Pharmacokinetics and pharmacodynamics of midazolam after intravenous and intramuscular administration in alpacas

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Objective—To determine pharmacokinetic and pharmacodynamic properties of midazolam after IV and IM administration in alpacas.

Animals—6 healthy alpacas.

Procedures—Midazolam (0.5 mg/kg) was administered IV or IM in a randomized crossover design. Twelve hours prior to administration, catheters were placed in 1 (IM trial) or both (IV trial) jugular veins for drug administration and blood sample collection for determination of serum midazolam concentrations. Blood samples were obtained at intervals up to 24 hours after IM and IV administration. Midazolam concentrations were determined by use of tandem liquid chromatography–mass spectrometry.

Results—Maximum concentrations after IV administration (median, 1,394 ng/mL [range, 1,150 to 1,503 ng/mL]) and IM administration (411 ng/mL [217 to 675 ng/mL]) were measured at 3 minutes and at 5 to 30 minutes, respectively. Distribution half-life was 18.7 minutes (13 to 47 minutes) after IV administration and 41 minutes (30 to 80 minutes) after IM administration. Elimination half-life was 98 minutes (67 to 373 minutes) and 234 minutes (103 to 320 minutes) after IV and IM administration, respectively. Total clearance after IV administration was 11.3 mL/min/kg (6.7 to 13.9 mL/min/kg), and steady-state volume of distribution was 525 mL/kg (446 to 798 mL/kg). Bioavailability of midazolam after IM administration was 92%. Peak onset of sedation occurred at 0.4 minutes (IV) and 15 minutes (IM). Sedation was significantly greater after IV administration.

Conclusions and Clinical Relevance—Midazolam was well absorbed after IM administration, had a short duration of action, and induced moderate levels of sedation in alpacas. (*Am J Vet Res* 2013;74:294–299)

Midazolam is a benzodiazepine that is used as a sedative and hypnotic in human and veterinary medicine.[1–6] Midazolam has been recommended for sedation prior to induction of anesthesia with ketamine in camelids, but the authors could not find reports describing the pharmacokinetics or pharmacodynamics properties of this drug in alpacas.[7,8] The pharmacokinetic properties of midazolam have been described in humans, dogs, and sheep.[9–11] The disposition of midazolam in humans has been described by a 2-compartment open model.[10] Midazolam has a half-life of approximately 2 hours, an apparent volume of distribution of 1.1 L/kg, and a total clearance of 0.38 L/kg/h in humans.[10] Absorption is rapid and complete after IM administration in dogs, with an apparent volume of distribution of 3 L/kg and a mean elimination half-life of 1.28 hours.[9] Plasma half-lives in both pregnant ewes and fetal lambs are approximately 1.5 hours and associated with high heart rates and mean arterial blood pressures.[11] Intramuscular administration of midazolam (0.4 mg/kg) causes sedation and sternal recumbency in goats, with higher doses causing loss of consciousness and lateral recumbency.[5] Midazolam causes weakness, ataxia, and transient agitation in dogs and may result in analgesia in sheep.[9,12] High heart rates with increases in respiratory rates are observed at higher doses.[5] The duration of anesthesia when midazolam is combined with ketamine in goats ranges from 16 to 39 minutes.[5]

Abbreviations

AUC	Area under the concentration versus time curve
Emax	Maximum sedation score

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Midazolam has been used in camelids for sedation prior to anesthesia and as part of balanced anesthetic techniques.[13,14] Midazolam (0.25 mg/kg, IV) and ketamine (5 mg/kg, IV) have been used to induce anesthesia in alpacas prior to maintenance of anesthesia with isoflurane in a study[13] assessing the effects of dobutamine and norepinephrine. Prior to catecholamine administration, heart rate was within reference range, and mean arterial blood pressure, central venous pressure, systemic vascular resistance, and stroke volume were decreased but within expected values for anesthetized alpacas.[13] In a case report,[14] a balanced anesthetic technique including midazolam, fentanyl, ketamine, and isoflurane was successfully used to provide anesthesia for extensive dental surgery of a female alpaca.

The purpose of the study reported here was to determine the pharmacokinetics of midazolam after IV and IM administration and determine its sedative effects and effects on heart rate and respiratory rate in alpacas.

