Research Article

EFFECT OF TRIKATU ON ORAL PHARMACOKINETICS OF CEFUROXIME AXETIL IN GOATS

Prabhat Kumar Padhi[1*], Vipin Katoch[2], Chandresh Varshneya[3]

ABSTRACT: The study was aimed at determining the intravenous pharmacokinetic variables of cefuroxime, and compare it with pharmacokinetic variables following its oral administration alone and in combination with trikatu, a herbal bioavailability enhancer. Six mountain Gaddi goats were administered cefuroxime sodium at dose rates of 10 mg kg^{-1} by intravenous route and cefuroxime axetil at 10, 20 and 40 mg kg^{-1} by oral route. Cefuroxime concentration in plasma samples collected at various time intervals was determined by microbiological assay using *Staphylococcus aureus* (ATCC 6538) as test organism. Following intravenous administration of cefuroxime, the pharmacokinetic behavior was best described by two compartment open model. The distribution half-life, elimination half-life, apparent volume of distribution and total body clearance were calculated to be 0.13 ± 0.01 h, 0.67 ±0.01 h, 0.39 ±0.05 L kg^{-1}, 411.81 ±16.38 ml kg^{-1}.h^{-1}, respectively. Cefuroxime is rapidly distributed and rapidly eliminated following intravenous administration in Gaddi goats. Cefuroxime axetil is not absorbed by oral route in goats and use of Trikatu did not lead to absorption of drug. Cefuroxime at the dose rate of 10 mg.kg^{-1} at 6 hourly intervals is likely to be effective against the highly susceptible bacteria when given by intravenous route.

Key words: Cefuroxime, Trikatu, Pharmacokinetics, Goats.

INTRODUCTION

Oral route of drug administration is preferred over other routes due to better owner compliance and less handling stress to animals. Many drugs like anti parasitic drugs, vitamins, minerals, and antibiotics in non-ruminants etc are given by oral route and have good owner compliance rates. However in compound stomach animals the use of antibiotics by oral route is rarely advised. Approaches such as use of esophageal groove closure and use of gastric protection, to bypass the compound stomach in animals have been suggested but these methods require involvement of skilled personnel and result in handling stress to animals. So Gastro Intestinal route is the most avoided route for

1. Krishi Vigyan Kendra (Odisha University of Agriculture and Technology),Jajpur, Odisha, India.
2. Department of Veterinary Microbiology CSKHPKV, Palampur-176062, India.
3. Department of Veterinary Pharmacology & Toxicology CSKHPKV, Palampur-176062, India.
*Corresponding author. e - mail: prabhat46@hotmail.com

antibiotic administration in ruminants. The use of orally administrable pro-drugs might provide solution against the problem.

Cefuroxime is a broad spectrum synthetic β–lactam antibiotic available in injectbale form and in a pro-drug form for oral use. It was the first β-lactam with a higher stability to β - lactamase hydrolysis due to its methoxy-imino side chain in position 7 of the cephem nucleus (Roberts *et al.,* 2004). It is available for parenteral use as cefuroxime sodium (poorly absorbed) and for oral use as cefuroxime axetil (moderately absorbed). The sodium salt is used in veterinary medicine for the treatment of clinical mastitis in lactating cattle, sub-clinical mastitis in dry cows and to prevent new infections during the dry period. Cefuroxime axetil is the orally active pro-drug form of cefuroxime (Sneader 2005). After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract in simple stomach animals and rapidly hydrolyzed by nonspecific esterases in the intestinal mucosa and blood to cefuroxime. Cefuroxime is subsequently distributed throughout the extracellular fluids. The antibacterial activity of the drug is due to the cefuroxime moiety. However the drug is poorly available from the GIT and has variable rates of elimination (Ruiz *et al.,* 1997). Use of herbal bioenhancer, Trikatu might provide a solution to the poor and variable absorption and elimination of cefuroxime.

Trikatu is an herbal drug having Piperine as the active principle. Piperine has been reported to increase the bioavailability of a number of antibiotics, NSAIDs and other drugs in different species of animals either by promoting rapid absorption from the gastrointestinal tract by increasing blood flow or by protecting the drug from being metabolized in its first passage

through the liver after being absorbed, or by a combination of these two mechanisms (Kang *et al.,* 2009). As cefuroxime is a drug with variable and poor bioavailability it could be co-administered with Trikatu for bioenhancing effects.

