PHARMACOKINETICS OF KETAMINE AND LIDOCAINE IN

SERUM AND MILK OF MATURE HOLSTEIN COWS

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PHARMACOKINETICS OF KETAMINE AND LIDOCAINE IN SERUM AND MILK OF MATURE HOLSTEIN COWS

Glen Sellers

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IN SERUM AND MILK OF MATURE

HOLSTEIN COWS

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Glen Sellers, son of Sam and Dania Sellers, was born January 23, 1976 in Tampa, Florida. He attended Seminole Presbyterian Elementary School and graduated from Jesuit High School in Tampa, June 1994. In September 1994 he entered the Animal and Dairy Sciences program at Auburn University and received a Bachelor of Science degree in 1998. He worked at the Auburn University Horse Teaching Unit and at the Auburn University College of Veterinary Medicine throughout his undergraduate career. He then accepted a position at the Auburn University College of Veterinary Medicine upon completion of his Bachelor's degree. He entered the Graduate program in Biomedical Sciences at Auburn University in the fall of 2002 and married Tonya Michea Andrews in October 2003.

THESIS ABSTRACT

PHARMACOKINETICS OF KETAMINE AND LIDOCAINE

IN SERUM AND MILK OF MATURE

HOLSTEIN COWS

Glen Sellers

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Ketamine and lidocaine are two commonly used anesthetics in veterinary medicine, with some animals occasionally being sent for slaughter following drug administration. The United States Department of Agriculture (USDA) and Food and Drug Administration (FDA) have a stern tolerance policy for drug residues in meat and milk. The objectives of this study were to investigate the pharmacokinetics of ketamine following administration of a single intravenous dose (5 milligrams per kilogram) and lidocaine administered via inverted L (100 milliliters total) and caudal epidural nerve blocks (0.22 milligrams per kilogram) and to utilize the information to recommend and help guide withdrawal times for meat and milk of these two anesthetics in mature Holstein cows.

Ketamine and 2% lidocaine were administered to nine healthy, mature, lactating Holstein cows with a 14 day washout period between the three treatments.

Serum samples were collected over 24 hours and milk samples were collected over 60 hours following drug administration. Samples were analyzed using a High Performance Liquid Chromatographic system and a standard curve linear equation was calculated for both drugs. Statistical analysis and pharmacokinetic parameters of ketamine and lidocaine were calculated using non-compartmental methods.

Ketamine administered intravenously as a single anesthetic dose of 5 milligrams per kilogram was detected from 0.083 to 8.0 hours in serum and from 0.5 to 48 hours in milk. The longest elimination half-life of ketamine in serum was approximately 3 hours (1.41 to 2.78 hours, mean 1.80 ± 0.50 hours). Calculating for safety, the meat withdrawal time is recommended as 30 hours or approximately 2 days. The last detectable ketamine concentration in milk was 48 hours with no residue detected at 60 hours (36 to 48 hours, mean 46 ± 4.90). Therefore, a milk withdrawal time of approximately 72 hours or approximately 3 days is recommended.

Lidocaine administered as an inverted L nerve block using a volume of 100 milliliters was detected in serum from 0.083 to 10 hours and in milk from 0.5 to 48 hours. The longest elimination half-life of lidocaine in the serum was approximately 8 hours (2.1 to 7.26 hours, mean 4.19 ± 1.69). Calculating for safety, the meat withdrawal time is recommended as 80 hours or approximately 4 days. The last detectable lidocaine concentration in milk was 48 hours with no residue detected at 60 hours (8 to 48 hours, mean 32.5 ± 16.2). Therefore, a milk withdrawal time of approximately 72 hours or approximately 3 days is recommended.

There was no detectable lidocaine concentration in the milk or serum samples at any time following caudal epidural administration at a dose of 0.22 milligrams per kilogram. Therefore this anesthetic technique may be performed without the potential for meat or milk contamination.

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Style manual or journal used Journal of American Veterinary Medical Association

Computer software used Microsoft Word

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

I. INTRODUCTION

The dairy industry contributes to the nation's food supply in a number of areas. The most known and recognized area is milk and milk products, yet market dairy cattle and veal calf producers help supply other sectors of the consumer meat market. Milk, usually collected from dairy cattle twice a day and offered to the consumer market daily, poses a unique challenge in the control of drug residues. Milk is not a one-time point of sale commodity like other agricultural products. For example, milk from one drug treated cow can contaminate a whole tank of milk collected over a number of days from a herd. Further and larger volumes of milk may be contaminated if this contaminated milk is mixed with those collected from other herds and sold as grade A milk to the consumer market.

There are a variety of regulatory agencies and laws that monitor and ensure the safety of the nation's food supply. The United States Department of Agriculture (USDA) along with the Food and Drug Administration (FDA) spearhead most of the agencies in cooperation with the Center for Veterinary Medicine (CVM), which is under the FDA, Center for Food Safety and Applied Nutrition (CFSAN), milk safety division, and State Department of Agriculture.[1] These agencies regulate and enact laws and restrictions to monitor and inspect the food supply to maintain a stern tolerance policy for drug residues in meat and milk.

Consumer awareness towards food safety has grown and continues to grow as more consumer health issues enter the media, for example, mad cow disease[2] and avian influenza.[3] It is expected that consumer expectations for safe milk and milk products is even higher since milk is perceived to be wholesome enough to feed our children. Thus, it is the responsibility of the dairy industry, the dairy producers, and the food animal veterinary practitioners to provide safe and residue free milk and meat products to the market.

One of the main challenges to dairy practitioners is the limitations of only five antibiotics, (ceftiofur sodium, neomycin, oxytetracyclin, penicillin G and tilmicosin) a sulfonamide, and five anesthetics (methoxyflurane, proparacaine, thiamyial sodium, magnesium sulfate, and lidocaine with epinephrine) approved by the FDA for administration in dairy cattle with a recognized milk withdrawal time.[4,5] A large number of drugs available for treatment and/or therapy of diseases of dairy cattle are not included in the limited approved drug list. Nevertheless, these unapproved drugs are a practical necessity, and when administered, are referred to as extra-label or off-label drugs, meaning the drug is administered in a manner other than its labeled directions. There are a number of extra-label drugs used in dairy cattle ranging from antibiotics, nonsteroidal anti-inflammatory drugs, sedatives, tranquilizers, analgesics, and general anesthetics. Anesthetics including ketamine, a dissociative anesthetic, and lidocaine, a local anesthetic, are commonly used in these animals for diagnostic and surgical procedures.

Ketamine hydrochloride is a short-acting, non-barbiturate, dissociative anesthetic commonly used alone or in combination with other anesthetics for chemical restraint, short term anesthesia, and pain management in cats, dogs, horses, cattle, small ruminants, humans, and exotic species.[6-8] Ketamine is approved for use in cats and subhuman primates for restraint and as an anesthetic for minor surgical and diagnostic procedures.[7] The use of ketamine in all other species is considered extra-label. In adult cattle ketamine has been used for induction of anesthesia at dosages ranging from 2.2 milligrams per kilogram intravenously, after administration of xylazine (intravenous or intramuscular) for sedation to 2.0 to 5.0 milligrams per kilogram intravenously without sedation.[6,9-12] After induction, anesthesia can be maintained with repeated administration of intravenous ketamine, intravenous infusion of ketamine solution (2-3 milligrams per milliliters), "Bovine Triple Drip" (xylazine 100 milligrams, ketamine 2000 milligrams in 1000 ml of 5% guaifenesin solution), or inhalation anesthetics after intubation.[6,9]

Lidocaine hydrochloride is an amide local anesthetic which is used to produce desensitization and anesthesia to skin, local tissue, and regional neuronal structures.[13,14] Lidocaine is frequently used for local infiltration and epidural nerve blocks in cattle.[13,14] Two of the most common local nerve blocks in adult cattle are the inverted L local infiltration and caudal epidural nerve blocks.[13] These nerve block techniques are utilized for numerous standing surgical procedures such as cesarean sections, obstetric manipulations, correction of a displaced abomasum, and perineal surgery.