Materials and Methods

Alpacas—Six alpacas (3 males and 3 females; mean ± SD age, 4.3 ± 3.3 years; mean ± SD body weight, 64.5 ± 14.5 kg) were included in the study. Physical examination, fecal analysis, CBC, and serum biochemical analyses were performed prior to inclusion in the study to confirm the health of the alpacas. The alpacas were housed in single-sex groups in The Ohio State University Veterinary Medical Center and fed hay. Water was available continuously. All procedures were approved by the Institutional Animal Care and Use Committee of The Ohio State University.

Experimental design—Twelve hours prior to midazolam administration, alpacas were restrained for aseptic placement of jugular venous catheters. Alpacas that were refractory to restraint were sedated with xylazine[a] (0.6 mg/kg, IM) to facilitate placement of IV catheters. Briefly, the hair over the right jugular vein was clipped and the skin was aseptically prepared. Lidocaine[b] (20 mg/site) was injected SC at the catheter insertion site to desensitize the skin. A 16-gauge, 3.25-inch catheter[c] was placed in the right jugular vein for collection of venous samples to determine midazolam concentrations. In the IV administration group, a 20-gauge, 2-inch catheter[d] was placed in the left jugular vein for IV administration of midazolam following aseptic skin preparation and SC lidocaine infiltration as described. The catheters were capped, heparinized, and covered with bandage material to protect them until initiation of the study, which occurred 12 hours after catheter placement. Alpacas were placed in single-sex stalls with access to food and water until midazolam administration. Alpacas received midazolam[e] (0.5 mg/kg, IM or IV) in a randomized crossover design. Midazolam was administered as a rapid IV bolus (< 5 seconds) through the left jugular catheter, followed immediately by 10 mL of heparinized saline (0.9% NaCl) solution. Midazolam was administered IM in the semimembranosus-semitendinosus muscles. There was a minimum 2-week washout period between treatments.

Blood samples—Ten milliliters of blood was drawn from the right jugular venous catheter prior to collection of the sample for analysis at each sampling time. A 10-mL blood sample for analysis was collected by use of a separate syringe and placed in a blood collection tube. The initial 10 mL of blood was injected back into the catheter, and the catheter was flushed with 10 mL of heparinized saline solution. Blood samples were collected at time 0 (immediately prior to drug administration) and at 3, 12, and 24 minutes and 1, 1.5, 3, 4.5, 8, 12, and 24 hours following IV administration of midazolam. Time points were calculated from the time after the midazolam was administered and flushed with 10 mL of saline solution. Blood samples were collected at time 0 (immediately prior to drug administration) and at 5, 15, and 30 minutes, and 1, 1.5, 3, 4.5, 8, 12, and 24 hours following IM administration of midazolam. Blood samples were centrifuged within 1 hour after collection. Serum was separated and frozen at –70°C until assayed.

Midazolam and nevirapine analytic standards—Stock solutions of 1 mg/mL concentration of the analyte (midazolam)[f] and internal standard (nevirapine)[g] were prepared in methanol. The midazolam solution was serially diluted with 50% methanol to prepare standard curves of 0.2, 0.5, 1, 2, 5, 10, 20, 50, 100, 200, 500, and 1,000 ng/mL. A fixed amount of nevirapine (1 µg/mL) was diluted in 50% methanol to provide a 10 ng/mL solution.

Sample preparation—One hundred microliters of blank alpaca serum and samples from IV and IM administration were dispensed into clean microcentrifuge tubes and supplemented with 10 µL of internal standard solution (nevirapine, 1 µg/mL). Samples were extracted with 0.8 mL of ethyl acetate for 15 minutes on a shaker. The samples were centrifuged at 13,400 × *g* for 1 minute, and the ethyl acetate fraction was collected and evaporated to dryness under dry nitrogen. The residue was dissolved in 100 µL of 50% methanol and subjected to liquid chromatography–triple quadrupole mass spectrometry analysis. Samples containing > 1,000 ng of midazolam/mL were diluted 1:4 with blank alpaca serum prior to extraction.

