RESEARCH ARTICLE

Pharmacokinetics of Cefquinome in Layer Birds Following Intramuscular and Intravenous Administration

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A B S T R A C T

Cefquinome is approved for use against many bacterial infections in a number of animal species. This study was conducted to evaluate the pharmacokinetics of Cefquinome after intramuscular (IM) and intravenous (IV) administration in layer birds for its safety evaluation. Twelve healthy layer birds were randomly allocated in two equal groups. Each group was administered with 5mg/kg b.w. of Cefquinome by intramuscular and intravenous routes. Highly sensitive high performance liquid chromatography with ultraviolet detection (HPLC-UV) method was developed for quantification of Cefquinome in layer bird's plasma with >80% recovery. The Limit of detection and quantification were 0.02 and 0.05µg/ml, respectively. The pharmacokinetic data showed that mean Area under the curve (AUC) after IM and IV administration were 7.838±0.165 and 11.729±0.346h×µg/ml, respectively. The maximum concentration (C_{max}) following IM administration (4.525±0.129 µg/ml) was almost same the mean C_{max} after IV administration (4.635±0.270µg/ml). Time to reach maximum concentration (T_{max}) after IV and IM administration were 0.1h and 0.5h, respectively. Cefquinome sulphate had a relatively shorter half-life (1.19±0.14h) after IV dose administration. The shorter half-life depicts a rapid elimination. Total recovery after each administration was greater than 75%. The mean resident time after IM and IV administration was found to be 1.528±0.09h and 1.988±0.0311h, respectively. The bioavailability after IM administration was 66.84±2.05%. This study indicated that Cefquinome sulphate has favorable pharmacokinetics following both administrations in healthy layer birds which can help to form optimum dosage regimes thus ultimately leading to its use for eradication of various systemic and local infections.

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INTRODUCTION

Cephalosporins are antibacterial agents that are active against many strains of Gram-positive and Gram-negative bacterial species. The key features of 4th generation cephalosporins include their wide range of spectrum, having resistance against degradation by β-lactamase enzymes and improved pharmacokinetic properties (Champawat *et al.,* 2018). Cefquinome is a new member of fourth generation injectable aminothiazolyl cephalosporin derivative. Globally, Cefquinome is approved for use against many bacterial infections in a lot of animal species (Shryock, 2004). Cefquinome is

developed for veterinary use and has been approved for many indications such as, respiratory tract diseases in equines and poultry; metritis-mastitis-aglactia syndrome, acute mastitis and foot rot disease (Limbert *et al.,* 1991). Cefquinome is stable against β-lactamase enzymes that are produced by various clinically significant bacteria (Dumka *et al.,* 2013). It is effective against the treatment of calf septicemia, foot rot in cattle, acute mastitis and pulmonary infections (Venkatachalam *et al.,* 2018).

Cefquinome has time dependent kinetics, the PK/PD model indicates the effectiveness of this drug is mostly related with the times the drug concentration in plasma surpass the MIC (minimum inhibitory concentration)

(Mckellar *et al.,* 2004). Therefore, the concentration of drug should be maintained above the MIC as long as possible during the dosing interval (T>MIC) for the best bactericidal effect (Derendorf and Meibohm 1999; Mckellar *et al.,* 2004; Owens and Ambrose 2007; Zonca *et al.,* 2011; Liu *et al.,* 2012).

The pharmacokinetic parameters of Cefquinome sulphate have been studied in several animals like; mice, ducks, horse, rabbits and cattle (Allan and Thomas 2003; Ehinger *et al.,* 2006; Li *et al.,* 2008; Al-Taher, 2010; Hwang *et al.,* 2011; Yuan *et al.,* 2011; Shan *et al.,* 2014; Ahmad *et al.,* 2015). Due to its zwitterions property, it possess good bioavailability and it can easily permeate into the cellular membranes (Guérin-Faublée *et al.,* 2003). Pharmacokinetic profile of Cefquinome revealed that it has poor absorption when administered orally; however, intramuscular and subcutaneous administration proceeds relatively quickly to C_{max} within 1.5-2 hours. Plasma protein binding is in the order of 5-15%. Plasma half-lives for Cefquinome are 1-2 hours in dogs and 1.5-3 hours in cattle. Only a small fraction of Cefquinome is metabolized. Excretion of Cefquinome is majorly by renal route (Uney *et al.,* 2018). In recent past, antimicrobial resistance against the available antibiotics was a significant problem in the treatment of life-threatening infections in veterinary. Therefore, the need for development of new generation antibiotics was emerged. Cefquinome being 4th generation cephalosporin was developed to cope up with the problem of antibiotic resistance. The spectrum of activity is very broad including *Staphylococcus aureus, Streptococci, Pseudomonas aeruginosa* and *enterobacteraceae* family i.e. *Escherichia coli, Salmonella species, Klebsilla species, Enetrobacter species, citobacter species* and *Serratiamarcescens.* Cefquinome is also active against methicillin-resistant bacterial strains including staphylococci and enterococci (Broens and van-Geijlswijk, 2018). Due to high prevalence of these bacterial infections in layer birds, this drug might be a good choice to use in poultry industry to reduce the economic loss due to highly resistant bacterial diseases.

