Academic International Journal of Veterinary Medicine
ISSN: 2984-7753
Aca. Intl. J. Vet. Med. 2024;2(2)34-42
Journal homepage: www.aipublishers.org/aijvm

Pharmacokinetic Profile of Ceftriaxone and Meropenem in Dogs

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(Received 6 June 2024, Revised 10 July 2024, Published 29 August 2024)

Abstract

The principal aim of the study was evaluating the pharmacokinetic of ceftriaxone and meropenem in dogs, eight healthy male dogs were used for this experiment. A microbiological assay was used to determine the pharmacokinetic indices of ceftriaxone and meropenem given intravenously. The values were then fitted to a two-compartment pharmacokinetic open model in order to assess the factors related to distribution and excretion. The obtained results showed that the half-life, volume of distribution, and total body clearance to the samples of plasma of ceftriaxone and meropenem were recorded (0.83 h., 0.35 L/kg and 0.28 L/hr/kg), (0.86 h., 0.48 L/kg and 0.33 L/hr/kg), and the ratio of plasma protein binding were 16.67 %; 9.58 %, respectively.

In conclusion, through the pharmacokinetic characteristics of meropenem and ceftriaxone in dogs, they possess an efficacious profile against K. pneumonia as same as other sensitive bacteria which were qualified to be a potential candidate to be one of the most commonly used parenterally administered antibacterial medicines in the treatment of acute bacterial cases that need to be treated quickly in veterinary therapy. However, the differences in the pharmacokinetic profile proved that the effectiveness of meropenem was more than ceftriaxone.

Keyword: Pharmacokinetic**,** *K.Pneumonia*, Microbiological Assay, Compartment Analysis.

How to cite: Orooba M.S. Ibrahim, Mohammed M. Shwaish. Pharmacokinetic Profile of Ceftriaxone and Meropenem in Dogs. *Aca. Intl. J. Vet. Med*. 2024;2(2) 34-42: https://doi.org/10.59675/V224

Introduction

The dog may have been the first animal to be domesticated, and it has been a devoted friend to humans ever since. Dogs and people have been demonstrated to have positive effects on each other's physical and emotional health, but owners are often unaware of the many diseases that can affect dogs. Many bacterial, viral, fungal, and parasitic illnesses [1]. Among dogs suffering from acute or chronic respiratory diseases, bacterial pneumonia continues to be one of the most prevalent clinical diagnoses. [2]. The common major health problems caused by *Klebsiella pneumoniae* so due to it colonizes the oropharyngeal and gastrointestinal tract mucosal surfaces; Then within the body, the bacteria can exhibit significant degrees of virulence and

drug resistance [3, 4]. Since *K. pneumoniae* produces a -lactamase, it preferably uses a broad-spectrum betalactam antibiotic (e.g. ceftriaxone, cefotaxim, piperacillin/tazobactam, ertapenem, or meropenem) [5]. The aminothiazol-cephalosporin ceftriaxone sodium (ceftriaxone) is a third generation cephalosporin [6]. Ceftriaxone has an optimum distribution and penetration in most bodily fluids and extracellular fluid of most tissues, especially when inflammation is present (which increases diffusion). Ceftriaxone has adequate penetration in the cerebrospinal fluid and is thus pharmacokinetically acceptable for the treatment of meningitis [7].

A new carbapenem called meropenem is usually used to treat multidrug-resistant gram-negative bacteria infection. Carbapenems, on the other hand, have been routinely utilized to cure severe infections caused by multi drug resistant bacteria since first report of their use against *K. pneumonia* [8].

In addition to pharmacodynamics, drug pharmacokinetics is essential for establishing the precise dosage that ensure the highest level of antibacterial effectiveness, the least amount of adverse effects, and the absence of bacterial resistance. [9, 10], Therefore, the purpose of this study is to determine the pharmacokinetic parameters of meropenem and ceftriaxone in dogs in order to offer exploratory data regarding drug ADME for use in clinical applications such as dose optimization using PK-PD modeling.

Material and Methods

Experimental Animal:

Eight dogs weighing 20-25 Kg with ages ranged from 8-12 months were used to perform the experiment of the present study. Experimental animals kept in separated clean and disinfected cages belonging to the Department of Surgery and Obstetrics \ College of Veterinary Medicine \ University of Baghdad for adaptation before experiment onset and fed on the commercial dry food pellets.

