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The Pharmacokinetics of Ceftazidime Following its Intravenous Administration in Dogs

Mustafa A. Al-Jumaili *[1], Nibras N. Al-Abbass [2], and Orooba M. S. Ibrahim [2]

[1]*Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Diyala, Iraq*
[2]*Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Baghdad, Iraq*

*Corresponding author's Email: mustafa.a@uodiyala.edu.iq

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ABSTRACT

Ceftazidime is a beta-lactam that is used in the treatment of bacterial infections in humans and companion animals, such as dogs and cats. It is prescribed to treat gram-negative infections, especially those caused by *Pseudomonas aeruginosa*. This study aimed to compare the pharmacokinetics of ceftazidime using a microbiological assay to evaluate the adequacy of the proposed dosage regimens for susceptible gram-negative bacteria. For this purpose, five healthy mongrel male dogs, with a mean age of four years and an average weight of 19.1 kg, were administered a single intravenous bolus dose of ceftazidime (20 mg/kg). Plasma concentrations were measured using a microbiological assay, and dosage regimens were established by integrating pharmacokinetics data with pharmacodynamics parameters. The results showed that ceftazidime was rapidly distributed to the peripheral tissues (0.189 L/kg), with a half-life of 1.15 hours and a clearance rate of 0.166 L/hr./kg. The results obtained from the pharmacokinetics-pharmacodynamic integration suggested 20 mg/kg q8 hours of ceftazidime for susceptible gram-negative bacteria with a Minimum Inhibitory Concentration of ≤ 8 µg/ml, and 20 mg /kg q12 hours of ceftazidime for susceptible gram-negative bacteria with a Minimum Inhibitory Concentration of ≤ 4 µg/ml. In conclusion, a mild correlation was observed between the dogs' weight and the ceftazidime half-life, which led to an adjustment of the proposed dosage regimen to 20 mg/kg q8 hours.

Keywords: Ceftazidime, Dog, Dosage regimen, Gram-negative microbe, Pharmacokinetic

INTRODUCTION

Dogs are the most common companion animals to humans because of their positive impacts on their owner's physical and mental status (Overgaauw et al., 2020). However, many bacterial diseases can affect the dogs' health and lead to a potentially unfavorable prognosis (Marks et al., 2011; De Sousa et al., 2023). Rational antibiotic therapy seems a solution to avoid undesirable complications (Wayne et al., 2011).

Ceftazidime belongs to the third generation of cephalosporins with a broad-spectrum bactericidal effect and high accessibility to most tissues, including hard and CNS tissues with unchanged excretion through the kidney (Budde and McCluskey, 2023). Ceftazidime is used to manage bacterial infections in dogs having bactericidal spectrum, including the susceptible pathogenic gram-negative bacteria, with additional activity against *Pseudomonas aeruginosa* (Papich, 2020).

Previous studies on the pharmacokinetics of ceftazidime in dogs, involving intravenous administration at doses ranging from 20 to 25 mg/kg in animals weighing 10.5-15.6 kg, have demonstrated that ceftazidime has rapid distribution, short half-life, and rapid elimination (Matsui et al., 1984; Kita et al., 1992; Sakamoto et al., 1993; Monfrinotti et al., 2010; Papich et al., 2022).

Pharmacokinetics plays a crucial role in establishing rational dosage regimens for antibiotics through integration with pharmacodynamics (PK/PD integration), which is considered a suitable solution to obtain the desired therapeutic response, minimizing adverse reactions, decreasing the risk of bacterial resistance, and reducing treatment costs (Guardabassi et al., 2018).

It is known that the diversity of dog breeds presents a challenge that could lead to a non-standardized pharmacokinetic profile of drugs due to potential unmatched digestive physiology, metabolic profile, kidney function, and protein binding (Tibbitts, 2003; Toutain et al., 2010). Therefore, this study aims to assess the pharmacokinetics of ceftazidime in local Mongrel dogs, compare the results with the previous studies conducted exclusively on Beagles, and determine whether adjustments to ceftazidime dosage regimen make any difference in treating susceptible gram-negative bacterial infections.

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MATERIALS AND METHODS

Ethical approval

The study was approved by the Ethical Committee of the College of Veterinary Medicine, University of Diyala, Iraq (Approval No. VM 301; November 2022).

