

Subcutaneous administration of ceftazidime at 20 and 40 mg/kg produces theoretically therapeutic plasma concentrations for at least 120 hours in red-eared sliders (*Trachemys scripta elegans*)

Kara Hiebert, DVM¹; Sherry Cox, PhD²; Shawna Hawkins, MS, DVM, DACZM^{1*}

¹Department of Surgical Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI

²Department of Comparative Medicine, College of Veterinary Medicine, University of Tennessee, Knoxville, TN

*Corresponding author: Dr. Hawkins (shawkins0902@gmail.com)

OBJECTIVE

To evaluate and compare the pharmacokinetic parameters of SC ceftazidime administered at 20 and 40 mg/kg to red-eared sliders.

ANIMALS

8 adult red-eared sliders (*Trachemys scripta elegans*).

METHODS

In a sequential, 2-period study with a 3-week washout period between treatments, ceftazidime was administered SC to turtles at 20 and 40 mg/kg. Blood samples were collected from the subcarapacial sinus at 0, 24, 48, 72, 96, and 120 hours after ceftazidime administration. Plasma ceftazidime concentrations were quantified using reversed-phase HPLC.

RESULTS

Mean plasma half-life after 20- and 40-mg/kg dosing was 39.75 ± 8.0 hours and 33.03 ± 6.56 hours, respectively. Mean maximum plasma concentration after 20- and 40-mg/kg dosing was 71.0 ± 15.93 $\mu\text{g/mL}$ and 120.0 ± 30.62 $\mu\text{g/mL}$, respectively. Mean plasma ceftazidime concentrations remained ≥ 8 $\mu\text{g/mL}$, the theoretical MIC for various reptile pathogens for all time points.

CLINICAL RELEVANCE

Results indicate that ceftazidime dosed at either 20 or 40 mg/kg produces plasma concentrations exceeding the theoretical MIC of various reptile pathogens for at least 120 hours. An ideal dosing interval could not be determined, as all plasma concentrations remained above the threshold of interest for all time points. Follow-up studies should focus on establishing a dosing interval and more rigorous monitoring for potential adverse effects.

Keywords: ceftazidime, red-eared slider turtle, *Trachemys scripta elegans*, pharmacokinetic, slider turtle

Freshwater turtles, such as red-eared sliders (*Trachemys scripta elegans*), have become common household pets throughout North America.¹ Pet turtles are often affected by bacterial infections, secondary to gram-negative species, some of which can pose a zoonotic risk in addition to impacting the animal's quality of life.^{2,3} Veterinarians treating turtles should practice appropriate antibiotic stewardship by using an evidence-based approach to select and administer an appropriate drug at its optimal dose

and frequency to eliminate infection and reduce the risk of developing antibiotic resistance.^{4,5} Sampling the site of infection for culture and sensitivity is considered the gold standard for antibiotic selection in human and veterinary medicine; however, the lack of pharmacokinetic data in turtles often makes it challenging to evaluate potential clinical efficacy despite the availability of sensitivity results.^{5,6}

Ceftazidime, a third-generation cephalosporin, is often used as an injectable empiric antibiotic option in turtle patients given its high efficacy against many common gram-negative reptilian pathogens, including *Pseudomonas* spp, despite commonly being designated as a second-line antibiotic.^{2,5,7} Ceftazidime

Received December 2, 2023

Accepted February 10, 2024

doi.org/10.2460/ajvr.23.11.0265

generally has a wide tissue distribution in mammals and is excreted primarily through the kidneys, with renal accumulation only documented in animals with preexisting renal disease.⁸ The tissue distribution and excretion of ceftazidime have not been described in turtle species, but the concern for toxicity appears low with no documentation of adverse effects in reptiles.^{6,8} The lack of adverse effect documentation in reptiles, however, may be due to a lack of complete investigation. Ceftazidime in humans can be associated with local inflammation at the site of injection, hypersensitivity reactions, gastrointestinal symptoms, CNS reactions, rare hemolytic anemia, and transient laboratory changes.⁹ Ceftazidime is a time-dependent antibiotic, meaning the dosing interval should be largely based on the time that plasma levels are above the MIC of the target pathogen.¹⁰

