Pharmacokinetics and clinical effects of a subanesthetic continuous rate infusion of ketamine in awake horses

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Objective—To determine the pharmacokinetics and clinical effects of a subanesthetic, continuous rate infusion of ketamine administered to healthy awake horses.

Animals—8 adult horses.

Procedures—Ketamine hydrochloride was administered to 2 horses, in a pilot study, at rates ranging from 0.4 to 1.6 mg/kg/h for 6 hours to determine an appropriate dose that did not cause adverse effects. Ketamine was then administered to 6 horses for a total of 12 hours (3 horses at 0.4 mg/kg/h for 6 hours followed by 0.8 mg/kg/h for 6 hours and 3 horses at 0.8 mg/kg/h for 6 hours followed by 0.4 mg/kg/h for 6 hours). Concentration of ketamine in plasma, heart rate, respiratory rate, blood pressure, physical activity, and analgesia were measured prior to, during, and following infusion. Analgesic testing was performed with a modified hoof tester applied at a measured force to the withers and radius.

Results—No signs of excitement and no significant changes in the measured physiologic variables during infusion rates of 0.4 and 0.8 mg of ketamine/kg/h were found. At 6 hours following infusions, heart rate and mean arterial pressure were decreased, compared with preinfusion measurements. An analgesic effect could not be demonstrated during or after infusion. Pharmacokinetic variables for 0.4 and 0.8 mg/kg/h infusions were not significantly different.

Conclusions and Clinical Relevance—Ketamine can be administered to awake horses at 0.4 or 0.8 mg/kg/h without adverse behavioral effects. The observed pharmacokinetic values are different than those reported for single-dose IV bolus administration of this drug. (Am J Vet Res 2006;67:1484–1490)

Nonsteroidal anti-inflammatory drugs, α₂-adrenoceptor agonists, and opioids are the most commonly used drug classes to provide analgesia in horses. Although each of these can be effective individually or in combinations, they can also have substantial adverse effects.¹⁻² Equine clinicians continue to search for drugs to be used for pain management that cause less severe cardiovascular, gastrointestinal, or behavioral changes than currently available analgesics.

Ketamine hydrochloride is a noncompetitive antagonist at N-methyl-D-aspartate receptors in the spinal cord.¹¹ It also has effects on opioid,¹² monoaminergic,¹⁴ and muscarinic receptors,¹３,¹５,¹６ as well as voltage-sensitive Ca²⁺ channels.¹⁷,¹⁸ Following IV administration, ketamine undergoes widespread distribution.¹⁹ Biotransformation occurs in the liver where the drug is converted to norketamine.²⁰ At anesthetic doses, ketamine has a variety of cardiovascular effects, including increases in cardiac index, mean aortic pressure, pulmonary arterial pressure, systolic and diastolic arterial pressure, and heart rate.²¹,²² Ketamine does not appear to have an effect on gastrointestinal motility and has only minimal and transient effects on ventilation.²³,²⁴ In fact, ketamine appears to decrease airway resistance in dogs and humans.²⁵,²⁶

Subanesthetic amounts of ketamine have been used to provide analgesia in small companion animal and human patients.²³,²⁵ Following oral or IM administration in people, serum concentrations of ketamine as low as 0.04 and 0.150 μg/mL, respectively, have been associated with analgesia.²⁶ Ketamine has been evaluated for its use in human patients with asthma,²⁷ limb amputations,²⁸ and chronic pain. It has also been examined for its analgesic effects following ovariohysterectomy and limb amputations in dogs.²⁹

