findings indicate a direct effect on the interstitial cells of Cajal pacemaker function (Guschlbauer *et al.* 2011). When additional lidocaine was added to the muscle samples, lidocaine was also able to decrease membrane permeability, however the underlying mechanism responsible for this decrease in permeability remains unknown. The authors concluded that initiating lidocaine during surgical correction of

colic lesions may improve lidocaine's prokinetic features by protecting the smooth muscle from effects of ischemia and reperfusion.

While the in vitro evidence of lidocaine appears promising, in vivo data for a direct prokinetic effect of lidocaine in horses remains inconclusive. More recent research suggests that lidocaine may mediate its prokinetic effects indirectly via its analgesic or anti-inflammatory properties. Three recent publications found varying results, however all included different populations of horses and differing study designs (Brianceau *et al.* 2002; Malone *et al.* 2006; Milligan *et al.* 2007). The first report included horses requiring surgical intervention for any type of colic (Brianceau *et al.* 2002). In this study, lidocaine-treated horses had significantly decreased jejunal cross-sectional area scores, jejunal diameter scores, and abdominal fluid as well as improved ultrasonographic intestinal function index (determined by duodenal and jejunal wall thickness, minimum and maximum duodenal and jejunal diameter, minimum and maximum duodenal and jejunal cross sectional area, small intestinal contractions per minute, and duodenal and jejunal intraluminal echogenicity) but increased abdominal fluid protein. There was no difference between groups in the presence of gastrointestinal sounds, time to passage of 1st feces, number of defecations in the 1st 24 hours, presence of gastric reflux, duodenal or jejunal wall thickness, maximum duodenal or jejunal diameter or cross sectional area, minimum duodenal diameter or cross-sectional area, duodenal and jejunal intraluminal echogenicity, small-intestinal contractions per minute, rate of complications, or outcome. However the low incidence of small-intestinal lesions (29%) and gastric reflux made it difficult to assess the use of lidocaine in the prevention of POI. Malone et al evaluated horses with POI or enteritis that refluxed >20 L or had been refluxing for >24 hours (Malone *et al.* 2006). Horses in the treatment group were administered lidocaine (1.3 mg/kg followed by 50 µg/kg/min) for 24 hours. Lidocaine treated

horses refluxed significantly fewer hours and were hospitalized for shorter durations, however overall outcome was the same between groups with no significant differences between groups in the amount of reflux per 24 hour or 6 hour period, physical or laboratory variables or complications. Horses treated with lidocaine did have a significantly decreased reflux rate after treatment compared to before treatment. It should be noted that 4/15 horses in the placebo group were given lidocaine after the 24 hour treatment period which may have affected survival scores and 3 horses (18%) developed muscle fasciculation's, 1 during the bolus and 2 during infusion. Lidocaine serum concentration determined during the episode in one horse during infusion was only 2.4 µg/mL, however this horse had a decreased serum protein concentration potentially leading to an increased proportion of free drug resulting in signs of lidocaine toxicity (Malone *et al.* 2006). The final study evaluated healthy horses with 4 electrodes sutured to the proximal jejunum to record electrical activity postoperatively (Milligan *et al.* 2007). Duration of the migrating myoenteric complex (MMC), the most common method for measuring small intestinal motility, remained unchanged in horses administered lidocaine (1.3 mg/kg bolus followed by 50 µg/kg/min) compared to placebo as did spiking activity and the number of phase III events (responsible for aboral propulsion of food), suggesting lidocaine does not influence proximal jejunal motility in healthy horses. While significance was not achieved, the data trended towards an increased MMC duration and a decreased number of phase III events which would be detrimental to motility. Taken together, while the in vitro evidence for the use of lidocaine to stimulate gastrointestinal motility appears promising, the data does not appear to correlate strongly with a clinical benefit. However, further research should be done in larger populations of post-operative clinical cases as the effects of lidocaine may be due to the analgesic and/or anti-inflammatory effects rather than a direct effect on motility.

Analgesic properties

One of the earliest reports in humans for the use of intravenous lidocaine during general anesthesia leading to reduced post-operative pain dates back to 1954 when investigators evaluated a lidocaine CRI in combination with a continuous infusion of succinyldicholine chloride, an ultra-short acting muscle relaxant, during general anesthesia with nitrous oxide in 900 patients (De Clive-Lowe *et al.* 1954). Despite not having a control group, the authors concluded that the infusion provided post-operative analgesia in 77% of cases with 25% having analgesia for up to 10 hours. Since that time, multiple investigations in humans have evaluated intravenous lidocaine and its effects on painful conditions including postoperative pain, neuropathic pain, burn patient pain, and renal colic pain. Two recent meta-analyses evaluated post-operative pain after intravenous lidocaine. The first included eight randomized controlled trials, 161 treated patients and 159 controls, administered a CRI of lidocaine or placebo during or after abdominal surgery; the analysis concluded that pain intensity 24 hours post-operation was significantly decreased (P=0.002) (Marret *et al.* 2008). The second included 29 randomized controlled trials and 1,754 patients which compared a lidocaine CRI to placebo or any comparative drug during anesthesia for any type of surgery; the analysis concluded that the 6-hour post-operative pain score was decreased at rest, during a cough and during movement and there was also a reduced opioid requirement in patients administered lidocaine (Vigneault *et al.* 2011). In 2005 a meta-analysis was performed evaluating neuropathic pain. Ten randomized controlled trials in humans were evaluated and concluded that systemically administered lidocaine was superior to placebo and equal to morphine, gabapentin, amitriptyline and amantadine for chronic neuropathic pain and more consistent for peripheral versus central pain. There has been minimal work evaluating burn patients, renal colic patients, and post-amputation

pain in humans after CRIs of lidocaine. A prospective randomized double-blinded clinical trial observed beneficial effects of CRIs of lidocaine for patients with renal colic (Soleimanpour *et al.* 2012). Another randomized double blinded crossover trial evaluating a CRI of morphine compared to lidocaine determined that lidocaine significantly diminished stump pain ($P<0.01$) but not phantom pain in human amputees. However, the evidence for burn patients has not revealed significant benefits compared to placebo (Wasiak and Cleland 2007; Wasiak *et al.* 2011).

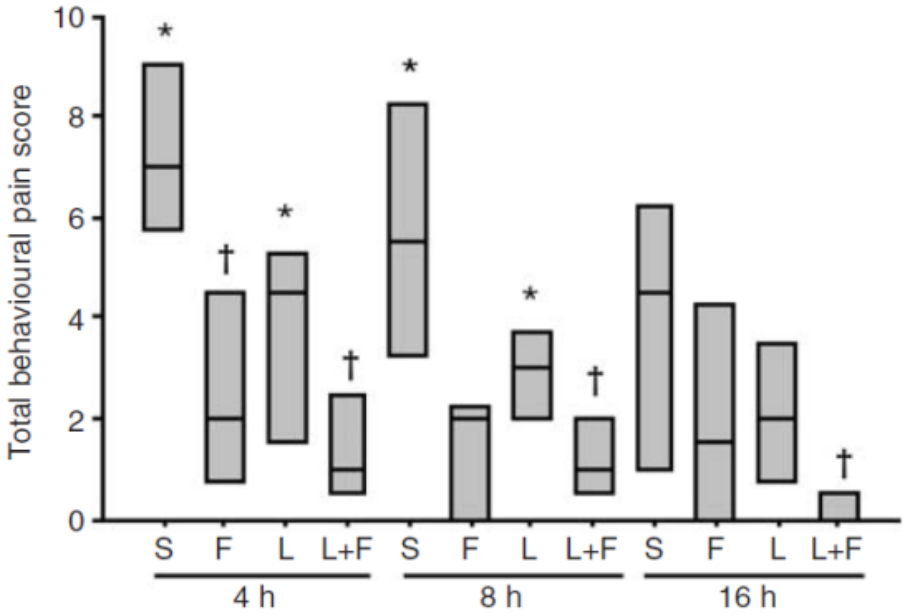
While evidence for the use of lidocaine as an analgesic in humans is promising, minimal research has been done in horses despite a need for alternative pain medications due to potentially severe unwanted side effects of opioids and NSAIDs. Opioids are well known for their inhibitory effects on gastrointestinal motility, especially in the horse. Butorphanol and morphine are both commonly used in horses however both have been shown to decrease borborygmi and defecation, especially when administered as a single injection (Sellon *et al.* 2001; Boscan *et al.* 2006). The most commonly used NSAIDs in equine medicine include flunixin meglumine, phenylbutazone and to a lesser extent, ketoprofen, firocoxib, and meloxicam all of which can lead to adverse effects including gastric glandular ulceration, right dorsal colitis and renal medullary crest necrosis. Gastric ulceration occurs in the glandular portion of the stomach due to decreased mucosal blood flow, decreased mucous production and increased hydrochloric acid secretion from prostaglandin inhibition (Videla and Andrews 2009). Right dorsal colitis is characterized by mucosal ulceration, edema, neutrophilic inflammation, and mural thickening of the right dorsal colon (Karcher *et al.* 1990; Jones *et al.* 2003). Renal medullary crest necrosis is characterized by sharply demarcated focal medullary necrosis that results in sequestration of fragments of the renal crest with secondary cortical segmental pallor

from tubular dilation, filtrate retention and interstitial edema (Read 1983; Black 1986). In contrast to the potentially life-threatening side effects of opioids and NSAIDs, the toxic effects of lidocaine are most commonly reported after administration errors and are transient, self-resolve, and include muscle fasciculations, ataxia, and occasional recumbency (Meyer *et al.* 2001). However human injuries may occur in cases of lidocaine toxicity in horses.

