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Population Pharmacokinetic Modeling of Gentamicin in dogs

Modelagem farmacocinética da gentamicina em cães: uma abordagem farmacocinética populacional (popPK)

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Highlights

Population pharmacokinetic modeling evaluated gentamicin dosing regimens in dogs.
Predicted therapeutic efficacy was assessed using PTA values ≥ 90%.
The 8 mg kg^{-1} regimen achieved PTA values ≥ 90% for pathogens with MIC ≤ 2 µg mL^{-1}.
Nephrotoxicity risk was evaluated by gentamicin thresholds and duration.
Mean time above the primary nephrotoxicity-risk threshold was 4–8 h.

Abstract

This study used population pharmacokinetic (popPK) modeling to predict therapeutic efficacy and assess nephrotoxicity risk associated with gentamicin administration in dogs. The model was developed in Monolix 2024 R1 (Lixoft SAS, Simulations Plus Company) using plasma concentration-time data obtained from the literature. Monte Carlo simulations were subsequently performed in Simulx 2024 (Lixoft SAS, Simulations Plus Company) for gentamicin doses of 2, 4, 6, and 8 mg kg^{-1} to evaluate

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therapeutic target attainment and exposure associated with nephrotoxicity risk. The model that best described the observed data was a two-compartment model with linear elimination. Predicted therapeutic efficacy was assessed using the Probability of Target Attainment (PTA) based on the PK/PD target fCmax/MIC ≥ 10 across a range of minimum inhibitory concentrations (MICs). Nephrotoxicity risk was evaluated according to the duration for which plasma gentamicin concentrations remained above the primary nephrotoxicity-risk threshold of 2 μg mL^{-1}. The 8 mg kg^{-1} regimen achieved PTA values ≥ 90% for pathogens with MIC ≤ 2.0 μg mL^{-1} and represented the highest-performing simulated regimen among those evaluated. For this regimen, the mean time above the 2 μg mL^{-1} nephrotoxicity-risk threshold ranged from 4 to 8 hours. These findings support the use of gentamicin against pathogens with MICs ≤ 2 μg mL^{-1} when administered using extended dosing intervals. However, dose and interval adjustments may be required in critically ill patients. Overall, the popPK approach provides a useful framework for precision dosing, supporting improved predicted efficacy and safety across different dosing regimens.
Key words: Aminoglycosides. Canine. Nephrotoxicity. Pharmacometrics. Population pharmacokinetics.

Resumo

O estudo teve como objetivo avaliar a eficácia e a nefrotoxicidade da gentamicina em cães a partir de um modelo de farmacocinética populacional (popPK). O modelo foi desenvolvido por meio do *software* Monolix 2024 R1 (Lixoft SAS, Simulations Plus Company), a partir de dados de concentração plasmática extraídos da literatura. Além disso, foram realizadas simulações para doses de 2, 4, 6 e 8 mg kg^{-1} de gentamicina, no *software* Simulx 2024 (Lixoft SAS, Simulations Plus Company), avaliando-se o sucesso terapêutico e o risco de toxicidade. O modelo que melhor se ajustou aos dados observados tinha dois compartimentos e eliminação linear. A eficácia terapêutica foi avaliada de acordo com a Probabilidade de Atingir o alvo (PTA) de diferentes concentrações inibitórias mínimas para gentamicina. Para se estimar o risco de toxicidade, foi considerado o tempo acima do limiar tóxico do antibiótico. Assim, com a dose de 8 mg kg^{-1}, foi alcançado um PTA ≥ 90% para bactérias com MIC ≤ 2.0 μg mL^{-1}, e o tempo médio acima da concentração tóxica de gentamicina (0.5 - 2 μg mL^{-1}) variou de 4 a 8 horas. Os resultados sugerem o uso da gentamicina para agentes com MICs ≤ 2 μg mL^{-1} e intervalo de dose prolongado; no entanto, o profissional deve ajustar a dose e intervalo em pacientes críticos. A abordagem popPK contribui para o aprimoramento da medicina de precisão, garantindo, assim, melhores níveis de eficácia e segurança para diferentes regimes de doses.
Palavras-chave: Aminoglicosídeos. Canino. Nefrotoxicidade. Farmacometria. Farmacocinética populacional.

