Pharmacokinetics of an intravenous constant rate infusion of a morphine-lidocaine-ketamine combination in Holstein calves undergoing umbilical herniorrhaphy

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OBJECTIVE
To describe the pharmacokinetics of morphine, lidocaine, and ketamine associated with IV administration of a constant rate infusion (CRI) of a morphine-lidocaine-ketamine (MLK) combination to calves undergoing umbilical herniorrhaphy.

ANIMALS
20 weaned Holstein calves with umbilical hernias.

PROCEDURES
Calves were randomly assigned to receive a CRI of an MLK solution (0.11 mL/kg/h; morphine, 4.8 μg/kg/h; lidocaine, 2.1 mg/kg/h; and ketamine, 0.42 mg/kg/h) for 24 hours (MLK group) or 2 doses of flunixin meglumine (1.1 mg/kg, IV, q 24 h) and a CRI of saline (0.9% NaCl) solution (0.11 mL/kg/h) for 24 hours (control group). For all calves, the CRI was begun after anesthesia induction. Blood samples were obtained immediately before and at predetermined times for 120 hours after initiation of the assigned treatment. Noncompartmental analysis was used to estimate pharmacokinetic parameters for the MLK group.

RESULTS
During the CRI, steady-state serum concentrations were achieved for lidocaine and ketamine, but not morphine. Mean terminal half-life was 4.1, 0.98, and 1.55 hours and area under the concentration-time curve was 41, 14,494, and 7,426 h•μg/mL for morphine, lidocaine, and ketamine, respectively. After the CRI, the mean serum drug concentration at steady state was 6.3, 616.7, and 328 ng/mL for morphine, lidocaine, and ketamine, respectively.

CONCLUSIONS AND CLINICAL RELEVANCE
During the CRI of the MLK solution, steady-state serum concentrations were achieved for lidocaine and ketamine, but not morphine, likely owing to the fairly long half-life of morphine. Kinetic analyses of MLK infusions in cattle are necessary to establish optimal dosing protocols. (*Am J Vet Res* 2020;81:17–24)

ABBREVIATIONS

$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 to ∞
AUC_{0-last}	Area under the concentration-time curve from time 0 to the last measurable concentration
$AUC_{\%extrap}$	Area under the concentration-time curve from the last measured time extrapolated to infinity and expressed as a percentage of the total area under the concentration-time curve
$AUMC_{0-\infty}$	Area under the first moment curve from time 0 to ∞
Cl	Clearance
C_{last}	Last analytically quantifiable plasma or serum concentration
C_{max}	Maximum serum or plasma concentration
CRI	Constant rate infusion
C_{ss}	Concentration at steady state
CV	Coefficient of variation
HPLC-MS-MS	High-performance liquid chromatography–tandem mass spectrometry
LLOQ	Lower limit of quantification
λ_z	Terminal rate constant
MEGX	Monoethylglycinexylidide (metabolite of lidocaine)
MLK	Morphine-lidocaine-ketamine
$MRT_{0-\infty}$	Mean residence time from time 0 to ∞
SPE	Solid phase extraction
$t_{1/2\lambda}$	Terminal half-life
t_{max}	Time to maximum concentration
Vd_{ss}	Volume of distribution at steady state
Vd_z	Volume of distribution during the terminal phase after IV administration

The use of analgesics in food animals has increased in recent years, in large part owing to a change in the attitudes of the farmers and veterinarians treating the animals and the general public.[1,2] The AVMA recommends that pain control strategies be tailored to individual animals, and this has increasingly become the strategy for practitioners of food animal medicine and surgery.[3] Veterinarians consider abdominal surgery to be one of the most painful surgical conditions of cattle, and almost all veterinarians who perform surgical procedures on cattle administer patients at least 1 dose of an analgesic during the perioperative period in addition to the use of local or regional anes-

thesia.[2,4,5] Analgesic protocols for use in cattle during the perioperative period are limited owing to food safety regulations and sparse research on the topic.[4] To our knowledge, studies to evaluate IV administration of an analgesic or combination of analgesics by CRI for alleviation of postoperative pain in cattle are lacking.

In both veterinary and human medicine, the combination of MLK is used to supplement the effects of general anesthesia and provide intraoperative and postoperative analgesia.[6–8] Lidocaine is an amide-linked local anesthetic that is extensively metabolized in the liver by cytochrome P450 to a number of metabolites including MEGX, 3-hydroxylidocaine, and 4-hydroxylidocaine.[9,10] It is used commonly, either alone or in combination with other drugs, as an IV analgesic in CRIs.[11–14] Ketamine, a dissociative anesthetic that inhibits *N*-methyl-D-aspartate receptors, is also commonly used in CRIs, often with lidocaine and xylazine, in multiple species.[6,11,14–18] Morphine is a pure μ-agonist opioid that is used in combination with other drugs in CRIs to provide analgesia in dogs[11,16,17] and horses.[19] The pharmacokinetics of lidocaine has been reported for adult cows,[20] and the pharmacokinetics of ketamine, both alone and in combination with other drugs, has been reported in cows[21,22] and calves.[23–25] The pharmacokinetics of morphine has not been described for cattle. The purpose of the study that is partially reported here was to describe the pharmacokinetics and analgesic efficacy of morphine, lidocaine, and ketamine associated with IV administration of an MLK solution as a CRI to calves undergoing umbilical herniorrhaphy. This article focuses solely of the pharmacokinetics aspect of the study; the analgesic efficacy of the MLK solution is described in another article.[26]

