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Original Research Article

Pharmacokinetics of cefquinome in goats after intramuscular administration alone and with meloxicam

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ABSTRACT

Background: Nonsteroidal anti-inflammatory drugs and antibiotics are commonly prescribed together. We aimed to study the kinetic profile of cefquinome (2 mg/kg b.wt.) following intramuscular administration of it alone and co-administered with meloxicam (0.2 mg/kg b.wt.) in goats.

Methods: Five Egyptian Baladi goats, each goat was injected intramuscularly at the dose rate of 2 mg/kg b.wt. Cefquinome into the deep gluteal muscle of hindquarter alone and then after fifteen days washout period, these animals also injected intramuscularly at the dose rate of 2 mg/kg b.wt. Cefquinome preceded with meloxicam at the dose rate of 0.2 mg/kg b.wt. The serum concentrations of cefquinome were detected by high performance liquid chromatography, two compartment model.

Results: Following a single dose intramuscular administration of cefquinome alone, peak plasma concentration (1.71 ± 0.0189 µg/ml) was obtained at 1.59 ± 0.0038 h. The absorption half-life ($t_{1/2ab}$), total body clearance (Cl_{tot}), elimination half-life ($t_{1/2el}$) and area under curve (area under concentration ($AUC_{(0-inf)}$) of cefquinome were 0.4 ± 0.0028 h, 0.068 ± 0.78 l/h/kg, 9.21 ± 0.178 h and 29.36 ± 0.78 µg.h.ml⁻¹, respectively. Following a single dose intramuscular co-administration of cefquinome and meloxicam, peak plasma concentration (1.60 ± 0.0124 µg/ml) was obtained at 1.49 ± 0.0092 h. The absorption half-life ($t_{1/2ab}$), total body clearance (Cl_{tot}), elimination half-life ($t_{1/2el}$) and area under curve ($AUC_{(0-inf)}$) of cefquinome were 0.396 ± 0.006 h, 0.094 ± 0.25 l/h/kg, 6.5 ± 0.221 h and 21.38 ± 0.696 µg/h/ml, respectively. Non significant alters were reported in the parameters following co-administration of Cefquinome with meloxicam.

Conclusions: From our results, may be concluded that intramuscular administration of meloxicam may be successfully co-administrated with cefquinome for combating bacterial infections with an inflammatory condition in goats without any antagonistic effect.

Keywords: Kinetic, Cefquinome, Meloxicam, Intramuscular, Goats

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) and antimicrobials are commonly prescribed together for the treatment of infectious diseases in goats.^{1,2}

Cefquinome is a β-lactam antibiotic of the cephalosporin class (a fourth generation cephalosporin). It has a broad spectrum of activity against both gram-positive and gram-negative bacteria, including *Actinobacillus pleuropneumoniae*, *Haemophilus spp.*, *Actinobacillus spp.*, *Corynebacterium*, *Erysipelothrix rhusiopathiae*,

Clostridium spp., *Streptococcus spp.* and *Pasteurella spp.* The shape of the Cefquinome molecule tends to facilitate distribution in treated animals and passage through bacterial cell walls, resulting in rapid bactericidal effect by inhibition to cell wall formation. It also increased resistant against inactivation by bacteria that produce β -lactamase enzyme.^{2,3} Fourth-generation cephalosporins are zwitterions that can penetrate the outer membrane of Gram-negative bacteria. They have a greater intolerance to β -lactamases than the third-generation cephalosporins. Many can cross the blood-brain barrier and are effective in meningitis.⁴

Meloxicam is a member of the oxycam group of NSAIDs whose mode of action may be related to inhibition of COX enzyme and it has anti-inflammatory, analgesic and antipyretic activities.⁵

Taking into consideration the above facts, this study was done in order to investigate pharmacokinetic parameters of cefquinome alone and co-administration between cefquinome and meloxicam after intramuscular injection in goats.

METHODS

Drugs

Cefquinome: It was obtained from Intervet International Company, Cairo, Egypt, under a trade name of (Cobactan 2.5%).

