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Original Article

Pharmacokinetics and Tissue Residues of Ceftiofur in Normal and *Escherichia Coli* Infected Chickens

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Abstract

The pharmacokinetics of ceftiofur was studied following intravenous and intramuscular (single & repeated) administrations. Following a single intravenous injection of 10 mg/kg body weight of ceftiofur in normal chickens, serum concentration-time curve was best described by a two compartments open model with elimination half life ($t_{0.5(\beta)}$) = 5.47 hour), volume of distribution (V_{dss}=198.60 ml/kg) and total clearance of the drug (CL_{tot}= 0.345 ml/kg/min). Following a single intramuscular administration of 10 mg/kg. body weight ceftiofur in normal chickens, The peak serum concentration (C_{max}) was 25.94 µg/ml was achieved at a maximum time (T_{max}) of 2.51 hour. The mean systemic bioavailability was 88.90%. The serum concentrations of ceftiofur following repeated intramuscular administration of 10 mg/kg body weight once daily for five consecutive days in normal and experimentally *Escherichia coli* infected chickens showed a lower significant values recorded in experimentally *Escherichia coli* infected chickens than in normal ones. Ceftiofur showed accumulative behavior in serum of chickens. Results of this study indicated that ceftiofur was useful for treatment of *Escherichia coli* infections in chickens. Ceftiofur was assayed in serum, heart, liver, spleen, kidney, fat, breast muscle, thigh muscle and skin after 24, 48, 72, 96 and 120 hours post last dose following administration of 10 mg/kg body weight every 24 hours.

Keywords: Pharmacokinetics, ceftiofur, tissue residues, chickens.

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Introduction

Ceftiofur sodium (Excenel)® is a chemotherapeutic agent is used in veterinary practice not only for large and small animals but also for poultry and fishes against Gram-positive and Gram-negative bacteria. Ceftiofur sodium (Excenel)® is one of the third generation cephalosporins.It is a broad spectrum antibiotic active against both Gram-positive and Gram-negative bacteria, including *β*-lactamase producing strains. It is bactericidal; destroying bacteria by preventing the synthesis of the cell wall.

The pharmacokinetics of ceftiofur has been investigated in many animal species including calves, chicken, pigs, foals, ducks, goats, elephants respectively. However, this study was done to investigate several data about pharmacokinetics of ceftiofur and tissue residues in chickens. Therefore, the aim of present work was undertaken to study the pharmacokinetic parameters of ceftiofur after intravenous and intramuscular administration in normal and experimentally *Escherichia coli* infected chickens. Also, the bioavailability of ceftiofur was calculated after intramuscular administration in normal chickens. Residues for ceftiofur in chicken's tissues were studied in normal and *Escherichia coli* infected chickens.

Materials and Methods

Drug

Ceftiofur was used in this study under the trade name (Excenel ®, sterile powder). Each vial contains ceftiofur sodium equivalent to 4 gm ceftiofur. Each ml of reconstituted solution contains ceftiofur sodium equivalent to 50 mg ceftiofur, which was manufactured by Pfizer, kalamazoo, USA.

Experimental Birds

Thirty one clinically normal Harbard chickens of 6 - 8 weeks age were used in this investigation. The mean weights of chickens were 1.900±0.053. Chickens were obtained from poultry farms in Benha city, El Qualubia government, Egypt. Chickens were feed balanced ration free from antibiotics for two weeks to ensure complete excretion of any drugs from their bodies. Water and feed free from antibacterial additives were ad-libitum.

Experimental Design

The chickens were divided into 3 groups:

Group 1

It included 7 normal chickens. Each bird was injected intravenously into the left wing vein with 10 mg ceftiofur /kg.b.wt. These chickens were left for 15 days after the intravenous injection to ensure complete excretion of ceftiofur from their bodies.

Then each chicken were injected intramuscularly into thigh muscle with 10 mg of ceftiofur /kg b.wt to calculate bioavaibility of ceftiofur in normal chickens.

