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Research paper

Bioavailability and pharmacokinetics of cefotaxime in Muscovy ducks

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Abstract

The pharmacokinetic profile of cefotaxime following a single intravenous (IV) and intramuscular (IM) injection was studied in Muscovy ducks. Cefotaxime was given at a dose rate of 25 mg/kg b.wt. for both routes. After IV injection, the plasma levels of cefotaxime estimated at 0.08 h was 70.87 µg/ml, which declined gradually and cefotaxime was detected up to 10 h (0.59 µg/ml). The mean values of CL, V_{dss} and $t_{1/2\beta}$ of cefotaxime in muscovy ducks were 0.22 l/kg/h, 0.51 l/kg and 1.81 h, respectively. After IM injection, maximum plasma concentration (C_{max}) was (14.72 µg/ml), time of maximal plasma concentration (t_{max}) was (2.3 h) and elimination half-life ($t_{1/2el}$) was (1.77 h). Bioavailability following IM injection was 79.61%, and *in vitro* protein binding percent was 31.48%. A recommended IM dosage for cefotaxime in muscovy ducks would be 30 mg/kg b.wt., repeated at 12 h intervals will provide a therapeutic plasma concentrations exceeding the MIC≤0.5 µg/ml for most susceptible pathogens in ducks.

Keywords:*Pharmacokinetics; Cefotaxime; Ducks.*

1. Introduction

Cefotaxime, is a third generation of cephalosporin antimicrobial drugs with an excellent bactericidal activity against a large variety of gram positive and gram negative micro-organisms, particularly β-lactamase producing strains (Neu, 1982a). Cefotaxime has an important location in antimicrobial drugs because of its expanded spectrum of antibacterial activity, greater resistance to β-lactamase (Kalager *et al*., 1982), low renal toxicity (Regamy, 1985), excellent disposition kinetics characteristics and least problem of bacterial resistance as well. It has minimum therapeutic concentration around 0.5 µg/ml for most of the susceptible micro-organisms (Neu, 1982b).

Pharmacokinetics of cefotaxime have been investigated in sheep (Guerrini *et al*., 1983), dogs (Guerrini *et al*., 1986), cats (HcElroy *et al*., 1986), goats (Atef *et al*., 1990; Dutta *et al*., 2004), cattle (Sharma *et al*., 1995), horses (Orsini *et al*., 2004) and buffaloes (Sharma *et al*., 2004; Sharma and Srivastava, 2006).

However, there is no information on pharmacokinetics of cefotaxime in Muscovy ducks. The aim of this study was to investigate cefotaxime pharmacokinetic profile and bioavailability in Muscovy ducks after intravenous (IV) and intramuscular (IM) injections.

2. Materials and methods

2.1. Drug (cefotaxime)

Cefotaxime (Cefotax®, EIPICO, Egypt, powder supplied for IV or IM injection in strengths equivalent to 1 g of cefotaxime sodium. The powder was dissolved in distilled water immediately before injection.

2.2. Experimental birds

Six healthy male Muscovy ducks, weighing from 4.2 and 4.8 kg, were obtained 2 weeks before the beginning of this study. Ducks allowed 3 weeks before starting of study to ensure the complete withdrawal of any previous drug from their bodies. Ducks were fed antibacterial-free commercial rations and drinking water was provided *ad-libitum*. This study was investigated in accordance with the guidelines set by Faculty of Veterinary Medicine.

2.3. Experimental design

Ducks were individually weighed before drug injection and the doses were calculated precisely. Ducks were given a single IV dose of cefotaxime at a dose of 25 mg/kg b.wt. into the left brachial vein. After 15 days the same ducks were given the same dose by IM route through the leg muscle.

Blood samples following the two routes of injections were collected from the right brachial vein in heparinised tubes before and at 0.16, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12 h after injection of cefotaxime. Blood samples were centrifuged at 3000 r.p.m for 10 min to separate the plasma. The plasma samples were frozen at – 20 ^{o}C until analysis.

2.4. Analytical procedures

Cefotaxime in plasma samples were carried out by microbiological assay method using *E.coli* (ATCC 25922) as a test organism (Bennett *et al*., 1966).

Standard curve was constructed using antibacterial free plasma collected from healthy ducks. Triplicates of 100 µg/ml from either standards or unknown plasma samples were added to wells in the assay perti-dishes. The lower detectable limit of cefotaxime assay was 0.1 µg/ml. The protein binding of the cefotaxime was deter-

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mined *in vitro* using the method of Craig and Suh (1980) with cefotaxime concentration of 0.5, 5, 10, 25, 50 and 100 µg/ml.

