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Ceftazidime pharmacokinetics in dogs after intravenous injection and delivered with the RxActuator Mini-Infuser infusion pump

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Abstract

Objective: To test the feasibility of an SC mini-infusion pump to deliver ceftazidime in dogs and produce plasma concentrations sufficient to reach a therapeutic target for 48 hours.

Setting: University research laboratory.

Animals: Six healthy Beagle dogs.

Interventions: Ceftazidime was administered by 2 routes to 6 healthy Beagle dogs. The first route was an IV bolus injection into a cephalic vein at a dose of 25 mg/kg. Blood samples were collected for 8 hours following injection. The second route was a SC infusion for 48 hours using the RxActuator Mini-Infuser wearable SC constant rate infusion pump. Blood samples were collected for 58 hours following application of the pump. All plasma samples were analyzed by high-pressure liquid chromatography and subject to pharmacokinetic analysis.

Main Results: After the IV bolus injection, there was rapid distribution and elimination. The elimination half-life was 0.95 hours, and the clearance was rapid at 0.176 ml/h/kg. After the 48-hour SC infusion, the half-life was slightly shorter, and the clearance was higher. The percent bioavailability from the SC infusion was approximately 72%. The SC infusion maintained plasma concentration near our target of 8 μg/ml for most of the dose interval but slightly lower after 24 hours. The concentrations below the target were attributed to slight drug loss, less than 100% bioavailability, and faster clearance from SC administration.

Conclusions: This study demonstrated the successful application of the RxActuator Mini-Infuser wearable SC constant rate infusion pump for delivering an antimicrobial needed for serious, and sometimes resistant, infections in dogs.

KEYWORDS
antimicrobial, canine, cephalosporin, half-life, mean inhibitory concentration

Abbreviations: AUC, area under the curve; CL, clearance; IACUC, Institutional Animal Care and Use Committee; MIC, minimal inhibitory concentration; USP, United States Pharmacopeia.

1 | INTRODUCTION

Ceftazidime[a] is a third-generation cephalosporin, approved for use in people but not approved for any veterinary species. However, it has become an important antimicrobial agent for dogs, cats, horses, marine mammals, exotic, and zoo animal species to treat infections that are resistant to other commonly used veterinary antimicrobial agents.[1–6] The most important organisms treated with ceftazidime are *Pseudomonas aeruginosa* and bacteria of the Enterobacterales order (primarily *Escherichia coli*) that are resistant to other antimicrobial agents. Because there are no veterinary-approved antimicrobial agents with a spectrum of activity that is equal to ceftazidime, veterinarians have relied on extralabel use of the human formulation.

The most important drawback for using ceftazidime in dogs is that it has a very short half-life of approximately 1 hour and rapid clearance. Because ceftazidime is a time-dependent antimicrobial for which it is important to maintain concentrations for as long as possible above the minimal inhibitory concentration (MIC),[6–8] 3–4 daily injections are needed, which is difficult for hospital staff and pet owners and can produce discomfort at the injection site .

Veterinarians often encounter resistant infections that are not responsive to veterinary-approved antimicrobials. They seek other options for their patients in order to avoid the use of carbapenems, amikacin, or newer agents available for use in human medicine. Ceftazidime may offer such an opportunity for an alternative agent if a convenient delivery method can be developed.

Ceftazidime for injection is supplied in sterile vials equivalent to 1 or 2 g of anhydrous ceftazidime. There were once several original brand names, but these are rarely available, and veterinarians rely on the generic formulations, which are available from various suppliers at an inexpensive cost affordable for veterinary use.

Clinical use is based on anecdotal experiences, pharmacokinetic studies in dogs,[1,9,10] and extrapolation from the use in human medicine. Based on these reports, recommended doses have ranged from 20 to 30 mg/kg (IV, IM, or SC), administered every 4, 6, or 8 hours in mammals.

Our hypothesis was that plasma concentrations of ceftazidime sufficient to meet therapeutic targets will be achieved in dogs with delivery by SC infusion using the RxActuator Mini-Infuser wearable SC constant rate infusion pump for 48 hours. To accomplish our objective, we performed a crossover study to compare a single IV bolus of 25 mg/kg to the SC infusion delivered over 48 hours.