Group 2

It included 12 chickens. Each bird was injected intramuscularly into thigh muscle with 10 mg ceftiofur /kg. b.wt, once daily for five consecutive days. Serum samples were taken and then intramuscular dose was administered every 24 hours for five consecutive days. Tissue samples were taken for assaying of drug residues after the last sampling.

Group 3

It included 12 chickens. Each bird was injected subcutaneously in the tissue of infraorbital sinues with 0.1 ml of Escherichia coli suspension (E.coli strain O78 serotype of poultry origin was obtained from poultry department, animal health research institute. Dokki, Giza, Egypt) from a concentration of 1X 106 C.F.U/1ml according to El-Sayed *et al.*, and Dalia 2013. After the appreance of symptoms of bacteraemia as diarrhea, lack of appetite and ruffled feathersly, each chicken was injected intramuscularly with 10 mg ceftiofur /kg.b.wt every 24 hours for five consecutive days. After that serum and tissue samples were taken for assaying of residues till disappearance of the drug from tissues.

Collection of Samples

Blood Samples

Blood samples were collected from either right or left wing vein following intravenous or intramuscular administration in normal and

experimentally infected chickens. Blood samples are collected after 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hours of administration in single study, and after 0.167, 0.25, 0.50, 1, 2, 4, 8, 12 and 24 hours in the first day, second, third, fourth and fifth dose in the same study in repeated intramuscular administration in normal and experimentally Escherichia coli infected chickens. Serum samples were separated by centrifugation and stored until assay of ceftiofur.

Tissue Samples

Three chicken were slaughtered at the end of the fifth day of repeated intramuscular administration of ceftiofur in normal and experimentally Escherichia coli infected chickens, Tissue samples from blood, liver, kidney, spleen, heart, breast muscle, thigh muscle, fat and skin were taken for assaying of residues of ceftiofur at 24, 48, 72, 96, 120 hours after the last sampling.

Analytical Procedures

Ceftiofur was assayed in serum by modified spectrophotometric method according to El-Sayed *et al.*, and Dalia 2013. The standard solution of ceftiofur was prepared by dissolving 25 mg ceftiofur in 25 ml distilled water to obtain a concentration of 1000 µg/ml. Standard concentrations were obtained by further dilution in distilled water and chicken serum to obtain concentrations of 0.313, 0.625, 1.25, 2.5, 5, 10, 25 and 75µg/ml for preparation of standard curve of ceftiofur. The pharmacokinetic parameters were calculated by winnonlin program, version 1.1 and other parameters according to El-Sayed *et al.*, and Dalia 2013. All statistical analysis was carried out according to El-Sayed *et al.*, and Dalia 2013.

Assay of Tissue Samples

Three milliliter of distilled water was added to one gram of the obtained tissue sample and homogenized in a porcelain morter by the aid of sterile sand. The homogenate was left in the refrigerator overnight then centrifuged. One milliliter of the supernatant was taken and subjected to the same procedures for assay in serum sample.

Results

Following a single intravenous injection of 10 mg /kg.b.wt. in normal chickens, ceftiofur could be detected therapeutically for 24 hours post intravenous injection. The serum concentration-time curve of ceftiofur following intravenous injection showed that the drug obeyed a two compartments open model. The disposition kinetics of ceftiofur following a single intravenous and intramuscular administration were recorded in tables (1) and showed in figure (1).

Table 1: Pharmacokinetic parameters of ceftiofur following a single intravenous and intramuscular injection of 10 mg/kg.b.wt. in normal chickens (n=7).

Parameter [1]	**Unit**	**Intravenous** $\bar{x}$ **± S.E.**	**Intramuscular** $\bar{x}$ **± S.E.**
B.wt	Kg	1.900±0.053	2.064±0.059
C^{o}	µg/ml	61.28±0.634	72.66±1.91
A	µg/ml	14.26±0.929	37.27±0.719
A	h^{-1}	1.34±0.105	-
$t_{0.5(\alpha)}$	H	0.536±0.043	-
K_{ab}	h^{-1}	-	0.921±0.036
$t_{0.5(ab)}$	h	-	0.759±0.030
AUC	µg/ml/h	388.52±9.04	345.17±6.62
$V^{1}c$	ml/kg	163.29±1.64	-
$V_{d(B)}$	ml/kg	212.92±3.04	-
$V_{d(\beta)}$	ml/kg	207.52±2.81	-
$V_{d(area)}$	ml/kg	206.74±2.60	-
V_{dss}	ml/kg	198.60±3.48	-
K_{el}	h^{-1}	-	0.126±0.005