Pain is difficult to assess in animals and experimental pain models do not necessarily correlate with clinical pain, however, researchers have attempted to characterize the analgesic properties of lidocaine in horses. In 2005, a randomized, blinded cross-over trial compared a CRI of lidocaine (2mg/kg bolus followed by 50 µg/kg/min for 2 hours) to saline in 6 horses to determine the effect on visceral and somatic nociception (Robertson *et al.* 2005). It was concluded that lidocaine may play a role in somatic analgesia as the thermal threshold of a heating element placed over the withers was increased significantly; however there were no significant differences in colorectal or duodenal distention threshold pressure indicating minimal effects of lidocaine on visceral nociception. That same year, there was another report on the use of lidocaine in anesthetized ponies undergoing castration procedures (Murrell *et al.* 2005). The authors determined that the median frequency (F_{50}), an electroencephalographic variable used as a monitor of anesthetic depth, increased with castration suggesting that it may be a specific marker for nociception in the horse (Murrell *et al.* 2003). Two years later, the same authors published their findings that horses undergoing the same castration procedure with a CRI of lidocaine did not have the same increase in F_{50} suggesting that lidocaine prevented a cortical response and may therefore be antinociceptive and contribute to the depth of anesthesia (Murrell *et al.* 2005).

While lidocaine by itself has not proved to be an effective analgesic for intensely painful conditions, there may be a synergistic effect when combined with other drugs such as flunixin meglumine. Lidocaine administration alone (1.3 mg/kg followed by 50 µg/kg/min) did not have an effect on behavioral pain scores in horses after undergoing a 2-hour ischemic event and was no different than saline treated horses. However when lidocaine was combined with flunixin meglumine, a significant decrease in pain scores was observed at 4, 8, and 16 hours post-ischemia compared to saline treated horses while flunixin meglumine alone was only different at 4 hours **(Fig. 2-4)** (Cook *et al.* 2008). While minimal research is available for the use of lidocaine as an analgesic in horses, these findings, taken together with human studies, suggests that lidocaine may have analgesic properties in certain situations and should be considered when formulating a pain management plan.

Figure 2-4 Behavior pain scores for horses treated with saline 1 mg/50 kg (S), flunixin meglumine 1 mg/kg (F), lidocaine 1.3 mg/kg followed by 50 µg/kg/min (L), or both flunixin meglumine and lidocaine (L + F) at 4, 8, and 16 hours after an ischemic event (Cook *et al.* 2008).



This material is reproduced with permission of John Wiley and Sons, Inc. * Is significantly (P<0.05) increased from preoperative score. † Is significantly lower (P <0.05) than score for saline treated horses at that time point

Lidocaine pharmacology and pharmacokinetics in adult horses

The disposition of lidocaine in healthy and unhealthy adult horses has been evaluated with a single bolus administration or a continuous infusion and in fed and fasted horses (Engelking *et al.* 1987; Feary *et al.* 2005; Feary *et al.* 2006; Milligan *et al.* 2006; Waxman *et al.* 2012). The most commonly studied dosage of intravenous lidocaine in horses is an initial bolus of 1.3 mg/kg followed by a continuous infusion of 50 µg/kg/min with a target steady state concentration of 1-2 µg/mL. This dosage led to mean plasma concentrations ranging from 1.37

to 1.78 µg/mL in healthy adult horses (Waxman *et al.* 2012), 1.50 ± 0.24 to 2.61 ± 0.38 µg/mL in healthy postoperative horses (Milligan *et al.* 2006), 0.891 ± 0.34 to 1.64 ± 0.85 µg/mL in post-operative colic patients (de Solis and McKenzie 2007), and from 1.46 ± 0.385 to 2.18 ± 0.263 µg/ml in horses undergoing general anesthesia with gastrointestinal disease (Feary *et al.* 2006). It should be noted that in the report by de Solís and McKenzie, there were multiple instances where the infusion was intermittently discontinued to walk the patient, therefore steady state concentration was not reached in these horses. Also, all reports included horses that received various other treatments that may affect the protein binding of lidocaine. In vitro research evaluating the effects of protein binding by other drugs **(Table 2-1)** revealed competition for protein binding sites with concurrently administered flunixin meglumine and ceftiofur (Milligan *et al.* 2006). While lidocaine alone was only moderately protein bound (53.1 ± 10.3%), the addition of the other highly protein bound drugs enhanced the amount of unbound free drug available to exert a pharmacologic effect and potential toxicity (Milligan *et al.* 2006). However, in vivo data in healthy horses determined that flunixin meglumine in conjunction with lidocaine did not lead to plasma concentrations of either drug outside their expected ranges (Waxman *et al.* 2012).

Table 2-1 In vitro percent protein binding of lidocaine alone and with flunixin meglumine and ceftiofur (Milligan *et al.* 2006).

	Lidocaine Protein Bound (%)	SD (%)
Lidocaine	53.1	10.3
Lidocaine + flunixin	34.1	21.5
Lidocaine + ceftiofur	27.3	9.72
Lidocaine + flunixin + ceftiofur	29.5	6.4

Engelking and colleagues evaluated the effects of fasting on serum lidocaine concentrations after a single intravenous bolus of 0.424 mg/kg. The authors determined that fasting for 3 days led to a decrease in clearance from 52.0 ± 11.7 to 43.7 ± 8.47 mL/min/kg when compared to fed horses and that plasma clearance in fed horses was more than twice estimated hepatic blood flow of 22.4 mL/min/kg (Engelking *et al.* 1985; Engelking *et al.* 1987). The authors explained the rapid clearance by four possibilities: intravascular degradation of lidocaine, lidocaine concentrated in erythrocytes, irreversible extrahepatic extravascular removal of lidocaine, or the estimated equine hepatic blood flow is low.