Animals

Five healthy male Mongrel dogs, provided by the Dogs Kennel of the College of Veterinary Medicine, University of Diyala, with an average age of 4 (± 0.5) years and an average weight of 19.1 kg (± 1.3), were utilized in this study. A comprehensive physical examination, including assessments of physical appearance, skin and coat integrity, lymph nodes, respiration rate and rhythm, pulse, and body temperature as well as general mouth and teeth examination was done by a certified veterinarian to ensure the dog was in good health. All dogs were free of antibiotics and other medications and were kept in an isolated kennel in the College of Veterinary Medicine, University of Diyala, for a week for behavioral adaptation. They were provided with free access to water and a balanced diet.

Drug administration

Ceftazidime (LDP Laboratories Torlan, Barcelona, Spain) was injected as an intravenous bolus via the right cephalic vein at 20 mg/kg dose for each dog (Monfrinotti et al., 2010).

Samples collection and analysis

One milliliter of blood was obtained from the left cephalic vein on 0.08, 0.16, 0.33, 0.5, 1, 2, 4, 8, 12, and 24 hours post-administration. The samples were kept in heparinized tubes, and plasma was separated by centrifugation and stored at -20C^{o} for further drug analysis. The microbiological assay was applied to estimate the concentration of ceftazidime using spores of *Bacillus subtilis* ATCC 6633 provided by the Department of Biology at the College of Science, University of Diyala, prepared as previously described by Sabath (1976). A drug-free plasma sample was used to prepare the standard curve for further determination of ceftazidime concentrations. additionally, the protein binding of ceftazidime was determined by calculating the partitioning ratio of ceftazidime between phosphate-buffered saline and plasma (Craig and Suh, 1991).

Pharmacokinetic analysis

The pharmacokinetic parameters of ceftazidime were calculated using Microsoft Excel®, following the equations outlined in Rosenbaum (2017). The Aikake Information Criterion (AIC) was applied to identify the most suitable model to fit the data points (Yamaoka et al., 1978).

Dosage regimen

The Minimum Inhibitory Concentration (MIC) breakpoints of ceftazidime against susceptible gram-negative bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were obtained from the Clinical and Laboratory Standards Institute (CLSI, 2024). The breakpoints were integrated with the pharmacokinetic parameters obtained in this study (PK/PD integration) to establish a dosage regimen for ceftazidime (Fratoni et al., 2021).

Statistical analysis

Pearson correlation coefficient (r) was applied to determine the relationship between body weight and the half-life of ceftazidime across different studies (Matsui et al., 1984; Kita et al., 1992; Sakamoto et al., 1993; Monfrinotti et al., 2010; Papich et al., 2022). Statistical analyses were performed using GraphPad Prism 8.0 for Windows (GraphPad Software, Boston, Massachusetts USA).

RESULTS

Clinical observations indicated no adverse effects from the intravenous administration of ceftazidime in the dogs. The microbiological assay employed to construct the ceftazidime standard curve in plasma showed a linear pattern, with an acceptable coefficient of determination (R^2 = 0.973), The limit of detection (LOD) for ceftazidime in plasma was 0.23 µg/ml, while the accuracy of the assay of ceftazidime analysis qualified by the limit of quantification (LOQ) was 0.78 µg/ml as listed (Table 1).

The two-compartment model selected to fit time-concentration points was based on AIC. The data points, depicted in Figure 1, show a clear bi-exponential decay of ceftazidime concentration over time. All the calculated primary and secondary pharmacokinetic parameters are summarized in Table 2. Briefly, ceftazidime was quickly distributed to peripheral tissues (0.189 L/kg), with a half-life of 1.15 hours and a clearance rate of 0.166 L/hour/kg.

The PK/PD integration results, reported in Table 3, suggested a dosage regimen of 20 mg /kg q8 hours of ceftazidime for susceptible *Pseudomonas aeruginosa* (MIC ≤ 8 µg/ml), while it proposed a dosage regimen of 20 mg /kg q12 hours of ceftazidime for susceptible *Enterobacterales* (MIC ≤ 4 µg/ml).

The correlation between the average body weight and the half-life of ceftazidime was established by analyzing data from previous works (Table 4) in conjunction with the present study. The analysis revealed a moderate positive relationship (r = 0.62) between body weight and ceftazidime half-life, as illustrated in Figure 2.