After surgical procedures, dairy cattle are often returned to production, but occasionally some of these animals may be sent for slaughter. These anesthetic-treated animals pose a risk to the food supply because of the potential residues which may be present in milk and meat. Because of the USDA's and FDA's stern tolerance policy for drug residues in meat and milk and their policy that some scientific information be available to guide withdrawal recommendations, the dairy industry, the dairy producers, and the food animal veterinary practitioners are left searching for the most updated information available. In regards to ketamine anesthesia, lidocaine administered via inverted L, or caudal epidural nerve blocks, there is limited information and no published data on meat and milk withdrawal times in dairy cattle. The information recommended for ketamine and lidocaine by the Food Animal Residue Avoidance Databank (FARAD), which is supported by the USDA, is based primarily on data collections and recommendations of other countries such as Switzerland and France, and the rapid absorption and metabolism of both drugs.[5] The information listed for ketamine is limited to plasma data in calves, sheep, and swine.[5] The listed information on lidocaine is based on the rapid metabolism of lidocaine after absorption without any specific data in cattle.[5]

The objectives of this study were to investigate the pharmacokinetics of ketamine following administration of a single intravenous dose, lidocaine administered via inverted L and caudal epidural nerve blocks, and to utilize the information to recommend and help guide the withdrawal time guidelines for meat and milk of these two anesthetics in mature Holstein cows.

II. LITERATURE REVIEW

There are a number of agricultural food products and commodities that enter the food chain daily that are considered a one time point of sale item.[4] One time point of sale items enters the food chain as steaks, chops, and other cuts of meat. These items are produced by cattle, swine, poultry and other animal products. They are a one time point of sale since the animal is slaughtered and the product is offered and sold only once. Other agricultural products which are offered into the food chain are products produced by the point of sale animals. These products are usually produced and marketed daily and are not considered point of sale items because they are reproduced daily. Milk, eggs, and cheeses are examples of reproducible products sold to the market.

Milk is a food product produced, collected, pasteurized, and offered to the food market as milk and as milk products, such as cheese and yogurt, on a daily basis. Since it is considered "Mother Nature's perfect food", and used to feed babies, infants and children, it is reasonable for the consumers to have higher expectations for milk and milk products than many other food products.[4]

There are a number of laws, regulations, and a variety of agencies established to protect and ensure a safe food policy in the United States. All grade A milk entering interstate commerce is regulated by the Pasteurized Milk Ordinance (PMO). [1,4,15] The PMO originated in the 1920's and is evaluated and revised every 2 years by the National Conference on Interstate Milk Shipments (NCIMS).[1,15,16] The NCIMS is a cooperative

conference set up between the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM), the Center for Food Safety and Applied Nutrition (CFSAN) Milk Safety Branch, the National Milk Producers Federation (NMPF), and the United States Department of Agriculture (USDA).[1,4] The enforcement of the PMO provisions are the responsibility of a check rating officer sent by the USDA.[1] However, with all the laws, enforcement, and regulations present, the primary responsibility for a residue free milk product lies with the dairymen and food animal practitioners. Therefore, it is essential to provide them with accurate information regarding drug residues in milk and meat.

In the early 1900's, tremetol, a toxin excreted in milk when a lactating animal consumes white snake root, is thought to be the first example of chemical residue affecting humans following milk consumption in the United States.[16] In the 1950's, penicillin was routinely administered to treat mastitis. With the recommended withdrawal times ignored or inadequate duration of sample collection, penicillin was considered a common adulterant causing large economic loss to milk processors of fermented products.[16] Due largely to the 1950 penicillin adulterant "problem", antibiotic testing in milk was recommended at least 4 times every 6 months by the Public Health Service Milk Ordinance in 1965.[16] In the 1980's, the USDA started a residue avoidance program leading to the development of the Food Animal Residue Avoidance Databank (FARAD), which is now one of the most used references for drug residue avoidance in food animals.[5,16] In 1991 the PMO changed to test every tank for β-lactams antibiotics.[1,16]

As of 1997 FARAD or FARAD digest listed only eight tranquilizers and anesthetics approved for use in dairy cattle: methoxyflurane, proparacaine, thiamylal sodium, lidocaine with epinephrine, chloral hydrate, magnesium sulfate, and pentobarbital.[5] These drugs are approved for use by the FDA, however these drugs are no longer used in clinical anesthetic practice because most are no longer marketed.[5,9,17] Therefore, a dairy practitioner must depend on extra label use of tranquilizers and anesthetics to induce local and general anesthesia. Two of the common anesthetic drugs used are ketamine hydrochloride and lidocaine hydrochloride.

Ketamine Hydrochloride

Ketamine is a phencyclidine derivative that produces a dissociative state of anesthesia. "Dissociative anesthesia" is characterized by a dissociation between the thalamo-cortical and limbic system on the electroencephalogram (EEG).[8,17-20] Subjects appear to be in a cataleptic state where the eyes remain open and often with a slow nystagmic gaze. Ketamine is chemically designated [2-(O-chlorophenyl)-2-methylaminocyclohexanonel] and has a molecular weight of 238.[6,18-20] Ketamine is a clear, odorless, and colorless drug which is water soluble and highly lipid soluble with a rapid onset of action. It has a pH of 3.5-5.5 making it mildly irritating to tissues but causes little tissue damage or necrosis.[7,8,18,19] Ketamine exists as two optical isomers in which only a racemic mixture of both isomers is available commercially. When studied separately, the (+) or (S) isomer produced more intense analgesia, longer hypnosis, a rapid metabolism leading to a rapid recovery, and a lower incidence of emergence

reaction than the (-) or (R) isomer.[8,18,21] The extreme lipid solubility of ketamine, which is five to ten times that of thiopental, allows a rapid transfer across the blood-brain barrier with peak plasma concentration occurring within 1 minute following intravenous administration.[6,8,18] This rapid transfer allows for the rapid loss of consciousness and onset of anesthesia. Once in the central nervous system (CNS), the thalamoneocortical projection system appears to be the primary site of action. The EEG evidence shows that ketamine stimulates parts of the limbic system, including the hippocampus, while selectively depressing neuronal function of the neocorticothalamic axis and the central nucleus of the thalamus.[18,22] There are a number of pharmacokintetic studies of ketamine reported in cats, swine, sheep, calves, and horses.[23-27] These studies indicate that ketamine is poorly bound to plasma proteins, which allows the drug to leave the brain quickly and redistributes into other tissues.[8,18,23-28] This redistribution of ketamine to other body tissues, primarily body fat, lung, liver and kidney, attributes to the rapid recovery from anesthesia, usually within 15 to 20 minutes after intravenous administration. However, the elimination half-life of the drug did not occur for at least 60 minutes in cats and calves and 2.3 hours in swine and horses.[23,25-27] The elimination half life is the result of high hepatic clearance rate of 1 liter per minute and large volume of distribution (Vd) of 3 liters per kilogram.[8,21] Ketamine is metabolized extensively by hepatic microsomal enzymes in the dog, horse, and humans.[8,18,26] In rats and cats, ketamine is excreted primarily unchanged via the kidney with very little hepatic metabolism.[6,18] Ketamine has also been reported to be able to cross the placenta rapidly in dogs, goats, and humans.[29,30] Ketamine anesthesia in pregnant goats showed an

increase in fetal blood pressure, heart rate, and arterial oxygen levels.[30] Furthermore, ketamine appeared to have a depressant effect on puppies delivered via cesarean section.[31]

Ketamine has a complex neuropharmacology. It binds to multiple receptor sites including *N*-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors, nicotinic and muscarinic cholinergic receptors, monoaminergic and opioid receptors, as well as interactions with voltage-dependent sodium (Na^{+}) and L-type Calcium (Ca^{++}) channels. The antagonism of NMDA receptors accounts for the majority of the analgesic, amnestic, psychotomimetic, and neuroprotective effects of ketamine. The NMDA receptor is an ionotropic receptor, which is an ion channel with excitatory properties when activated by glutamate, the most abundant excitatory neurotransmitter in the CNS.[8,18,21,32] These ion channels are permeable to Ca^{++}. Ketamine is a noncompetitive antagonist for the Ca^{++} channels of the NMDA receptors and phencyclidine receptor binding site which leads to the inhibition of the NMDA receptor activity.[8,18,21,32]