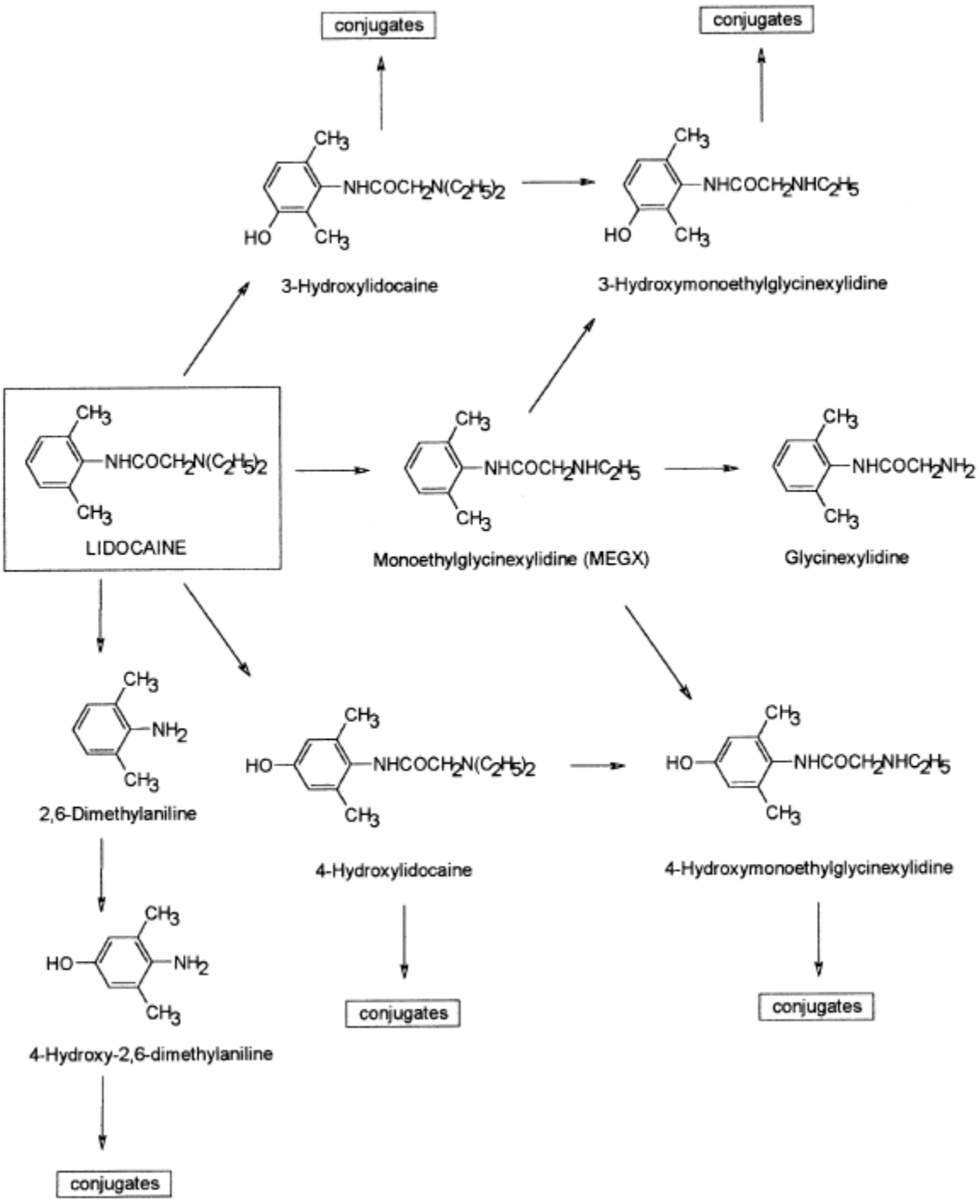
Lidocaine metabolites

While the pharmacokinetics, disposition, and clinical effects of lidocaine have been studied extensively in adult horses, there is limited information regarding the effects of the metabolites. Validated techniques to measure certain metabolite concentrations have only recently been developed, therefore it is impossible to draw conclusions related to their pharmacologic effects. Lidocaine undergoes extensive metabolism before being excreted in the urine **(Fig. 2-5)**. It is metabolized in the liver by cytochrome P450 oxidative dealkylation resulting in MEGX and glycine xylidide (GX). Monoethylglycine xylidide is then broken down to monoethylglycine and xylidide, which have sodium channel activities of 75% and 10% respectively (Riviere and Papich 2009). Further metabolism occurs resulting in a number of metabolites that are excreted in the urine with the primarily metabolites in the horse being MEGX, GX, 3-hydroxyliodcaine (3-OH-LID) and 4-hydroxylidocaine (4-HO-LID) (Nelis *et al.* 2010). Studies evaluating the clearance of lidocaine and its metabolites found that serum lidocaine concentrations decreased below detectable limits by 4-6 hours after discontinuation in adult horses with the most noticeable difference in the first 30 min explained by a rapid

distribution and elimination (Feary *et al.* 2005; Feary *et al.* 2006; Dickey *et al.* 2008). On the other hand, the concentrations of MEGX and GX were not below detectable limits until 24 hours after discontinuing the infusion (de Solis and McKenzie 2007; Dickey *et al.* 2008).

In evaluating the accumulation of lidocaine and its metabolites over time, three reports advised caution when using intravenous lidocaine for prolonged periods. Milligan et al evaluated a 12-hour intravenous lidocaine infusion (1.3 mg/kg followed by 50 µg/kg/min) to postoperative healthy horses and found a significant increase in plasma concentrations from 4-12 hours compared to hours 1-3; the authors concluded that a lower lidocaine infusion rate may be needed when administered to horses for a prolonged period of time (Milligan *et al.* 2006). Another report found a steady increase in the mean concentrations of lidocaine, MEGX and GX when evaluating infusions lasting over 12 hours in post-operative colic patients and also concluded that prolonged infusions should be used with caution (de Solis and McKenzie 2007). The third report evaluated a 96-hour lidocaine infusion to healthy horses and found that while lidocaine and MEGX did not accumulate, GX did accumulate significantly up to 48 hours after which time the concentration remained constant (Dickey *et al.* 2008). The authors in this study concluded that while prolonged infusions appear safe in healthy horses, the accumulation of GX is cause for concern.

Figure 2-5 Structure of lidocaine and its metabolites (Harkins *et al.* 1998).



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Lidocaine toxicity

While the target steady state concentration in horses is reported to be between 1-2 µg/mL, clinical signs of toxicity have been observed at serum concentrations as low as 1.85 µg/mL (range 1.85-4.53 µg/mL; mean 3.24 ± 0.74 µg/mL) (Meyer *et al.* 2001). Toxicity may not only result from overdoses but also from the accumulation of metabolites, rapid exposure of brain cells to lidocaine, increases in unbound lidocaine and acidosis (Blumer *et al.* 1973; Narang *et al.* 1978; Scott 1986; de Solis and McKenzie 2007). Milligan et al evaluated a loading dose of 1.3 mg/kg over 15 minutes followed by a 12-hour infusion of 50 µg/kg/min to 6 postoperative healthy horses. While the infusion was well tolerated in 5/6 horses, one horse developed tremors and collapsed 5.5 hours into the infusion (Milligan *et al.* 2006). The corresponding serum concentration at 6 hours in that horse was only 2.74 µg/mL. Waxman et al evaluated the same dosage over a 6-hour infusion to 6 horses. Five of the six horses did not display sings of toxicity. One horse experienced an episode of Hyperkalemic Periodic Paralysis 2.5 hours after discontinuing the infusion; it was unclear whether the response was triggered by the study protocol or if it was a random occurrence (Waxman *et al.* 2012). In another report of 10 horses administered prolonged lidocaine infusions after an exploratory laparotomy, 2 horses experienced an episode of moderate ataxia during the infusion with serum concentrations at the time of occurrence under the reported toxic concentrations (de Solis and McKenzie 2007). While lidocaine does display a narrow therapeutic index, the drug is redistributed from the plasma after approximately 8 minutes (Roden 1996), therefore, the side effects resolve rapidly after the drug is discontinued.

Lidocaine pharmacokinetics in adults and neonates of other species

The pharmacokinetic properties of intravenous lidocaine have been evaluated in newborn piglets (Satas *et al.* 1997), sheep (Morishima *et al.* 1979) and children (Finholt *et al.* 1986) and differences and similarities exist between and amongst species. For example, newborn sheep are reported to have a 20 percent greater clearance of lidocaine compared to adult sheep (Morishima *et al.* 1979). This finding is in contrast to newborn piglets, who have a significantly decreased clearance (Satas *et al.* 1997), and humans, who have no difference in clearance compared to their adult counterparts (Finholt *et al.* 1986). With regard to half-life, neonatal piglets and sheep have a longer half-life of intravenously administered lidocaine compared to adults; this finding has been attributable to a larger volume of distribution due to a higher percentage of body water (Morishima *et al.* 1979; Satas *et al.* 1997). The exact age at which the pharmacokinetics in young animals behave similar to adults will vary amongst species. Finholt and colleagues found that once children were over 6 months of age there were no significant differences compared to adults when evaluating the pharmacokinetics of lidocaine and concluded that both age groups distribute and eliminate intravenous lidocaine in the same manner (Finholt *et al.* 1986).

Protein binding is another important component of the volume of distribution of lidocaine as only unbound drug is available to exert its pharmacological effects (Satas *et al.* 1997). Milligan et al found that at serum concentrations of 2µg/mL, the in vitro plasma protein binding of lidocaine in adults is 53 percent (Milligan *et al.* 2006). Lidocaine in the plasma is mainly bound to α_1-acid glycoprotein and different concentrations of this protein in neonatal circulation leads to differences in free lidocaine concentrations. At birth, piglets were reported to have 14,263 µg/mL of α_1-acid glycoprotein (Itoh *et al.* 1992) compared to an undetectable (<20 µg/mL) concentration in newborn foals (Taira *et al.* 1992). The concentration increases in foals

throughout the first year of life to reach detectable concentrations by 14 days of age and a concentration of 99.23 ± 26.90 μg/mL by one year. Significant differences in clearance, half-life, volume of distribution and protein binding in adults versus neonates necessitates determination of serum concentrations and pharmacokinetics of intravenous lidocaine infusions to foals.

Pharmacokinetic differences in adult horses and foals

While the data specific to foal physiology is scarce, a few generalizations have been made and should be considered when a dosing regimen is developed for use in foals (Magdesian 2015). Foals are rapid growing creatures gaining 1.15 ± 0.17 kg/day and therefore constant dosage adjustments must be made, especially in drugs with a narrow therapeutic index. As with most young animals, the volume of distribution in foals is larger when compared to adults due to a relatively high water content and minimal fat, which results in lower plasma concentrations of drugs in foals compared to adults. Foals generally have lower total serum protein concentrations which may lead to more free drug and greater risk for toxic concentrations. Foals also have a decreased metabolic and excretory capacity compared to adults as maturation of hepatic function primarily occurs in the first 1-2 weeks postpartum. This is especially important for drugs that are metabolized by the liver as the hepatic microsomal enzyme pathways are not completely developed at birth which could result in longer elimination half-lives and decreased clearance. In contrast, the renal function in foals is fully functioning by 1-2 days of age however, foals generally have more acidic urine than adults, therefore tubular resorption of weak acids readily occurs and weak bases may be trapped in the urine. All of these factors should be considered as they may affect distribution, metabolism and excretion of drugs.

