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Pharmacokinetics of intravenous gentamicin in healthy young-adult compared to aged alpacas

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Abstract

The study objective was to evaluate the effects of age on aminoglycoside pharmacokinetics in eight young-adult (<4 years) and eight aged (≥ 14 years) healthy alpacas, receiving a single 6.6 mg/kg intravenous gentamicin injection. Heparinized plasma samples were obtained at designated time points following drug administration and frozen at –80°C until assayed by a validated immunoassay (QMS®). Compartmental and noncompartmental analyses of gentamicin plasma concentrations versus time were performed using WinNonlin (v6.4) software. Baseline physical and hematological parameters were not significantly different between young and old animals with the exception of sex. Data were best fitted to a two-compartment pharmacokinetic model. The peak drug concentration at 30 min after dosing (23.8 ± 2.1 vs. 26.1 ± 2 µg/ml, $p = .043$) and area under the curve (70.4 ± 10.5 vs. 90.4 ± 17.6 µg hr/ml, $p = .015$) were significantly lower in young-adult compared to aged alpacas. Accordingly, young alpacas had a significantly greater systemic clearance than older animals (95.5 ± 14.4 and 75.6 ± 16.1 ml hr⁻¹ kg⁻¹; $p = .018$, respectively). In conclusion, a single 6.6 mg/kg intravenous gentamicin injection achieves target blood concentrations of >10 times the MIC of gentamicin-susceptible pathogens with MIC levels ≤ 2 µg/ml, in both young-adult and geriatric alpacas. However, the observed reduction in gentamicin clearance in aged alpacas may increase their risk for gentamicin-related adverse drug reactions.

1 | INTRODUCTION

Advanced age may cause physiological and anatomical changes in both animals and humans that can modify the pharmacokinetic disposition of drugs and the related pharmacodynamic response (Dowling, 2005). In various species, aging correlates with declines in basal metabolic rate; renal, hepatic, and cardiac function; and the water-to-adipose compartment ratio of the body (Aucoin, 1989; Harper, 1998; Modric & Martinez, 2011; Mosier, 1989),

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AUTHOR CONTRIBUTION

All authors have read and approved the final manuscript. Individual contributions include design, data collection, sample and statistical analyses, data interpretation, and scientific writing (AG, DB, MC); pharmacokinetics analysis and scientific writing (IZ, MC).

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

which may increase the risk of drug-related toxicities in the elderly. In fact, a sevenfold increase in the rate of drug toxicities was observed in geriatric humans, rising from 3% at 20–29 years of age to 21% at 70–79 years of age (Beard, 1992). The potential for drug-related toxicity in any species is particularly important for medications with a low therapeutic index.

The aminoglycoside gentamicin is a potentially nephrotoxic and ototoxic drug that shows its best bactericidal activity as a concentration-dependent antimicrobial against gram-negative bacteria (Fraisie et al., 2014). While the efficacy of gentamicin is determined by peak plasma concentrations, its nephrotoxicity is primarily a result of the length of renal drug exposure. Therefore, extended-interval dosage regimens are designed to limit the duration of drug exposure to the kidneys while still achieving appropriately high plasma levels (Magdesian, Hogan, Cohen, Brumbaugh, & Bernard, 1998; Mueller & Boucher, 2009). Unfortunately, a recent study in people reported a high number of inadequate plasma concentrations of aminoglycosides in the elderly (Fraisie et al., 2014). This finding underscores the need for targeted pharmacokinetic studies in aged veterinary patients to not only minimize adverse drug reactions (ADRs) but also to circumvent treatment failure and the development of antimicrobial resistance due to subtherapeutic drug concentrations.