Liquid chromatography–triple quadrupole mass spectrometry analysis of serum midazolam concentrations—Serum concentrations of midazolam were determined by means of liquid chromatography–triple quadrupole mass spectrometry[h] under electrospray ionization conditions with a high-performance liquid chromatography pump[i] and autosampler.[j] The sample extracts were analyzed on a column (length, 50 mm; internal diameter, 2.1 mm; particle diameter, 5 µm).[k] The mobile phase A (10mM ammonium formate containing 0.2% formic acid) and mobile phase B of methanol were used in isocratic mode with 0.1 mL/min flow rate for each. The analysis was conducted in positive mode, and the parameters, including capillary voltage, auxiliary gas pressure, and sheath gas pressure, were optimized to give the maximum sensitivity during the day of analysis. Transfer line temperature was 325°C. The tandem mass spectrometry conditions were set to detect the M + H ion of midazolam at 326 m/z and the

fragment ion at 291 m/z, with a collision energy of 37%. The tandem mass spectrometry conditions were set to detect the M + H ion of nevirapine at 267 m/z and the fragment ion at 226 m/z, with a collision energy of 25%.

Method validation—Under isocratic analytic conditions, the retention times of midazolam and internal standard were 2.9 and 2.1 minutes, respectively. The serum calibrators for midazolam determination were prepared separately at concentrations of 0.2, 0.5, 1, 2, 5, 10, 20, 50, 100, 200, 500, and 1,000 ng/mL at a fixed internal standard concentration as described. The ratios of the peak area of analyte and internal standard peaks were calculated and plotted against concentrations of each calibrator. The calibration curves were linear within the concentration ranges of 1 to 1,000 ng/mL for midazolam with $R^2 > 0.999$. The intra- and interday validation of the method inaccuracy and precision were performed in replicates (n = 6) of 1, 5, 50, and 500 ng/mL concentrations.

Pharmacokinetic analysis—Pharmacokinetic analysis of the individual concentration versus time data was performed with a computer program.[1] Briefly, data from each alpaca for the IV and IM administrations were plotted to determine number of compartments, and the data were subjected to compartmental analysis. The most appropriate model was chosen by evaluation of the correlation coefficient, Akaike information criterion, and residuals analysis. The best fit was obtained with a 2-compartment open model. Data for each alpaca for the primary pharmacokinetic parameters, secondary parameters, and derived data were tabulated, and the median and range were determined. In similar fashion, concentration versus time data for midazolam after IM administration were subjected to 2-compartment analysis with first-order absorption. The AUC from time 0 to the last time point was used to determine fractional absorption (bioavailability) after IM administration. Systemic availabilities after IM administration were tabulated and the median and range determined.

Pharmacodynamic measurements—Heart rate and respiratory rate were measured immediately prior to drug administration and 3, 12, 24, and 45 minutes and 1, 1.25, 1.5, 1.75, 2, 3, 4.5, 8, 12, and 24 hours following IV administration of midazolam and at 0, 5, 15, 30, and 45 minutes and 1, 1.25, 1.5, 1.75, 2, 3, 4.5, 8, 12, and 24 hours following IM administration of midazolam. Time to onset of sedation, time to peak sedation, and time to return to baseline sedation were recorded. The quality of sedation was graded on a scale of 0 to 4 on the basis of a published sedation scale used in llamas,[15] where grade 0 corresponded to no sedation; grade 1 corresponded to mild sedation characterized by slight lowering of the head or ear position, protrusion of the lower lip, delayed response to surroundings, or extension of the head and neck; grade 2 corresponded to obvious sedation with the same criteria for grade 1 with prolapsed nictitating membranes, decreased awareness, and mild ataxia without recumbency; grade 3 corresponded to obvious sedation with the same criteria for grade 2 with recumbency and rising easily with stimulation; and grade 4 corresponded to obvious sedation and recumbency, without rising after stimulation. Sedation scores were assessed at each time point that blood was collected and at any other time there was a noticeable change in sedation level. A subjective assessment of behavior was recorded during assessment of sedation. All sedation scores were assessed by 2 independent observers. Sedation and behavior were assessed first, followed by heart rate and respiratory rate, and then blood samples were collected to minimize the effect of handling on subjective and cardiorespiratory variables.