The pharmacokinetics for a variety of drugs have been evaluated in both foals and adult horses although there are limited studies directly comparing the two groups. Prescott et al

compared a 5 mg/kg dosage of erythromycin in foals ranging from 1-7 weeks of age to adult horses (Prescott *et al.* 1983). Foals had an increased clearance, larger volume of distribution and similar half-lives (**Table 2-2)**. Cummings et al compared the pharmacokinetics of gentamicin (4 mg/kg) in foals throughout the first 30 days of life to mares **(Table 2-3**) (Cummings *et al.* 1990). While the volume of distribution decreased over time, as expected in young animals, the half-life also decreased with age. Finally, indirect comparisons of flunixin meglumine in newborn foals revealed a larger volume of distribution, increased clearance and a longer half-life in foals compared to adults **(Table 2-4)** (Semrad and Moore 1987; Toutain *et al.* 1994; Crisman *et al.* 1996; Coakley *et al.* 1999).

Table 2-2 Pharmacokinetic parameters in 1-7 week old foals compared to adults administered a single intravenous injection of erythromycin (5 mg/kg) (Prescott *et al.* 1983).

Parameter	Foals	Adults
Cl (mL/kg/h)	2.9 ± 1.0	1.9 ± 0.4
V_d (L/kg)	3.7 ± 1.1	2.3 ± 0.6
$t_{1/2}$ (h)	1.0 ± 0.4	1.0 ± 0.5

Cl= clearance, V_d= volume of distribution, $t_{1/2}$= elimination half life

Table 2-3 Pharmacokinetics of gentamicin (4 mg/kg) in neonatal foals after a single intravenous injection compared to adults (Cummings *et al.* 1990).

	Foals					Adults
	1 day	5 days	10 days	15 days	30 days	
Cl (mL/kg/min)	1.75 ± 0.47	2.98 ± 1.48	2.60 ± 0.96	2.4 ± 0.87	3.66 ± 1.93	1.69 ± 0.65
$V_{d(ss)}$ (mL/kg)	306 ± 30	350 ± 66	344 ± 95	325 ± 48	279 ± 34	155 ± 22
$H_{t1/2}$ (min)	127 ± 23	90 ± 32	101 ± 33	106 ± 33	60 ± 31	65 ± 55

Cl= clearance, $V_{d(ss)=}$ volume of distribution at steady state, $H_{t1/2}$= harmonic mean half life

Table 2-4 Pharmacokinetics of flunixin meglumine (1.1 mg/kg) in neonatal foals less than 24 hours old compared to adults (Semrad and Moore 1987; Toutain *et al.* 1994; Crisman *et al.* 1996; Coakley *et al.* 1999).

	Foals	Adults	Adults	Adults
Cl (mL/kg/hr)	17	63 ± 12	59 ± 20	66 ± 12
V_d (mL/kg)	220	154 ± 51	199 ± 28	117 ± 16
$t_{1/2}$ (hr)	8.5	4.2 ± 2.1	2.5 ± 0.6	N/A

Cl= clearance, V_d= volume of distribution, $t_{1/2}$= half-life

Chapter 3 - Materials and Methods

All procedures were approved by the Kansas State University Institutional Animal Care and Use Committee.

Phase I

The objective of this phase was to determine the pharmacokinetics and plasma concentrations of lidocaine and MEGX in healthy foals less than three months of age.

Experimental design and sample collection

Healthy foals less than 3 months of age were used. Foals were weighed and determined to be healthy based on a physical examination, complete blood count, serum biochemistry analysis and assessment of adequate passive transfer of maternal antibody performed in the first week of life. Foals were maintained in a divided stall with their dam and not allowed to nurse during the 6-hour treatment period, although milk was provided in a bucket and free access to water and hay were available at all times.

A double lumen (16 gauge) over the wire catheter was aseptically placed in the left jugular vein using 2 mL of bupivacaine as a local anesthetic. One port was designated for the lidocaine infusion and the other port for sampling of lidocaine plasma concentrations. A single lumen short term (16 g, 5-inch) catheter was placed in the right jugular vein in the same fashion as the double lumen catheter; the right-sided catheter was only used for plasma lidocaine concentration sampling. The purpose of having two catheters was to determine the accuracy of obtaining samples from the same catheter (different lumen) as the lidocaine infusion. The results were used to determine accuracy of samples obtained in phase II.

Lidocaine hydrochloride was administered as a loading dose (1.3 mg/kg) intravenously over 15 minutes followed by an intravenous infusion of 50 µg/kg/min. An infusion pump was used to administer the lidocaine for a period of 6 hours. Blood, 5 mL per time point, was collected from the single lumen catheter into heparinized tubes before (time 0), at the midpoint (0.125 h), and at completion (0.25 h) of the loading dose, during the infusion at time points 0.5, 1, 1.5, 2, 3, 4, and 6 hours, and after discontinuation of the infusion at time points 6.25, 6.5, 7, 7.5, 8, and 10 hours. Blood, 5 mL per time point, was also collected into heparinized tubes from the port designated for sampling on the double lumen catheter at time points 1, 2, 4, and 6 hours after initiation of the lidocaine infusion. Plasma lidocaine concentrations from both catheters were compared. Heart rate and respiratory rate were also recorded at each time point. Foals were subjectively evaluated for adverse effects such as skeletal muscle fasciculations, anxiety, ataxia, and/or collapse.

Phase II

The objective of this phase was to determine plasma concentrations of lidocaine and MEGX in unhealthy foals less than 6 months of age presented to a referral hospital or academic institution. Owner consent was obtained prior to inclusion of all foals.

Experimental design and sample collection

Foals less than 6 months of age admitted to a private equine practice or Kansas State University from March 1 through September 1, 2013 necessitating lidocaine treatment were included in the study. Older foals were included in this part of the study to increase sample size. A physical examination, complete blood counts and serum biochemistry analysis were performed prior to lidocaine administration. A weight tape or visual assessment was used to determine the

weights of foals at the private practice as it was not feasible to weigh the foals in this clinical setting. A scale was used to weigh foals at Kansas State University. Foals were not allowed to nurse during the treatment period, instead they were supplemented nutritionally with intravenous dextrose formulations, total parenteral, or partial parenteral nutrition.

A double lumen, over the wire catheter was aseptically placed into either the right or left jugular veins using 1-2 mLs of lidocaine. At least 20 minutes elapsed between catheter placement and initiation of lidocaine treatment. Lidocaine hydrochloride was administered as a loading dose (1.3 mg/kg) intravenously over 15 min followed by an intravenous infusion of 50 µg/kg/min using the estimated or actual weight as described above. An infusion pump was used to administer the lidocaine. Blood, 5 mL per time point, was collected from the port designated for sampling into heparinized tubes after administration of the lidocaine infusion (between 0.25-0.75 h) and then between 4-12 hours, 12-24 hours, and 24-48 hours during the infusion. Foals were subjectively evaluated for adverse effects such as skeletal muscle fasciculations, anxiety, ataxia, and collapse. The breed, gender, age, diagnosis, outcome and other treatments administered were also recorded.

Plasma Drug Analysis and Pharmacokinetic Determinations

Plasma was separated and stored frozen at -70°C before analysis. Plasma was analyzed for lidocaine concentrations by high pressure liquid chromatography (HPLC) with mass spectrometry. Plasma samples and standards (0.1mL) were treated with 0.4 mL methanol containing mepivacaine (250 ng/mL) as the internal standard (IS). The mass spectrometry determined lidocaine (m/z 235→86) and MEGX (m/z 207→58), quantitatively using mepivacaine as the IS (m/z 247→98), and GX (m/z 179→122), 3-OH-L and 4-OH-L (m/z 251→86) were qualitatively evaluated. The m/z is the mass to charge ratio and (XX→XX) are

the qualifying and quantifying ions, respectively. The mobile phase consisted of acetonitrile and 0.1% formic acid with a phenyl column achieving separation (150x3mm, 5 µM, Thermo Hypersil, ThermoFisher, Waltham, MA, USA). Plasma parameters were calculated using non-compartmental analysis. The pharmacokinetic parameters that were calculated were AUC, AUMC, Cmax, Tmax, MRT, ʎ, and elimination t ½.