Pharmacokinetics study

Eight dogs divided equally for 2 drugs. Ceftriaxone was given to the first group, and meropenem was given to the second group as a single intravenous bolus dose of 24 mg/kg BW and 20 mg/kg BW, respectively. Our two drugs were injected slowly into the jugular vein in less than 5 min, 3ml of blood sample was obtained from the (cephalic vein or jugular vein) directly in K4 hepatized tubes at different time (0.083, 0.16, 0.25, 0.3, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hrs). Each obtained blood samples were exposed to centrifuge at 3000 rpm for 15 minutes to gain supernatant and left the sediment and then kept in deep freeze about -20 ºC till time of making analysis by microbiological assay [11].

Ceftriaxone and meropenem concentrations in various samples were measured using a microbiological technique, which is based on assessing drug potency against growth of specific isolate of organism. The department of Pharmacology at the College of Veterinary Medicine, University of Baghdad, kindly provided *K. pneumonia*, which was used as a test microorganism to determine the concentration of meropenem and ceftriaxone in blood plasma. [12]. Plasma without any antibacterial was used to create the standard ceftriaxone and meropenem curves. The Craig approach[13], which is based on the calculation of ceftriaxone and meropenem partitioning between two media, was evaluate the percent of plasma protein binding of these drugs. This formula was used to calculate the amount of protein bound at each concentration:

$$Protien\ binding(\%) = \frac{Zone\ of\ inhibition\ in\ buffer - Zone\ of\ inhibition\ in\ plasma}{Zone\ of\ inhibition\ in\ buffer} x100$$

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Pharmacokinetics Analysis

The parameters of pharmacokinetics after administration of ceftriaxone and meropenem were calculated with spreadsheets algorithm of Microsoft Excel according to [14]. It had been done for plasma samples to calculate the following parameters. Using the trapezoidal approach, the area under the curve (AUC0-last), or 0−∞, was determined. Recorded final concentration at the end time and the elimination constant of the 1st order models. According to Yamaoka et al. [15], the statistical Akaike information criterion (AIC) indicated that the two compartmental pharmacokinetic studies were the best model to fit plasma concentrations versus time.

Standard curve drawing

Series of dilution were made in various concentrations of both ceftriaxone and meropenem 2, 4, 8, 16, 32, 64, 128 and 256 µg/ml and 1, 2, 4, 6, 8 and 10µg/ml, respectively. This concentration (Log unit µg/ml) was calculated using microbiological assay. These concentrations were used to determine the Pharmacokinetic parameter.

Result

Results the standard curve of ceftriaxone and meropenem in plasma showed that the inter-assay the coefficient (R2) of ceftriaxone and meropenem concentration in plasma are (0.97 and 0.98), respectively. Both standard curves showed near clear linearity, where the value of the coefficient of determination (R2) for both curves approached to 1, Figure (1) and (2).

