

Pharmacokinetic of Cefquinome After Single I.V Administration Alone and Concurrent with Meloxicam in Goats

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**ABSTRACT:**

The active profile of cefquinome in goats was concentrated after single intravenous organization of cefquinome alone and single intravenous organizations in goats pretreated with meloxicam at a portion of 2 mg/kg b.wt. Serum groupings of cefquinome were dictated by utilizing superior fluid chromatography (HPLC). Following compartmental examination, a two-compartment open model best portrayed the fixation time information of cefquinome after i.v. organization. The outcomes uncovered that after a solitary intravenous injection, cefquinome was distinguished till 24 hours, dispersion half-life ( $t_{1/2\alpha}$ ) of cefquinome was  $0.281 \pm 0.055$  h, elimination half-life ( $t_{1/2\beta}$ ) was of  $5.46 \pm 0.22$  h and clearance (CL) was  $0.04 \pm 0.0013$  (L/kg/h), volume of distribution at steady state ( $V_{dss}$ ) was  $0.31 \pm 0.018$  (L/kg). Following a single intravenous injection pretreated with meloxicam, distribution half-life ( $t_{1/2\alpha}$ ) was  $0.227 \pm 0.07$  h, elimination half-life ( $t_{1/2\beta}$ ) was of  $3.63 \pm 0.055$  h and clearance (CL) was  $0.056 \pm 0.0022$  (L/kg/h), volume of distribution at steady state ( $V_{dss}$ ) was  $0.296 \pm 0.0163$  (L/kg). From this examination, we inferred that organization of meloxicam (0.2 mg/kg b.wt.) may be successfully co-administrated with cefquinome (2 mg/kg b.wt.) for combating bacterial infections with an inflammatory condition in goats without any antagonistic effect on the kinetics of cefquinome.

**Keywords:** Cefquinome – Goats – Meloxicam.

**INTRODUCTION**

Cephalosporins are a class of  $\beta$ -lactam antibiotics obtained from the *Cephalosporium acremonium* fungus. Cephalosporins were categorized into five generations according to their chronological growth sequence. New generation cephalosporins came to overcome bacteria-producing resistant  $\beta$ -lactamases and are distinguished by widespread range against several microorganisms. The advantage of the beta lactam antibiotics is high degree of safety in the target animal.

Cefquinome is the first fourth generation cephalosporin antibiotic developed for use in veterinary medicine and is highly stable to beta-lactamases, that could be produced by most of important clinical pathogens. (Yuan *et al.*, 2011; Zhou *et al.*, 2015). It has broad spectrum

activity against most of gram positive and gram-negative bacteria. Its mechanism is disrupting the synthesis of the peptidoglycan layer forming the bacterial cell wall. It had been approved for treatment of many diseases such as respiratory diseases, mastitis and foot rot in cattle. Binding plasma protein plays a vital role in drug distribution, elimination, and therapeutic efficiency by reducing renal excretion. It is used in estimating the effectiveness of the drug. Pharmacokinetic studies had been previously published in mice, calves, pigs, piglets, ducks, rabbits and camels following IV and IM administration (Li *et al.*, 2008; Al-Taher, 2010; Hwang *et al.*, 2011; Yuan *et al.*, 2011; Zhou *et al.*, 2015).

Non-Steroidal Anti-inflammatory Drugs (NSAIDs) are widely used for the management of pain, fever and inflammation,

particularly arthritis (Tariq Ali *et al.*, 2012). Meloxicam is one of these non-steroidal anti-inflammatory drugs that might be given with antimicrobial. Meloxicam has a plasma half-life of approximately 20 hours, making it convenient for once-daily administration. Meloxicam is eliminated after biotransformation to 4 pharmacologically inactive metabolites, which are excreted in urine and faeces. Meloxicam and its metabolites bind extensively to plasma albumin. Substantial concentrations of meloxicam are attained in synovial fluid, the proposed site of action in chronic inflammatory arthropathies (Davies and skjodt 1999).

