International Journal of Livestock Research, Vol. 10 (8) Aug' 2020
http://www.ijlr.org
eISSN: 2277-1964
NAAS Rating 2020 – 5.36

Original Research

Pharmacokinetics of Cefquinome on Single Intramuscular Administration in Osmanabadi Goats by Microbiological Assay Technique

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How to cite this paper: Patil, M., Somkuwar, A., & Patil, P. (2020). Pharmacokinetics of Cefquinome on Single Intramuscular Administration in Osmanabadi Goats by Microbiological Assay Technique. *International Journal of Livestock Research*, 10(8), 150-155. doi: http://dx.doi.org/10.5455/ijlr.20200418104458

Received : Apr 18, 2020
Accepted : Jul 12, 2020
Published : Aug 31, 2020

Abstract

Experiment was performed on six healthy Osmanabadi goats of either sex having age above 9 months and weighing around 30 to 35 kg to study the different pharmacokinetic parameters after single intramuscular administration @ 2 mg/kg body weight by microbiological assay technique. The peak serum concentration, absorption half-life, distribution half-life, elimination half-life, volume of distribution, total body clearance, AUC, AUMC, MRT and bioavailability values found were 1.77 ± 0.113 mcg/ml, 0.23 ± 0.03h, 0.29 ± 0.04 h, 2.69 ± 0.07h, 1.89 ± 0.18L/kg (Vd(B)) and 2.01± 0.24 L/kg (Vdss), 0.50 ± 0.05 L/kg.h-1, 4.17 ±0.34 µg/ml.hr, 16.50 ±1.15 µg/ml.hr2, 3.99 ± 0.14 h and 100 % respectively. It may be concluded that the elimination half-life of cefquinome was 2.54 h in goats indicating the repeating of doses at 12 to 15 h intervals in goats. The loading dose would be double than the maintenance dose of cefquinome after intramuscular administration.

Keywords: Cefquinome, Intramuscular, Microbiological Assay Technique, Osmanabadi Goats, Pharmacokinetics

Introduction

In veterinary medicine, the cephalosporin cefquinome is approved and used for several animal species in many countries worldwide (Aarestrup and Skov, 2010). In comparison with the third- generation cephalosporins, it shows a higher degree of activity against gram-negative bacteria (Suhren and Knappstein, 2003). Fourth-generation show marked resistance to β-lactamases and increased outer membrane permeability when compared with third-generation cephalosporins (Hancock and Bellido, 1992). Also, it has a broad spectrum and is susceptible to clinically important bacteria such as *Streptococcus* spp., *Staphylococcus* spp., *Pseudomonas* spp., *Moraxella* spp., *Haemophilus* spp., *Corynebacteriae, Enterococci, Escherichia coli* and gram- positive anaerobes tested *in vitro* (Limbert *et al.*, 1991; Murphy *et al*., 1994; Shpigel *et al.*, 1997). Cefquinome has been shown to have good activity against respiratory tract infections, diarrheoa and mastitis in cattle and buffalo (Kikuchi *et al*., 1995; Wilson *et al.*, 1996; Barkema *et al*., 1998). Moreover, it is highly stable to β-lactamases produced by most of the pathogenic bacteria. It is approved for the treatment of respiratory tract diseases and mastitis for livestock worldwide.

The pharmacokinetics of cefquinome is studied in different animals such as camel, sheep, piglets, chicken, mice, dogs, pigs and calves. However, these studies are conducted in different parts of the world and there are no data available from India. Further, no data on pharmacokinetic study in goats was observed. Thus, many data is required to be produced in different species of animals by using different routes of administration for its use in veterinary practice on a large scale.

Materials and Methods

For this study, six goats of either sex were selected. All the animals were kept under observation for a period of two weeks prior to the experiment. During the entire period of experimentation, the animals were provided ad-libitum dry as well as green fodder, concentrates and clean drinking water. Group of goats comprising six animals was administered with cefquinome @ 2mg/kg bwt by intramuscular route. In the present study microbiological assay was performed for estimation of serum cefquinome concentrations. For this assay, *Escherichia coli* (MTCC 739) were procured from Microbial Type Culture Collection (MTCC), Chandigarh, UT.

Microbiological Assay Technique

Agar Plate Preparation

The sterilized assay plate stand was leveled with adjustable screws, using a spirit level for getting uniform thickness of melted medium. The sterilized large assay plate was placed on the stand. The molten assay medium was allowed to cool to the temperature of 45^0C to 50^0C. About 1.0ml of bacterial suspension was added into the medium and was gently shaken to distribute the bacteria's uniformly. The lid of the surface of the glass plate rapidly to form uniform layer of medium and was allowed to solidify for 20 to 25 minutes. One hundred ml of agar produced a uniform layer of media of about 2.5 to 2.7 mm thickness.