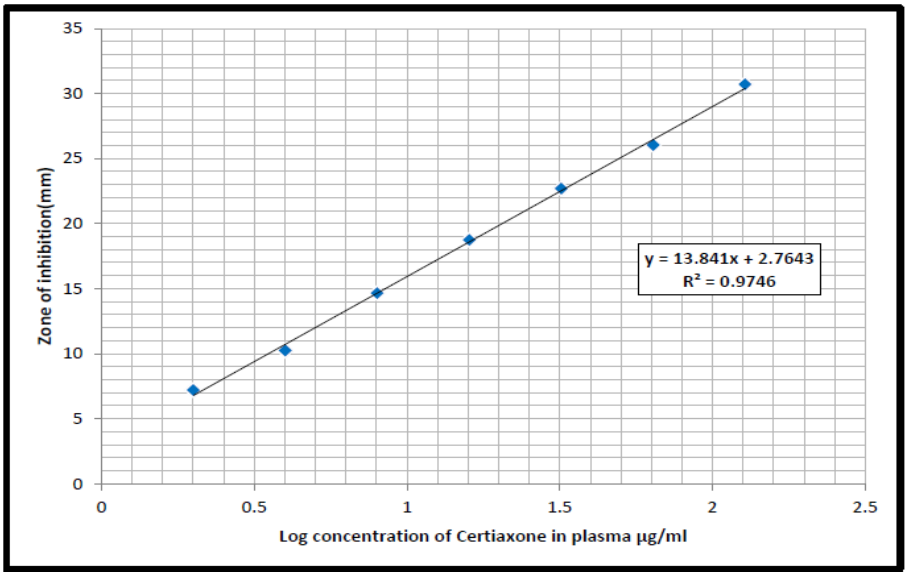

Figure (1): Standard curve of ceftriaxone in plasma

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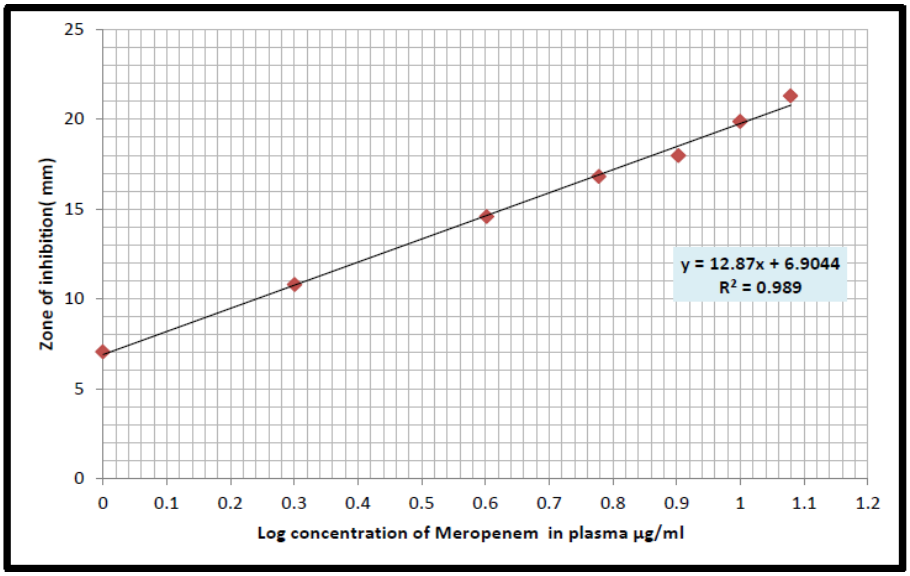

Figure (2): Standard curve of meropenem in plasma

The concentration at zero time (Cp0) of ceftriaxone and meropenem was 206.75 ± 50.34 and 270.22 ± 50.34µg/ml respectively, and the calculated rate constant of ceftriaxone and meropenem (K12) listed in Table (1) was 0.846 ± 1.01 and 0.943 ± 1.2h-1 respectively. Simultaneously, the half-lives (t1/2β) for ceftriaxone and meropenem were found to be 0.98 and 0.98 hours, respectively. The area under the curve (AUC) determined revealed that the body was exposed to 86.72 and 59.101 (h*µg)/ml. The protein binding percentage of ceftriaxone and meropenem were calculated for plasma results reported in the Table (1) revealed that the plasma protein binding of ceftriaxone and meropenem were 16.67%, 9.58%, respectively. Based on our clinical observations, no adverse effects were resulting from ceftriaxone and meropenem single intravenous bolus administration at the site of injection.

Dogs' plasma concentrations of ceftriaxone and meropenem over specified periods were measured using the mean and standard deviation. The compartmental pharmacokinetic analysis was performed using dogs that were selected based on the Akaike information criterion (AIC). The open two compartmental pharmacokinetics consider as the best model to fit our data. Results of two compartmental analyses that listed in the Table (1) and graphed in Figures (3) and (4)

Table (1): ceftriaxone and meropenem parameter of compartmental and non-compartmental pharmacokinetic (Single I.V. bolus dose) in plasma.

Parameters	Units	Mean ±SE of Ceftriaxone	Mean ±SE of Meropenem
Cmax	µg/ml	N. A.	N. A.
AUC*	(h*µg)/ml	86.72 ± 2.16	59.101 ± 1.56
Cl*	L/hr/kg	0.28 ± 0.05	0.33 ± 0.02
TMax	h	N. A.	N. A.
λ z	h-1	0.83 ± 0.37	1.01 ± 0.10
T1/2 λz	h	0.83 ± 0.11	0.68 ± 0.01
MRT	h	1.026± 0.13	0.84 ± 0.02
Cp0 *	µg/ml	206.75 ± 50.34	270.22 ± 50.34
t1/2α*	h	0.10 ± 0.04	0.07 ± 0.07
t1/2β *	h	0.98 ± 0.1	1.1 ± 0.4
K10 *	h-1	0.82 ± 0.2	0.69 ± 0.10
K10 *	h-1	0.82 ± 0.2	0.69 ± 0.10
K12 *	h-1	0.846 ± 1.01	0.943 ± 1.2
K21 *	h-1	5.6 ± 0.03	8.95 ± 0.01
A *	µg/ml	194.72 ± 2.0	209.37 ± 1.09
α *	h-1	6.55 ± 2.01	9.9 ± 1.03
B *	µg/ml	40.033 ± 8.77	23.84 ± 4.77
β *	h-1	0.7± 0.13	0.62 ± 0.13
Vd *B* *	L/kg	0.35 ± 0.13	0.48 ± 0.02
VC *	L/kg	0.11 ± 0.10	0.08 ± 0.14
Vdss *	L/kg	0.12± 0.02	0.08 ± 0.05
Protein binding	%	16.67 ± 0.12	9.58± 0.12

