Distribution and Elimination of the Third Generation Cephalosporins in Dogs: A Comparative Study

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Abstract

Members of the third generation of cefalosporins are well regarded as a therapeutic choice due to their extended bactericidal effect against gram-negative pathogenic bacteria in addition to their pharmacokinetics-pharmacodynamics favorable features. Cefatoxime is active against gram-negative *bacilli* and *Streptococci* in contrast to *Pseudomonas aeruginosa*, while, Ceftazidime shows a greater antibacterial activity against *P. aeruginosa*. pharmacokinetic studies of Ceftazidime and Cefotaxime in local Mongrel dogs are almost non-existent. Therefore, this study aims to enrich the therapeutic profile of the third generation of cefalosporins with data by subjecting each ceftazidime and cefotaxime to study their distribution and elimination features, and to compare their pharmacokinetic profiles. The pharmacokinetic study ran a crossover design where a single intravenous bolus of Ceftazidime (20 mg/kg) was administered. then, after a washout period of two weeks, a bolus of Cefotaxime (25 mg/kg) was injected intravenously. The microbiological assay was used to find the concentrations of the two antibiotics. The Noncompartmental pharmacokinetic model was applied to calculate the distribution and elimination parameters of Ceftazidime and Cefotaxime. The results found the concentration at zero time (C^0) and the areas under the curve (AUC & AUMC) parameters were significantly higher in the plasma of the dogs that were given Ceftazidime compared to those whom Cefotaxime administered. In contrast, Cefotaxime displayed larger volumes of distribution (Vd_{ss} and V_z) than Ceftazidime. The mean residence time (MRT) and the half-life ($t_{1/2}$) are longer in Cefotaxime than in Ceftazidime, also body clearance (Cl) was higher in Cefotaxime.

The Study concluded that the distribution and elimination of Ceftazidime and Cefatoxime in local mongrel dogs is slightly variable compared to the distribution and elimination in most recent studies done on dogs considering the difference in dose, the used

dog species, the method of analysis, and the pharmacokinetics calculations. and, the comparison between the two drugs showed a better distribution of Cefatoxime to the peripheral tissues, a longer half-life, and a mild rapid elimination compared to Ceftazidime which achieved a greater concentration at the zero time accompanied by a larger area under the curve, such as paradoxical events may require a further study for the pharmacokinetics of both drugs especially Cefatoxime due to lack of adequate and recent pharmacokinetic studies for this drugs in dogs compared to Ceftazidime.

Keywords: Cefotoxime, Ceftazidime, Dogs, Pharmacokinetics, Noncompartmental analysis, Distribution, Elimination

1. Introduction

Bacterial infections are considered the most common type of infection that affects dogs causing different infectious conditions in the oral, respiratory, gastrointestinal, urogenital, and skin tissues (1, 2) in addition to supportive care, the use of antibiotics is the only available strategy to cure bacterial infections (3). Different groups of antibiotics are used to treat infections with determinant criteria to select the suitable antibiotic for a specific bacterial infection depending on its pharmacokinetics-pharmacodynamics properties, potential adverse effects, toxicity, infection severity, and antibiotic spectrum .(4)

Cephalosporins are regarded as popular β-lactam antibiotics used against bacterial diseases that affect man and animals (5). Their bactericidal effect is exerted by interfering with cell wall synthesis leading to the loss of its integrity and, consequently, the death of bacteria .(6) Many references classified Cephalosporins in different manners, but, Bacterial sensitivity especially gram-negative microbes toward different cephalosporins is a criterion that classifies them into five generations which is the most adopted currently .(7)

Members of the third generation of cefalosporins are well regarded as a therapeutic choice due to their extended

bactericidal effect against gram-negative pathogenic bacteria, and their pharmacokinetics-pharmacodynamics favorable features (8). Different members of the injectible third generation of Cephalosporins like Cefotaxime and Ceftazidime are considered therapeutically against resistant bacterial infections in small animals (9). Cefatoxime is active against gram-negative bacilli and Streptococci with less activity against Staphylococcus aureus, with no activity against Pseudomonas aeruginosa in contrast to Ceftazidime that shows a greater antibacterial activity against P. aeruginosa .(10)

2. Materials and Methods

2.1. Ethical approval

The study was permitted by the ethical committee of the College of Veterinary Medicine, University of Diyala, Iraq (Approval Order No. VM, 422, 9, 2023).