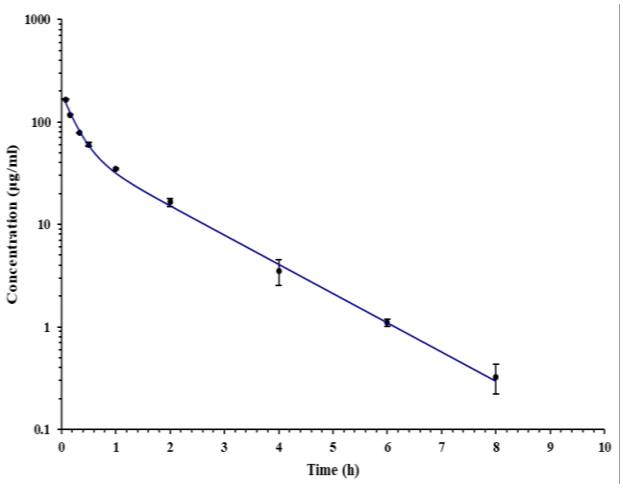

Figure 1. Ceftazidime concentrations in the plasma of dogs after a single Intravenous bolus administration (20 mg/kg).

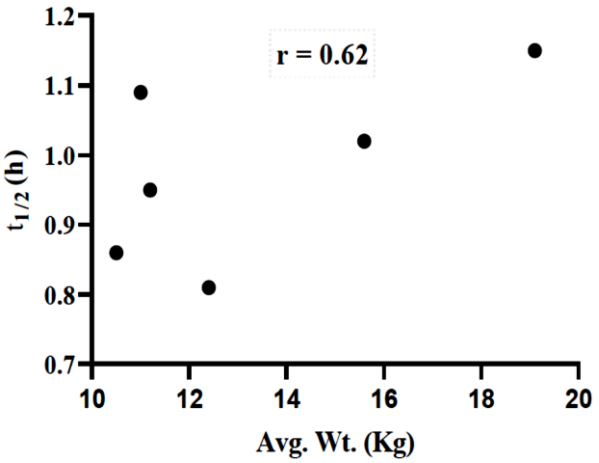

Figure 2. Relationship between dog body weight and the half-life of Ceftazidime through different studies. $t_{1/2}$, half-life; Avg. wt.: Average weight

Table 1. Standard curve of Ceftazidime microbiological assay

Parameter	Value
CV%	3
Slope	13.87
Intercept	12.871
R^2	0.97
LOD (µg/ml)	0.23
LOQ (µg/ml)	0.78

CV: Variation coefficient; R^2: Determination coefficient; LOD: The limit of detection; LOQ: The limit of quantification

Table 2. Pharmacokinetics of Ceftazidime administration in plasma of dogs

Parameter	Unit	Mean	SD
A	µg/ml	135.75	13.41
α	1/h	3.83	2.04
$t_{1/2\alpha}$	h	0.24	0.16
AUC	(h*µg)/ml	120.01	7.07
AUMC	µg/ml*h^2	137.61	13.75
B	µg/ml	48.39	26.67
β	1/h	0.61	0.11
$t_{1/2\beta}$	h	1.15	0.21
Cl_T	L/hr./kg	0.166	0.009
Cp^0	µg/ml	184.14	39.75
K_{12}	1/h	1.37	1.05
K_{21}	1/h	1.56	0.84
MRT	h	1.13	0.05
V_C	L/kg	0.113	0.026
Vd_{ss}	L/kg	0.189	0.004
Protein binding	%	12.3	1.02

A: Distribution intercept; α: Distribution rate constant; $t_{1/2\alpha}$: Distribution half-life; AUC: Area under the curve; AUMC: Area under the moment curve; B: Elimination intercept; β: Elimination rate constant; $t_{1/2\beta}$: Elimination half-life; Cl_T: Total body clearance; Cp^0: Zero-time concentration; K_{12} and K_{21}: Micro-distribution rate constants; MRT: Mean residence time; Vc: Volume of distribution of central compartment; Vd: Volume of distribution at steady state

Table 3. Dosage regimens of Ceftazidime in dogs

τ (h.)	%T>MIC (1 µg/ml)	%T>MIC (2 µg/ml)	%T>MIC (4 µg/ml)	%T>MIC (8 µg/ml)	No. doses/day
8	96.68	82.30	67.93	53.55	3
12	64.45	54.87	45.29	35.70 [N.A.]	2