Materials and Methods

Animals

All study procedures were reviewed and approved by The Ohio State University Clinical Research Advisory Committee and Institutional Animal Care and Use Committee. Owner consent was obtained for each animal prior to its enrollment into the study. Weaned Holstein calves that were admitted to The Ohio State University Veterinary Medical Center for surgical correction of an umbilical hernia were considered for the study. Only calves that were determined to be free of concurrent disease on the basis of results of a physical examination were eligible for study enrollment. All calves were obtained from 1 premises and examined by the same investigator (AKH) at hospital admission. Twenty calves were enrolled in the study.

Study design

The study was a prospective blinded case-control clinical trial. A random number generator was used to assign calves to 1 of 2 treatment groups (MLK and control groups; 10 calves/group). Blood samples were collected for determination of the serum or plasma drug concentrations necessary for pharmacokinetic analyses before and at predetermined times after treatment administration. Personnel responsible for assessing calves for signs of pain following surgery and performing laboratory and pharmacokinetic analyses remained unaware of (ie, were blinded to) the assigned treatment group for all calves throughout the observation period.

MLK group

Calves in the MLK group received a CRI of an MLK solution. The MLK solution consisted of 1,000 mL of a 2% lidocaine solution, 4 g of ketamine (concentration, 100 mg/mL; volume, 40 mL), and 45 mg of morphine (concentration, 15 mg/mL; volume, 3 mL), which resulted in a solution with a lidocaine concentration of 19 mg/mL, ketamine concentration of 3.8 mg/mL, and morphine concentration of 0.04 mg/mL. The MLK solution was administered through a jugular catheter at a rate of 0.11 mL/kg/h; thus, the dose of lidocaine delivered was 2.1 mg/kg/h (35 μg/kg/min), the dose of ketamine delivered was 0.42 mg/kg/h (7 μg/kg/min), and the dose of morphine delivered was 4.8 μg/kg/h (0.08 μg/kg/min). The CRI was begun after anesthesia induction and orotracheal intubation and was continued for 24 hours.

Control group

Calves in the control group received 2 doses of flunixin meglumine (1.1 mg/kg, IV, q 24 h). The first dose was administered 30 minutes before the start of surgery, and the second dose was given 24 hours later. To ensure observers remained blinded to treatment group assignment, calves in the control group received a CRI of sterile saline (0.9% NaCl) solution at the same infusion rate (0.11 mL/kg/h) as the CRI administered to calves in the MLK group. The CRI was begun after anesthesia induction and orotracheal intubation and was continued for 24 hours.

Anesthesia and surgical procedure

For each calf, food but not water was withheld for 12 hours prior to anesthesia induction. On the day of surgery, a physical examination was performed on each calf before anesthesia induction, and the calf's body weight, rectal temperature, heart rate, respiratory rate, mucous membrane color, hydration status, PCV, serum total protein concentration, and hernia size were recorded. A 14-gauge catheter[a] was aseptically placed in each jugular vein; 1 catheter was used for drug and fluid administration, and 1 catheter was used for blood sample collection. Anesthesia was induced with a combination of guaifenesin (50 mg/mL) and ketamine (1 mg/mL), administered IV to effect; the dose of the guaifenesin-ketamine combination administered was recorded. Following orotracheal intubation, anesthesia was maintained with isoflurane, and the CRI of the assigned treatment (MLK or saline

solution) was begun, with the time of CRI initiation recorded in the anesthesia record. Once anesthetized, each calf was positioned in dorsal recumbency, and the ventral aspect of the abdomen was clipped and aseptically prepared for surgery in a routine manner. An open herniorrhaphy was performed, and any abnormal findings were recorded.

Blood sample collection

From each calf, a blood sample (4 mL) was collected from the designated jugular catheter at 0 (prior to anesthesia induction and initiation of CRI; baseline), 1, 2, 4, 8, 12, 18, and 24 hours after initiation of the CRI and at 3, 6, 12, 18, 30, 45, 60, 75, and 90 minutes and 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, and 96 hours after discontinuation of the CRI. At each sample acquisition time, blood was collected into a blood collection tube that contained EDTA as an anticoagulant to obtain plasma and a blood collection tube without any additives to obtain serum. All blood samples were centrifuged, and serum or plasma was harvested, divided into two 1-mL aliquots, placed in cryovials (ie, for each sample acquisition time, 2 serum and 2 plasma aliquots were obtained), and stored at –70°C until analysis.