In horses, ketamine has been used for more than 2 decades as an injectable anesthetic agent in conjunction with α₂-adrenoceptor agonists such as xylazine. Ketamine is usually administered IV at a dose of 2.2 mg/kg, and anesthesia is maintained with circulating concentrations of approximately 1 μg of ketamine/mL.³⁰ Infusions of ketamine have been shown to decrease the minimum alveolar concentration of halothane in horses.³¹ Without prior medication with drugs such as xylazine or diazepam, this dose of ketamine can cause undesirable excitation and muscular rigidity.³² More recently, ketamine has been...
used by caudal epidural injection to provide analgesia for the perineal region and locally for peripheral nerve blocks in the distal portion of the limbs of horses. Pharmacokinetic properties of a single dose of ketamine in horses, mules, and donkeys have been evaluated. The disappearance half-life ranged from 42 to 65 minutes in horses. To provide long-term analgesia in people, ketamine administration at 0.3 to 1.2 mg/kg/h as a CRI has been recommended. This regimen allows the effects of ketamine to be titrated as well as prevents substantial variation in analgesic effects as serum concentrations fluctuate between subsequent doses. To our knowledge, no reports exist on the pharmacokinetics or clinical assessment of a CRI of subanesthetic amounts of ketamine to horses.

Ketamine could represent an analgesic drug for use in equine patients that are systemically compromised from cardiovascular, respiratory, or gastrointestinal diseases. On the basis of clinical experience and research with other species, we hypothesize that ketamine can be used safely as an analgesic agent in horses. The purposes of the study reported here were to determine an appropriate dose, evaluate clinical physical examination and hemodynamic parameters associated with this dose, and describe the pharmacokinetics of CRI ketamine in horses.

Materials and Methods

Animals—Eight horses (2 for a pilot study and 6 for the principal study) were used. The pilot study horses consisted of a 10-year-old Quarter Horse gelding with a body weight of 550 kg and a 22-year-old Arabian mare with a body weight of 384 kg. The 6 principal study horses included 2 breeds (3 Quarter Horses and 3 Thoroughbreds) with a median body weight of 498 kg (range, 366 to 623 kg). Three of the principal study horses were mares, and 3 were geldings. Approval of the study was obtained from the University Laboratory Animal Care Committee at Texas A&M University.

Prior to the start of the infusions, body weight of each horse was recorded by use of a digital walk-on scale, a complete physical examination was performed, and catheters were placed in both jugular veins of each horse. Ketamine hydrochloride was diluted in saline (0.9% NaCl) solution to a concentration of 3 mg/mL and administered IV through the left-sided catheter with an infusion pump.

Pilot study—Each horse was maintained in a padded recovery stall during the infusion of ketamine and for 2 hours following the end of infusion. Feed was withheld during the infusion, but intermittent access to water was provided. The first horse received ketamine HCl at a rate of 0.4 mg/kg/h for 6 hours, followed by 0.8 mg/kg/h for 6 hours, with a total infusion time of 12 hours. The second horse received ketamine HCl at a rate of 0.8 mg/kg/h for 6 hours, followed by 1.6 mg/kg/h for 2 hours. The latter infusion was stopped prematurely as a result of behavioral changes in this horse.

Throughout the infusion, horses were under continuous observation and the heart rate was recorded every 15 minutes. Activity, as measured by the number of right forelimb footstep within a 2-minute period, was also recorded every 15 minutes according to a previously described technique. Blood samples, approximately 20 mL, were serially collected throughout the infusions and processed as will be described.

Principal study—The 6 horses used in this part of the study were housed in indoor stalls for a total of 84 hours (48 hours prior to infusion, 12 hours during infusion, and 24 hours following infusion) with free access to feed (Bermuda grass hay) and water. The dose of ketamine HCl was randomized as follows: 3 horses received the high dose (0.8 mg/kg/h) for 6 hours, followed by the low dose (0.4 mg/kg/h) for 6 hours. The other 3 horses received the low dose (0.4 mg/kg/h) for 6 hours, followed by the high dose (0.8 mg/kg/h) for 6 hours.