Alpacas contribute significantly to the non-food-producing livestock population, with 253,336 alpacas currently registered in the United States and an unknown number of unregistered animals (Alpaca Owners Association, 2017). Bacterial infections are a significant cause of morbidity and mortality in this species, including gastrointestinal, respiratory, urinary, dental, reproductive, and systemic disease (Fowler, 1994). In a retrospective study of 0.2 to 17-year-old South American Camelids, *Archaeobacterium*, *Actinobacillus spp.*, and *E. coli* were common pathogens associated with dental abscessation, but gentamicin resistance was found in only 17.3% (17 of 98) of bacterial isolates (Niehaus & Anderson, 2007). Gentamicin may be a particularly important treatment option of gram-negative infections for which alternative antimicrobial choices are not available.

Few veterinary studies have suggested drug–dose adjustments in older patients to date, whereas current therapeutic protocols in humans advise reductions in dose and/or dosing frequency for patients greater than 65 or 70 years of age (Koo, Tight, Rajkumar, & Hawa, 1996; Triggs & Charles, 1999). The latter age group is estimated to correspond to an approximate age of 14–15 years in alpacas, given an expected life span of 15–20 years. The total life span of production animals, such as alpacas, is often shortened due to economic considerations that may favor euthanasia following senile infertility (Fowler, 1994). It has been suggested that dose adjustments for geriatric animals may be extrapolated based on information found in human drug package inserts for the use in elderly patients (Dowling, 2005). However, various studies have documented that age-related alterations in physiological variables, such as total body water and plasma protein binding, may differ significantly between species (Koyanagi, Yamaura, Yano, Kim, & Yamazaki, 2014; Modric & Martinez, 2011). Thus, extrapolation of pharmacokinetic differences across species should be pursued only with extreme caution.

The purpose of this study is therefore twofold: (i) to establish baseline gentamicin pharmacokinetics in young-adult alpacas and (ii) to determine the pharmacokinetic differences between young-adult and geriatric alpacas receiving a 6.6 mg/kg intravenous dose of gentamicin. We hypothesized that plasma levels of gentamicin will remain higher for longer in aged versus young-adult animals as reflected by a greater AUC and decreased drug clearance.

2 | MATERIALS AND METHODS

2.1 | Animals

Sixteen client-owned huacaya alpacas from a single farm were enrolled and divided into two age-based study groups (young adults: eight alpacas <4 years; aged animals: eight alpacas 14 years). All procedures were approved by the Institutional Animal Care and Use Committee of the Cummings School of Veterinary Medicine at Tufts University and completed following written owner consent. Study animals were visited on-farm prior to enrollment and deemed clinically healthy on the basis of owner history, physical examination, complete blood count, fibrinogen, and serum chemistry analyses.

Study alpacas were acclimated to the Cummings Hospital for Large Animals for a minimum of 24 hr prior to gentamicin administration. Throughout their 2½–3 days of hospitalization, all animals were provided with ad libitum water, ad libitum second-cut timothy hay, and eight oz/animal twice daily commercial alpaca pellets.

2.2 | Gentamicin administration and sample collection

All animals were outfitted with two jugular venous catheters (Milacath® Short Term; Mila International, Inc., Erlanger, KY, USA) using aseptic technique, following sedation with intramuscular (IM) xylazine (AnaSed® injection, 100 mg/ml; LLOYD, Inc.®, Shenandoah, IA, USA; mean dose 0.15 mg/kg IM). A minimum wash-out period of 18 hr from the time of xylazine administration was observed prior to gentamicin administration. All catheters were flushed with heparinized 0.9% NaCl solution (0.9% Sodium Chloride Injection USP; Baxter Healthcare Corporation, Deerfield, IL; with Heparin Sodium Injection, USP, 1,000 USP Units/ml; APP Pharmaceuticals LLC, Schaumburg, IL; 1 ml Heparin per 500 ml solution) every 6 hr until study completion (for sample collection catheters) or the end of gentamicin injection (drug administration catheters).