Serum and plasma drug concentrations

Determination of serum concentrations of morphine, lidocaine, and ketamine—Serum concentrations of lidocaine, morphine, and ketamine and their associated metabolites were determined by use of HPLC-MS-MS performed in accordance with a previously described[23] enzyme hydrolysis and SPE method for bovine plasma. The HPLC-MS-MS system consisted of a pump, autosampler, and column compartment[b] coupled to an ion trap mass spectrometer.[c] To each 0.5 mL of serum was added 0.5 mL of acetate buffer (pH, 4.5) containing 2,000 units of β-glucuronidase (derived from *Helix pomatia*)/mL and 10 µL of an internal standard mixture that contained 6 deuterated compounds. The internal standard for morphine was d_3-morphine. The internal standard for lidocaine was lidocaine-d_{10}. The internal standards for the 3 lidocaine metabolites (3-hydroxylidocaine, 4-hydroxylidocaine, and MEGX) evaluated were d_{10}-3-hydroxylidocaine and d_5-norlidocaine. The internal standard for ketamine was d_4-ketamine, and the internal standard for the 2 ketamine metabolites (norketamine and dehydroketamine) evaluated was d_4-norketamine. The concentration of each compound in the internal standard mixture was 5 ng/µL. The resulting mixture underwent hydrolysis overnight (approx 12 hours), after which 2 mL of 0.1M ammonium acetate buffer (pH, 4.7) was added to the mixture, and the samples were centrifuged at 2,000 × *g* for 20 minutes. The supernatant was applied to a conditioned strong-cation SPE column[d] and washed with buffer and methanol. The compounds of interest were eluted from the SPE column with two 0.75-mL portions of 5% ammonium hydroxide in acetonitrile. The eluate was dried with a stream of nitrogen at 50°C in an evaporator. The dry residue was reconstituted with 100 µL of 25% (vol/vol) acetonitrile in water and vortexed. Fifty microliters of water was added to the reconstituted residue, and the mixture was vortexed again. The mixture was transferred to an autosampler vial fitted with a glass insert. The injection volume was 10 µL. The mobile phase consisted of 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B). The flow rate was 0.25 mL/min. The mobile phase began at 10% B for 1 minute with a linear gradient to 95% B at 9 minutes, which was maintained for 1.5 minutes, and then re-equilibration to 10% B. Separation was achieved with a C18 column[e] maintained at 40°C. Full-scan mass spectrometry of the pseudomolecular ion of each drug or drug metabolite yielded 1 to 6 ions for identification and quantitation. Morphine yielded 6 fragmented ions. Lidocaine, 3-hydroxylidocaine, and 4-hydroxylidocaine each yielded 1 fragmented ion with an m/z of 86, whereas the corresponding d_{10} internal standards (lidocaine-d_{10} and d_{10}-3-hydroxylidocaine) each yielded a fragmented ion with an m/z of 96. Ketamine and its 2 metabolites (norketamine and dehydronorketamine) yielded 2 to 4 fragmented ions for quantitation. Sequences consisting of blank serum samples, calibration spikes, quality control samples, and bovine serum samples were batch processed. For each sample, the processing method automatically identified and integrated each peak and calculated the calibration curve on the basis of a weighted (1/X) linear fit. Concentrations of the parent drugs and their metabolites in study animal serum samples were calculated on the basis of the respective calibration curves by a commercially available software program,[f] and results were viewed with that program.

For all drugs and drug metabolites, the standard curves for bovine serum were linear at concentrations ranging from 0.25 to 2,000 ng/mL, with correlation coefficients > 0.995. The LLOQ was 0.250 ng/mL for morphine, 2.0 ng/mL for lidocaine, 0.125 ng/mL for 3-hydroxylidocaine, 0.125 ng/mL for 4-hyrdroxylidocaine, 1.0 ng/mL for MEGX, 2.0 ng/mL for ketamine, 5.0 ng/mL for norketamine, and 0.250 ng/mL for dehydronorketamine.

