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Comparative pharmacokinetic and renal clearance study of ceftiofur in cross breed Friesian and Buffalo calves

A. A. M. El-Gendy [1*], M. A. Tohamy [1], M. Ismail [2]

[1]*Pharmacology Department, Faculty of Veterinary Medicine, Beni-Suef University, Beni-Suef,Egypt*
[2]*Pharmacology Department, Faculty of Veterinary Medicine, Cairo University, Giza, Egypt*

The pharmacokinetic profile of ceftiofur sodium, a third generation cephalosporin, was studied in both Friesian and buffalo calves following a single intravenous and intramuscular administration of 2.2 mg kg^{-1} b.wt. in a cross over study with 15-day wash out period. After i.v administration the serum concentration-time curve of ceftiofur sodium was best fitted using two-compartments open model, with distribution half-lives ($t_{½(\alpha)}$) of 0.384 and 0.176 h., elimination half-lives ($t_{½(\beta)}$) of 5.047 and 1.607 h., mean residence time (MRT) of 6.926 and 2.072 h., volumes of distribution at steady-state (Vd_{ss}) of 0.206 and 0.134 L kg^{-1} and total body clearance (Cl_B) of 0.029 and 0.065 L kg^{-1} h^{-1} in Friesian and buffalo calves, respectively. Following intramuscular administration, the drug absorbed with half-lives of absorption ($t_{½(ab)}$) of 1.010 and 0.217 h., maximum serum concentrations (C_{max}) of 5.539 and 9.663 µg ml^{-1} which attained after (t_{max}) of 3.147 and 0.825 h. and the drug was eliminated with half-lives ($t_{½(el)}$) of 5.239 and 1.750 h. in Friesian and buffalo calves, respectively. The systemic intramuscular bioavailabilities were 89.82 and 99.7 %, while the in-vitro serum protein-binding tendencies were 39.68 and 14.44 % in Friesian and buffalo calves, respectively.

Ceftiofur sodium is a third-generation cephalosporin which is approved for use in cattle, pigs, poultry, horses and dogs in united states (Crosier *et al*., 1996). It has a broad-spectrum activity against Gram-positive and Gram-negative aerobic and some anaerobic bacteria. Owing to the antibiotic's high efficacy *against Pasteurella haemolytica, Pasteurella multocida* and *Haemophilus somnus* (Anonymous, 1991; Jaglan *et al*., 1992) ceftiofur sodium is approved in many countries worldwide for the treatment of bovine respiratory disease affecting beef and lactating dairy cattle (Clarke *et al*., 1996). In beef cattle, ceftiofur sodium is used primarily to treat shipping fever, an acute bronchopneumonia that often occurs following transport to feed lots (Sweeney and Smith, 1990). In dairy cattle, ceftiofur sodium is indicated for the treatment of enzootic calf pneumonia (Sweeney and Smith, 1990; Anonymous, 1991).

The pharmacokinetics of ceftiofur in various species was reviewed by Brown *et al.* (1991). Since that time, additional reports have appeared for cattle (Soback *et al*., 1991; Halstead *et al*., 1992; Erskine *et al*., 1995; Whittem *et al*., 1995; Brown *et al*., 1996), horses (Meyer *et al*., 1992; Jaglan *et al*., 1994), dogs (Brown *et al*., 1995), sheep (Craigmill *et al*., 1997) and dairy goats (Courtin *et al*., 1997). A preliminary report on the pharmacokinetics of ceftiofur in sheep (Craigmill *et al*., 1991) showed that the pharmacokinetics in sheep were very similar to those seen in cattle. Another preliminary report (Courtin *et al*., 1994) showed the pharmacokinetic parameters in goats to be similar to sheep.

However, there is no published information about the pharmacokinetics of ceftiofur sodium in buffalo calves. The purpose of this study was to determine the pharmacokinetic, bioavailability and renal clearance of ceftiofur sodium in buffalo calves compared to Friesian calves after a single intravenous and intramuscular injection in order to establish adequate dose regimen for potential clinical use in infection of calves with susceptible microorganisms.