Hence a study was designed to calculate the pharmacokinetic parameters of cefuroxime in goats following its intravenous and oral administration alone and in combination with Trikatu. Effect of oral administration of cefuroxime on the flora and fauna of rumen in goats was also investigated.

MATERIALS AND METHOD.

Animals: Six adult male Gaddi goats weighing six between 18-22 kg were used. They had been kept under close observation before the commencement of experiment and were acclimatized to the new environment. Goats were housed in the Animal shed of Clinical Complex, College of Veterinary Sciences, Palampur. They were maintained on feed procured from Department of Animal Nutrition, College of Veterinary and Animal Sciences, Chaudhury Sarwan Kumar Himachal Pradesh Krishi Vishvavidyalaya (CSKHPKV), Palampur and were allowed to browse. Permission to conduct studies on animals was obtained from Institutional Animal Ethics Committee of CSKHPKV, Palampur.

Drugs : 1. Cefuroxime : Cefuroxime sodium -750 powder and cefuroxime axetil-500 tablets (Brand name Altacef of Glenmark Pharmaceuticals Ltd., Mumbai India) were used in the studies. Cefuroxime sodium contains cefuroxime 702 mg and sodium 42mg in 750 mg of cefuroxime sodium and 500 mg of cefuroxime per tablet respectively.

2. Trikatu: Dried fruits of Piper *longum*

(Pipli) and *Piper nigrum* (Black pepper) and dried rhizomes of *Gingiber officinale* (Ginger) were procured from the local market in post-monsoon period (October-November). These were thoroughly ground to make fine powder using kitchen grinder. Equal parts (1:1:1) of these herbs were mixed to prepare Trikatu and it was standardized for the presence of Piperine content in it by High performance thin layer chromatography (HPTLC) method developed at R & D Laboratory, Indian Herbs, Saharanpur. The Piperine content was 2.02 per cent.

Administration of drug: 1.Cefuroxime 10.0 percent solution of cefuroxime sodium was administered into the jugular vein of goats at the dose rate of 10 mg.kg^{-1} for intravenous study and intramuscular study and the tablet mixed with jaggery was fed orally to goats for oral study.

2. Trikatu: Trikatu mixed with jaggery in 1:2 ratio was fed to goats at the dose rate of 1.5 gm of Trikatu per Kg body weight for 14 days prior to start of study.

Collection of Samples: Blood samples were collected from jugular vein of goats in heparinised vials. The samples were centrifuged at 3000 rpm for 10 minutes to separate the plasma. The plasma samples were stored analyzed as soon as possible or they were stored at -20ºC until their analysis.

Assay of cefuroxime : The concentration of microbiologically active cefuroxime in plasma was determined by an agar plate diffusion method (Arret *et al.,* 1971) with some modifications. In this technique, only a seed layer with bacterial suspension is poured on assay plates and the wells were prepared by punching the solidified media (Bennet *et al.,* 1966). The detailed procedure of the estimation by this method is given below:

1. 30.5 gram of antibiotic media No. 1 (HiMedia Laboratories, Mumbai India) was dissolved in one liter of distilled water. The suspension is then sterilized by autoclaving for 15 minutes at 15 pounds. Final pH of medium = 6.6±0.2.

2. Staphylococcus aureus (ATCC 6538) was obtained from Indian Veterinary Research Institute, Izatnagar, Bareilly and was maintained in 5 per cent Sheep Blood Agar, kept under refrigeration and subcultured at 15 days interval to maintain its viability

3. Agar puncher: A stainless steel well puncher was prepared with inside diameter of 4 ± 0.1 mm.

Preparation of test organism: Suspension of test organism used for drug estimation was prepared as follows:

1. Test organism was streaked on sterilized plate of Medium No. 1 and incubated at 37ºC for 17-18 hours.

2. Few colonies from the resulting bacterial growth were transferred to nutrient broth and incubated at 37ºC for 3 hours.

3. The optical density (OD) of resulting growth was adjusted to 0.045 at 580 nm, using spectrophotometer.

4. At OD of 0.045, the bacterial suspension of this organism comprised of approximately 10^7 CFU/ml, as determined by pour plate method of bacterial cell counting. This suspension was prepared daily and used to prepare seed layer. (Simon and Yin 1970)

Assay Plates: Assay plates were prepared by putting 25 ml of seed layer (Punch Method) of Medium No. 1. One ml of bacterial suspension containing 10^7 CFU was added to 10 ml of molten Medium No. 1. This suspension was used to prepare assay plates so that after incubation, the growth of bacteria gave clarity

and required dimensions of zone of inhibition with reference concentration of cefuroxime (0.625 mg ml^{-1}). Appropriate volume of bacterial suspension to be added for preparing seed layer was determined by conducting preliminary trials. Twenty five ml of media was added per plate and was allowed to solidify at room temperature.