For its effective clinical use in veterinary, its pharmacokinetics in different animal species must be known. The pharmacokinetic data of these studies provide a theoretical basis to access the rational clinical use of Cefquinome in equine and other animals. However, no data is available on bioavailability and pharmacokinetic properties of Cefquinome in layer birds. This study was designed to investigate the pharmacokinetics of Cefquinome in layer birds following IM and IV administration. These results could apply for assessment of efficacy, safety, and the suggestion of dosage regimens for clinical use in layers.

MATERIALS AND METHODS

Chemicals: Cefquinome sulphate 2.5% was imported from Shanghai Tongren Pharmaceutical Company Ltd. Cefquinome sulphate analytical standard was purchased from Sigma-Aldrich Co. LLC. Methanol and Acetonitrile were HPLC grade and purchased from Merck. Sodium di-hydrogen phosphate buffer was also procured from Merck. Purified water was obtained from university

Quality operation lab. All supplementary reagents used were of high analytical grade.

Animals: Twelve healthy layer birds with 16 weeks of age and 1.5-1.8kg weight were used in this study. These birds were kept in animal shed and fed with antibiotic free feed and water was available around the clock. All the procedures regarding use and care of laboratory animals were performed following university guidelines. All the ethical issues were according to the Institutional Guidelines of Ethical Review Committee No. DR/04, regarding the experimental use of layer birds were kept in consideration (Cristofol *et al.,* 2000).

Chromatographic conditions: An HPLC method was developed and validated for the quantification of Cefquinome sulphate in the plasma of layer birds. The HPLC separation was carried out by a reverse phase chromatography with analytical column of C18, 4.6x 250mm and 10µm dimensions. The mobile phase was consisted of a mixture of ACN (acetonitrile) and phosphate buffer in a ratio of 15:85 v/v and run at a flow rate of 1.0ml/min. The temperature of column was maintained at 25-30°C and the wavelength was set at 265nm.

Standard stock and working solution preparation: Stock solution was prepared (1000µg/ml) by dissolving 6.18mg of Cefquinome sulphate of analytical standard in 5ml of purified water. By diluting the stock solution, standard working solutions were prepared with different concentrations ranges of 0.05, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2 and 6.4µg/ml. Standard curves were plotted against the corresponding concentration of Cefquinome sulphate.

Method validation: The validation of HPLC method was performed according to the guidelines provided by FDA for appropriateness of the method for quantification of Cefquinome sulphate in the plasma of layer birds (Baber, 1994; Naidis and Turpeinen, 2009). First selectivity was checked by running concentration ranges 0.05-6.4µg/ml ensuring any endogenous interference at retention time. To obtain the linear relationship and standard curves, concentration of 0.05-6.4µg/ml were prepared for both spiked plasma and standard solution for three consecutive days. Correlation coefficient, intercept and slope of each standard curve were calculated based on least square regression method. Limit of detection (LOD) and limit of quantification (LOQ) were calculated based on signal-to noise ratio of 3:1and10:, respectively. Precision was calculated on basis of coefficient of variation (CV) and determined by preparing three different concentrations (1, 2 and 4LOQ) of spiked plasma and standard solution. Three sets of each concentration were run for intraday analysis while three replicates of each concentration were run for three consecutive days for inter-day analysis. Accuracy was calculated on the basis of recovery obtained by comparing the peak areas of spiked samples with that of peak areas of standard solution.