Drug dosing in turtles is typically extrapolated across reptilian taxa or chosen based on anecdotal reports when pharmacokinetic and pharmacodynamic data in a species of interest are not available. Allometric scaling based on pharmacokinetic and pharmacodynamic data in multiple species can potentially be used to extrapolate a dose in an unstudied species; however, the appropriateness of these scaled doses is limited by drug- and species-dependent factors that cannot always be accounted for.¹¹ The most frequently cited dose for ceftazidime in reptiles is 20 to 40 mg/kg, SC or IM, every 24 to 72 hours.¹² Despite these published recommendations, pharmacokinetic studies evaluating ceftazidime in turtles are limited. When a single injection of 20 mg/kg ceftazidime, IM or IV, was evaluated in loggerhead sea turtles (*Caretta caretta*), plasma levels were shown to exceed the MIC for *Pseudomonas* spp, defined as $\geq 8 \mu\text{g/mL}$, for up to 60 hours.¹³ When the same dose of ceftazidime was administered IM to eastern box turtles (*T. carolina carolina*), yellow-bellied sliders (*Trachemys scripta scripta*), and river cooters (*Pseudemys concinna*), population-based pharmacokinetics data showed plasma levels exceeded the MIC of *Pseudomonas* spp ($\geq 8 \mu\text{g/mL}$) for up to 120 hours.¹⁴

These prior studies compare plasma ceftazidime concentrations to the theoretical MIC of only *Pseudomonas* spp, but it is important to note that ceftazidime can be effective for other common reptile pathogens, depending on the individual isolate's MIC. In snakes, *Pseudomonas* spp, *Aeromonas* spp, *Proteus* spp, and *Enterobacter* spp were all isolated with documented MICs ranging from 0.062 to 1 $\mu\text{g/mL}$ for ceftazidime.¹⁵ Given that these values are below the previously noted MIC of *Pseudomonas* spp from loggerhead turtles, a clinical threshold of 8 $\mu\text{g/mL}$ will be used in this study when the MIC of common reptile pathogens is referenced.

Pharmacokinetic parameters after SC administration of ceftazidime have not yet been evaluated in reptiles. In amphibians, SC administration has been shown to produce clinically relevant plasma concentrations for up to 5 days in eastern hellbenders (*Cryptobranchus alleganiensis alleganiensis*)

and up to 24 hours in Northern leopard frogs (*Lithobates pipiens*); however, there was no direct comparison to IM administration.^{16,17} A different third-generation cephalosporin, ceftiofur crystalline-free acid, produced more reliable plasma concentrations in bearded dragons when administered SC over IM, suggesting the SC route may be advantageous; however, species-, drug-, and formulation-dependent factors would prevent direct extrapolation to ceftazidime dosing in turtles.¹⁸

This study's objective was to evaluate the pharmacokinetic parameters of SC administration of ceftazidime in red-eared sliders at 2 different doses. We aimed to measure plasma ceftazidime concentrations after a single dose of 20 and 40 mg/kg administered SC. We hypothesized that the plasma concentrations would exceed the theoretical MIC for common reptile pathogens ($\geq 8 \mu\text{g/mL}$)^{13,15} for a longer duration after the 40-mg/kg dose as compared to the 20-mg/kg dose.

Methods

This study protocol was approved by the University of Wisconsin-Madison School of Veterinary Medicine Institutional Animal Care and Use Committee (protocol No. V006636).

Animals

Red-eared sliders ($n = 8$; 5 female, 3 male) with a mean body weight of 532 g (range, 410 to 740 g) were obtained from a commercial supplier (Niles Biological Inc). Turtles were housed in a group pond enclosure with a filter pump, underwater hides, and multiple haulouts with a ceramic heat lamp and a full spectrum UV lamp. Average daily ambient temperature was maintained between 24 and 27 °C, and average daily ambient humidity was maintained between 19% and 25%. Complete water changes were performed twice weekly, while water pH, ammonia levels, and nitrite levels were monitored weekly and maintained at 6.0 to 8.5, $< 1.0 \text{ mg/L}$, and $< 2 \text{ mg/L}$, respectively. Water temperature was monitored daily and kept between 20 and 24 °F. Turtles were fed a pelleted diet formulated for aquatic turtles (TetraFauna ReptoMin) every other day. Turtles were housed in their enclosure for at least 4 weeks before initiating this study. Two weeks before baseline samples were taken, each turtle underwent a physical examination and was administered 50 mg/kg fenbendazole (100 mg/mL; 10% Panacur Suspension; Merck Animal Health) orally via metal gavage needle for prophylactic endoparasite treatment. During the physical exam, 1 mL blood was collected from the subcarapacial plexus and placed into lithium heparin microtainers (Becton Dickinson). This phlebotomy site was chosen based on ease of access as study animals were not amenable to restraint for alternative phlebotomy sites such as the jugular vein or brachial plexus. For each turtle, 200 μL of whole blood was submitted within 2 hours of the first blood collection for biochemistry evaluation using