Antimicrobials and NSAIDs are used mostly in multiple drug prescription. Coadministration of drugs results in either enhancing the action against bacteria or increasing toxic effect.

The aim of this study was to estimate the pharmacokinetic parameters of cefquinome after single i.v of cefquinome at adose of (2mg/kg b.wt) alone and after concurrent administration of cefquinome with (0.2mg/kg b.wt) of meloxicam (nonsteroidal anti-inflammatory drugs).

## MATERIAL AND METHODS

### 1- Materials

#### Drug

Cefquinome was obtained from Intervet International Company, Cairo, Egypt, under a trade name: Cobactan 2.5% and meloxicam (nonsteroidal anti-inflammatory drugs) Under trade name (mobitol®) from MUP.

#### Animals

Ten clinically normal goats were used in this study. The tested goats weighting 20-33 kg and 30-36-month-old were used. they were housed in hygienic stables and were fed on concentrated ration, barseem and water was provided *ad-libitum*. The goats were divided into two equal groups.

### 2- Methods

#### 2.1. Experimental design

##### Experiment (1):-

The first group was injected intravenously into the left jugular vein with a single dose 2mg /kg.b.wt of cefquinome alone (El-Hewaity *et al.*, 2014).

##### Experiment (2):-

The second group was given 0.2 mg/kg b.wt meloxicam (Tiwari *et al.*, 2015) by single intravenous injection, followed immediately by

2 mg/kg b.wt cefquinome by single intravenous injection.

#### 2.2. Blood samples:

After intravenous injection, blood samples (0.5 to 1 ml) were gathered through the contrary jugular vein of every goat in first and second analyses at 5, 15 and 30 minutes and 1, 2, 4, 8, 12- and 24-hours post-injection. All blood samples were left to clot; the clear sera were separated by centrifugation of samples at 3000 r.p.m for 15 minutes. The serum samples were put away in clean plastic Eppendorf's tubes at -20° C in fridge until examined.

#### 2.3 HPLC ASSAY:

##### A) Assay of cefquinome in blood:

Cefquinome was assayed in serum by HPLC method according to (Uney *et al.*, 2011). This method for the quantification of the total concentration of cefquinome involved a deproteinization of the plasma and a back-extraction of acetonitrile with dichloromethane. 400 µl of acetonitrile was added to 200 µl of plasma for deproteinization and vortex – mixed. After centrifugation of the samples for 10 minutes at 10000 g, the supernatant was brought into a new Eppendorf vial. Then 600 µl of dichloromethane was added. After vortex-mixing for 15 seconds, the samples were again centrifuged at 10000 g, for 10 minutes. The top layer was transferred into an auto sampler vial condition of High-Performance Liquid Chromatography (HPLC). The mobile phase consistence and chromatographic conditions are carried out according to (Li *et al.*, 2008). The mobile phase was filtered and degassed. The injection volume of samples was 20 µl, the flow rate was fixed at 1.0 ml/min, column temperature was 30° C and the ultra violet detector wavelength was set at 268 nm.

##### B) Pharmacokinetic analysis:

The two-compartment open model provided the best fit to the data in all goats. and the estimation of the model-dependent pharmacokinetic parameters were made with the help of a computerized curve- stripping program (R-strip, Micromath Scientific Software, Salt Lake City, UT, USA). Analyses were run for each data set independently.

The pharmacokinetic parameters were calculated according to Baggot (1978).

#### 2.4. Statistical analysis:

Information got in this investigation were statically examined for fluctuation (Combined examples T test) with certainty limits set as 95% (noteworthiness at  $p \leq 0.05$  likelihood

