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Pharmacokinetic Studies Of Ceftiofur (Ceftiprima In Calves)

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ABSTRACT:

The kinetic profile of ceftiofur in calves was studied after single intramuscular and intravenous administrations at a dose of 2.2 mg ceftiofur/kg b.wt. Serum concentrations of ceftiofur were determined by using high performance liquid chromatography (HPLC). Following compartmental analysis, a two-compartment open model best described the concentration-time data of ceftiofur after i.m. and i.v. administration. After intramuscular administration, the drug reached its maximum serum concentrations (C_{max}) of 6.51 ± 0.123 µg/ml at maximum time (T_{max}) of 2.49 ± 0.073 h,absorption half-life ($t_{1/2ab}$) was 0.57 ± 0.035 h and (AUC_{0-t}) was 100. 8 ± 0.69 µg/ml.h.Following a single intravenous injection, the drug was detected till 24 hours, distribution half-life ($t_{1/2\alpha}$) was 0.11 ± 0.01 h, elimination half-life ($t_{1/2\beta}$) was of 11.07 ± 0.12 h and clearance (CL) was 0.013 ± 0.005 (L/kg/h), volume of distribution at steady state (V_{dss}) was 0.16 ± 0.004 (L/kg) and bioavailability was 64.66±0.39%.

Keywords: ceftiofur – *Bioavailability –HPLC – calves.*

INTRODUCTION

Cephalosporins are a class of β-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 β-lactamases and are distinguished by widespread range of microorganism activity (Petri., 2006).

Ceftiofur is an antibiotic created primarily for veterinary use in the third generation of cephalosporin.In addition to its activity against gram-negative bacteria, in previous generations it also has excellent activity against anaerobic bacteria.Ceftiofur – a third-generation antibiotic with cephalosporin has good anaerobic activity including gram-negative bacteria.

Ceftiofur has been used solely to treat certain respiratory diseases in bovine beef animals as well as dairy cattle, interdigital dermatitis in bovine animals and other animals (Salmon *et al*., 1995).This antimicrobial is also used exclusively for the treatment of mastitis and septic circumstances in livestock (Erskine *et al*., 1995 and Stanek and Kofler 1998).Ceftiofur may also treat intrauterine infections that cause metritis, retained placenta (Scott *et al.,* 2005).

Binding plasma protein plays a crucial role in drug distribution, elimination, and therapeutic efficacy. Ceftiofur's biological half-life rises due to protein binding as well as reduced kidney elimination by preventing β lactam ring from breaking. Plasma protein binding should be known for evaluating the potential effectiveness of antibacterial (Hornish and Kotarski 2002).

Pharmacokinetic studies that provide a basis for determining a suitable dosage regime are important when performed in the species where the antimicrobials are to be clinically used (Sharma and UlHaq, 2012).

Ceftiofur pharmacokinetics were studied in cattle (Brown *et al.,* 1996, Halstead *et al.,* 1992, Okker *et al.,* 2002, Liu *et al.,* 2010 and Tohamy, 2008).

Taking into consideration the above facts, this study was done in order to investigate ceftiofur pharmacokinetic parameters after intravenous, intramuscular injection in calves.

MATERIAL AND METHODS

1- Materials

Drug

Ceftiofur sodium : sterile powder for injection Itwas obtained from Badr Pharma for Pharmaceutical Industries for Pharma Cure Pharmaceutical Industries as sterile powder for injection under trade name (Ceftiprima® one gram)

Animals

Five clinically normal calves were used in this investigation. The body weight and age of the tested calves ranged from 90 -100 kg and from 60-80 days old. They were housed in hygienic stable, mainly fed on milk from its dams and eat small amount of concentrate with tibn. Water was provided *ad-libitum*.

Experimental design

1.Experiment(1):-

Each calf was injected intravenously into the left jugular vein with a single dose of 2.2mg ceftiofur /kg.b.wt.**(Brown *et al*.,1996).**

These five calves were left for 15 days after the intravenous injection to insure complete excretion of ceftiofur from their bodies.