the VetScan Whole Blood Analyzer with the Avian/Reptile Profile Plus rotors (Abaxis). The remainder of the sample for each animal was centrifuged (E8 Porta-Fuge; LW Scientific Centrifuge) at 1,534 X *g* for 10 minutes, and plasma was removed via pipette, pooled in cryovials, and frozen at -80 °C. Once the pooled plasma was frozen, it was shipped overnight on dry ice to the University of Tennessee College of Veterinary Medicine Pharmacology Laboratory for assay validation.

Study design

All turtles were administered ceftazidime (100 mg/mL; 1-g vial of ceftazidime; WG Critical Care LLC) at 20 and then 40 mg/kg, SC, in the ante-brachial area of a forelimb in a sequential, 2-period study with a 3-week washout period between doses. On the day of drug administration, a 1-g vial of ceftazidime was reconstituted with 10 mL sterile water to 100 mg/mL according to the instructions on the package insert. Reconstituted ceftazidime was used within 1 hour of reconstitution; a new vial was reconstituted for each sampling period. Before drug administration for each sampling period, every turtle was handled for weight measurement and collection of blood from the subcarapacial plexus for baseline plasma ceftazidime measurement. The injection site was gently wiped with 70% isopropyl alcohol-soaked gauze before drug administration, and then gentle digital pressure was applied after injection for 5 to 10 seconds to prevent drug leakage. Animals were evaluated by a veterinarian once daily during the sample period for visible redness, swelling, or discoloration at the injection site. During handling, the animals were also monitored for expected behaviors including strong retraction into the shell and rapid retreat into the water after handling. Animals were otherwise not observed between blood samples.

To monitor ceftazidime plasma levels over time, 0.5 mL blood was collected from the subcarapacial plexus from every turtle at 24, 48, 72, 96, and 120 hours after ceftazidime administration and placed in a lithium heparin microtainer. Within 30 minutes of sample collection, blood samples were centrifuged (E8 Porta-Fuge; LW Scientific Centrifuge) at 1,534 X *g* for 10 minutes, and plasma was removed via pipette and placed in cryovials. All plasma samples were frozen at -80 °C until the conclusion of both sampling periods. Samples were stored frozen for up to 4 weeks and then shipped on dry ice to the University of Tennessee College of Veterinary Medicine Pharmacology Laboratory for analysis. All samples arrived frozen and were immediately placed in a -80 °C freezer before analysis.

Sample analysis

Measurement of ceftazidime concentration in plasma samples was performed as previously described.^{16,19} A reversed-phase HPLC method was used to analyze the samples. Compounds were separated on a C18 column (4.6 X 250 mm; 5 μm) with a 5-μm guard column (Symmetry Shield C18 column;

Waters Corp). The mobile phase was a mixture of 10 mM potassium phosphate monobasic (pH of 2.5) and acetonitrile-mixture (90:10 ratio). Absorbance was measured at 260 nm with a flow rate of 0.9 mL/min. Ceftazidime was extracted from plasma samples via centrifugation. One hundred microliters of plasma was transferred to a 13 X 100-mm glass tube followed by 10 μL of cefotaxime (internal standard, 100 μg/mL) and 140 μL of distilled water. The tubes were vortexed for 30 seconds and then loaded into a centrifugation filter unit (Millipore Amicon Ultra [0.5 mL] and Ultracel [30 K] filters; MilliporeSigma) and centrifuged for 20 minutes at 16,060 X *g*. The resulting solution (approx 200 μL) was transferred into HPLC vials, and 100 μL was injected into the chromatography system. Standard curves for plasma analysis were prepared by fortifying untreated turtle plasma, collected, and pooled during the initial physical exam as stated above, with ceftazidime, which produced a linear concentration range of 0.1 to 100 μg/mL. The average recovery was 91% for ceftazidime. Precision and accuracy were assessed by analyzing 5 replicates at 0.35, 7.5, 35, and 75 μg/mL. The precision ranged from 3% to 11% and the accuracy from 98% to 101%, and the lower limit of quantification was 0.1 μg/mL.