Sample preparation: Plasma samples were thawed for one hour followed by vortexing for 15sec. before extraction to ensure homogeneity. 500µl of plasma

aliquots were added in 350µl of methanol for deproteination and then vortexes for 15sec. The mixture was centrifuged at 10000 rpm for 10mins. An aliquot of the top layer was shifted to another Eppendorf tube, filter through syringe filters and transferred to HPLC vials. A 20µl of this was injected onto the column of HPLC system for analysis.

Pharmacokinetic study: For this study, the layer birds were arbitrarily distributed to 2 equal groups. One group was injected Cefquinome sulphate IM (intramuscularly) at a dose of 5mg/kg.b.w. While, 2nd group was injected intravenously at dose 5mg/kg b.w. Blood samples (1ml) were collected in heparin containing tubes from brachial vein of birds. Blood samples (1ml) were collected before (0 hours) and 0.25, 0.5,1, 2, 4, 6, 8, 12 and 24 hours following IM administration and at 0, 0.1,0.5,1, 2, 4, 6, 8, 12 and 24 hours following IV administration. The plasma were separated by centrifugation at 4000rpm for 10min. and stored at -20°C until analysis. Sample preparation was done and subjected to HPLC for analysis.

Data analysis: Plasma concentration v/s time data of Cefquinome sulphate was analyzed through non-compartmental model based on statistical moment theorem. Pharmacokinetic data were calculated using commercially available software (Win-Nolin 5.2.1, Pharsight Corp., CA, USA). Pharmacokinetics parameters such as maximum concentration of drug (C_{max}), Time to reach maximum concentration (T_{max}), clearance of drug, area under the plasma drug concentration time curve from zero to infinity ($AUC_{0-\infty}$), minimum resident time (MRT), half-life ($T_{1/2}$) of drug, were measured. The bioavailability and dose were calculated by using the following formulas.

F % = (AUC_{IM}x $Dose_{IV}$) / (AUC_{IV} x $Dose_{IM}$) x100
Dose = AUC (area under curve) × CI (clearance)

All the data were expressed as the mean±SD. All the descriptive statistical parameters such as Mean, Standard deviation were calculated using Microsoft Excel, 2010.

RESULTS

HPLC method validation
Selectivity: The selectivity of the method was proved by absence of interference at the retention time of Cefquinome sulphate. There was no peak observed in blank plasma samples while the spiked plasma showed peak at 6.84 minutes (Fig. 1).

Calibration curves and linearity: The calibration curves were linear over concentration ranges 0.05-6.4µg/ml for three consecutive days. The coefficient of determination (R^2) was found to be 0.999 for both standard and plasma samples (Table 1). The mean regression equation for Cefquinome sulphate was y= 37846x+10032.

Limit of detection and limit of quantification: The LOD and LOQ determined on the basis of signal to noise ratio 3:1 and 10:1. The Limit of detection and quantification were 0.02 and 0.05µgml^{-1}, respectively.
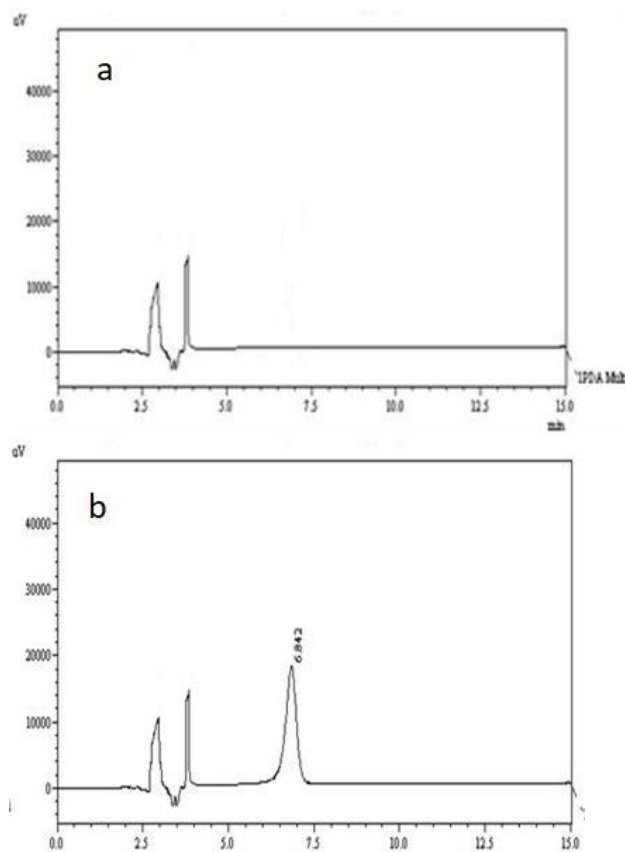