* Corresponding author. Tel.: +20 105380875;
fax: +20 822327982.
E-mail address: elgendyab@yahoo.com
(A.A.M. El-Gendy).

Materials and Methods

Antimicrobial agent. Ceftiofur sodium (Excenel^{TM}, sterile powder, Upjhon Limited, Animal Health Crawley, RH10 2LZ, U.K.) was used. Each vial contains ceftiofur sodium, equivalent to 4 gm ceftiofur. Each ml of reconstituted solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

Animals. Five healthy, 6-9 months-old, female animals of each of cross-breed Friesian calves (weighing 163-209 kg b.wt.) and buffalo calves (weighing 144-351 kg b.wt.) were obtained from the animal farm, Faculty of Veterinary Medicine, Beni-Suef University. Animals were kept under good hygienic condition, feed on hay, concentrated mixture and green fodder and water *ad-libitum.* None of the animals were treated with antibiotics for one month prior to the study.

Experimental protocol. Two-way crossover design studies were used, with a 2 weeks washout period between successive experiments, where all animals were administered 2.2 mg kg^{-1} ceftiofur sodium (Folz *et al*., 1992; Halstead *et al*., 1992; Mahrt 1992; Meyer *et al*., 1992; Jaglan *et al*., 1994; Brown *et al*., 1995; Brown *et al*., 1996; Erskine *et al*., 1996; Courtin *et al*., 1997; Craigmill *et al*., 1997; Drew *et al*., 2004; Chenault *et al*., 2004; Wenz *et al*., 2005) as an intravenous bolus and after 2 weeks the animals were given the same dose by an intramuscular route. Blood samples were collected via vein puncture from jugular vein before and 5, 10, 15 and 30 min., 1, 2, 4, 6, 8, 12 and 24 h. post-administration. Blood samples were left to clot for 30 min. then centrifuged at 3000 r.p.m for 15 min. to obtain clear serum that was kept in deep freezer until being assayed. For urine collection each animal was catheterized using a folly balloon catheter No. 16 (Timedco, Atlanta, GA, USA). The urinary bladder was emptied before drug administration. Urine samples were collected prior and at 0.5, 1, 2, 4, 6, 8, 12 and 24 h. after drug administration. The amount of urine voided at each sampling time was measured and a 10 ml aliquot was stored at -20ºC until used for assessment.

Drug bioassay. Serum concentrations of ceftiofur sodium were determined by agar well-diffusion microbiological assay according to the method of Bennett *et al*. (1966) using *Micrococcus luteus* (American Type Culture Collection ATCC 9341) as an indicator organism (Erskine *et al*., 1995) and Mueller-Hinton agar (Oxoid LTD., Basingstoke, Hampshire, England). Standard concentrations of ceftiofur sodium were prepared in antibiotic-free calf serum and phosphate buffer saline (pH 6.2). The standard curves for serum and buffer were linear between 0.6 and 40 µg ml^{-1} ceftiofur sodium with a typical correlation coefficient > 0.99 for serum and buffer. The minimal quantification level for the assay method was 0.6 ug ml^{-1}. The difference of inhibition zone diameter between serum and buffer was used to calculate the *in-vitro* serum protein-binding tendency of ceftiofur sodium according to (Craig and Suh, 1980) by the following equation:

$$\text{Protein binding \%} = \frac{\text{Zone of inhibition in buffer} - \text{Zone of inhibition in serum}}{\text{Zone of inhibition in buffer}} \times 100$$

Estimation of endogenous creatinine clearance. The creatinine concentrations were measured in serum and urine samples according to the method described by Siest *et al*. (1985) using a commercial creatinine diagnostic kit (Bio Merieux, Paris, France). The endogenous creatinine and renal clearance (Cl_{cr} and Cl_R) were calculated according to formulas of Schirmeister *et al*. (1981):

$$Cl_{cr}(\text{ ml/min/10 kg b.wt }) = \frac{\text{Creatinine concentration in urine (µg/ml) x rate of urine flow(ml/min)}}{\text{Creatinine concentration in serum (µg/ml) x body weight (kg)/10}}$$

$$Cl_R(\text{min/10 kg b.wt.}) = \frac{\text{Drug concentration in urine (mg/dl) x rate of urine flow(ml/min)}}{\text{Drug concentration in serum (mg/dl) x body weight (kg)/10}}$$