K_{12}	h^{-1}	0.274±0.011	-
K_{21}	h^{-1}	0.997±0.036	-
B	µg/ml	47.02±0.689	35.48±1.39
B	h^{-1}	0.127±0.0025	-
$t_{0.5(\beta)}$	h	5.47±0.112	5.56±0.182
K_{13}	h^{-1}	0.161±0.0006	-
C_{max}	µg/ml	-	25.94±1.03
T_{max}	h	-	2.51±0.088
Cl_{tot}	ml/kg/min	0.345±0.009	0.285±0.004

[1]A & B, Zero time serum drug concentration intercepts of biphasic intravenous disposition curve. The coefficient B is based on the terminal exponential phase (µg/ml); α & β, Hybrid rate constant of biphasic intravenous disposition curve values of α and β are related to the slopes of distribution and elimination phase respectively, of biexponential drug disposition curve (h-1); AUC, Total area under the serum drug concentration versus time curve from t = 0 to t = α after administration of a single dose; C°, Drug concentration in the serum at zero time immediately after a single intravenous injection (µg/ml); C max, Maximum serum concentration of drug in blood after extra vascular administration (µg/ml); Cl tot, The total clearance of a drug, which represents the sum of all clearance processes in the body (ml/kg /min); Kab , Apparent first order absorption rate constant (h-1); Kel, First - order elimination rate constant for disappearance of drug from central compartment (h-1); K12 , First - order transfer rate constant for drug distribution from central to peripheral compartment (h^{-1}); K21 , First order transfer rate constant for drug distribution from peripheral to central compartment (h^{-1}); K13 , First - order elimination rate constant for disappearance of drug from central compartment (h^{-1}); t 0.5(ab), The absorption half- life (h); t 0.5(α), Distribution half - life (h); t 0.5(β), Elimination half - life (h); t max , The time at which the maximum concentration of drug was reached after extravascular administration (h); V1 c, The apparent volume of central compartment (ml/kg); Vd(B), The apparent volume of distribution Which calculated by extrapolation method (ml/kg); Vd(area), The apparent volume of distribution which was calculated by the area method (ml/kg); Vdss, The apparent volume of distribution which was calculated by Steady - state method (ml/kg).

Table 2: Pharmacokinetic parameters of ceftiofur in normal (N) and experimentally *Escherichia coli* infected chickens (I) during repeated intramuscular injections of 10 mg /kg. b.wt. once daily for five consecutive days (n=7).