Experiment(2):-

Each calf was injected intramuscularly with a single dose of 2.2mg ceftiofur /kg.b.wt. **(Brown *et al*.,1996).**

2. Blood samples:

Blood samples (0.5 to 1 ml) were collected from the left jugular vein of each calf. After intravenous injection, samples were collected at 5,15, and 30 minutes and 1, 2, 4, 8, 12,18 and 24 hours of administration. After intramuscular injection, samples were collected at 10, 20and 30 minutes and 1,2,4,8,12,18 and 24 hours of administration. All blood samples were centrifuged at 3000 rpm for 10 minutes, and serum was harvested and stored frozen at -20 ºC until analyzed for ceftiofur sodium.

The injection volume of samples was 20 µl, the flow rate was fixed at 1.0 ml/min, column temperature was 25ºC and the ultra violet detector wavelength was set at 256 nm.

3. Preparation of standard curves of ceftiofur in serum:

Ceftiofur Sodium (clarity ≥ 98.0%) was obtained from Sigma (3050 Spruce Street, Saint Louis, MO 63103, USA). A standard solution 1000 µg/ml of Ceftiofur in deionized H2O was prepared. All standard solutions were kept at $+4^0$C. Functioning solutions of Ceftiofur used to confound plasma were arranged at 10.00, 1.00 and 0.10 µg/ml concentrations from standard solutions by attenuating with deionized water. Standard concentrations were gotten by extra attenuation in drug free normal calves serum to attain concentrations 0.05, 0.10, 0.25, 0.50, 1.00, 5.00, 10.0 and 25.0 µg/ml for creation of standard curve of ceftiofur according to (Altan *et al.,* 2017) .

Drug free normal calves serum was pointed with ceftiofur from the formerly prepared concentration. Ceftiofur was take out according to (Altan *et al.,* 2017). In an eppindorf tube, Inpassing, nearly 200 µl of each serum sample was taken and 200 µl of methanol was added then samples were vortexed for 30 sec. Later centrifugation at 13,000 g for 10 min at 22°C, clear supernatant was reassigned to 2 ml micro centrifuge tubes, 100 µl of 10% dithioerythritol in borate buffer was extra to each tube, and each tube was sited in a H2O bath at 50°C for 15 min. Tubes were moved from the H2O bath and permitted to reach room temperature then 100 µl of 23.3% iodoacetamide in phosphate buffer was added to each tube, tubes were covered in aluminum foil and shaken at 350 rpm for 45 min at room temperature. 25 µlof formic acid was extra to each tube. Following derivatization, samples were vortexed for 30 sec after stirring at 22°C, and were centrifuged for 10 min at 13,000 rpm. An aliquot of 20 µlof supernatant was filtrated with 0.45 µm and transferred into the auto-sampler vial for analysis.

4. Pharmacokinetic analysis:

The pharmacokinetic parameters were calculated by PKSolver: An add-in program for Microsoft Excel, version 2.

5. Statistical analysis:

The data were calculated as mean ± standard deviation. All statistical analysis was carried out according to (**Berly and Lindgren 1990**). The pharmacokinetic parameters of drug in normal chickens were compared with the experimentally infected chicken by the Student's (t) probability test, which was performed according to the following equation:

$$t = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{SE_1^2 + SE_2^2}}$$

Where:

$\overline{X}_1$= mean of data of normal chicken.

$\overline{X}_2$ = mean of data of the diseased chicken.

$(S.E)_1$= Standard error of the normal chicken.