Preparation of Standard Curve: The working standards solutions of cefuroxime containing known concentrations of drug in pooled plasma of goats not given any drugs were used to prepare standard curve for analysis of samples.

Assay of Samples: The plasma samples were thawed at room temperature. Three plates were used for each sample. One well on each plate was filled with reference concentration (0.625 mg ml^{-1}). The remaining three wells were filled with 50 µL of the samples. The plates were then incubated for 17-18 h at 37^{0}C. At the end of incubation, diameter of each zone of inhibition was measured using vernier calipers and the values for zone of inhibition were obtained. The drug concentrations in the test samples were calculated in mg ml^{-1} of plasma.

Effect of cefuroxime on the flora and fauna of rumen: Cefuroxime was administered orally at the dose rates of 40 mg/kg bodyweight. Rumen liquor was collected before the administration of drug and at 1 and 2.5 hours after administration of drug. The pH, color and consistency of the collected samples were recorded. Rumen protozoa count was done at under 10X magnification and the protozoa count was qualitatively expressed in a + to + + + + + grading scale. Bacterial count of rumen liquor was done using pour plate technique and anaerobic culture (Jackson and Cockcroft 2007).

Pharmacokinetic analysis: Different pharmacokinetic parameters were calculated according to the "method of residual yields" (Gibaldi and Perrier 1982) and dosage regimen of cefuroxime was calculated as per method suggested by Corvasier *et al* (1998) using T>MIC as the criterion.

Statistical analysis: The differences between the mean values of individual observations were determined by student's t test. The data were analyzed statistically using Instat Graphpad Software. Statistical analysis was done at 5 per cent and 10 per cent levels of significance.

RESULTS AND DISCUSSION

Pharmacokinetics after intravenous administration:

The mean plasma concentration of cefuroxime was 63.43 ± 4.7 µg ml^{-1} at 5 minutes which declined rapidly to 12.09 ± 0.91 µg ml^{-1} at 30 minutes and was not detectable after 120 minutes (Table 1).

The disposition curve is divided into distribution and elimination components, which is presented in Fig. 1 as least square regression lines. The pharmacokinetic mean values can be written in bi-exponential equation as:

$$Cp(t) = 95.14e^{-5.74t} + 12.88e^{-1.13t}.$$

Pharmacokinetic parameters which describe the distribution and elimination of cefuroxime in goats listed in Table 2. The distribution rate constant was 5.74 ± 0.48 h^{-1} (3.80 h^{-1} - 7.04 h^{-1}). The mean distribution half-life was 0.10 ± 0.01 h and elimination half-life was 0.67 ± 0.01 h. The K_{12} and K_{21}, which represent the rate of transfer of cefuroxime from central to peripheral compartment and from peripheral to central compartment were 1.02 ± 0.14 h^{-1} and 1.54 ± 0.22 h^{-1}, respectively. The drug was calculated to have volume of central

Table 1: Plasma concentration of cefuroxime in ìg.ml⁻¹ in goats following its single intravenous administration at the dose rate of 10 mg kg⁻¹ body weight.

Time in minutes	Mean ± SE
5	63.43 ± 4.7
10	48.16 ± 4.07
15	29.18 ± 2.05
20	19.69 ± 1.61
30	12.09 ± 0.91
40	8.14 ± 0.73
50	5.54 ± 0.81
60	3.75 ± 0.38
70	2.78 ± 0.19
80	1.96 ± 0.18
90	1.5 ± 0.07
100	1.23 ± 0.06
110	1.1 ± 0.02
120	Non detectable
150	Non detectable

compartment (V_c) and an apparent volume of distribution ($V_{d(area)}$) of 0.21 ±0.00 L Kg⁻¹ and 0.39 ±0.05 L Kg⁻¹, respectively. Total body clearance (Cl_B) which is sum of all excretory processes, area under curve (AUC) and ratio of drug concentration in peripheral and total duration of pharmacological effect were calculated to be 411.81 ±16.38 ml Kg⁻¹h⁻¹, 24.47 ±0.96 µg ml⁻¹h and 2.67 ±0.4 h respectively.

