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Research Article

PHARMACOKINETIC OF CEFTIOFUR SODIUM IN KANKREJ COW CALVES FOLLOWING A SINGLE INTRAMUSCULAR INJECTION

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Abstract: The present investigation on pharmacokinetics of the ceftiofur alone (following intramuscular administration) in six healthy Kankrej cow calves @ 4.4 mg/kg was conducted to explore the disposition and arrive at the clinically effective dosage regimens. The blood samples were collected at predetermined intervals following drug administration in cow calves and plasma was separated for quantification of ceftiofur by UHPLC with UV detector. The concentration vs time data were analyzed using PK 2.0 Solver software with non-compartment approach. Following IM administration of ceftiofur alone, the drug was detected for up to 24 h with last concentrations of 0.59 µg/ml, A peak ceftiofur (alone) concentration (C_{max}) by intramuscular route was observed as 11.45 µg/ml at 45 min of drug administration. After administration of ceftiofur alone @ 4.4 mg/Kg intramuscularly in cow calves, the value of pharmacokinetic parameters was observed ast1/2β =6.92 h, AUC = 69.40µg.h/ml, AUMC = 622.03 µg.h2/ml, MRT = 8.90 h, Vd(area) = 0.66 L/kg and ClB = 0.06 L/h/kg.

Keywords: *Sodium, Intramuscular Route, Non-Compartment, Pharmacokinetics*

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Introduction

Antimicrobials are likely one of the most successful kinds of chemotherapy in medical history. Prior to the turn of the twentieth century, infectious illnesses were a major cause of morbidity and mortality over the world. Sir Alexander Fleming's (1881-1955) discovery of penicillin in 1928 signalled the beginning of the antibiotic revolution. The veterinary exclusive antimicrobials were introduced to resolve the few of these challenges and are now getting popularity among clinician community.

Ceftiofur is one of few veterinary exclusive third generation semi-synthetic cephalosporin being widely accepted and approved by veterinary drug regulatory authorities all over the world for use in veterinary medicine. Ceftiofur has good spectrum of activity against Gram-positive as well as Gram-negative bacteria, including β lactamase producing strains because of presence of additional methoxyimino side-chain to the aminothiazole [1,2,3].The primary use of ceftiofur in domestic livestock is for the treatment of respiratory diseases. Ceftiofur is typically active against Gram negative bacteria and is resistant to many β-lactamases [4]. Ceftiofur is also considered as an effective approach for treating and controlling respiratory distress in horses caused by *Streptococcus zooepidemicus* [5].

Pharmacokinetics describes the temporal course of a medication in the body using mathematical equations (models), allowing us to better understand, interpret, and even determine the type and amount of the biological effects (therapeutic or harmful) of a medicine. It is a critical stage in the development of a new medicine. The pharmacokinetic studies of cephalosporin antimicrobial in cattle and buffalo species demonstrated the noteworthy differences between these two species of domestics animals, and the findings provides strong evidences that inter-species extrapolation of pharmacokinetics is not recommended [6].

Keeping the above facts in view, the present study was conducted to investigate concentrations of ceftiofur after intramuscular administration in healthy cow calves.

Materials and Methods

Six healthy male cattle calves of Kankrej breed having age 1-2 years and weight between 150-200 kg, were used in the present study. Total six healthy animals were selected for the pharmacokinetic study of ceftiofur.

Drug Administrations

For intramuscular (IM) administration of ceftiofur alone, exactly 250 mg of drug powder was dissolved in 5 ml of water for injection and administered at the dose of 4.4 mg/kg body weight. Disposable needles of 18G × 38mm size were used. Intramuscular injection was given in either side of neck muscle.

Collection of blood samples

Six cattle calves were used for pharmacokinetic studies. Maximum 3.0 ml of blood was collected in heparinized test tube at 0 min (pre administration), 5, 15, 30, 45 min and at 1, 2, 4, 8, 12, 24 and 36 hours after intramuscular administration of drug.