Introduction

Gentamicin (GM) is an aminoglycoside widely used in small-animal medicine for local treatment, such as otitis externa (Heuer et al., 2024), and for systemic infections, including urinary tract infections (Santis et al., 2022) and sepsis (Jessen et al., 2019). Despite its clinical utility, systemic gentamicin administration is associated with nephrotoxicity and ototoxicity, particularly following prolonged exposure and sustained concentrations above toxicity-related thresholds (Santis et al., 2022; Yamada et al., 2021).

Gentamicin remains an attractive therapeutic option because resistance rates among bacterial pathogens are low, indicating high susceptibility this antimicrobial (Souza et al., 2020). In dogs with sepsis, aminoglycosides and amoxicillin-clavulanate have been associated with lower resistance rates than other microbial classes, supporting their use in selected clinical situations (Camargo et al., 2020).

Population pharmacokinetic and pharmacokinetic/pharmacodynamic (PK/PD) modeling have become important tools for optimizing antimicrobial therapy. These approaches support dose selection, regimen optimization, simulation of drug exposure, and assessment of efficacy and safety profiles (Mi et al., 2022; Ren et al., 2022). For example, Felix et al. (2023) used PK/PD integration to establish dosing regimens for sodium cloxacillin in goats based on the probability of target attainment across different bacterial MIC distributions. Given the need to maximize antimicrobial efficacy while minimizing toxicity, population pharmacokinetic (popPK) modeling offers a valuable framework for evaluating gentamicin dosing strategies. Therefore, this study aimed to predict therapeutic efficacy and assess nephrotoxicity risk associated with gentamicin administration in dogs using a popPK model.

Material and Methods

Pharmacokinetic data

The popPK model was developed using raw plasma concentration-time data from the study of Widerhon et al. (2005). That study included six clinically healthy male mixed-breed dogs with a mean body weight of 12 ± 3 kg and a mean age of 2 ± 0.25 years. Gentamicin (Gentamicin 40, Laboratorios Río de Janeiro, Santa Fe, Argentina) was administered intravenously through the left cephalic vein at a dose of 2 mg kg^{-1}. Blood samples were collected from the right cephalic or femoral vein at 5, 10, 15, 20, and 30 min, and at 1, 2, 3, 4, and 6 h after administration.

Population pharmacokinetic modeling

Gentamicin concentration-time data were analyzed using a nonlinear mixed-effects model (NLEM) in Monolix 2024 R1 (Lixoft SAS, Simulations Plus Company). Pharmacokinetic parameters were estimated by maximum likelihood using the Stochastic Approximation Expectation-Maximization (SAEM) algorithm (Mould & Upton, 2013; Traynard et al., 2020).

Candidate structural models included one- and two-compartment models with linear elimination, alternative parameterization (rate or clearance based), and constant, proportional or combined residual error structures.

Model development accounted for both interindividual variability and residual unexplained variability. Interindividual variability in clearance (Cl) and volume of distribution (Vd) was modeled using log-normal distributions, whereas residual unexplained variability was described using a proportional error model.

Model selection was based on standard pharmacometrics diagnostics, including goodness-of-fit plots, observations versus predictions, individual weighted

residuals (IWRES), normalized prediction distribution errors (NPDE), prediction-corrected visual predictive checks (pcVPC), changes in objective function value, and correlations among random effects. Akaike's Information Criterion (AIC), the Bayesian Information Criterion (BIC), and a parameter precision expressed as relative standard error (RSE) were also considered. Model robustness was further evaluated using a nonparametric bootstrap procedure with 1,000 replicates and 95% confidence intervals (Lavielle & Ribba, 2016; Mould & Upton, 2013; Nguyen et al., 2017; Savic & Karlsson, 2009).

Monte Carlo simulations and PK/PD analyses

The final popPK model was implemented in Simulx 2024 (Lixoft SAS, Simulations Plus Company) to simulate gentamicin dosing regimens of 2, 4, 6, and 8 mg kg^{-1}. Monte Carlo simulations were performed using a virtual population of 10,000 dogs.