Para meter	Unit	1st day		2nd day		3rd day		4th day		5th day	
		N	I	N	I	N	I	N	I	N	I
A	µg/ml	32.83± 1.255	34.67± 0.162*	27.58± 0.554	27.93± 0.146	24.56± 0.794	22.99± 0.255*	23.46± 0.574	21.93± 0.241**	26.59± 0.718	21.79± 0.359***
K_{ab}	h^{-1}	0.797± 0.018	0.804± 0.030	0.993± 0.041	0.859± 0.034**	1.019± 0.043	0.924± 0.005**	0.828± 0.017	0.800± 0.019	1.08± 0.019	0.693± 0.010***
$t_{0.5(ab)}$	H	0.872± 0.019	0.868± 0.031	0.705± 0.034	0.700± 0.116	0.688± 0.031	0.750± 0.004*	0.840± 0.018	0.866± 0.023	0.639± 0.024	0.999± 0.035***
B	µg/ml	35.35± 0.883	34.99± 0.194	33.30± 0.596	33.35± 0.26	35.75± 0.428	33.76± 0.442***	40.38± 1.031	36.73± 1.19**	46.40± 0.366	41.82± 0.966***
K_{el}	h^{-1}	0.130± 0.001	0.165± 0.003***	0.075± 0.003	0.111± 0.002***	0.060± 0.002	0.072± 0.002***	0.057± 0.001	0.059± 0.001*	0.056± 0.001	0.058± 0.001*
$t_{0.5(\beta)}$	H	5.35± 0.045	4.22± 0.090***	9.35± 0.402	6.22± 0.096***	11.57± 0.344	9.69± 0.213***	12.11± 0.254	11.15± 0.274**	12.34± 0.268	11.95± 0.283***
C°	µg/ml	67.51± 1.627	69.63± 0.268	60.88± 1.140	61.32± 0.266	59.76± 0.734	56.80± 0.519***	65.26± 2.353	58.66± 1.88**	72.98± 2.218	63.61± 1.97***
C_{max}	µg/ml	26.89± 0.403	23.24± 0.346***	28.22± 0.407	24.77± 0.111***	30.23± 0.390	27.21± 0.279***	32.55± 0.513	29.83± 1.28*	42.53± 0.825	33.33± 1.36***
t_{max}	H	2.76± 0.090	2.547± 0.047*	2.56± 0.074	2.66± 0.045	2.88± 0.029	2.97± 0.031*	2.14± 0.013	3.52± 0.115***	2.77± 0.146	3.91± 0.143***
Cl_{tot}	ml/kg/ min	0.308± 0.005	0.375± 0.011***	0.210± 0.007	0.297± 0.005***	0.180± 0.004	0.202± 0.002***	0.148± 0.002	0.168± 0.005***	0.130± 0.001	0.152± 0.003***

* P<0.05, ** P<0.01, *** P<0.001.

Intramuscular administration of 10 mg/kg.b.wt every 24 hours for five consecutive days in normal and Escherichia coli infected chickens revealed a lower significant serum ceftiofur concentration at all time sampling in Escherichia coli infected chickens than in normal chickens. The pharmacokinetic parameters of ceftiofur after repeated intramuscular administration in normal chickens were compared to those in Escherichia coli infected chickens in table (3).

Table 3: Serum (µg/ml) and tissue(µg/g) concentrations of ceftiofur (µg/ml) in normal (N) and experimentally *Escherichia coli* infected chickens (I) during repeated intramuscular injections of 10 mg /kg.b.wt. once daily for five consecutive days (n=3).

	After 24 hours		After 48 hours		After 72 hours		After 96 hours		After 120 hours	
Tissue	**N**	**I**	**N**	**I**	**N**	**I**	**N**	**I**	**N**	**I**
Serum	15.93± 0.320	12.54± 0.856***	1.430± 0.078	-	-	-	-	-	-	-
Heart	23.43± 0.183	7.60± 0.694***	6.900± 0.247	0.46± 0.070***	0.300± 0.054	-	-	-	-	-
Liver	40.42± 0.117	14.78± 1.554***	18.98± 0.376	5.27± 0.379***	8.940± 0.193	0.25± 0.068***	1.17± 0.070	-	-	-
Spleen	33.72± 0.415	12.14± 0.882***	16.64± 0.151	1.91± 0.306***	7.390± 0.744	-	0.39± 0.110	-	-	-
Kidney	43.16± 0.137	20.58± 1.196***	25.65± 0.078	8.63± 0.657***	11.55± 0.324	0.63± 0.075***	1.67± 0.058	-	-	-
Fat	27.35± 0.115	12.75± 0.497***	9.020± 0.072	1.52± 0.182***	0.860± 0.047	-	-	-	-	-
Breast muscle	32.09± 0.440	9.44± 0.356***	18.48± 0.129	1.13± 0.126***	7.640± 0.240	-	0.85± 0.046	-	-	-
Thigh muscle	22.86± 0.058	4.84± 0.631***	8.280± 0.495	-	0.460± 0.066	-	-	-	-	-
Skin	10.07± 0.487	1.63± 0.179***	1.040± 0.073	-	-	-	-	-	-	-

*** P<0.001.

Tissue residues for ceftiofur in heart, liver, spleen, kidney, fat, breast muscle, thigh muscle, skin after repeated intramuscular administration in normal chickens were compared to those in Escherichia coli infected chickens were recorded in table (4).