$(S.E)_2$=Standard error of the diseased chicken

RESULTS:

After a single intravenous and intramuscular administration of ceftiofur (2.2 mg/kg b.wt.), HPLC assessed the pharmacokinetic profile of ceftiofur in serum of calves and recorded in **(table 1).**

A comparison of serum ceftiofur concentration following a single intravenous and intramuscular injection were designed on arithmetic coordinates **(fig.1).**

Kinetic disposition of Ceftiofur after intramuscular administration:

Analytical results following i.m injection of 2.2mg ceftiofur /kg b.wt. ceftiofur showed that the serum concentration-time data was best equipped for an open model of two compartments. Ceftiofur was identified in serum in a therapeutic level for 24 hours with mean value 0.87±0.042 µg/ml.The obtained results exposed that the distribution half-life $t_{0.5(ab)}$ was 0.57±0.035 h. After a maximum time equivalent to (T_{max}) 2.49±0.073h, Ceftiofur achieved its maimum concentration (C_{max}) 6.51±0.12µg / ml.The elimination half-life $t_{0.5(el)}$ was 8.30±0.158 h.The area under serum concentration time (AUC) was 100.8 ± 0.69 µg/ml.h and the bioavailability was 64.66 ± 0.39 % as tabulated in **table 1**.

Kinetic disposition of ceftiofur after intravenous administration:

Analytical results following i.v injection of 2.2mg ceftiofur /kg b.wt. ceftiofur showed that the serum concentration-time data was best equipped for an open model of two compartments. Ceftiofur was identified in serum in a therapeutic level for 24 hours with mean value 1.59±0.11µg/ml.The obtained results exposed that the distribution half-life $\mathbf{t_{0.5(\alpha)}}$was 0.11±0.01h.The distribution phase **[α]** equivalent to 6.86 ± 0.44 h-1,volume of distribution at steady state **(Vdss)** was 0.16±0.004 (mg/kg)/(µg/ml). Ceftiofur's elimination half-life ($\mathbf{t_{0.5(\beta)}}$ was 11.07±0.12 hand the area under the curve **(AUC)** was 155.95±1.32µg/ml.h. Ceftiofur was cleared by all clearance processes ($\mathbf{Cl_{tot}}$) in the body at rate of 0.013±0.005L/kg/h.

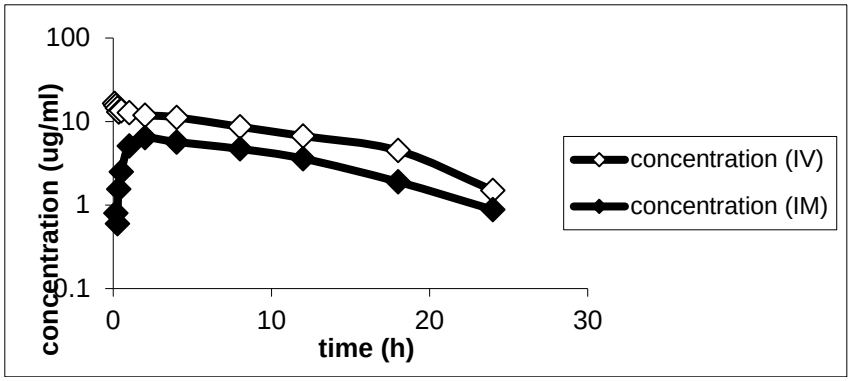

Fig. 1. Semilogarithmic graph illustrating the time progression of **ceftiofur**(µg/ml) in serum after a single intravenous and intramuscular injection of 2.2mg/kg.b.wt.in calves (n = 5).

Table 1. Mean±SD pharmacokinetics parameters of ceftiofur after single intramuscular and intravenous administration of 2.2mg ceftiofur/kg b.wt. (n=5).