Meloxicam: It was obtained from Medical Union Pharmaceuticals (MUP) company, Egypt as injectable solution under a trade name of (Mobitil 15 mg/1.5 ml ampoule).

Animals

The experiment was performed on five Egyptian Baladi goats of 1-2 years of age and weighing between 15 to 22 kg. The animals were housed in separate pens and provided standard ration with *ad libitum* water. Goats were kept under observation for two weeks before the experiment and put under clinical examination to exclude the probability of any diseases. The experiment was performed in accordance with the guidelines set by the Ethical Committee of Sadat city University, Egypt.

Experimental design

Each goat was injected intramuscularly at the dose rate of 2 mg/kg b.wt. cefquinome (cobactan 2.5%) into the deep gluteal muscle of hindquarter alone and then after fifteen days washout period, these animals also injected intramuscularly at the dose rate of 2 mg/kg b.wt. Cefquinome preceded with meloxicam at the dose rate of 0.2 mg/kg b.wt.^{2,6,7}

Blood samples

Blood samples (2 ml) were collected after intramuscular injection of Cefquinome alone at (0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 h post administration and after concurrent intramuscular injection of Cefquinome (2 mg/kg b.wt.) and meloxicam (0.2 mg/kg b.wt.) at (0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 h post administration. All blood samples were left to clot for 30 min., centrifuged at 3000 rpm for 15 min. and the obtained clear sera were transferred to eppendorf's tubes and kept at -20 C°. Samples were analyzed to quantify Cefquinome concentration using high performance liquid chromatographic (HPLC).

Analytical analysis

Serum concentrations of cefquinome were determined using a HPLC method. Sample analysis, solutions and HPLC.⁸ 0.5 ml of serum or supernatant of tissues was added to 3 ml of acetonitrile in centrifugation tubes and was mixed for 1 min by vortex, samples was centrifuged at 3000 rpm for 20 min, then the supernatant was transferred to other centrifuge tube and was evaporated under nitrogen flow to dryness, then 150 μ l of mobile phase and 400 μ l of hexane was added to dry sample and mixed for 1 min by vortex, samples were centrifuged at 3000 rpm for 20 min, the supernatant was discarded and 50 μ l was injected to HPLC.⁹

Pharmacokinetic analysis

Serum concentrations of cefquinome versus time curve were generated, and best fitted by the aid of computer poly-exponential curve stripping program, (R-Strip Micromath, software, USA). Data from each goat was fitted individually and the pharmacokinetic variables were computed by the aid of the software programs. The hybrid rate constants of the distribution and elimination phase (α and β), the first order absorption and elimination rate constants (K_{ab} and K_{el}), corresponding extrapolated zero time intercepts (A and B), absorption, distribution & elimination half-lives ($t_{0.5ab}$, $t_{0.5\alpha}$, $t_{0.5\beta}$, $t_{0.5el}$), transfer rate constants (K_{12} and K_{21}), the area under the curve from zero to infinite time area under concentration ($AUC_{0-\infty}$), mean residence time (MRT), maximum serum concentration (C_{max}) and time to be achieved (T_{max}) were calculated. The other pharmacokinetic parameters as total body clearance, the volume of the central compartment (V_c), the volume of distribution at steady state (V_{dss}) were calculated.¹⁰ The results were expressed as mean (\pm) SE and the obtained data statistically using student "t" test.¹¹

RESULTS

Single intramuscular administration of cefquinome alone

The serum cefquinome concentrations following its single intramuscular administration of 2 mg/kg b.wt. were recorded in Table 1. Cefquinome was firstly detected in

serum 10 minutes following its intramuscular administration with a mean value of (0.95±0.11 µg/ml). The mean peak serum level (1.96±0.026 µg/ml) achieved 2 hour post intramuscular administration. The drug was still detected in a concentration of (0.53±0.017 µg/ml) at 24 hours in serum of goats.

Table 1: Mean serum concentration (µg/ml) of cefquinome in goats after a single intramuscular administration.