2 | METHODS

2.1 | Animals

Six healthy research Beagle dogs with a mean weight of 11.15 kg (±1.43 kg) were obtained from the college's Laboratory Animal Resources. The dogs were housed in the college's Laboratory Animal Facilities throughout the study and maintained on their regular diet. An Institutional Animal Care and Use Committee (IACUC)-approved protocol was available prior to the start of the project (IACUC approval #19-814).

2.2 | Procedure

On the day prior to drug administration, jugular IV catheters were inserted to facilitate blood collection. Mild sedation was administered with dexmedetomidine injection at a dose of 10 μg/kg (IM) to decrease discomfort associated with the catheter insertion. The catheters were flushed with 0.9% sterile saline solution between collection times to prevent blood clotting in the catheter. Each dog was allowed a recovery time of 24 hours prior to administration of ceftazidime.

In the first phase of the study, ceftazidime was administered as a rapid IV injection in the cephalic vein, at a dose of 25 mg/kg. Ceftazidime was reconstituted with sterile water according to the manufacturer's instructions. After IV ceftazidime administration, blood samples were collected at 0 (predose), 2, 10, 20, 30, and 40 minutes, 1 hour, 1.5 hours, and then at 2, 3, 4, 6, and 8 hours. Following a washout period of 48 hours to allow for clearance of the IV dose, SC ceftazidime was administered to the same dogs, using the RxActuator Mini-Infuser pump.[b] The SC pump reservoir was filled with 10 ml of ceftazidime solution. The pump is designed to deliver at a rate of 0.2 ml/h for 50 hours. Ceftazidime vials (1-g vial) were diluted with sterile water to obtain an average concentration of 89.2 mg/ml, with a precise amount calculated for each dog according to the dog's body weight. The RxActuator Mini-Infuser device was attached to the dogs' backs (on the dorsal thorax) and secured with 2 skin sutures and a light wrap.

The total dose delivered was 1.6 mg/kg/h for a duration of 48 hours, with a total dose during the 48-hour period of 76.8 mg/kg. This dose was based on a calculation of average clearance from previously published studies[1,9,10] (mean clearance, 0.197 L/kg/h), which was rounded up to 0.2 L/kg/h. The target steady-state plasma drug concentration was 8 μg/ml, based on the MIC for targeted bacteria.[11] Thus, the infusion rate was calculated as

Infusion rate (mg/kg/h) = [Target concentration] × [Clearance].

After pump activation, the SC catheter was inserted in each dog in a space approximately between the shoulder blades on the dogs' dorsum. Blood samples were collected at 0, 1, 2, 4, 6, 8, 12, 24, 30, 36, 42, and 48 hours. The pump was then disconnected and additional samples collected at 50, 52, 56, and 58 hours. Samples after 48 hours were intended to measure post-pump drug disposition. After the pump was disconnected, the residual volume and concentration remaining in the pump was measured.

All blood samples were collected into heparinized tubes. After collection, the blood was immediately placed on ice to inhibit lysis of RBCs. Samples were centrifuged, plasma harvested, and stored at −70°C until analysis. Animals were observed for adverse effects from drug administration by licensed and board-certified veterinarians.

2.3 | Plasma drug analysis

Ceftazidime samples in plasma were all analyzed within 48 hours of collection with high-pressure liquid chromatography. After thawing, the samples were analyzed using a method validated in the investigator's laboratory following methods described in other studies.[3,5] A partial validation was performed by fortifying blank canine plasma with known concentrations of ceftazidime and confirming that the assay performed according to our laboratory's acceptance criteria. For each batch of samples analyzed, a fresh calibration curve and quality control samples were prepared to ensure the assay met the laboratory's acceptance criteria. Our lower limit of quantification was 0.05 μg/ml for the assay. The precision and accuracy of the assay was 4.7%–6.2% and 100%, respectively.