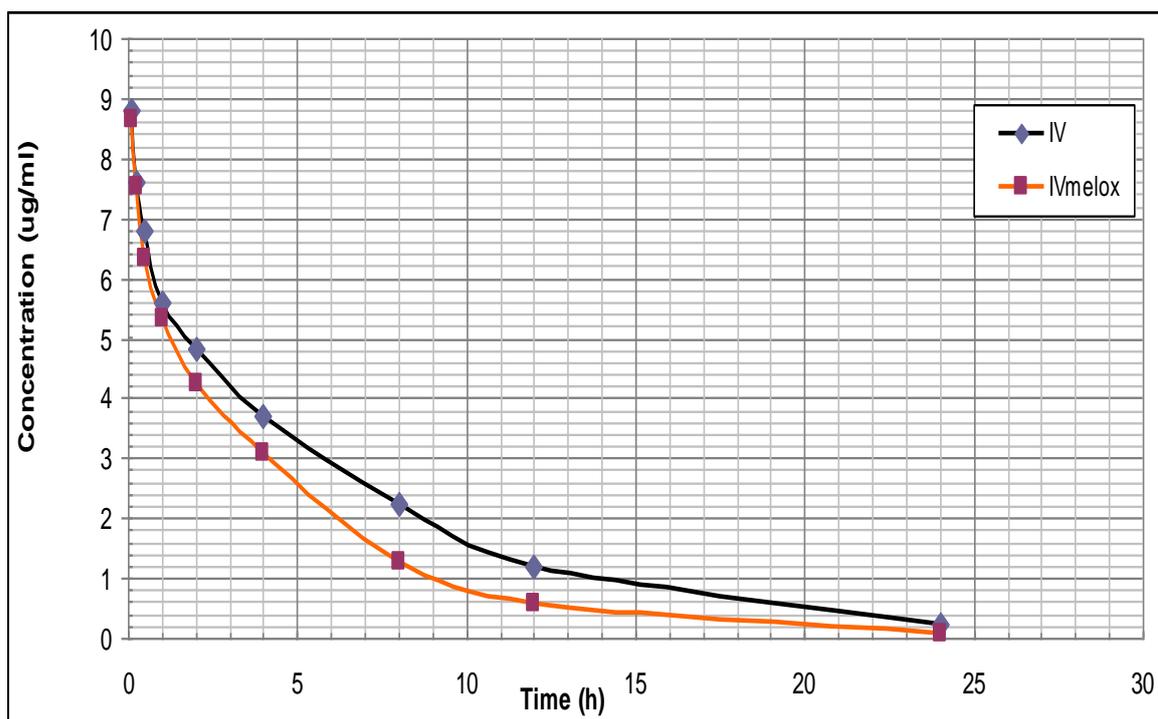
level). The results were determined as mean  $\pm$  standard mistake. All measurable examination was done by Snedecor (1969)

## RESULTS

No clinical indications of enemy impacts or narrow mindedness were seen to cefquinome after IV injection. Semilogarithmic chart outlining the time movement of Cefquinome ( $2\mu\text{g/ml}$  b.wt.) in serum after a single intravenous injection alone at a dose rate of  $2\text{mg/kg}$  b.wt and concurrent with ( $0.2\text{mg/kg}$ .b.wt) of meloxicam in goats. Figures (1). These data are best fitted to a two-compartment open model. The initial serum drug concentration following IV injection was  $9.43$  and  $9.56$   $\text{mg/mL}$  in cefquinome alone and co-administered with meloxicam, respectively, and was recognized previously. Mean  $\pm$ SE pharmacokinetics parameters of cefquinome after single intravenous administration of  $2.2$   $\text{mg}$  cefquinome/kg b.wt alone and co-administrated with meloxicam ( $0.2\text{mg/kg}$  b.wt) are abridged in Tables (1).

Following IV injection of cefquinome alone and in combination with meloxicam, there are no huge changes in the pharmacokinetic parameters. The area under serum concentration-time curve  $\text{AUC}_{(0-\text{inf})}$  was significantly decreased ( $\text{AUC}_{(0-\text{inf})}$ ,  $35.7 \pm 1.314$   $\mu\text{g.h/ml}$ ) in meloxicam pretreated goats compared to that of control goats ( $\text{AUC}_{(0-\text{inf})}$ ,  $50.26 \pm 1.51$   $\mu\text{g.h/ml}$ ).

