Pharmacokinetics of intravenously administered caffeine in healthy alpacas (Lama pacos) and llamas (Lama glama)

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Objective—To determine the pharmacokinetic disposition of IV administered caffeine in healthy Lama spp camelids.

Animals—4 adult male alpacas and 4 adult female llamas.

Procedures—Caffeine (3 mg/kg) was administered as an IV bolus. Plasma caffeine concentrations were determined by use of high-performance liquid chromatography in 6 animals and by use of liquid chromatography–mass spectrometry in 2 llamas.

Results—Median elimination half-life was 11 hours (range, 9.3 to 29.8 hours) in alpacas and 16 hours (range, 5.4 to 17 hours) in llamas. The volume of distribution at steady state was 0.60 L/kg (range, 0.45 to 0.93 L/kg) in alpacas and 0.75 L/kg (range, 0.68 to 1.15 L/kg) in llamas. Total plasma clearance was 44 mL/h/kg (range, 24 to 56 mL/h/kg) in alpacas and 42 mL/h/kg (range, 30 to 109 mL/h/kg) in llamas.

Conclusions and Clinical Relevance—High-performance liquid chromatography and liquid chromatography–mass spectrometry were suitable methods for determination of plasma caffeine concentrations in alpacas and llamas. Plasma caffeine concentration-time curves were best described by a 2-compartment model. Elimination half-lives, plasma clearance, volume of distribution at steady state, and mean residence time were not significantly different between alpacas and llamas. Intravenous administration of caffeine at a dose of 3 mg/kg did not induce clinical signs of excitement. (Am J Vet Res 2006;67:1063–1069)

Hepatic lipidosis in camelids is a relatively uncommon clinical entity that can be difficult to treat.1–4 It is a multifactorial disease characterized by excessive fat mobilization secondary to negative energy balance, and clinical signs are often not apparent until later stages of the disease.5 A negative energy balance may result from concurrent disease conditions; inadequate nutrition; and stress associated with transport, parturition, or lactation.2 Excessive fat mobilization leads to hepatic lipidosis.1 The hepatic lipidosis syndrome in South American camelids is characterized by inappetence; weight loss; high serum concentrations of glucose, bilirubin, bile acids, and nonesterified fatty acids; high serum alkaline phosphatase, γ-glutamyltransferase, and sorbitol dehydrogenase activities; and decreased responses to insulin.6,9 Lactating and pregnant camelids appear to be at greater risk for developing hepatic lipidosis because of increased energy demands imposed by the mammary gland and developing fetuses.1,5

Serum biochemical markers used to assess hepatocyte integrity (eg, sorbitol dehydrogenase and aspartate aminotransferase activities), biliary function (eg, γ-glutamyltransferase activity), and liver excretion (eg, concentration of bile acids) increase earlier in feed-restricted llamas that develop hepatic lipidosis, compared with llamas that do not develop hepatic lipidosis.5 Those findings suggest that feed restriction during periods of increased energy demand may result in subclinical liver dysfunction.6 Definitive diagnosis of lipidosis is typically made on the basis of results of histologic examination of liver biopsy specimens.1,12,13 However, less invasive tests of hepatic function may prove useful in assessing hepatopathy and hepatocyte damage in animals that are at risk.

Reference values for caffeine clearance have been determined for multiple species. Caffeine clearance is a useful measure of hepatic function because caffeine has low toxicity, is simple to measure, and has an elimination half-life that is highly correlated with hepatic function.14–15 The purpose of the study reported here was to determine total plasma clearance and elimination half-life of caffeine in clinically normal alpacas and llamas.

Materials and Methods

Animals—Four castrated adult male alpacas and 4 adult female llamas were used. Animals were housed on fescue pasture and received supplemental grass hay. All were determined to be healthy on the basis of complete physical exam-
ination and results of a CBC and serum biochemical analysis. Animals were placed in stalls in groups of 2 and allowed to acclimate to confinement for 1 week prior to initiation of the study. All llamas and alpacas were observed to be consuming grass hay and water and urinating and defecating normally. On the day before the start of the study, each animal was weighed and an IV catheter was placed in each jugular vein; 1 catheter was used for drug administration, and the other was used for blood sampling. Prior to drug administration, after drug administration, and after sample collection, catheters were flushed with heparinized saline (0.9% NaCl) solution. Procedures were reviewed and approved by the institutional animal care and use committee of each institution (ie, University of Missouri and The Ohio State University).