A single dose of 6.6 mg/kg gentamicin sulfate solution (100 mg/ml; Henry Schein®, Dublin, OH, USA) was injected intravenously over 2 min via a dedicated jugular catheter. Venous blood samples (7 ml) were collected from the opposite jugular catheter at 0, 5, 15, 30, 45 min, 1, 2, 4, 6, 8, 12, 18, and 24 hr from the time of drug administration. This dose was selected with the intent of achieving peak plasma concentrations >20 µg/ml, which corresponds to 8–10 times the reported gentamicin breakpoint MIC of 2 µg/ml, for bacteria isolated from animals (Papich, 2013), and was based on preliminary data in two alpacas prior to the study. Ten milliliters of heparinized blood was withdrawn from the catheter prior to each sample collection and subsequently returned to the subjects to prevent dilution effects. All samples were immediately placed into heparinized tubes (6 ml Vacuette® NH

Sodium Heparin; Greiner Bio-One North America, Inc., Monroe, NC), chilled on wet ice and centrifuged within 30 min of collection at $2,000 \times g$ for 10 min at 4°C. Plasma was immediately separated and stored at -80°C pending analysis of the gentamicin concentration. An additional 1 ml of blood was taken from each animal at the 0- and 24-hr time points ($t = 0$ and $t = 24$) and utilized for the comparison of PCV/TS and creatinine between the beginning and the end of the 24-hr blood collection window. Free catch urine samples were collected for analysis prior to and following completion of the study.

2.3 | Assay validation and sample analysis

Heparinized alpaca plasma was used to validate a commercially available liquid phase competitive binding immunoassay utilizing photometric measurement (QMS® Gentamicin Immunoassay; Thermo Fisher Scientific, Waltham, MA), prior to the study. Gentamicin-free alpaca plasma (dilution plasma) was assayed three times, and zero recovery was confirmed. Manufacturer-provided gentamicin sulfate solution (Henry Schein®, Dublin, OH, USA) was subsequently diluted in alpaca plasma using fixed volume pipettes to obtain three separate reference solutions of 100, 50, and 5 µg/ml (high, medium, and low concentrations). A single gentamicin concentration was analyzed 10 times to determine precision of the assay and produced an acceptable intra-assay variation of 4%. Maximum (initial) plasma concentrations were expected to range between 60 and 100 µg/ml following IV drug infusion for study alpacas receiving 6.6 mg/kg gentamicin IV. This indicated the likely need for dilution of study samples from early collection time points to obtain concentrations within the assay's published range of linearity of 0.3–10 µg/ml. Each gentamicin reference solution (100 µg/ml, 50 µg/ml, and 5 µg/ml) was therefore diluted to obtain five samples per concentration within the range of assay linearity. The obtained recoveries (with their coefficients of variation) were 98.3 (2.3)%, 98.0 (3.1)%, and 103.8 (5.9)% for the reference solutions of 100, 50, and 5 µg/ml, respectively. Subsequently, all study samples that required dilution were both diluted and assayed in duplicate, and the mean result was reported. An intra-sample variation of 5.5% was considered acceptable.

2.4 | Pharmacokinetic analysis

Compartmental and noncompartmental analyses of plasma gentamicin concentrations were performed using pharmacokinetic software (Phoenix WinNonlin version 6.4; Pharsight Inc. Mountain View, CA). The individual plasma concentrations were best described by a two-compartment model as determined by the coefficients of variation in the estimated parameters, the lowest sum of squares, and Akaike criteria. The distribution (α and $T_{1/2\alpha}$) and elimination (β and $T_{1/2\beta}$) phases were calculated using the two-compartment first-order equation ($C_t = Ae^{-\alpha t} + Be^{-\beta t}$), where the values of A and B are the extrapolated concentrations to time 0 of the distribution and elimination phases. The area under the plasma concentration–time curve ($AUC_{0-\infty}$) and the area under the first moment curve ($AUMC_{0-\infty}$) were determined using the trapezoidal method with extrapolation to infinity. The systemic clearance (CL) was calculated using the dose/AUC, and the mean residence time (MRT) was obtained from the ratio of $AUMC_{0-\infty}$ to $AUC_{0-\infty}$. The volume of distribution of the central compartment (V_c) was calculated from the dose/ C_0 (where $C_0 = A + B$). The volume of distribution area (V_{darea}) was also determined from CL/β . The apparent steady-state volume of distribution ($V_{dss} = CL \times MRT$) was calculated. C_{peak} is an observed

value 30 min after drug administration, which approximates the time of transition from the distribution to elimination phase ($T_{1/2\alpha} \times 4$) and was defined on the basis of convention in therapeutic drug monitoring protocols in veterinary and human literature (Bauquier, Boston, Sweeney, Wilkins, & Nolen-Walston, 2015; Moore, Lietman, & Smith, 1987).