2.5. Pharmacokinetic analysis

Parameters for pharmacokinetic study were determined for each duck. Plasma concentrations of cefotaxime following a single IV and IM injection were subjected to non-compartmental and compartmental analysis using computerized program, WinNonlin 4.1 (Pharsight, Mountain View CA, USA). The priming and maintenance doses were calculated according to formula mentioned by Chaudhary *et al*., (1999).

3. Results

Plasma concentrations of cefotaxime-time profiles following IV and post IM of 25 mg/kg b.wt. were shown in Figure (1). The pharmacokinetic variables corresponding to IV and IM routes were given in Table (1). Following IV injection of 25 mg cefotaxime/kg, the plasma concentration-time data were described by the two compartments open model as shown (Figure 1). The distributional half life ($t_{1/2\alpha}$) was rapid (0.32 h). Volume of distribution at steady state (Vd_{ss}) was 0.51 l/kg.

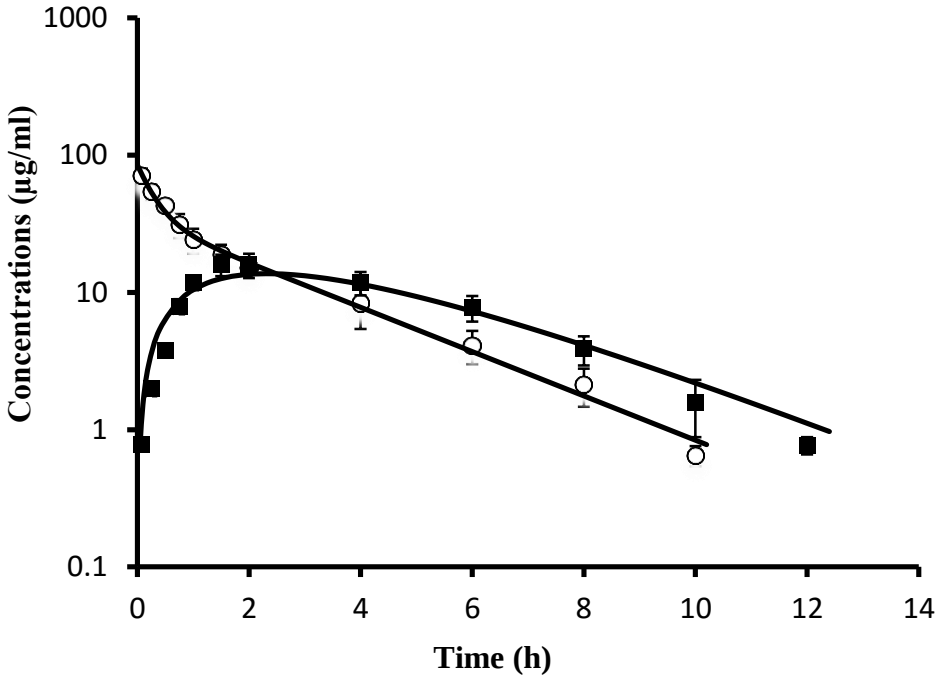


Fig. 1: Semi-Logarithmic Graph Depicting the Time-Concentration of Cefotaxime in Plasma of Muscovy Ducks after A Single IV (○) and IM (■) Administration Of 25 mg/kg b.w.t (n=6).

Table 1: Mean ± SE Plasma Pharmacokinetic Parameters of Cefotaxime in Muscovy Ducks Following A Single IV and IM Administration of 25 mg/kg b.wt. (n=6).

Parameter	Unit	IV	IM
α (k_{ab})	h^{-1}	2.12 ± 0.07	0.43 ± 0.01
$t_{1/2\alpha}$ ($t_{1/2ab}$)	h	0.32 ± 0.008	1.58 ± 0.04
β (k_{el})	h^{-1}	0.38 ± 0.007	0.39 ± 0.01
$t_{1/2\beta}$ ($t_{1/2el}$)	h	1.81 ± 0.05	1.77 ± 0.04
AUC	µg ml^{-1} h^{-1}	111.19 ± 4.28	88.55 ± 3.41
AUMC	µg ml^{-1} h^{-2}	254.67 ± 11.03	377.56 ± 9.35
MRT	h	2.29 ± 0.06	4.26 ± 0.07
MAT	h	—	1.97 ± 0.03
Vd_{ss}	l kg^{-1}	0.51 ± 0.004	—
Cl_{tot}	l kg^{-1} h^{-1}	0.22 ± 0.008	—
C_{max}	µg ml^{-1}	—	14.72 ± 0.29
t_{max}	h	—	2.30 ± 0.02
F	%	—	79.61 ± 1.82