Validation methods for the parent drugs (morphine, lidocaine, and ketamine) and their metabolites (3-hydroxylidocaine, 4-hydroxylidocaine, norlidocaine, and norketamine) were chosen by the cooperating analytical chemistry laboratory (Pharmacology Analytical Support Team, Iowa State University Veterinary Diagnostic Laboratory, Ames, Iowa). Accuracy was > 94% and precision was < 20% for all assays. Linearity was assessed by ensuring that the coefficient of determination (R^2) was > 0.98 for all calibrators (C1 through C12). The mean ± SD variation in the slopes of calibration curves was 0.004173 ± 0.000482 (CV, 11.5%) for morphine, 0.010177 ± 0.000790 (CV, 7.3) for lidocaine, 0.01075 ± 0.000573 (CV, 5.6) for 3-hydroxylidocaine, 0.010202 ± 0.001290 (CV, 12.6) for 4-hydroxy lidocaine, 0.000496 ± 0.00005 (CV, 10.1) for norlidocaine, 0.008403 ± 0.000580 (CV, 7.29) for

ketamine, and 0.010726 ± 0.000790 (CV, 7.28) for norketamine. Assay of quality control samples with drug or drug metabolite concentrations of 10 ng/mL and 50 ng/mL, which were analyzed over 5 days (ie, n = 5 samples at each concentration) were deemed acceptable on the basis of Iowa State University analytical laboratory methods (Racing Medication and Testing Consortium). The laboratory did not provide the limit of detection for any of the drug or drug metabolites evaluated in this study. The LLOQs for the compounds of interest were as previously described.

Determination of plasma concentration of flunixin— The plasma flunixin concentration was determined by means of HPLC-MS-MS as described.[27] Briefly, plasma samples were thawed and vortexed to ensure plasma constituents were evenly suspended in the samples. For each sample, a 100-µL aliquot was transferred to a vial along with 400 µL of flunixin D-3 (internal standard; concentration, 50 mg/mL) in acetonitrile with 0.1% formic acid. Standards were prepared by spiking 100-µL aliquots of blank plasma with flunixin to achieve solutions with flunixin concentrations of 0.005, 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1, 2, 5, and 10 µg/mL. Quality control samples were prepared by spiking 100-µL aliquots of blank plasma with flunixin to achieve solutions with flunixin concentrations of 0.03, 0.3 and 3 µg/mL. All test, standard, and quality control samples were vortexed and centrifuged at 2,500 × *g* for 20 minutes. The supernatant was decanted. The samples were dried, reconstituted with 200 µL of 25% acetonitrile in water, vortexed, transferred to an autosampler vial with a glass insert, and centrifuged again at 2,500 × *g* for 20 minutes before being analyzed with HPLC-MS-MS.

The mass spectrometer[g] was coupled to a pump and autosampler.[h] The mobile phase consisted of 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B). The flow rate was 0.5 mL/min. The mobile phase began at 2% B and transitioned along a linear gradient to 80% B at 7.27 minutes and 99% B at 7.37 minutes, and then returned to 2% B at 11 minutes. Separation was achieved with a C18 column.[i] The 3 ions measured for flunixin in negative ion mode had an m/z of 295→251, 210, and 197 at a retention time of 5.60 minutes. The standard curve had a quadratic form in bovine plasma at flunixin concentrations ranging from 0.005 to 10 µg/mL. Test samples with flunixin concentrations > 10 µg/mL were diluted with blank bovine plasma and reanalyzed.

All calibration curves had an $R^2 > 0.99$. Quality control samples passed when calculated levels were within 20% of expected levels. The accuracy and CV for flunixin were 101% and 4.5%, respectively. The LLOQ for flunixin was 0.005 µg/mL, and the limit of detection was 0.003 µg/mL.

Pharmacokinetic analyses

For each calf and drug and drug metabolite measured, the serum concentration over time was plotted. The C_{max} and t_{max} were determined by visual observation of the serum concentration–time curves. For calves in the MLK group, a commercially available computer software program[j] was used to conduct noncompartmental analysis of the serum concentration-versus-time data with the data weighted 1/concentration.[2] The parent drug (function 1) was modeled with each of its metabolites (eg, lidocaine had 3 metabolites designated as functions 2, 3, and 4 and ketamine had 2 metabolites designated as functions 2 and 3) simultaneously and results represented the summation for the parent drug and its metabolites. For the calves in the control group, serum concentration-versus-time data were analyzed from baseline to the last time that the serum flunixin concentration exceeded the LLOQ (0.005 µg/mL).

For the 3 parent drugs in the MLK infusion (morphine, lidocaine, and ketamine) and their metabolites, the λ_z was estimated by linear regression of time versus the logarithmic serum or plasma drug concentration following discontinuation of the CRI; the slope of the linear regression line included a minimum of 3 concentration-time data points. The $t_{1/2\lambda}$ was calculated as $\ln 2/\lambda_z$. The AUC_{0-last} was calculated by the trapezoidal rule, and the $AUC_{0-\infty}$ was calculated as $AUC_{0-last} + C_{last}/\lambda_z$. The $AUC_{\%extrap}$ was recorded for each drug quantitated. The Cl for each parent drug was calculated from the dose administered and the $AUC_{0-\infty}$. The $AUMC_{0-\infty}$ was calculated as the concentration × time. The Vd_z was calculated as the dose administered/λ_z × $AUC_{0-\infty}$, and the V_{ss} was calculated as (dose administered/ AUC_{0-last}) × mean residence time. The $MRT_{0-\infty}$ was estimated as $AUMC_{0-\infty}/AUC_{0-\infty}$. Steady-state serum concentrations of morphine, lidocaine, and ketamine were estimated as the dose rate/Cl.