Experimental design—Caffeine was administered (dose, 3 mg/kg IV) as caffeine and sodium benzoate in a sterile pyrogen-free normal saline solution (concentration, 50 mg of caffeine/mL of solution) through 1 of the catheters. Hemiparetic blood samples (7 mL) were withdrawn from the contralateral catheter at the time of administration and 3, 6, 12, 30, and 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 4.5, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours after administration. Sampling point times were similar to those previously report.

Plasma was harvested by centrifugation of heparinized whole blood at 1,000 X g for 10 minutes, placed in individual cryovials, and stored at –70°C until analyzed. Four sets of alpaca blood samples and 2 sets of llama blood samples were analyzed via HPLC at the University of Missouri. The 2 remaining sets of llama samples were analyzed via LC-MS at The Ohio State University.

Preparation of caffeine stock solutions for use in HPLC determination of plasma caffeine concentrations—Stock solutions (A) of caffeine were prepared by dissolving 100 mg of caffeine in 10 mL of methanol-water (50:50, vol/vol; end concentration, 10 mg of caffeine/mL). Stock solution A was stored in darkness at 4°C. Working standard solutions of caffeine were prepared daily by dilution of stock solution A in methanol-water (50:50, vol/vol) to 1 mg/mL (B), 0.1 mg/mL (C), and 0.01 mg/mL (D). Appropriate volumes of stock solutions A, B, C, and D were added to 0.25 mL of blank alpaca plasma for preparation of plasma caffeine calibrators ranging in concentration from 0.031 µg of caffeine/mL to 64 µg of caffeine/mL. Plasma caffeine calibrators were prepared, extracted, and analyzed with each set of experimental samples. In addition, negative control samples (ie, blank alpaca plasma with no detectable caffeine) were prepared and extracted with each batch of experimental samples.

Sample preparation for HPLC determinations—Plasma samples were thawed at ambient temperature and mixed to assure homogeneity. Three 250-µL aliquots of each plasma sample were pipetted into individual tubes. Samples were prepared according to a described protocol involving acid precipitation of protein and injection of the protein-free supernatant solutions onto the chromatograph. In brief, to each 250-µL aliquot of plasma, an equal volume of 0.8M perchloric acid was added; resulting samples were mixed vigorously and centrifuged at 14,000 X g for 20 minutes at 21°C. A 200-µL aliquot of clarified supernatant solution was transferred from each tube to an autosampler vial containing 10 µL of 4M NaOH. Vials were capped and mixed, and 50 µL was injected onto the liquid chromatograph.

HPLC system—An HPLC pump and controller, autosampler, and dual-wavelength UV detector were used for analyses. The mobile phase was modified from a previously used mixture to optimize retention time and peak shape with the column (25 X 0.46 cm; 5-µm particle size) used in the present study. The mobile phase was 20M phosphate buffer (pH, 3.0)-acetonitrile, 85:15 (v/v), at a flow rate of 1 mL/min. Caffeine in test samples was quantified on the basis of characteristic retention time and UV absorbance at 273 nM, in comparison with caffeine standards.

Data were recorded by use of a computer workstation and chromatography software. Daily sample analysis included the running controls, calibrators, and experimental samples, all of which were prepared, extracted, and analyzed together.

Preparation of caffeine and 8-chlorocaffeine stock solutions for use in LC-MS determination of plasma caffeine concentrations—Caffeine reference standard solutions (1.0 mg/mL) were obtained from commercial sources. Working standard solutions (10 ng/µL; A and B) were prepared by diluting 0.1 mL of each of the reference standard solutions with methanol to a volume of 10.0 mL. Further 10-fold dilutions of A and B were made to prepare 1.0 ng/µL standard solutions (C and D). The gravimetric reference standard solution of 8-chlorocaffeine (E; internal standard with a concentration of 1.0 mg/mL) was prepared by dissolving 50 mg of 8-chlorocaffeine in 50 mL of methanol. Working internal standard solution (F; 10 ng/µL) was prepared by diluting 0.1 mL of the gravimetric standard solution to a volume of 10 mL with methanol. Stock solutions were stored in darkness at 4°C.