2.5 | Statistical analysis

Hematological and urine analyses data were compared between groups using independent samples *t*-test or Mann–Whitney U analysis, dependent upon data normality as measured by the Shapiro–Wilk test. Hematological and physical parameters pre-and post-treatment were evaluated via paired samples *t*-test or Wilcoxon rank test based on the normality of data distribution. The Levene’s test for variance was used to compare the variability in PK parameters between age groups. All results are presented as mean $\pm$ *SD* or median, range. Statistical analyses were performed using specialized statistical software (IBM SPSS 22), with $p < .05$ considered significant.

3 | RESULTS

Baseline physical examination and hematological parameters were not significantly different between young-adult and older alpacas (Table S1). Similarly, mean prestudy creatinine (1.18 ± 0.28 mg/dl vs. 1.21 ± 0.27 mg/dl, $p = .75$) and BUN values (19 ± 4 mg/dl vs. 19 ± 3 mg/dl, $p = .88$) did not differ significantly between young and aged animals. The young-adult group was composed of eight male alpacas aged 2.5 ± 0.7 years (mean $\pm$ *SD*), while the older group consisted of seven females and one male, aged 15.9 ± 1.1 years. Neither mean body weight (young-adult 59.5 ± 4.1 kg, aged 63.3 ± 11.8 kg, $p = .34$) nor median body condition score (young-adult BCS 3 (3–4) vs. aged BCS 2.75 (2.5–3.5), $p = .21$) was significantly different between age groups. No abnormal urine sediment was noted, and all samples were free of glucose and significant ($>$ trace) protein. All alpacas remained clinically healthy without evidence of adverse drug reactions or documented complications during or subsequent to the study period. Gentamicin administration and sample collection were not associated with statistically significant changes in creatinine or packed cell volume from baseline in either age group.

The plasma concentration–time curves and pharmacokinetic parameters following administration of 6.6 mg/kg IV gentamicin in eight young-adult and eight aged alpacas are represented in Table 1 and Figure 1. The measured C_{peak} was significantly lower in young-adults compared to aged animals (23.8 ± 2.1 $\mu\text{g/ml}$ and 26.1 ± 2.0 $\mu\text{g/ml}$, respectively; $p = .043$). Systemic clearance was significantly greater in young versus aged animals (95.5 ± 14.4 $\text{ml hr}^{-1} \text{ kg}^{-1}$ and 75.6 ± 16.1 $\text{ml hr}^{-1} \text{ kg}^{-1}$, $p = .02$) and associated with a lower gentamicin exposure in young alpacas, represented by the AUC (70.4 ± 10.5 $\mu\text{g hr/ml}$ and 90.4 ± 17.6 $\mu\text{g hr/ml}$, respectively; $p = .02$). Levene’s test for equality of variance revealed no significant differences in intragroup variability between young and aged animals for any of the pharmacokinetic parameters. Noncompartmental analysis indicated there was no significant difference in MRT between age groups.

The mean time at which gentamicin trough levels reached 2 $\mu\text{g/ml}$ (common MIC for large-animal pathogens) was significantly shorter in young-adults (6.7 ± 1 hr) versus aged animals

(8.7 ± 1.9 hr; $p = .03$). Only one of eight young animals and three of eight aged alpacas showed measurable plasma levels ($0.3 \mu\text{g/ml}$ vs. $0.3\text{--}0.6 \mu\text{g/ml}$) at 18 hr following gentamicin administration, while gentamicin was detectable ($0.3 \mu\text{g/ml}$) until 24 hr after injection in one aged alpaca. Similarly, median gentamicin concentrations were statistically lower in young ($0.35 \mu\text{g/ml}$; range $0\text{--}0.7$) versus old animals ($0.65 \mu\text{g/ml}$; range $0.4\text{--}1.6$; $p = .021$) at 12 hr following drug administration.