Blood samples were collected from the right jugular vein prior to the start of the infusions, at 30-minute intervals throughout the infusion, and at 30-minute intervals for 6 hours following the end of infusion. All blood samples were collected into evacuated tubes containing lithium heparin. Values for physiologic variables were recorded prior to the start of infusion, at 1-hour intervals during the infusion and at 1-hour intervals for 6 hours following the end of infusion. Heart rate was evaluated by cardiac auscultation, and respiratory rate was recorded by observation of thoracic movement. Indirect blood pressure measurements were made by use of a tail cuff and a recorder according to product guideline and as previously described. Tail cuffs were placed prior to the start of the study and fixed in place with adhesive tape to ensure consistency of placement throughout the study.

Analgesic testing was performed prior to the start of infusion, at 6 hours into the infusion (immediately before dose change), at 12 hours into the infusion (immediately before stopping), and at 6 hours after the end of infusion. Testing was performed with a modified hoof tester fitted with an electronic force transducer (load cell) to measure isometric force applied to the withers and radius. The force was manually applied and increased until either the point of gross purposeful movement or a total elapsed period of 1 minute. Gross purposeful movement was defined as lifting of the leg when the stimulus was applied to the radius and reflex skin twitch when the stimulus was applied to the withers. The applied force was amplified, displayed by a signal processor, and then recorded. Locations for placement of the hoof tester were identified prior to the study, and the overlying hair was clipped to maintain consistent placement between measurements. The location at the withers was approximately 5 cm to either side of the highest point. The location at the radius was approximately 6 cm proximal to the accessory carpal bone. All measurements were performed 3 times with a 1-minute interval of rest between each force application.

Plasma ketamine concentrations—Plasma was harvested after centrifugation and frozen at 80°C until analyzed. Following solid-phase extraction, concentrations of ketamine in plasma were determined by HPLC. Samples were extracted in triplicate and randomly analyzed. Mepivacaine (8.72 μg) was added as an internal standard to 4 mL of plasma followed by addition of 5 mL of 0.2M phosphate buffer (pH, 5.2). Samples were loaded onto a preconditioned (5 mL of methanol and 5 mL of HPLC grade water; followed by 3 mL of 1N acetic acid) 300-mg C8-aromatic sulfonic acid mixed-bed solid-phase extraction column. The column was rinsed with 5 mL of 0.2M phosphate buffer, followed by 3 mL of 1N acetic acid and then 5 mL of methanol. It was then dried for 15 minutes under a vacuum of 10 to 15 inches of mercury, followed by washing with 5 mL of hexane and then 5 mL of methanol. Ketamine was eluted with 5 mL of a solution of dichloromethane:methanol:ammonium hydroxide (60:40:4; vol:vol:vol). Samples were dried under nitrogen at 45°C. The residue was dissolved in 300 μL of a solution of dichloromethane:isopropanol (10:1; vol:vol) and then transferred into an HPLC vial. Samples were dried under nitrogen and resuspended in 60 μL of HPLC solvent.
The HPLC instrument was equipped with a C-18 column (2.0 X 250 mm). The mobile phase was acetonitrile (water with 3% triethylamine:3% tetrahydrofuran; pH adjusted to 5.3 with phosphoric acid [7.93; vol/vol]). The injection volume was 20 μL. Wavelengths monitored were 208 nm (used for quantification) and 210 nm. The flow rate was 0.2 mL/min. Calibrators were prepared in duplicate by addition of appropriate volumes of ketamine to 4 mL of blank plasma. Calibrators had internal standards added and were extracted as already described. Calibrators were prepared by the addition of the appropriate volume of ketamine to produce concentrations of 1.084, 0.650, 0.434, 0.325, 0.217, and 0.108 μg/mL. Quality control samples were prepared in triplicate at each concentration and extracted as already described. Quality control samples were prepared by spiking 4 mL of blank equine plasma with the appropriate volume of ketamine to produce concentrations of 0.615, 0.383, and 0.182 μg/mL.