Predicted therapeutic efficacy was evaluated using the PK/PD index fCmax/MIC, where fCmax represents the maximum free-drug concentration and MIC represents the minimum inhibitory concentration of the infecting pathogen (Hodiamont et al., 2022). The established aminoglycoside target of fCmax/MIC ≥ 10 (Farkas et al., 2022) was used to calculate the probability of target attainment (PTA) across MIC values ranging from 0.5 to 8 μg mL^{-1}. Dosing regimens achieving PTA values ≥ 90% were considered to provide an acceptable probability of therapeutic success (Toutain et al., 2019). Simulations assumed a plasma free fraction of 85% for gentamicin (Riviere et al., 1985). No specific bacterial species were evaluated; therefore, analyses were conducted across the predefined MIC distribution.

Nephrotoxicity risk was assessed by quantifying the duration of exposure above clinically relevant gentamicin concentration thresholds A plasma concentration of 2 μg ml^{-1} was used as the primary nephrotoxicity-risk threshold based on evidence associating elevated trough concentrations with increased nephrotoxicity risk (Santis et al., 2022; Yamada et al., 2021). A more conservative therapeutic monitoring target of 0.5 μg ml^{-1} was also evaluated (Sundaram et al., 2017). Previous studies have suggested that trough concentrations should remain below these thresholds at least 2–4 h before the subsequent dose (Burton et al., 2013; Santis et al., 2022). Total plasma gentamicin concentrations were used for all analyses.

Results

Pharmacokinetic analysis of gentamicin in dogs

Gentamicin pharmacokinetics were best described by a two-compartment model with linear elimination, no delay component, and clearance-based parameterization (Figure 1). Bootstrap median estimates and their corresponding 95% confidence intervals were consistent with the final model estimates, supporting model stability and robustness (Table 1). In addition, all parameter estimates exhibited acceptable precision, with RSE values below 30%.

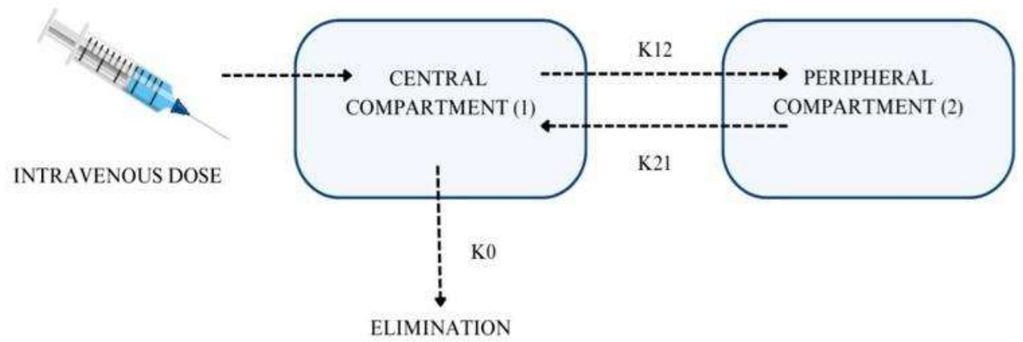

Figure 1. Graphical representation of the final two-compartment pharmacokinetic model. Abbreviations: K0, elimination constant; k12, intercompartmental transfer rate constant from the central compartment to the peripheral compartment; k21, intercompartmental transfer rate constant from the peripheral compartment to the central compartment.

Table 1

Final population pharmacokinetic model parameter estimates and bootstrap results for gentamicin following intravenous administration in dogs. Abbreviations: RSE, relative standard error; CI, confidence interval; Cl, clearance; V, volume of distribution; Q, intercompartmental clearance between the central (V1) and peripheral (V2) compartments; Corr, correlation coefficient