Sample preparation for use in LC-MS determinations—Appropriate volumes of working standard caffeine solutions (A and C) were added to 0.5 mL of blank alpaca plasma for preparation of 2 sets of caffeine calibrators (0.025 to 1.0 µg/mL and 1.0 to 20.0 µg/mL) in blank alpaca plasma. Control samples were prepared from negative control plasma by adding appropriate volumes of working standard solutions (B and D). To each experimental sample, calibrator, and control sample, 0.25 µg of 8-chlorocaffeine was added, samples were vortexed, and 2 mL of 1M sodium acetate buffer (pH, 5) was added. After mixing, 4 mL of methylene chloride-isopropanol (9:1, vol/vol) was added, tube contents were vortexed for 10 minutes, and tubes were centrifuged at 1,000 X g for 5 minutes. Bottom (solvent) layers were transferred to clean tubes and evaporated under nitrogen at 40 ± 5°C. Dried residues were dissolved in 35 µL of methanol, and that mixture was added to 215 µL of aqueous 30 mM ammonium formate (pH, 6.5). Sample extracts were transferred to autosampler vials and injected onto the LC-MS system. Control samples included negative control (ie, no detectable caffeine), positive controls (0.03, 0.8, 1.2, and 16.0 µg of caffeine/mL; 0.25 µg of 8-chloro-

LC-MS system—Plasma caffeine concentrations were determined by use of LC-MS in 2 llamas. Briefly, caffeine was quantified by use of an LC-MSD trap/equipped with a guard column (2.1 X 12.5 mm; 5 µm) and C18 (2.1 X 150 mm; 3 µm) analytical column. The mobile phase (solvent A, 30 mM ammonium formate with pH of 6.5; solvent B, methanol) was delivered at a flow rate of 0.3 mL/min. The gradient developed was 1% solvent B from time 0 to time 1.0 minute, with ramp from 1% to 85% solvent B from time 1.0 minute to time 6.5 minutes; hold from time 6.5 minutes to time 8.5 minutes; and 16% solvent B from time 8.5 minutes to time 15.0 minutes. Column temperature was maintained at 35°C, and 10 µL of each sample extract was injected. The mass spectrometer was operated in positive-ion mode at normal resolution with nitrogen flow at 9 L/min (dry gas temperature, 365°C). The mass spectrometer was tuned to m/z 305 at 20 V (skimmer), 110-V capillary exit, octapole 1 (14 V), octapole 2 (2.5 V), octapole RF (80 V), lens 1 voltage (–5 V), and lens 2 voltage (–60 V). Mass spectrometer parameters were as follows: caffeine transition: m/z 195 → 110,
method validation: standard curves, detection limit, and recovery—The limit of quantitation for determining caffeine concentration in plasma via HPLC was estimated by injection of a standard solution of caffeine in mobile (0.0625, 0.5, 8.0, and 64 µg/mL), and a minimum of 3 replicates was analyzed at each fortification level. Each replicate was injected in triplicate, and the mean concentration of caffeine in each replicate was used to determine concentration from the intercept and slope of the line of that day's calibration curve. Those plasma fortifications were prepared and analyzed on 4 separate days. Within-day accuracy was determined on the basis of the lowest concentration with a signal-to-noise ratio of 3.1. Known concentrations of caffeine in plasma were used to determine recovery of caffeine from acid-precipitated plasma samples. Recovery was calculated by use of this equation:

\[
\% \text{ Recovery} = \frac{PA_{\text{extracted}} \times 100}{PA_{\text{non-extracted}}}
\]

where PA is peak area of caffeine extracted from plasma by acid precipitation or peak area of the same quantity of caffeine added directly to mobile phase in an autosampler vial.

HPLC accuracy and precision—Blank alpaca plasma was used to prepare control samples at 4 fortification levels (0.0625, 0.5, 8.0, and 64 µg/mL of caffeine/mL), and a minimum of 3 replicates was prepared at each fortification level. Each replicate was injected in triplicate, and the mean value of the peak area of caffeine in each replicate was used to determine concentration from the intercept and slope of the line of that day's calibration curve. Those plasma fortifications were prepared and analyzed on 4 separate days. Within-day accuracy was determined each day for each fortification level as the difference in concentration between caffeine detected and caffeine added and determining the relative SD for difference between days.

