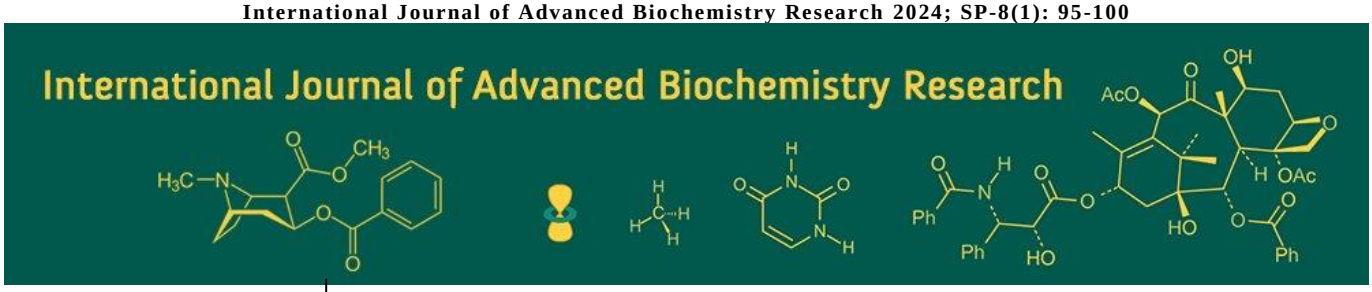

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Effect of meloxicam co-administration on pharmacokinetics of Cefquinome following intramuscular administration in dromedary camel (*Camelus dromedarius*)

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Abstract
The present study was planned to investigate the pharmacokinetics study of Cefquinome (a fourth generation cephalosporin) when administered intramuscularly at the dose rate of 1 mg.kg^{-1} body weight either alone and in combination with meloxicam (a NSAID) at the dose rate of 0.6 mg.kg^{-1} body weight in camel. Cefquinome concentrations in plasma were determined by HPLC Method. The plasma concentration-time profile of Cefquinome following intramuscular administration was best described by two-compartment open model. The peak plasma concentration ($C_{max\ cal.}$) of 1.013±0.038 µg.ml^{-1} was achieved at 5.257±0.067 h ($t_{max\ cal.}$). The absorption half-life ($t_{½ka}$), elimination half-life ($t_{½\beta}$), area under plasma drug concentration-time curve (AUC) and apparent volume of distribution (Vd_{area}) of Cefquinome were 3.401±0.042 h, 3.754±0.072 h, 14.417±0.621 µg.ml^{-1} h and 0.379±0.016 L.kg^{-1}, respectively. No significant alterations were observed in pharmacokinetic parameters of cefquinome in camel after meloxicam co-administration and therefore, dose regimen for cefquinome need not be altered when meloxicam is used in combination. Any adverse drug effects could not be detected in camel during or after single intramuscular co-administration of cefquinome with meloxicam for five consecutive days. Integration of pharmacokinetic data generated from the present study and minimum inhibitory concentration of common bacterial pathogens suggest that the cefquinome can be administered at the dose rate of 1 mg.kg^{-1} body weight through intramuscular route, either alone or in combination with meloxicam to combat susceptible bacterial infections in camel.

Keywords: Camel, cefquinome, meloxicam, intramuscular, pharmacokinetics, compartmental open model

Introduction
Non-steroidal anti-inflammatory drugs (NSAIDs) are extensively used to reduce inflammation and associated pain in rheumatic diseases and other disorders. Combinational use of antibiotics and NSAIDs is very common in veterinary practice to reduce inflammation and pain and to combat different bacterial infections efficiently (Deleforge *et al*., 1994) [6]. Meloxicam an enolic acid, Non-Steroidal Anti-inflammatory Drug, preferentially inhibits inducible enzyme cyclooxygenase-2 (COX-2) over cyclooxygenase-1 (COX-1) and has anti-inflammatory, analgesic and antipyretic activities (Euller-Ziegler *et al.*, 2001) [10]. It is quite effective in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and other rheumatological conditions. Other advantages include no effect on platelet aggregation or renal prostaglandin synthesis, sparing action on COX-1 and low ulcerogenic potential (Engelhardt *et al*., 1996; Alencar *et al*., 2002) [9, 2]. These attributes make it an ideal and suitable NSAID for use in animals (Busch *et al*., 1998). Meloxicam has also been reported to be effective in pain management in camel in osteoarthirits or post-operative cases (Flower *et al*., 2014; Jenna and Sahoo, 2014) [11, 12]. However, meloxicam can alter the pharmacokinetics of certain antibiotics like gatifloxacin and ceftizoxime when administered simultaneously (Dumka *et al.*, 2010; Ranjan *et al*., 2011) [10, 18]. So, The present research aimed to investigate the pharmacokinetic study of cefquinome (a fourth generation cephalosporin) when administered intramuscularly at the dose rate of 1 mg.kg^{-1} body weight either alone and in combination with meloxicam (a NSAID) at the dose rate of 0.6 mg.kg^{-1} body weight in camel.

