ORIGINAL RESEARCH

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Serum Concentrations of Lidocaine and Its Metabolites MEGX and GX During and After Prolonged Intravenous Infusion of Lidocaine in Horses after Colic Surgery

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ABSTRACT

Lidocaine is the most commonly used prokinetic after gastrointestinal surgery in horses. Cardiovascular status, hepatic function, and duration of therapy are the primary determinants of lidocaine metabolism, and these factors could affect equine patients after colic surgery. This study examined the systemic concentrations of lidocaine and its active metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX), in horses that had undergone colic surgery and subsequently received prolonged postoperative lidocaine infusions. The mean lidocaine concentration increased over the course of treatment but did not exceed the therapeutic range. Concentrations of MEGX and GX increased progressively, and concentrations exceeding 1,000 ng/ml were observed frequently after 72 hours of infusion. None of the horses in the study developed severe signs of toxicity; however, the progressively increasing concentrations of lidocaine, MEGX, and GX are cause for concern in clinically ill patients receiving prolonged lidocaine therapy. The potential contribution of MEGX and GX should be considered when evaluating adverse reactions to prolonged lidocaine infusions.

Keywords: Horse; Intravenous lidocaine; Postoperative colic; Metabolites; Prolonged infusion

INTRODUCTION

Lidocaine is the most common prokinetic drug and the first-choice prokinetic strategy after equine gastrointestinal surgery.[1] Lidocaine is a sodium-channel blocker with a number of properties that favor its use in horses with acute abdomen. The mechanism by which lidocaine reduces ileus and pain is not fully understood, however. Several different properties of lidocaine may play a role, because lidocaine is an anesthetic-sparing drug[2,3] and has analgesic[4-6] and prokinetic properties.[7-11] Lidocaine also is an antioxidant and inflammation modulator, potentially useful in preventing ischemia reperfusion injury.[12] Metabolism of lidocaine occurs mainly by phase I oxidative reactions (dealkylation, hydrolysis, and hydroxylation) by microsomal mixed function oxidases in the liver. Its two major metabolites are monoethylglycinexylidide (MEGX) and glycinexylidide (GX).[13] Cardiovascular status, hepatic function, and duration of therapy are the three main determinants influencing lidocaine metabolism.[14-18] All of these factors may potentially affect an equine patient receiving lidocaine therapy after colic surgery. Other factors reported to affect lidocaine metabolism in other species are dosage, age, renal disease, elevated plasma concentrations of MEGX, and the presence of other drugs, such as cimetidine, erythromycin, and omeprazole.[13,19-25]

Lidocaine infusion is commonly administered to equine patients until the clinical signs of ileus or pain are resolved. However, in initial reports on the use of lidocaine as a prokinetic, both in humans and in horses, the infusion was initiated intraoperatively and continued for only 24 hours postoperatively.[9,11] A recent publication suggests that prolonged infusions of lidocaine are probably not necessary and should be avoided.[8] In other species, prolonged intravenous infusion is associated with variable and unpredictable serum concentrations of lidocaine.[14,15,17,26,27] Although lidocaine administration for up to 96 hours has been reported in normal horses without adverse effects,[28] no studies have investigated the safety of prolonging intravenous infusions of lidocaine beyond 24 hours or the effects of the duration of therapy on the disposition of the drug in clinically ill horses.

High plasma concentrations of lidocaine in horses can result in toxicity affecting the central nervous system (CNS) as well as the cardiovascular and musculoskeletal systems. Nerve conduction in horses has been suggested to be more sensitive to sodium-channel blockade; therefore, toxic side effects develop at concentrations well tolerated by other species.[6,18,28] Signs of toxicity reported in horses include alteration in visual function, rapid and intermittent eye blinking, attempts to inspect objects closely, anxiety, mild sedation, ataxia, collapse, seizures, and death.[28,29]

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Other side effects reported in horses are delayed detection of laminitis pain, potentially increased incisional infection rates, and lower quality of anesthetic recovery after intraoperative infusion.[9,29] Altered patterns of lidocaine metabolism have been found in human patients showing signs of CNS toxicity, and adverse reactions have been attributed in some cases to accumulation of lidocaine and in other cases to accumulation of its metabolites MEGX and GX.[30]

To study the concentrations of lidocaine and its two main metabolites, MEGX and GX, in horses receiving prolonged intravenous infusion after gastrointestinal surgery, we performed a prospective study measuring the serum concentrations of lidocaine, MEGX, and GX in a group of horses after colic surgery that were receiving the standard prokinetic dose of lidocaine for 48 hours or longer. We hypothesized that lidocaine, MEGX, and GX would accumulate during prolonged intravenous infusions.