Pharmacokinetic analysis—Pharmacokinetic analysis was performed with commercial software. The mean value of the trapezoidal analysis for concentrations of ketamine in plasma was used for modeling. All values below the limit of quantification (0.047 μg/mL) were excluded. Concentration-time course for each horse was analyzed individually, and the values reported as median (range) for the group were analyzed statistically. Noncompartmental pharmacokinetic analysis was used on the basis of a prerequisite of achieving an absorption and distribution equilibrium.

The following measurable parameters were estimated by use of pharmacokinetics software: Cw was the concentration of drug in plasma at steady state; AUC was the area under the time-concentration curve to the last time point of infusion, estimated by use of the trapezoidal method; AUMC was the area under the moment curve versus time from time zero to infinity; K10 was the elimination rate constant, estimated by use of the plasma concentration at time points during the approach to steady state. The following derived parameters were then calculated with the pharmacokinetics program with the following equations:

\[
Cl = k_i/C_{ss}
\]

where Cl is total body clearance and \(k_i\) is the infusion rate,

\[
V_{ss} = \frac{\text{Dose} \times \text{AUMC}}{\text{AUC}}
\]

where \(V_{ss}\) is the apparent volume of distribution at steady state and dose = \(k_i\) (time of infusion),

\[
MRT = \frac{\text{AUMC}}{\text{AUC}}
\]

where MRT is the mean residence time,

\[
K_d = 1/MRT
\]

where \(K_d\) is the rate constant of disappearance,

\[
T_{1/2d} = 0.693/K_d
\]

where \(T_{1/2d}\) is the half-life of disappearance, and

\[
T_{1/2e} = 0.693/K_{10}
\]

where \(T_{1/2e}\) is the half-life of elimination and \(K_{10}\) is the rate constant of elimination from the central compartment.

Ketamine analysis—The limit of quantitation for ketamine (signal to noise > 10 and the quantitative level was within ± 20% of target) was 0.047 μg/mL. Within- and between-day precision was calculated by use of a 1-way ANOVA and values for the mean sum of squares. Mean accuracy was 114%, 102%, and 112% for the 0.615, 0.383, and 0.182 μg/mL concentrations, respectively. Estimates of within-day coefficients of variation for concentrations of 0.615, 0.383, and 0.182 μg/mL of plasma were 14.8%, 13.9%, and 16.8%; between-day coefficients of variation were 22.9%, 15.9%, and 17.2%.

Statistical analysis—Statistical analysis was performed with commercial software. Comparisons of physiologic variables were made between values obtained from low-dose ketamine administration in all 6 horses and values obtained from high-dose ketamine administration in all 6 horses. Specifically, the preinfusion value, the 6-hour infusion value, the 12-hour infusion value, and the 6-hour postinfusion value were compared by use of a nonparametric ANOVA (Kruskal-Wallis) test. When overall group differences were significant (P < 0.05), pairwise comparisons were made with the post hoc Dunn test. Values for the respective pharmacokinetic parameters were compared between the 2 doses by use of a Wilcoxon matched-pairs test. Values of P < 0.05 were considered significant.

Results

Pilot study—The first horse (0.4 and 0.8 mg/kg/h) did not have any signs of adversity. The second horse did not have any abnormal behavior at the lower dose (0.8 mg/kg/h for 6 hours), but approximately 2 hours after the start of infusion of the high dose (1.6 mg/kg/h), the horse had signs of excitation. The previously described activity score, as measured by the number of right forelimb footsteps within a 2-minute course for each horse was analyzed individually, and the values reported as median (range) for the group were analyzed statistically. Noncompartmental pharmacokinetic analysis was used on the basis of a prerequisite of achieving an absorption and distribution equilibrium.