Materials and Methods

Animals and Experimental Protocol

The study was carried out in five apparently healthy male dromedary camels in the age group of 3 to 4 years, weighing in between 400-450 kg. The experimental animals were kept under constant observation for two weeks prior to the experiment at National Research Centre on Camel, Bikaner, Rajasthan and examined periodically to exclude any possibility of localized or systemic disease. The animals were maintained under an intensive system of management and fed daily with guar (*Cyamopsis tetragonoloba*) meal (mixture of 30-33% hull, 27-30% endosperm, and 43-47% germ) and groundnut (*Arachis hypogaea*) haulms. The experimental protocol was approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Govt. of India (F. No. 25/19/2018-CPCSEA, Dated 22.11.2018). The ethical standards and guidelines of CPCSEA were followed throughout the experiment.

Cefquinome sulphate (Cobactan 2.5% MSD Animal Health, Pune, India) when administered intramuscularly at the dose rate of 1 mg.kg^{-1} body weight either alone (phase I) and in combination with Meloxicam injection (Melonex®; 0.5%, Intas Pharmaceuticals Limited, Ahmedabad, India) at the dose rate of 0.6 mg.kg^{-1} body weight either along (phase II) in the caudal cervical epiaxial muscles located in the lower neck region after aseptic preparation of the injection site. Blood samples were collected in heparinized test tubes, immediately before administration of cefquinome alone (Phase I) or cefquinome and meloxicam (Phase II) (0h) and at 0.25, 0.5, 1.0, 2, 4, 6, 8, 10, 12, 24, 36 and 48 h after administration of the drug (s). Plasma was separated from the collected blood samples by centrifugation at 3000 rpm for 15 minutes at 4 °C and stored at -80 °C till analysis.

Analytical procedure

Cefquinome concentrations in plasma samples were determined using high performance liquid chromatography (HPLC) as per the method described by Uney *et al.* (2011) [21]. Briefly, 200 µl of plasma sample was mixed with 400 µl of methanol in a 2-ml microcentrifuge tube and vortexed for 10 seconds. The resultant mixture was centrifuged at 4000 g for 10 min, 300 µl of clear supernatant was filtered into a fresh vial and 150 µl of HPLC grade water was added and mixed for 10 seconds. The mixed clear supernatant (200 µl) was pipetted into an autosampler vial.

The HPLC system (Perkin Elmer, series 200, Waltham, USA) was fitted with a single pump, a degasser and an autosampler injector. The reverse-phase chromatography was performed with an analytic C_{18} column (Sun fire, Particle size 5µ, 4.6 X 150 mm, Waters, USA). In present method, binary gradient mobile phase was used with water containing 0.1% trifluroacetic acid (Sigma-Aldrich) as mobile phase A and acetonitrile (Sigma-Aldrich) as mobile phase B. The gradient elution was programmed with the ratio of mobile phases A: B as 90: 10 for 7 min, followed by 50: 50 for 3 min and 90:10 for 5 min. The injection volume was kept 50µl and flow rate was maintained as 0.9 ml.min^{-1}. The detection was performed using a UV/VIS detector set at 268 nm. The Total Chrom software (version 6.1) was used for running the HPLC system and data analysis. The retention time of cefquinome was about 6.48 min and calibration curve for cefquinome was linear at concentrations of 0.05-50 µg/ ml with correlation coefficients (r) above 0.996. The limit of detection (LOD) and limit of quantification (LOQ) were determined by signal-to-noise ratio evaluations of samples spiked from 0.01 to 0.1 µg/ml. The LOD and LOQ of cefquinome were determined to be 0.02 µg/ml and 0.04 µg/ml, respectively and were based on a signal-to-noise ratio of 3:1. The accuracy % for intra and inter day assay were found above 90% and above 95%, respectively. The recoveries of the three different concentration 0.4 µg/ml, 6.25 µg/ml, 25 µg/ml were found to be 93.32%, 89.56% and 95.51%, respectively within the day analysis and 91.16%, 88.39% and 95.03%, respectively between the day analysis.