Chapter 4 - Results

Phase I

Six healthy Quarter Horse foals (3 fillies and 3 colts) between 4-10 weeks of age and 93-142 kg were used. All foals were determined to be healthy prior to inclusion into the study with no adverse effects observed during lidocaine administration. Lidocaine was well tolerated in all foals during the study. Heart rate and respiratory rate remained consistent and within normal reference ranges for all foals during the infusion. Difference in the plasma concentrations between the double lumen and single lumen catheter were minimal (mean 98.2% ± 13%); the largest difference was observed at 1 hour at which time the single lumen catheter was 86% of the concentration of the double lumen catheter **(Table 4-1)**. Steady state was reached by 1.5 hours with a mean plasma concentration of 0.670 µg/mL ± 0.074 (min 0.484 µg/mL; max 0.785 µg/mL) from 1.5-6 hours. The metabolites MEGX, GX, and 4-hydroxy-2,6-xylidine were present; only MEGX was quantified **(Table 4-2; Fig. 4-1)**. Mean plasma lidocaine concentration was undetectable by 2 hours after discontinuation of the CRI while the MEGX concentration decreased at a slower rate **(Table 4-3; Fig. 4-2)**. Pharmacokinetic parameters were determined using non-compartmental analysis **(Table 4-4)**.

Table 4-1 Mean plasma lidocaine concentration comparison between a catheter designated only for sampling (single lumen) compared to a double lumen catheter used for sampling and infusion of a continuous intravenous infusion of lidocaine (1.3 mg/kg followed by 50 µg/kg/min) to 6 healthy young foals.

	Mean Plasma Lidocaine Concentration (µg/mL)		
Time (h)	Double Lumen (Infusion and Sampling)	Single Lumen (Sampling)	Difference (%)
1	0.690	0.594	86%
2	0.677	0.659	97%
4	0.684	0.626	92%
6	0.684	0.626	92%

Table 4-2 Raw mean, SD, and range of lidocaine and MEGX plasma concentrations following a lidocaine CRI (1.3 mg/kg followed by 50 µg/kg/min) for 6 hours in 6 healthy young foals

	Lidocaine Plasma Concentration (µg/mL)			MEGX Plasma Concentration (µg/mL)		
Time (h)	Mean ± SD	Min	Max	Mean ± SD	Min	Max
0	0.000 ± 0.000	0.000	0.000	<0.010	0.000	<0.010
0.125	0.388 ± 0.119	0.232	0.550	0.016 ± 0.008	<0.010	0.025
0.25	0.782 ± 0.088	0.636	0.902	0.063 ± 0.015	0.038	0.080
0.5	0.557 ± 0.062	0.474	0.628	0.131 ± 0.033	0.089	0.166
1.0	0.594 ± 0.076	0.465	0.681	0.183 ± 0.051	0.121	0.241
1.5	0.653 ± 0.088	0.503	0.744	0.238 ± 0.074	0.153	0.335
2.0	0.659 ± 0.060	0.546	0.727	0.270 ± 0.075	0.181	0.379
3.0	0.669 ± 0.057	0.568	0.727	0.314 ± 0.095	0.209	0.436
4.0	0.699 ± 0.075	0.602	0.785	0.335 ± 0.117	0.197	0.477
6.0	0.672 ± 0.099	0.484	0.762	0.340 ± 0.143	0.190	0.574

Figure 4-1 Mean ± SD plasma concentrations of lidocaine and MEGX following a lidocaine CRI (1.3 mg/kg followed by 50 µg/kg/min) for 6 hours to 6 healthy young foals

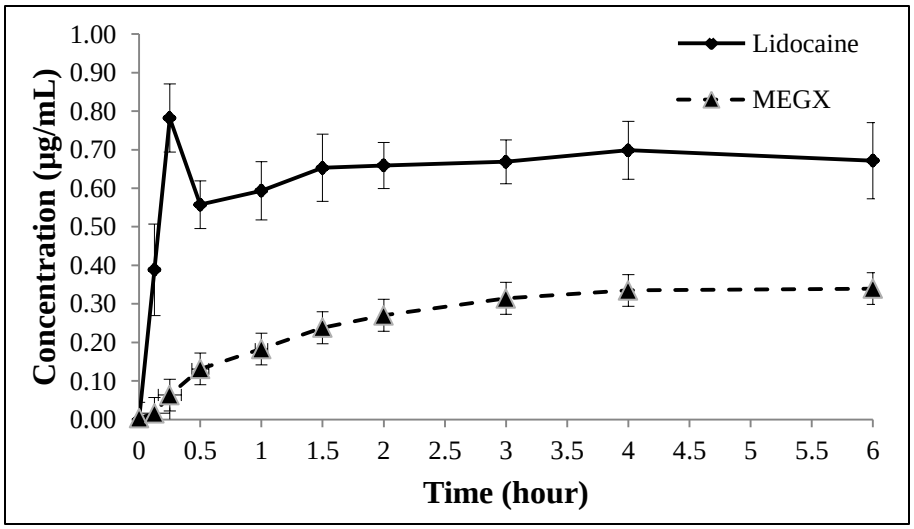


Table 4-3 Mean ± SD and range of lidocaine and MEGX plasma concentrations after discontinuation of a 6-hour lidocaine CRI (1.3 mg/kg followed by 50 µg/kg/min) in 6 healthy young foals

	Lidocaine Plasma Concentration (µg/mL)			MEGX Plasma Concentration (µg/mL)		
Time (h)	Mean ± SD	Min	Max	Mean ± SD	Min	Max
6.25	0.414 ± 0.065	0.325	0.495	0.302 ± 0.122	0.162	0.505
6.5	0.291 ± 0.060	0.191	0.372	0.267 ± 0.125	0.120	0.487
7.0	0.111 ± 0.058	0.000	0.155	0.196 ± 0.094	0.091	0.349
7.5	0.015 ± 0.037	0.000	0.091	0.139 ± 0.070	0.060	0.258
8.0	0.000 ± 0.000	0.000	0.000	0.095 ± 0.050	0.040	0.179
10.0	0.000 ± 0.000	0.000	0.000	0.028 ± 0.017	<0.010	0.054

Figure 4-2 Mean ± SD plasma concentrations of lidocaine and MEGX following discontinuation of a 6-hour lidocaine CRI (1.3 mg/kg followed by 50 µg/kg/min) to 6 healthy young foals

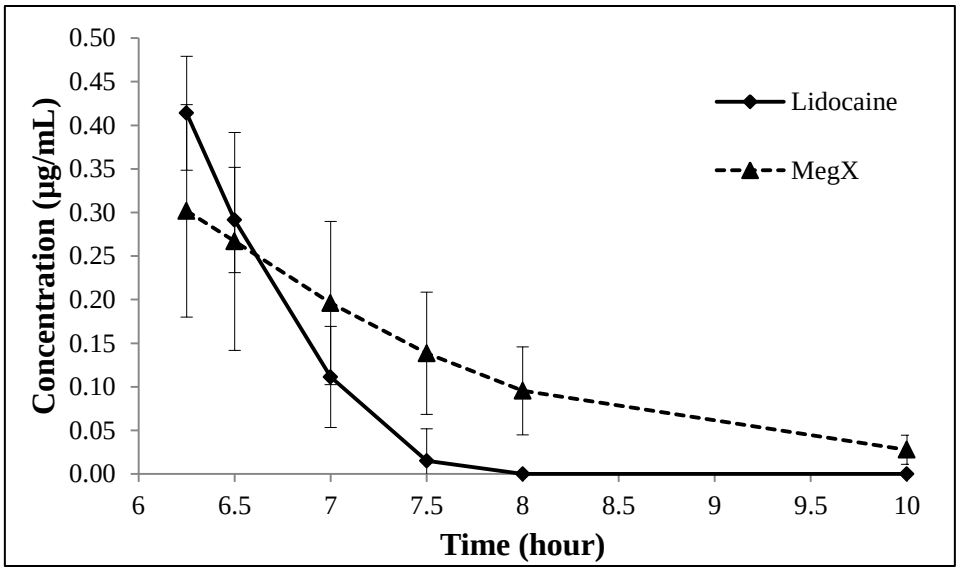


Table 4-4 Pharmacokinetic parameters of lidocaine and MEGX after administration of a lidocaine bolus (1.3 mg/kg) followed by a CRI of lidocaine (50 µg/kg/min) for 6 hours to 6 healthy young foals.

