Estimations of Milk and Meat Withdrawal Times of Ketamine and Lidocaine in Adult Holstein Cows

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Introduction

Ketamine is a dissociative anesthetic commonly used for short-term and induction of anesthesia in bovine species. Ketamine has recently become popular for use as a constant-rate infusion for continuous pain relief. Lidocaine, a local anesthetic, is frequently used for local infiltration and epidural nerve blocks. Two of the most common local blocks in adult cattle are the inverted-L local infiltration and caudal epidural nerve blocks. These blocks are utilized for numerous standing surgical procedures such as cesarean sections, obstetric manipulations, correction of a displaced abomasum and perineal surgery. These animals may occasionally be sent for slaughter following a surgical procedure, and the Food and Drug Administration (FDA) has a zero-tolerance policy for drug residues in meat and milk. There is limited information and no published data on meat and milk withdrawal times for ketamine anesthesia or lidocaine administration via these two different techniques. The objectives of this study were to investigate the pharmacokinetics of ketamine following administration of a single intravenous dose and lidocaine administered via inverted-L and caudal epidural nerve blocks, and to establish the withdrawal times for meat and milk of these two anesthetics in mature Holstein cows.

Materials and Methods

Ketamine and lidocaine dosing and sample collection

Nine healthy, mature lactating Holstein cows were weighed (mean 1260 ± 156 lb; 573 ± 71 kg) before administration of ketamine and lidocaine. A ketamine dosage of 5 mg/kg was administered via jugular catheter to induce anesthesia. Two different techniques for lidocaine administration were studied: inverted-L local infiltration blocks and caudal epidural nerve blocks. The inverted-L infiltration blocks were performed by using a total volume of 100 ml of 2% lidocaine injected subcutaneously via an18-gauge, 1.5-inch (40 mm) needle. The site of injection was along the caudal border of the last rib and a line ventral to the lumbar transverse processes from the last rib to the fourth lumbar vertebra. The caudal epidural blocks were achieved with 0.22 mg/kg of 2 % lidocaine administered into the neural canal using an 18-gauge, l.5-inch needle placed between the first and second coccygeal vertebre. Treatments were randomly assigned to the cows with a 14-day washout period.

Blood samples were collected via jugular catheter over 24 hours (0, 0.083, 0.166, 0.333, 0.5, 0.667, 0.833, 1, 2, 4, 6, 8, 12 and 24 hours) following drug administration. Blood samples were centrifuged at 39°F (4°C) for 15 minutes; the plasma was extracted then stored at –112°F (–80°C) until analyzed.

Milk was collected by stripping approximately 1-2 mls per quarter and rotating quarters until a total of 10 mls of milk were collected into a collection tube. Milk samples were collected over 60 hours (0.5, 1, 2, 4, 8, 12, 24, 36, 48 and 60 hours) following drug administration and stored at –112°F (–80°C) until analyzed.

Analytical method for ketamine in plasma samples

Two aliquots of plasma samples were mixed with lidocaine hydrochloride (internal standard) and borate buffer (pH 9.0), and samples were extracted with a mixture of isopropanol-chloroform (1:9, v/v). The mixture was vortexed for one minute and centrifuged at 1000 g for 10 minutes at 39°F (4°C). The organic layer was aspirated and dried to a residue. This residue was reconstituted with mobile phase and analyzed with a DIONEX High-Performance Liquid Chromatography (HPLC) system.

The HPLC system included a C-18 reversed phase column and UV detection set at 210 nm. The aqueous portion (65%) of mobile phase consisted of 100 mM monobasic phosphate with 30 mM triethylamine dissolved in distilled water. The organic portion (35%) of the mobile phase consisted of 60% acetonitrile and 40% methanol (v/v). The flow rate was set for one mL per minute. The peak of ketamine was detected at 8.5 minutes, while the peak of lidocaine was detected at 12 minutes.

