Pharmacokinetic Evaluation Of Cefotaxime After Intramuscular Administration In Chickens

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ABSTRACT

Pharmacokinetics of cefotaxime was investigated in clinically healthy chickens following single intramuscular injection of three doses (5, 10 and 20 mg/kg.bwt.). An increase in concentration of the drug was found with increasing dose at all the sampling times in each subject. The peak serum concentrations (Cmax) of cefotaxime was 4.5, 8.0 and 21.60μg/ml at maximum time at which the drug reach maximum concentration (tmax) of 28, 29 and 30 minutes, respectively. The serum concentrations was decreased with elimination half lives (t0.5e) of 0.72 ,0.70 and 0.71 hours and The area under serum drug concentration (AUCo-∞) was 7.09, 12.32 and 32.58 $\mu g.ml^{-1}.h$ for the three doses, respectively.

Pharmacokinetic/pharmacodynamic integration index (time of drug concentration in serum ≥ minimum inhibitory concentration) for Cefotaxime as a concentration-independent drug was 4.5, 5.0 and 6.1 hours with therapeutic duration of 4.1, 4.6 and 5.5 hours for three doses, respectively.

INTRODUCTION

Cefotaxime was the first of the third generation cephalosporins to be released in the market for Veterinary therapy. It is a broad spectrum antibiotic and highly resistant to the action of β-lactamase enzyme. Against gram negative micro organisms, it exhibits greater *in vitro* activity than any of the previous cephalosporins *(1)*.

Cefotaxime inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested *(2)*.

The Pharmacokinetic properties of Cefotaxime have been investigated in humans *(3)*, rats *(4)*, Sheep *(5,6)*, dogs *(7)*, cats *(8)*, goats *(9,10)* and cattle *(11,12)*, buffaloes *(13)*, but, few articles were published about Cefotaxime in poultry farms as efficacy against *Salmonella spp.* and *Escherichia coli* isolated from chickens *(14-17)* with insufficient data about pharmacokinetic properties of cefotaxime in chickens.

The aim of this study was to determine the pharmacokinetic properties (as a comparative study) of cefotaxime after single intramuscular administration of three doses (5, 10 and 20 mg/kg b.wt.) in chickens.

MATERIAL AND METHODS

Drug

Cefotaxime (Cefotax - EPICO - Egypt) was diluted with sterile distilled water before administration. The drug was administered at therapeutic dose of 5 mg/kg b.wt., double therapeutic dose (10 mg/kg b.wt.) and forth fold therapeutic dose (20 mg/kg b.wt.).

Chickens

Fifteen clinically healthy chickens (1.5-2.0 kg body weight and 30 days age) were used for the study. The chickens were kept for 15 days without any medication before the study, fed on prepared ration and kept under observation before starting and during the experiment.

Study design

The chickens were divided into three groups (each of 5) and the study of dosing was performed in a three-way crossover design with one weeks washout period (total fifteen chickens per treatment).

Blood sampling

After single intramuscular injection of 5, 10 and 20 mg of Cefotaxime/ kg.bwt. for the three group by the three-way crossover design, blood samples were withdrawn from wing vein in sterile tubes prior and at 10, 20 and 30 minutes, 1, 2, 4, 6, 8 & 12 hours after drug injection. Sera were separated and kept at -20°C till drug analysis.

Drug Analysis

Concentration of Cefotaxime was determined in serum by microbiological assay method *(18)* using *Bacillus Subtilis* ATCC 6633 (BD, USA) as a standard test organism. The correlation coefficient (r^2) of linearity of standard curve was 0.99.

Minimum inhibitory concentration (MIC)

Minimum inhibitory concentration (MIC) of Cefotaxime against *E.Coli* O157:H7 (BD, USA) was performed using agar plate diffusion technique *(19)*.

Data analysis:

Data were expressed as mean ± SE *(20)*. Pharmacokinetic analysis was performed using serum concentration-time profile *(21,22)*.

RESULTS AND DISCUSSION

The mean ± SE for the intramuscular pharmacokinetic parameters of three doses of Cefotaxime (5, 10 and 20 mg/kg.bwt.) in clinically healthy chickens based on the serum level-time profile of Cefotaxime are presented in Table 1, and the average plasma concentrations of the drug against time are plotted in Figure 1.