Pharmacokinetic analysis

Pharmacokinetic parameters for ceftazidime were calculated using Phoenix 64 WinNonlin (version 8.1; Certara Co). Values for the elimination rate constant, plasma half-life, maximum plasma concentration, area under the plasma concentration time curve from time 0 to infinity ($AUC_{0-\infty}$), AUC from time 0 to the last measured concentration, percentage of the $AUC_{0-\infty}$ that was extrapolated to infinity, and mean residence time from 0 to infinity were calculated by noncompartmental analysis. The AUC was calculated with the log-linear trapezoidal rule. Mean residence time was calculated as $AUMC_{0-\infty}/AUC_{0-\infty}$, where $AUMC$ is the area under the first moment curve to infinity. Variability in pharmacokinetic parameters was expressed as the SD.

Statistical analysis

Plasma concentrations and calculated pharmacokinetic parameters between the 20- and 40-mg/kg sampling periods were analyzed and compared using commercial statistics software (SigmaPlot 13; Systat Software). Normality of plasma ceftazidime concentration distribution at each sampling time point as well as the distribution of each calculated pharmacokinetic parameter was assessed using the Shapiro-Wilks test. Comparison of plasma ceftazidime concentrations and calculated pharmacokinetic parameters between treatment groups at each time point was performed using the paired *t* test if data were normally distributed or the Wilcoxon signed rank test if data were not normally distributed. *P* values of < .05 were considered significant. Mean ceftazidime plasma concentrations and SD were calculated for each treatment group at each time point

for normally distributed time points; median and IQR were calculated for each nonnormally distributed time point.

Results

Vetscan biochemistry results were compared to published reference ranges and all values were within normal limits for each turtle.^{20,21} Pharmacokinetic parameters for each ceftazidime dose evaluated, 20 and 40 mg/kg, are summarized (**Table 1**). Ceftazidime was not detected in any plasma samples taken at time point 0 for both sampling periods. Mean ceftazidime plasma concentrations were detectable above the MIC for *Pseudomonas* spp for all time points from both doses evaluated (**Figure 1**). Statistical analysis of calculated pharmacokinetic parameters and ceftazidime plasma concentrations at each time point between the 2 ceftazidime doses are summarized (**Table 2**). No cutaneous redness, swelling, or discoloration was noted at any injection sites and all turtles had strong retraction into their shells and rapid retreat into the water at each sampling point.

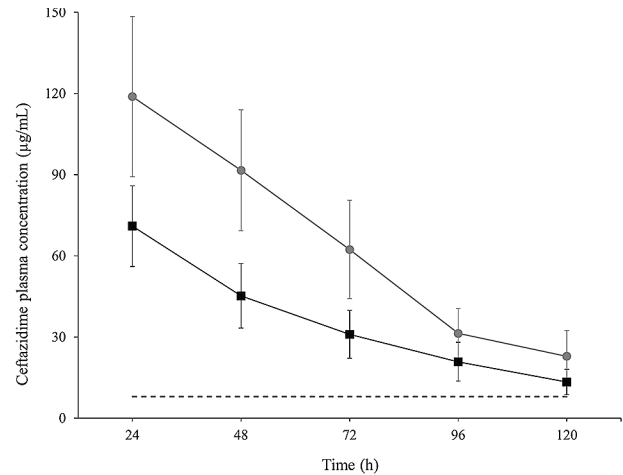


Figure 1—Mean ± SD plasma ceftazidime concentrations in red-eared sliders (*Trachemys scripta elegans*) following administration of a single ceftazidime dose at 20 mg/kg, SC (n = 8; black squares), and 40 mg/kg, SC (8; gray circles). The dashed line indicates the theoretical MIC ($\geq 8 \mu\text{g/mL}$) of *Pseudomonas* spp in loggerhead sea turtles (*Caretta caretta*) and other common reptile pathogens.^{13,15}

Table 1—Ceftazidime pharmacokinetic parameters in red-eared sliders.

Pharmacokinetic parameter	20 mg/kg (mean ± SD)	Minimum	Maximum	40 mg/kg (mean ± SD)	Minimum	Maximum
$t_{1/2}$ (h)	39.75 ± 8.22	30.37	56.74	33.03 ± 6.56	25.74	43.45
λ_z (1/h)	0.017 ± 0.004	0.012	0.023	0.021 ± 0.004	0.016	0.027
t_{max} (h)	24.0 ± 0	24	24	27.0 ± 8.49	24	48
C_{max} (µg/mL)	71.0 ± 15.93	37	90	120.0 ± 30.62	80	163
$\text{AUC}_{0-\infty}$ (h·µg/mL)	5,028 ± 1,451	2,619	7,198	8,783 ± 2,555	6,031	12,630
$\text{AUC}_{0-\text{Last}}$ (h·µg/mL)	4,196 ± 1,112	2,220	5,880	7,589 ± 1,966	5,388	10,308
$\text{AUC}_{\text{Extrap}}$ (%)	15.92 ± 5.17	7.69	24.29	12.97 ± 4.95	6.61	18.86
$\text{MRT}_{0-\infty}$ (h)	71.75 ± 9.83	57.12	87.36	66.69 ± 9.09	55.24	77.41