Ketamine has a number of clinical applications in human and veterinary medicine. It has been used extensively for pain relief in burn patients, anesthesia for aged or critically ill patients, obstetrical anesthesia, outpatient surgery, in conjunction with local and regional anesthesia, and cardiothoracic anesthesia in human medicine.[20,21] However, due to its potential side effects and newer drugs, its use in human medicine is limited today. In veterinary medicine, ketamine has been mainly used for chemical restraint and anesthesia.[6,33] Approved by the FDA for use in cats and primates only, ketamine has been used as an extra label drug in a wide variety of species ranging from

domesticated animals (dogs, horses, goats, pigs, cattle and sheep), to wild mammals, reptiles, and birds. Ketamine was first synthesized in 1963 and was approved for clinical uses in 1970 with high expectations of being an "ideal" intravenous anesthetic agent in clinical anesthesia for both human and veterinary medicine.[6,20] Yet, ketamine's clinical usefulness quickly became limited in humans once its cardiovascular stimulating properties and high incidences of rough and disturbing emergence reactions became apparent. The cardiovascular stimulating properties, such as high blood pressure, tachycardia, and increased cardiac output, are primarily sympathomimetic actions as a result of stimulation of the central sympathetic nervous system.[34,35] The postanesthetic emergence reactions of ketamine are characterized as changes in body image, mood state, out-of-body experiences, floating, vivid dream, illusions, and occasional delirium.[36] The illusions and vivid dreams usually disappear once the patient is awake but reoccur as flashbacks for weeks after ketamine administration in adults and children.[37-39] There is also evidence of post anesthesia emergence reactions in cats following ketamine anesthesia. The form of emergence reaction as indicated by catalepsy is followed by ataxia and increased motor activity.[6] The cats are also hypersensitive to touch with some becoming aggressively violent.[6] Most cats recovered within several hours without further recurrences.[6]

For humans, the FDA and Drug Enforcement Administration (DEA) categorize ketamine as a category III control substance because it is highly addictive and its abuse potential. Despite this, ketamine is widely used in burn units for bandage changes, wound dedridements, and skin grafting procedures in children and adults.[20] It has been

observed that an apparent tolerance to ketamine develops after receiving two exposures to the drug and the dose had to be progressively increased in patients receiving repeated administration.[20] Ketamine has also been successfully used at low doses for outpatient oral surgery procedures in children, with some reports citing significant cardiovascular stimulation, airway obstruction, and minor postanesthetic complications, including illusions and unpleasant dreams.[20,37,40] Side effects, such as illusions, out of body experiences, and potential tolerance build-up, make ketamine a dangerous street drug known as "special k" or "kitkat". The potential risk of ketamine abuse on the streets is the reason for its control drug status as a category III control substance, which makes it illegal to possess on the street.

Despite the dangerous side effects of ketamine, it is still used in human medicine and commonly used in veterinary medicine, especially in combination with other drugs, which helps to minimize some of the potential side effects. In fact, ketamine is one of the only available intravenous agents that can provide unique sedative, amnestic, analgesic, and anesthetic properties in a number of species.[6,18,20,21] Ketamine has been useful for chemical restraint, surgical anesthesia, and pain relief, and management.[6,11,18,32] Ketamine provides a fast onset of anesthesia and loss of consciousness with good analgesic effects which appear greater for somatic pain than for visceral pain.[6,18] The high level of somatic analgesic effects explains its popularity in burn patients and oral surgery in humans. Primarily due to the high lipid solubility and poor protein binding, ketamine is quickly redistributed throughout the body, allowing for a rapid recovery, usually 15-20 minutes.[8,18] This fast onset and rapid recovery from

anesthesia, coupled with its analgesic properties, makes ketamine a very versatile drug that could be used for years.

Lidocaine Hydrochloride

Local anesthetics are commonly used anesthetics by the food animal practitioner due to the concern of cost for surgery and the potential risks associated with general anesthesia. Local anesthetics are drugs that reversibly block the propagation of action potentials along nerve axons. These local anesthetics interrupt impulse transmissions to autonomic, somatic sensory, and somatic motor function producing autonomic nervous system blockage, sensory anesthesia, and skeletal paralysis in the area affected by the nerve.[14,41,42] The primary action of local anesthetics is interference with voltage-gated sodium channels, but this is not the only effect. Local anesthetics are also used for other purposes, for example, lidocaine is used for treatment of cardiac ventricular arrhythmias and pain management via topical application or continuous rate infusion.[14,42]

Cocaine was the first local anesthetic introduced in 1884 by Kollar for use in ophthalmology.[14,42] Procaine, an ester derivative with less addictive and toxic qualities than cocaine, was the first synthetic local anesthetic introduced in 1905 by Einhorn.[14,42] Lidocaine was synthesized in 1943 by Nils Lofgren and Bengt Lundqvist as an amide derivative of diethylaminoacetic acid.[14,42] Unlike procaine, lidocaine produces more rapid, intense, and longer lasting effects which can be administered topically and intravenously.[14,42] Lidocaine, with these effects, became the prototype and standard for the synthesis of other amide-linked local anesthetics.

Local anesthetics prevent the generation of a propagated action potential by inhibiting passage of sodium ions through ion-selected sodium channels in the neuronal tissues.[14,42,43] Failure of the sodium ion channel to increase its permeability slows the rate of depolarization where the threshold potential can not be reached and an action potential will not be initiated.[14,42,43] However, local anesthetics do not directly affect the resting transmembrane potential or the threshold potential.[14]

Absorption and metabolism of local anesthetics depend on the site of injection, dose, use of epinephrine, and pharmacological characteristics of the drug.[42] Amide local anesthetics, such as lidocaine, are metabolized at varying rates by microsomal enzymes in the liver.[14] While in the liver, lidocaine undergoes oxidative dealkylation to monoethyl-glycinexylidide (MEGX) which is then hydrolyzed to xylidide or 2,6-Dimethylaniline (2,6-DMA).[14,44] In humans, approximately 75% of 2,6-DMA is excreted in the urine as 4-hydroxy-2,6-dimethylaniline.[14] 2,6-DMA has been identified as a nasal carcinogen and may also act as a tumor promoter in rats.[44] There is no direct evidence that 2, 6-DMA is a human carcinogen.[44]

Lidocaine has been well documented in rapid placental transfer in pregnant women following intravenous or epidural administration.[45-51] Intravenous lidocaine administered to the mother at a dose of 2 or 3 milligrams per kilogram found lidocaine in the umbilical cord within 2 minutes and measurable quantities remained for 30-45 minutes in the infant.[51] Following epidural administration, lidocaine was absorbed from the site of injection into maternal circulation within 3 to 5 minutes, with peak concentration occurring within 5 minutes and peak fetal lidocaine concentration in 9 and

10 minutes.[47-49] In a study following a standard paracervical block (post-PCB), lidocaine was also associated with a number of cases of fetal bradycardia at peak fetal lidocaine concentration time of 9 to 10 minutes.[49] Yet this high level of lidocaine (2.45 micrograms per milliliter) could not be necessarily associated with the fetal bradycardia since it was also seen with normal concentrations of lidocaine (0.85 micrograms per milliliter).[49] In the neonate, lidocaine was present for at least 48 hours following local infiltration of the perineum.[52] In all cases, studies have shown that the fetus and neonate were able to metabolize lidocaine. The maternal elimination half-life following epidural anesthesia was 113.9 ± 5.6 minutes.[46] The neonate was reported to have a longer elimination half-life based on a 3-day postpartum study which indicated higher levels of lidocaine in the neonatal urinary excretion when compared to the mother.[50] Therefore, caution must be taken against the possible accumulation of lidocaine in the neonate because of immature liver function, as commonly seen in newborns.[53]

Lidocaine has also been reported to be excreted in the milk of breast feeding mothers.[54] In one case, a lactating women was administered 0.8 micrograms per milliliter of lidocaine for treatment of ventricular arrhythmia.[54] Lidocaine in the milk was observed at 40% of the serum level and was present in the milk sample 2 hours after the last treatment.[54] Plasma concentrations of lidocaine have been reported ranging from 1.19 to 3.10 micrograms per milliliter in women receiving epidural lidocaine.[55] In this study the concentration of lidocaine in breast milk is exceedingly small. However, the clinical practitioner should be aware that lidocaine is present and that the infant or neonate will ingest these small amounts. It is noted that the infant or neonate can still

nurse safely since less than 30% of the lidocaine is bio-available after it is ingested.[54,55] Caution should be taken with infants or neonates with poor hepatic function, where lidocaine or its metabolite may accumulate. In healthy infants or neonates, any adverse reaction is usually limited to a mild allergic reaction.[54]

The results of these studies emphasize the importance of determining the pharmacokinetics of lidocaine in dairy cattle following intravenous and epidural administration of lidocaine to prevent potential residue problems and potential health risks to consumers.