Ceftiofur sodium clearance and creatinine clearance ratio were calculated according to (Osbaldiston, 1971) to determine the pathway of ceftiofur sodium elimination through the kidney.

Pharmacokinetic analysis. Serum concentrations (log_{10}) versus time curve were generated and best fitted by the aid of computer poly-exponential curve stripping program (R-strip, Micromath, Scientific software, USA). Data from each animal were fitted individually and the pharmacokinetic variables were computed by the aid of the software program. The hybrid rate constants of distribution and elimination phase (α and β), first order absorption and elimination rate constants [K_{ab} and K_{el}] and the corresponding extrapolated zero time intercepts (A and B), absorption, distribution and elimination half lives ($t_{½(ab)}$, $t_{½(\alpha)}$, $t_{½(\beta)}$ and $t_{½(el)}$), transfer rate constants (K_{12} and K_{21}), mean residence time (MRT), maximum serum concentration (C_{max}) and time to be achieved (t_{max}), volume of central compartment (V_c), apparent volume of distribution at steady state

(Vd_{ss}), total body clearance (Cl_B) were calculated according to Baggot (1978). Area under the serum concentration-time curve (AUC) was calculated by trapezoidal rule, whereas the intramuscular bioavailability (F) was calculated according to the following equation: (AUC i.m /AUC i.v) x 100, (Gibaldi and Perrier 1982). The statistical analysis were carried out according to (Snedecor and Cochran 1976).

Results

The serum concentration-time curves following intravenous and intramuscular administration of 2.2 mg kg^{-1}b.wt of ceftiofur sodium in Friesian and buffalo calves are shown (Fig.1,2). Following i.v administration, the serum concentration-time curves obeyed two-compartments open model in both Friesian and buffalo calves. The pharmacokinetic parameters were summarized (Table1). Ceftiofur sodium was distributed in buffalo calves significantly ($p<0.05$) faster rate than in cattle calves as evidenced by long distribution rate constant (α) 3.949 $h.^{-1}$ and short distribution half-life ($t_{½(\alpha)}$) 0.176 h. in buffalo calves compared to 1.804 $h.^{-1}$ and 0.384 h., respectively in Friesian calves.

Small volumes of the central compartment (V_c) 0.132 and 0.076 L kg^{-1} and of distribution (Vd_{ss}) 0.206 and 0.134 L kg^{-1} were obtained in Friesian and buffalo calves, respectively. The results indicated a limited distribution of the drug. The drug was eliminated at slower rate in Friesian calves ($p<0.01$) than in buffalo calves as indicated by long elimination half-lives ($t_{½(\beta)}$) 5.047 h. compared to 1.607 h., respectively. Table (2) shows the resulting pharmacokinetic parameters following intramuscular administration. The concentrations in serum reached a peak at a significant ($p<0.01$) long time (t_{max}) of 3.147 in Friesian calves compared to 0.825 h. in buffalo calves and the respective C_{max} values were 5.539 and 9.663 ug ml^{-1}, respectively. Ceftiofur sodium was absorbed in buffalo calves in significantly ($p<0.01$) faster rate compared with Friesian calves as indicated by long absorption rate constant (k_{ab}) 3.200 $h.^{-1}$ and short absorption half-life ($t_{½(ab)}$) 0.217 h. in buffalo calves compared to 0.686 $h.^{-1}$ and 1.010 h. in Friesian calves, respectively. Elimination half-lives of 5.239 and 1.750 h., systemic bioavailabilities of 89.82 and 99.7 % and serum protein-binding tendencies of 39.68 and 14.44 % were recorded in Friesian and buffalo calves, respectively. Ceftiofur sodium was found to be excreted at high concentrations in urine of Friesian and buffalo calves following both i.v. and i.m. routes and extends up to 24 h. in Friesian calves and 8-12 h. in buffalo calves post-administration (Table 3). Also the ceftiofur sodium to creatinine clearance was less than one (Tables 4, 5).