Preparation of Standards

Cefquinome powder having a known potency was used to prepare standard. Initial standard was prepared by adding 01 ml of distilled water to this powder to give the concentration of 10mg/ml. Further dilutions were done to obtain concentrations of 5.0, 2.5, 1.0, 0.5, 0.25, 0.125, 0.625, 0.313, and 0.157 mg/ml. For each assay the cefquinome concentrations were freshly prepared to compensate for deterioration of activity.

Preparation of Reservoirs

The heat resistant porcelain beads (No. 2) which are generally used as insulators, were used in the present study as reservoirs, having diameter of 5mm and 7mm height. These beads held about 0.2ml of sample solution. The beads were cleaned with extreme care and were boiled in 4% concentrated hydrochloric acid for 30 minutes and were rinsed thoroughly in water, dried overnight. Batch of 100 beads each then dispensed in test tubes and were heated in the hot air oven at 160^0C for 2 hours.

Application of Samples and Standards

Dilutions of standard and test samples were placed in shallow wells of Perspex plate. The plate was initially swabbed liberally with absolute alcohol and sterilized under ultraviolet lamp before used. The reservoir beads were held with a bent forcep on the surface of the sample and were allowed to be filled by capillary action without tilting. These were gently placed in the position on a agar surface without piercing the medium. A guiding chart placed beneath the assay plate helped in placing the bead at right position and also in identifying the corresponding sample while results were recorded. After putting beads on the agar, a ring of the fluid appeared at base of porcelain beads. This did not indicate leakage. All the test samples were assayed preferably in triplicates and care was taken that the standard dilutions of antibiotic were invariably put on each assay plate processed. The test samples and standard dilutions were given code numbers to facilitate placing them at the predetermined spot in a sequential randomization pattern as recommended by Bennet *et al.* (1966) and thereafter by various researchers. After placing the beads in position, plate was covered with the lid and kept at room temperature for half an hour and then incubated at 37^0C overnight (18-24 hours). The zones of inhibition were measured by inverting the plate and results were averaged.

Cefquinome was diluted with sterile distilled water and administered @ 2 mg/kg body weight in Osmanabadi goat. Intramuscular (IM) injection of the drug was given to the left side of neck using 20G x 25mm sterile needle. The site of prick for blood collection was washed, shaved and cleaned with alcohol. After intramuscular administration of the drug, blood samples (4 ml each) of Osmanabadi goats were collected from external jugular vein using disposable needles in clot activator tubes at different time intervals. The schedule of blood collection for pharmacokinetic studies after intramuscular administration was at 0, 15, 30 min and 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 hr. Serum obtained in clot activator tubes was collected in sterilized plastic vials and stored in refrigerator until assayed. The serum levels of cefquinome were estimated by microbiological assay technique using large glass plate (Bennett *et al*., 1966; Black *et al*., 1983; Burrows *et al*., 1987). The different pharmacokinetics parameters like distribution rate constant, elimination rate constant, absorption half-life, distribution half-lives, elimination half-lives, volume of distribution, body clearance of drug, bioavailability, area under curve, mean residence time, zero-time plasma drug concentration, AUMC, drug concentration between tissue and plasma. peak plasma drug concentration, time of peak plasma drug concentration, loading dose, Maintenance dose etc. were calculated manually by using pharmacokinetic formulae's as described by (Baggot, 1977; Gibaldi and Perrier, 1982; Riviere *et al*., 2011). Data of various pharmacokinetic parameters was analysed and depicted the results as per Snedecor and Cochran,1994.