Pharmacokinetic analysis

The appropriate pharmacokinetic model was determined by visual examination of plasma cefquinome concentration versus time curves and different pharmacokinetic parameters were calculated by PK Solver: An Add in Programme for Microsoft Excel, Version 2 (Zhang *et al.*, 2010) [23]. The pharmacokinetic variables obtained were expressed as mean ± S.E.

Results and Discussion

Intramuscular administration of cefquinome at the rate of 1 mg per kg body weight appeared safe as no clinical signs suggestive of adverse effects or drug intolerance was evident in any camel. The mean plasma drug concentration-time curve for cefquinome in dromedary camel following its single intramuscular administration is depicted in Fig 1. The plasma cefquinome concentrations could be detected up to 36 h in the collected samples, but at 48h, it could not be detected.

After concurrent intramuscular administration of cefquinome and meloxicam at the rate of 0.6 mg.kg^{-1} body weight, The mean plasma drug concentration-time curve for cefquinome along meloxicam in dromedary camel following its single intramuscular administration is depicted in Fig 2, the drug concentration decreased gradually there after to reach a level at 36 h. No drug could be detected in plasma samples collected after 48 h in all animals. The value of different pharmacokinetic parameters obtained are presented in Table 1.

The present study was to determine any possible alterations in the pharmacokinetic parameters of cefquinome after meloxicam co-administration in camel. The comparison of mean ± SE values of various pharmacokinetic parameters is depicted in table 1. The values were analysed statistically applying Student's t-test using SPSS.

Mean ± SE values of absorption ($T_{1/2ka}$) and elimination ($T_{1/2\beta}$) half-life were 3.555±0.111 h and 3.622±0.020 h, respectively. The values of area under the plasma drug concentration versus time curve $(AUC)_{0\text{-}t}$, area under the first moment curve (AUMC) and apparent volume of distribution (Vd_{area}) were 12.425±0.068 µg/ml*h, 127.456±1.210 µg/ml*h^2 and 0.472±0.003 L/kg respectively. The mean residence time (MRT) was 10.187±0.053 h and apparent total body clearance was 0.077±0.003 (mg/kg)/ (µg/ml)/h respectively.

Mean values of A, B, $C_{max\ (cal)}$, $AUC_{0\text{-}t,}$ $AUC_{0\text{-}inf}$ and AUMC differed significantly (p<0.05) in between the two groups. However, the majority of vital pharmacokinetic parameters did not show any significant difference in between the cefquinome alone and with meloxicam co-treated groups.

In the present study, a generalized trend of lower plasma drug concentration at different observation period was recorded in animals co-treated with meloxicam in comparison to those receiving cefquinome alone. Calculated value of mean peak plasma cefquinome concentration (C_{max}) of animals co-treated with meloxicam was significantly lower in comparison to those receiving cefquinome alone. It is widely assumed that most of NSAIDs compete with antibiotics in plasma protein binding sites leading to increase in free antibiotic concentration in plasma (Ranjan *et al*., 2011) [18]. Hence, it is a novel finding that warrants further investigation. Perusal of available literature did not reveal any report on pharmacokinetic interaction of antibiotics with meloxicam in camel; hence results of the present study could not be compared. Variable activities of drug-metabolizing enzymes and peculiar ability to biotransform and eliminate xenobiotics in camel in comparison to other animal species may be a possible reason behind this observation (Alquarawi and Ali, 2000) [3]. Meloxicam has also been reported to have different pharmacokinetic behavior and metabolic pattern in camel in comparison to other domestic animals (Wasfi *et al*., 2011) [22]. Cefquinome chemistry and its interaction with meloxicam may be another possible reason behind this observation. In goat, C_{max} of cefquinome was reported to decrease, albeit non-significantly following co-administration of flunixin (Champawat *et al.*, 2018) [5] which supports results of the present study. Likewise, co-administration of meloxicam failed to produce any significant alteration in C_{max} of cefquinome in goat (Tiwari *et al*., 2015) [20]. However, peak plasma drug concentration (C_{max}) of cefquinome was reported to increase significantly following co-administration of tolfenamic acid in sheep (Rana *et al*., 2015) [17]. There are several reports documenting meloxicam co-treatment results into increase in peak plasma concentration of different antibiotics like ceftizoxime in febrile sheep (Ranjan *et al*., 2011) [18] and ofloxacin in yak and cattle (Ahmed *et al*., 2015) [1].