Parameters	Final Model		Bootstrap (N=1000)	
	Estimate	RSE (%)	Median	95% CI
Fixed Effects				
Cl_pop (ml/min^{-1} kg^{-1})	2.29	12.36	2.27	1.78 – 2.90
V1_pop (L kg^{-1})	0.12	7.63	0.13	0.10 – 0.14
Q_pop (mL min^{-1})	49.53	13.11	48.93	36.75 – 61.48
V2_pop (L kg^{-1})	0.09	12.88	0.09	0.07 – 0.12
Random Effects (Interindividual Variability)				
ω Cl (%)	0.39	15.36	0.38	0.25 – 0.47
ω V1 (%)	0.34	18.35	0.32	0.21 – 0.41
Correlations				
Corr_V1_Cl	0.87	8.49	0.89	0.67 – 0.96
Residual Error Model Parameters				
Proportional error, b (%)	0.18	10	0.17	0.17 – 0.2

Goodness-of-fit diagnostics indicated satisfactory model performance. The observed-versus-predicted plots showed no evidence of model misspecification (Figure 2), and observed concentrations were in good agreement with model predictions. Inspection of the individual weighted residuals (IWRES) and normalized prediction distribution errors (NPDE) revealed no apparent trends or systematic bias.

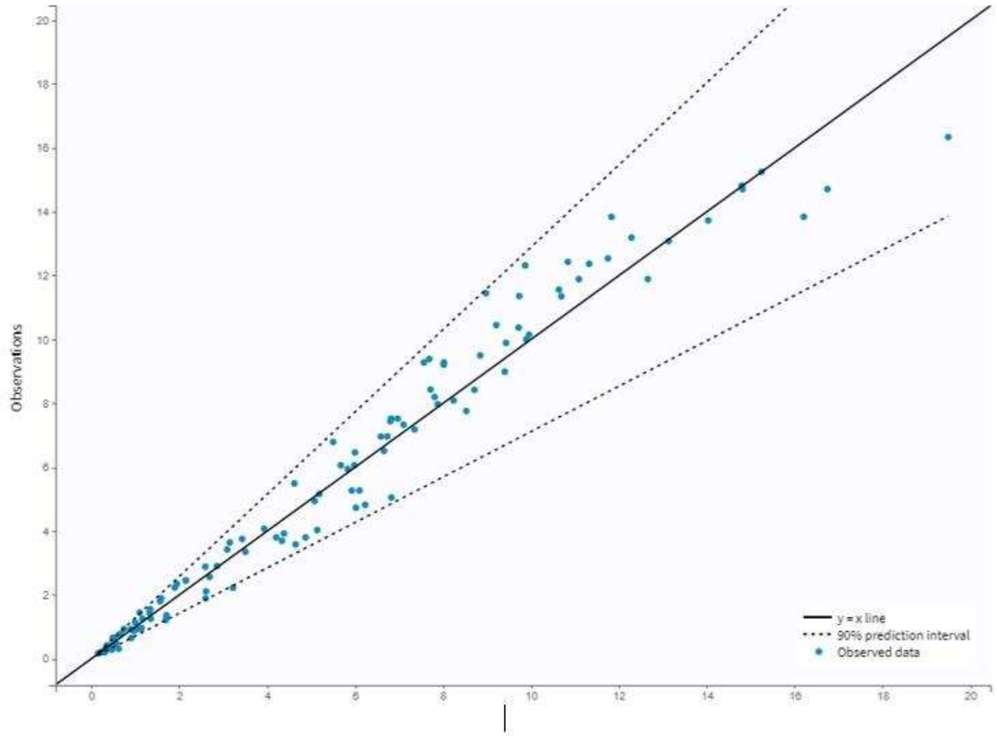

Figure 2. Observed-versus-predicted plot for the final population pharmacokinetic model of gentamicin in dogs. The solid line represents the line of identity (y = x), and the dashed lines represent the 90% prediction interval.

The prediction-corrected visual predictive check (pcVPC) further demonstrated adequate model performance (Figure 3). The observed median concentrations and the 10th, 50th and 90th percentiles were well captured within the corresponding 95% confidence intervals, indicating that the model adequately described both the central tendency and variability of the observed data.