λ_z = Elimination rate constant. $\text{AUC}_{0-\infty}$ = Area under the plasma concentration time curve from time 0 to infinity. $\text{AUC}_{\text{Extrap}}$ = Percentage of the $\text{AUC}_{0-\infty}$ extrapolated to infinity. $\text{AUC}_{0-\text{Last}}$ = Area under the plasma concentration time curve from time 0 to last time point. C_{max} = Maximum plasma concentration. $\text{MRT}_{0-\infty}$ = Mean residence time from time 0 to infinity. $t_{1/2}$ = Terminal half-life. t_{max} = Time to maximum plasma concentration.

Table 2—Statistical analysis between pharmacokinetic parameters in red-eared sliders given 2 doses of ceftazidime SC.

Pharmacokinetic parameter	20 mg/kg (mean ± SD)	40 mg/kg (mean ± SD)	Statistical test	P value
$t_{1/2}$ (h)	39.75 ± 8.22	33.03 ± 6.56	Paired t test	.064
λ_z (1/h)	0.017 ± 0.004	0.021 ± 0.004	Paired	.065
t_{max} (h)	24.0 (24.0–24.0) [†]	24.0 (24.0–24.0) [†]	Wilcoxon signed rank	1.000
C_{max} (µg/mL)	71.0 ± 15.93	120.0 ± 30.62	Paired	< .001*
$\text{AUC}_{0-\infty}$ (h·µg/mL)	5,028 ± 1,451	8,783 ± 2,555	Paired	< .001*
$\text{AUC}_{0-\text{Last}}$ (h·µg/mL)	4,196 ± 1,112	7,589 ± 1,966	Paired	< .001*
$\text{AUC}_{\text{Extrap}}$ (%)	15.92 ± 5.17	12.97 ± 4.95	Paired	.265
$\text{MRT}_{0-\infty}$ (h)	71.75 ± 9.83	66.69 ± 9.09	Paired	.296
C_{24} (µg/mL)	71.00 ± 15.93	118.88 ± 31.61	Paired	< .001*
C_{48} (µg/mL)	45.25 ± 12.70	91.63 ± 23.89	Paired	< .001*
C_{72} (µg/mL)	31.00 ± 9.47	62.38 ± 19.37	Paired	< .001*
C_{96} (µg/mL)	18.5 (16.25–26.75) [†]	27.00 (24.25–38.50) [†]	Wilcoxon signed rank	.008*
C_{120} (µg/mL)	13.37 ± 4.98	22.88 ± 10.16	Paired	.023*

λ_z = Elimination rate constant. C_{max} = Maximum plasma concentration. C_x = Plasma concentration at time point x. $\text{AUC}_{0-\infty}$ = Area under the plasma concentration time curve from time 0 to infinity. $\text{AUC}_{\text{Extrap}}$ = Percentage of the $\text{AUC}_{0-\infty}$ extrapolated to infinity. $\text{AUC}_{0-\text{Last}}$ = Area under the plasma concentration time curve from time 0 to last time point. $\text{MRT}_{0-\infty}$ = Mean residence time from time 0 to infinity. $t_{1/2}$ = Terminal half-life. t_{max} = Time to maximum plasma concentration.

*Difference in parameters between 20 and 40 mg/kg is statistically significant with a set at $P < .05$. [†]Median and IQR are used in place of mean ± SD for groups of data that were nonnormally distributed.

Discussion

The results of this study demonstrate sustained detectable plasma ceftazidime concentrations above the theoretical MIC for common reptile pathogens for at least 120 hours after SC administration of either 20 or 40 mg/kg ceftazidime, SC, in red-eared sliders. These results are similar to the findings of a study¹⁴ evaluating 20 ceftazidime, IM, in wild North American freshwater turtles, which found similar sustained plasma levels for 120 hours after administration using a population-based pharmacokinetic study design. This differs from loggerhead sea turtles, in which plasma concentrations above 8 µg/mL were only sustained for up to 60 hours after IV and IM administration of 20 ceftazidime, which highlights an interspecies variation in metabolism regardless of administration route.¹³

This is the first ceftazidime pharmacokinetic study to evaluate both 20- and 40-mg/kg doses in freshwater turtles via the SC route. While the half-lives for both doses were not significantly different, the 40-mg/kg dose produced higher ceftazidime concentrations at every time point. Despite lower plasma ceftazidime concentrations produced by the 20-mg/kg doses, all concentrations were above our predetermined clinical threshold of 8 µg/mL.