Pharmacokinetic and pharmacodynamic analyses—Quality of sedation after IV and IM administration of midazolam (0.5 mg/kg) was evaluated by modeling the drug concentrations observed in serum to measurements of sedation observed during the pharmacokinetic study. Pharmacodynamic effect was assessed by constructing drug concentration–drug response curves on the basis of the sigmoidal Emax model[1]:

$$E = (Emax \times C^{\gamma})/(C^{\gamma} + EC_{50}^{\gamma})$$

where E is the relative sedation response observed after IV or IM administration with 0.5 mg of midazolam/kg, C is the serum concentration, γ is the curve shape parameter, and EC_{50} is the serum drug concentration inducing 50% of the Emax.

Statistical analysis—Physiologic data were determined to be normally distributed by use of a Kolmogorov-Smirnov test and reported as mean ± SD values. A repeated-measures 1-way ANOVA was performed on the physiologic data in each treatment group with a Dunnett posttest. Time to onset of sedation, time to peak sedation, and time to return to baseline sedation were compared via a 1-tailed Wilcoxon signed rank test and results reported as median (range) values. Serum concentrations of midazolam at each time point were described as the median and range for both administration routes.

Pharmacokinetic values were determined by compartmental analysis of data with a computer program[1] to determine the best fit of the data. Pharmacokinetic-pharmcodynamic modeling was conducted on the basis of the sigmoidal effect model.[1] Method inaccuracy was expressed as relative SD at each concentration, whereas method precision was deter-

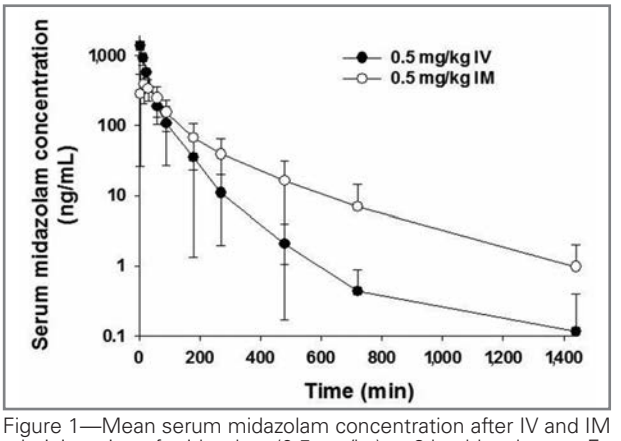

Figure 1—Mean serum midazolam concentration after IV and IM administration of midazolam (0.5 mg/kg) to 6 healthy alpacas. Error bars represent SD.

Table 1—Pharmacokinetic parameters for a 2-compartment open model after IV and IM administration of midazolam (0.5 mg/kg) to 6 healthy alpacas.

Parameter	IM	IV
A (ng/mL)	457 (49–413)	1,317.5 (1,111–1,412)
B (ng/mL)	48 (10.9–128)	57 (8.5–91.5)
α (1/min)	0.0017 (0.009–0.026)	0.037 (0.015–0.055)
β (1/min)	0.003 (0.002–0.007)	0.007 (0.0019–0.01)
$AUC_{0-tlast}$ (min•ng/mL)	44,556 (33,617–89,243)	47,073 (39,003–83,927)
k_{10} (1/min)	—	0.033 (0.014–0.038)
k_{12} (1/min)	—	0.003 (0.006–0.013)
k_{21} (1/min)	—	0.009 (0.002–0.0121)
Maximum serum concentration (ng mL)	411 (217–675)	1,394 (1,150–1,503)
Total body clearance (mL/min/kg)	—	11.3 (6.7–13.9)
Volume of distribution at steady state (mL/kg)	—	525 (446–798)
Distribution half-life (min)	41 (30.2–79.8)	18.7 (12.6–46.5)
Elimination half-life (min)	234 (102–320)	98 (67–373)
Bioavailability (%)	92 (78–125)	—

Data are median (range).
— = Not applicable. A = Zero-time intercept for the initial phase. α = Rate constant associated with the initial phase. $AUC_{0-tlast}$ = Area under the curve from time 0 to the last quantifiable time point. B = Zero-time intercept for the terminal phase. β = Rate constant associated with the terminal phase. k_{10} = Microrate constant for central compartment to outside body. k_{12} = Microrate constant for transfer from central to peripheral compartment. k_{21} = Microrate constant for transfer from peripheral compartment to central compartment.

mined via a 1-way ANOVA. Values of $P < 0.05$ were considered significant.