No. of dogs = 8. For ceftriaxone and meropenem.
All data represent free concentrations of ceftriaxone and meropenem.
(*) calculated by compartmental analysis.
N.A. (Not applicable).

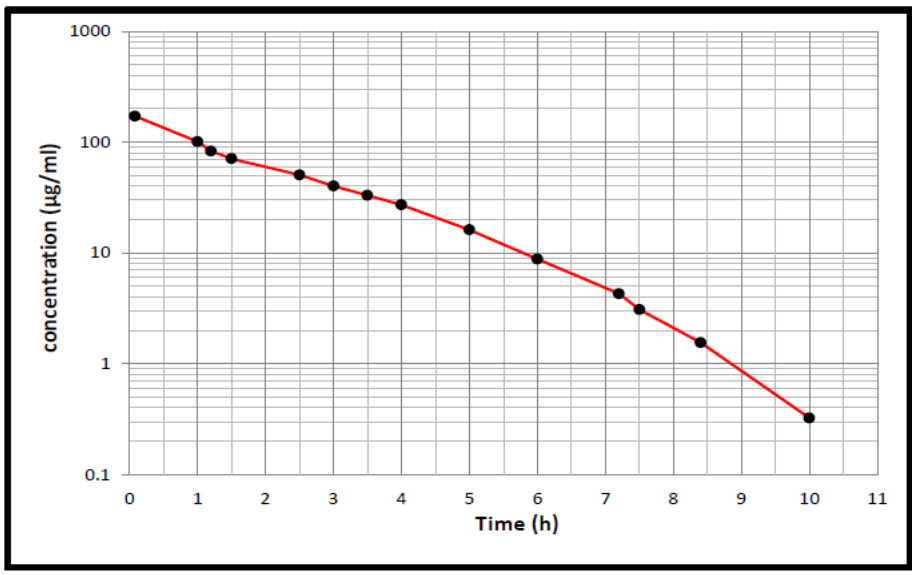

Figure (4): Two compartmental model of ceftriaxone in plasma

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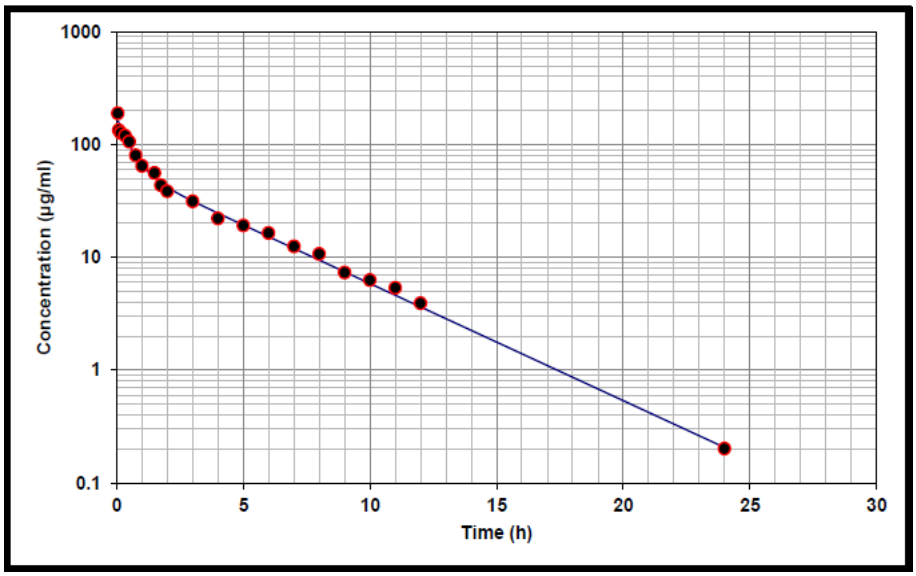