Chromatographic conditions for ceftiofur

The chromatographic conditions and parameters for UHPLC analysis of ceftiofur concentrations in plasma sample was, Mobile phase was mixture of buffer and acetonitrile (82:18). The buffer was prepared by dissolving trifluoracetic acid (TFA) in HPLC grade water to yield strength of 0.1% TFA buffer (v/v).

It was filtered by 0.45 µm pore size filter (Millipore®, Merck Life Science Pvt. Ltd., Bangalore) by using vacuum pump and degassed using ultrasonic sonicator (Frontline Ultrasonic cleaner, Ahmedabad, India) before use. During sample run, intermittent washing of manual micro syringe were done with washing solution (80 Acetonitrile: 20 HPLC water)to avoid carry over effect.

Extraction and sample preparation

After administration of ceftiofur, normally it is rapidly converted to the biologically active metabolite, desfuroylceftiofur (DFC) in the body of animals. Therefore, plasma DFC concentrations were determined for the pharmacokinetics of ceftiofur and plasma DFC concentration is represented as a ceftiofur concentration. Ceftiofur was extracted from plasma using derivatization method that converts ceftiofur to its metabolites desfuroylceftiofur (DFC). At first, exactly 200 µl of each plasma sample was brought to room temperature and transferred to 2 ml micro centrifuge tubes. To this, 200 µl of methanol was added, and samples were vortexed for 30 seconds. This was followed by centrifugation of samples at 13,000 rpm for 10 min at 22°C.

The clear supernatant was transferred to 2 ml micro centrifuge tubes. Exactly 100 µl of 10% dithioerythritol (prepared in borate buffer) was added to each tube, and each tube was placed in a water bath at 50°C for 15 min. The tubes were moved from the water bath and allowed to reach room temperature. Next, each tube was wrapped in aluminium foil followed by addition of 100 µl of 10 % iodoacetamide (prepared in phosphate buffer). The contents in micro centrifuge tube were centrifuged at 350 rpm for 45 min at 22°C temperature. Formic acid (25 µl of 2%) was added to each sample. Following derivatization, samples were vortexed for 30 seconds and then were centrifuged for 10 min at 13,000 rpm. An aliquot of the resulting supernatant (50 µl) was injected into the UHPLC system. The retention time was 10 ± 0.4 and total run time was 15 minutes.

Preparation of standard calibration curve in plasma

Initially, a stock solution of ceftiofur in drug free cattle calf plasma was prepared by mixing 10 mg of drug powder in 1 ml of plasma. This stock was used for making different standard concentrations of ceftiofur ranging from 0.156 to 20 µg/ml. Working standard solutions were mixed properly in pooled drug-free plasma with a vortex mixture. Final ceftiofur concentrations in plasma were 0.156, 0.312, 0.625, 1.25, 2.5, 5, 10 and 20 µg/ml. In UHPLC, each of these standards were run in triplicate (n=3) to get peak area response.

Pharmacokinetic Analysis

The plasma concentration-time curves of individual calf were subjected to non-compartmental analysis (NCA) for working out targeted pharmacokinetic (PK) parameters of ceftiofur, following intramuscular administrations either given alone or with blood level enhancing vehicle. Values of pharmacokinetic parameters were presented as a mean ± standard error (SE) using data set of 6 calves.

Non-compartmental methods can be used to determine certain PK parameters without fitting data in any compartmental model. The basic calculations are based on the area under the plasma concentration versus time curve (Zero moment) and the first moment curve (AUMC). The area under the curve (AUC) and area under first moment curve (AUMC) can be calculated by using the trapezoidal rule without making any assumption concerning the number of compartments [7].

Statistical Analysis

All the data have been presented in Mean ± SE. The effect of blood level enhancing vehicle on concentrations and pharmacokinetics of ceftiofur in cattle calves were statistically compared by 'Paired sample T-test' using software IBM SPSS (version 20), where $P<0.050$ was considered as statistically "significant" and $P<0.010$ was considered as statistically "highly significant".