Results

Calves

The 10 calves assigned to the MLK group included 5 heifers and 5 steers and had a mean ± SD age of 148.8 ± 29.9 days and body weight of 146.2 ± 36.7 kg. The 10 calves assigned to the control group included 8 heifers and 2 steers and had a mean ± SD age of 160.7 ± 27.6 days and body weight of 150.5 ± 35.7 kg.

Pharmacokinetic parameters

The mean serum concentrations of morphine, lidocaine, and ketamine over time were plotted **(Figure 1)**. The pharmacokinetic parameters for morphine **(Table 1)**, lidocaine and its metabolites **(Table 2)**, and ketamine and its metabolites **(Table 3)** were summarized.

For the calves in the MLK group, the mean C_{max} for morphine was 5 ng/mL and the mean t_{max} for morphine was approximately 12 hours after initiation of the CRI. The mean ± SD serum morphine concentration was 2.65 ± 1.8 ng/mL throughout the duration of the 24-hour CRI. Morphine was widely distributed throughout the body with a mean ± SD V_{ss} of 1.25 ±

0.44 L/kg, and Cl was fairly limited (mean ± SD, 0.2 ± 0.13 L/h). The geometric mean $t_{1/2\lambda}$ was 4.1 hours (range, 2.3 to 7.5 hours). The 24-hour CRI was insufficient for morphine to achieve a steady state in some calves.

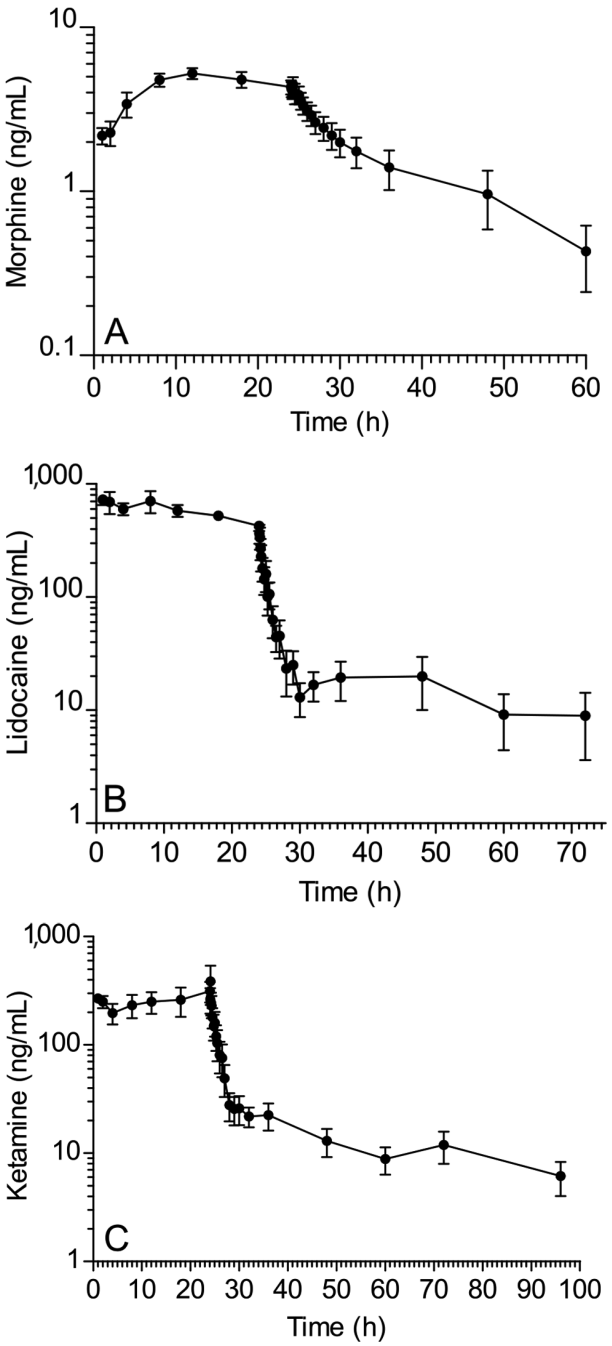

Figure 1—Mean ± SD serum concentrations of morphine (A), lidocaine (B), and ketamine (C) over time for 10 Holstein calves that underwent umbilical herniorrhaphy and received a CRI of an MLK solution for 24 hours beginning immediately after anesthesia induction and orotracheal intubation (MLK group). The MLK solution had a morphine concentration of 0.04 ng/mL, lidocaine concentration of 19 mg/mL, and ketamine concentration of 3.8 mg/mL. It was administered through a jugular catheter at a rate of 0.11 mL/kg/h; thus, the dose of morphine delivered was 4.8 µg/kg/h (0.08 µg/kg/min), the dose of lidocaine delivered was 2.1 mg/kg/h (35 µg/kg/min), and the dose of ketamine delivered was 0.42 mg/kg/h (7 µg/kg/min).