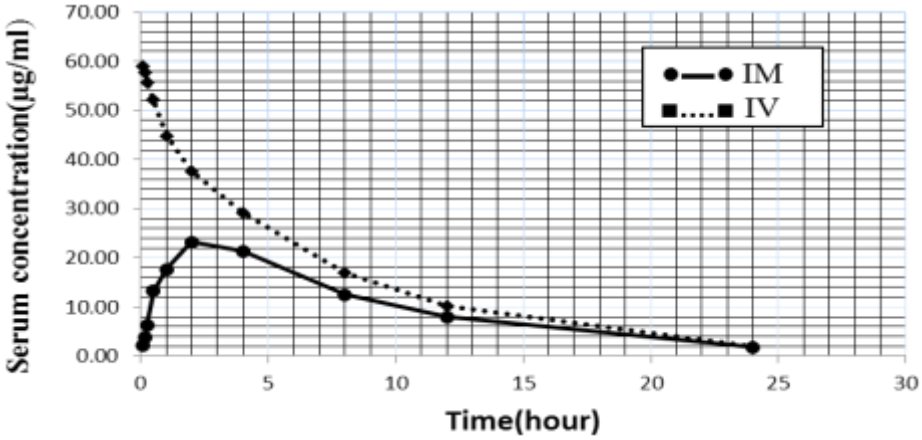

Fig. 1: Arithmetic plot of serum of ceftiofur concentrations in normal chicken following a single intramuscular injection of 10 mg/kg bwt.(●—●) in chicken previously given the same dose *by* a single intravenous injection (■….■) (n=7).

Discussion

In the present investigation, intravenous injection of 10 mg ceftiofur /kg.b.wt. in normal chickens, showed that the drug disposition best fitted a two-compartments open model, compartment of plasma and rapid equilibrating tissues, and a deeper slower compartment. The obtained result was consistent with those reported for ceftiofur in ducks, in neonatal foals, and for cefquinome in chicken.

The Vdss is a clearance-independent volume of distribution that is used to calculate the drug amount in the body under equilibrium conditions. The Vdss for ceftiofur was 198.60 ml/kg, suggesting limited penetration through biological membranes and tissue distribution after intravenous administration in broiler chickens. The obtained value agreed with the data reported after intravenous administration of ceftiofur in calves (0.200 L/kg) by El-Sayed *et al.*, and Dalia 2013. On the other hand, volume of distribution was shorter than those recorded in calves (0.284 L/kg), in goats (0.25 L/kg), in foals (0.83 L/kg) and in ducks (0.48 L/kg). Ceftiofur was transferred from central to peripheral compartment at a slower rate (K12 = 0.274 h-1) than its passage from peripheral compartment to central compartment (K21 = 0.997 h-1). These values were nearly similar to that reported for ceftiofur in cows (K12 = 0.473 h-1) and (K21 = 0.950 h-1) by El-Sayed *et al.*, and Dalia 2013.

The elimination half-life (t0.5(β)) of ceftiofur following a single intravenous injection was equal to 5.47 h. This observation agreed with the data reported after intravenous administration of ceftiofur in calves and cows (t0.5(β)) =5.05, 5.09 h by El-Sayed *et al.*, and Dalia 2013 respectively. On contrast, this obtained value was longer than those recorded in other species as chickens (4.23 h), camels (3.18 h), ducks (2.28 , 3.64 h). On the other hand, it was shorter than those showed in cattle (7.12 h) and in foals (7.8 h).

The rate of total body clearance (CLtot) of ceftiofur following intravenous injection was 0.345±0.009 ml/kg/min. This value was close to other cephalosporins as ceftriaxone (0.37 L/h/kg) in cats and cefquinome (0.22, 0.35 L/h/kg) in ducks and chickens, respectively.