The calculated values of volume of distribution of the central compartment ( $V_c$ ), the apparent volume of distribution of peripheral compartment ( $V_\beta$ ), the total body clearance ( $\text{Cl}_{\text{tot}}$ ) and the volume of distribution at steady state ( $V_{d_{\text{ss}}}$ ) were significantly unchanged in meloxicam pretreated goats compared to that of control goats. they were recorded in meloxicam pretreated goats as ( $V_c \rightarrow 0.211 \pm 0.005$  L.kg,  $V_\beta \rightarrow 0.34 \pm 0.0163$  L.kg,  $\text{Cl}_{\text{tot}} \rightarrow 0.05 \pm 0.002$  L.kg,  $V_{d_{\text{ss}}} \rightarrow 0.296 \pm 0.0098$  L.kg). and recorded in control goats as ( $V_c \rightarrow 0.33 \pm 0.014$  L.kg,  $V_\beta \rightarrow 0.34 \pm 0.0143$  L.kg,  $\text{Cl}_{\text{tot}} \rightarrow 0.04 \pm 0.013$  L.kg,  $V_{d_{\text{ss}}} \rightarrow 0.31 \pm 0.018$  L.kg).



**Fig. 1.** Semilogarithmic graph illustrating the time progression of Cefquinome ( $2\mu\text{g/ml}$  b.wt.) in serum after a single intravenous injection alone at a dose rate of  $2\text{mg/kg}$  b.wt and concurrent with meloxicam ( $0.2\text{mg/kg}$ .b.wt).in goats (  $n = 5$ ).

Mean $\pm$ SE Pharmacokinetic Parameters of Cefquinome			
Parameters	Units	i.v	
		cefquinome alone	cefquinome + meloxicam
C <sub>0</sub>	mg/ml	9.43 $\pm$ 0.145	9.56 $\pm$ 0.171
$\alpha$	h <sup>-1</sup>	2.78 $\pm$ 0.392	3.276 $\pm$ 0.453
$\beta$	h <sup>-1</sup>	0.131 $\pm$ 0.005	0.191 $\pm$ 0.003
t <sub>0.5(<math>\alpha</math>)</sub>	h	0.281 $\pm$ 0.055	0.227 $\pm$ 0.027
t <sub>0.5(<math>\beta</math>)</sub>	h	5.46 $\pm$ 0.221	3.63 $\pm$ 0.0554
k <sub>12</sub>	h <sup>-1</sup>	1.07 $\pm$ 0.161	1.254 $\pm$ 0.186
k <sub>21</sub>	h <sup>-1</sup>	1.84 $\pm$ 0.426	2.213 $\pm$ 0.291
V <sub>d(area)</sub>	L/kg	0.21 $\pm$ 0.003	0.318 $\pm$ 0.0092
V <sub>dss</sub>	L/kg	0.31 $\pm$ 0.18	0.296 $\pm$ 0.0098
AUC	mg.h/ml	50.26 $\pm$ 1.51	35.7 $\pm$ 1.314
Cl <sub>tot</sub>	L/kg/h	0.04 $\pm$ 0.0013	0.0564 $\pm$ 0.0022
MRT	h	7.54 $\pm$ 0.317	5.078 $\pm$ 0.085

**Table 1.** Mean  $\pm$ SE pharmacokinetics parameters of cefquinome after single intravenous administration of 2.2mg cefquinome/kg b.wt alone and co-administrated with meloxicam(0.2mg/kg b.wt) (n=5).

## DISCUSSION

Following a single intravenous administration, the half-life of distribution ( $T_{1/2\alpha}$ ) was extremely short ( $0.281 \pm 0.055$ h) in goats injected with cefquinome in a single dose of 2 mg/kg. The distribution half-life of cefquinome is intently like that recently detailed in broiler chickens ( $0.155$  h, Maha, 2005), healthy piglets ( $0.27 \pm 0.21$ h Li *et al.*, 2008), healthy ducks ( $0.196 \pm 0.05$ h Yuan *et al.*, 2011), Beagle dogs ( $0.12 \pm 0.05$ h Zhou *et al.*, 2015) and wild boar ( $0.22 \pm 0.04$ h LIU *et al.*, 2011). Longer half-life of distribution was recorded for cefquinome in chickens ( $0.768 \pm 0.023$  h El Sayed *et al.*, 2015), sheep ( $1.49 \pm 0.06$ h Corum *et al.*, 2019) and goats ( $1.17 \pm 0.22$ h Dumka *et al.*, 2013).