Analytical method for ketamine in milk samples

The analytical method for determination of ketamine in milk samples was the same method as that for ketamine plasma samples, but milk samples were filtered (pore size: 0.45 mm) before being injected into the HPLC system because of calcium precipitation in the samples. The process of milk samples through the HPLC system was the same as that of the ketamine plasma samples.

Analytical method for lidocaine plasma sample

The analytical method for determination of lidocaine in plasma samples was the same method as that for ketamine plasma samples except this time, ketamine was used as the internal standard. The peak of ketamine was detected at 8.5 minutes, while the peak of lidocaine was detected at 12 minutes.

Analytical method for lidocaine in milk samples

The analytical method for determination of lidocaine in milk samples was the same method as that for lidocaine plasma samples, but milk samples were filtered (pore size 0.45 mm) before being injected into the HPLC system because of calcium precipitation in the samples. The HPLC system used the same condition as plasma samples.

Pharmacokinetic calculations for ketamine

Noncompartmental method was used to estimate the pharmacokinetic values of ketamine from plasma and milk concentrations. Data from six cows was used to calculate the pharmacokinetic parameters. The terminal rate constant beta was determined by linear regression of the natural log (LN) drug concentration versus time from the terminal decline in plasma concentrations. The elimination half-life (*t1/2*) was calculated as 0.693/beta. The area under the drug concentrations versus time curve (AUC) and its first moment (AUMC) were estimated by the linear trapezoidal rule, with the last portion estimated to zero or by using terminal constant rate beta. The total body clearance (CL) was determined by Dose/AUC and the mean residual time (MRT) as AUMC/AUC. The steady-state volume of distribution (Vss) was calculated as Vss=MRT*CL and the volume of distribution based on area (Varea) as Varea=CL/beta. The time to reach peak plasma concentrations (Tmax) and the maximal plasma concentrations (Cmax) were based on observed values. To compare milk concentrations relative to plasma concentrations, the ratios of their AUCs were determined.

Pharmacokinetic calculations for lidocaine

Noncompartmental method was also used to estimate the pharmacokinetic values of lidocaine from plasma and milk concentrations. Data from eight cows were used to calculate the pharmacokinetic parameters. The terminal rate constant beta was determined by linear regression of the LN drug concentration versus time from the terminal decline in plasma concentrations. The estimation for AUC, AUMC, Tmax, Cmax, calculations for *t1/2*, the CL uncorrected for the extent of absorption (CL/F=Dose/AUC), and MRT were similar to those used for ketamine. Since the extent of absorption is not known and the terminal decline in plasma concentrations could be absorption-limited, no volume of distribution parameters were determined. To compare milk concentrations relative to plasma concentrations, the ratios of their AUCs were determined.

Results

Following ketamine administration, plasma Tmax was 0.083 hours and plasma Cmax was 18,135 ng/ml. The mean AUC for plasma was 4484 ±1398 ng/hr/ml. Plasma *t1/2* was 1.80±0.50 hours and MRT was 0.794 ±0.318 hours, with Cl of 1.29 ±0.70 hours. The mean plasma Vss was calculated at 0.99 ±0.53 L/kg, and Varea calculated at 3.23±1.51 L/kg. The last measurable time of ketamine in plasma was detected at 8.0 hours, with a mean concentration of 24.9 ±11.8 ng/ml. Ketamine Tmax in milk was detected at 0.67 ±0.26 hours, with Cmax at 2495±904 ng/ml. Milk AUC last was 6711±2615 ng/hr/ml, with mean AUC milk to AUC plasma ratio of 2.02 ±2.15. The last measurable time that ketamine was detected in milk was 46 ± 4.90 hours, with a mean concentration of 13.35 ±9.98 ng/ml.