The corresponding concentration was the limit of quantitation for determinations of the peak area ratio versus the caffeine concentration in the corresponding calibrator. Plasma caffeine concentrations determined from analyses of positive control samples (nominally 0.03, 0.8, 1.2, and 16.0 µg of caffeine/mL) by use of LC-MS analysis were subjected to similar calculations to determine assay accuracy and precision. Positive control samples from 2 sources were used to independently verify results.

HPLC method validation: standard curves, detection limit, and recovery—The ratio of peak area of caffeine-to-peak area of 8-chlorocaffeine was calculated for each calibrator, control sample, and experimental sample extract. Concentrations of caffeine in experimental and control samples were calculated from the slope and intercept of the equation for the calibration line obtained by linear regression analysis of the peak area ratio versus the caffeine concentration in the corresponding calibrator. Plasma caffeine concentrations determined from analyses of positive control samples (nominally 0.03, 0.8, 1.2, and 16.0 µg of caffeine/mL) by use of LC-MS analysis were subjected to similar calculations to determine assay accuracy and precision. Positive control samples from 2 sources were used to independently verify results.

Pharmacokinetic analysis—Plasma concentration-versus-time data were summed, and mean ± 1 SD was determined for alpacas (n = 4) and llamas (4). Log plasma concentration-versus-time data underwent compartmental analysis by use of commercially available software. Zero-time plasma drug concentration intercepts of the biphasic IV disposition curve (A, B) were determined via the computer program by extrapolation of the plasma caffeine concentration to t = 0 for the distribution phase (A) and terminal exponential phase (B). The hybrid rate constants of the biphasic IV disposition curve (α and β) are related to the slopes of the distribution and elimination phase, respectively. The first-order elimination rate constant for disappearance of the drug from the central compartment is K121, whereas the first-order transfer rate constants for drug distribution between the central and peripheral compartments are K12 and K21, respectively. The total plasma clearance was estimated according to this equation:

\[
Cl_{\text{tot}} = \frac{IV_{\text{dose}}}{AUC}
\]

where AUC is area under the concentration-versus-time curve.

The apparent volume of the central (V1) and peripheral (V2) compartments and volume of distribution at steady state (Vss) were estimated from this equation:

\[
V_{\text{ss}} = \frac{IV_{\text{dose}} \cdot AUMC}{(AUC)^2}
\]

where A is the zero-time plasma drug concentration intercept for the distribution phase and B is the zero-time plasma drug concentration intercept for the terminal exponential phase (B).

This equation was used to calculate Vss:

\[
V_{\text{ss}} = \frac{IV_{\text{dose}} \cdot AUMC}{(AUC)^2}
\]

where AUMC is the area under the first moment of the curve.

This equation was used to calculate V2:

\[
V_2 = \frac{Cl_{\text{tot}}}{K_{21}}
\]

Distribution half-life (h) was calculated by use of the following equation:

\[
T_{1/2\alpha} = \ln 2 \div \alpha
\]

where ln 2 = 0.693 and α is the slope of the initial log-linear segment of the concentration-time curve.
Elimination half-life was calculated by use of the following equation:

$$T_{1/2} = \frac{\ln 2}{\beta}$$

where \(\ln 2 = 0.693\) and \(\beta\) is the slope of the terminal log-linear segment of the concentration-time curve.

The maximum plasma concentration for each data set is represented by \(C_{\text{peak}}\).

Area under the curve from time of dosing to infinity was calculated by use of this equation:

$$\text{AUC} = \frac{A + B}{\alpha} \frac{\alpha}{\beta}$$

The AUMC from time of dosing to infinity was calculated by use of the following equation:

$$\text{AUMC} = \frac{A + B}{\alpha} \frac{\alpha^2}{\beta^2}$$

Mean residence time was determined from the ratio of AUMC to AUC according to the following equation:

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}}$$

The compartmental model that best described the data for each animal was chosen on the basis of the Akaike information criterion.\(^1\) Individual animal coefficients of the compartmental models and variables derived from those coefficients were reported as median and range. Pharmacokinetic variables obtained from alpaca and llama data were compared by use of the rank sum test.

**Results**

Plasma caffeine concentrations were readily determined in alpaca and llama plasma by use of the HPLC-UV method. Retention time of caffeine in the system was 9.5 to 10.4 minutes. Recovery of caffeine from camelid plasma was good (> 85%) over the range of concentrations examined (Table 1). When caffeine-fortified samples prepared in alpaca plasma (at concentrations of 0.0625, 0.5, 8.0, and 64 \(\mu\)g of caffeine/mL) were assayed via HPLC, recoveries were 106%, 87%, 94%, and 89%, respectively.