2.4 | Stability testing of ceftazidime solution

The strength of the ceftazidime solution was tested over time to ensure that during the 48-hour infusion time the drug retained the strength within the acceptance criteria specified in the United States Pharmacopeia (USP) compendial standard for ceftazidime solution. To meet the USP standard, solutions should retain potency at ±10% of the nominal concentration. The strength of the reconstituted solution was tested at 0, 24, and 48 hours after reconstitution using a validated high-pressure liquid chromatography method in our laboratory.[3]

2.5 | Pharmacokinetic analysis

2.5.1 | Compartmental analysis

Drug plasma concentrations were analyzed using computer software and compartmental methods.[c] For the IV bolus administration, 1-, 2-, and 3-compartment models were fit to the data. After examination of the diagnostic plots and predicted versus observed plots, a 2-compartment model with bolus input was selected for the IV data according to the equation:

$$C(t) = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t}$$

where C is the concentration at time t, A is the y-axis intercept for the initial steep portion of the curve, with accompanying rate constant (α), and B is the intercept for the terminal (elimination) portion of the curve with the accompanying rate constant (β). Secondary parameters calculated included the half-life, area-under-the-curve (AUC), systemic clearance (CL), mean residence time, and volumes of distribution (V_1 and V_{SS}). A weighting factor of 1/predicted Y^2 was applied to the data.

The SC infusion data used a similar approach in which various models were tested and diagnostic plots examined to determine the model that best fit the data. For the SC infusion dose, a 1-compartment model with infusion was fitted to these data according to the equation:

$$C(T) = (D/T_I) \times \frac{1}{V \times \mathrm{K10}} \times (e^{(-\mathrm{K10} \cdot t^*)} - e^{(-\mathrm{K10} \cdot t)})$$

where $C(T)$ is the concentration at time T; D is the dose; T_I is time of infusion (48 h); V is the volume of distribution; K10 is the elimination rate constant; and t^* is $T - T_I$ when $T > T_I$ and 0 when $T \leq T_I$.

Secondary parameters included the AUC, CL, and elimination half-life. Also measured from the SC infusion data was the bioavailability, which was calculated from

$$\%\text{bioavailability} = \frac{AUC\ SC\ \text{infusion}}{AUC\ IV\ \text{bolus}} \times \frac{Dose\ IV}{Dose\ SC\ \text{infusion}} \times 100.$$

2.5.2 | Noncompartmental analysis

Noncompartmental analysis was performed using the Phoenix software[c] for the purpose of calculating partial AUC values during the 48 hour infusion. The analysis is based on the measurement of the AUC using the trapezoid method from time 0 to the last measured time point and adding the terminal portion of the AUC from the last measured concentration divided by the terminal rate constant. Partial AUCs were measured from time 0 to 24 hours and from 24 to 48 hours.

3 | RESULTS

3.1 | Observations

There were no adverse effects observed from administration of the IV bolus of ceftazidime or the SC infusion over 48 hours. All dogs completed both phases of the study without any observed problems. At the end of the 48-hour infusion, the mean residual volume remaining in the reservoir of the RxActuator Mini-Infuser device was approximately 0.4 ml, which agrees with the anticipated calculated amount. The RxActuator pump was designed to deliver at a rate of 0.2 ml/h . The reservoir was filled with 10 ml of ceftazidime solution and was removed at 48 hours. Thus, it was anticipated that 4% of the solution would be retained.

3.2 | Drug analysis

The assay performed according to our criteria used in previous studies.[3,5] The calibration curves were linear, with a R^2 of 0.99 or higher. The accuracy and precision of the assay met our acceptance criteria of ±15% at concentrations above the lower limit of quantification, which was 0.05 μg/ml.