	Lidocaine			MEGX		
	Mean ± SD	Min	Max	Mean ± SD	Min	Max
$AUC_{0\infty}$ (µg·min/mL)	259.27 ± 25.02	212.63	283.40	n/a	n/a	n/a
Cl (mL/min/kg)	72.17 ± 7.83	65.45	87.24	n/a	n/a	n/a
C_{max} (µg/mL)	0.794 ± 0.067	0.706	0.902	0.361 ± 0.141	0.209	0.574
$t_{1/2}$ (min)	26.3 ± 3.7	21.9	29.7	62.5 ± 6.0	54.0	68.8
Terminal rate (L/min)	0.027 ± 0.004	0.023	0.032	n/a	n/a	n/a
$MRT_{0\infty}$ (min)	26.06 ± 6.86	15.50	34.00	n/a	n/a	n/a
T_{max} (min)	72.5 ± 140.8	15.0	360.0	280.0 ± 90.3	180.0	360.0
$V_{d(ss)}$ (L/kg)	1.85 ± 0.41	1.35	2.47	n/a	n/a	n/a

Values were generated using noncompartmental analysis. $AUC_{0\infty}$= area under the plasma concentration-time curve from time 0 to infinity, Cl= clearance, $C_{max=}$ maximal plasma concentration, $t_{1/2=}$ terminal half-life, MRT= mean residence time, T_{max}= time of maximal plasma concentration, $V_{d(ss)}$= apparent volume of distribution at steady stat

Phase II

One Quarter Horse and 7 Thoroughbred foals were included in the study. There were 3 fillies and 5 colts ranging from 2-136 days of age. The seven Thoroughbred foals were estimated to weigh between 52- 227 kg; the Quarter Horse foal weighed 82 kg. Six foals survived to discharge and 2 were euthanized. There were a variety of diagnoses and concurrent treatments administered **(Table 4-5)**. Lidocaine appeared to be well tolerated in all foals during the study. No adverse effects were observed, however foal #8 presented recumbent and never stood without assistance; therefore, the ability to monitor for adverse effects in this foal was difficult. A complete blood count and serum biochemistry analysis were performed in all cases except foal #6 in which only a complete blood count and electrolyte concentrations were performed **(Table 4-6)**. Plasma lidocaine concentrations and MEGX concentrations are reported in **Table 4-7** and **Fig. 4-3** and **Fig. 4-4**. Plasma lidocaine concentrations for foals #1-7 were within or below the ranges reported for healthy horses **(Fig. 4-3)**. Foal #8 had a peak plasma lidocaine concentration of 8.43 µg/mL after the bolus infusion, however, the bolus was administered to this foal over 5 minutes.

Table 4-5 Description, concurrent treatments administered, diagnosis and outcome in 8 unhealthy foals administered a CRI (1.3 mg/kg followed by 50 µg/kg/min) of lidocaine

Foal	Age (d)	Weight (kg)	Breed	Gender	Other treatments	Diagnosis	Outcome
#1	79	227*	TB	Filly	LRS, K-pen, gentamicin, flunixin meglumine, omeprazole, probiotic paste	Enteritis, pneumonia	DC
#2	31	114*	TB	Colt	LRS + dextrose, sucralfate, ranitidine, metronidazole, omeprazole, biosponge, probiotic paste, gastrocote	Colitis	DC
#3	70	140*	TB	Colt	LRS + dextrose, K-pen, gentamicin, flunixin meglumine, hyaluronate sodium, sucralfate, lactaid, omeprazole, probiotic paste	SI volvulus	DC
#4	2	52*	TB	Filly	LRS, TPN, ceftiofur sodium, sucralfate, biosponge, gastrocote, ketoprofen, lactaid, probiotic paste, metronidazole, pysillium	Enteritis	DC
#5	61	122*	TB	Colt	LRS + dextrose, probiotic paste, ketoprofen, sucralfate, omeprazole	Enteritis	DC
#6	136	181*	TB	Colt	LRS + dextrose, dopamine CRI, equioxx, ranitidine, omeprazole, sucralfate	Gastric ulceration	E
#7	4	69*	TB	Colt	LRS + dextrose, oxytetracycline, lactaid, metronidazole, sucralfate, probiotic paste, ketoprofen	Salmonella Unilateral CNS signs	DC
#8	47	82	QH	Filly	TPN, LRS, K-pen, gentamicin, famotidine, sucralfate, omeprazole, flunixin meglumine, metoclopramide	SI volvulus, mesenteric rent	E

* Estimated weight performed; foal #8 was weighed. TB= Thoroughbred, QH= Quarter Horse, TPN= total parenteral nutrition, LRS= lactated ringers solution, K-pen= potassium penicillin, DC= discharged, E= euthanized.

Table 4-6 Important complete blood count and serum biochemistry findings in 8 unhealthy foals administered a CRI of lidocaine (1.3 mg/kg followed by 50 µg/kg/min) during hospitalization.

	Reference Range (#1-7)	Foal #1	Foal #2	Foal #3	Foal #4	Foal #5	Foal #6	Foal #7	Foal #8	Reference range (#8)
WBC x 10^3	7.0-12.0	6.4	10.8	9.7	8.9	10.0	74.6*	10.5	7.4	6.0-12.0
PCV (%)	30-44	38.3	35.4	31.9	35.8	29.7*	54.4*	35.7	43	32-48
Fibrinogen (mg/dL)	200-400	500*	600*	500*	400	600*	600*	300	200	100-400
TP (g/dL)	5.4-7.6	6.6	6.0	5.6	6.0	6.0	9.3*	5.3*	5.9*	6.0-8.5
Albumin (g/dL)	2.4-5.0	3.0	2.8	2.7	2.8	2.5	N/A	2.8	2.8	2.7-3.7
AST (U/L)	80-250	316*	223	215	161	191	N/A	108	400	244-543
CK (U/L)	50-250	264*	176	790*	212	278*	N/A	88	1218*	192-565
SDH	0.8-4.2	12.3*	2.3	3.4	5.6*	8.7*	N/A	9.2*	<0.3	N/A
GGT (U/L)	6-24	13	36*	14	25*	30*	N/A	12	17	6-24
Creatinine (mg/dL)	0.8-2.0	1.1	0.8	1.3	1.0	1.1	9.9*	1.0	1.7	0.8-1.8
BUN (mg/dL)	8-26	17	12	16	6	11	N/A	6	21	9-22

* Indicates value outside of the reference range**.** WBC= white blood count, PCV= packed cell volume, TP= total protein, AST= aspartate transaminase, CK= creatine kinase, SDH= sorbitol dehydrogenase, GGT= gamma glutamyltransferase, BUN= blood urea nitrogen

Table 4-7 Plasma lidocaine and MEGX concentrations in 8 unhealthy foals administered a CRI of lidocaine (1.3 mg/kg followed by 50 µg/kg/min) during hospitalization

	Sample #1			Sample #2			Sample #3			Sample #4		
Foal	Time (hr)	Lidocaine (µg/mL)	MEGX (µg/mL)	Time (hr)	Lidocaine (µg/mL)	MEGX (µg/mL)	Time (hr)	Lidocaine (µg/mL)	MEGX (µg/mL)	Time (hr)	Lidocaine (µg/mL)	MEGX (µg/mL)
#1	0.30	0.523	0.139	4.50	0.455	0.261	18.50	0.867	0.573	38.00	0.478	0.285
#2	0.50	0.284	0.090	6.50	0.538	0.385	17.50	0.761	0.620	42.00	0.301	0.411
#3	0.50	0.379	0.244	4.75	0.599	0.476	19.00	0.671	0.524	43.50	0.768	0.547
#4	0.25	0.180	0.032	5.50	0.602	0.787	15.50	0.456	0.629	43.75	0.745	0.857
#5	0.25	0.270	0.049	4.25	0.586	0.317	15.75	0.417	0.256	38.75	0.725	0.239
#6	0.30	0.365	0.054	9.00	0.865	0.541	23.25	1.160	1.130	42.00	1.450	1.560
#7	0.30	0.144	0.061	5.50	0.481	0.562	17.75	0.597	1.180	42.00	0.558	1.140
#8	0.60	8.430	0.215	5.00	0.958	0.582	22.00	1.080	0.504	45.50	3.130	0.449

Figure 4-3 Plasma lidocaine concentrations in 8 unhealthy foals administered a CRI (1.3 mg/kg followed by 50 µg/kg/min) of lidocaine during hospitalization