III. MATERIALS AND METHODS

Animals

Nine healthy, mature, lactating Holstein cows were randomly selected from the Auburn University Large Animal Clinic dairy teaching herd in Auburn, Alabama. Cows were randomly assigned to each anesthetic treatment and allowed at least a two-week washout period between treatments (Table 1). All cows were weighed before each treatment (mean body weight of 551 ± 77 kilograms) for accurate drug dosing (Table 1). A catheter was placed the night before treatment administration in either the right or left jugular vein, alternating between treatments. A 0.5 milliliter lidocaine bleb was deposited subcutaneously at the catheter site and a stab skin incision was performed prior to placement of a 14-gauge, 140 mm Abbocath®-T Radiopaque FEP intravenous [a] catheter into the selected jugular vein. A 51 cm Baxter extension set [b] and an Arrow Luer-Lock injection plug [c] were attached to the catheter and both were sutured in place and flushed with 10 milliliters of heparinized saline every 3 hours. This study was approved by the Institutional Animal Care and Use Committee of Auburn University (IACUC/PRN # 2002-0172).

Drug Treatments

Two anesthetic drugs, ketamine and lidocaine were studied. Cows receiving ketamine were removed from feed for 24 hours and water for 12 hours before treatments. Ketamine HCl[d] (100 milligrams per milliliter) was administered intravenously at a

dosage of 5 milligrams per kilogram to induce anesthesia. Following administration, cows assumed sternal recumbency and were maintained in that position by the support of hay bales until they regained consciousness and stood. Lidocaine HCl[c] was administered via two different techniques: inverted L local infiltration blocks and caudal epidural nerve blocks. A 2% or 20 milligrams per milliliter veterinary grade solution of lidocaine without epinephrine was administered for both techniques. The inverted L infiltration blocks were established using a total volume of 100 milliliters of lidocaine administered subcutaneously with an 18-gauge, 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 by administering 0.22 milligrams per kilogram of lidocaine into the neural canal using an 18-gauge, 40 mm needle placed between the first and second coccygeal vertebra.

Sample Collection

Blood sample collections for both drugs was accomplished by aspirating 20 milliliters of blood back from the catheter and discarded as that removed the heparinized saline diluted blood in the extension set and catheter, after which 10 milliliters was collected into red top Vacutainer tubes [f] with no additives and cooled in the refrigerator until centrifuged. The catheter was flushed with 10 milliliters of heparinized saline. Blood samples were collected over 24 hours after drug administration. Samples were collected prior to drug administration (time 0) and 0.083, 0.166, 0.333, 0.5, 0.667, 0.833, 1, 2, 4, 6, 8, 12, and 24 hours post treatment. Blood samples time 0, 0.083, 0.166, 0.333,

0.5, 0.667, 0.833 and 1 hour were centrifuged after time 1 hour sample was collected, while samples 2, 4, 6, 8 and 12 hours were centrifuged after the collection of time 12 hour sample, and sample 24 hour was centrifuged immediately after collection. All blood samples were centrifuged for 15 minutes, and the serum was extracted and then stored in a 2 milliliter graduated free-standing screw cap Fisherbrand microcentrifuge tube [g] at –80 degrees centigrade until assayed.

Milk collection was accomplished by cleaning and stripping all 4 teats on the udder. Approximately 1 to 2 milliliters of milk per teat were collected into a Falcon 14 milliliter polystyrene round-bottom collection tube [h]. Milk collection was rotated per teat until a total of 10 to 12 milliliters of milk were collected. Teats were then dipped in a barrier solution for teat protection. Milk samples were collected before each treatment (time 0) and over 60 hours post treatment at 0.5, 1, 2, 4, 8, 12, 24, 36, 48 and 60 hours and stored at -80 degrees centigrade until assayed. All cows were kept on a regular milking schedule being milked twice a day.

Analytical Method for Ketamine Serum Samples

To aliquots of serum samples were added lidocaine HCl as an internal standard and a borate buffer (pH 9.0). Samples were then extracted with a mixture of isopropanol-chloroform (1:9, v/v). The mixture was vortexed for 1 minute and centrifuged at 1000 g for 10 minutes at 4 degrees centigrade using a Fisher Scientific centrifuge Marathon Model 22KBR [g]. 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 nanometers. The HPLC system also included a DIONEX mobile phase gradient pump model GP40, a DIONEX auto sampler model AS 3500 and DIONEX UV absorbance detector model AD 20. 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 milliliter per minute and the injection volume was 25-100 microliters. The peak for ketamine was detected at 8.5 minutes, while the peak for lidocaine was detected at 12 minutes. The standard curve ranged from 7.625 to 305 nanograms per milliliter with a correlation coefficient of 0.9991. The serum and injection volumes were selected based on expected concentrations. The limit of quantiation was 3.05 nanograms per milliliter and the inter- and intra-day variation was less than 12%.

Analytical Method for Ketamine Milk Samples

The analytical method for determination of ketamine in milk samples used the same method as that used for ketamine serum samples, but milk sample extracts were filtered (pore size: 0.45 micrometer) before being injected into the HPLC system because of calcium precipitation in the samples. The process for milk samples by the HPLC method was the same as that of the ketamine serum samples. The standard curve ranged from 7.625 to 305 nanograms per milliliter with a correlation coefficient of

0.9991. The limit of quantiation was 3.05 nanograms per milliliter and the inter- and intra-day variation was less than 12%.

Analytical Method for Lidocaine Serum Samples

To aliquots of lidocaine serum samples were added ketamine as an internal standard and a borate buffer (pH 9.0). The samples were then extracted with a mixture of isopropanol-chloraform (1:9, v/v). Then the mixture was vortexed for 1 minute and centrifuged at 1000 g for 10 minutes at 4 degrees centigrade using a Fisher Scientific centrifuge Marathon Model 22KBR[g]. The organic layer was aspirated and dried down under a gentle stream of air. The residue was reconstituted with mobile phase and analyzed with a DIONEX HPLC system. The HPLC system included a C-18 reversed phase column and UV detection set at 210 nanometers. The HPLC system also included a DIONEX mobile phase gradient pump model GP40, a DIONEX auto sampler model AS 3500 and DIONEX UV absorbance detector model AD 20. The aqueous portion (65%) of the 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% of methanol (v/v). The flow rate was set for 1 milliliter per minute and the injection volume was 25 to 100 microliters. The peak for ketamine was detected at 8.5 minutes, while the peak for lidocaine was detected at 12 minutes. A standard curve linear equation was obtained from 20.4 to 400.8 nanograms per milliliter with a correlation coefficient of 0.9979. The serum and injection volumes were selected based on expected concentrations. The lower limit of quantiation was

10.02 nanograms per milliliter and the variation, both inter- and intra-day was less than 10%.

Analytical Method for Lidocaine Milk Samples

The analytical method for lidocaine milk samples was the same method as serum samples. However, the milk sample extracts were filtered (pore size: 0.45 micrometer) before being injected into HPLC system due to the calcium precipitates. The HPLC conditions were the same as for the serum samples. The standard curve in milk ranged from 10.02 to 200.4 nanograms per milliliter with a correlation coefficient of 0.994. The limit of quantiation was 10.02 nanograms per milliliter and variation was less than 13%.

Pharmacokinetic Calculations for Ketamine

A noncompartmental method was used to estimate the pharmacokinetic values of ketamine from serum and milk concentrations.[56] Data from six cows was used to calculate the pharmacokinetic parameters. Three cows were excluded from the pharmacokinetic analysis due to extremely high initial levels, secondary peaks, or curving or flattening in terminal phase. These observations could be due to sample time errors, assay errors, or physiological changes in animals during anesthesia. The terminal rate constant beta was determined by linear regression of the natural log (LN) drug concentration versus time from the terminal decline in serum concentrations. The elimination half-life ($t_{½\beta}$) 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 residence 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 serum concentrations (Tmax) and the maximal serum concentrations (Cmax) were based on observed values. To compare milk concentrations relative to serum concentrations, the ratios of their AUCs were determined.

Pharmacokinetic Calculations for Lidocaine

A noncompartmental method was also used to estimate the pharmacokinetic values of lidocaine from serum and milk concentrations.[56] The data from eight cows was used to calculate the pharmacokinetic parameters. One cow was excluded from the pharmacokinetic analysis since measurable serum concentrations were only noted for up to 1 hour. The terminal rate constant beta was determined by linear regression of the LN drug concentration versus time from the terminal decline in serum concentrations. The AUC and its AUMC were estimated by the linear trapezoidal rule with the last portion estimated to zero or by using terminal rate constant beta. The CL was determined by Dose/AUC and the MRT as AUMC/AUC. Since the extent of absorption is not known and the terminal decline in serum concentrations could be absorption limited, no volume of distribution parameters were determined. To compare milk concentrations relative to serum concentrations, the ratios of their AUCs were determined.