Discussion

Interpretation of results of the present study takes into consideration the assay method used (microbiological) and its sensitivity. The microbiological assay method did not, however distinguish between the parent drug (ceftiofur) and its active metabolite (desfuroylceftiofur). The presence of active metabolite may not necessarily interfere with determination of a therapeutic dosage regimen (Sams, 1994 and Gavrielli *et al*., 1995). Cephalosporins offer the advantages of low toxicity and a broad antimicrobial spectrum (Caprile, 1988). Ceftiofur sodium is favored due to its wide range of antimicrobial therapy and its long storage stability after reconstitution, 7 days when refrigerated and frozen reconstituted solutions are stable for up to 8 weeks (Plumb, 1995). Following intravenous administration of ceftiofur sodium to Friesian and buffalo calves at a dose of 2.2 mg kg-1., the drug concentration-time data for each animal was best fitted individually using a two-compartment open model. A similar kinetic profile was recorded in dairy cattle (Whittem *et al*., 1995), calves (Halstead *et al*., 1992; Vermeersch *et al*., 1996), dairy goats (Courtin *et al*., 1997) and sheep (Craigmill *et al*., 1997).

Disappearance of the drug from the serum of Friesian and buffalo calves was characterized by slower ($p<0.05$) distribution phases ($t_{½(\alpha)}$) and slower ($p<0.01$) elimination phases ($t_{½(\beta)}$) in Friesian calves than in buffalo calves as indicated by values of 0.384 and 5.047 h. vs. 0.176 and 1.607 h., respectively. This result may be due to lower serum protein binding tendency of the drug in buffalo than Friesian calves. The result of $t_{½(\alpha)}$ in Friesian (0.384 h.) is nearly similar to those recorded in sheep 0.457 h. (Craigmill *et al*., 1997) and dairy goats 0.470 h. (Courtin *et al*., 1997). While, the $t_{½(\alpha)}$ in buffalo calves 0.176 h. is nearly similar to that reported in sheep 0.108 h. (Craigmill *et al*., 1997). Ceftiofur sodium has been shown to have a relatively long elimination half-life similar to that reported in cattle 7.12 and 6.6 h. (Soback *et al*., 1991 and Whittem *et al*., 1995), calves 3.2 h. (Vermeersch *et al.,* 1996), dairy goats 2.86-4.23 h.(Courtin *et al*., 1997) and sheep 4-5.83 h.

Table (1): Mean (±SE) kinetic parameters of ceftiofur sodium following a single intravenous administration of 2.2 mg kg^{-1} b.wt in Friesian and buffalo calves (n=5).

Parameter	Unit	Friesian calves	Buffalo calves
C_p^o	µg ml^{-1}	16.604 ± 1.28	28.929 ± 1.9 **
A	µg ml^{-1}	7.009 ± 0.459	16.006 ± 1.40 *
B	µg ml^{-1}	9.595 ± 0.561	12.922 ± 1.16
α	h^{-1}	1.804 ± 0.097	3.949 ± 0.263 **
β	h^{-1}	0.137 ± 0.040	0.431 ± 0.071 *
k_{21}	h^{-1}	1.100 ± 0.079	2.003 ± 0.099 **
K_{el}	h^{-1}	0.225 ± 0.011	0.851 ± 0.046 **
k_{12}	h^{-1}	0.616 ± 0.069	1.527 ± 0.078 **
$t_{½(\alpha)}$	h	0.384 ± 0.071	0.176 ± 0.022 *
$t_{½(\beta)}$	h	5.047 ± 0.399	1.607 ± 0.066 **
MRT	h	6.926 ± 0.477	2.072 ± 0.092 **
AUC	µg ml^{-1} h^{-1}	75.38 ± 9.224	34.812 ± 2.98 *
AUMC	µg ml^{-1} h^{-1}	510.77 ± 41.5	70.470 ± 8.01 **
Vc	L kg^{-1}	0.132 ± 0.077	0.076 ± 0.004
Vd_{ss}	L kg^{-1}	0.206 ± 0.032	0.134 ± 0.024
Cl_B	L kg^{-1} h^{-1}	0.029 ± 0.008	0.065 ± 0.001 *