Results

The ratios of midazolam to nevirapine (internal standard) versus concentration in calibrators were linear over the range of 1 to 1,000 ng/mL ($R^2 > 0.999$). The lower limit of quantification of this method was 1 ng/mL, and the lower limit of detection was 0.2 ng/mL. The within-day method inaccuracy was 5.8%, 0.86%, 1.6%, and 2.1% at the tested concentrations of 500, 50, 5, and 1 ng/mL, respectively. The between-day method inaccuracy was 4.4%, 3.4%, 2.4%, and 5% over this same range of calibrators. The within-day method precision was 2.8%, 1.6%, 2.2%, and 6.6% at the tested concentrations of 500, 50, 5, and 1 ng/mL, respectively. Between-day precision was 4.6%, 4.8%, 4.7%, and 5.5% at the tested concentrations of 500, 50, 5, and 1 ng/mL, respectively.

The serum concentration versus time data best fit a 2-compartment open model (**Figure 1**). Midazolam was detectable in 1 of 6 alpaca serum samples 24 hours after IV administration. Median maximum serum concentration of midazolam measured after IV administration was observed at the first sample time (3 minutes after injection; **Table 1**). The distribution half-life was 18.7 minutes, and the elimination half-life was 98 minutes. The total clearance of midazolam from alpaca serum after IV administration was 11.3 mL/min/kg of body weight. The volume of distribution at steady state was 525 mL/kg of body weight.

Serum concentrations of midazolam after IM administration were detectable in 4 of 6 alpacas at 24 hours. Median maximum midazolam concentrations (411 ng/mL) were observed between 5 and 30 minutes after administration (Table 1). The distribution half-life after IM administration was 41 minutes, and elimination half-life after IM administration was 234 minutes. Comparing the AUC after IM administration to that after IV administration, systemic availability of midazolam in alpacas was 92%.

Table 2—Cardiopulmonary variables in 6 healthy alpacas administered midazolam (0.5 mg/kg) IV or IM.

	Heart rate		Respiratory rate	
Time	IV	IM	IV	IM
0 min	59 ± 8	56 ± 8	33 ± 10	30 ± 9
3 min	83 ± 18*	—	52 ± 28*	—
5 min	—	59 ± 4	—	31 ± 7
12 min	76 ± 18	—	36 ± 12	—
15 min	—	64 ± 9	—	34 ± 15
24 min	78 ± 23*	—	42 ± 23	—
30 min	—	65 ± 7	—	30 ± 11
45 min	70 ± 9	62 ± 9	41 ± 7	31 ± 10
1 h	67 ± 12	59 ± 10	31 ± 7	27 ± 8
1.25 h	61 ± 7	55 ± 5	32 ± 7	27 ± 6
1.5 h	57 ± 5	55 ± 8	29 ± 6	27 ± 9
1.75 h	63 ± 6	53 ± 5	26 ± 6	24 ± 4
2 h	57 ± 4	56 ± 5	27 ± 3	26 ± 5
3 h	59 ± 3	53 ± 3	28 ± 6	25 ± 5
4.5 h	53 ± 3	55 ± 7	23 ± 4	25 ± 4
8 h	53 ± 8	59 ± 5	26 ± 4	26 ± 4
12 h	59 ± 9	52 ± 7	23 ± 3	22 ± 2
24 h	54 ± 7	57 ± 6	24 ± 4	25 ± 4

Data are mean ± SD.
*Value is significantly ($P < 0.05$) different from the baseline value for the same treatment group.
— = Not applicable.

Pharmacodynamic results—Heart rate and respiratory rate increased in all alpacas within 3 minutes after IV administration of midazolam (**Table 2**). Heart rate was not different at 12 minutes but was increased at 24 minutes in the IV group. Heart rate and respiratory rate did not change in alpacas following IM administration of midazolam. The time to peak sedation in the IV group was 0.4 minutes (**Table 3**). The time to peak sedation in the IM group was 15 minutes. The degree of sedation was significantly higher in the IV group (peak sedation score, 4) than the IM group (peak sedation score, 2). The peak sedative effect occurred significantly faster in the IV group (0.4 minutes) than in the IM group (22.5 minutes). There was no difference in time to return to baseline sedation between the IV and IM groups.

Table 3—Sedation variables in 6 healthy alpacas administered midazolam (0.5 mg/kg) IV or IM.