4 | DISCUSSION

Gentamicin pharmacokinetics have not been previously reported in alpacas of any age. However, the observed V_{dss} in this study (0.21 ± 0.018 L/kg in young vs. 0.21 ± 0.024 L/kg in aged alpacas) is comparable to that reported in llamas receiving a single intravenous injection of 5 mg/kg gentamicin (V_{dss} : 0.25 ± 0.03 L/kg) (Lackey, Belknap, Greco, & Fettman, 1996). In contrast, a lower clearance (CL: 66 ± 8.4 ml hr⁻¹ kg⁻¹) and slightly longer elimination half-life ($t_{1/2\beta}$: 2.76 ± 0.34 hr) were previously observed in llamas, compared to results of the current report (CL: 95.5 ± 14.4 ml hr⁻¹ kg⁻¹ and $t_{1/2\beta}$: 1.69 ± 0.22 hr in young alpacas vs. CL: 75.6 ± 16.1 ml hr⁻¹ kg⁻¹ and $t_{1/2\beta}$: 2.09 ± 0.50 hr in aged alpacas). Separately, Dowling et al. (Dowling, Ferguson, & Gibney, 1996) investigated the use of 4 mg/kg IV gentamicin in six healthy llamas. Results were presented as harmonic means of clearance (CL: 30.6 ml hr⁻¹ kg⁻¹), V_{dss} (0.12 L/kg),¹ and elimination half-life ($t_{1/2\beta}$: 3.03 hr).¹ Despite similar study doses of gentamicin, the two llama studies reported notably different values for CL and V_{dss} , which may reflect variations in study techniques and/or animals. Based on these discrepancies and on the observed differences in PK parameters between llamas and alpacas for compounds studied in both species (Pentecost, Niehaus, Werle, & Lakritz, 2013, 2015), it remains difficult to derive dose selections in untested camelid species based upon work in another camelid species (Hunter & Isaza, 2008). It is, therefore, critical to assess individual pharmacological compounds, particularly those with a low therapeutic index, in individual species and patient populations to gauge efficacy and safety.

Aged alpacas showed a significantly lower gentamicin clearance than young-adult alpacas in this study, which is likely associated with age-related declines in renal efficiency. The effects of aging on renal blood flow and/or glomerular filtration (GFR) in alpacas have not been investigated to date. However, previous research has documented age-related decreases in cardiac output and renal perfusion (increased peripheral vascular resistance), and/or reduced creatinine clearance (Hilmer, McLachlan, & Le Couteur, 2007; Mangoni & Jackson, 2004; Modric & Martinez, 2011) in humans (Boss & Seegmiller, 1981; Dick & Davies, 1949; Rowe, Andres, Tobin, Norris, & Shock, 1976) and some other species, including dogs (Kaufman, 1984), cows (Deetz, Tucker, Mitchell, & DeGregorio, 1982), and horses (McKeever, Eaton, Geiser, Kearns, & Lehnhard, 2010). Thus, a gradual age-related decline of renal function appears to be similar across species and supports the notion that a detectable decline in GFR occurs in alpacas with increasing age. As a result of decreased clearance, a higher AUC and prolonged elimination half-life were also observed in the aged cohort in this study. Etzel et al. reported that people with lower total body weight and

¹Original units were converted for direct comparison

advanced age demonstrated a significantly greater aminoglycoside V_{dss} and, thus, longer drug elimination half-life (Etzel, Nafziger, & Bertino, 1992). However, as there was no significant difference in body weight or V_{dss} between age groups in this study, the lower drug clearance in older alpacas is most likely related to decreased renal function. Additionally, higher trough levels (median plasma concentration at 12 hr after drug administration) were observed in the aged alpaca population, as compared to young alpacas. As aminoglycoside adverse drug reactions (e.g., ototoxicity and nephrotoxicity) are related to trough levels, or duration of drug exposure, the aged animals may become more susceptible to drug toxicity, particularly given gentamicin's narrow therapeutic index. The use of extended-interval administration (once daily gentamicin dosing) is expected to minimize these concerns, as 12-hr trough levels reached values of <0.5 – 2 $\mu\text{g/ml}$ in all alpacas. The latter suggests adequate renal drug by 12 hr, irrespective of age.