In test samples, retention times of caffeine (7.4 to 7.5 minutes) and the internal standard (8.9 to 9.0 minutes) as determined by use of LC-MS were within ± 2% of values observed in the corresponding standards, and no interference from other substances was observed. Caffeine recoveries from positive-control plasma samples (at concentrations of 0.03, 0.8, 1.2, and 16 \(\mu\)g/mL) as assayed by use of LC-MS were 92%, 95%, 95%, and 105%, respectively (Table 1).

Regression analysis of 6 calibration curves generated by use of HPLC indicated that the relationship between peak area and caffeine concentration was linear over the range examined (\(r^2 > 0.994\)). The limit of quantitation for the HPLC assay for caffeine in plasma was 0.0625 \(\mu\)g/mL. Regression analysis of the 5 calibration curves generated by use of LC-MS indicated that the relationship between the ratio of peak area (caffeine/internal standard) and caffeine concentration was linear over the range examined (\(r^2 > 0.993\)). The limit of quantitation for the LC-MS method was approximately 0.025 \(\mu\)g/mL.

Within-and between-day accuracy for HPLC analysis as determined by the relationship between concentration added and concentration detected indicated that there was < 15% variation in replicate determinations at all fortification levels on the 4 days (Table 1). Assay precision was < 15% for within-day and < 15% for between-day determinations at all concentrations except 0.0625 \(\mu\)g/mL, for which the relative SD for between-day precision was < 20%. Both within- and within-day accuracies for the LC-MS assay were < 10% for concentrations from 0.030 \(\mu\)g/mL to 16 \(\mu\)g/mL.

Plasma caffeine concentrations remained above the HPLC-method limit of quantitation for 72 hours in all alpaca samples and in the 2 samples from llamas. Plasma caffeine concentrations remained above the HPLC-method limit of quantitation for 120 hours in 1 llama and above the LC-MS limit of quantification for 120 hours in the 2 llamas.

Plasma concentrations of caffeine in alpacas and llamas were summarized (Figure 1). Concentration-time data were best described by a biexponential equation corresponding to a 2-compartment open-pharmacokinetic model. Pharmacokinetic variables for alpacas and llamas derived from 2-compartment analysis of concentration-time data were summarized (Table 2). No significant differences between

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**Table 1**—Summary of data from HPLC and LC-MS assays for between- and within-day accuracy and precision and percentage recovery of drug after extraction over the range of concentrations used to prepare the standard curves. Data represent percentages of values observed in the corresponding standards.

<table>
<thead>
<tr>
<th>Concentration ((\mu)g/mL)</th>
<th>Between-day</th>
<th>Between-day</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>accuracy</td>
<td>precision</td>
<td></td>
</tr>
<tr>
<td>HPLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>11.2</td>
<td>0.4</td>
<td>5.0</td>
</tr>
<tr>
<td>8</td>
<td>1.9</td>
<td>0.6</td>
<td>4.6</td>
</tr>
<tr>
<td>0.5</td>
<td>1.8</td>
<td>0.8</td>
<td>3.4</td>
</tr>
<tr>
<td>0.0625</td>
<td>0.8</td>
<td>0.6</td>
<td>3.5</td>
</tr>
<tr>
<td>LC-MS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>5.2</td>
<td>0.4</td>
<td>10.5</td>
</tr>
<tr>
<td>1.2</td>
<td>5.3</td>
<td>0.4</td>
<td>9.5</td>
</tr>
<tr>
<td>0.8</td>
<td>6.3</td>
<td>0.4</td>
<td>9.5</td>
</tr>
<tr>
<td>0.03</td>
<td>2.5</td>
<td>0.4</td>
<td>9.5</td>
</tr>
</tbody>
</table>

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\(^1\) The compartmental model that best described the data for each animal was chosen on the basis of the Akaike information criterion.
pharmacokinetic variables for alpacas and llamas were detected ($P < 0.05$).