In the present study, disposition kinetics of cefquinome along with meloxicam was described by two compartment open model. Following intramuscular administration of cefquinome with meloxicam in camel, most of the pharmacokinetic parameters did not alter significantly in comparison to the animals receiving cefquinome alone, except A (zero-time intercept of distribution phase), B (zero-time intercept of elimination phase), $C_{max\ (cal.)}$ (maximum plasma drug concentration), AUC_{0-t} (area under plasma drug concentration versus time curve) AUC_{0-inf} (area under plasma drug concentration versus time curve to infinity) and AUMC (area under the first moment curve). Similar observations were also recorded by Champawat *et al*., (2018) [5] in goat after co-administration of flunixin with cefquinome, which supported findings of the present study.

The absorption half-life ($t_{1/2ka}$) of cefquinome in camel co-treated with meloxicam was 3.555±0.111 h which was almost similar to $t_{1/2ka}$ in camel receiving cefquinome alone (3.401±0.042 h), indicating no significant effect of meloxicam on the absorption of cefquinome after intramuscular administration in camel. Similarly, no significant alteration was observed in absorption half-life ($t_{1/2ka}$) of cefquinome (0.15±0.01h to 0.16±0.01 h) in goat when co-administered with meloxicam (Tiwari *et al*., 2015) [20] which was in support to the present study. Likewise, Champawat *et al*., (2018) [5] also recorded no significant alteration in $t_{1/2ka}$ of cefquinome in goat following co-administration of flunixin. There are several reports documenting no effect of NSAIDs on absorption half-life of different antibiotics like flunixin on cefepime in goat (El-Hewaity, 2014) [8], Ketoprofen on Cefepime in goat (Patel *et al*., 2012a) [14] Ketoprofen on cefepime in cow calf (Patil *et al.,* 2012) [16] and paracetamol on ceftriaxone in cattle calf (Singh *et al*., 2008) [19]. All these findings supported the result of the present study. On the contrary, significant decrease in $t_{1/2ka}$ values of different antibiotics was reported after co-administration of NSAIDs, for example ceftriaxone with paracetamol in goat (Jimoh *et al*., 2011) [13] and cefquinome with flunixin in sheep (Rana *et al*., 2015) [17]. But, significant increase $t_{1/2ka}$ value of cefepime was reported in sheep when co-administered with ketoprofen (Patel *et al*., 2012b) [15].

The elimination half-life ($t_{1/2\beta}$) of cefquinome co-administered with meloxicam in camel was found 3.622±0.020 h, which is lower, albeit non-significantly than camel receiving cefquinome alone (3.754±0.072 h). In goat, $t_{1/2\beta}$ of cefquinome was reported to decrease following co-administration with meloxicam (1.75±0.08 h vs 1.60±0.05 h; Tiwari *et al*., 2015) [20] which further supported findings of the present study. Changes in value of elimination half-life of cefquinome appear to vary after NSAIDs co-administration. In a study, $t_{1/2\beta}$ of cefquinome did not alter significantly, albeit values decreased (12.29±2.62 h vs9.00±0.51 h) after co-administration of tolfenamic acid in goat (Rana *et al*., 2015) [17]. Likewise, no significant alteration in $t_{1/2\beta}$ of cefepime was found after ketoprofen co-administration (5.32±0.32 h vs 5.13±0.27 h) in goat (Patel *et al.,* 2012a) [14]. On the contrary, Champawat *et al*., (2018) [5] recorded increase in $t_{1/2\beta}$ of cefquinome following co-administration of flunixin in goat. Significant increase in the value of $t_{1/2\beta}$ of ceftizoxime was also reported in cross bred calves after paracetamol co-administration (4.08±0.54 h) in comparison to those given ceftizoxime alone (1.44±0.12 h) by Singh *et al*., (2008) [19]. Paracetamol co-administration has also been reported to increase $t_{1/2\beta}$ of ceftriaxone (5.34±1.85 h vs 0.58±0.012 h) in goat (Jimoh *et al.* 2011) [13].