Mean ± SD Pharmacokinetic Parameters of Ceftiofur			
Parameters	Units	intravenous	intramuscular
B	h^{-1}	0.062±0.006	----------
k_{12}	h^{-1}	1.70±0.13	----------
k_{21}	h^{-1}	4.80±0.40	----------
$t_{o.5(\alpha)}$	h	0.11±0.01	----------
$t_{0.5(\beta)}$	h	11.07±0.12	
$t_{0.5(ab)}$	h	____	----------
$t_{0.5(el)}$	h	-------	0.57±0.035
$V_{d(area)}$	L/kg	0.20±0.003	8.30±0.158
V_{dss}	L/kg	0.004±0.16	----------
T_{max}	h	____	----------
C max	µg/ml		
AUC	µg/ml.h	____	2.49±0.073
Cltot	L/kg/h	155.95±1.32	
MRT	h	0.013±0.005	0.12±6.51
F	%	9.058±0.03	100.8±0.69
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			64.63± 0.39

B,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});**t0.5(ab)**,The absorption half- life (h). **;t0.5(α)**,Distribution half - life (h);**t0.5(β)**and**t0.5(el)**,Elimination half - life (h);**T_{max},**The time at which the maximum concentration of drug was reached after extra vascular administration (h);**C_{max},**maximum concentration of drug;**Vd(area)**,The apparent volume of distribution which was calculated by the area method (L/kg);**Vdss**,The apparent volume of distribution which was calculated by Steady - state method (L/kg);**CLtot**,The rate of total body clearance;**MRT**,Mean residence time;**AUC**,Area under the concentration–time curve;**F**(%),bioavailability.

DISCUSSION

In the current study, ceftiofur pharmacokinetics were determined in calves following a single i.v and i.m administration of 2.2mg ceftiofur / kg b.wt.by a two-compartment open model.

After intramuscular administration of ceftiofur sodium , it was identified in calves serum up to 24h after 2.2 ceftiofur mg/kg.b.wt. pharmacokinetic research of an antibiotic is a prerequisite for clinical recommendation. The extent to which a drug is systemically absorbed depends on its route of administration. If animal condition is not critical, the intramuscular route is recommended. Drug absorption within intramuscular route is useful due to better muscle blood supply.The extent of systemic absorption differs between drugs and drugs and between species and species.Pharmacokinetic research of ceftiofur is crucial because the i.m route used on the field.Once ceftiofur sodium was injected by i.m route, parent drug as well as its metabolite were detected in calves serum up to 24 h.Administration was better situated separately into an open two-compartment model consistent with the calves model reported in calves (Halstead *et al*., 1992 and Brown *et al*., 1996), sheep (Craigmill *et al*.,1997), goats (Courtin*et al*., 1997), and cows (Tohamy, 2008).

Following a single intramuscular injection of 2.2 mg ceftiofur / kg.b.wt, the drug absorped very quickly with a short half-life absorption [$t_{0.5(ab)}$] of 0.56±0.035 h. The results achieved are compatible with those for ceftiofur reported in calves (0.38 and 0.37h, Brown *et al*.,1996 and Altan*et al*.,2017), cattle (0.35h,Tohamy, 2008)and camels (0.34h,Goudah, 2007). And also compatible with the result obtained from other cephalosporin as i.m administration of cefepime in ewes (0.49h,Ismail , 2005a) and cefqinome in piglet (0.4h, Li *et al*.,2008).This value is lower than ceftiofur in cows (1.30h, Liu *et al*.,2010),but longer than those results in non lactating goats (0.26h Courtin *et al*.,1997) and this may be due to its high enzyme levels and the result in buffalo calves (0.11h, (Sudamrao, 2015) . Ceftiofur reached a maximum serum concentration after (2.48±0.07h) this result is similar to ceftiofur reported in cattle and water buffalo (2.00 and 2.87h ,Nie et al.,2015 and Gorden et al.,2015). The present result is nearly similar to the results in calves (1.82 and 1.5h;Halsteadet al.,1992 and Altan et al.,2017).however disagreed with those stated in sheep (0.81h,Craigmill et al.,1997), goats (1.17h, Courtin et al., 1997), camel (1.22h,Goudah, 2007), buffalo calves (0.33h,Sudamrao,2015) and cattle (0.67h,Hornish and Kotarski 2002). After comparison to other cephalosporin, the time studied to reach the maximum serum concentration (T_{max}) was agreed with those reported in cefqinome in broiler chicken (2.8h,El-Mahdy *et al*., 2015)