Results and Discussion

The various pharmacokinetic parameters estimated were depicted in Table 1. The average peak serum cefquinome (IM) concentration, absorption half-life, distribution half-life ($t_{1/2(\alpha)}$), elimination half-life ($t_{½(\beta)}$), volume of distribution $Vd_{(B)}$ and (Vd_{ss}), total body clearance, AUC, AUMC and mean residence time in goats were found to be 1.77 ± 0.113 mcg/ml, 0.23 ± 0.03h, 0.29 ± 0.04 h, 2.69 ± 0.07h, 1.89 ± 0.18L/kg ($Vd_{(B)}$) and 2.01± 0.24 L/kg (Vd_{ss}), 0.50 ± 0.05 L/kg.h^{-1}, 4.17 ±0.34 µg/ml.hr, 16.50 ±1.15 µg/ml.hr^2, 3.99 ± 0.14 h, respectively after intramuscular administration of single dose of cefquinome. Errecalde *et al.* (2002) reported the absorption half-life and distribution half-life of cefquinome in calves as 0.57 ± 0.06 h and 0.59 ± 0.12 h, respectively these values are higher than the values obtained in the present study. The average elimination half-life and total body clearance of 1.76 ± 0.27h and 1.20 L/hr/kg, respectively in goats after intramuscular administration of cefquinome @ 2 mg/kg bwt reported by Errecalde *et al.* (2002). The average elimination half-life was towards lower side as compared to the range of half-life reported in the present study and total body clearance was higher as compared to that observed in the present study in goats and buffalo calves, which might be due to species variation. Tohamy (2011) studied half- lives of intramuscular cefquinome (10mg/kg bwt) in different age groups of sheep and observed it as 2.411 ± 0.19, 2.475 ± 0.31 and 3.333 ± 0.22 h respectively in one year, six months and one-month old sheep. Our results are in agreement with this study. The variation observed might be because of age factor as described above. Uney *et al.* (2011) noted less Vd_{ss} as 0.36 ± 0.06 L/kg of cefquinome (@ 2mg/kg bwt IV in sheep as compared to goats in the present study. Uney *et al.* (2011) studied pharmacokinetics of cefquinome (@ 2mg/kg bwt) in sheep and observed the AUC 5.19 ± 0.25 mcg.hr/ml after IM administration. These AUC values are comparable to the AUC values of goats obtained in the present study. It might be due to variation in method used for study of cefquinome concentration in blood and method may be one of the factors for difference in values.

Table 1: Pharmacokinetic parameters in Osmanabadi goats (@ 2mg/kg bwt) after intramuscular administration of cefquinome

Parameters	Units	Goats	
		Mean	**± S. E.**
A	µg/ml	6.23	0.84
B	µg/ml	1.1	0.09
A’	µg/ml	0.2	0.06
$t_{½\beta}$	hr	2.69	0.07
$t_{½\alpha}$	hr	0.29	0.04
$t_{½ka}$	hr	0.23	0.03
B	hr^{-1}	0.26	0.01
A	hr^{-1}	2.59	0.26
Ka	hr^{-1}	3.18	0.31
AUC	µg/ml.hr	4.17	0.34
AUMC	µg/ml.hr^2	16.5	1.15
MRT	hr	3.99	0.14
K_{21}	hr^{-1}	0.61	0.04
K_{12}	hr^{-1}	1.14	0.14
K_{el}	hr^{-1}	1.1	0.12
C_{max}	µg/ml	1.89	0.06
T_{max}	hr	0.61	0.04
Vd_B	L/kg	1.89	0.18
Vd_{ss}	L/kg	2.01	0.24
Cl_B	L/kg.hr	0.5	0.05
Fc		0.25	0.02
T/P		3.24	0.39
Td	hr	14.18	
F	%	150.58	
$C_{p(min)}{}^{\alpha}$		0.00714	
LD	mg/kg	3.982	
MD	mg/kg	1.99	

Errecalde *et al.* (2002) reported MRT as 1.64 ±0.23 h in calf after administration of cefquinome (IM) at the dose rate of 1 mg/kg bwt which was lower than the value reported in present study. The bioavailability (F) recorded in the present study was 150.58 % in goats after single intramuscular administration of cefquinome intramuscularly. Maha (2005) reported the bioavailability in broiler chickens as 103.17% after administration of cefquinome @ 1mg/kg bwt. At the same dose, Yang *et al.* (2009) reported it as 102.37 % in pigs. The values of bioavailability reported by Maha (2005) and Yang *et al.* (2009) were lower than the value reported in present study. This difference in bioavailability was might be due to difference in absorption, food effect, drug metabolism/ biotransformation, energy dependent efflux transporters, physico-chemical factors and first pass metabolism.

Conclusion

From the results it may be concluded that the elimination half-life of cefquinome was 2.69 h in goats indicating the repeating of doses at 12 to 15 h intervals in goats. The bioavailability of cefquinome in goats was found to be 150.58 %. Further it is concluded that the loading dose would be double than the maintenance dose of cefquinome after intramuscular administration and the microbiological assay technique was found to be suitable for the estimation of serum cefquinome concentration in the laboratories where the LC/MS facilities are not available.

Acknowledgements

The authors are very much thankful to Associate Dean, college of Veterinary and Animal Sciences, Udgir dist. Latur for providing essential facilities for this research.

Conflict of Interests

There is no conflict of interest.

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