**Discussion**

The HPLC method used in the present study for determination of plasma caffeine concentration was modified from methods used in previous studies by changing the length of the column (to 250 mm from 150 mm) and by increasing the buffer strength (to 20mM from 7.3mM phosphate at pH 3.0) and acetonitrile concentration (to 15% from 13%) in the mobile phase. Those modifications improved peak shape, retention time, and separation of the caffeine peak from interfering peaks. To reduce the effects of a strong base on column packing material, the volume of 4M NaOH solution that was added to each sample prior to injection was reduced (to 10 µL from 27 µL), compared with the volume of solution reported previously. Those changes were not associated with alterations in peak shape or retention time (9.5 to 10.4 minutes) of caffeine in alpaca and llama plasma, and there was no interference from early peaks associated with injection events. The accuracy and precision of the results of these determinations indicate that both HPLC and LC-MS analytic methods are suitable for analysis of caffeine in alpaca and llama plasma.

The pharmacokinetic variables determined by compartmental analysis of concentration-versus-time data for caffeine administered IV at a dose of 3 mg/kg were not significantly different between alpacas and llamas. Results also revealed that the pharmacokinetic properties of caffeine in alpacas and llamas were similar to disposition of the drug in other species. Values for total plasma caffeine clearance, elimination half-life, and mean residence time in adult alpacas and llamas were similar to those reported for horses, donkeys, sheep, cattle, and dogs. The combination of lower total plasma clearance and a comparable volume of distribution results in longer elimination half-life. Values for total plasma caffeine clearance, elimination half-life, and mean retention time in camels differ substantially from values in alpacas, llamas, other domesticated livestock species, and dogs. In camels, the combination of lower total plasma clearance and a comparable volume of distribution results in longer elimination half-life.

Variation among individual animals and in method may have limited detection of differences in caffeine clearance between alpacas and llamas. The small number of animals limited the power of the study for detect-
under similar conditions as those described \(^{13,18}\) for caffeine, theobromine, and paraxanthine (both of which are metabolites of caffeine). \(^{13} \) Little information regarding drug metabolism pathways for South American camelids is available at present. Because expression of hepatic cytochrome P450 isozymes is specific and the various isoforms of P450 are substrate selective, determination of caffeine clearance and metabolic fate of caffeine in camelids may improve our understanding of hepatic metabolism of other drugs in those species. \(^{13} \) For example, the metabolic fate of phenylbutazone in cattle is markedly different from that in a number of other species. The elimination half-life of phenylbutazone in mature dairy cows (40 hours) and bulls (62 hours) is longer than that in llamas (2 hours). \(^{23,26} \) Because phenylbutazone is metabolized primarily in the liver, species differences in metabolic pathways or phenylbutazone disposition may reflect differences in expression or activity of hepatic drug–metabolizing enzymes. Assessment of caffeine metabolite profiles after caffeine administration may prove useful in understanding which metabolic pathways are used for caffeine clearance by alpacas and llamas, information that has been determined in other species. \(^{13,30,31} \) Reduction in caffeine metabolite–caffeine ratios may be a more sensitive indicator of reduced hepatocyte function than caffeine clearance alone. \(^{10} \)

Caffeine clearance is substantially reduced in humans with chronic liver disease \(^{19} \) and in dogs with experimental liver disease. \(^{30} \) Development of liver function tests such as caffeine clearance may prove useful for determining severity of hepatic injury, for modification of drug dosages, and in assessing response to treatment. \(^{20,27,28} \) Those assertions are supported by work in calves and goats, in which reduction in plasma clearance and prolongation of elimination half-life of caffeine, antipyrine, sulfdamidine, and paracetamol were observed after feed and water restriction. \(^{12,23,30} \) The decreased plasma clearance and increased elimination half-life observed in those capacity-limited drugs were proposed to result from changes in hepatocyte oxidative and conjugative metabolism. \(^{32,33,30} \) Less severe hepatic dysfunction, as is observed in camelids with transient inappetence, would be associated with less marked reductions in caffeine clearance.