Following a single intramuscular administration of 10 mg ceftiofur /kg.b.wt, the drug reached its maximum serum concentrations after 2 hours of administration (23.20 µg/ml). Ceftiofur could be detected in serum in a therapeutic level (1.77 µg/ml) at 24 hours. The mean peak serum concentrations of ceftiofur (Cmax) was (25.94 µg/ml) achieved at maximum time (tmax = 2.51 h). These values were similar to those recorded for ceftiofur in chickens (27.83 µg/ml at 2.39 hours). On contrast, the obtained results were higher than those reported in in camels (10.34 µg/ml at 1.22 hours), in cows (7.83 µg/ml at 1.55 hours), in ball python (7.09 µg/ml at 2.17 hours), in guinea fowl (5.26 µg/ml at 19.3 hours), in ducks (6.44 µg/ml at 0.49 hours) and in chickens (3.04 µg/ml), but shorter than those reported in pigs (28.3 µg/ml at 2 hours). These variations might be attributed to anatomical differences between species, healthy status and the dose administered in each case.

The bioavailability of ceftiofur in normal chickens was (88.90%). This value referred to a good absorption of ceftiofur from its site of intramuscular administration. This value was similar to those recorded for ceftiofur in calves (89.82%) and for ceftiofur in ducks (89.54%). On the other hand, this value was higher than that recorded for ceftiofur in camels (68.70%) and in ducks (79.25%). On contrast, this value was lower than that reported for ceftiofur in horses (100%) and for cefquinome in ducks (93.28%), cefquinome in chickens (95.81%).

The obtained blood levels of ceftiofur in Escherichia coli infected chickens were significally lower than those in normal chickens following repeated intramuscular administrations. These lower blood concentrations in infected chickens might be attributed to the higher penetrating power of ceftiofur to the diseased tissues. The relative higher serum concentrations of ceftiofur after the last dose compared to the first doses indicated the accumulation of ceftiofur in blood during multiple dosing at 24 hours intervals for five consecutive

days. These observations agreed with data reported by El-Sayed *et al.,* and Dalia 2013, who found that progressive daily increase in the mean serum concentrations following the intramuscular injection of ciprofloxacin in lactating goats in a daily dose of five mg/kg.b.wt. for five consecutive days and who recorded a progressive daily increase in mean concentration in blood following intramuscular injection of ceftiofur in weanling foals at a daily dose of 6.6 mg/kg.b.wt. for four consecutive days. The obtained result was inconsistent with that reported by El-Sayed *et al.,* and Dalia 2013, who found that little drug accumulated after multiple dosing of norfloxacin in dogs. Neither serum nor urine concentration increased significantly after two weeks of drug administration.

Repeated intramuscular administration of 10 mg ceftiofur /kg.b.wt every 24 hours for five consecutive days in normal and experimentally Escherichia coli infected chickens revealed that the drug could be detected only in blood and muscle with skin till 48 hours post last dose and till 96 hours post last administration in liver, spleen, kidney and breast muscle. The high clearance of ceftiofur indicated the reduced possibility of finding residues of ceftiofur in chickens after treatment and shorter withdrawal time for this antimicrobial (five days). Results showed that kidney and liver contained the highest drug concentrations (43.16, 40.42 µg/g respectively), while the lowest drug concentrations was found in thigh muscle and skin (22.86, 10.07 µg/g respectively), 24 hours after the stoppage of drug medication.

This result slightly agreed with that recorded for ceftiofur in swines that reported by El-Sayed *et al.,* and Dalia 2013, who found that the highest concentration in kidney (2.589 µg/g) at 12 hours, while the concentration of ceftiofur in all of tissues at three days was lower than the Maximum Residue Limit (MRL). Also, their results indicated that the elimination rate was skin/ fat> muscle> liver> kidney> injection site, with the elimination half-life of 28.99, 35.80, 36.76, 55.72, 160.8 hours, respectively.

Conclusion

The intramuscular bioavailability of ceftiofur is excellent, so it is recommended to be used against enteric and systemic Escherichia coli infection. Repeated intramuscular administrations of 10 mg/kg.b.wt. ceftiofur once daily for five consecutive days would provide an effective concentration against Escherichia coli in broiler chickens. Treated chickens must not be slaughtered before 5 days from last dose of repeated administration of ceftiofur to withdraw the drug residues from all tissues of treated chickens.

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