The mean peak ceftiofur serum concentration (C_{max}) was (6.50±0.12 µg/ml) after intramuscular administration of 2.2 mg ceftiofur /kg.bw these values are consistence with those in water buffalo (6.2µg/ml, Nie *et al*.,2015),buffalo calves (6.6µg/ml ,Sudamrao, 2015), calves (7.73 µg/ml,Altan *et al*.,2017), sheep (7.13µg/ml,Craigmill *et al*.,1997) and cows (7.8µg/ml,Tohamy, 2008). This result not resemble the result had been stated in beef calves (8.78µg/ml Halstead *et al*.,1992, cattle (13.9 ,14.5 ,9.58 and 1.09µg/ml,Brown *et al*.,1996;Hornish and Kotarski 2002;Gorden, *et al*.,2015 and Wang *et al*., 2018) respectively. Even though there are many differences throughout the values of maximum ceftiofur serum levels, the literature on β-lactam antibiotics mentions that effectiveness does not correlate with the maximum concentration of plasma or tissue but depends on the length of time at which the drug levels stay above MIC of the susceptible pathogen (Sudamrao, 2015).

The elimination half life of ceftiofur $t_{0.5(el)}$ subsequent single intramuscular administration was (8.30±0.158 h).This obtained result **is** similar to those stated in cattle (8.13 and 9.20h,Gorden, *et al*.,2015 and Wang *et al*., 2018) and nearly similar to those results in cattle (10.3h,Hornish and Kotarski 2002),but not similar to the results of intramuscular administration of ceftiofur in calves (3.56,Halstead*et al*.,1992),buffalo calves (17 h,Sudamrao, 2015),neonatal calves (19.9h ,Altan*et al*.,2017),dairy goats (2.6h,Courtin*et al*., 1997),camels (3.2h,Goudah, 2007), water buffalo (12.72h,Nie*et al*.,2015) and cattle (5.03

and 15.3h, Liu *et al*.,2010 and Tohamy, 2008).The differences between the value systems calculated for pharmacokinetic parameters can be directly linked to the species of animal, formulations 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 even inter-individual variations, as well as the drug analysis method (Riond *et al*., 1989).

The longer elimination time($t_{0.5(el)}$) in calves may be largely related to less maturation of eliminating organs and/or elimination processes of ceftiofur and its metabolite particularly in comparison to adult and old animals of various species (Brown *et al*.,1996). On the opposite, lower elimination time (19.9 h) in calves (Altan *et al*.,2017) relative to the current inquiry may be owing to varieties in the enzymatically catalyzed metabolism and ceftiofur renal excretion, including effective renal secretion through organic acid transporters, and also glomerular filtration in such animals (Brown *et al*., 1996).

The area under curve (AUC) in this study is (100.8µg/ml.h) and is consistence with those of cattle (108.4µg/ml.h,Hornish and Kotarski 2002), Goats (124.1 µg/ml.h,Courtin *et al*., 1997). This result is not consisted with the results in calves (66.17 ,77.3 and 153µg/ml.h,Halstead *et al*.,1992; Brown *et al*., 1996 and Altan *et al*.,2017) respectively, buffalo calves (26.8 µg/ml.h,Sudamrao,2015),sheep(33.7µg/ml.h,Craigmill *et al*.,1997),water buffalo (65.4µg/ml.h,Nie *et al*.,2015) and cattle (163µg/ml.h,Liu *et al*.,2010).This may be because of differences in the quantity of body fluids between species and different ages. The bioavailability of ceftiofur sodium found in this research about 65% that may similar to the result obtained from dairy cows (Wang *et al*., 2018) that was 70.5%and buffalo calves (Sudamrao, 2015) that was 75%.

After 2.2 mg ceftiofur / kg.b.wt single intravenous injection in calves, The drug demonstrates high serum concentration (16.72±0.2µg / ml) in calves at 5 minutes after injection, Then it gradually reduced its concentration until its minimum level reached 24 hours after injection (1.59±0.11µg / ml).