2.2. Animals

Five local mongrel male dogs weighing about 19.1 ($\pm$ 1.3) kg. kindly provided by the animal house of the College of Veterinary Medicine\ University of Diyala and housed in dogs Kennel were used as models for our study. a one week of adaptation was allowed with free access to

Despite the recognized pharmacokinetic studies of Ceftazidime and Cefatoxime in dogs that were done mostly on the Beagles breed (11, 12). but, pharmacokinetic studies of Ceftazidime and Cefotaxime in local mongrel dogs are almost non-existent. Therefore, the purpose of this study is to enrich the therapeutic profile of the third generation of cefalosporins with data by subjecting ceftazidime and cefotaxime to study their distribution and elimination features in local mongrel dogs, and to compare their pharmacokinetic profiles for further applications in the therapeutic field.

food and water. all animals are subjected to physical examination and general hematological and biochemical evaluation for liver and kidney functions.

2.3. Drug administration

Each Ceftazidime and Cefotoxime (LDP Laboratorios Torlan, Barcelona, Spain) had been purchased from a registered pharmacy in the Al-harthia neighborhood in Baghdad\Iraq. The pharmacokinetic study ran a crossover design where a single intravenous bolus of Ceftazidime (20 mg/kg). then, after a washout period of two

weeks, the Cefotaxime (25 mg/kg) was injected intravenously .(10, 13)

2.4. Samples collection and analysis

Veinous Blood samples (1 ml) were collected on 0.08, 0.16, 0.33, 0.5, 1, 2, 4, 8, 12, and 24 hours and kept in Lithium heparin tubes. plasma separated by centrifugation, and kept at 20 C° for future drug analysis. The microbiological assay was used to find the concentrations of the two antibiotics, and, the Sabath method was used to prepare spores of *Bacillus subtilils* ATCC 6633 that was used as a biodetector as recommended.(14)

3. Results

The observations after the injection of each antibiotic showed no adverse reactions in the injection site, also no clinical reports of any side effects were noticed in animals during the two experiments. The noncompartmental analysis (NCA) was used to analyze the pharmacokinetics of both Ceftazidime and Cefotaxime. Figure 1 shows a progressive decline of both drug concentrations inverse proportionally to the time.

The comparison between the pharmacokinetic profile of cefotaxime and

2.5. Pharmacokinetic Analysis

The Noncompartmental pharmacokinetic model was applied to calculate the distribution and elimination parameters of Ceftazidime and Cefotaxime.(15)

2.6. Statistical Analysis

Statistical analysis was done by applying the two-independent t-student test ($p < 0.05$) to compare Ceftazidime and Cefatoxime pharmacokinetic parameters (16) by using GraphPad Prism 8.0 for Windows.

ceftazidime illustrated in Table 1, found both concentration (C^0 & C_{max}) and the areas under the curve (AUC & AUMC) parameters were significantly higher in the plasma of the dogs that were exposed to Ceftazidime compared to those whom Cefotaxime administered. In contrast, Cefotaxime displayed larger volumes of distribution (Vd_{ss} and V_z) than Ceftazidime. The mean residence time (MRT) and the half-life ($t_{1/2}$) are longer in Cefotaxime than in Ceftazidime, also body clearance (Cl) was higher in Cefotaxime.
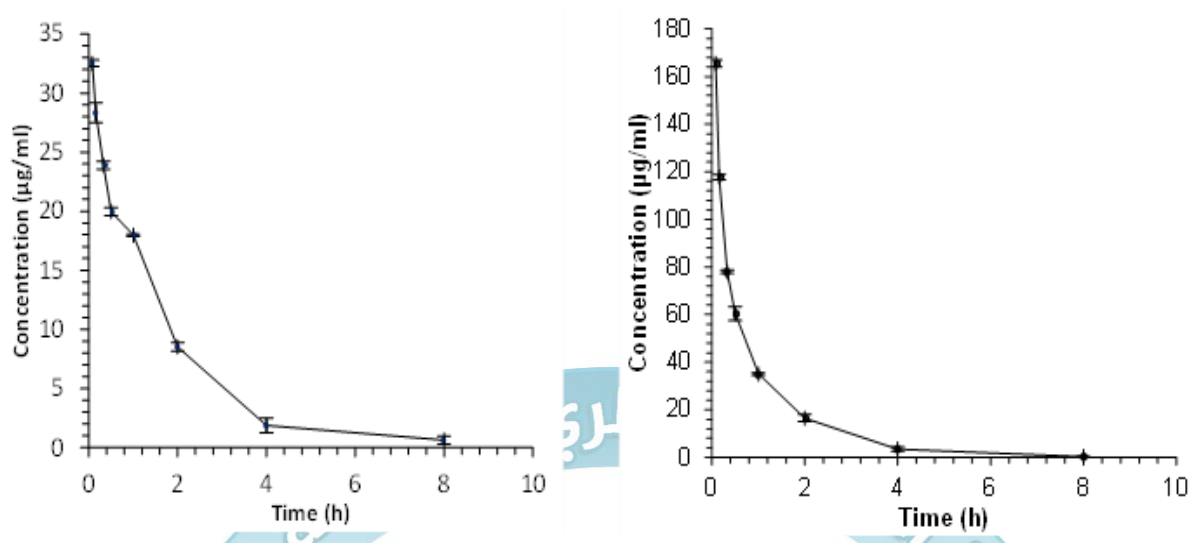
Figure (1) Cefatoxime (left) and Ceftazidime (right) concentrations in plasma of dogs after a single Intravenous bolus administration.