* $p<0.05$ ** $p<0.01$

C_p^o ceftiofur concentration at zero time; A, B zero-time intercepts of the biphasic disposition curve; α, β hybrid rate constants representing the slopes of distribution and elimination phases, respectively; k_{21} first-order constant for transfer from peripheral to central compartment; K_{el} elimination rate constant; k_{12} first-order constant for transfer from central to peripheral compartment; $t_{½(\alpha)}$ distribution half-life; $t_{½(\beta)}$ elimination half-life; MRT mean residence time; AUC area under curve; AUMC area under moment curve; Vc apparent volume of the central compartment; Vd_{ss} volume of distribution at steady state; Cl_B total body clearance.

Table (2): Mean (± SE) kinetic parameters of ceftiofur sodium following a single intramuscular administration of 2.2 mg kg^{-1} b.wt in Friesian and buffalo calves (n=5).

Parameter	Unit	Friesian calves	Buffalo calves
k_{ab}	h^{-1}	0.686 ± 0.043	3.200± 0.196 **
K_{el}	h^{-1}	0.132 ± 0.025	0.396± 0.053 **
$t_{½(ab)}$	µg ml^{-1}	1.010 ± 0.088	0.217± 0.033 **
$t_{½(el)}$	h	5.239 ± 0.308	1.750± 0.083 **
C_{max}	h	5.539 ± 0.471	9.663± 0.083 **
t_{max}	h	3.147 ± 0.345	0.825± 0.057 **
AUC	µg ml^{-1} h^{-1}	67.712 ± 4.98	34.700± 1.85 **
AUMC	µg ml^{-1} h^{-1}	559.17 ± 39.5	92.94± 7.730 **
MRT	h	9.015 ± 0.492	2.837± 0.194 **
F	%	89.82 ± 6.761	99.7± 7.009

** $p<0.01$

Protein binding % in Friesian calves was 39.68±3.07 and 14.44±0.89 in buffalo calves. k_{ab} first-order absorption rate constant; K_{el} first-order elimination rate constant; C_{max} maximum serum concentration; t_{max} time to peak serum concentration; $t_{0.5(ab)}$ absorption half-life; $t_{0.5(el)}$ elimination half-life; F fraction of drug absorbed systemically after i.m injection.

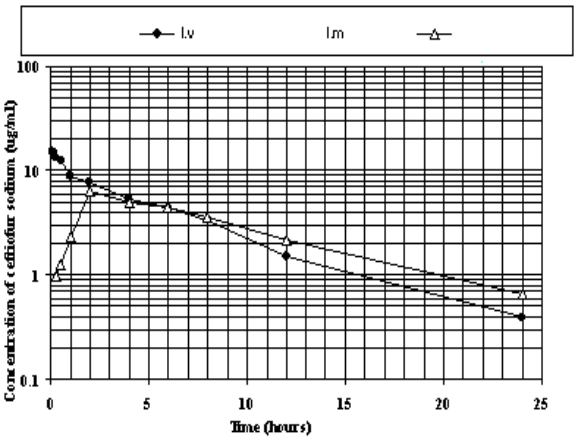

Fig. (1): Semilogarithmic graph depicting the time-concentration of ceftiofur sodium in serum of Frisian calves after a single intravenous and intramuscular injection of 2.2 mg/kg b.wt.