Serum concentrations of lidocaine increased and achieved a steady state rapidly following initiation of the CRI and declined rapidly after the CRI was discontinued (Figure 1). The mean ± SD serum lidocaine concentration was 764 ± 222 ng/mL throughout the duration of the 24-hour CRI. The mean ± SD V_{ss} was 7.8 ± 12 L/kg and Cl was 3.7 ± 1.0 L/h/kg. The geometric mean $t_{1/2\lambda}$ was 0.98 hours (range, 0.64 to 1.5 hours). The mean ± SD C_{max} and t_{max} for MEGX were 75 ± 38 ng/mL and 1.7 ± 0.9 hours, respectively. The serum concentrations of the hydroxylated metabolites of lidocaine (3-hydroxylidocaine and 4-hydroxylidocaine) were much lower and the $t_{1/2\lambda}$ were 2- to 3-fold longer than the corresponding values for lidocaine and MEGX.

Ketamine was similar to lidocaine in that the serum ketamine concentration increased and achieved a steady state rapidly following initiation of the CRI and declined rapidly after the CRI was discontinued (Figure 1). The mean ± SD V_{ss} for ketamine was 14.7 ± 13.0 L/kg, and the Cl was 1.9 ± 1.2 L/h/kg. The geometric mean $t_{1/2\lambda}$ was 1.55 hours (range, 1 to 3.7 hours). The geometric mean $t_{1/2\lambda}$ for norketamine and dehydroketamine were approximately 0.5 to 2 hours longer than the geometric mean $t_{1/2\lambda}$ for ketamine.

The mean ± SD plasma flunixin concentration over time for the calves in the control group was plotted **(Figure 2)**. The mean ± SD C_{max} and t_{max} for the flunixin dosage regimen were 4,664 ± 3,540 ng/mL and 1 hour after administration of the first dose, respectively. The mean plasma flunixin concentration 1 hour after administration of the second dose (and 25 hours after administration of the first dose) was 931 ng/mL, which was greater than that at the preceding observation point but was severalfold lower than the C_{max}.

Table 1—Pharmacokinetic parameters for morphine following administration of a CRI of an MLK solution to 10 Holstein calves that underwent umbilical herniorrhaphy.

Parameter	Value
λ_z (h^{-1})	0.18 (0.09–0.31)*
$t_{1/2\lambda}$ (h)	4.1 (2.3–7.5)*
$AUC_{0-\infty}$ (h•ng/mL)	41 ± 27
$AUC_{\%extrap}$ (%)	12 ± 6
Vd_z (L/kg)	0.99 ± 0.5
Cl (L/h/kg)	0.2 ± 0.13
Vd_{ss} (L/kg)	1.25 ± 0.44
$AUMC_{0-\infty}$ (h•h•ng/mL)	454 ± 399
$MRT_{0-\infty}$ (h)	8.9 ± 4
C_{ss} (ng/mL)	6.3 ± 4

Values represent the mean ± SD unless otherwise indicated. The MLK solution had a morphine concentration of 0.04 ng/mL, lidocaine concentration of 19 mg/mL, and ketamine concentration of 3.8 mg/mL. It was administered through a jugular catheter at a rate of 0.11 mL/kg/h; thus, the dose of morphine delivered was 4.8 µg/kg/h (0.08 µg/kg/min), the dose of lidocaine delivered was 2.1 mg/kg/h (35 µg/kg/min), and the dose of ketamine delivered was 0.42 mg/kg/h (7 µg/kg/min). The CRI was begun immediately after anesthesia induction and orotracheal intubation and was continued for 24 hours. Pharmacokinetic parameters were estimated by noncompartmental analysis.

*Geometric mean (range).

Table 2—Pharmacokinetic parameters for lidocaine and its metabolites following administration of a CRI of an MLK solution to 10 Holstein calves that underwent umbilical herniorrhaphy.