The area under the curve (AUC) $_{0-t}$ of cefquinome when co-administered with meloxicam (12.425±0.068 µg/ml*h) was significantly lower in comparison to camel receiving cefquinome alone (14.417±0.621 µg/ml*h). In corroboration of the present study, Champawat *et al*., (2018) [5] also recorded non-significant decrease in AUC (14.44±0.82 to 13.67±0.57 µg/ml*h) following flunixin co-administration in goat. Likewise, Jimoh *et al.* (2011) [13] reported lower value of AUC in goats when ceftriaxone co-administered with paracetamol (42.14±2.11 µg ml^{-1}*h) in comparison to ceftriaxone given alone (144.10±1.71 µg ml^{-1}*h). However, AUC of cefquinome evidenced non-significant increase after tolfenamic co-administration in goat (Rana *et al*., 2015; 16.65±0.57 to17.52±0.14 µg/ml*h) [17] and after meloxicam co-administration in goat (Tiwari *et al*., 2015; 17.16±0.42 to 18.49±0.74 µg/ml*h) [20]. AUC of some other cephalosprins has been reported to increase non-significantly following NSAIDs co-administration, for example AUC of cefepime after ketoprofen co-administration in goat (Patel *et al*., 2012a) [14] and sheep (Patel *et al*., 2012b) [15] and AUC of ceftizoxime after paracetamol co-administration in calve (Singh *et al*., 2008) [19].

The area under the first moment curve (AUMC) of cefquinome when co-administered with meloxicam in camel was (127.456±1.210 µg ml^{-1} h^2) which is significantly lower than AUMC observed in cefquinome alone (154.028±8.188 µg ml^{-1} h^2) administered camel. Champawat *et al*., (2018) [5] observed non-significant decrease in AUMC of cefquinome after co-administration of flunixin in goat which supported findings of the current study. In corroboration to the present observation, significant decrease in AUMC of ceftriaxone in goat was noted after co-administration with paracetamol (313.50±6.156 µg ml^{-1} h^2 to 167.14±54.34 µg ml^{-1} h^2; Jimoh *et al*., 2011) [13]. However, no significant alteration was noted in AUMC of cefquinome in goat when co-administered with the meloxicam (Tiwari *et al*., 2015) [20]. Non-significant alteration in AUMC was also reported in calves when cefepime was co-administered with ketoprofen (338.77±23.35µg $ml^{-1}h^2$) in comparison to cefepime given alone (367.26±36.00µg ml^{-1} h^2)(Patil *et al.,* 2012) [16]. Patel *et al.,* (2012b) [15] also reported no significant alteration in AUMC of cefepime in sheep after ketoprofen co-administration.

Mean residence time (MRT) of cefquinome when co-administered with meloxicam in camel (10.187±0.053 h) was non-significantly lower than those calculated in camel receiving cefquinome alone (10.569±0.155 h). In corroboration to the present finding, Champawat *et al*. (2018) [5] recorded non-significant decrease in MRT of cefquinome in goat after flunixin co-administration (2.64±0.07 h to 2.56±0.36 h). Likewise, non-significant decrease in the MRT of cefquinome in goat was noted after meloxicam co-treatment (2.44±0.06 to 2.25±0.05 h; Tiwari *et al.,* 2015) [20]. Rana *et al*. (2015) [17] also recorded non-significant decrease in MRT of cefquinome in sheep after tolfenamic acid co-administration. No significant alteration in MRT of other cephalosporins after NSAIDs co-administration have been reported in other animal species, for example cefepime with ketoprofen in calve (Patil *et al*., 2012) [16], cefepime with ketoprofen in sheep (Patel *et al*., 2012b) [15] and goat (Patel *et al*., 2012a) [14].

The apparent volume of distribution (Vd_{area}) of cefquinome increased, albeit non-significantly after meloxicam co-administration in camel. Champawat *et al*., (2018) [5] also recorded significant (p<0.01) increase in Vd_{area} of cefquinome after flunixin co-administration in goat (0.29±0.02 L/kg to 0.42±0.04 L/kg), which supported findings of the present study. Contrary to the present observation, meloxicam co-administration was also reported to increase the Vd_{area} of ceftizoxime in sheep (Ranjan *et al*., 2011) [18]. Likewise, Jimoh *et al*., (2011) [13] reported significant decrease in volume of distribution of ceftriaxone when co-administered with paracetamol in goat, while no significant alteration was reported after ketoprofen co-administration by Patel *et al*. (2012a) [14]. Rana *et al.* (2015) [17] also reported non-significant decrease in volume of distribution of cefquinome after tolfenamic co-administration (2.07±0.36 L kg^{-1} to 1.48±0.08 L kg^{-1}) in sheep.