Variable	IV	IM
Time to onset of sedation (min)	0.4 (0.25–0.5)*	15 (5–30)
Peak sedation score	4 (4)*	2 (1–4)
Time to peak sedation (min)	0.4 (0.25–0.5)*	22.5 (15–30)
Time to return to baseline sedation (min)	105 (90–120)	105 (75–270)

Data are median (range).
*Value is significantly ($P < 0.05$) different from IM treatment group.
Timed sedation data were measured from the time that midazolam was administered.

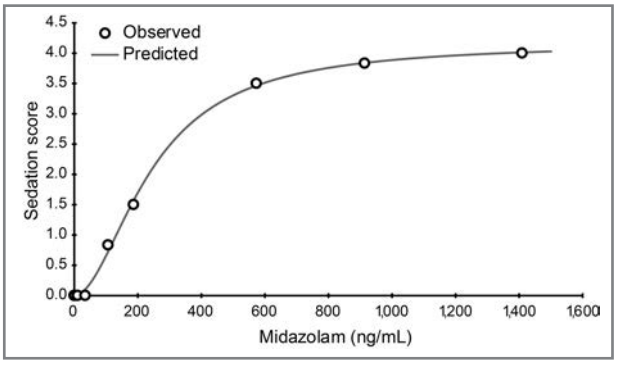

Figure 2—Results of the Hill equation ($E = [4.16 \times C^{188}]/[C^{188} + 244^{188}]$) for midazolam (0.5 mg/kg) administered IV to 6 healthy alpacas.

Pharmacokinetic and pharmacodynamic correlation—The highest sedation scores occurred within 3 minutes after IV administration. Sedation scores remained increased at their maximal level for 12 minutes in 5 of 6 alpacas, 24 minutes in 4 of 6 alpacas, and 75 minutes in 1 of 6 alpacas. Sedation scores gradually decreased and returned to baseline status by 90 minutes after administration in 3 of 6 alpacas and by 120 minutes in all alpacas. Sedation scores after IM administration of midazolam differed from those after IV administration. Moderate sedation (scores 2 or 3) was observed in 4 of 6 alpacas from 15 to 45 minutes, after which sedation scores decreased to baseline between 75 and 105 minutes after midazolam administration. A sedation score of 1 was observed within 5 minutes after IM administration in one alpaca, and another had a sedation score of 4 (deepest sedation) from 30 to 45 minutes. Serum concentrations of midazolam in alpacas after IV administration correlated well with the observed sedation scores as assessed by the sigmoidal Emax model (**Figure 2**). Further, there was no observed delay in the onset of sedation between serum concentration and sedation (the sedation score at a serum drug concentration of 0 ng/mL was 0). The Emax after IV midazolam administration was 4.0 ± 0.09 (at 1,410 ng/mL), the serum drug concentration inducing 50% of the Emax was 244 ± 11.8 ng/mL, and the curve shape coefficient (Hill constant) was 1.88 ± 0.12.

Discussion

Midazolam induced sedation in alpacas after IV and IM administration. The level of sedation was greater after IV administration and the duration of sedation varied in each group. The level of sedation correlated to serum concentrations in the IV administration group but could not be correlated in the IM administration group. Midazolam was rapidly and almost completely absorbed after IM administration. Increases in heart rate and respiratory rate occurred in both groups.

Obvious sedation (sedation scores > 0) was observed in alpacas from 3 to 75 minutes after IV administration of midazolam. Midazolam did not cause restlessness, agitation, or a state of heightened arousal in healthy alpacas as has been observed in dogs and cats.[9,16,17] Following IV administration, sedation with recumbency (lateral or sternal) occurred within 30 seconds in all alpacas, similar to the responses seen in goats and humans.[5,10] Healthy human test subjects fell asleep following IV administration of 5 mg of midazolam and continued to sleep for up to 2 hours.[10] Sedation and increased approachability occurred within 15 minutes following IM administration of midazolam, with 4 of 6 alpacas assuming sternal or lateral recumbency. Sedation and ataxia were correlated in this study because of the qualitative scale used for the pharmacodynamic parameters. Muscle relaxation was not evaluated independently but presumably was present and was assessed in conjunction with sedation and ataxia and resultant sternal or lateral recumbency. Muscle relaxation was considered substantial in cats after high doses of midazolam (5.0 mg/kg) were administered IV or IM but was also present after lower doses were administered IV or IM.[16] In the present study, duration of recumbency following IV administration was variable, with 5 of 6 alpacas standing within 45 minutes. This is consistent with other species and reflects the large volume of distribution, short half-life, and rapid clearance of midazolam.