Time (h)	Groups (X±S.E.)	
	Cef. I.M	Cef. I.M±melox.
0.083	0.95±0.011	0.75±0.018
0.25	1.21±0.011	1.05±0.019
0.5	1.32±0.015	1.24±0.018
1	1.65±0.0181	1.52±0.017
2	1.96±0.026	1.81±0.014
4	1.31±0.015	1.12±0.018
8	0.98±0.0195	0.75±0.021
12	0.79±0.018	0.58±0.014
24	0.53±0.017	0.38±0.019

Mean serum concentration (µg/ml) of cefquinome in goats after a single intramuscular (IM) administration. of 2 mg/kg b.wt. alone (Cef. I.M.) and pretreated with meloxicam (Cef. I.M±melox) intramuscular at a dose rate of 0.2 mg/kg b.wt. (n= 5).

Table 2: Mean pharmacokinetic parameters of cefquinome in goats after a single intramuscular administration.

Parameter	Units	X±S.E.	
		Cef. I.M.	Cef. I.M.±melox
A	µg/ml	1.23±0.0102	1.432±0.017
K _{ab}	h ⁻¹	1.75±0.012	1.82±0.036
T _{0.5(ab)}	h	0.4±0.0028	0.396±0.006
B	µg/ml	2.01±0.017	1.98±0.0139
K _{el}	h ⁻¹	0.075±0.0015	0.11±0.003
T _{0.5(el)}	h	9.21±0.178	6.5±0.221**
C _{max}	µg/ml	1.71±0.0189	1.6±0.0124
T _{max}	h	1.59±0.0038	1.49±0.0092
AUC _(0-inf)	µg.h/ml	29.36±0.78	21.38±0.696**
MRT	h	13.63±0.254	9.77±0.309**
IBD	h	36.15±0.25	24.56±0.27**
Cl _{tot}	l/h/kg	0.068±0.78	0.094±0.25

Mean pharmacokinetic parameters of cefquinome in goats after a single intramuscular (IM) administration of 2 mg/kg b.wt. alone (Cef. I.M.) and pretreated with meloxicam (Cef. I.M.±melox.) IM at a dose rate of 0.2 mg/kg b.wt. (n=5). ***p≤0.001, **p≤0.01, *p≤0.05.

The pharmacokinetic parameters of cefquinome following intramuscular administration of 2 mg/kg b.wt. were recorded in Table 2. The results revealed that, Cefquinome was rapidly absorbed after its intramuscular administration with an absorption rate constant (k_{ab}) of 1.75±0.012 h⁻¹ and the calculated value for t_{0.5ab} was found to be 0.4±0.0028 h. The maximum serum concentration

(C_{max}) was found to be 1.71±0.0189 µg/ml reached at 1.59±0.0038 h. post intramuscular administration. The elimination half-life (t_{0.5el}) was 9.21±0.178 h., the mean residence time (MRT) was 13.63±0.254 h., the calculated AUC (0-inf) was found to be 29.36±0.78 µg.h.ml⁻¹. The calculated interval between doses (IBD) was found to be 36.15±0.25h and total body clearance was 0.068±0.78 l/h/kg.

Single intramuscular co-administration of cefquinome and meloxicam

The serum cefquinome concentrations after a single intramuscular administration of 2 mg/kg b.wt. in goats pretreated with meloxicam were recorded in Table 1 and Figure 1. The mean peak serum level (1.81±0.014 µg/ml) was achieved 2 hour post administration. The drug was still detected in a concentration of 0.38±0.019 µg/ml at 24 hours post administration in serum of meloxicam pretreated goats.