Dosage regimen of cefuroxime for microorganisms of different susceptibility is presented in Table 3.

Plasma cefuroxime concentrations could not be undetected following oral administrations at the dose rates of 10, 20, 40 mg.kg⁻¹. Following treatment of goats with Trikatu plasma levels of cefuroxime remained undetectable at all dose rates.

Effect of cefuroxime on the flora and fauna of rumen

The protozoa and bacterial levels in rumen of goats are presented in Table 4 and Table 5, respectively. Rumen pH was in the range of 6-7 in all the samples of rumen liquor taken before and after administration of drug. The color and

Table 2: Disposition kinetic values of cefuroxime following its single intravenous administration at 10 mg Kg⁻¹.

Parameter	Unit	MEAN ± SE	Parameter	Unit	MEAN ± SE
A	µg ml⁻¹	95.14 ± 12.38	K_{el}	h⁻¹	4.31 ± 0.39
α	h⁻¹	5.74 ± 0.48	K_{21}	h⁻¹	1.54 ± 0.22
B	µg ml⁻¹	9.96 ± 2.7	K_{12}	h⁻¹	1.02 ± 0.14
β	h⁻¹	1.13 ± 0.14	Vc	L Kg⁻¹	0.1 ± 0.01
$t_{1/2\alpha}$	h	0.13 ± 0.01	Vd (area)	L Kg⁻¹	0.39 ± 0.05
$t_{1/2\beta}$	h	0.67 ± 0.1	Cl_B	ml Kg⁻¹h⁻¹	411.81 ± 16.38
AUC	µg ml⁻¹h	24.47 ± 0.96	T/P	ratio	3.31 ± 0.86
AUMC	µg ml⁻¹h²	10.12 ± 0.7	MRT	h	0.41 ± 0.02
Cp⁰	µg ml⁻¹	105.09 ± 10.2	td	h	2.67 ± 0.4

**Table 3: Dosage regimen of cefuroxime for intravenous administration at the dose rate of 10mg.kg^{-1}.**

MIC in μg/ml	T>MIC hrs	Dosing interval hrs
0.625	2.67	6
1	2.22	6
2	1.55	4
3	1.16	3
4	0.88	2.5
5	0.66	1.5

consistency of the samples were also found to be similar.

Cefuroxime is used in treatment of infections of soft tissues (Barbour *et al.,* 2009), urogenital tract (Vazquez and Villar 2003), respiratory tract (Fiocchi *et al.,* 2009) and central nervous system (Halperine 2013) and ocular tissue infection (Garcia *et al.,* 2010) in human medicine. It is available for veterinary use in treatment of sub clinical mastitis in dry cows and for prevention of new infections during the dry period (Shelgren *et al.,* 2007). However it has not been extensively used in the treatment of systemic infections in animals.