IV. RESULTS

Ketamine

Following ketamine administration, serum Tmax was 0.083 hours and serum Cmax was 18,135 nanograms per milliliter (Table 2 and Figure 1). The mean AUC for serum was 4484 ± 1398 nanograms per hour per milliliter (Table 3). The serum elimination half-life was 1.80 ± 0.50 hours and MRT was 0.794 ± 0.318 hours with CL of 1.29 ± 0.70 liters per kilogram per hour (Table 3). The mean serum Vss was calculated as 0.990 ± 0.530 liters per kilogram and Varea was calculated as 3.23 ± 1.51 liters per kilogram (Table 3). The last measurable time for ketamine in serum was noted at 8.0 hours with a mean concentration of 24.9 ± 11.8 nanograms per milliliter (Table 2 and Figure 1). Ketamine Tmax in milk was detected at 0.67 ± 0.26 hours with Cmax at 2495 ± 904 nanograms per milliliter (Tables 4, 5 and Figure 2). Milk AUC last was 6711 ± 2615 nanograms per hour per milliliter with mean AUC milk to AUC serum ratio of 2.02 ± 2.15 (Table 5). Cow 7 displayed very high ketamine milk concentrations compared to the other cows. Excluding cow 7, the milk AUC/serum AUC was 1.14 ± 0.14. The last measurable time that ketamine was detected in milk was 46 ± 4.90 hours with a mean concentration of 13.35 ± 9.98 nanograms per milliliter (Table 5 and Figure 2).

Lidocaine

Following lidocaine administration for the inverted L nerve block, mean serum Tmax was 0.521 ± 0.226 hours and serum Cmax was 572 ± 207 nanograms per milliliter (Tables 6, 7 and Figure 3). The AUC for serum was 1348 ± 335 nanograms per hour per milliliter (Table 7 and Figure 3). The apparent serum elimination half-life 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 liters per kilogram per hour (Table 7). The last measurable time of lidocaine in serum was detected at 8.5 ± 1.4 hours with a mean concentration of 51 ± 30 nanograms per milliliter (Tables 6, 7 and Figure 3). Milk Tmax was detected at 1.75 ± 0.46 hours with Cmax at 300 ± 139 nanograms per milliliter (Tables 8, 9 and Figure 4). Milk AUC last was 1869 ± 459 (AUC to 60 hrs) nanograms per hour per milliliter with the mean AUC milk to AUC serum ratio of 1.439 ± 0.374 (Table 9 and Figure 4). The last measurable time that lidocaine was detected in milk was 32.5 ± 16.2 hours with a mean concentration of 46 ± 30 nanograms per milliliter (Tables 8, 9 and Figure 4).

There was no detectable lidocaine concentration in the milk and serum samples at any time following caudal epidural administration.

V. DISCUSSION

Dairy cattle and calves supply a number of sectors in the consumer market. The most recognized sectors being meat and milk. Milk sold on a daily basis is consumed by the nations' most precious and vulnerable consumers, children, along with a number of adults. Milk is also processed for use in cheeses, yogurts, and many other food products. Dairy cattle and calves support major sectors of the meat market such as the veal ground beef market. The dairy industry, dairy producers, and food animal practitioners are aware of the potential dangers that drug residues in milk and meat can have on consumer health and the economical impact on the dairy industry. They are also aware that potential drug residue dangers are always changing as new drugs, the environment, and consumers demand changes. Therefore, it is vital to provide the most updated information to the dairy producers and food animal practitioners to ensure residue free milk and meat products.

The USDA and FDA both play an important role in keeping residue-free milk and meat products on the market. The FDA and USDA, along with FARAD, provide the most collective and updated scientific information to the dairy producers and the food animal practitioners. The FARAD data, with regards to ketamine and lidocaine, is primarily based on data collected and recommended by foreign countries, mainly Switzerland and France. The USDA and FDA have limited information available on meat and milk withdrawal times for ketamine and lidocaine but have a stern tolerance

policy for drug residues in meat and milk. Because of this limited information on withdrawal times of ketamine and lidocaine in dairy cattle, the stern tolerance policy set forth by the USDA and FDA and potential health risks of the two drugs to the consumers, an investigation into the pharmacokinetics of ketamine following intravenous administration and lidocaine administered via inverted L and caudal epidural nerve blocks, and the establishment of the withdrawal time recommendations for meat and milk of these two anesthetics in mature Holstein cows was warranted.

Ketamine and lidocaine are two of the most commonly used anesthetics in veterinary medicine, particularly in food animals, considering financial concerns of other drugs. However, these two anesthetic drugs do carry the risk of residue and there is limited information available to the dairy producers and food animal practitioners on milk and meat withdrawal times. Most information listed for ketamine is limited to plasma data in calves, sheep, and swine, along with foreign country withdrawal times.[5,24,27] Switzerland lists ketamine as having a milk withdrawal time of 72 hours and meat withdrawal time of one day while France has no recommended meat or milk withdrawal times.[5] FARAD recommends a ketamine meat withdrawal time of three days and milk withdrawal time of 48 hours.[5] Data for lidocaine is more limited than for ketamine, with most information primarily based on its rapid metabolism.[5] FARAD recommends a lidocaine meat withdrawal time of one day and milk withdrawal time of 24 hours.[5]

In veterinary practice, ketamine is used not only as an anesthetic but also for postoperative pain management via continuous rate infusion. Ketamine, categorized as a

schedule III controlled substance by the FDA and DEA because of its moderate abuse and addictive potential, is also linked to a number of side effects such as illusions and flashback episodes, floating, vivid dreams, and occasional delirium in humans.[36] The residue potential of ketamine increases these risks in consumers, especially children. In a recent study, government researchers have been using ketamine for the treatment of depression but admits that more work is required due to potential side effects.[57]

Actual values for ketamine administered intravenously as a single anesthetic dose of 5 milligrams per kilogram was detected in serum from 0.083 to 8.0 hours and 0.5 to 48 hours in milk (Tables 2, 4 and 5 and Figures 1 and 2). The longest calculated elimination half-life of ketamine in serum was approximately 3 hours (actual values: 1.41 to 2.78 hours, mean 1.80 ± 0.50 in Table 3). Calculating for safety with the withdrawal time as ten times the elimination half-life, the meat withdrawal time will be recommended as 30 hours or 2 days, which is shorter than previously recommended by FARAD.[5] The pharmacokintic calculation of ten times the elimination half life with normal renal and hepatic function will eliminate 99.9 percent of any drug residue. The last detectable ketamine concentration in milk was 48 hours (actual values: 36 to 48 hours, mean 46 ±5.0 in Table 5). However, five of the six cows showed residues at 48 hours and no residues were detected at 60 hours (Table 4 and Figure 2). Therefore approximately 72 hours or a milk withdrawal time of 3 days is recommended, which is longer than previously recommended by FARAD.[5]

Lidocaine has fewer dangerous side effects with regards to the abuse and addictive potential than ketamine. However, caution should still be taken with the

potential for residues in milk and meat. Lidocaine can cause allergic reactions and systemic toxicity as a result of high plasma and tissue concentrations in humans.[54] The bioavailability of lidocaine after ingestion is poor; approximately 30% of lidocaine was detected in the blood circulation.[54] Nevertheless, consumers are at risk since lidocaine or its metabolite may accumulate, especially in the extremely young or those with compromised hepatic function.

Actual values for lidocaine administered by inverted L nerve blocks using a volume of 100 milliliters was detected in serum from 0.083 to 10 hours and 0.5 to 48 hours in milk (Tables 6 and 8 and Figures 3 and 4). The longest elimination half-life of lidocaine in the serum was approximately 8 hours (actual values: 2.1 to 7.26 hours, mean 4.19 ±1.69 in Table 7). Calculating for safety with the withdrawal time as ten times of the elimination half-life, the meat withdrawal time would be recommended as 80 hours or 4 days, which was four times longer than that recommended by FARAD.[5] The pharmacokintic calculation of ten times the elimination half life with normal renal and hepatic function will eliminate 99.9 percent of any drug residue. The last detectable lidocaine concentration in milk was 48 hours (actual values: 8 to 48 hours, mean 32.5 ± 16.2 in Table 8 and 9). However, five of the eight cows showed residues at 48 hours with no detectible residues at 60 hours. Therefore, approximately 72 hours or a milk withdrawal time of 3 days is recommended, which was also three times longer than that recommended by FARAD.[5]

There was no detectable lidocaine concentration in the milk or serum samples following caudal epidural administration at a dose of 0.22 milligrams per kilogram.