Although we used this threshold as a benchmark for ceftazidime concentrations based on previously published MICs for common reptile pathogens, there are no reptile-specific breakpoints established for any antibiotic drugs to measure bacterial sensitivity against. Prior studies²²⁻²⁵ reviewing susceptibility patterns of reptile bacterial isolates reference established Clinical and Laboratory Standards Institute and European Committee on Antibiotic Susceptibility Testing breakpoints as the standard for susceptibility of the isolates of interest without publication of MICs. Common bacterial pathogens isolated from turtle species include *Pseudomonas* spp, bacteria within the Enterobacteriaceae family, *Aeromonas* spp, *Morganella* spp, and *Proteus* spp^{3,7,26} Based on the Clinical and Laboratory Standards Institute and European Committee on Antibiotic Susceptibility Testing databases, all of these bacterial species have a breakpoint of ≤ 8 µg/mL, which is consistent with previously published MIC data from pathogens isolated from loggerhead sea turtles and various snake species suggesting this is an appropriate threshold.^{13,15,24,26} However, given the lack of established breakpoints for reptiles and the higher plasma concentrations produced by the 40-mg/kg ceftazidime dose, it may be feasible to consider this higher dose for bacterial isolates with MICs of > 8 µg/mL. This would require careful interpretation of culture and susceptibility results. Additionally, adverse effect monitoring in this study was limited to the visual appearance of the injection site and behavior monitoring during handling sessions. Histologic evidence of injection site pathology could have been missed as well as manifestations of adverse effects that were not sufficient to alter behavior. Cautious monitoring for adverse effects,

especially if using the higher 40-mg/kg dose, should be implemented.

An additional consideration when making dosing recommendations based on the pharmacokinetic data from this study is the temperature at which turtles are maintained. During this study, water temperature was maintained between 20 and 24 °C with an ambient temperature between 24 and 27 °C; a basking area was also provided, but maximum basking temperature was not measured. Because all turtles in this study were housed in the same enclosure, the effects of ambient temperature on pharmacokinetic data could not be assessed but are considered consistent for all individuals. Previously in gopher tortoises, it has been shown that ambient temperature significantly affects the pharmacokinetic parameters after amikacin injection.²⁷ Similar effects may be possible in this species, so red-eared sliders should ideally be housed with similar ambient temperature parameters if making dosing recommendations based on the data reported in this study.

Further, these animals were group housed during the study period, and despite continuous filtration and twice-weekly water changes, there was some degree of exposure to urate, urine, and feces. In red-eared sliders, the rate of excretion as well as the drug form that is excreted in urinary and fecal waste has not been documented. Thus, it is unknown whether animals were reexposed to ceftazidime through their environment during the study period, which could potentially affect pharmacokinetic parameters. Previous studies^{13,14} evaluating the pharmacokinetics of ceftazidime in aquatic turtles did not provide housing information to correlate whether this could have been a factor in previously published data. Despite the possible effects of this study's animal housing on pharmacokinetic parameters, this may not significantly impact the clinical relevance of this data as aquatic turtles under veterinary care are generally housed in similar conditions.

This study had several limitations. The first is infrequent sampling times, which can cause an unreliable AUC measurement as well as the elimination rate constant. To account for this, we have reported the extrapolated percentage of the AUC, which should ideally be as small as possible but should not exceed 20% for the AUC measurement to be deemed reliable. The extrapolated percentage of the AUC is < 20% for both the 20- and 40-mg/kg doses. While more frequent sampling times would have been preferred, this frequency was chosen to minimize the total blood sampled during the study period and handling stress on the animals.

This study essentially served as pilot data for the pharmacokinetics of SC ceftazidime in red-eared sliders, so the sampling period length was based on the prior studies^{13,14} evaluating IM administration of ceftazidime in loggerhead sea turtles and freshwater turtles. Thus, an additional limitation is that the sampling period did not exceed the period of time that ceftazidime plasma levels were detectable. This means that we can draw conclusions about the minimum time that ceftazidime plasma levels will be

above a certain MIC but cannot determine the maximum time ceftazidime plasma levels will be detectable, thus making dosing interval recommendations challenging based on this study alone. Future studies evaluating ceftazidime pharmacokinetics in red-eared sliders should include additional time points beyond 120 hours postadministration.