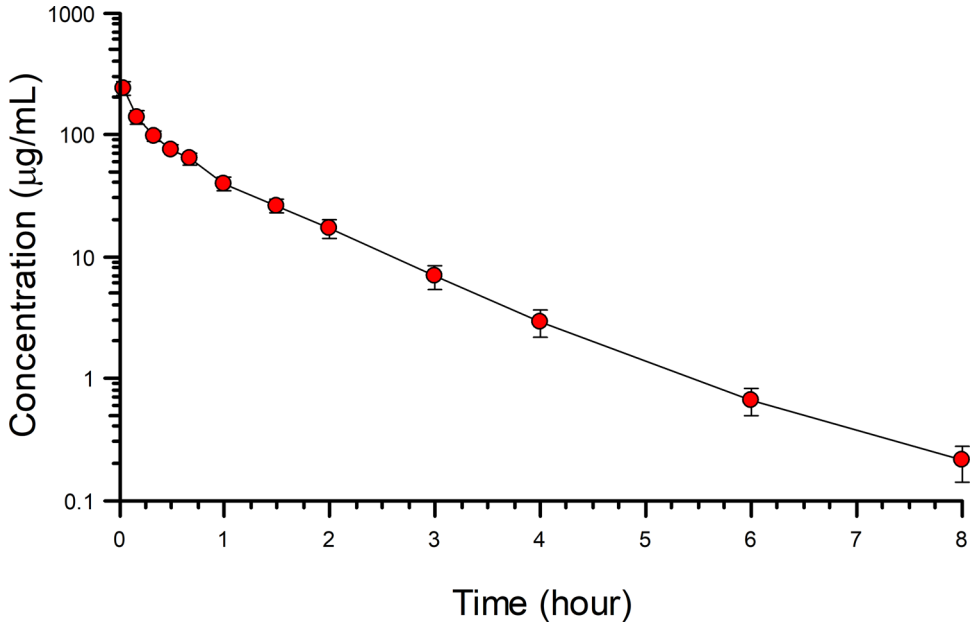

FIGURE 1 Ceftazidime concentrations in 6 dogs after IV injection of 25 mg/kg. Each point represents the mean ± SD

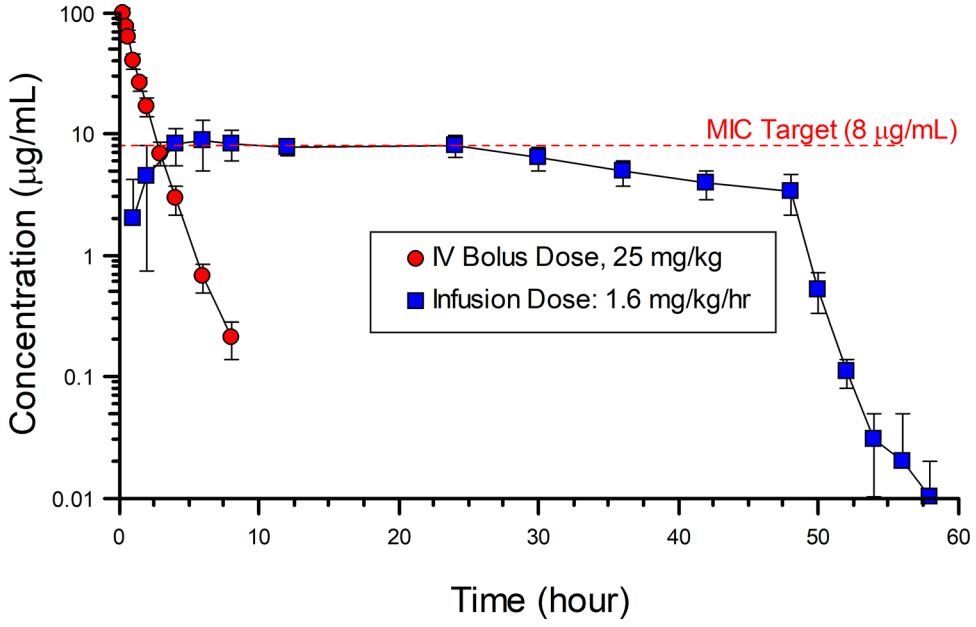

FIGURE 2 Plasma ceftazidime concentration after IV injection of 25 mg/kg in 6 dogs, and after SC infusion for 48 hours at a rate of 1.6 mg/kg/h. Each point represents the mean ± SD. Red circles, IV infusion; blue squares, SC infusion. The lower limit of quantification (LLQ) for the assay was 0.05 μg/ml

3.3 | Plasma concentrations and pharmacokinetics

The ceftazidime plasma concentrations after the IV bolus are shown in Figures 1 and 2. Also shown in Figure 2 are the ceftazidime concentrations measured during, and after, the 48-hour SC infusion of 1.6 mg/kg/h. The average concentration at steady state, during the SC infusion, was 6.65 μg/ml (SD, 2.78).