Therefore this technique may be performed without the potential for meat or milk contamination.

The results of this study revealed differences in the meat and milk withdrawal times of ketamine and lidocaine compared to the recommendations in the FARAD data bank. Several factors may be attributable to these differences. First is the formulation of the drugs, especially with respect to using lidocaine with or without epinephrine and may be attributed partially to the differences. The presence of epinephrine in the lidocaine injectable solution will slow the uptake of lidocaine by the circulation and prolong the duration of the local anesthesia of the tissue as a result of vasoconstriction produced by epinephrine.[14] Secondly is the difference in the routes of administration of the drugs. The data for lidocaine provided by FARAD is primarily based on the rapid metabolism and elimination after absorption of the lidocaine in most species.[5] It is likely that this data is based on pharmacokinetic studies following systemic administration of lidocaine, which may not take into account the slow absorption of the drug following administration by inverted L and caudal epidural nerve blocks in the present study. In the present study, the data of ketamine is based on samples collected from adult, lactating dairy cattle, and not extrapolated from other species. Therefore, differences in the age and species of the animals studied will also account for the difference of the pharmacokinetics observed in the present study. Furthermore, the data for ketamine available in FARAD is based on the pharmacokinetics of ketamine in serum and plasma from calves, sheep, and swine along with foreign established drug withdrawal times.[5] Lastly, the increase in sensitivity of the assays may also contribute to the differences

observed in the study. It is possible that the increase in sensitivity of the HPLC assay in recent years has allowed detection of much lower concentrations of the drugs in serum and milk samples. The improvements of sensitivity of the HPLC system thus reflected in the longer elimination half-life and prolonged meat and milk withdrawal times

In conclusion, the present study recommends a ketamine meat withdrawal time of 2 days, which is one day shorter than the FARAD recommendation of 3 days. This study also recommends a 72 hours milk withdrawal time for ketamine, which is 24 hours longer than the FARAD recommendation of 48 hours. With regards to lidocaine, this study concludes a meat withdrawal time of 4 days and a milk withdrawal time of 72 hours for lidocaine administered via an inverted L nerve block. However, lidocaine administered via a caudal epidural nerve block had no withdrawal times for meat or milk since no lidocaine was detected in the samples. FARAD withdrawal recommendations for lidocaine are one day for meat and 24 hours for milk. 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 stern tolerance for meat and milk residues as regulated by the FDA and enforced by the USDA.

Manufactures' addresses:

[a] Abbocath-T, Abbott Ireland, Sligo, Republic of Ireland
[b] Baxter HealthCare Corp., Deerfield, IL, USA
[c] Arrow International, Inc., Reading, PA, USA
[d] *Ketaset*® ,Fort Dodge Animal Health, Fort Dodge, IA,USA
[e] Abbott Laboratories, North Chicago, IL,USA
[f] Sterile Interior, Franklin Lakes, NJ,USA
[g] Fisher Scientific, Pittsburgh, PA, USA
[h] Becton Dickinson Lab ware, Franklin Lakes, NJ,USA

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TABLES

Date	cow #	Treatment	Weight (lbs)	Weight (kgs)	Age (yrs)
5/22/2003	1	T2	1131	514	3
5/27/2003	2	T3	1450	659	4
5/28/2003	3	T2	1030	468	3
5/29/2003	4	T3	1285	584	3
6/12/2003	5	T3	1210	550	3
6/26/2003	3	T1	960	436	3
6/26/2003	6	T1	1360	618	7
6/26/2003	5	T1	1200	545	3
6/27/2003	7	T1	1220	555	3
6/27/2003	8	T3	1265	575	3
7/11/2003	8	T1	1175	534	3
7/11/2003	4	T1	1210	550	3
7/10/2003	9	T1	960	436	3
7/10/2003	3	T3	950	432	3
7/31/2003	2	T2	1490	677	4
7/24/2003	9	T2	1000	455	3
7/17/2003	1	T3	1180	536	3
8/14/2003	4	T3	1200	545	3
8/14/2003	8	T2	1220	555	3
8/15/2003	9	T3	1000	455	3
8/29/2003	1	T1	1160	527	3
9/11/2003	7	T2	1100	500	3
9/12/2003	2	T1	1510	686	4
9/10/2003	6	T1	1495	680	7
9/25/2003	4	T2	1200	545	3
9/24/2003	5	T2	1310	595	3
9/24/2003	6	T2	1470	668	7
		Mean	1212.6	551.2	3.6
		MN Std Dev	170.1	77.3	1.3

Table 1: Sample collection dates corresponding with cow ear tag number and followed by designated treatment, weights, and age. The mean and standard deviation for weights and ages are located at the bottom of the table. Treatments: T1 = Ketamine (5 milligrams per kilogram, intravenous), T2 = 2 % Lidocaine epidural (0.22 milligrams per kilogram) and T3 = 2 % Lidocaine inverted L block (100 milliliters).

Time	Cow							
(hours)	2 t1	6 t1	3 t1	8 t1	9 t1	7 t1	Mean	STD
0.083	9612	6026	4989	14069	10073	64042	18135	22720
0.166	3809	512		4046	1531	2246	2429	1503
0.333	2184	831	1499	2117	1276	611	1420	648
0.500	1332	149	873	1173	710	393	772	452
0.666	1293	757	873	916	667	1013	920	219
0.833	807	327	544	798	585	716	629	183
1.00	609	281	501	781	429	673	546	180
2.00	363		408	278	352	269	334	59
4.00	101.4	53.3	114.7	94.8	90.4	73.2	88.0	21.8
6.00	70.9	13.0	37.2	79.9	37.0	32.2	45.0	25.3
8.00	38.8	6.7	35.8	24.2	25.9	17.7	24.9	11.8

Table 2: Serum concentration of ketamine in nanograms per milliliter vs. time following an intravenous administration of 5 milligrams per kilogram to six dairy cows.

Parameter		Cow 2	6	3	8	4	7	Mean	STD
AUC	(ng-hr/mL)	4656	4395	4717	5840	5441	1852	4484	1398
AUMC	(ng-hr^2/mL)	5924	1564	4848	4380	3743	1236	3616	1861
Cl	(L/hr/kg)	1.07	1.14	1.06	0.86	0.92	2.70	1.29	0.70
Varea	(L/kg)	4.31	2.31	2.70	1.96	2.29	5.81	3.23	1.51
Vss	(L/kg)	1.366	0.405	1.090	0.642	0.632	1.802	0.990	0.530
beta	(hr^{-1})	0.249	0.493	0.393	0.437	0.402	0.465	0.406	0.086
t1/2	(hr)	2.78	1.41	1.76	1.59	1.73	1.49	1.80	0.50
MRT	(hr)	1.27	0.36	1.03	0.75	0.69	0.67	0.794	0.318

Table 3: Calculated pharmacokinetics of ketamine (5 milligrams per kilogram) in serum following intravenous administration to six dairy cows.

AUC: total area under curve

AUMC: first moments under curve

CL: total body clearance

Varea: volume of distribution based on area

Vss: steady-state volume of distribution

Beta: time after peak drug concentration

$t_{½}$: half-life

MRT: mean resident time

Time	cow							
(hours)	2	6	3	8	4	7	Mean	STD
0	0	0	0	0	0	0	0	
0.5	1628	1845	2363	1678	2568	4229	2385	980
1	2215	1626	2002	1750	1851	3815	2210	813
2	731	800	1132	1147	1280	2238	1221	542
4	379	218	301	451	266	868	414	237
8	55.8	72.3	0.0	49.6	20.6	137.9	56.0	47.8
12	41.6	11.4	0.0	0.0	22.9	0.0	12.7	16.9
24	30.9	19.9	0.0	3.3	34.2	18.9	17.9	14.0
36	16.5	3.8	0.0	1.5	16.4	0.0	6.4	8.0
48	23.6	0.0	7.2	5.9	27.7	11.9	12.7	10.8

Table 4: Concentrations of ketamine (5 milligrams per kilogram) in milk (nanograms per milliliter) vs. time for each cow with mean and standard deviation for each cow following intravenous administration to six dairy cows.