Figure (3): Two compartmental model of Meropenem in plasma

Discussion

It is well recognized that the explanation and construction of the standard curve is essential for any analytical technique; pharmacokinetics is not excluded, where the standard curve is constructed to link known serial concentrations of an active drug with their equivalent physical, chemical, or biological phenomena [16]. Standard curves approached to 1, where the achieved zones of inhibition (Independent variables) and the applied concentrations (dependent variables) are implied to have a perfect relationship by such a result [17].

It is well known that plasma protein binding has a vital role in the pharmacokinetic and pharmacodynamic profile of antibacterial agents due to its impact on tissues distribution [18]. Through that the ratios of binding were 16.67%, 9.58%, respectively. Our results are in line with several investigations conducted on plasma from humans, baboons, rabbits, dogs, and rats, all of which revealed that ceftriaxone exhibits a high plasma protein binding [19].

In commonly, many factors can effect on pharmacokinetic results of drugs including;
the used animals in the study and even species/subspecies physiological differences, the used dose and its pharmaceutical formula, the route and the type of administration, the way that samples were collected, the method by which concentrations were detected and the method that researcher had been utilized to analyze and report his results [20].

Our quantitative data, which was obtained from the concentrations of ceftriaxone and meropenem in plasma following an intravenous bolus administration in a predetermined chronological order, was mathematically fitted into both compartmental and non-compartmental models. In order to fit and compute our data on the plasma concentration-time curve of ceftriaxone and meropenem, which was graphed in figures (3) and (4), two compartmental models were chosen based on the curve's shape, which revealed a first order and bi-exponential decrement with distinct distribution and elimination phases [21, 22].

AUC, or area under the curve, represents the degree of exposure after a drug is administered. This helps to smooth the calculation of other parameters like clearance, elimination half-life, time to maximum plasma concentration (Tmax), and maximal concentration (Cmax). In addition, the non-compartmental method is the starting point for pharmacokinetic analysis [23].

Ceftriaxone, as expected, displayed a mild to long distribution phase (A) to the interstitial compartment as a normal consequence of that phase's long half-life (t1/2α). This was attributed to the drug's low distribution from the plasma (central) compartment to the peripheral tissues because of a high plasma-protein binding ratio, which was previously reported and is similar to our findings [9, 24]. As though As other β-lactams, meropenem displayed a long distribution phase (A) to the interstitial compartment as a normal consequence of that phase's long half-life (t1/2α), which was linked to the drug's high distribution from the plasma (central) compartment to the peripheral tissues as a result of the previously reported low plasma-protein binding ratio [25].

One of the calculated volumes at steady state, in addition to the apparent volume of distribution (Vd B), central volume of distribution (Vc), and peripheral volume of distribution (Vp), is the volume of distribution (Vdss). It is distinguished by its accuracy and independence from any elimination process or constant [26]. Vdss has been used to determine interspecies dose extrapolation, loading and maintenance dosages in different dosing regimens [27].
The distribution of Meropenem was mainly restricted to extravascular compartments, such as lung tissue, as indicated by the relatively small Vdss of our results, which were calculated in both compartmental and non-compartmental analysis at 0.12 and 0.08 of ceftriaxone and meropenem L/kg, respectively [28, 29] that recorded the Vdss of meropenem in dog 0.337 L/kg. The area under the concentration-time curve (AUC) is one of the pharmacokinetic parameters that measure the exposure time to the drug; the AUC value submitted to the effect dose, absorption, and clearance [30, 31].

According to our accomplishment, the elimination T1/2 of in plasma by meropenem was 0.68 hours, and the total body clearance was 0.63 L/hr/kg. The obtained t1/2 and ClT values are in line with the expected results for β-lactams in general and meropenem in particular. Meropenem has a short t1/2 and a high ClT, which when combined with its low Vdss will quickly bring about a state of equilibrium between the concentration in the extracellular compartments and the central compartment given their penetration ratio [28].
Our results indicated that meropenem is more effective against *K.pneumonia* which can be used in cases of pneumonia, in addition. Meropenem has been shown to penetrate efficiently about 1 h after intravenous injection into interstitial fluid of dogs more than ceftriaxone [32, 33].

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