The following measurable parameters were estimated by use of pharmacokinetics software: Cw was the concentration of drug in plasma at steady state; AUC was the area under the time-versus-concentration curve to the last time point of infusion, estimated by use of the trapezoidal method; AUMC was the area under the moment curve and was the plot of time versus concentration X time from time zero to infinity; K10 was the elimination rate constant, estimated by use of the plasma concentration at time points during the approach to steady state. The following derived parameters were then calculated with the pharmacokinetics program with the following equations:

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where \(K_d\) is the rate constant of disappearance,

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T_{1/2d} = 0.693/K_d
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where \(T_{1/2d}\) is the half-life of disappearance, and

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where \(T_{1/2e}\) is the half-life of elimination and \(K_{10}\) is the rate constant of elimination from the central compartment.

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<table>
<thead>
<tr>
<th>Time relative to CRI of ketamine</th>
<th>Prior to low dose</th>
<th>During low dose</th>
<th>During high dose</th>
<th>After ketamine infusion</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>34 (28–40)*</td>
<td>32 (28–36)</td>
<td>30 (24–36)</td>
<td>26 (24–32)*</td>
<td>0.02</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>20 (16–32)</td>
<td>20 (12–36)</td>
<td>22 (8–28)</td>
<td>12 (8–36)</td>
<td>0.34</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>125 (101–140)</td>
<td>124 (102–137)</td>
<td>130 (98–134)</td>
<td>119 (93–133)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>92 (77–100)</td>
<td>88 (84–96)</td>
<td>89 (79–96)</td>
<td>81 (74–94)</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>105 (95–108)*</td>
<td>99 (72–109)</td>
<td>102 (90–107)</td>
<td>91 (86–106)*</td>
<td>0.02</td>
</tr>
<tr>
<td>Activity (footsteps/min)</td>
<td>2.5 (0–6)</td>
<td>2.0 (0–6)</td>
<td>5.5 (0–8)</td>
<td>2.5 (0–8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Analgesia at withers (ft-lb)†</td>
<td>12 (9–16)*</td>
<td>7.5 (2–11)</td>
<td>10 (2–14)</td>
<td>5 (3–8)*</td>
<td>0.02</td>
</tr>
<tr>
<td>Analgesia at radius (ft-lb)/f</td>
<td>12 (6–17)*</td>
<td>8 (5–9)</td>
<td>6 (3–14)</td>
<td>6 (3–7)*</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Significant (P < 0.05) difference between time points. †Multiply by 0.1383 to convert to meter-kilogram.
period, ranged from 0 to 29 during low-dose ketamine administration in this horse but ranged from 32 to 57 during high-dose ketamine administration. Initially, that horse had exaggerated responses to movement, light, and noise. The behavior increased in severity to the point that the infusion was discontinued. A blood sample that was obtained shortly before the onset of those signs had a concentration of 0.28 μg of ketamine/mL of plasma. After the infusion of ketamine was discontinued, 0.01 mg of detomidine/kg was administered IV. All signs of excitation ceased, and the horse did not have any other abnormal behavior during the following 2 hours of observation.

Principal study—All horses in the principal study tolerated infusions well, and none had any abnormal behavior during or following the infusion. Throughout the infusions, all horses continued to eat, defecate, and urinate normally. Heart rate and mean arterial blood pressure decreased significantly (P = 0.02 for both comparisons) at 6 hours after infusion, compared with before infusion values (Table 1; Figures 1 and 2). Significant differences in pharmacokinetic parameters were not found between the 2 groups of horses (ie, horses given ketamine at 0.8 mg/kg/h for 6 hours, followed by 0.4 mg/kg/h for 6 hours and vice versa; Table 2; Figures 3 and 4).

Discussion

Reluctance to use ketamine in horses without prior sedation is primarily the result of concerns about the possibility for an excitatory response. However, the administered dose or circulating concentration of ketamine at which excitement or abnormal behavior may occur has not been identified. No recognized differences were observed between sexes regarding response to ketamine, and our study was not designed to determine that. Results of our study indicate that ketamine can be administered to horses at a dose up to 0.8 mg/kg/h for 6 hours without adverse behavioral effects. Higher rates of ketamine administration may be possible (0.9 to 1.5 mg/kg/h) but were not evaluated in our study.