Parameter		cow 2	6	3	8	4	7	Mean	STD
Tmax	(hr)	1.00	0.50	0.50	1.00	0.50	0.50	0.67	0.26
Cmax	(ng/mL)	2215	1845	2363	1750	2568	4229	2495	904
AUClast	(ng-hr/mL)	6117	4661	5370	5552	6707	11858	6711	2615
AUCmilk/AUCserum		1.31	1.06	1.14	0.95	1.23	6.40	2.02	2.15
last measurable time	(hr)	48	36	48	48	48	48	46.0	5.0
conc	(ng/mL)	23.6	3.8	7.2	5.9	27.7	11.9	13.4	10.0

Table 5: Pharmacokinetics of ketamine (5 milligrams per kilogram) in milk with mean and standard deviation for each cow following intravenous administration to six dairy cows.

Tmax: Time to reach peak drug concentration

Cmax: peak concentration of drug

AUC last: last area under curve

AUC milk/AUC serum: milk area under curve divided by serum area under curve

Time (hr)	Cow										
	2	6	3	5	8	4	7	1	9	Mean	SD
0	0	0	0	0	0	0	0	0	0		
0.083	138	207	0	140	261	273	213	332	513	231	143
0.167	413	224	597	277	341	289	250	354	539	365	129
0.333	215	240	432	370	433	331	472	618	854	441	197
0.5	451	472	689	377	355	360	433	414	998	505	210
0.667	272	517	492	316	297	300	403	438	559	399	108
0.833	200	263	111	353	279	323	335	378	474	302	105
1	175	300	100	726	279	225	282	253	281	291	175
2	161	147	0	189	81	170	166	112	37	118	66
4	101	54	0	75	83	80	90	0	55	60	37
6	67	0	0	56	0	102	81	56	34	44	38
8	2	0	0	79	36	62	39	48	0	30	31
10	108	20	0	0	0	0	23	0	0	17	35
12	0	0	0	0	0	0	0	0	0	0	0

Table 6: Serum concentrations (nanograms per milliliter) of lidocaine Vs time with means and standard deviations for each cow following administration of 100 milliliters of 2% lidocaine via inverted L nerve block.

Parameters		Cow									
		2	6	5	8	4	7	1	9	Mean	SD
Dose	(mg/kg)	3.0	2.9	3.6	3.5	3.4	3.7	3.7	4.4	3.5	0.5
Weight	(kg)	659	680	550	575	584	545	536	455	573	71
Tmax	(hr)	0.500	0.667	1.000	0.333	0.500	0.333	0.333	0.500	0.521	0.226
Cmax	(ng/mL)	451	517	726	433	360	472	618	998	572	207
AUC	(ng-hr/mL)	1955	917	1567	968	1513	1270	1285	1312	1348	335
beta	(hr-1)	0.118	0.202	0.334	0.189	0.148	0.254	0.182	0.096	0.190	0.076
t1/2	(hr)	5.86	3.44	2.08	3.68	4.69	2.73	3.81	7.26	4.19	1.69
MRT	(hr)	10.34	3.15	3.61	4.15	6.20	3.66	4.54	5.40	5.13	2.33
Cl/F	(l/hr/kg)	1.53	3.16	2.30	3.62	2.25	2.91	2.88	3.35	2.75	0.68
last measurable time	(hr)	10	10	8	8	8	10	8	6	8.5	1.4
concentration	(ng/mL)	108	20	79	36	62	23	48	34	51	30

Table 7: Calculated serum pharmacokinetics of lidocaine following 100 milliliters of 2 % lidocaine administered via inverted L nerve blocks to eight cows.

Tmax: Time to reach peak drug concentration

Cmax: peak concentration of drug

AUC: total area under curve

Beta: time after peak drug concentration

$t_{½}$: half-life

MRT: mean resident time

CL/F: total body clearance not accounting for absorption

Time (hr)	Cow										
	2	6	3	5	8	4	7	1	9	Mean	SD
0	0	0	0	0	0	0	0	0	0	0	0
0.5	0	119	216	0	87	145	114	185	334	133	105
1	158	179	193	155	124	250	265	472	334	237	110
2	211	187	277	259	169	180	299	323	552	273	118
4	114	64	0	154	72	0	190	215	108	102	76
8	73	90	30	119	45	56	96	105	31	72	33
12	0	0	0	23	0	0	0	0	13	4	8
24	0	26	0	0	0	0	43	0	0	8	16
36	35	0	0	0	37	73	0	0	0	16	26
48	0	23	0	0	0	79	0	0	21	14	26
60	0	0	0	0	0	0	0	0	0	0	0

Table 8: Concentrations of lidocaine in milk (nanograms per milliliter) vs. time in eight dairy cows following 100 milliliters of 2% lidocaine administered via inverted L nerve block.

Parameters		Cow									
		2	6	5	8	4	7	1	9	Mean	SD
Dose	(mg/kg)	3.0	2.9	3.6	3.5	3.4	3.7	3.7	4.4	3.5	0.5
Weight	(kg)	659	680	550	575	584	545	536	455	573	71
Tmax	(hr)	2	2	2	2	1	2	1	2	1.75	0.46
Cmax	(ng/mL)	211	187	260	169	250	299	472	552	300	139
AUClast	(ng-hr/mL)	1485	1623	1625	1234	2599	2185	2027	2174	1869	450
AUCmilk/AUCserum		0.760	1.770	1.037	1.275	1.717	1.717	1.577	1.657	1.439	0.374
last measurable											
time	(hr)	36	48	12	36	48	24	8	48	32.5	16.2
concentratio	(ng/mL)	35	23	23	37	79	43	105	21	46	30

Table 9: Calculated milk pharmacokinetics of lidocaine after administration of 100 milliliters of 2 % lidocaine via inverted L nerve block to eight cows.

Tmax: Time to reach peak drug concentration

Cmax: peak concentration of drug

AUC last: last area under curve

AUC milk/AUC serum: milk area under curve divided by serum area under curve

FIGURES

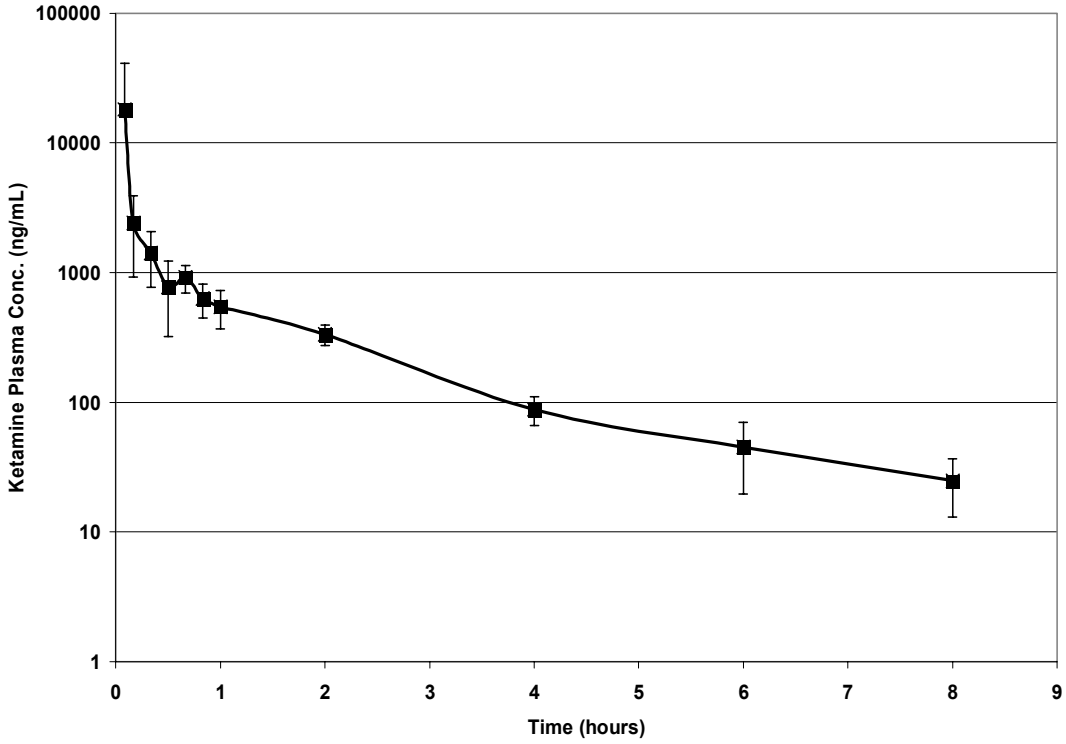

Figure 1: Serum concentration in nanograms per milliliter vs. time following intravenous administration of 5 milligrams per kilogram of ketamine to six dairy cows.