The intravenous injection of 2.2 mg ceftiofur / kg.b.wt in the preset investigation in calves, It was shown that the drug disposition best suited a two-compartment open model ; a serum and fast balancing tissue compartment, and a deeper, slower compartment. The result obtained was compatible with the results reported for ceftiofur in calves (Brown *et al*., 1996), cattle (Whittem *et al*.,1995; Brown *et al*.,1996;Tohamy, 2008 and Liu *et al*., 2010), dairy goats (Courtin *et al*., 1997), sheep (Craigmill *et al*., 1997), camels (Goudah.,2007),subsequent intravenous dosing.This phenomenon is also agreement with those stated for other cephalosporines as cefquinome in yellow cattle administered 1 mg/kg i.v and i.m (Shan *et al*.,2013).

After single intravenous administration of (2.2mg ceftiofur/.kg.b.wt) in calves, distribution half life ($t_{o.5(\alpha)}$= 0.11h).This is almost consistent with the results reported in buffalo calves $t_{o.5(\alpha)}$(0.19h.(Sudamrao, 2015)and sheep by the dose of 1.1mg ceftiofur/k.g .b.wt.(0.10h,Craigmill *et al*.,1997).While longer half-life of distribution of ceftiofur was recorded of ceftiofur cattle (0.462h; Tohamy, 2008),camel (0.48h;Goudah, 2007), bull calves 6 and 9 months (0.88, 0.74h;Brown *et al*.,1996), lactating andnonlactating goats (0.69h, 0.8h;Courtin *et al*., 1997), sheep (4.8h;Craigmill *et al*.,1997).The differences between the value systems calculated for pharmacokinetic parameters can be directly linked to the species of animal, formulations 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 even inter-individual variations, as well as the drug analysis method (Riond *et al*., 1989).This result of half-life of the distribution $t_{o.5(\alpha)}$, compared to other cephalosporins, is almost comparable to that earlier reported in cefquinome in yellow cattle (0.29 h, Shan *et al*.,2013),cefepime in goats (0.20 h;El-Hewaity, 2014),cefepime in sheep (0.2h, Patel *et al*.,2010),cefepime in calves (0.2 h;0.25h, Ismail, 2005b; Pawar and Sharma 2008),cefepime in ewes (0.18 h, Ismail,2005a)and cefepime in buffalo calves (0.18 h, Joshi and Sharma 2007).

The V_{dss} is an independent clearance volume of the distribution used to calculate the amount of

drug in the body under conditions of equilibrium.Distribution volume ($V_{d(area)}$) and distribution volume at steady state (V_{dss}) in calves after i.v. administration were (0.2 L/kg) and (0.15 L/kg) respectively, referring to a moderate distribution of the parent drug and its metabolite in different body tissues and fluids.Thisresult of distribution volume at steady state (V_{dss}) almost consistent with the results of ceftiofur administration intravenously in lactating goats (0.18L/kg, Tohamy, 2008 and Fernández-Varón *et al*.,2016) ,camels (0.13L/kg Goudah, 2007),calves (0.25L/kg, Brown *et al*.,1996) , cattle (0.20 L/kg, Whittem *et al*.,1995), non lactating goats (0.25L/kg,courtin *et al*.,1997), water buffalo (0.25L/kg,Nie *et al*.,2016) .

The volume of distribution (V_{dss}) in this study was lower than that stated after intravenous administration of ceftiofur in in a 7-day,1month and 9 months age calves (0.34,0.33,,0.300L/kg, Brown *et al*.,1996) respectively,buffalo calves(0.53L/kg,Sudamrao, 2015) and cows (0.30L/kg,Liu *et al*., 2010).