The pharmacokinetic results from the compartmental analysis are shown in Table 1 for the IV bolus injection at 25 mg/kg and Table 2 for the 48-hour SC infusion. The parameters are defined in the table legend. Also shown is the fraction of dose absorbed from SC administration, calculated from a ratio of the AUC values. The pharmacokinetic results from the noncompartmental analysis are shown in Table 3 for the IV bolus injection and SC infusion.

TABLE 1 Compartmental pharmacokinetic parameters in 6 dogs after IV ceftazidime injection of 25 mg/kg

Parameter	Units	Geo Mean	Geo CV%
A	μg/ml	170.20	16.09
Alpha	1/h	3.35	41.45
Alpha T½	h	0.21	41.45
AUC	h·μg/ml	142.04	10.96
B	μg/ml	59.98	59.28
Beta	1/h	0.73	9.13
Beta T½	h	0.95	9.13
CL	ml/h/kg	176.01	10.96
C_0	ug/ml	234.64	19.83
K12	1/h	0.83	120.51
K21	1/h	1.48	39.55
MRT	h	0.98	6.73
V_1	ml/kg	106.55	19.83
Vss	ml/kg	171.66	6.69

Abbreviations: A, *y*-axis intercept for distribution phase with accompanying rate constant α (alpha) and half-life (T½); AUC, area under the curve; B, elimination phase intercept with accompanying rate constant β (beta) and half-life (T½); C_0, peak concentration; CL, systemic clearance; K21 and K12, microdistribution rate constants; MRT, mean residence time; V_1, volume of distribution for the central compartment; V_{SS}, volume of distribution at steady state. Geo Mean and Geo CV% are geometric mean and CV% generated from transformed data.

TABLE 2 Compartmental pharmacokinetic parameters in 6 dogs after SC infusion of ceftazidime at a rate of 1.6 mg/kg/h for 48 hours

Parameter	Units	Geo mean	Geo CV%
AUC	h·μg/ml	313.09	17.45
CL/F	ml/h/kg	245.29	17.45
CMAX	μg/ml	6.52	17.45
K10	1/h	0.84	18.14
K10 T½	h	0.82	18.14
MRT	h	1.19	18.14
V/F	ml/kg	291.81	34.00
% F	%	71.75	16.21

Abbreviations: AUC, area under the curve; CL/F, systemic clearance per fraction absorbed; CMAX, peak concentration; F, fraction of the dose absorbed (bioavailability); K10, elimination rate constant and accompanying half-life (T½); MRT, mean residence time; V/F, volume of distribution per fraction absorbed. Geo Mean and Geo CV% are geometric mean and CV% generated from transformed data.

3.4 | Measurement of strength of injection solution

Injection vials of ceftazidime (1 g) were reconstituted in the same manner as prepared for the IV and SC administration studies. These vials were stored at room temperature for 48 hours to measure the strength after storage. After initial reconstitution, the concentration was 109% of the stated strength on the label; at 24 hours, the strength was 111% of the stated strength; and at 48 hours, the concentration was 104% of the stated strength on the label. Thus, at 48 hours the concentration was still within accepted limits of ±10% allowed by the USP but was approximately 5% lower than the original concentration.

4 | DISCUSSION

This study showed that an IV bolus of ceftazidime in dogs has a rapid clearance and elimination half-life of less than 1 hour (0.95 h in this study). Ceftazidime is a time-dependent antimicrobial. The effectiveness is dependent on the time that drug concentrations remain above the MIC for susceptible bacteria.[6–8,12] Therefore, to maintain effective concentrations in dogs for treating serious infections, multiple injections per day are needed.

On the other hand, we showed that an SC infusion of ceftazidime at a rate of 1.6 mg/kg/h for 48 hours using the RxActuator Mini-Infuser pump produces sustained steady-state concentrations near the targeted concentration of 8 μg/ml. The selection of this concentration as a target is described in more detail in the following section. This device offers an obvious advantage for veterinarians and pet owners who wish to avoid repeated IV injections or hospitalizations in order to treat serious bacterial infections in dogs.