The volume of distribution ( $V_{dss}$ ) in our examination ( $.31 \pm .018$  L/Kg) is firmly identified with cefquinome that recently detailed in wild boars ( $0.31 \pm 0.03$ L/kg, Liu *et al.*, 2011), sheep ( $0.28 \pm 0.01$ L/Kg, Corum *et al.*, 2019), Beagle dogs ( $0.30 \pm 0.03$ L/Kg, Zhou *et al.*, 2015) and goats ( $0.32 \pm 0.01$ L/Kg, SAgar *et al.*, 2015). What's more, was not like that recorded in chickens ( $0.389 \pm 20.65$  L/Kg, EL Sayed *et al.*, 2015), goats ( $0.21 \pm 0.03$ L/Kg, Dumka *et al.*, 2013), Rabbits ( $0.21 \pm 0.03$ L/Kg, Hwang *et al.*, 2011), Piglets ( $0.46 \pm 0.10$ L/Kg, Li *et al.*, 2008), and Ducks ( $0.41 \pm 0.04$ L/Kg, Yuan *et al.*, 2011).

The area under the concentration time curve from 0 to infinity ( $AUC_{(0-\infty)}$ ) of cefquinome in our examination ( $50.26 \pm 1.51$   $\mu$ g.h/ml). it is like that detailed in chickens ( $41.24 \pm 1.40$   $\mu$ g.h/ml, EL Sayed *et al.*, 2015), goats ( $43.57 \pm 1.31$   $\mu$ g.h/ml, Sagar *et al.*, 2015), goats ( $33.83$

$\pm 2.53$   $\mu$ g.h/ml, Dumka *et al.*, 2013) and Ducks ( $25.12 \pm 2.31$   $\mu$ g.h/ml, Yuan *et al.*, 2011). What's more, not like that recorded in Wild boars ( $13.85 \pm 2.57$   $\mu$ g.h/ml, Liu *et al.*, 2011), Sheep ( $16.05 \pm 0.37$   $\mu$ g.h/ml, Corum *et al.*, 2019), Rabbits ( $11.08 \pm 4.06$   $\mu$ g.h/ml, Hwang *et al.*, 2011), Piglets ( $8.07 \pm 1.91$   $\mu$ g.h/ml, LI *et al.*, 2008) and Beagle dogs ( $8.51 \pm 1.27$   $\mu$ g.h/ml, Zhou *et al.*, 2015).

The half-life elimination ( $T_{1/2(\beta)}$ ) of cefquinome after single i.v administration ( $5.46 \pm .221$  h) is concurred with that announced in in Goats ( $5.76 \pm 0.19$  h Dumka *et al.*, 2013), Goats ( $6.21 \pm 0.51$ h, Sager *et al.*, 2015) and chickens ( $4.92$  h, Maha, 2005), And couldn't help contradicting that detailed in chickens ( $1.29 \pm 0.10$  h, Xie *et al.*, 2013), healthy ducks ( $1.57 \pm 0.06$  h, Yuan *et al.*, 2011), chickens ( $0.712 \pm 0.050$  h, El Sayed *et al.*, 2015), healthy piglets ( $1.85 \pm 1.11$  h, Li *et al.*, 2008) and wild boars ( $1.64 \pm 0.42$ h Liu *et al.*, 2011).