<table>
<thead>
<tr>
<th>Pharmacokinetic variable</th>
<th>Units</th>
<th>Alpaca</th>
<th>Llama</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A)</td>
<td>(\mu g/mL)</td>
<td>8.84 (6.7–13.4)</td>
<td>3.3 (2.8–3.5)</td>
</tr>
<tr>
<td>(\alpha)</td>
<td>(1/h)</td>
<td>7.1 (2.0–10.3)</td>
<td>1.0 (4.1–2.1)</td>
</tr>
<tr>
<td>(B)</td>
<td>(\mu g/mL)</td>
<td>6.6 (4.9–6.8)</td>
<td>3.8 (1.9–4.2)</td>
</tr>
<tr>
<td>(\beta)</td>
<td>(1/h)</td>
<td>0.03 (0.02–0.074)</td>
<td>1.0 (0.04–1.1)</td>
</tr>
<tr>
<td>(C_{\text{max}})</td>
<td>(\mu g/mL)</td>
<td>0.017 (0.13–0.20)</td>
<td>0.09 (0.07–0.24)</td>
</tr>
<tr>
<td>(K_{10})</td>
<td>(1/h)</td>
<td>4.4 (0.4–6.7)</td>
<td>0.43 (0.13–0.89)</td>
</tr>
<tr>
<td>(K_{21})</td>
<td>(1/h)</td>
<td>2.8 (0.03–3.4)</td>
<td>0.61 (0.18–1.1)</td>
</tr>
<tr>
<td>(C_{\text{trt}})</td>
<td>(mL/h/kg)</td>
<td>44 (24–56)</td>
<td>42 (30–109)</td>
</tr>
<tr>
<td>(V_1)</td>
<td>(mL/kg)</td>
<td>0.22 (0.15–0.43)</td>
<td>0.45 (0.41–0.55)</td>
</tr>
<tr>
<td>(V_2)</td>
<td>(mL/kg)</td>
<td>0.39 (0.30–0.50)</td>
<td>0.32 (0.23–0.46)</td>
</tr>
<tr>
<td>(V_3)</td>
<td>(mL/kg)</td>
<td>0.40 (0.45–0.53)</td>
<td>0.75 (0.68–1.15)</td>
</tr>
<tr>
<td>(T_{1/2\alpha})</td>
<td>(h)</td>
<td>0.10 (0.07–0.39)</td>
<td>1.00 (0.33–1.7)</td>
</tr>
<tr>
<td>(T_{1/2\beta})</td>
<td>(h)</td>
<td>11.0 (5.3–29.8)</td>
<td>16 (5.0–17)</td>
</tr>
<tr>
<td>(AUC_{0-h})</td>
<td>(\mu g/mL)</td>
<td>0.88 (0.59–1.24)</td>
<td>76 (27–59)</td>
</tr>
<tr>
<td>(AUMC_{0-h})</td>
<td>(g/mL)</td>
<td>9.8 (6.7–13.4)</td>
<td>3.3 (2.8–3.5)</td>
</tr>
<tr>
<td>(AUMC_{\text{trt}})</td>
<td>(g/mL)</td>
<td>198 (70–2,285)</td>
<td>1.66 (203–2,290)</td>
</tr>
<tr>
<td>(MRT)</td>
<td>(h)</td>
<td>15.0 (13.0–15.8)</td>
<td>21 (7.4–23)</td>
</tr>
</tbody>
</table>

\(A\) = Zero-time plasma drug concentration intercept of initial distribution phase of the biphasic IV disposition curve. \(\alpha\) = Hybrid rate constant of the distribution phase of the biphasic IV disposition curve. \(B\) = Hybrid rate constant of the elimination phase of the biphasic IV disposition curve. \(C_{\text{max}}\) = Maximum plasma concentration. \(K_{\text{10}}\) = First-order elimination rate constant. \(K_{\text{21}}\) = First-order rate transfer constants for drug distribution between the central and peripheral compartments, respectively. \(C_{\text{trt}}\) = Total body clearance or plasma clearance of drug (sum of all clearance processes). \(V_1, V_2\) = Apparent volume of central and peripheral/ or tissue compartments, respectively. \(V_3\) = Apparent volume of distribution at steady state. \(T_{1/2\alpha}\) = Half-life of the distribution phase. \(T_{1/2\beta}\) = Half-life of the elimination phase. \(AUC_{0-h}\) = Total area under the plasma concentration-versus-time curve to infinity. \(AUMC_{0-h}\) = Area under the moment curve to infinity. \(MRT\) = Mean residence time.

Caffeine is metabolized in hepatocytes via demethylation to related compounds (ie, theophylline, theobromine, and paraxanthine) that may be detected under similar conditions as those described. \(^{10,11,12,20} \) Caffeine clearance reflects the rate at which the compound is delivered to the liver. \(^{10,11,13,20} \)
References