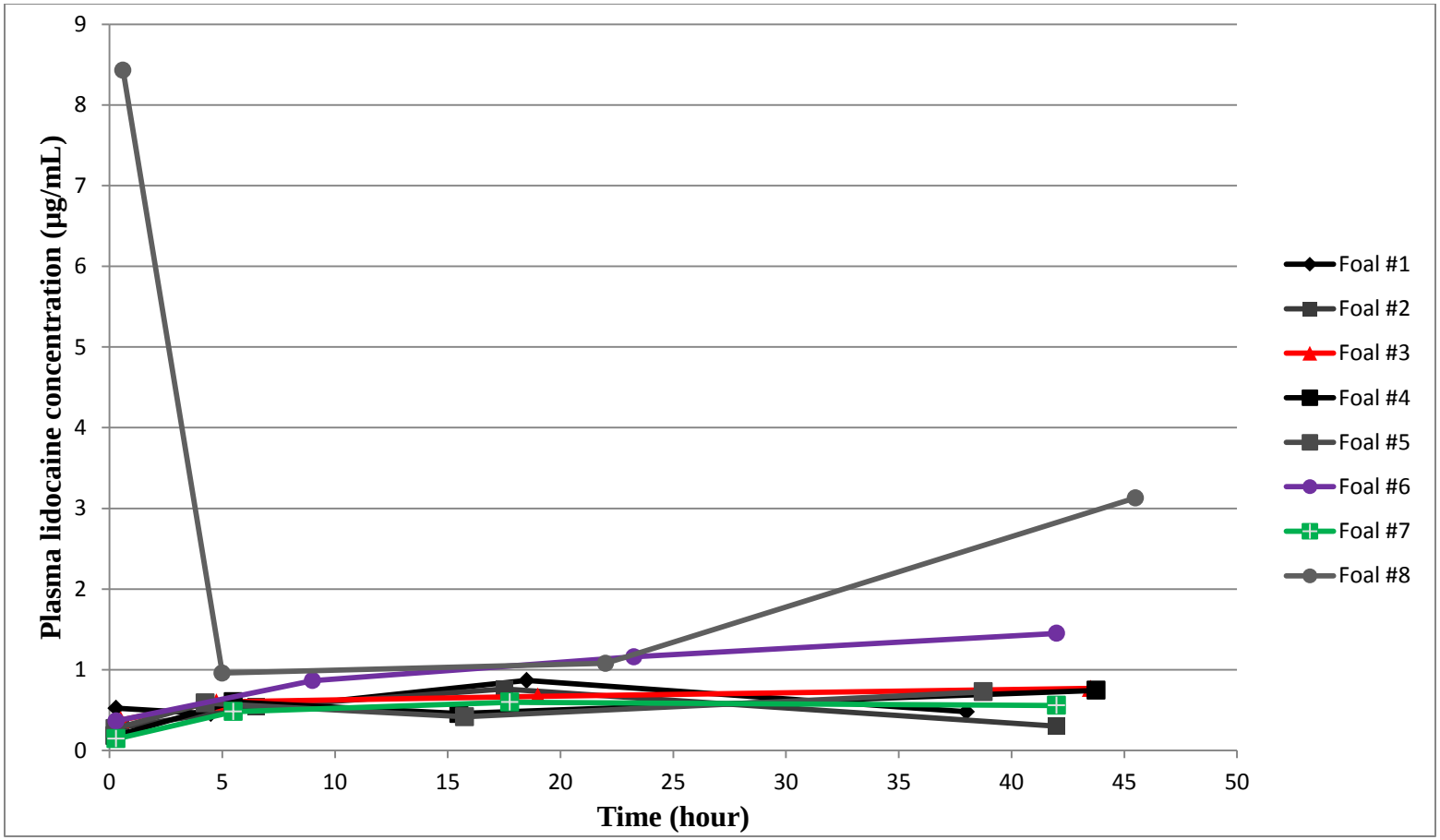
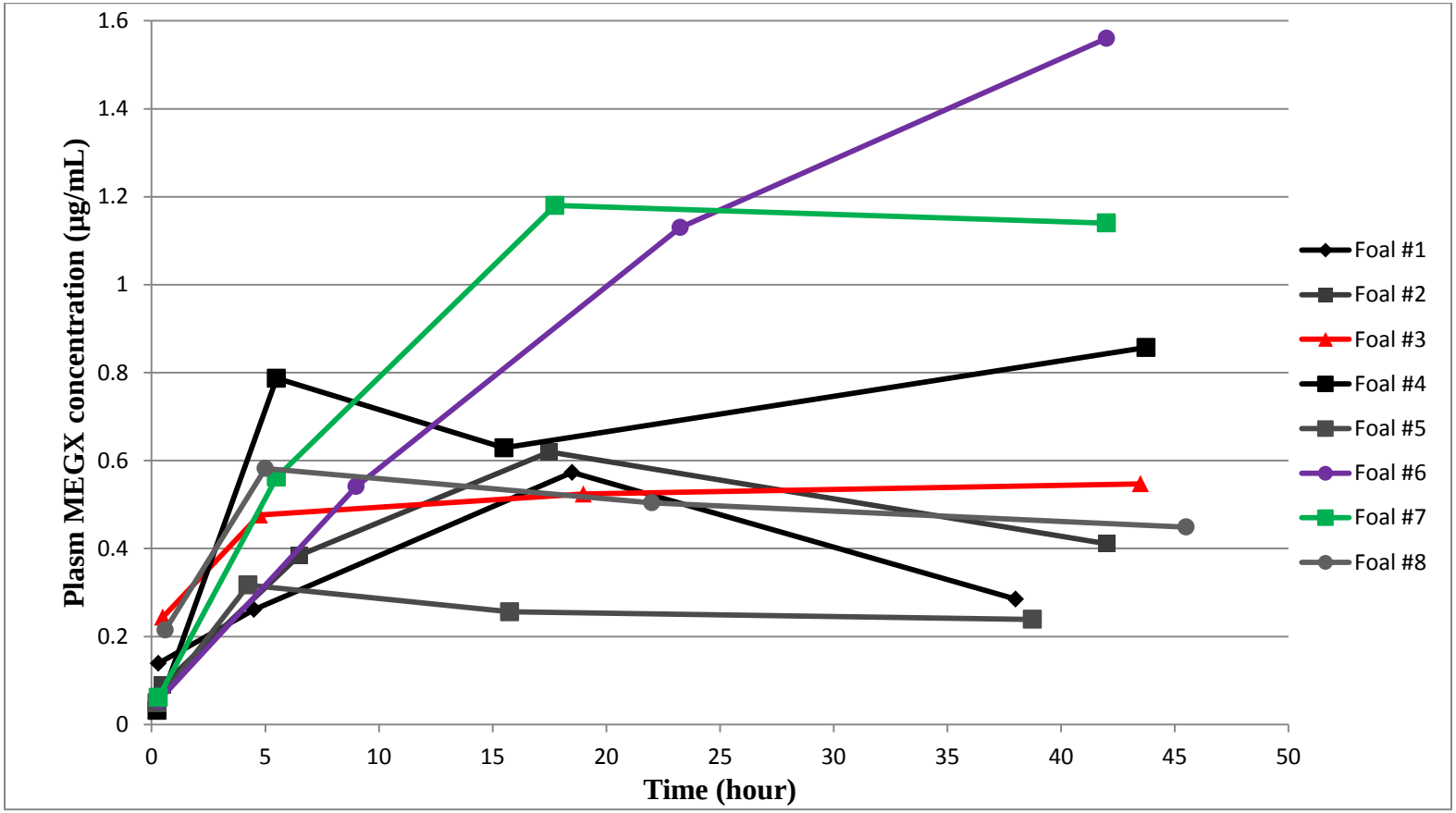


Figure 4-4 Plasma MEGX concentrations in 8 unhealthy foal administered a CRI (1.3 mg/kg followed by 50 µg/kg/min) of lidocaine during hospitalization



Chapter 5 - Discussion

In the clinical setting, intravenous lidocaine is used in foals for any one of its purported properties. The most common clinical dosage used is a loading dose of 1.3 mg/kg followed by a CRI of 50 µg/kg min. While there are no data on plasma concentrations or pharmacokinetics with the use of this dosage in foals, clinicians commonly use the same adult dosage in younger patients. As this is a logical starting place, lidocaine has a narrow therapeutic index and therefore caution is advised when extrapolating to younger animals.

Despite the narrow therapeutic index, in this study using the adult dosage, no adverse effects were observed in any of the healthy foals and the heart rate and respiratory rates monitored during each sampling in these foals remained within normal limits consistent with previously published data (Meyer *et al.* 2001). Clinical signs of toxicity would not be expected to occur at the plasma concentrations achieved in foals #1-7 (phase II) as they were well below the reported toxic range of 1.85-4.53 µg/mL (Meyer *et al.* 2001). Foal #8 was recumbent with altered mention at presentation and throughout hospitalization, therefore signs of toxicity were difficult to assess due to confounding clinical signs from the foals primary disease. The most likely explanation for the high plasma concentration in this foal was that the bolus was administered over 5 minutes rather than the suggested10-15 minutes. However, this would not explain the increased concentration after the third sample. Therefore, other possible explanations include a dose miscalculation, a malfunctioning infusion pump, altered hemodynamics affecting hepatic blood flow and therefore lidocaine extraction (clearance), protein binding by other concurrent medications, increased vascular permeability or decreased drug clearance despite normal hepatic and renal enzymes (Milligan *et al.* 2006; Riviere and Papich 2009). It is also possible this is an artifact of sampling. For example, if the sample was obtained immediately

after the bolus then the local concentrations within the vasculature and tissues immediately surrounding the infusion may not be representative of systemic plasma concentrations and biased high. Interestingly, the concentration of MEGX in this foal did not appear different from the other clinical foals supporting the fact that further studies evaluating the behavior and effects of lidocaine metabolites are needed.

Variations in dosing and protocols have been suggested in adult horses including halving the lidocaine dosage during general anesthesia to maintain the same plasma concentrations as in conscious horses, not administering a loading dose as steady state is reported to occur within 3 hours, and decreasing the infusion rate after 3-4 hours to decrease the risk for accumulation and toxicity (Brianceau *et al.* 2002; Milligan *et al.* 2006; Dickey *et al.* 2008). While there did not appear to be accumulation of lidocaine or its metabolites in healthy foals or foals that survived to discharge in phase II, the results of this study suggest that further research evaluating accumulation in diseased/compromised foals is needed (**Fig. 4-3**, foals #6 & #8). Evaluating larger populations of hospitalized foals would allow dosage recommendations to be made for foals during anesthesia or during prolonged infusions, however eliminating the loading dose should be considered as this would eliminate concerns for toxicity during rapid administration.