The RxActuator device was simple to prepare for attachment to the dog, with infusion directed SC using a simple catheter. There was no observed discomfort or attempt by the dogs to dislodge the device. (It should be noted that these were healthy active dogs, which are likely different from a clinical patient.)

The pharmacokinetics observed in this study compare favorably to other studies. The pharmacokinetics of ceftazidime were reported for dogs.[1,9,10,13,14] For comparison, a summary of pharmacokinetics in dogs, averaged from all the canine studies, is listed in Table 4.

In previous studies (Table 4), the average clearance (CL) was 0.198 L/kg/h. We used this value (rounded up to 0.2 L/kg/h) to calculate the infusion rate of 1.6 mg/kg/h to reach a target of 8 μg/ml. (Infusion rate = CL × Target Concentration.) The actual IV clearance in these dogs was 0.176 L/kg/h; therefore, it was slightly lower than other studies and accounts for some of the discrepancy between our predicted concentrations and the actual concentrations measured. The half-life was slightly longer in the dogs in the current study and the volume of distribution slightly smaller compared to other studies.

An earlier study examined absorption from a single SC injection of ceftazidime in dogs.[10] The reported bioavailability from SC injection to dogs in that study[10] was 70.3%. In the current study, the value was 71.75%, which is essentially identical. The previous study[10] also reported a slight (approximately 1 h) delay before the peak concentration was attained, which is also an observation from the current study (Figures 1 and 2). Because SC absorption was less than 100%, some discrepancy is accounted for between our predicted concentrations and the measured concentrations. Our target concentration used during the design of the study was 8 μg/ml to coincide with susceptible bacteria targets,[11] and the measured concentration at steady state during the SC infusion was 6.65 μg/ml (SD, 2.78).

TABLE 3 Noncompartmental pharmacokinetic parameters in 6 dogs after a single IV bolus injection of 25 mg/kg and an SC infusion of ceftazidime at a rate of 1.6 mg/kg/h for 48 hours

		IV Bolus		48-hour Infusion	
Parameter	Units	Geo Mean	CV%	Geo Mean	CV%
AUC (% extrapolated)	%	0.16	24.23	0.01	59.38
AUC (0 to infinity)	h·μ/ml	144.86	11.51	305.62	14.91
AUC (0 to Cn)	h·μg/ml	144.62	11.49	305.58	14.92
C_0 (IV) or C_{MAX} (SC)	μg/ml	275.27	13.64	10.05	22.05
Clearance or CL/F	ml/h/kg	172.58	11.51	251.29	14.91
Half-life	h	0.95	8.48	1.01	19.67
Lambda-Z	1/h	0.73	8.48	0.69	19.67
MRT	h	0.94	6.31	22.01	8.48
VD	ml/kg	162.32	7.92	364.89	30.94
Partial areas for infusion dose					
0–24	h·μg/ml			175.75	20.70
24–48	h·μg/ml			124.10	12.80

Abbreviations: AUC, area under the curve, listed as time 0 to infinity, time 0 to the last measured time point (Cn), and partial areas from time 0 to 24 hours and 24 hours to 48 hours; CL/F, systemic clearance per fraction absorbed; C_0, initial concentration after an IV bolus; C_{MAX}, peak concentration; lambda-Z is the terminal rate constant; MRT, mean residence time; VD, apparent volume of distribution. Geo Mean and Geo CV% are geometric mean and CV% generated from transformed data.

TABLE 4 Ceftazidime pharmacokinetics in dogs (mean across all studies)

	T½	Kel	VD	CL	AUC	C_{MAX}	T_{MAX}
	h	–	L/kg	L/kg/h	μg h/ml	μg/ml	h
Mean IV	0.866	0.778	0.229	0.1976	103.25	156.5	–
SD	0.11	0.087	0.03	0.018	4.6133	49.25	–
Mean SC	1.24	0.71	0.194	–	149.5	47.35	1.06
SD	0.445	0.245	0.047	–	41.55	12.3	0.42

Note: Bioavailability (F): 70.3% (SC), from Monfrinotti et al.[10] The data used for the estimates in Table 4 are from studies reported for dogs.[1,9,10,13,14]
Abbreviations: AUC, area-under-the-curve; CL, clearance; C_{MAX}, peak concentration (C_0 for IV dose); Kel, elimination rate constant; T½, half-life; T_{MAX}, time to peak concentration; VD, volume of distribution (VD/F for the SC dose).