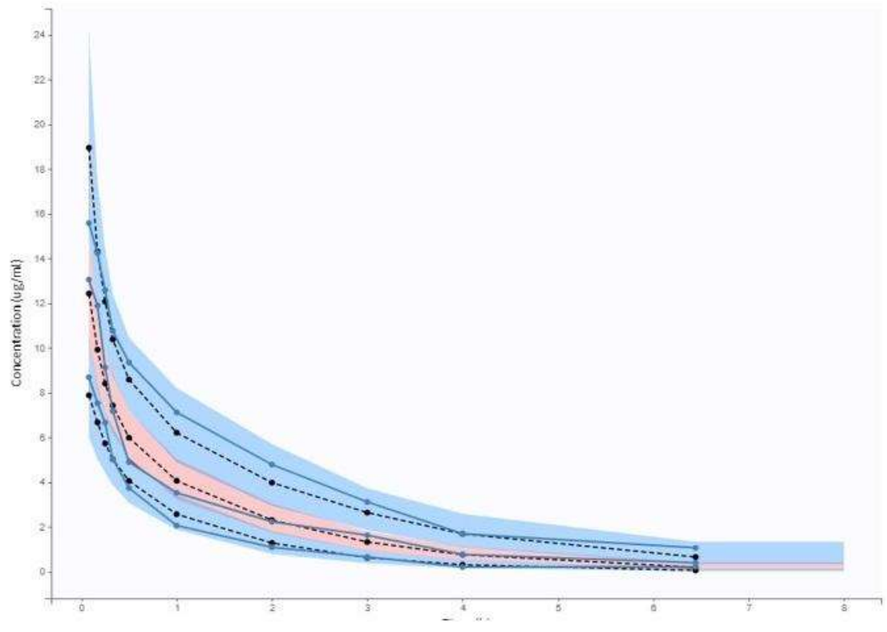

Figure 3. Prediction-corrected visual predictive check (pcVPC) for the final population pharmacokinetic model following intravenous administration of 2 mg ml^{-1} gentamicin in healthy dogs. The figure shows the observed concentration–time data and the corresponding model-predicted percentiles with their associated confidence intervals.

Monte Carlo simulations and PK/PD analyses

Monte Carlo simulations were performed using the PK/PD target *f*Cmax/MIC ≥ 10 across an MIC distribution ranging from 0.5 to 8 µg mL^{-1} (Table 2). The PTA analysis indicated that the 8 mg kg^{-1} regimen was the highest-performing simulated regimen, achieving PTA values ≥ 90 for pathogens with MICs up to 2.0µg mL^{-1}.

Table 2
Probability of Target Attainment (PTA, %) for simulated gentamicin dosing regimens in dogs (n = 10,000), based on the PK/PD target fCmax/MIC ≥ 10

	MIC (µg mL^{-1})				
Dose (mg kg^{-1})	**0.5**	**1.0**	**2.0**	**4.0**	**8.0**
2	99.96	79.07	3.64	0	0
4	100	99.89	77.84	3.65	0
6	100	100	98.67	40.44	0.11
8	100	100	99.89	78.44	3.70

Nephrotoxicity risk was evaluated based on the duration of exposure above the primary nephrotoxicity-risk threshold of 2 µg mL^{-1}. Across the simulated single-dose regimens, the mean time above this threshold ranged from 4 to 8 hours (Figure 4 and Table 3).