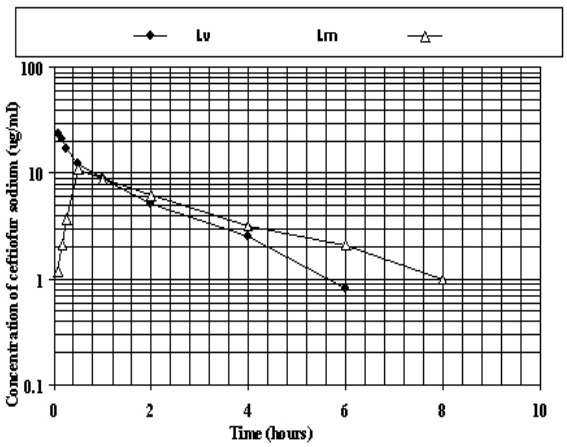

Fig. (2): Semilogarithmic graph depicting the time-concentration of ceftiofur sodium in serum of buffalo calves after a single intravenous and intramuscular injection of 2.2 mg/kg b.wt.

Table (3): Urine concentration of ceftiofur sodium following intravenous (i.v) and intra-muscular (i.m) administration of 2.2 mg kg^{-1} b.wt. in Friesian and buffalo calves (n= 5).

Time (h)	Urine concentration of ceftiofur sodium µg ml^{-1}(Mean ± SE)			
	Friesian calves		Buffalo calves	
	i.v	i.m	i.v	i.m
0.5	127.4 ± 10.2	86.18 ± 7.3	243.0 ± 22.4	178.2 ± 17.3
1	192.1 ± 15.6	105.1 ± 9.5	466.3 ± 44.6	330.1 ± 31.4
2	288.9 ± 22.4	167.4 ± 13.4	263.9 ± 28.0	198.2 ± 17.6
4	211.4 ± 18.7	136.3 ± 12.7	163.1 ± 14.6	112.8 ± 9.12
6	168.7 ± 19.1	109.2 ± 9.5	96.3 ± 8.07	79.45 ± 7.03
8	139.3 ± 14.2	85.8 ± 9.61	9.36 ± 0.77	26.34 ± 3.21
12	74.46 ± 7.34	43.42 ± 6.10	B	5.11 ± 0.20
24	4.65 ± 0.185	7.04 ± 0.42	B	B

*B:Below the limit of the sensitivity of the assay method used.

Table (4): Ceftiofur sodium / creatinine clearance ratio following intravenous and intramuscular administration of ceftiofur sodium at a dose of 2.2 mg kg^{-1} b.wt. in Friesian calves (n=5).

Time (h)	i.v			i.m		
	Ceftiofur sod. clearance ml min^{-1} 10 kg^{-1}	Creatinine clearance ml min^{-1} 10 kg^{-1}	Ratio	Ceftiofur sod. clearance ml min^{-1} 10 kg^{-1}	Creatinine clearance ml min^{-1} 10 kg^{-1}	Ratio
0.5	2.93±0.12	18.69±1.3	0.157±0.07	6.46±0.052	7.00±0.54	0.923±0.07
1	2.42±0.17	11.69±0.91	0.207±0.02	3.74±0.18	9.71±0.88	0.385±0.02
2	3.63±0.22	11.36±1.01	0.320±0.01	1.57±0.21	9.72±0.65	0.162±0.04
4	3.79±0.19	11.96±1.37	0.317±0.04	1.50±0.09	6.93±0.34	0.216±0.06
6	1.78±0.08	6.18±0.53	0.288±0.06	0.87±0.03	3.29±0.21	0.264±0.03
8	1.18±0.06	5.04±0.34	0.234±0.06	0.58±0.01	3.52±0.22	0.165±0.04
12	1.84±0.10	6.01±0.61	0.306±0.07	1.12±0.09	5.85±0.36	0.191±0.02

ND:Not detected.

Table (5): Ceftiofur sodium / creatinine clearance ratio following intravenous and intramuscular administration of ceftiofur sodium at a dose of 2.2 mg kg^{-1} b.wt. in buffalo calves (n=5).