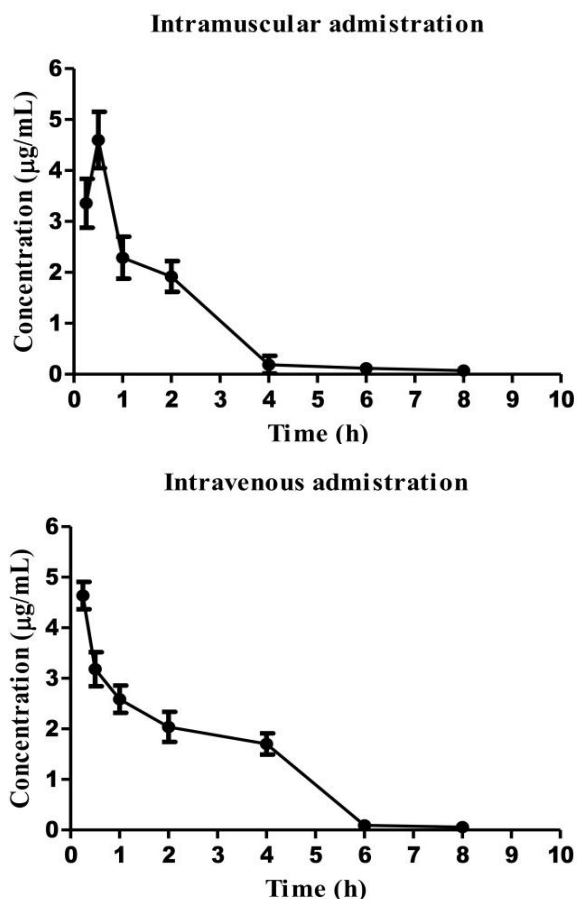**Fig. 1:** Chromatogram of blank plasma (a) and plasma spiked with Cefquinome sulphate @1µg/ml (b).

Fig 2: Plasma concentrations of Cefquinome sulphate at different time intervals following IM and IV administration in layer birds. (n=6)

Table 1: Calibration Curve and Regression data of Cefquinome in layer bird's plasma

Parameters	Plasma
LOD(µg/ml)	0.02
LOQ(µg/ml)	0.05
Linearity range(µg/ml)	0.05-6.4
Correlation coefficient	0.999
Slope	37846
Intercept	10032

LOD (Limit of Detection), LOQ (Limit of Quantification).

Recovery, precision and accuracy: For determination of precision and accuracy, three different concentrations 1LOQ, 2LOQ and 4LOQ were analyzed. The recovery of drug from spiked plasma was more than 78% for low, medium and high concentration. The intra-day Coefficient of variation (CV) was less than 10%, while inter-day CV% was less than 20% (Table 2).

Pharmacokinetics of cefquinome: The pharmacokinetics of Cefquinome in layer bird's plasma was evaluated after intramuscular and intravenous administration. Pharmacokinetic data were measured by a non-compartmental analysis. The plasma concentrations versus time profiles are illustrated in Fig. 2(a) and 2(b).

When the drug was administered by IM and IV routes, the highest concentration was observed after 30 min and 0.1h, respectively, and then the drug decreased gradually. After 8 hours, the drug concentration was observed below the LOQ. No adverse effects were observed after IM and IV administration. After IM administration, the elimination half-life of Cefquinome sulphate was 2.22h that show a rapid elimination following intramuscular administration of drug. The $AUC_{0-\infty}$ (area under the concentration time curve) was 7.837 ± 0.165h×µg/ml. The mean resident time was 1.528 ± 0.096h. After IV administration, the elimination half-life was 1.19 h and $AUC_{0-\infty}$ was 11.729 ± 0.346 h×µg/ml. The mean peak plasma concentration after the IM route is almost same as IV route 4.525 ± 0.128 and 4.635 ± 0.27µg/ml, respectively. Dose calculated following both IM and IV administration were 4.82 ± 0.003 and 4.94 ± 0.004mg/kg, respectively. The absolute bioavailability after IM administration was $66.84\pm2.05\%$. The estimated pharmacokinetic parameters after IM and IV administration are showed in Table 3.