In the present study microbial assay method with S*taphylococcus aureus* ATCC 6538 as the test organism, has been used for analysis of cefuroxime pharmacokinetics. Bioassay in addition to being less expensive is also reliable with respect to cefuroxime (Schmidt *et al.,* 2009). Bioassay studies on cefuroxime has also been conducted by using *Micrococcus luteus* (ATCC 9341) (Macedo *et al*., 2012) and *Bacillus subtillis* (ATCC 6633) (El-Sooud *et al.,* 2000)
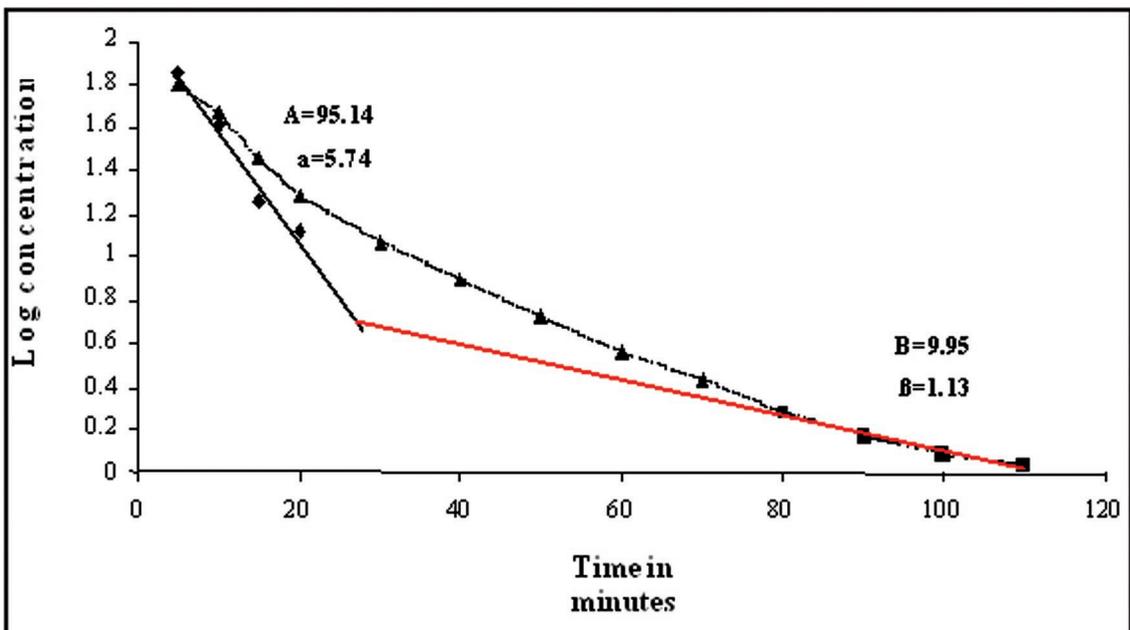
Fig. 1: Disposition curve depicting bi-exponential decline of plasma cefuroxime concentration in goats following single intravenous administration at the dose rate of 10mg.kg^{-1}.

Table 4: Qualitative protozoa count in rumen liquor of goats before and after administration of oral cefuroxime.

Time (h)	Animal number					
	1	2	3	4	5	6
0	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +
1	+ + +	+ +	+ + +	+ + +	+ + +	+ + +
2.5	+ + +	+ +	+ +	+ +	+ + +	+ + +

Table 5: Bacterial count (in 10^9) in rumen liquor of goats before and after administration of oral cefuroxime.

Time(h)	Animal number			Mean ± SE
	1	2	4	
0	45	48	83	58.67 ± 7.04
1	32	58	93	61 ± 10.2
2.5	116	47	72	78.33 ± 11.64

as test organism.

Pharmacokinetic study following intravenous administration of cefuroxime was done at the dose level 10 mg.kg^{-1}. Intravenous pharmacokinetics of this drug has been studied in goats (El-Sooud *et al.,* 2000), cow calves (Chaudhary *et al.,* 2001 and Soback *et al.,* 1989), buffalo calves (Chaudhary *et al.,* 1999). Maximum detectable plasma concentration were 63.43 ± 4.7 µg ml^{-1} following dosage at the rate of 10 mg.kg^{-1} in the present study. The duration for which the plasma concentrations remained above detectable levels was 110 minutes. However, Chaudhary *et al.,* (2001) reported a maximal obtainable concentration of 87.8 µg ml^{-1} in plasma and a detectable level of nearly 1 µg ml^{-1} up to 8 hours in cow calves which are in contrast with respect of duration of detectable drug concentration found in present study. In goats, plasma concentrations have been detected for longer periods by El-Sooud *et al* (2000). The distribution and elimination half-lives were found to be 0.13 ± 0.01 h and 0.67 ± 0.1 in the present study. In cow calves similar elimination half life following intravenous administration has been recorded (Soback *et al.,* 1989). In other studies in goats distribution and elimination half-lives of 0.25 h and 1.482 h at 20 mg.kg^{-1} dose level have been recorded (El-Sooud *et al.,* 2000). In cow calves distribution and elimination half lives of 0.064 h and 1.47 h at 10 mg.kg^{-1} dose level have been recorded (Chaudhary *et al.,* 2001). The variation in value of distribution and elimination half life in different studies suggests that variations in species, breed, and climatic conditions could have marked effect on pharmacokinetics of cefuroxime. The short distribution half life and faster elimination half life in the present study indicates that the drug has unique intravenous pharmacological features in Gaddi goats.