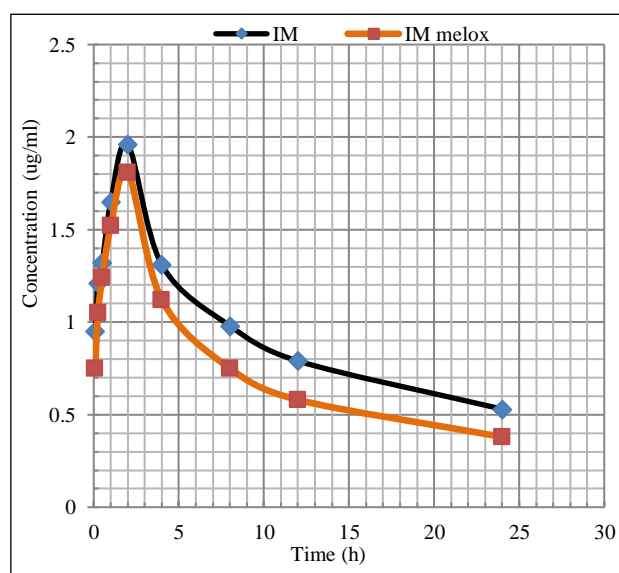


Figure 1: The time course of cefquinome in serum of goats after a single intramuscular dose of 2 mg/kg b.wt. alone (IM) and co-administration with meloxicam (IM. melox.).

The pharmacokinetic parameters of cefquinome following a single intramuscular administration of 2 mg/kg b.wt. in goats pretreated with meloxicam were recorded in Table 2. The results revealed that cefquinome was rapidly absorbed post intramuscular administration with an absorption rate constant (k_{ab}) of 1.82±0.036 h⁻¹. The maximum serum concentration (C_{max}) of 1.6±0.0124 µg/ml was reach at 1.49±0.0092 h. The elimination half-life (t_{0.5el}) was 6.5±0.221 h. The MRT was 9.77±0.309 h. The AUC_(0-inf) was found to be 21.38±0.696 µg.h/ml. The calculated interval between doses IBD was found to be 24.56±0.27 hours and total body clearance was 0.094±0.25 l/h/kg.

DISCUSSION

In the present study, following intramuscular administration of Cefquinome with meloxicam, a significant decrease in elimination half-life ($t_{1/2el}$) (6.5 ± 0.221 h), $AUC_{(0-inf)}$ (21.38 ± 0.696) and MRT (9.77 ± 0.309) was observed. Whereas all other pharmacokinetic parameters were not significantly altered as compared to Cefquinome only.

A non-significant difference was in peak plasma concentration (C_{max}) of Cefquinome alone or co-administrated with meloxicam in goats (1.71 ± 0.0189 & 1.60 ± 0.024 $\mu\text{g/mL}$), respectively as compared. Similarly, to inquiry mentioned that there were non-significant differences in the C_{max} of cefepime following concomitant intramuscular administration of ketoprofen in goats.¹²

In the present study, following intramuscular administration of cefquinome with meloxicam in goats; the major pharmacokinetics parameters were not significantly altered in comparison to goats administered cefquinome alone. Similarly, the major pharmacokinetic parameters of cefmenoxime remained unaffected following concomitant diclofenac sodium administration in rabbits, which supports the results of our study.¹³ No significant alterations were found in the major pharmacokinetic parameters of cefepime following its concomitant intramuscular administration with ketoprofen in sheep, which is in agreement with the present study.¹⁴ And also as studies mentioned that following intramuscular administration of cefquinome with tolfenamic acid in sheep, the major pharmacokinetics parameters were not significantly altered in comparison to sheep administered cefquinome alone.¹

In contrast to the present study, Barot reported a significant increase in the C_{max} of cefpirome following co-administration of it with ketoprofen in goats.¹⁵ The major parameters of cefquinome following co-administration with meloxicam in goats stated a significant increase when compared with cefquinome only.² Reports of alterations in the pharmacokinetic parameters of cephalosporin when co-administered with NSAIDs may be due to differences in the species of animal and the chemical nature of the drugs.

The results of our study showed that non-significant changes in the major pharmacokinetic parameters of cefquinome were observed following its concomitant administration with meloxicam in goats. So, it may be concluded that intramuscular administration of meloxicam (0.2 mg/kg) may be successfully co-administrated with cefquinome (2 mg/kg) for combating bacterial infections with an inflammatory condition in goats without antagonistic effect.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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