α; β hybrid rate constant representing the slope of distribution and elimination phase after IV injection; K_{ab}; K_{el} absorbtion and elimination rate constant after IM injection; $t_{1/2(\alpha)}$ distribution half-life after IV injection; $t_{1/2(ab)}$ absorption half-life after IM injection; $t_{1/2(\beta)}$ elimination half-life after IV injection; $t_{1/2(el)}$ elimination half-life after IM injection; AUC area under plasma concentration-time curve; AUMC area under moment curve; MRT mean residence time; MAT mean absorption time; Vd_{ss} volume of distribution at steady state; Cl total body clearance. C_{max} maximum plasma concentration; t_{max} time to peak plasma concentration; F fraction of drug absorbed systemically after IM injection.

The results showed that, plasma concentrations of cefotaxime following IM injection were peaked 14.72 µg/ml at 2.30 h, with elimination half-life ($t_{1/2el}$) of 1.77 h. These results reveal a better absorption of cefotaxime after IM injection with respective bioavailability of 79.61%. Cefotaxime was bound to plasma protein at a percent 31.48%.

4. Discussion

After IV injection of cefotaxime at a dose of 25 mg/kg b.wt., concentrations of cefotaxime in plasma against time indicated that cefotaxime pharmacokinetics in Muscovy ducks, was best fitted by the two-compartment open model. The two compartment open model was observed for cefotaxime after IV injection in goats (Atef *et al*., 1990). Elimination half-life ($t_{1/2\beta}$) of cefotaxime was

1.81 h, indicating a rapid elimination of cefotaxime in ducks, and this observation agreed with cefquinome in ducks (1.57 h; Yuan *et al*., 2011) and chickens (1.29 h; Xie *et al*., 2013). Compared with other cephalosporins, $t_{1/2\beta}$ of cefotaxime in Muscovy ducks was shorter than ceftiofur in chickens (4.23 h; Amer *et al*., 1998). The Vd_{ss} of cefotaxime in ducks (0.51 l/kg), indicating limited distribution of cefotaxime in ducks, which might attributed to high protein binding activity (31.48%). Obtained result was nearly similar to that recorded for cefquinome in broiler chickens (0.49 l/kg; Xie *et al*., 2013). Total body clearance of cefotaxime in ducks was 0.22 l/kg/h, which lower than cefotaxime in sheep (0.65 l/kg/h; Guerrini *et al*., 1983) and calves (0.81 l/kg/h; Sharma *et al*., 1995).

Following IM injection of cefotaxime in ducks, absorption half-life ($t_{1/2ab}$) was (1.58 h). This value was longer than cefquinome (0.12 h) in ducks (Yuan *et al*., 2011). The IM absorption was reflected by moderate MAT (1.97 h). The elimination half-life ($t_{1/2el}$) was (1.77 h) was nearly similar to cefquinome (1.79 h) in ducks (Yuan *et al*., 2011). Maximal plasma concentration (C_{max}) was 14.74 µg/ml achived at (t_{max}) of 2.30 h. These values were higher than cefquinome (9.38 µg/ml at 0.38 h) in ducks (Yuan *et al*., 2011) and broier chickens (3.04 µg/ml at 0.25 h; Xie *et al*., 2013). The systemic bioavailability was (79.61%) which lower than cefquinome in ducks (93.28%; Yuan *et al*., 2011) and broiler chickens (79.61%; Xie *et al*., 2013).

The main aim of this study was to determine a satisfactory dosage regimen of cefotaxime in ducks to be effectively used clinically for treatment of different mild to severe bacterial infections in ducks, without having first conducted a detailed pharmacokinetic study. The minimum inhibitory concentration (MIC_{90}) of cefotaxime has been reported to be 0.016-1 µg/ml (Knudsen *et al*., 1997). Using a MIC of cefotaxime as 0.5 µg/ml, the suitable dosage regimen of cefotaxime in Muscovy ducks should be 30.71 mg/kg (priming dose) followed by 30.42 mg/kg (maintenance dose) at 12 h intervals.

5. Conclusions

Clinically, cefotaxime is very useful in treatment of different bacterial infections in Muscovy ducks with MIC≤0.5 µg/ml and the recommended dose is 30 mg/kg bwt given by IM route at 12 h intervals.

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