The observed, statistically significant differences in C_{peak} between young-adult and geriatric alpacas (23.8 ± 2.1 $\mu\text{g/ml}$ vs. 26 ± 2.0 $\mu\text{g/ml}$; $p = .043$) are relatively small in absolute terms and may thus have minimal clinical significance in healthy animals. Contemporary gentamicin dose regimens in most species are designed to achieve peak plasma concentration eight to 10 times the MIC of the target organism (Godber, Walker, Stein, Hauptman, & Derksen, 1995; Lackey et al., 1996; Moore et al., 1987). These high gentamicin C_{peak} :MIC concentrations potentiate the aminoglycoside postantibiotic effect (PAE), which is characterized by persistent suppression of bacterial growth at sub-MIC or even undetectable gentamicin concentrations (Mueller & Boucher, 2009). Considering a reported gentamicin break point MIC of 2 $\mu\text{g/ml}$, for bacteria isolated from animals (Papich, 2013), the C_{peak} values observed in this study result in estimated C_{peak} :MIC ratios of 11.9 ± 1 in young adults and 13 ± 1 in aged alpacas, both well above the recommended target range of eight to 10 times MIC (Bauquier et al., 2015; Fraisse et al., 2014; Tudor, Papich, & Redding, 1999). For infectious organisms with intermediate susceptibility (MIC 4 $\mu\text{g/ml}$), the extrapolated C_{peak} :MIC ratio of 6.0 ± 0.5 in young adults and 6.5 ± 0.5 in aged alpacas would not reach a target of 8 – $10 \times$ MIC in either group. Irrespective of age group, intravenous dose of 6.6 mg/kg of gentamicin in alpacas is, therefore, only indicated to target susceptible bacterial organisms, rather than those with intermediate sensitivity.

In addition to mean differences in pharmacokinetic parameters between young and geriatric patients, the assessment of intragroup variability is useful in considering the risk for therapeutic failure. Previous studies in humans have identified that increased physiological heterogeneity and resultant pharmacokinetic variability is a significant contributor to an increased risk of adverse drug reactions (ADRs) in geriatric patients (Kinirons & O'Mahony, 2004; Modric & Martinez, 2011). However, increased pharmacokinetic variability within the aged compared to young population, as measured by the Levene's test for variance, was not observed in the current study of alpacas.

The availability of predominantly young male and aged female alpacas generated an inadvertent sex disparity between animal groups, which is a potentially confounding variable. Previous research has identified pharmacokinetic differences between male and female study patients. The physiological bases for some of these differences include evidence of increased renal blood flow in male compared to female subjects in other species

(Hoang et al., 2003; Meibohm, Beierle, & Derendorf, 2002; Modric & Martinez, 2011; Schwartz, 2003). As such, renal processes of glomerular filtration, tubular secretion, and tubular reabsorption appear to be faster in men compared to women (Schwartz, 2003). Although differences in volume of distribution of gentamicin have been related to weight, age, and sex in human beings (Goncalves-Pereira, Martins, & Pova, 2010; Hilmer et al., 2007), the volume of distribution was not significantly affected by sex in alpacas of the current investigation ($p > .05$). Similarly, merely age and body weight, but not gender, were related to disposition of gentamicin in a population pharmacokinetic study of horses (Martin-Jimenez, Papich, & Riviere, 1998). Therefore, gender-based PK differences in one species should only be extrapolated to another species with extreme caution (Christian, 2001). Additionally, previous studies have concluded that it is rare for detectable PK differences between males and females to result in clinically significant differences in treatment outcomes (Modric & Martinez, 2011; Thurmman, 2007). It is the authors' observation that in the Northeast United States, female alpacas are more likely than males to reach advanced age as a result of breeding management practices. Although the effect of a sex disparity between cohorts cannot be completely ruled out in this study, the aged alpaca group likely reflects a representative gender sample of older animals most commonly seen in clinical practice.