The pharmacokinetic properties of midazolam in alpacas were comparable to those reported in other species.[6,9–11] The volume of distribution of midazolam in alpacas was smaller than that observed in dogs and humans, the elimination half-life of midazolam in alpacas after IV administration was similar to that in dogs and shorter than in humans, and total body clearance in alpacas was greater than in humans but less than in dogs.[9,10] The elimination half-life of midazolam after IM administration was more than twice that observed after IV administration in alpacas, whereas in dogs, the elimination half-life following IV administration was comparable to the elimination half-life following IM administration of midazolam.[9] Plasma concentrations of midazolam were prolonged after IM administration in comparison to the same dose administered IV. Four alpacas had detectable midazolam at 24 hours, but only 3 had quantifiable concentrations of midazolam (the midazolam concentration in 1 alpaca was less than the limit of quantification), resulting in a longer elimination time and longer elimination half-life in the IM administration group. However, the AUC after IM administration was nearly the same as that determined after IV administration, indicating good absorption and high bioavailability following IM administration (92%), similar to that measured in dogs (> 90%).[9] This compared well with bioavailability observed in other spe-

cies, making IM administration a clinically relevant mode of inducing sedation in alpacas that are difficult to approach or restrain.[9]

The pharmacodynamic parameters derived from the sigmoidal Emax equation indicated that serum concentrations of midazolam were highly correlated with the observed qualitative sedation scores in alpacas. Estimating the sedative effects of midazolam on the basis of an administered dose appears possible, although correlation of dose with quality of sedation requires further evaluation. For example, a constant rate infusion of midazolam to maintain serum concentrations in a specific range could help to define doses needed for a specific sedative effect.

Transient increases in heart rate and respiratory rate occurred immediately following administration, confirming that the physiologic response to midazolam in the alpacas was similar to sheep, humans, and dogs.[6,11,17] Mean heart rate increased by 24 beats/min (71% increase) and mean respiratory rate increased by 19 breaths/min (63% increase) by 3 minutes following IV administration of midazolam. In comparison, heart rate increased in dogs following IV midazolam administration by 15% and in goats by 25%.[5,18] Additionally, mean arterial blood pressure decreased in dogs and cardiac output increased slightly following administration of midazolam at doses of 1 and 10 mg/kg, IV.[18] Other cardiovascular variables such as mean arterial blood pressure and cardiac output were not evaluated in the present study, but given the increases in heart rate observed in alpacas, it is possible that arterial blood pressure may decrease and overall cardiac output would increase. Further study is necessary to define these cardiovascular effects in alpacas.

Although it is possible that the administration of xylazine may have affected these results, it is unlikely given the 12-hour interval between xylazine administration and the administration of midazolam and the finding that no alpaca had residual sedation immediately prior to midazolam administration. In addition, all alpacas received xylazine for catheter placement, limiting the confounding of the results. At present, the pharmacokinetics and pharmacodynamics of midazolam following IV and IM administration indicate that midazolam provides a short duration of action with moderate levels of sedation and minimal cardiovascular or behavioral adverse effects.

a. Xylazine, Vedco Inc, St Joseph, Mo.
b. Lidocaine, Vedco Inc, St Joseph, Mo.
c. Angiocath, Parke, Davis & Co, Sandy, Utah.
d. Surflo catheter, Terumo Medical Corp, Elkton, Md.
e. Midazolam, Hospira Inc, Lake Forest, Ill.
f. Midazolam, United States Pharmacopeia, Rockville, Md.
g. Nevirapine, Boehringer Ingelheim Pharmaceutics Inc, Ridgefield, Colo.
h. TSQ Vantage triple stage quadrupole mass spectrometer, ThermoFisher Scientific, San Jose, Calif.
i. LC-20AD HPLC pump, Shimadzu, Columbia, Md.
j. LC-20AC Autosampler, Shimadzu, Columbia, Md.
k. Betabasic, 8 column, ThermoFisher Scientific, San Jose, Calif.
l. WinNonlin, version 5.2, Pharsight Corp, St Louis, Mo.

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