Table (1) Pharmacokinetics of Cefatoxime and Ceftazidime (Single IV bolus dose) in plasma of dogs.

Parameter	Unit	Cefatoxime	Ceftazidime	Student's t-test p-value
λ_z	h^{-1}	0.52 ± 0.06	0.68 ± 0.05	0.004
$t_{1/2}$	h	1.3 ± 0.17	1.02 ± 0.08	0.006
C_0	µg/ml	37 ± 0.94	232 ± 5.7	0.000
AUC_{0-t}	µg.h/ml	49 ± 1.8	125 ± 4.4	0.000
$AUC_{0-\infty}$	µg.h/ml	50 ± 2.2	125 ± 4.4	0.000
$AUMC_{0-\infty}$	µg.h^2/ml	90 ± 15	141 ± 13	0.000
MRT	h	1.8 ± 0.24	1.1 ± 0.07	0.000
V_z	L/kg	0.96 ± 0.09	0.24 ± 0.02	0.000
Cl	L/kg/h	0.5 ± 0.02	0.16 ± 0.01	0.000
Vd_{ss}	L/kg	0.9 ± 0.8	0.19 ± 0.01	0.000

Abbreviations: λ_z; Terminal elimination rate constant, $t_{1/2}$; Elimination half-life, C_0; Concentration at the zero time, C_{max}; the maximal concentration, AUC_{0-t}; Area under the curve from zero time to the last measurable concentration, $AUC_{0-\infty}$; Area under the curve from zero time to the infinity, $AUMC_{0-\infty}$; Area under the moment curve from zero time to the infinity, **MRT**; Mean residence time, **Cl**; body clearance, V_z; Volume of distribution at the terminal phase, Vd_{ss}; Volume of distribution at steady state.

4. Discussion

Studying drug pharmacokinetics including distribution and elimination is an important tool because it decides the required numbers of drug molecules that achieve the full effect of that drug with minimal side effects (17). Based on the results listed in Table 1, Ceftazidime achieved a low concentration at zero time compared to Papich et al. study (12). This can be presumed due to the administered dose in our study (20 mg/kg) compared to the previously mentioned study that used 25 mg/kg of ceftazidime, which in turn affected the distribution of the drug onto different body tissues (18). The area under the curve was minorly smaller than that of Papich et al. (12) due to the low concentration of Ceftazidime at zero time which lead to mild shrinkage in the area under the curve (19)

The half-life of ceftazidime is lower than that in Papich et al study(12) this impact is a result of the decrease in the volume of distribution that is influenced by the decrement in the administered dose, while there is no sensible change in the value of the elimination due to the mathematical correlation among the three parameters (Vd, CL and the $t_{1/2}$) (20).

The information about the pharmacokinetics of Cefatoxime is listed in Table 1, which showed no difference in the concentration at the zero time of cefotaxime compared to Sumano et al. study (21). The area under the curve in the present study is much lower than that found in the study of Sumano et al. (21), with a slow distribution of cefotaxime to the different tissues with a longer half-life and slower elimination.

Many factors could contribute to such variation in the results including the difference in the weight of the animal of the present study, besides the difference in the administered dose. also the the way of drug analysis, and the difference in the method of pharmacokinetic calculations (22).

The comparison between Ceftazidime and Cefatoxime in the present study revealed that Cefatoxime has a significant rapid distribution to the peripheral tissues, a long half-life, and a mild rapid clearance compared to Ceftazidime due to the physicochemical differences between both drugs especially the side chains and substituents that differs between the two drugs (23).

5. Conclusions

The distribution and elimination of Ceftazidime and Cefatoxime in local mongrel dogs is slightly variable compared to the distribution and elimination in most recent studies done on dogs considering the difference in dose, the used dog species, the method of analysis, and the pharmacokinetics calculations.

The comparison between the two drugs showed a better distribution of Cefatoxime to the peripheral tissues, a longer half-life, and a mild rapid elimination compared to Ceftazidime which achieved a greater concentration at the zero time accompanied by a larger area under the curve, such paradoxical events may require a further study for the pharmacokinetics of both drugs especially Cefatoxime due to lack of adequate and recent pharmacokinetic studies for this drugs in dogs compared to Ceftazidime.

Conflict of interest

There is no conflict of interest as all authors declared.

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