In summary, statistically significant pharmacokinetic differences were observed between young-adult and geriatric alpacas, leading to reduced drug clearance and higher drug exposure in aged animals. However, the magnitude of these differences has limited clinical implications in healthy animals and may be confounded by observed sex disparities in aged animals. A single 6.6 mg/kg intravenous dose of gentamicin achieves therapeutic blood concentrations against susceptible pathogens with an MIC $\leq 2 \mu\text{g/ml}$ in both young adult and geriatric alpacas. Further studies are required to establish the common pathogens and their MICs in alpacas, as well as the likelihood of drug toxicity following repeated dosing, particularly for aged animals, where decreased clearance and increased drug exposure create a greater risk of ADRs and/or therapeutic failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1. Mean [$\pm$ *SD*] plasma concentration–time profile after single-dose intravenous dose of gentamicin (6.6 mg/kg) to eight healthy young-adult and eight aged alpacas

TABLE 1

Pharmacokinetic (PK) parameters of gentamicin (6.6 mg/kg) administered intravenously to healthy young-adult and aged alpacas

PK Parameter	Young-adult Alpacas		Aged Alpacas		p value
	Mean	SD (CV)	Mean	SD (CV)	
A (mg/ml)	27.888 ± 5.385		36.736 ± 11.179		.0633
α (hr ⁻¹)	5.276 ± 0.745		6.402 ± 1.870		.136
B (mg/ml)	26.680 ± 2.037		28.483 ± 2.952		.177
β (hr ⁻¹)	0.417 ± 0.061		0.352 ± 0.099		.14
t _{1/2α} (hr)	0.133 ± 0.017		0.118 ± 0.039		.319
t _{1/2β} (hr)	1.693 ± 0.224 (13.2)		2.085 ± 0.495 (23.7)		.060
AUC _{0-∞} (μg hr/ml)	70.4 ± 10.5 (14.9)		90.4 ± 17.6 (19.5)		.015
AUMC _{0-∞} (μg hr ² /ml)	162.6 ± 44.3 (27.2)		264.7 ± 104.3 (39.4)		.023
CL (ml hr ⁻¹ kg ⁻¹)	95.5 ± 14.4 (15.1)		75.6 ± 16.1 (21.3)		.018
MRT (hr)	2.27 ± 0.32 (14.1)		2.83 ± 0.68 (24.0)		.056
V _c (L/kg)	0.122 ± 0.014 (11.5)		0.105 ± 0.020 (19.0)		.063
V _{darea} (L/kg)	0.091 ± 0.011 (12.1)		0.101 ± 0.015 (14.9)		.192
V _{dss} (L/kg)	0.214 ± 0.018 (11.9)		0.205 ± 0.024 (11.7)		.436
C ₀ (μg/ml)	54.568 ± 6.514		65.219 ± 13.157		.059
C _{peak} (μg/ml) ^a	23.8 ± 2.1		26.1 ± 2.0		.043

A, extrapolated concentrations to time 0 of the distribution phase; AUC_{0-∞}, area under the plasma concentration–time curve from 0 to infinity; AUMC_{0-∞}, area under the first moment curve from 0 to infinity; B, extrapolated concentrations to time 0 of the elimination phase; C₀–initial concentration; C_{peak}, peak plasma concentration; CL, systemic clearance; MRT, mean residence time; t_{1/2α}, distribution half-life; t_{1/2β}, elimination half-life; V_c, volume of distribution in the central compartment; V_{darea}, volume of distribution by area; V_{dss}, volume of distribution at steady-state; α, rate constant of distribution phase; β, rate constant of elimination phase. Statistically significant differences between groups, based on P < .05, are identified in bold.

^a observed value.