No analgesic effect could be demonstrated during or following the ketamine infusion. Ketamine did not appear to produce any sedation, and horses may have become conditioned to the stimulus over time. In fact, a small but significant increase in sensitivity in both testing regions was observed, as shown by a response to a smaller amount of stimulus with each subsequent

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Table 2—Median (range) values of pharmacokinetic parameters for low-dose (0.4 mg/kg/h for 6 hours; n = 3) and high-dose (0.8 mg/kg/h for 6 hours; 3) ketamine infusion in horses.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Low-dose data</th>
<th>High-dose data</th>
<th>Combined data</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (μg/mL)</td>
<td>0.067 (0.052–0.095)</td>
<td>0.137 (0.056–0.175)</td>
<td>0.076 (0.053–0.176)</td>
<td>0.0625</td>
</tr>
<tr>
<td>Cl (mg/[h(μg/mL)])</td>
<td>2.966 (2.065–4.335)</td>
<td>3.113 (2.455–6.101)</td>
<td>3.113 (2.065–6.101)</td>
<td>0.5625</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>3.11 (3.07–3.61)</td>
<td>3.26 (3.07–3.61)</td>
<td>3.11 (3.07–3.61)</td>
<td>0.8438</td>
</tr>
<tr>
<td>AUC (h×[μg/mL])</td>
<td>0.401 (0.310–0.570)</td>
<td>0.820 (0.336–1.055)</td>
<td>0.459 (0.310–1.055)</td>
<td>0.0625</td>
</tr>
<tr>
<td>AUMC (h×h×[μg/mL])</td>
<td>1.34 (1.00–1.74)</td>
<td>2.55 (1.03–3.69)</td>
<td>1.43 (1.00–3.69)</td>
<td>0.0625</td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td>19.9 (12.9–26.7)</td>
<td>18.2 (15.9–47.8)</td>
<td>18.2 (12.9–47.8)</td>
<td>0.3125</td>
</tr>
<tr>
<td>Kd (1/h)</td>
<td>0.321 (0.277–0.326)</td>
<td>0.307 (0.277–0.326)</td>
<td>0.321 (0.277–0.326)</td>
<td>0.8438</td>
</tr>
<tr>
<td>T1/2d (h)</td>
<td>2.16 (2.13–2.50)</td>
<td>2.26 (2.13–2.50)</td>
<td>2.16 (2.13–2.50)</td>
<td>0.8438</td>
</tr>
<tr>
<td>T1/2E (h)</td>
<td>0.081 (0.05–0.22)</td>
<td>0.181 (0.05–0.422)</td>
<td>0.078 (0.05–0.422)</td>
<td>0.8438</td>
</tr>
</tbody>
</table>

Cmax = Maximum plasma concentration of ketamine. Cl = Total body clearance of ketamine. MRT = Mean residence time. AUC = Area under the time-versus-concentration curve. AUMC = Area under the moment curve. Vss = Volume of distribution at steady state. Kd = Rate constant of disappearance. T1/2d (equivalent to 0.693 × MRT) = Half-life of disappearance. Kd = Rate constant of elimination from the central compartment. T1/2E (equivalent to 0.693 × Kd) = Half-life of elimination.
reported values. Although the median heart rate and ketamine administration were similar to previously some other species.

Similar types of pain models have been used to evaluate the concentration of metabolites and cardiovascular changes associated with subanesthetic doses of ketamine have not been previously described. The decrease in heart rate and mean arterial blood pressure after ketamine administration was unexpected but could be attributable to the action of a persistent metabolite. Alternatively, these effects may represent a compensatory response following the termination of the sympathomimetic effects of the drug. The decrease in heart rate could be clinically important, as 3 of the 6 horses developed a bradycardia of 24 beats/min. Additional studies are needed to evaluate the concentration of metabolites and cardiovascular effects. It is also possible that this difference could have occurred as the result of normal diurnal variation.