Following lidocaine administration for the inverted-L nerve block, mean plasma Tmax was 0.521±0.226 hours and plasma Cmax was 572± 207 ng/ml. The AUC for plasma was 1348±335 ng/hr/ml. Plasma *t1/2* was 4.19 ±1.69 hours and MRT was 5.13±2.33 hours, with clearance uncorrected for the extent of absorption (Cl/F) of 2.75±0.68 hours. The last measurable time of lidocaine in plasma was detected at 8.5±1.4 hours, with a mean concentration of 51 ±30 ng/ml. Milk Tmax was detected at 1.75±0.46 hours with Cmax at 300 ±139 ng/ml. Milk AUC last was 1869 ±459 ng/hr/ml, with mean AUC milk to AUC plasma ratio of 1.439 ±0.37. The last measurable time that lidocaine was detected in milk was 32.5 ±16.2 hours, with a mean concentration of 46±30 ng/ml.

There was no detectable lidocaine concentration in the milk and plasma samples following caudal epidural administration.

Significance

Ketamine administered as a single anesthetic dose of 5 mg/kg was detected in plasma from 0.083 to 8.0 hours and 0.5-50.9 hours in milk. The *t1/2* of ketamine

in plasma was approximately three hours (1.3-2.3 hours, mean 1.80 ±0.50). Calculating for safety, the withdrawal time as 10 times of the *t1/2*, the meat withdrawal time will be recommended as 30 hours or two days. The last detectable ketamine concentration in milk was 51 hours (41.1-50.9 hours, mean 46 ±4.90). Therefore, approximately 72 hours, or a milk withdrawal time of three days, is recommended.

Lidocaine administered for inverted-L nerve blocks using a volume of 100 mls was detected in plasma from 0.083 to 9.9 hours and 0.5 to 48.7 hours in milk. The longest *t1/2* of lidocaine in the plasma was approximately six hours (2.5-5.88 hours, mean 4.19 ±1.69). Calculating for safety, the withdrawal time as 10 times of the *t1/2*, the meat withdrawal time will be recommended as 60 hours or three days. The last detectable lidocaine concentration in milk was 49 hours (16.3-48.7 hours, mean 32.5 ±16.2). Therefore, approximately 72 hours, or a milk withdrawal time of three days, is recommended.

There was no detectible lidocaine concentration in the milk or plasma samples following caudal epidural administration at a dose of 0.22mg/kg. Therefore, this technique may be performed without the potential for meat or milk contamination.

Based on the results of this study, to include any residue left below the detectable tolerance of the assay, the recommendations of meat and milk withdrawal times for ketamine and lidocaine support the zero tolerance for meat and milk residues as regulated by the FDA.

The Efficacy of Meloxicam as an Adjunct Therapy in the Treatment of Neonatal Calf Diarrhea Complex

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Introduction

Neonatal calf diarrhea complex has a significant impact on the dairy industry. The National Animal Health Monitoring System reports that diarrhea accounts for greater than 60% of pre-weaned calf deaths. A recent field study in Europe has identified beneficial effects of Meloxicam therapy in calves with diarrhea. This controlled trial examined the efficacy of Meloxicam administration in combination with oral electrolyte and antibiotic therapy for the treatment of calf diarrhea. Compared to control animals, the Meloxicam-treated calves experienced significant improvements in clinical parameters, such as hydration status, fecal consistency, rectal temperature and signs of visceral pain. Overall, calf recovery from the episode of diarrhea was improved for calves receiving Meloxicam therapy, compared to placebo-treated calves. The objective of the current study was to examine the effects of Meloxicam administration on calf health, behavior and performance in calves with neonatal calf diarrhea complex in Ontario.

Materials and Methods

A double-blind, controlled trial was designed to study Meloxicam administration as an adjunct therapy in the treatment of diarrhea in neonatal dairy calves. Holstein bull calves were purchased at birth from three commercial dairy operations in eastern Ontario and moved to the calf research facility at Kemptville College, University of Guelph. For the duration of the trial, the calves were housed in individual hutches and managed under conditions representative for Ontario. At the onset of diarrhea, the experimental calves were enrolled on the study and randomly assigned to receive a single subcutaneous injection (0.5 mg/kg BW) of