4.1 | Establishing therapeutic targets

The therapeutic targets for ceftazidime plasma concentrations are established based on the analysis by the Clinical and Laboratory Standards Institute (CLSI).[11,15] The CLSI has approved a breakpoint for susceptible bacteria isolated from dogs. The ceftazidime breakpoint is ≤4 μg/ml for Enterobacterales (eg, *Escherichia coli*) and ≤8 μg/ml for *P. aeruginosa*.[11] This is identical to the human breakpoint.[16] Importantly, some extended-spectrum beta-lactamase–producing isolates may be treatable using these breakpoints for ceftazidime.[16] The extended-spectrum beta-lactamase–producing bacterial isolates (eg, *E. coli*, *Klebsiella pneumoniae*) are some of the most serious infections encountered in veterinary medicine. *Pseudomonas aeruginosa* is often encountered in chronic and difficult-to-treat infections and may not be susceptible to oral antimicrobial agents, such as fluoroquinolones.

When calculating pharmacokinetic–pharmacodynamic targets, the unbound fraction of the antibiotic should be used.[17] However, protein-binding studies were unnecessary for this study because protein binding was previously reported as 10.2% in dogs,[13] with a free fraction (*fu*) of 0.898. This is negligible for predicting clinical efficacy from pharmacokinetic–pharmacodynamic parameters. Thus, a correction for protein binding was not needed, which simplifies the calculation of infusion rates.

There are important observations from this study that allow precise dose adjustments to apply this infusion device for clinical use and administer ceftazidime in dogs for 48 hours. The concentrations at the early time points in some dogs (Figure 2) were above the targeted concentration. We speculate that this occurred because the reconstituted vial concentration was slightly higher than the concentration on the label, although still within the USP-accepted standard of ±10% deviation. On the other hand, Figure 2 shows a slight decrease in the concentration lower than the target of 8 μg/ml after approximately 24 hours. The average concentration at steady state during the SC infusion was slightly lower than our target of 8 μg/ml. We speculate that this occurred because our dose rate calculations were based on an assumption of 100% bioavailability. The value we calculated was lower (approximately 71.75%) but is in agreement with an earlier study.[10] We recommend that a dose adjustment should be applied in the future to account for less than 100% bioavailability. We also observed a slight drug loss in the reservoir after 24 hours. The strength of the solution measured after 24 hours was approximately 5% lower than that at the beginning of the infusion. We also observed that mean drug clearance was higher in these dogs from the SC infusion compared