METHODS

Study Population

The study included 10 adult horses (mean age, 11.4 years; range, 2–23 years) presenting with acute onset of abdominal pain to the Marion duPont Scott Equine Medical Center during 2004 and 2005 that underwent exploratory laparotomy and to which lidocaine was given as part of the postoperative treatment for 48 hours or longer (Table 1). Horses were weighed at presentation to the hospital, with a mean weight of 547.6 kg (range, 463–625 kg). Preoperative and postoperative therapy followed normal hospital protocol and included intravenous administration of crystalloid solutions, ampicillin (20 mg/kg intravenously 3 times daily), gentamicin (6.6 mg/kg intravenously once per day), and flunixin meglumine (0.9–1.1 mg/kg intravenously twice per day) in all horses. Other treatments used as prescribed by the attending clinician included enrofloxacin (5 mg/kg intravenously once per day), metronidazole (15 mg/kg orally 3 times daily or per rectum), chloramphenicol (50 mg/kg orally 4 times daily), bethanecol (0.025 mg/kg subcutaneously 4 times daily), metoclopramide (0.04 mg/kg/hour constant rate infusion), 10% dimethylsulfoxide (DMSO) (100 ml diluted in 1l 0.9% NaCl per horse intravenously twice daily for 5 doses), 50% dextrose solution, partial parenteral nutrition, omeprazole (4 mg/kg orally once per day), sucralfate, DTO smectite (Biosponge; Platinum Performance, Buellton, CA), *Saccharomyces boulardii,* polymyxin B (3×10^6 units in 5% dextrose per horse every 8 hours for three doses). Horses experiencing postoperative pain were treated with either detomidine (10 mg intravenously once) or butorphanol (10 mg intravenously once). One horse received butorphanol as a CRI at a dose of 17 μg/kg/hour (30 mg in 500 ml 0.9% NaCl at 166 ml/hour for 24 hours) to treat persistent abdominal discomfort.[31]

During surgery, 8 of 10 horses received a loading dose (0.8–1.3 mg/kg intravenously) of lidocaine hydrochloride followed by a CRI of 50 μg/kg/minute. Two horses did not receive lidocaine during surgery. The infusion was stopped during the anesthetic recovery period. Serum concentration of lidocaine was measured before initiation of the infusion after surgery. After return to the stall, the horses received a second loading dose (1.3 mg/kg intravenously over 15 minutes) followed by a 50 μg/kg/minute intravenous CRI for the period the clinician considered appropriate, ranging between 62 and 168 hours. Lidocaine was given by an infusion pump as a 0.33% solution in lactated Ringer's solution (Veterinary LRS, Abbot Labs, Inc., North Chicago, IL) (10 g 2% lidocaine hydrochloride solution [Hospira, Inc., Lake Forest, IL] in 3 liters lactated Ringer's solution). Fluid rates were adjusted individually to meet the dosage requirements for loading and CRI lidocaine based on the body weight of each patient.

Venous blood samples were collected before and after administration of the postanesthetic bolus, and at 1, 3, 6, 12, and 24 hours and every 24 hours after initiation of the CRI, at the end of the infusion, and 1, 3, 6, 12, and 24 hours after discontinuing the infusion of lidocaine. Blood was collected by venipuncture from the facial sinus in 5 of 10 horses and from the intravenous catheter placed in the jugular vein in 6 of 10 horses (one horse had 11 samples drawn from the catheter and 2 from the facial sinus). If the blood was drawn from the intravenous catheter, the intravenous infusions were stopped, the catheter flushed with 20 ml heparinized 0.9% sodium chloride, 20 ml drawn and discarded, and other 20 ml collected and used as the sample to be analyzed. The blood was collected into non-anticoagulated vacuum tubes, centrifuged at 3000 rpm for 10 minutes, and the serum separated and frozen at –80°C until shipped on dry ice to the University of Tennessee, College of Veterinary Medicine Pharmacology Laboratory (2407 River Drive, Room A305, Knoxville, TN 37996) for analysis. Lidocaine and metabolites (MEGX and GX) analysis was performed using a previously described high-performance liquid chromatography (HPLC) method.[2] The lower limit of detection for the lidocaine, MEGX, and GX assays is 50 ng/ml.

Vital signs and other parameters of the general physical examination were recorded as part of the routine postoperative care. This information was not analyzed statistically but rather provided information regarding possible adverse reactions to lidocaine infusion. In addition, any overt adverse reactions were recorded by the attending nursing technician or clinician when noted. The study protocol was approved by the Virginia Polytechnic and State University Animal Care and Use Committee.

Statistical Analysis

Statistical comparisons were made using the nonparametric Mann-Whitney *U* test (Minitab 13; Minitab, Inc., State College, PA), and graphs were made using Statistica 6.0 (StatSoft, Inc., Tulsa, OK). Systat 11.0 (Systat Inc., Richmond, CA) was used to fit the terminal concentrations (Y) to the decay equation $Y=ke^{-\lambda(time)}$, and the half-life ($t_{1/2}$) was estimated from the slope, λ, using $t_{1/2} = 0.693/\lambda$.