The volume of distribution(V_{dss}) of ceftiofur in this study after i.v injection was agreed with other cephalosporin as cefepime intravenously in calves (0.21L/kg mg/kg, Ismail, 2005b) , bull camels(0.10L/kg mg/kg,Goudah *et al*.,2009).The result of (V_{dss}) in this study not agreeable with that reported in intravenous administration of ceftiofur in lactating Holstein dairy cows (1.33L/kg,Wang *et al*.,2018).

The differences between the value calculated for pharmacokinetic parameters can be related to the species of animal, formulations 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 (Riond *et al*., 1989).

The mean residence time (MRT) in this study is (9.05h) and agreed with the result recorded in 3and 9months calves (9.50 and 9.02h,Brown *et al*.,1996) , lactating Holstein dairy cows(8.60h, Wang *et al*.,2018) and water buffalo (8.4h, Nie *et al*.,2016). But not agree with result of 6 months old calves (6.76h,Brown *et al*.,1996), lactating and non lactating goats (3.8h,courtin *et al*.,1997), sheep (5.75h,Craigmill *et al*., 1997), camel (3.6h, Goudah, 2007)and lactating goats (4.27h, Fernández-Varón*et al*.,2016).And totally disagree with those reported in 7-day and 1month old calves (19.43 and 19.78h, Brown *et al*.,1996).The differences between the value calculated for pharmacokinetic parameters can be related to the species of animal, formulations 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 (Riond *et al*., 1989).

The rate of total body clearanceof ceftiofur (Cl_{tot}) was (0.013L/kg/h).In support of extended half-life distribution,lower(Cl_{tot}) of ceftiofur, added evidence in the current investigation for slower ceftiofur elimination after intravenous administration of 2.2mg/kg b.w.This (Cl_{tot}) value was almost comparable to those reported in7- day and1month old calves (0.017and 0.016L/kg/h,Brown *et al*.,1996), goats (0.013L/kg/h,Liu *et al*.,2010),water buffalo (0.029L/kg/h,Nie *et al*.,2016),bullcalves(0.03L/kg/h;Tohamy,2008), camel (0.03L/kg/h,Goudah, 2007),cattle(0.032L/kg/h,Whittem *et al*.,1995) and cows (0.033L/kg/h, Brown *et al*.,1996) . And nearly comparable to those reported in ceftiofur in goats (0.04L/kg/h, Fernández *et al*.,2016) and ceftiofur in buffalo calves (0.07 L/kg/h,Sudamrao, 2015) . But the results of (Cl_{tot}) in this study disagreed with those reported for ceftiofur in lactating and non lactating dairy goats (1.38 and 1.11L/kg/h, Courtin *et al*.,1997) and lactating holstein dairy cows (0.12L/kg/h,Wang *et al*., 2018).

After intravenous injection of ceftiofur in calves, the results showed elimination half-life ($t_{0.5(\beta)}$) (11.07 h) that nearly reliable with buffalo calves (12.6h,Sudamrao, 2015) and 3months old calves (8.22h,Brown *et al*.,1996).

The half-life of elimination of ceftiofur was longer in cows (15.3h, Liu *et al.,* 2010) and in 7-day and 1month old calves(16.10 and 17.16h,Brown *et al*.,1996) than in this

investigation. But this study result's slighty differ from those result from intravenous administration of ceftiofur in cattle (7.12h,Whittem *et al*.,1995), 9months and 6months old calves (7and 5.95h,Brown *et al*.,1996), water buffalo (7.8h,Nie *et al*.,2016)and lactating holstein dairy cows (7.45h,Wang *et al*.,2018).But disagree with the results from ceftiofur intravenous administration in sheep (4h,Craigmill *et al*., 1997), goats (4.23h,Courtin *et al*.,1997), camel (3.18h,Goudah, 2007), cows (5.10h,Tohamy,2008) and goats (4.21h,Fernández *et al*.,2016). The longer drug removal in calves may be owing to less maturation of bodies and/or removal procedures of ceftiofur and its metabolite relative to adult animals of distinct species (Brown *et al*., 1996).

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