Further, since this was not a repeated dosing study, we are unable to evaluate cumulative plasma ceftazidime concentrations or any cumulative adverse effects that may occur. Pharmacokinetic data after repeated ceftazidime administration in veterinary medicine have not been reported; in humans, repeated ceftazidime administration twice daily over 8 days did not have a cumulative effect, and no additional adverse effects were noted over time.²⁸ However, this dosing interval is markedly different than the dosing interval used in reptiles, meaning this precedent may not hold true in reptiles.

In conclusion, this study reports sustained, detectable ceftazidime plasma concentrations for at least 120 hours after administration of either 20 or 40 mg/kg ceftazidime, SC, to red-eared sliders with the higher dose producing higher plasma concentrations. No adverse effects were seen in any of the turtles during the study period. Depending on the target therapeutic plasma concentration, the dose recommendation for ceftazidime in red-eared sliders would be 20 mg/kg with an expected duration of action of at least 5 days.

Acknowledgments

None reported.

Disclosures

The authors have nothing to disclose. No AI-assisted technologies were used in the generation of this manuscript.

Funding

Funding was provided by the Companion Animal Grant Fund.

References

1. Reavill DR, Griffin C. Breeders, wholesalers, and retailers. In: Divers SJ, Stahl SJ, eds. *Mader's Reptile and Amphibian Medicine and Surgery*. 3rd ed. Elsevier; 2019:1406–1413.
2. Isaza R, Jacobson ER. Antimicrobial drug use in reptiles. In: Giguère S, Prescott JF, Dowling PM, eds. *Antimicrobial Therapy in Veterinary Medicine*. Wiley; 2013. doi:10.1002/9781118675014.CH37
3. Hossain S, Heo GJ. Pet-turtles: a potential source of human pathogenic bacteria. *Arch Microbiol*. 2021;203(7):3785–3792. doi:10.1007/S00203-021-02428-X/FIGURES/1
4. Fishman N. Antimicrobial stewardship. *Am J Infect Control*. 2006;34(5):S55–S63. doi:10.1016/J.AJIC.2006.05.237
5. Hedley J, Whitehead ML, Munns C, et al. Antibiotic stewardship for reptiles. *J Small Anim Pract*. 2021;62(10):829–839. doi:10.1111/JSAP.13402
6. Flanagan JP. Turtles (turtles, tortoises). In: Miller RE, Fowler ME, eds. *Fowler's Zoo and Wild Animal Medicine*. Vol 8. W.B. Saunders; 2015:27–38.
7. Tang PK, Divers SJ, Sanchez S. Antimicrobial susceptibility patterns for aerobic bacteria isolated from reptilian samples submitted to a veterinary diagnostic laboratory: 129 cases (2005–2016). *J Am Vet Med Assoc*. 2020;257(3):305–312. doi:10.2460/javma.257.3.305.
8. Plumb DC. Ceftazidime. In: Plumb DC, ed. *Plumb's Veterinary Drug Handbook*. 9th ed. John Wiley & Sons; 2018:214–216.
9. Ceftazidime. Package insert. USDA. Revised September 2021. Accessed January 16, 2024. <https://www.accessdata.fda.gov/spl/data/fa5dc130-c774-440f-94f6-ea404c0e5ddb/fa5dc130-c774-440f-94f6-ea404c0e5ddb.xml>
10. Eylar RF, Shvets K. Clinical pharmacology of antibiotics. *Clin J Am Soc Nephrol*. 2019;14(7):1080–1090. doi:10.2215/CJN.08140718
11. Hunter RP, Isaza R. Concepts and issues with interspecies scaling in zoological pharmacology. *J Zoo Wildl Med*. 2008;39(4):517–526. doi:10.1638/2008-0041.1
12. Carpenter JW, Klaphake E, Gibbons PM, Sladky KK. Reptile formulary. In: Divers SJ, Stahl SJ, eds. *Mader's Reptile and Amphibian Medicine and Surgery*. 3rd ed. Elsevier; 2019:1191–1211.