Parameter	Lidocaine	3-Hydroxylidocaine	4-Hydroxylidocaine	MEGX
λ_z (h^{-1})	0.71 (0.45–1.0)*	0.22 (0.07–0.35)*	0.26 (0.06–0.39)*	0.72 (0.32–1.53)*
$t_{1/2\lambda}$ (h)	0.98 (0.64–1.5)*	3.1 (1.96–9.8)*	2.6 (1.8–12)*	0.97 (0.45–2.1)*
t_{last} (h)	73 ± 35	39 ± 8	40 ± 10	45 ± 27
C_{last} (ng/mL)	6.2 ± 4.4	0.5 ± 0.2	0.5 ± 0.37	2.1 ± 0.97
AUC_{last} (h•ng/mL)	14,484 ± 3,289	173 ± 84	113 ± 68	292 ± 105
$AUC_{0-\infty}$ (h•ng/mL)	14,494 ± 3,286	175 ± 85	115 ± 69	295 ± 106
$AUC_{\%extrap}$ (%)	8.1 ± 9.3	1.6 ± 0.95	1.9 ± 1.2	1.2 ± 0.7
Vd_z (L/kg)	5.7 ± 2.7	1.9 ± 1.4	2.2 ± 0.93	0.3 ± 0.18
Cl (L/h/kg)	3.7 ± 1	0.42 ± 0.3	0.58 ± .25	0.2 ± 0.08
Vd_{ss} (L/kg)	7.8 ± 12	1.5 ± 1.75	2.9 ± 2.5	0.93 ± 0.51
$AUMC_{0-\infty}$ (h•h•ng/mL)	211,007 ± 74,695	2,548 ± 1,340	1,861 ± 1,065	3770 ± 3038
$MRT_{0-\infty}$ (h)	2.4 ± 3.5	2.9 ± 2.2	4.7 ± 3	11.7 ± 6.4
C_{ss} (ng/mL)	616.7 ± 191	—	—	—

— = Not calculated. t_{last} = Time to last measurable concentration.
See Table 1 for remainder of key.

Table 3—Pharmacokinetic parameters for ketamine and its metabolites following administration of a CRI of an MLK solution to 10 Holstein calves that underwent umbilical herniorrhaphy.

Parameter	Ketamine	Norketamine	Dehydronorketamine
λ_z (h^{-1})	0.45 (0.19–0.64)*	0.32 (0.2–0.47)*	0.23 (0.15–0.34)*
$t_{1/2\lambda}$ (h)	1.55 (1–3.7)*	2.2 (1.5–3.3)*	3.2 (2–4.6)*
t_{last} (h)	91 ± 23	53 ± 28	72 ± 17
C_{last} (ng/mL)	13.3 ± 14	8.2 ± 3.5	0.4 ± 0.16
$AUC_{0-\infty}$ (h•ng/mL)	7,426 ± 1,050	8,920 ± 3,673	1,462 ± 510
$AUC_{\%extrap}$ (%)	0.46 ± 0.55	0.32 ± 0.13	0.15 ± 0.11
Vd_z (L/kg)	3.9 ± 2	—	—
Cl (L/h/kg)	1.9 ± 1.2	—	—
Vd_{ss} (L/kg)	14.7 ± 13	—	—
$AUMC_{0-\infty}$ (h•h•ng/mL)	156,093 ± 86,269	130,163 ± 68,405	21,520 ± 8,708
$MRT_{0-\infty}$ (h)	9 ± 7.3	2 ± 1.9	3.2 ± 1
C_{ss} (ng/mL)	328 ± 174	—	—

See Tables 1 and 2 for key.

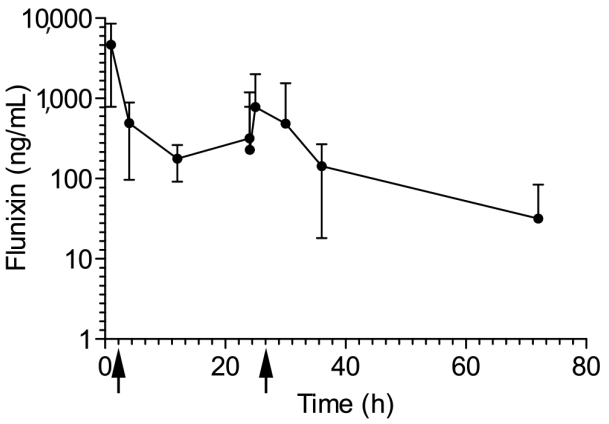

Figure 2—Mean ± SD plasma flunixin concentration over time for 10 Holstein calves that underwent umbilical herniorrhaphy and received 2 doses (arrows) of flunixin meglumine (1.1 mg/kg, IV, q 24 h; control group). The first dose was administered 30 minutes before the start of surgery.

Discussion

In the present study, results of pharmacokinetic analyses revealed that lidocaine and ketamine, but not morphine, achieved steady-state serum concentrations when an MLK solution (morphine concentration, 0.04 ng/mL; lidocaine concentration, 19 mg/mL; and ketamine concentration, 3.8 mg/mL) was administered as a CRI at a rate of 0.11 mL/kg/h to Holstein calves that underwent umbilical herniorrhaphy. The CRI was begun immediately after anesthesia induction and orotracheal intubation and was continued for 24 hours. For most drugs, it generally takes at least 5 half-lives for the drug to reach a steady state. Given that the geometric mean half-life for morphine was 4.1 hours (range, 2.3 to 7.5 hours) for the calves of the present study, it is likely that morphine achieved a steady state in only some of the calves during the 24-hour CRI. However, the half-lives of lidocaine (0.98 hours; range, 0.64 to 1.5 hours) and ketamine (1.55 hours; range, 1.0 to 3.7 hours) were much shorter. Thus, those drugs readily achieved a steady state, and the serum concentrations of those 2 drugs plateaued prior to discontinuation of the 24-hour CRI. These findings suggested that a CRI of MLK can result in drug residues, and we strongly recommend that the Food Animal Residue Avoidance and Depletion Program (United States) or a similar entity (countries other than the United States) be contacted for guidance in establishing an appropriate withdrawal interval when this protocol is used in food animal species.