The present study showed that no significant alteration in major pharmacokinetics parameters of cefquinome were observed following its co-administration with meloxicam in camel. so, meloxicam at the rate of 0.6 mg/ kg body weight intramuscularly can be successfully co-administration with cefquinome at the dose rate of 1 mg/ kg body weight intramuscular for combating bacterial infections with an inflammatory condition in camel. meloxicam co-administred with cefquinome in camel, cause no alteration in most of the pharmacokinetics parameters of cefquinome. In the present study, plasma cefquinome levels above the MIC were maintained >24 h following single intramuscular administration of cefquinome. Therefore, a dose rate of 1 mg/kg at 24 h dosing interval may be recommended for intramuscular administration of cefquinome in camel.

Table 1: Values (mean ± S.E.) of different pharmacokinetic parameters following its single intramuscular injection (@1mg/ kg body weight) alone and along with meloxicam (@ 0.6 mg/kg body weight) in camel

Parameter	Unit	Cefquinome alone	Cefquinome with meloxicam
A	µg/ml	17.887±4.196	30.170±1.700*
Alpha	1/h	0.176±0.006	0.191±0.001
B	µg/ml	8.809±1.923	15.435±0.610*
Beta	1/h	0.185±0.003	0.191±0.001
K_a	1/h	0.204±0.002	0.202±0.001
$T_{1/2\ alpha}$	H	3.965±0.144	3.626±0.019
$T_{1/2\ beta}$	H	3.754±0.072	3.622±0.020
$T_{1/2ka}$	H	3.401±0.042	3.555±0.111
CL/F	(mg/kg)/(µg/ml)/h	0.069±0.003	0.077±0.003
$T_{max(cal)}$	H	5.257±0.067	5.091±0.026
$C_{max(cal)}$	µg/ml	1.013±0.038*	0.905±0.005
AUC_{0-t}	µg/ml*h	14.417±0.621*	12.425±0.068
AUC_{0-inf}	µg/ml*h	14.548±0.633*	12.499±0.075
AUMC	µg/ml*h^2	154.028±8.188*	127.456±1.210
MRT	H	10.569±0.155	10.187±0.053
Vd area	L/kg	0.379±0.016	0.421±0.003

A, zero time intercept of the least square regression line of the absorption phase; B, zero time intercept of the least square regression line of the elimination phase, α and β, distribution and elimination rate constants; K_a, first order rate constant; $T_{1/2\alpha}$ and $T_{1/2\beta}$, distribution and elimination half-life; $T_{1/2ka}$, absorption half-life; CL/F, body clearance corrected for bioavailability; $T_{max\ (cal)}$, the time point of maximum plasma concentration; $C_{max(cal)}$, maximum plasma drug concentration; $AUC_{0-t}$and AUC_{0-inf}, area under plasma drug concentration vs time curve to 36 h and to infinity; AUMC, area under the first moment curve; MRT, mean residence time; Vd_{area}, apparent volume of distribution of drug

*: Significant at p< 0.05; NS: Non-significant

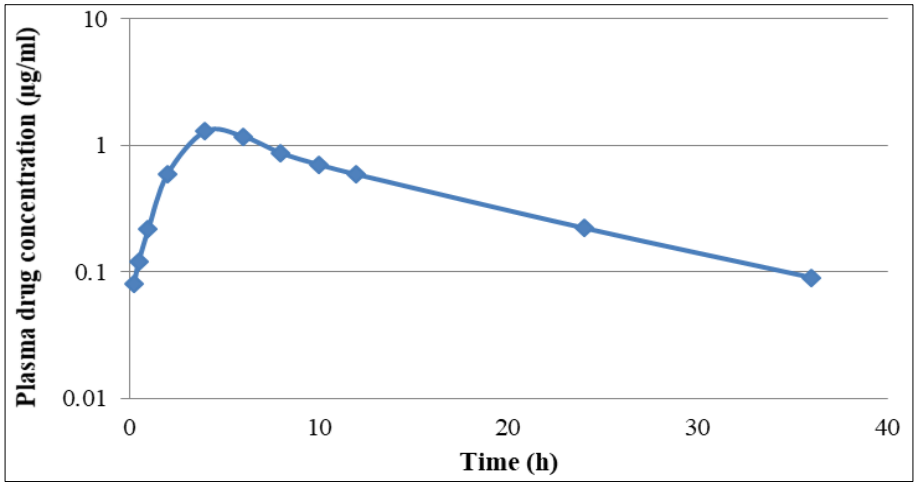


Fig 1: A semi logarithmic plot of plasma cefquinome conc. after single intramuscular administration of cefquinome @ 1 mg/ kg body weight in dromedary camel