Time (h)	i.v			i.m		
	Ceftiofur sod. clearance ml min^{-1} 10 kg^{-1}	Creatinine clearance ml min^{-1} 10 kg^{-1}	Ratio	Ceftiofur sod. clearance ml min^{-1} 10 kg^{-1}	Creatinine clearance ml min^{-1} 10 kg^{-1}	Ratio
0.5	1.58±0.08	10.12±0.9	0.156±0.03	2.43±0.10	15.11±1.14	0.161±0.02
1	3.19±0.41	5.82±0.36	0.548±0.07	1.94±0.21	6.94±0.74	0.280±0.04
2	3.00±0.34	5.80±0.55	0.517±0.06	1.19±0.30	4.51±0.61	0.264±0.05
4	6.20±0.70	6.26±0.34	0.990±0.08	2.46±0.19	6.96±0.68	0.353±0.04
6	4.40±0.35	9.22±0.77	0.477±0.06	1.54±0.17	3.94±0.044	0.391±0.07
8	ND	0.62±0.08	-	1.35±0.31	5.00±0.67	0.270±0.01
12	ND	4.52±0.37	-	ND	7.05±0.35	-

ND:Not detected.

(Craigmill *et al*., 1997).

The volume of distribution at steady-state (Vd_{ss}) is an accurate indication of the diffusion of the drug into the body tissues (Gilman *et al*., 1980; Galinsky and Svensson, 1995). The small volumes of distribution of ceftiofur sodium at steady-state (Vd_{ss}) 0.206 and 0.134 L kg^{-1} in Friesian and buffalo calves, respectively, indicating poor distribution of the drug to the extra-vascular tissues. This poor distribution is probably due to its poor lipid solubility and relatively low pka (Amer *et al.,* 1998). These values were close to the values reported in dairy cattle 0.200 L kg-1 (Whittem *et al.,* 1995), calves 0.284-0.345 L kg-1 (Brown *et al.,* 1996) and dairy goats 0.25-0.31 L kg-1 (Courtin *et al.,* 1997). The drug has been showed a significant longer mean residence time (MRT) ($p<0.01$) in Friesian calves 6.926 h. than in buffalo calves 2.072 h. The result in Friesian calves was supported by those recorded in dairy cattle 6.48 h. (Whittem *et al.,* 1995) and sheep 5.75-7.38 h. (Craigmill *et al.,* 1997).

In the present study, the total body clearance (Cl_B) of ceftiofur sodium was very slow in Friesian and buffalo calves (0.030 and 0.065 L kg^{-1} $h.^{-1}$), indicating that ceftiofur excretion is not only by glomerular filtration but also by extra-renal pathway (Soback *et al*., 1989). These values were similar to that reported in dairy cattle 0.032 L kg^{-1} $h.^{-1}$ (Whittem *et al*., 1995), dairy goats 0.067-0.089 L kg^{-1} $h.^{-1}$ (Courtin *et al*., 1997) and calves 0.0167 L kg $h.^{-1}$ (Brown *et al*., 1996). The drug cleared at a significant faster rate ($p<0.05$) in buffalo calves than in Friesian calves as indicated by large Cl_B in buffalo calves 0.065 L kg^{-1} $h.^{-1}$ compared to 0.030 L kg^{-1} $h.^{-1}$ in Friesian calves. This result may be attributed to the lower protein binding capacity of the drug in buffalo calves than in Friesian calves.