The MLK solution appeared to provide adequate postoperative analgesia for the calves of the present study. However, because the 3 drugs were administered in combination, we could not determine the contribution of each individual drug to the analgesic state achieved. Future studies should involve a larger number of cattle than evaluated in the present study and assess multiple MLK dosage regimens.

For the calves of the MLK group, the mean ± SD serum morphine concentration was 2.65 ± 1.8 ng/mL throughout the 24-hour infusion period, which is well below the serum morphine concentration range (9.3 to 80 ng/mL) considered therapeutic for human patients.[28] However, the effects of concurrent administration of ketamine and lidocaine on the analgesic efficacy of morphine are unknown. A low dose of morphine was administered to the calves of the present study in an effort to avoid some of its unwanted effects, such as ileus. To our knowledge, the present study was the first to describe the pharmacokinetics of morphine in cattle.

Concentrations of lidocaine and 3 of its metabolites (3-hydroxylidocaine, 4-hydroxylidocaine, and MEGX) were detected in the serum of calves of the MLK group. Monoethylglycinexylidide is an active metabolite of lidocaine, whereas 3-hydroxylidocaine and 4-hydroxylidocaine are inactive metabolites that are believed to have a role in the toxic effects of lidocaine. In another study,[20] MEGX was not detected in the serum of adult cows following a single injection of lidocaine (1.5 mg/kg, IV). Similar to morphine, the mean ± SD serum lidocaine concentration (764 ± 222 ng/mL) for the calves of the MLK group throughout the 24-hour infusion period was well below the serum lidocaine concentration range (1,000 to 5,000 ng/mL) considered therapeutic for human patients.[29]

Concentrations of ketamine and its metabolites norketamine and dehydronorketamine were also detected in the serum of the calves of the MLK group. Ketamine and norketamine bind to μ-opioid and κ-opioid receptors, which produces analgesia.[30] Norketamine is believed to be only one-third as potent as ketamine.[31] The activity of dehydronorketamine is not well understood; nevertheless, it and norketamine are the primary metabolites of ketamine, and it may have a role in the clinical effects of ketamine.[32] The mean serum ketamine concentration achieved for the calves in the MLK group throughout the 24-hour infusion period was consistent with the serum ketamine concentration (40 to 150 ng/mL) considered therapeutic in human patients.[33]

The plasma flunixin concentrations achieved for the calves of the control group were consistent with blood flunixin concentrations reported following IV administration of the drug to cattle of other studies.[34,35]

It is important to note that administration of anesthetics and analgesics by CRI to cattle is often not practical owing to staffing or facility limitations. Animals need to be carefully monitored during CRI of drugs such as morphine, lidocaine, and ketamine because alterations in the infusion flow rate can rapidly lead to toxicosis or death.

Results of the present study indicated that a CRI of MLK provided adequate postoperative analgesia to calves that underwent umbilical herniorrhaphy. The CRI was begun immediately after anesthesia induction and orotracheal intubation and was continued for 24 hours. However, animals must be closely monitored during the CRI, so the described protocol may not be practical in all settings and is most applicable to hospital settings. All calves of the present study were healthy and systemically normal aside from the umbilical hernia. Because drug absorption and metabolism may be altered by disease, further research is necessary before administration of a CRI of MLK can be recommended for analgesia in clinically ill calves. Kinetic analyses of MLK infusions in cattle are also necessary to establish optimal dosing protocols and appropriate withdrawal intervals.

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Footnotes

a. Abbocath-T, Abbott Ireland, Sligo, Ireland.
b. Agilent Technologies, Santa Clara, Calif.
c. LTQ, Thermo Scientific, San Jose, Calif.
d. Strata X-C (100 mg, 3 mL), Phenomenex, Torrance, Calif.
e. ACE 3 C18 (150 mm X 2.1 mm, 3-μm particles), Mac-Mod Analytical, Chadds Ford, Pa.
f. Xcalibur Software, Thermo Scientific, San Jose, Calif.
g. ABSciex, Framingham, Mass.
h. 1260 Infinity pump and autosampler, Agilent Technologies, Santa Clara, Calif.
i. Gemini C18 (50 mm X 2mm, 3-μm particles), Phenomenex, Torrance, Calif.
j. Phoenix WinNonlin, version 6.2, Pharsight-Certara, Cary, NC.

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