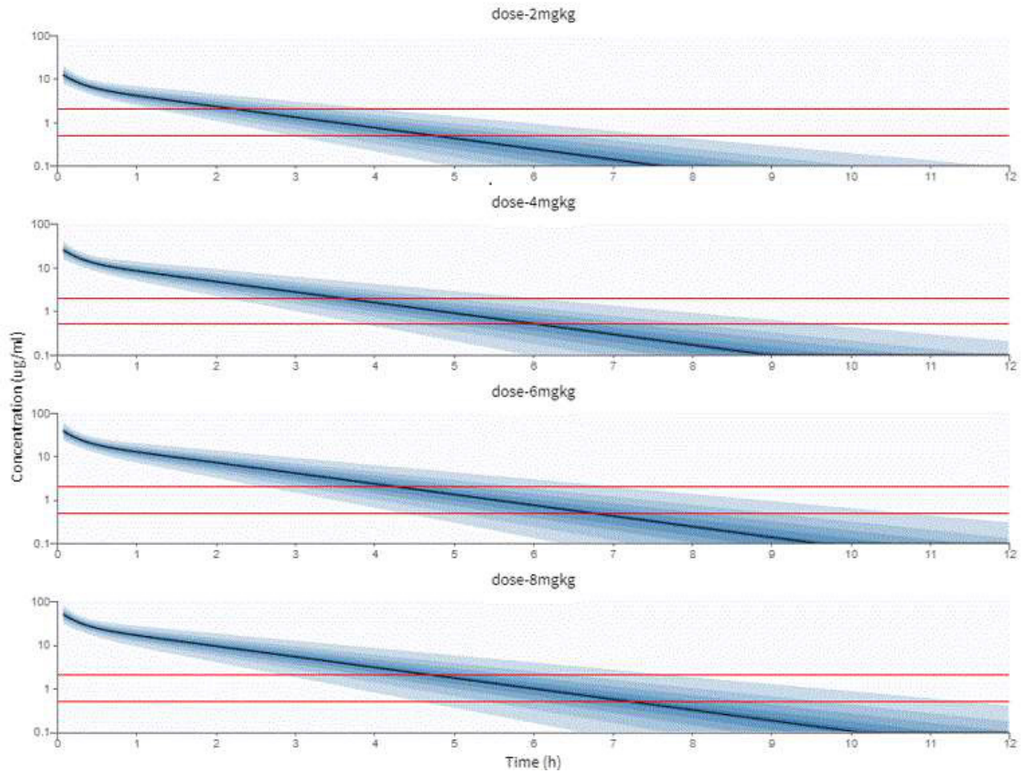

Figure 4. Simulated gentamicin concentration-time profiles in dogs following administration of four dosing regimens (2, 4, 6, and 8 mg kg^{-1}). Black lines represent the median predicted concentrations, and shaded areas represent prediction intervals. Red lines indicate the concentration thresholds of 0.5 µg ml^{-1} (conservative therapeutic monitoring target) and 2 µg ml^{-1} (primary nephrotoxicity-risk threshold) used to evaluate exposure associated with nephrotoxicity.

Table 3
Simulated duration of exposure above gentamicin concentration thresholds in dogs (n= 10,000) following administration of different dosing regimens

	Time (h) above plasma gentamicin concentration			
	0.5 µg mL^{-1}		2 µg mL^{-1}	
Dose (mg kg^{-1})	Median	P05 – P95	Median	P05 – P95
2	2.16	(1.08 - 3.9)	4.64	(2.83 – 7.51)
4	3.49	(1.99 - 5.77)	5.95	(3.77 – 7.92)
6	4.15	(2.45 - 6.85)	6.62	(4.23 – 7.92)
8	4.65	(2.74 - 7.64)	7.12	(4.48 – 7.92)

Discussion

Aminoglycosides are classified by the World Health Organization as critically important antimicrobials [World Health Organization], 2024). This class of antimicrobials may therefore be preferred over those associated with higher resistance rates, such as quinolones and third-generation cephalosporins, when clinically appropriate. At the same time, prolonged exposure to aminoglycosides increases the risk of cumulative nephrotoxicity (Santis et al., 2022). Consequently, optimizing gentamicin dosing regimens represents as important strategy for maximizing efficacy while minimizing toxicity in dogs.

In response to increasing antimicrobial resistance, antimicrobial stewardship programs have been implemented to promote the prudent and responsible use of antimicrobial agents. These programs emphasize that antimicrobials considered essential for human health should be reserved for situations in which they are necessary for the treatment, control, or prevention of disease. In addition to appropriate antimicrobial selection, optimization of dose, treatment duration, and route of administration is essential to preserve the efficacy of currently available drugs (Guardabassi & Prescott, 2015; Lloyd & Page, 2018). The Food and Drug Administration has established goals to support implementation of this approach in veterinary medicine [Food and Drug Administration & National Agricultural Statistics Service], 2024. Consequently, antimicrobial stewardship strategies have been adopted across several sectors of veterinary medicine, particularly in companion and food-producing animals (Guardabassi & Prescott, 2015; Lloyd & Page, 2018; Patel et al., 2020; Weese et al., 2015). The present model provides a framework for MIC-guided dose selection, supporting precision dosing strategies that aim to achieve therapeutic targets while minimizing unnecessary antimicrobial exposure.