Results and Discussion

Following IM administration of ceftiofur, the drug concentration of individual animal at first time point of collection i.e., at 0.083 h observed to be ranging from 1.01 to 2.63 µg/ml with a mean of 1.71 µg/ml. The mean peak plasma drug concentration (C_{max}) of 11.45 ± 0.61µg/ml was achieved at 0.75 h (T_{max}), which declined rapidly to 2.87 ± 0.43 at 8 h and further to 1.70 ± 0.22 µg/ml at 12 h post drug administration. The lowest concentration at 24 h was observed as 0.59 ± 0.08 µg/ml, which declined to nondetectable level at 36 h.

Similar values of C_{max} (10.34 µg/ml) in camel was detected [8]. The relatively lower values of peak plasma concentration in goat (2.7 µg/ml), cow (7.73 µg/ml) and horses (6.38 µg/ml) were observed [9,10,11]. Higher peak plasma concentration after intramuscular administration observed in present study can be attributed to higher dose of ceftiofur (4.4 mg/kg). Apart from this, anatomical and physiological distinctness affecting vascular permeability, protein binding, site of injections and physic-chemical properties of drug are important determinant for peak plasma concentration after extra vascular administration [13].

Pharmacokinetic profile

Following IM administration of ceftiofur, the values of elimination rate constant (β) varied from 0.089 to 0.112 h^{-1} with an average of 0.10 ± 0.04 h^{-1}. The corresponding mean value of elimination half-life (t1/2β) was calculated to be 6.92 ± 0.29h. The respective values of AUC and AUMC in present investigation were observed to be 69.40 ± 6.76 µg.h/ml and 622.03 ± 76.62 µg.h2/ml. The mean values of MRT, Vd(area)and ClBof 8.90 ± 0.44h, 0.66 ± 0.06 L/kg and 0.06 ± 0.07 L/h/kg were observed in cow calves following intramuscular administration of Ceftiofur @ 4.4 mg/kg. Mean intramuscular bioavailability of ceftiofur (4.4 mg/kg, IM) was observed to be 76.44 ± 7.57%.

Pharmacokinetic Parameters of Ceftiofur after Intramuscular Administration in Cow Calves

Elimination rate constant (β)

Following single dose IM administration of ceftiofur, the mean value of elimination rate constant was 0.10 h^{-1} in calves. Similar values of elimination rate constant in horses and camel were reported.By Macpherson *et al*. (2016) [11] and Goudah*et al*. (2007) [8], respectively. In contrary to these findings, relatively higher value was reported in cow (1.86 h^{-1}) by Altan *et al*. (2017) [10]. The values of elimination rate constant reflect the rate at which the drug is removed from the system. Elimination of a drug refers to its specific rate of elimination in amount of drug per unit time, the rate constant for elimination (Kel) or the half-time of elimination (t1/2β), the time when half the drug is eliminated. Both half-life and elimination and constantgive direct information about the rate of elimination of a drug [13].

Elimination half-life (t½β)

Following single dose IM administration of ceftiofur, the mean value of elimination half- life was found to be 6.92 h in cow calves. Lower value of elimination half-life as 2.71 and 4.10 h were reported in goats and horses, respectively [9,11]. Half-life represents the amount of time for reducing the concentration of drug to half and is largely depends on drug metabolizing and eliminating capacity of particular individual more specifically. There are factors which causes wide variation in these leading to huge variation in the half-life values of similar drug among different livestock species. The present study revealed relatively longer half-life of ceftiofur indicating slower rate of metabolism and excretion from body in Kankrej cattle calves as compared to goats and horse.

Volume of distribution (Vd)

Volume of distribution (Vd) is necessary to know the extent of penetration of drugs in body tissues and to compute optimal dosage regimen of drug that must be given to achieve and maintain its therapeutic concentration in the body. Lipid solubility can affect volume of distribution, as highly lipid-soluble drugs have good cell penetration, resulting in high value of volume of distribution.