DISCUSSION

Pharmacokinetics is proposed to study the ADME scheme that includes the absorption, the distribution, the metabolism and the elimination of drugs in man and animal. A single pharmacokinetic profile of a drug may be well compiled by C_{max}, T_{max}, $t_{1/2}$ and AUC evaluation (Urso et al., 2002).

This study was designed to evaluate the pharmacokinetic profile of Cefquinome sulphate, a 4th

generation Cephalosporin with enhanced activity against pathogenic bacteria including both zoonotic and commensals. Cefquinome is evolved solely for veterinary. It has better pharmacokinetic parameters like it absorbed quickly after intramuscular and intravenous administration, low MIC and reached to C_{max} very quickly. It is less toxic with a small amount of residues (Wang and Chen, 2004).These features make Cefquinome a better alternate for antibiotics against many bacterial infections.

An HPLC system that was highly sensitive and selective, utilized for pharmacokinetic analysis of Cefquinome in layers. Trials were performed using different mobile phase compositions, extraction method, pH effect, type of column to ensure the optimization conditions for proper separation and high resolution. The method was evaluated on the bases of several parameters i.e. LOD and LOQ, linearity, accuracy and precision. The method was found to be linear for a range of 0.05-6.4µg/ml having R^2 of 0.999 with LOD and LOQ of 0.02 and 0.05µg/ml, respectively in the plasma of layer bird. Recovery found to be greater than 78%.

Route of administration as well as formulation is important for kinetic studies. Therefore, intramuscular and intravenous routes of administration were selected for comparative pharmacokinetic study. Pharmacokinetic analysis was well described by non-compartmental analysis. Results showed that Cefquinome sulphate is quickly eliminated from plasma with a half-life of almost 60min after IV administration these results were quite similar to half-life of Cefquinome in ducks (Yuan et al., 2011). In comparison to other Cephalosporin, the elimination half-life of cefquinome in layers following IV administration was shorter (4.23 ± 0.05h) than that of ceftiofur in healthy chickens (Tell et al., 1998) and similar to half-life of ceftriaxone (0.60-1.40h) in broilers (Li et al., 1995).

Following IM administration of Cefquinome sulphate as single dose of 5mg/kg, the kinetic data was evaluated by a non-compartment analysis with first-order absorption, which has also been reported in young pigs given Cefquinome sulphate IV at a dose of 2mg/kg. The bioavailability of Cefquinome sulphate after intramuscular route is $66.84\pm2.05\%$. In the present case the lower bioavailability might be resulted due to flip-flop kinetics (Hwang et al., 2011). However, the absorption of Cefquinome sulphate following IM administration was rapid and nearly complete as mentioned in literature. The variation in bioavailability might be due to species difference.

Cefquinome sulphate had a relatively shorter half-life (1.19 ± 0.14h) after IV administration as compared to the half-lives of pigs, camel, horses, and piglets (2.32 ± 0.47, 10.24 ± 0.08, 2.77 ± 1.03, 1.85 ± 1.11h, respectively). The shorter half-life depicts a rapid elimination. The total body

Table 2: Recovery, intra-day and inter-day accuracy and precision of Cefquinome sulphate

Sample/Day	Concentration (0.05µg/ml)		Concentration (0.1µg/ml)		Concentration (0.2µg/ml)	
	Recovery (%)	Intraday CV (%)	Recovery (%)	Intraday CV (%)	Recovery (%)	Intraday CV (%)
1	81.73	4.33	79.29	4.62	78.54	4.91
2	79.91	5.23	80.86	4.04	82.43	2.47
3	80.71	6.00	78.60	3.2	82.82	2.71
Inter-day CV (%)	16.9		15.0		16.66	

Table 3: Pharmacokinetic parameters of Cefquinome after IM and IV administration in layer birds

Parameters	Units	Intramuscular dose 5mg/kg Mean± SD	Intravenous dose 5mg/kg Mean± SD
L_z	l/h	0.415 ±0.23	0.575±0.070
$T_{1/2}$		2.22±1.20	1.194±0.144
C_{max}	µg/ml.	4.525±0.129	4.635±0.270
$T_{max.}$	h	0.5	0.1
$AUC_{0-\infty}$	h×µg/ml.	7.838±0.165	11.729±0.346
Cl	L/h/Kg	0.616±0.02	0.421±0.012
V_z	L/Kg	1.954 ± 1.020	0.739 ± 0.088
MRT	h	1.528 ±0.09	1.988 ±0.0311
Dose	mg/kg.b.w.	4.82±0.003	4.94±0.004
F	%	66.84±2.05	--
V_{ss}	L/Kg	--	0.871± 0.034