τ: Time interval; %T > MIC: Percentage of time over the minimum inhibitory concentration; N.A.: Not applicable (T > MIC is below 45 %). No: Number

Table 4. Comparison across different studies of Ceftazidime pharmacokinetics in dogs (IV Bolus)

Study	Avg. Wt. (Kg)	VDss (L/kg)	$t_{1/2}$ (h)	AUC (µg.h/ml)	CL (L/kg/h)
Matsui et al. (1984)	12.4	0.218	0.81	93	0.215
Kita et al. (1992)	10.5	0.210	0.86	105	0.192
Sakamoto et al. (1993)	11.0	0.353	1.09	89	0.228
Monfrinotti et al. (2010)	15.6	0.206	1.02	126	0.159
Papich et al. (2022)	11.2	0.171	0.95	142.4	0.176
Average	12.14	0.232	0.95	111.08	0.194
Present study	19.1	0.189	1.15	120.01	0.166

Avg. wt.: Average weight; Vdss, Volume of distribution at steady state; t1/2: Elimination half-life; AUC: Area under the curve; Cl: Total body clearance

DISCUSSION

The accuracy of the assay of drug analysis, determined by the limit of quantification (LOQ), was higher than what the was quantified in the current study. This issue, known as data below the limit of quantification (BLOQ), is typically managed by discarding values below LOQ (Barnett et al., 2021).

The current study found that the volume of distribution at steady state (VD_{ss}), the area under the curve (AUC), and the drug clearance (Cl) values of ceftazidime were within the range as reported in previous studies. However, the half-life observed in this study was slightly longer than that reported in most previous research (Matsui et al., 1984; Kita et al., 1992; Sakamoto et al., 1993; Monfrinotti et al., 2010; Papich et al., 2022).

The half-life correlates proportionally to the volume of distribution and inversely to the clearance (Smith et al., 2018). In the current study, the clearance was lower than the average reported in previous studies (Matsui et al., 1984; Kita et al., 1992; Sakamoto et al., 1993; Monfrinotti et al., 2010; Papich et al., 2022), which may explain the moderately long half-life of ceftazidime (Lieberman and Murti Vemuri, 2015). According to the obtained data, the observed difference could be attributed to the marginally greater body weight of the dogs in the current study in comparison to those in earlier research (Table 4). The increment in the body weight linearly increases the volume of the distribution and extends the half-life as denoted previously in other beta-lactams such as aminopenicillins (Lashev and Pashov, 1992), and subsequently slow elimination (Zamboni et al., 2023).

The PK/PD integration results from this study align with most dosage regimens recommended by different texts (Grayson et al., 2017; Riviere and Papich, 2018; Papich, 2020). Specifically, the authors of this study suggest a dosage regimen of 20 mg /kg q12 hours of ceftazidime for susceptible *Enterobacterales* (MIC ≤ 4 µg/ml) and a dosage regimen of 20 mg /kg q8 hours of ceftazidime for susceptible *Pseudomonas aeruginosa* (MIC ≤ 8 µg/ml). This suggestion is based on the conclusion of Muller et. al. (2013) who recommend a 45 % time over MIC ratio for ceftazidime to achieve a favorable bactericidal effect against gram-negative microbes (Muller et al., 2013).

CONCLUSION

The pharmacokinetics of ceftazidime in the local Mongrel dogs used as a model in this study were comparable to the mean of those observed in Beagle dogs in similar studies, except for a slightly longer half-life. This finding may be attributed to the larger average body weight of the dogs in the current study, which could impact the recommended dosage regimen of 25 mg/kg q8 hours for ceftazidime in dogs as suggested by veterinary texts. However, the dosage

regimen suggested in the current study still requires further validation due to the small sample size used, which was limited by ethical considerations, and the lack of multiple statistical simulations.

DECLARATIONS

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Availability of data and materials
All data for the current study are available from the corresponding author upon reasonable request.

Authors' contributions
All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Mustafa A. Al-Jumaili, Nibras N. Al-Abbass, and Orooba M. S. Ibrahim. The first draft of the manuscript was written by Mustafa A. Al-Jumaili and all authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

Conflict of interests
The authors have no competing interests to declare.

Ethical considerations
The authors declare that this manuscript is original and is not being considered elsewhere for publication. Other ethical issues, including consent to publish, misconduct, fabrication of data, and redundancy, have been checked by the authors.

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