Disposition kinetics of cefuroxime was best fitted using two compartment open model after intravenous administration. This has also been observed in other studies in goats (El-Sooud *et al.,* 2000) and in normal cow calves (Chaudhary *et al.,* 2001) by intravenous route. Apparent volume of distribution ($V_{d(area)}$ which gives an estimate of the extent of distribution of drug in the body was found to be comparable to the value obtained by in cow calves (Chaudhary *et al.,* 2001). This suggests that the extent of protein binding in these two species is almost identical. In the present study AUC was found to be 24.47 ± 0.96 ìg ml^{-1}h. But in calves a higher AUC of 79.6 ìg ml^{-1}h has been reported by at 10 mg.kg^{-1} dose level (Chaudhary *et al.,* 2001). This difference might be due to the persistence of cefuroxime for a longer time in cow calves.

The total body clearance (CL_B) is an important pharmacokinetic parameter that represents the characteristics of drug elimination. High values of CL_B were obtained in the present study (411.81 ± 16.38 ml Kg^{-1}h^{-1} at 10 mg.Kg^{-1}) which is high in comparison to value in cow calves (266.9 ml Kg^{-1}h^{-1}) (Chaudhary *et al.,* 2001) suggesting that the drug is more rapidly cleared in goats.

MRT provides a mean estimate of the duration of persistence of the drug in the body. Mean residential time was found to be 0.41 ± 0.02 h. In studies by other workers MRT values were found to be much higher than this value (El-Sooud *et al.,* 2000, Chaudhary *et. al.,* 2001, Soback *et al.,* 1989). Such differences also indicate species and breed variation in the disposition kinetics of the drug.

Piperine present in trikatu has bio-enhancing effect on the absorption of a number of co-administered drugs such as Tetracycline, Rifampicin, Phenytoin, Pentobarbitone,

Nimesulide (Patil *et al.,* 2011). Trikatu has also been reported to enhance the bioavailability of antibiotic Pefloxacin in goats (Dama *et al.,* 2008). The mechanisms suggested for its bio-enhancing effect include enhanced blood flow due to gastrointestinal vasodilatations and reduced metabolism of the drug in its first passage after absorption (Kang *et al.,* 2009). Despite the reported bio-enhancing effects of Trikatu, in the present study it was observed that the oral absorption of cefuroxime in goats is almost negligible which remained unaffected by prior administration of Trikatu. The detectable concentration in the present studies could not be obtained despite increasing the dose of cefuroxime in geometric progression suggesting that possible vasodilatation caused by Trikatu might not be sufficient to compensate for first pass metabolism of cefuroxime axetil and the enzymes responsible for first pass metabolism in gastrointestinal tract of goats might not be targets of piperine.

The disposition kinetic values could not be calculated for want of detectable plasma concentrations at various time intervals. It has been reported that the absorption of cefuroxime from gut lumen is carrier mediated and obeys Michaelis-Menten equation (Mosher *et al.,* 1992). Moreover the extent of hydrolysis of cefuroxime axetil by the esterases in gut and blood might have a marked effect on the degree of absorption of cefuroxime axetil. It is thus apparent from the present studies that cefuroxime has got significant first pass metabolism in goats and lack of absorption could also be due the lack of a carrier in the gut of goats. Alternate methods such as Chitosan based intragastric delivery of cefuroxime axetil (Senel *et al.,* 2004, Nagar and Yadav 2012, Kanehara *et al.,* 1985) could be better in causing

enhanced absorption of the drug.

To determine the effect of cefuroxime on the microbes of rumen like rumen pH, color, consistency and protozoal and bacterial counts were evaluated before and after administration of cefuroxime axetil (40 mg kg^{-1}) by oral route. The effect of antibiotic, cefuroxime was further studied under *in vivo* conditions to know if the antibiotic has any detrimental effect on normal flora and fauna. However no significant difference was observed in these parameters before and after administration of drug. It is thus apparent that cefuroxime axetil does not have any antibacterial activity before its conversion to cefuroxime in the body (Harding *et al.,* 1984). Cefuroxime at the dose rate of 10 mg.kg^{-1} at 6 hourly intervals is likely to be effective against the highly susceptible bacteria when given intravenously.

CONCLUSION

Cefuroxime is rapidly distributed and rapidly eliminated following intravenous administration in Gaddi goats and its pharmacokinetic behavior following intravenous administration can be best described using two compartment open model. Cefuroxime axetil is not orally absorbed in goats even when administered after pre-treatment with trikatu and hence it may not be given orally. However Cefuroxime at the dose rate of 10 mg.kg^{-1} at 6 hourly intervals is likely to be effective against the highly susceptible bacteria when given by intravenous route.

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