13. Stamper AM, Papich MG, Lewbart GA, May SB, Plummer DD, Stoskopf MK. Pharmacokinetics of ceftazidime in loggerhead sea turtles (*Caretta caretta*) after single intravenous and intramuscular injections. *J Zoo Wildl Med*. 1999;30(1):32–35.
14. Cerreta AJ, Lewbart GA, Dise DR, Papich MG. Population pharmacokinetics of ceftazidime after a single intramuscular injection in wild turtles. *J Vet Pharmacol Ther*. 2018;41(4):495–501. doi:10.1111/JVP.12500
15. Lawrence K, Muggleton PW, Needham JR. Preliminary study on the use of ceftazidime, a broad spectrum cephalosporin antibiotic, in snakes. *Res Vet Sci*. 1984;36(1):16–20. doi:10.1016/s0034-5288(18)31994-5
16. Hawkins SJ, Cox SK, Sladky KK. Pharmacokinetics of ceftazidime in Northern leopard frogs (*Lithobates pipiens*) at two different doses and administration routes. *Am J Vet Res*. 2021;82(7):560–565. doi:10.2460/AJVR.82.7.560
17. Musgrave KE, Hanley CS, Papich MG. Population pharmacokinetics of ceftazidime after a single subcutaneous injection and normal oral and cloacal bacterial flora survey in eastern hellbenders (*Cryptobranchus alleganiensis alleganiensis*). *J Zoo Wildl Med*. 2021;52(1):90–96. doi:10.1638/2020-0145
18. Churgin SM, Musgrave KE, Cox SK, Sladky KK. Pharmacokinetics of subcutaneous versus intramuscular administration of ceftiofur crystalline-free acid to bearded dragons (*Pogona vitticeps*). *Am J Vet Res*. 2014;75(5):453–459. doi:10.2460/ajvr.75.5.453
19. Bergman J, Harvill L, Hawkins S, Sladky K, Cox S. Determination of ceftazidime in plasma by RP-HPLC and ultraviolet detection. *Biomed Chrom*. 2021;35(7):1–6. doi:10.1002/bmc.5104
20. Crawshaw GJ, Holz P. Comparison of plasma biochemical values in blood and blood-lymph mixtures from red-eared sliders, *Trachemys scripta elegans*. *Bull Assoc Reptil Amphib Vet*. 1996;6(2):7–9. doi:10.5818/1076-3139.6.2.7
21. Klaphake E, Gibbons PM, Sladky KK, Carpenter JW. Reptiles. In: Carpenter JW, Marion CJ, eds. *Exotic Animal Formulary*. 5th ed. Elsevier; 2018:81–166.
22. Bertelloni F, Chemaly M, Cerri D, Le Gall F, Eban VV. *Salmonella* infection in healthy pet reptiles: bacteriological isolation and study of some pathogenic characters. *Acta Microbiol Immunol Hung*. 2016;63(2):203–216. doi:10.1556/030.63.2016.2.5
23. Dec M, Stepien-Pysniak D, Szczepaniak K, Turchi B, Urban-Chmiel R. Virulence profiles and antibiotic susceptibility of *Escherichia coli* strains from pet reptiles. *Pathogens*. 2022;11(2):127. doi:10.3390/pathogens11020127

24. 2023 Breakpoints in use toolkit. Clinical & Laboratory Standards Institute. Accessed September 2, 2023. <https://clsi.org/meetings/ast/breakpoints-in-use-toolkit/>
25. Breakpoint tables for interpretation of MICs and zone diameters. Version 13.1. 2023. The European Committee on Antibiotic Susceptibility Testing. Accessed September 2, 2023. https://www.eucast.org/clinical_breakpoints
26. De Silva BCJ, Hossain S, Wimalasena SHMP, Pathirana HNKS, Dahanayake PS, Heo GJ. Comparative in vitro efficacy of eight essential oils as antibacterial agents against pathogenic bacteria isolated from pet-turtles. *Vet Med (Praha)*. 2018;63(7):335-343. doi:10.17221/142/2017-VETMED
27. Caligiuri R, Kollias GV., Jacobson E, McNab B, Clark CH, Wilson RC. The effects of ambient temperature on amikacin pharmacokinetics in gopher tortoises. *J Vet Pharmacol Ther*. 1990;13(3):287-291. doi:10.1111/J.1365-2885.1990.TB00778.X
28. Kemmerich B, Warns H, Lode H, Borner K, Koeppel P, Knothe H. Multiple-dose pharmacokinetics of ceftazidime and its influence on fecal flora. *Antimicrob Agents Chemother*. 1983;24(3):333. doi:10.1128/AAC.24.3.333