Plasma-protein binding, particularly to albumin, reduces volume of distribution, while tissue binding increases the volume. Unlike the IV pharmacokinetics, IM study consists of calculation of only the apparent volume of distribution (Vd(area)). The mean ± SE value of apparent volume of distribution (Vd(area)) calculated following single dose IM administration of ceftiofur (4.4 mg/kg) in present study was 0.66 ± 0.07 L/kg in cow calves. This indicates the limited distribution of drug to extra vascular space. Lower value was reported in cattle (0.212 L/kg) by Altan *et al*. (2017) [10].

Area under curve (AUC)

Area under the curve or AUC is a pharmacokinetic statistic used to describe the total exposure to a drug. More specifically, it is the time-averaged concentration of drug circulating in the body fluid analyzed (normally plasma, blood or serum).

The mean ± SE value of AUC following single dose IM administration of ceftiofur in the present study was 69.40 ± 6.76 µg·h/ml. The value recorded in present experiment is in close agreement with the value of 55.28 µg·h/ml reported in horses [11], whereas relatively higher values of 100.8 µg·h/ml in cattle and 68.70 µg·h/ml in camel were reported [14,8]. Moderate AUC values suggest that ceftiofur covers vast area upon IM administration in calves.

Total body clearance (ClB)

Total body clearance of the drug following single dose IM administration was found to be 0.06 ± 0.07 L/h/kg in present study. Lower values of total body clearance were observed in cow as 0.013 ± 0.005 and 0.014 L/h/kg by Mohamed *et al*. (2019) [14] and Altan *et al*. (2017) [10].

Mean residence time (MRT)

The mean value of MRT calculated following single dose IM administration of ceftiofur was found as 8.90 ± 0.44 h, this is in partial agreement with the value reported in horse (6.38 h) by Macpherson *et al*. (2016). Lower values were detected in goat (4.48 h) by Courtin *et al*. (1997) [9] and camel (5.21 h) by Goudah *et al*. (2007) [8]. The considerable higher values of MRT observed in the present study reflects longer stay in body and this may be due to higher dose and slower elimination of ceftiofur.

Bioavailability (F)

Bioavailability is the pharmacokinetic parameter which expresses the proportion of a drug administrated by non-vascular route that gain access to systemic circulation. Following single dose IM administration of ceftiofur at the dose rate of 4.4 mg/kg body weight, the calculated mean ± SE value of bioavailability was 76.44 ± 7.57 %. Higher value was reported in camel (97.40 % by Goudah *et al*., 2007) [8] and buffalo (89.57 % by Nie *et al*., 2016) [15]. Comparatively lower values of bioavailability were observed in cow (64.66% by Mohamed *et al*., 2019) [14] and (70.52% by Woodrow *et al*., 2015) [16].

Conclusion

Following IM administration of ceftiofur (alone) in cow calves, the mean peak plasma drug concentration (C_{max}: 11.45 µg/ml) was achieved at 0.75 h (T_{max}). Based on PK-PD integration, ceftiofur administered IM at the dose rate of 4.4 mg/kg is promising for treating the susceptible bacteria having MIC value ≤ 0.25 µg/ml in Kankrej cow calves

Application of research: The present study throws insight to favorable pharmacokinetic profile of ceftiofur alone following IM route of administration.

Research Category: Veterinary science

Abbreviations: mg/kg-Milligram per kilogram body weight, IM-Intramuscular, MIC-Minimum Inhibitory Concentration, MRT-Mean Residence Time, PK-PD-Pharmacokinetic- Pharmacodynamic, UHPLC-UltraHigh Performance Liquid Chromatography

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Study area / Sample Collection: Livestock Research Station (LRS), Sardarkrushinagar, Dantiwada, Gujarat

Breed name: Kankrej Cattle Breed

Conflict of Interest: None declared

Ethical approval: This study was prior recommended and approved by Institutional Animal Ethics Committee (IAEC) of Department of Veterinary Pharmacology & Toxicology, College of Veterinary Science & Animal Husbandry, Sardarkrushinagar, 385505, Kamdhenu University, Gandhinagar, 382010, Gujarat, India
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