The aim of beta-lactam therapy including Cephalosporins is to keep the antibiotic plasma concentration above the minimum inhibitory concentration (MIC) at which bacteria are inhibited from growth *(23)*. The increase in the serum concentration of Cefotaxime was shown with increasing dose and this increase seems to be dose dependent.

After single intramuscular administration of Cefotaxime in clinically healthy chickens (5, 10 and 20 mg/ kg.bwt.), the drug attained the maximum serum concentrations (Cmax) of 4.5, 8.0and 21.6 µg/ml after 28, 30 and 38 minutes of drug administration (tmax) with increase the absorption rate constant (3.81, 3.99 and 5.13 h^{-1}) and decrease absorption half-life (0.18, 0.17 and 0.14 h) for the three doses, respectively.

The rapid appearance of Cefotaxime in plasma suggests that, this drug quickly enters into the systemic circulation following intramuscular administration and this is confirmed by the high value for the absorption rate constant which increase with increase the dose.

The AUCo- ∞ values were noted to be 7.09, 12.32 and 32.58 µg.h/ml after the administration of intramuscular doses of 5, 10 and 20 mg/kg which is dose dependent in comparable with increase of drug level in serum.

The elimination half-life (t1/2e) was observed to be 0.72, 0.70 and 0.71 hours after a doses of 5, 10 & 20 mg/kg body weight and these values are shorter than its half-life in cow calves and buffalo calves, similar to half-life in cats and dogs, but longer than that reported in sheep and goats and these differences may be attributed to the variation in the dosage form, species and route of drug administration. The elimination half-lives of Cefotaxime in cow calves *(12)*, buffalo calves *(24,25)*, cats *(8)*, dogs *(7)*, sheep *(5)* and goats *(9)* have been reported to be 3.48, 1.31, 0.98, 0.74, 0.38 and 0.36 h, respectively.

Time of drug concentration in serum (T) ≥ minimum inhibitory concentration (MIC) is the best pharmacokinetic/ pharmacodynamic integration index for a concentration-independent drug as Cefotaxime and this index is required for clinical cure depending on the host or pathogen *(22)*.

Our results indicated that, the concentrations of Cefotaxime in serum after single intramuscular administration of three doses (5, 10 & 20 mg/kg body weight) to clinically healthy chickens was enough to overwcome the minimum inhibitory concentration (MIC) of *E. coli* (≥ 0.1 µg/ml) for 4.5, 5.0 and 6.1 hours with therapeutic duration of 4.1, 4.6 and 5.5 hours. This data mean that, using of Cefotaxime as a chemotherapeutic agent in chickens at

recommended and even at high doses not enough as a one dose per day.

However, the parenteral administration of the drugs in chickens more than one dose per day along the course of treatment is very difficult to be applied. So, we can suggest, the intramuscular administration of cefotaxime can be use as a initial dose to sure that the drug reach to the diseased chickens which were unable to drink medicated water, then, followed by oral route as a maintenance dose).

Table 1. Pharmacokinetic parameters (mean ± SE) of cefotaxime after single intramuscular injection of three doses (5, 10 and 20 mg/kg.b.wt.) in chickens.

parameters	Unit	Dose (mg/kg.b.wt.)		
		5 *Therapeutic*	10 *Double therapeutic*	20 *Forth fold therapeutic*
A	$\mu g.ml^{-1}$	8.75±0.12	16.24±2.65	58.15±3.66
K_a	h^{-1}	3.81±0.06	3.99±0.21	5.13±0.21
$t_{0.5a}$	h	0.18±0.01	0.17±0.02	0.14±0.01
B	$\mu g.ml^{-1}$	8.83±0.15	15.76±0.99	40.51±1.55
K_e	h^{-1}	0.96±0.02	0.99±0.03	0.97±0.21
$t_{0.5e}$	h	0.72±0.13	0.70±0.11	0.71±0.10
C_{max}	$\mu g.ml^{-1}$	4.5±0.25	8.0±0.35	21.6±1.11
t_{max}	min.	28±1.69	30±2.00	38±2.00
$AUC_{o-\infty}$	$\mu g.ml^{-1}.h$	7.09±1.33	12.32±2.98	32.58±2.00
MIC (*E.Coli*)	µg.ml		0.1	
T ≥ MIC	h	4.5±0.11	5.5±0.12	6.1±0.10
td	h	4.1±0.21	4.6±0.30	5.5±019