L_z= elimination rate constant; $T_{1/2}$= elimination half-life; C_{max} = maximum concentration of drug; T_{max} = time to reach maximum conc.; $AUC_{0-\infty}$= area under plasma conc. - time from $0-\infty$; Cl = clearance rate; F= bioavailability; V_z = volume of distribution; V_{ss}= volume of distribution at steady state; MRT= mean resident time, Data are presented as Mean±SD.

clearance (Cl_B) of Cefquinome sulphate in layer birds (0.62±0.02L/h/kg) is comparable to the Cl_B of other animal species like ducks, sheep, and piglets but much higher than other animals, predicting a rapid clearance in small animals. The apparent volume of distribution (V_{ss}) is a measure of distribution of drug in the body tissues. The V_{ss} of Cefquinome sulphate is 0.87±0.03L/kg. The small value of V_{ss} illustrates the limited distribution of Cefquinome sulphate due to low lipid solubility. Time to reach the maximum concentration T_{max} after IV and IM administration was 0.1h & 0.5h, respectively, while other animal species showed a T_{max} of 0.25h-0.38h after IM administration. Relatively lower T_{max} and higher Cl_B demonstrate the rapid elimination of the drug in layer birds. C_{max} of Cefquinome sulphate in layers was observed as 4.52±0.13µg/ml that is almost similar to the C_{max} of 4.01µg/ml in piglets. While, C_{max} in ducks, piglets and pigs were found to be 9.38, 4.01 and 3.36µg/ml, respectively.

Clinically, the use of Cefquinome sulphate has not been applied to poultry yet. Only a few publications report that Cefquinome is effective against bacteria of poultry origin. The specific bacterial strains of poultry origin, such as chicken, were *E. coli* O78 and *Salmonella* strain C79-13 that were extremely sensitive to a lower serum concentration of Cefquinome. MICs (Minimum Inhibitory Concentration) of these strains were 0.063 and 0.25 mg/ml, respectively (Aarestrup *et al.,* 2010). *Pasturella multocida* strains isolated from poultry such as geese, ducks, chicken, turkeys and pheasants were susceptible to Cefquinome (Sellyei *et al.,* 2009). The current study showed that serum concentrations of Cefquinome sulphate in layer birds were higher than MIC for 3-4 hours following IV and IM route of administration at a dose of 5mg/kg b.w. For achieving favorable therapeutic activity of many cephalosporin, the time in which plasma levels remain above the MIC should be >40% of the dosing interval (Nie *et al.,* 2016). Hence, to keep the plasma concentration of Cefquinome sulphate above the MIC, 2-3 times repeated doses per day, might be suggested at a dosage of 5mg/kg.b.w. in layer birds. In present study, the dosages calculated are 4.82 and 4.94mg/kg.b.w. following IM and IV routes of administration respectively, suggesting that good therapeutic efficacy could be achieved at given dose.

The misuse and overuse of antibacterial drugs have also responsible for the resistance, because the bacteria are no longer sensitive to the available antibacterial (Zhang *et al.,* 2017). This prevailing antimicrobial resistance is a major hazard to human and animal health (Lan *et al.,* 2016). There is a dire need of new antibiotics having lesser side effects and having effect against many pathogenic organisms. Therefore, evaluation of pharmacokinetic profile of Cefquinome sulphate was necessary to design an optimum dosage regimen and to correlate the pharmacological actions with pharmacokinetics.

Conclusions: This study gives insight knowledge of the pharmacokinetic profile of Cefquinome sulphate which will not only improve our understanding about pharmacology and toxicology of this drug but also help us to design dosage regimen and comprehensively paved way to possible replacement of antibiotics extensively used in poultry and consequently abolishing the threat of antibiotic resistance in humans consuming chicken products.

Authors contribution: Conceived and designed the experiments: AS, MAH. Performed the experiments: RS, MA. Analyzed the data: AS, AJ. Contributed reagents/ materials/analysis tools: AG. Wrote the paper: AS, RS.

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