Phase I confirmed that plasma concentrations in healthy foals administered a dose of 1.3 mg/kg followed by 50 µg/kg/min were lower than the targeted adult concentrations of 1-2 µg/mL. Steady state concentrations were also lower than those reported in adult horses (Milligan *et al.* 2006; de Solis and McKenzie 2007; Waxman *et al.* 2012) with the highest plasma concentration achieved during steady state of only 0.785 µg/mL. While different analytical methods were used to determine mean plasma concentrations in healthy adult horses (Milligan *et al.* 2006), the data suggest that mean plasma concentrations in foals may vary by up to 40% from

those reported in adult horses **(Table 5-1)**. However since these were 2 different studies extrapolation between them should be done cautiously.

Table 5-1 Comparison of mean plasma concentrations between healthy adult horses (Milligan *et al.* 2006) and healthy foals 4-10 weeks of age.

	Mean Plasma Concentration (µg/mL) ± SD		
Time (hr)	Adults	Foals	% Difference
0.5	2.25 ± 0.47	0.56 ± 0.06	25%
1	1.50 ± 0.24	0.59 ± 0.08	40%
2	1.70 ± 0.17	0.66 ± 0.06	39%
3	1.72 ± 0.18	0.67 ± 0.06	39%
4	2.45 ± 0.40	0.70 ± 0.08	29%
6	2.30 ± 0.49	0.67 ± 0.10	29%

This table is only to illustrate the reported differences between adults and foals and care should be taken when making direct comparisons as different analytical methods were used.

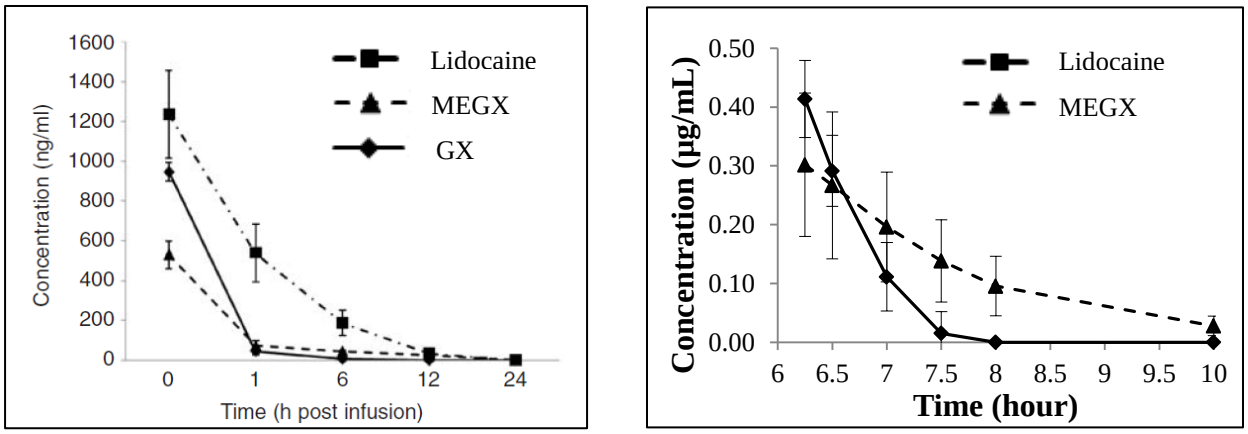
The pharmacokinetic parameters reported in adult horses vary from the findings in healthy foals reported here **(Table 5-2)**. Healthy foals in this study had an increased clearance, decreased C_{max}, shorter $t_{1/2,}$ longer time to peak concentration (T_{max}) and a larger volume of distribution at steady state which would all be expected as younger animals tend to have higher metabolic rates, increased volumes of distribution and lower total protein concentrations. Despite the difference in pharmacokinetic parameters between foals and adult horses, similarities exist in terms of elimination times for lidocaine and MEGX (de Solis and McKenzie 2007; Dickey *et al.* 2008) **(Fig. 5-1)**.

Table 5-2 Pharmacokinetic parameters in foals 4-10 weeks of age compared to adult horses (Feary *et al.* 2005; Feary *et al.* 2006).

		Foals[+]	Adults[a+]	Anesthetized adults[a+]	Anesthetized adults with gastrointestinal disease[b+]
	Units	Mean ± SD[+]	Mean ± SD	Mean ± SD	Mean ± SD
Cl	mL/min/kg	72.2 ± 7.8	29 ± 7.6	15 ± 3.3	25 ± 3
C_{max}	µg/mL	0.79 ± 0.07	2.0 ± 0.27	3.8 ± 0.55	2.3 ± 0.4
$t_{1/2}$	min	26.3 ± 4	79 ± 41	54 ± 14	65 ± 33
$MRT_{0-\infty}$	min	26.0 ± 6.9	28 ± 7.8	27 ± 5.4	27 ± 10
T_{max}	min	72.5 ± 140.8	22 ± 28	23 ± 21	48 ± 44
$V_{d(ss)}$	L/kg	1.8 ± 0.4	0.79 ± 0.16	0.40 ± 0.09	0.70 ± 0.31
$AUC_{0-\infty}$	(µg•min/mL)	259 ± 25	210 ± 52	410 ± 84	184 ± 31

This table is only to illustrate the reported differences between adults and foals and care should be taken when making direct comparisons as different analytical methods were used. [+] Non compartmental analysis, [a](Feary *et al.* 2005), [b](Feary *et al.* 2006) 75-105 min infusion; horses also received other treatments. Cl= clearance, C_{max}= peak concentration of the drug, $t_{1/2=}$ terminal half-life, MRT_{∞}= mean residence time, T_{max}= time to peak concentration, $V_{d(ss)}$= apparent volume of distribution at steady state, AUC= area under the curve

Figure 5-1 Mean ± SD concentrations of lidocaine and its metabolites GX and MEGX over time following discontinuation of a lidocaine CRI in adults (left) and foals (right) (Dickey *et al.* 2008).



This material is reproduced with permission of John Wiley and Sons, Inc. Left values reported in ng/mL; right values reported in µg/mL.

In this study, the primary lidocaine metabolites, MEGX and GX, were present in healthy and unhealthy foals, however only MEGX was quantified as a reference standard for GX was unavailable at the time of analysis. A review of the literature suggests that lidocaine metabolites are inconsistently present in horses following lidocaine administration. The metabolites MEGX and GX have been detected in the plasma of adult horses administered lidocaine for acute onset abdominal pain (mean ± SD peak MEGX: 1.379 µg/mL ± 0.896; mean ± SD peak GX: 1.166 ± 0.900 µg/mL) (de Solis and McKenzie 2007) and in the serum of healthy horses administered prolonged infusions (mean ± SD peak MEGX: 0.529 µg/mL ± 0.063; mean ± SD peak GX: 1.234 µg/mL ± 0.221) (Dickey *et al.* 2008). The metabolites MEGX, GX, 3-HO-LID, and 4-HO-LID have also been detected in the urine and plasma of a healthy adult Thoroughbred and 3-HO-LID in the urine of Thoroughbred mares as an indicator of illegal lidocaine use in racehorses (Nelis *et al.* 2010).

Limitations to phase II of this study include a small sample size with a relatively wide age and weight range, a variety of different concurrent treatments administered and multiple clinical diseases in the foals included. Ideally, a larger number of hospitalized foals would have been included to determine clinical significance in this population as well as pharmacokinetic determination by including samples during the elimination phase. The other major limitation during phase II was the inability to accurately weigh all but one of the foals. While the accurateness of the clinicians' visual assessment and weight tape measurement in this population has not been determined, the clinician is confident from previous experience that her estimations were reasonably close to the true weight of each foal. The plasma concentrations were within a similar range as healthy foals which may also suggest the weights were reasonably accurate, however it is also possible that true PK differences were present but not detected due to inaccurate weights.

In conclusion, the data obtained from these investigations suggest that lidocaine can be safely administered to healthy foals and the majority of hospitalized foals had plasma lidocaine concentrations within normal ranges with no adverse effects observed. One of the hospitalized foals, however, did have much higher than expected lidocaine concentrations. Therefore, further studies in larger populations are needed to assess if this is a true finding or an artifact of the study design and methodology as well as further characterize the disposition of lidocaine and its metabolites in clinical patients to determine if a dose adjustment is necessary. In the meantime, evaluating each patient on an individual basis, especially in terms of the hemodynamic status and hepatic and renal function, in conjunction with the results of this report and monitoring for adverse effects should help guide practitioners in their usage of intravenous lidocaine in foals.

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