The total body clearance (CL) of cefquinome following a single i.v administration in the present study is ( $.04 \pm .0013$  L/Kg/h), this got outcome was concurred with that recorded in Chickens ( $0.048 \pm 0.002$  L/Kg/h, El Sayed *et al.*, 2015), Goats ( $0.04 \pm 0.001$  L Kg/h, Sager *et al.*, 2015) and goats ( $0.06 \pm 0.004$  L/Kg/h, Dumka *et al.*, 2013). Furthermore, couldn't help contradicting that recorded in Wild boars ( $0.15 \pm 0.03$  mg/kg/h, Liu *et al.*, 2011), Sheep ( $0.16 \pm 0.00$  L/kg/h, Corum *et al.*, 2019), Rabbits ( $0.18 \pm 0.05$  L/kg/h, Hwang *et al.*, 2011), piglets ( $0.26 \pm 0.08$  L/kg/h, Li *et al.*, 2008), healthy ducks ( $0.22 \pm 0.02$  L/kg/h, Yuan *et al.*, 2011) and beagle dogs ( $0.24 \pm 0.03$  L/kg/h, Zhou *et al.*, 2015).

Following i.v administration of meloxicam (0.2mg/kg b.wt) concurrent with cefquinome. in our study the distribution half time ( $T_{1/2(\alpha)}$ ) was ( $0.227 \pm 0.027$ h) it concurred with of cefepime (10 mg/kg b.w.) in combination with flunixin (2.2 mg/kg b.wt.IM) following a single intravenous injection in goats ( $T_{1/2(\alpha)}$   $0.20 \pm 0.003$ h, EL Hewaity, 2014).

The volume of distribution ( $V_{dss}$ ) was ( $.296 \pm .0098$  L/kg). this result agreed with of ceftiofur in cattle after a single intravenous administration dose of (2mg/kg b.wt) ceftiofur sodium preceded by a single intravenous administration dose of (26 mg/kg b.wt) acetyl salicylate (aspirin) that was (0.253 L/kg Whitem *et al.*, 1995). and not agreed with of cefepime (10 mg/kg b.w.) in combination with flunixin (2.2 mg/kg b.wt. IM) following a single intravenous injection in goats ( $V_{dss}$   $0.47 \pm 0.04$ L/kg, EL Hewaity, 2014).

The area under the concentration-time curve from 0 to infinity ( $AUC_{(0-\infty)}$ ) was ( $35.7 \pm 1.314$   $\mu$ g/h/ml). And disagreed with ceftiofur in cattle after a single intravenous bolus dose of (2mg/kg b.wt) ceftiofur sodium preceded by a single intravenous bolus dose of (26 mg/kg b.wt) acetyl salicylate (aspirin) that was (63.8 mg/h/L. Whitem *et al.*, 1995).

The elimination half-life in our study was ( $t_{1/2el}$   $3.63 \pm .0554$ h). Compared with other cephalosporins. it agreed with of cefepime (10 mg/kg b.w.) in combination with flunixin (2.2 mg/kg b.wt. IM) following a single intravenous injection in goats ( $t_{1/2el}$   $3.50 \pm 0.23$ h, EL Hewaity, 2014). And not agreed with ceftiofur in cattle after a single intravenous bolus dose of (2mg/kg b.wt) ceftiofur sodium preceded by a single intravenous bolus dose of (26 mg/kg b.wt) acetyl salicylate (aspirin) that was recorded (9.10h, Whitem *et al.*, 1995).

The variation between the value calculated for pharmacokinetic parameters can be related to the species of animal, chemistry of the drug used, the sex, size or age of the animals, discrepancies in deposits of fatty tissue between breeds or species of animals, and inter-individual variations, as well as the drug analysis method.

Following intravenous administration cefquinome (2mg/kg b.wt) in goats either alone or concurrent with meloxicam. no adverse effects or toxic manifestations were observed. The pharmacokinetic parameters of cefquinome in meloxicam pretreated goats not

alarmed altogether contrasted and in goats given cefquinome alone except elimination half time and area under curve. pharmacokinetic parameters of ceftiofur were unchanged following concurrent with acetyl salicylate (aspirin) in cattle which support results of our study.

## CONCLUSION

It can be concluded that administration of meloxicam (0.2 mg/kg b.wt.) may be successfully and efficiently co-administrated intravenously or intramuscularly with cefquinome (2 mg/kg b.wt.) for combating bacterial infections with an inflammatory condition in goats without any antagonistic action.

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