A retrospective study evaluating antimicrobial resistance among bacteria isolated from dogs and cats in southern Brazil between 2013 and 2017 identified gentamicin as one of the antimicrobials with the lowest resistance rates, indicating

high bacterial susceptibility (Souza et al., 2020). These findings suggest that gentamicin may represent an effective therapeutic option for bacterial infections in dogs, although susceptibility testing remains essential whenever possible. To evaluate how pathogen susceptibility may influence dosing performance, the present study used raw data from Widerhon et al. (2005) to perform Monte Carlo simulations in a virtual population of 10,000 dogs and assessed an MIC distribution ranging from 0.5 to 8 μg mL^{-1} based on values reported by EUCAST. This approach enables evaluation of dosing regimens across a broad range of clinically relevant susceptibility profiles and may contribute to the more rational use of gentamicin in veterinary practice. Pharmacokinetic modeling has become an important tool for evaluating dosing regimens by integrating efficacy and safety considerations (Duong et al., 2021; Gonzaga et al., 2024). Such models can be used to estimate attainment of pharmacodynamic targets as well as exposure above toxicity-related thresholds (Felix et al., 2024; Tosca et al., 2021). In the present study, nephrotoxicity was assessed according to the duration of exposure above the primary nephrotoxicity-risk threshold of 2 μg mL^{-1} (Yamada et al., 2021). This approach is consistent with contemporary pharmacometric strategies designed to balance predicted therapeutic efficacy and safety.

The estimated pharmacokinetic parameters were consistent with previously published data, supporting the validity of the final model. The estimated volume of distribution (0.12 L kg^{-1}) was comparable to values reported by Dix et al. (1986) (0.12 L kg^{-1}), Batra et al. (1983) (0.12–0.16 L kg^{-1}), and Frazier and Riviere (1987) (0.13 L kg^{-1}). Similarly, the estimated clearance (2.29 mL min^{-1} kg^{-1}) closely matches values reported by Isoherranen and Soback (2000) (2.63 mL min^{-1} kg^{-1}) and Brown and Riviere (1991) (2.27 mL min^{-1} kg^{-1}). Together, these findings support the physiological plausibility of the parameter estimates obtained in the present analysis.

The final model was a two-compartment model, consistent with several previous studies of gentamicin pharmacokinetics in dogs, including investigations of nephrotoxicity and pharmacokinetic alterations (Dix et al., 1986; Frazier & Riviere, 1987; Riviere & Coppoc, 1981). Similar findings have also been reported in studies evaluating the therapeutic use of gentamicin (Batra et al., 1983; Behrend et al., 1994). In contrast, noncompartmental approaches have been used to investigate gentamicin pharmacokinetics, including studies of individual gentamicin components (Isoherranen & Soback, 2000), hemorrhagic shock (Dickson et al., 1987), and diabetes-associated pharmacokinetic changes (Brown & Riviere, 1991). Whittem et al. (1996) described a three-compartment model while evaluating the effects of poly-L-aspartic acid on gentamicin pharmacokinetics. Such differences are expected because model selection depends on study objectives, data structure, and model discrimination criteria.

In both humans and dogs, elevated gentamicin trough concentrations are associated with an increased risk of nephrotoxicity (Yamada et al., 2021; Albarellos et al., 2004). Consequently, prolonged exposure above nephrotoxicity-risk thresholds increases the likelihood of renal injury. Understanding the pharmacokinetic

behavior of gentamicin is therefore essential for optimizing dosing regimens. Aminoglycosides are excreted largely unchanged by the kidneys, with approximately 90% eliminated renally and about 10% accumulating in the renal cortex (Germovsek et al., 2017; Nagai & Takano, 2004). Higher gentamicin exposure is associated with a greater risk of nephrotoxicity. In the present study, the duration of exposure above the primary nephrotoxicity-risk threshold was estimated to support dosing strategies aimed at minimizing toxicity in dogs.