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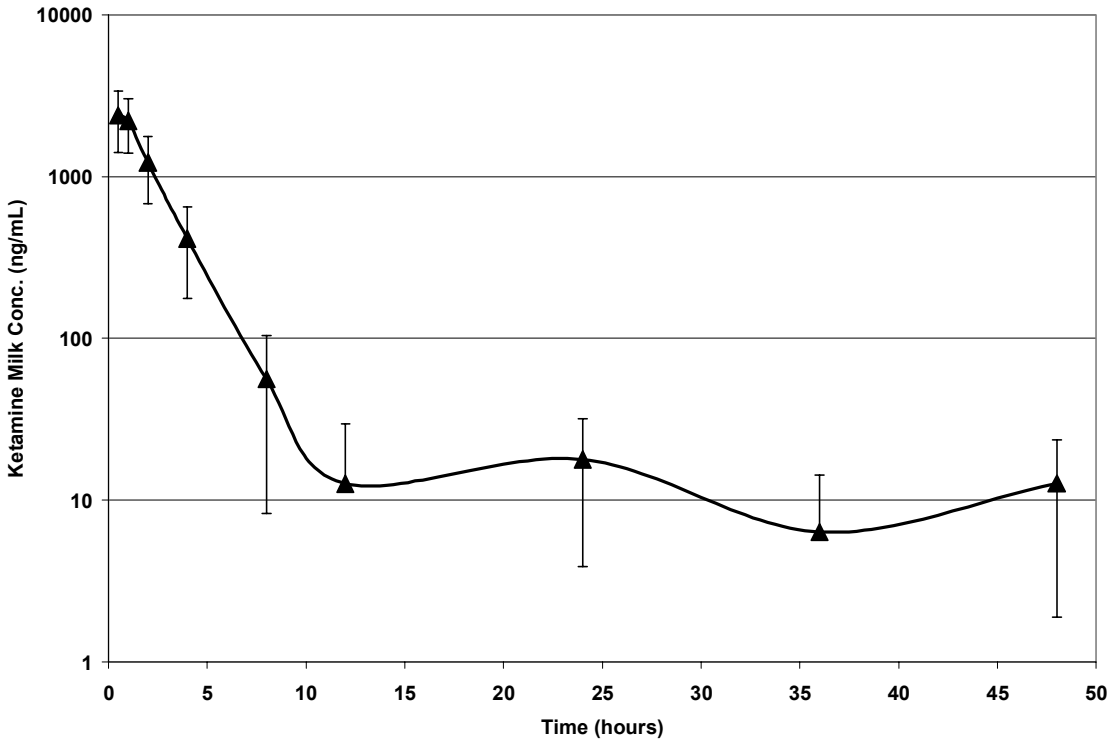

Figure 2: Milk concentrations in nanograms per milliliter vs. time following intravenous administration of 5 milligrams per kilogram of ketamine to six dairy cows.

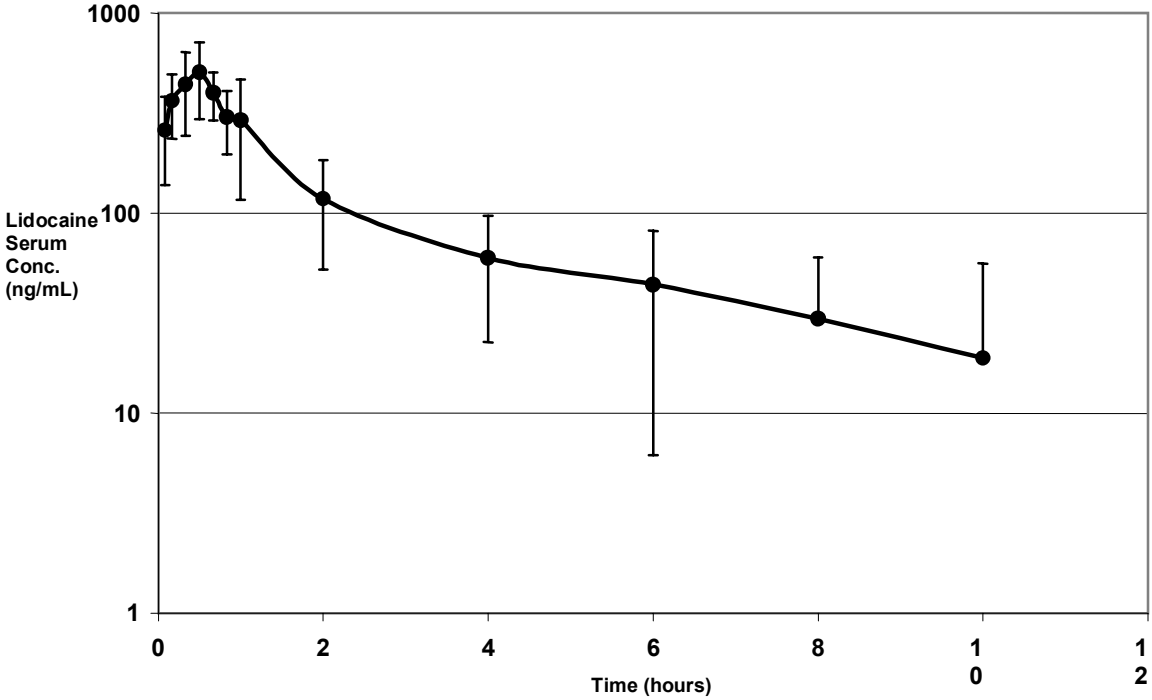

Figure 3: Serum concentrations in nanograms per milliliter vs. time following administration of 100 milliliters of 2 % lidocaine via inverted L nerve block to eight dairy cows.

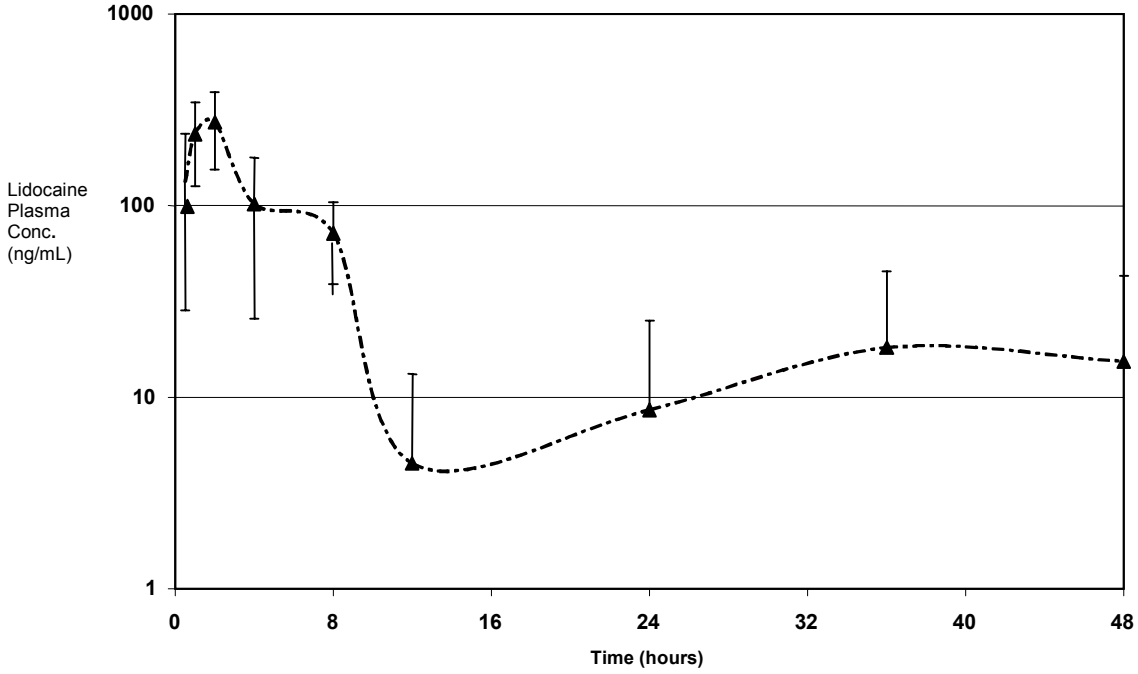

Figure 4: Milk concentrations in nanograms per milliliter vs. time following administration of 100 milliliters of 2 % lidocaine via inverted L nerve block to eight dairy cows.