The median respiratory rate remained relatively constant throughout the ketamine infusion. This is consistent with previous findings that suggest that ketamine does not have a substantial effect on the respiratory system. Activity reported for horses in our study is consistent with a lack of sedation but also did not demonstrate an increase in movement.

The maximum plasma concentrations of ketamine (median, 0.137 μg/mL; range, 0.056 to 0.176 μg/mL) obtained during the 0.8 mg/kg/h infusion rate was approximately twice that (median, 0.067 μg/mL; range, 0.052 to 0.095 μg/mL) obtained during the infusion rate of 0.4 mg/kg/h. Those concentrations were above those needed to provide analgesia after IV administration in people. Our study was not able to establish a minimum concentration that provided analgesia in horses. Clinical trials or alternative models may be required to identify that value.

Values for pharmacokinetic parameters in our study differed from those reported for studies with horses after single-dose IV bolus and short infusion. Specifically, our study found a shorter elimination half-life, longer distribution half-life, higher volume of clearance, and larger apparent volume of distribution, compared with other studies. Our data indicate that steady state was achieved after infusion at each rate.

Two important differences exist between the design of our study and prior studies, and these may explain, at least in part, the pharmacokinetic values obtained. One is the use of premedications or inhalation anesthetics in other studies. With horses after single-dose IV bolus and short infusion. Specifically, our study found a shorter elimination half-life, longer distribution half-life, higher volume of clearance, and larger apparent volume of distribution, compared with other studies. Our data indicate that steady state was achieved after infusion at each rate.

The second major difference between our study and prior research is the achievement and maintenance of a steady-state concentration by continuous infusion. Values for pharmacokinetic parameters from a study with a single IV bolus estimates the distribution and elimination half-lives based on the assumption that the initial rapid decrease in plasma concentration is the result of distribution and that the slower terminal phase represents elimination. Although this assumption holds true for many drugs, our data suggest that this may not be true for ketamine in horses. It is possible that the terminal half-life reported in prior studies may reflect elimination but may be limited by kinetics of distribution and redistribution. That difference must be the result of the delayed distribution of ketamine in horses relative to its elimination.

Observations made in prior studies evaluating ketamine in people provide some support for this interpretation of data. Specifically, during continuous infusions of ketamine, the reported elimination half-life was 79 ± 8 minutes, whereas values for the same parameter following a single IV injection has ranged from...
155 ± 12 minutes to 299 ± 94 minutes, depending on the condition of the patient. Additional studies in which ketamine was administered to people by longer-term CRIs found an elimination half-life of approximately 1 hour, with 85% of the drug being eliminated within 2 hours.

Observations made in our study may have been strengthened by more samples at time points during the early part of infusion and immediately following the cessation of infusion. Our study design was based on a reported elimination half-life of 42 minutes. Additionally, because concentrations of ketamine rapidly decreased to less than the limit of quantitation after infusion was discontinued, it was necessary to eliminate some data points following the cessation of infusion, restricting our ability to calculate, for some horses, the terminal half-life after the infusion was stopped.

In conclusion, subanesthetic doses of ketamine up to 0.8 mg/kg/h for 6 hours did not cause signs of excitement in horses, but an analgesic effect was not obtained with the method of analgesic testing used in our study. Mild, postinfusion bradycardia and hypotension were associated with that dose of ketamine. Pharmacokinetic results of our study indicate that in horses, ketamine may have greater clearance, longer distribution half-life, and shorter elimination half-life than previously described.

a. Ketaset (100 mg/mL), Fort Dodge Animal Health, Fort Dodge, Iowa.


g. InStat 3.0 for Windows, GraphPad Software Inc, San Diego, Calif.

References