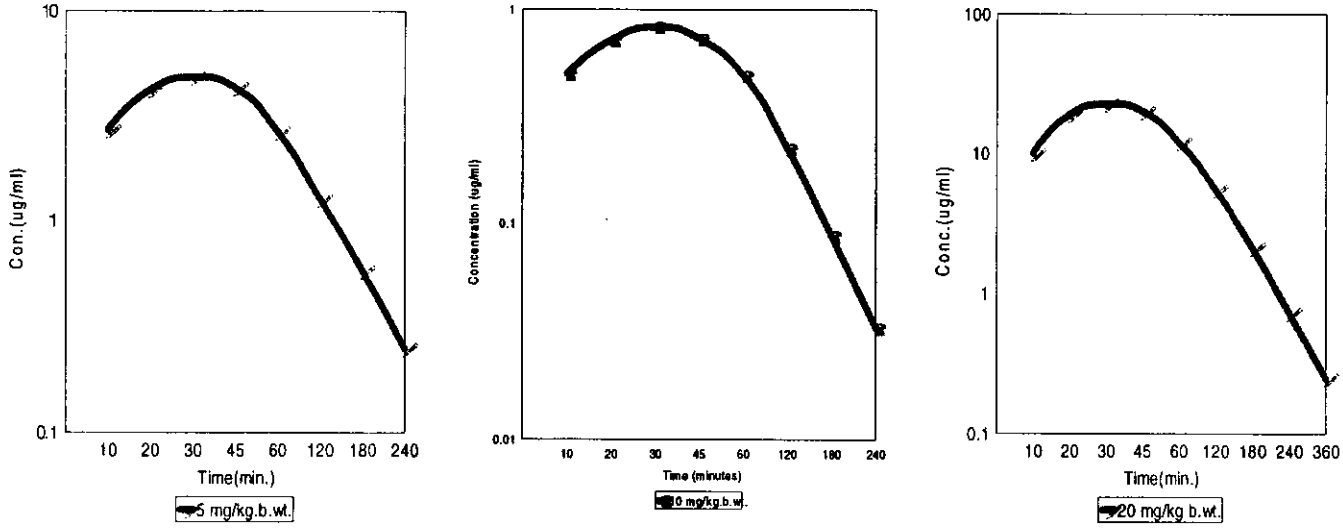

Figure 1. Mean Serum concentrations (mean±SE) of Cefotaxime after single intramuscular injection of three doses (5, 10 and 20 mg/kg.b.wt.) in chickens.

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الملخص العربى

تقييم الحركة الدوائية للسيفوتاكسيم بعد الحقن العضلى في الدجاج

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تم دراسة الحركة الدوائية للسيفوتاكسيم بالجرعة العلاجية (5 مجم / كجم وزن حي) ومضاعفاتها (10 و 20 مجم / كجم وزن حي) عن طريق الحقن بالعضل في الدجاج.

أشارت النتائج الى أن الدواء تم امتصاصه خلال نصف ساعة بعد الحقن ووصل اعلي تركيز للسيفوتاكسيم في البلازما الي 4.5 ، 8.0 و 21.60 ميكروجرام/مل والمساحة تحت المنحني الي 7.09 ، 12.32 و 32.58 ميكروجرام/ مل. ساعة وذلك للجرعات الثلاث بالتتابع.

كما دلت مؤشرات علاقة التوافق الحركي مع الفاعلية الدوائية الى أن اعلي تركيز للدواء في البلازما ≤ اقل تركيز لمنع نمو ميكروب القولون العص وي كانت 4.5 ، 5.0 و 6.1 ساعات ومدة فاعلية الدواء 4.1 ، 4.6 و5.5 ساعات وذلك للجرعات الثلاث بالتتابع.