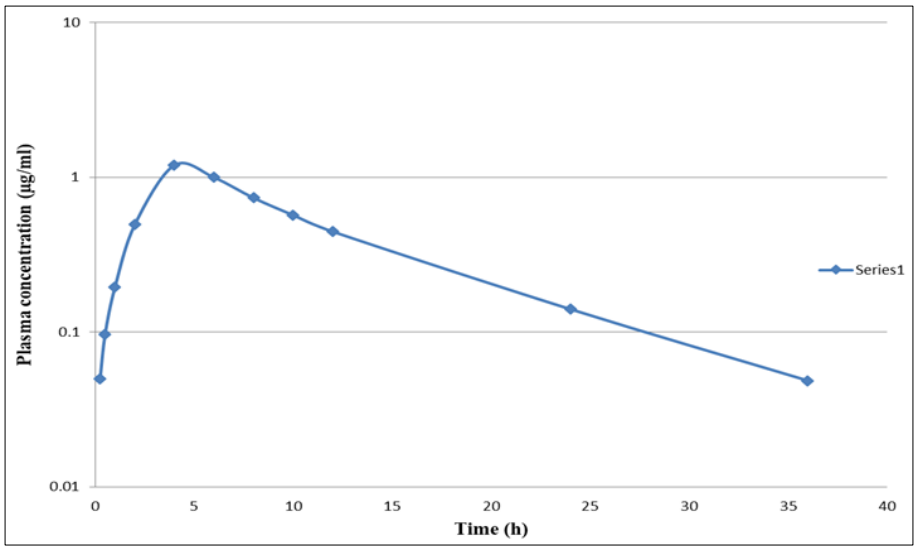
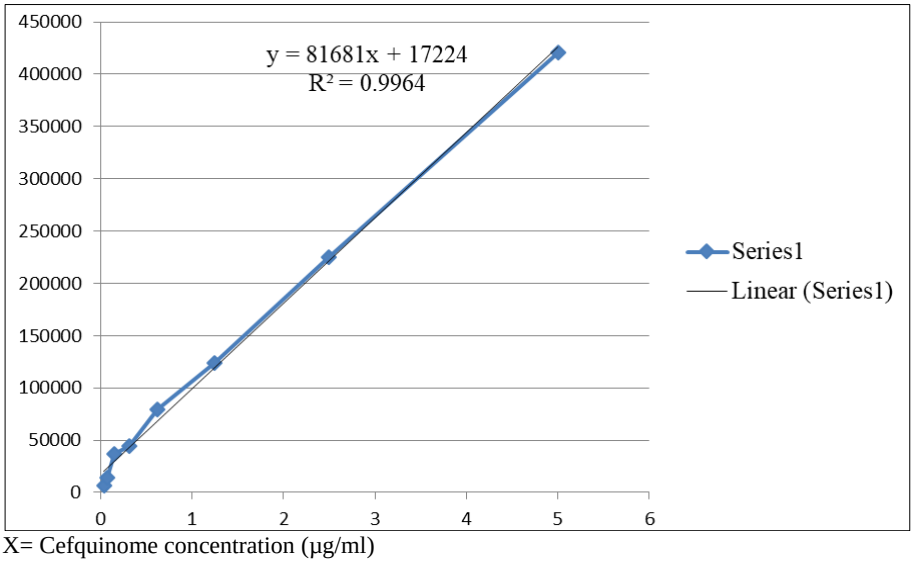


Fig 2: A semi logarithmic plot of plasma cefquinome conc. after single intramuscular administration of cefquinome @ 1 mg/ kg and meloxicam @ 0.6 mg/kg body weight in dromedary camel



X= Cefquinome concentration (µg/ml)
Y = Peak area (mAU)

Fig 3: Calibration curve of cefquinome in camel plasma

Conclusion

The study revealed that the therapeutically effective level of cefquinome in camel blood is maintained for more than 24h. Co-administration of meloxicam at the rate of 0.6 mg/ kg body weight q24h does not have significant effect on pharmacokinetic parameters of cefquinome in camel.

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