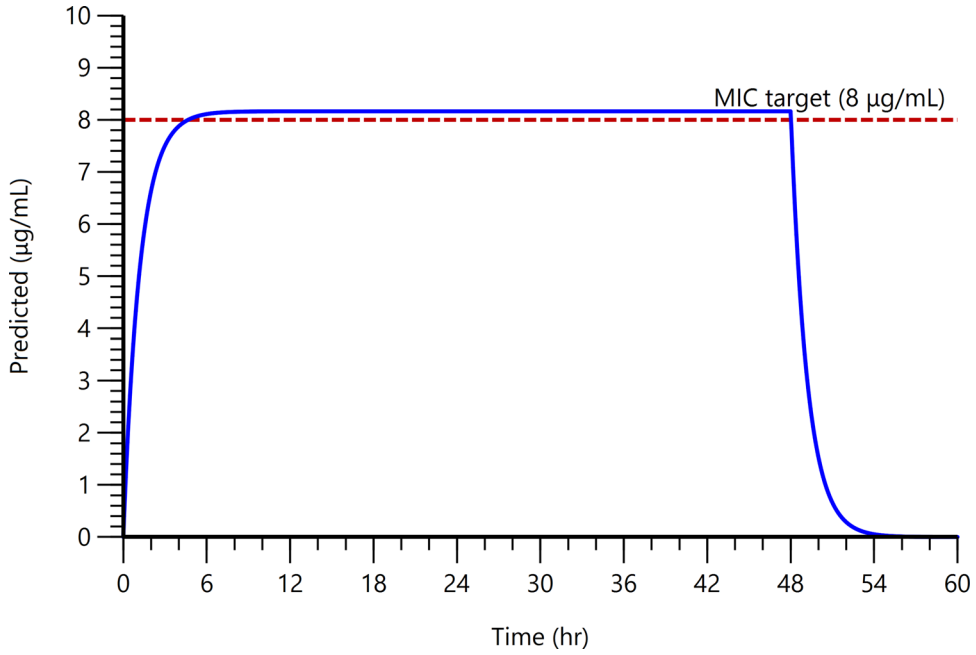

FIGURE 3 Simulated ceftazidime plasma concentration from CL/F and V/F values reported in Table 2 to reach a target of 8 μg/ml, using an SC infusion dose of 2 mg/kg/h delivered over 48 hours. CL/F, systemic clearance per fraction absorbed; V/F, volume of distribution per fraction absorbed. Solid line is the predicted concentration; dashed line is the MIC target

to IV administration and higher when compared to the value used to calculate the infusion rate. Based on previous data, we used a clearance value of 0.2 L/kg/h to calculate the infusion dose of 1.6 mg/kg/h for this study. However, the actual clearance measured was 0.245 L/kg/h (±0.017). Faster clearance results in lower plasma drug concentrations.

4.2 | Potential clinical application

Ceftazidime is an ideal short-term antibiotic to administer to dogs during periods of critical illness for patients with drug-resistant infections that cannot be treated with approved antimicrobial agents. Unfortunately, repeated injections of ceftazidime are necessary because of the short half-life. These regimens are inconvenient, stressful for the patient, and could be a challenge for a busy hospital or for at-home treatment. The results reported here using the RxActuator device offer an option for administration. The device can be applied in the hospital to free up valuable time from the veterinary technician, and when treatment is needed in dogs in an outpatient setting so that the owner can care for the dog at home without the need to administer frequent and painful injections or maintain IV infusion lines.

A duration of 48 hours would be an ideal interval for the administration of ceftazidime. Many infections treated are acute, severe, and often life-threatening. These patients require frequent reassessment every 48 hours in order to make critical clinical decisions or modify the treatment. Often, the first 24–48 hours are the most critical for determining the outcome.[18] Therefore, the ability to administer ceftazidime using a portable wearable pump that can administer the drug subcutaneously to dogs for 48 hours may be helpful for the treatment of these canine patients. An important advantage of this delivery of ceftazidime at a constant rate is that it can maintain antibiotic concentrations above the MIC throughout the dosage interval, which is important for β-lactam antibiotics.[6–8,12] A long duration above the MIC from a constant rate infusion provides better therapeutic outcomes compared to intermittent IV injections for treating infections using time-dependent antibiotics such as ceftazidime.

To use the RxActuator pump for clinical administration of ceftazidime in dogs, a dose adjustment should be applied using the considerations identified in our study. A dose adjustment will account for drug loss, lower bioavailability, and higher clearance. A dose adjustment using the clearance value measured in this study (0.245 L/kg/h) to target a concentration of 8 μg/ml results in an infusion dose of 1.96 mg/kg/hr over 48 hours. (We suggest rounding up to 2 mg/kg/h.) To illustrate the outcome of this dose adjustment, a simulation using Phoenix software[c] was developed and is presented in Figure 3. A mean target of steady-state concentration of 8 μg/ml is attainable with these simple dose adjustments.

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Notes

[a] Ceftazidime solution for injection, USP, WG Critical Care, LLC, Paramus, NJ.

[b] RxActuator Mini-Infuser wearable subcutaneous constant rate infusion pump, RxActuator, Inc., Tucson, AZ. www.rxactuator.net.

[c] Phoenix, WinNonlin, Certara, St. Louis MO.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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