Therapeutic drug monitoring (TDM) of gentamicin is well established in several species. In human medicine, TDM commonly involves monitoring peak (Cmax) and trough (Cmin) plasma concentrations to optimize efficacy while minimizing toxicity. Bayesian approaches may also be used to individualize dosing based on patient-specific pharmacokinetic profiles (Hodiamont et al., 2022). Similar strategies are applied in horses, where gentamicin is commonly administered intravenously at 10 mg kg^{-1} every 24 hours, and both peak and trough plasma concentrations are monitored to ensure adequate exposure while limiting nephrotoxicity risk (Schoster et al., 2021). Published studies suggest that target trough concentrations should remain below 2 μg mL^{-1} and, in some cases, below the more conservative target of 0.5 μg mL^{-1} (Burton et al., 2013; Santis et al., 2022). Trough concentrations are influenced by the dosing interval, elimination half-life, and patient-specific physiological or pathological factors. Consequently, they represent a key parameter in therapeutic drug monitoring. Once-daily administration and extended dosing intervals generally maintain trough concentrations below 2 μg mL^{-1} (Pacifici, 2009), whereas concentrations exceeding this threshold have been associated with an increased risk of nephrotoxicity and ototoxicity. Concentrations above 12 μg/ml are considered overtly toxic (Biénès et al., 2023). Given the narrow therapeutic window of gentamicin, monitoring trough concentrations remains essential for minimizing renal injury.

For aminoglycosides, therapeutic efficacy is best predicted by the PK/PD index Cmax/MIC, with bactericidal activity generally associated with Cmax/MIC values ≥ 10 μg mL^{-1} (Biénès et al., 2023). In addition, aminoglycosides exhibit a pronounced post-antibiotic effect (PAE), allowing suppression of bacterial growth even after drug concentrations fall below the MIC of the target pathogen. This characteristic supports the use of extended dosing intervals while maintaining therapeutic efficacy (Santis et al., 2022). Accordingly, the present study evaluated the performance of different dosing regimens across a range of MIC values to identify regimens capable of achieving PK/PD targets while maintaining acceptable safety profiles (Table 2 and 3).

Despite these promising findings, several limitations should be acknowledged. Because gentamicin is frequently administered in combination with other drugs, particularly in septic patients, potential drug interactions should be considered. The Practical Guide to Antimicrobial Therapy in Sepsis (Instituto Latino Americano de Sepse [ILAS], 2022) describes incompatibilities between gentamicin and antimicrobials such as ampicillin and oxacillin, as well as interactions of clinical relevance, including concomitant administration with piperacillin,

which may increase nephrotoxicity risk. Future studies should therefore evaluate the population pharmacokinetics of gentamicin in critically ill dogs and in animals with renal impairment to support safer and more individualized dosing recommendations.

The PK/PD approach applied in this study complements antimicrobial stewardship strategies by enabling evaluation and optimization of antimicrobial dosing regimens through pharmacometric modeling. Such approaches can improve antimicrobial use by aligning dose selection with pathogen susceptibility while limiting unnecessary drug exposure. Future refinement of this strategy could incorporate MIC data obtained directly from clinical isolates at individual veterinary hospitals, allowing more precise, site-specific dosing recommendations. Administering the lowest regimen capable of achieving PK/PD targets may contribute to reducing selection pressure and limiting the development of antimicrobial resistance.

Conclusions

The population pharmacokinetic model was useful for evaluating gentamicin dosing regimens in dogs across a range of pathogen MIC values and nephrotoxicity-risk scenarios. Among the simulated regimens, the 8 mg kg^{-1} regimen achieved PTA values ≥ 90% for pathogens with MICs ≤ 2 μg mL^{-1}. The model also enabled assessment of exposure above nephrotoxicity-risk thresholds, supporting evaluation of dosing strategies with respect to predicted therapeutic efficacy and safety. Further studies are needed to evaluate model performance in clinical patients and refine dosing recommendations for critically ill dogs and other special populations.

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