Following intramuscular administration, the peak concentrations (C_{max}) achieved with 2.2 mg kg-1 dose were 5.539 µg ml^{-1} in Friesian calves and 9.663 ug ml^{-1} in buffalo calves. The value of C_{max} in buffalo calves is similar to those recorded in calves 8.8 µg ml^{-1} (Halstead *et al*., 1992) and sheep 7.13 µg ml^{-1} (Craigmill *et al*., 1997). Also the value of C_{max} in Friesian calves is similar to those recorded in dairy goats 4.57 ug ml^{-1} (Courtin *et al*., 1997) and sheep 4.33 µg ml^{-1} (Craigmill *et al*., 1997). This study show that ceftiofur sodium was absorbed at a faster rate ($p<0.01$) in buffalo calves than Friesian calves as indicated by a doubling of C_{max} 9.663 µg ml^{-1} and short absorption half-life ($t_{½(ab)}$) 0.217 h. in buffalo calves as compared to 5.539 µg ml^{-1} and 1.010 h. in Friesian calves. This result was supported by the lower protein binding capacity of the drug in buffalo calves than in Friesian calves. Peak serum concentration attained at a shorter ($p<0.01$) time (tmax) 0.825 h. in buffalo calves than in Friesian calves 3.147 h.

Absorption of ceftiofur sodium was rapid in buffalo calves than in Friesian calves as indicated by large absorption rate constant (k_{ab}) 3.200 $h.^{-1}$ and short absorption half-life ($t_{½(ab)}$) 0.217 h. compared to 0.686 $h.^{-1}$ and 1.010 h., respectively. The $t_{½(ab)}$ in buffalo calves is similar to that in dairy goats 0.20-0.27 h. (Courtin *et al*., 1997).

Ceftiofur sodium was eliminated at slower rate ($p<0.01$) in Friesian calves than in buffalo calves as indicated by long elimination half-lives ($t_{½(el)}$) and mean residence time (MRT) in Friesian calves 5.239 h. and 9.015 h. compared to 1.750 h. and 2.837 h. in buffalo calves. The previously mentioned results of $t_{½(el)}$ and MRT in Friesian calves are close to values recorded in sheep 6.48-7.65 h. and 7.85-9 h. (Craigmill *et al*., 1997).

Intramuscular bioavailability of ceftiofur sodium was 89.82 % in Friesian calves and 99.7 % in buffalo calves, reflexing good absorption of the drug from the site of i.m injection. These values are similar to that recorded in dairy goats and sheep 100 % (Courtin *et al*., 1997; Craigmill *et al*., 1997). Bioavailability of ceftiofur sodium is complete in calves after intramuscular injection (Brown *et al*., 1996). Serum protein-binding capacity of the drug is significantly higher ($p<0.01$) in Friesian calves than in buffalo calves as indicated by a percent of binding 39.68 % in Friesian calves compared to 14.14 % in buffalo calves.

The higher concentrations of ceftiofur sodium were found in urine, indicating that the drug may be an efficacious drug for treating urinary tract infections caused by susceptible microorganisms. The ratios between ceftiofur clearance to creatinine clearance was less than one, indicating that the glomerular filtration is the main pathway for ceftiofur elimination through the kidney. This finding was in agreement with results reported for other 4^{th} generation cephalosporin (cefepime) in humans (Barbhaiya *et al*., 1992; Kalman *et al*. 1992), Friesian calves (Ismail, 2005a) and ewes (Ismail, 2005b).

Ceftiofur sodium has been shown to have excellent in vitro activity against a variety of gram-negative veterinary respiratory pathogens such as *P. haemolytica, P. multocida, H. somnus and Escherichia coli* (Yancey *et al*., 1987; Watts *et al*., 1994; Salmon *et al*., 1995).

The minimum inhibitory concentration (MIC90) of the drug for *P. haemolytica*, *P. multocida* and *H.somnus* was < 0.03 ug ml^{-1} (Salmon *et al*., 1996). Its MIC_{90s} for *Actinobacillus pleuropneumonia,* Haemolytic streptococci, *Klebsiella pneumoniae* and *E. coli* were in the range of < 0.03-1 µg ml^{-1} (Salmon *et al*., 1996; Deshpande *et al*., 2000).

Conclusion

Based on the pharmacokinetic parameters observed in this study and if we make a relationship between the concentrations of ceftiofur sodium in serum and urine with the MIC_{90s} of microorganisms isolated from other animal species, dosage regimen of 2.2 mg kg^{-1} administered two times daily in Friesian calves and three times daily in buffalo calves could be an appropriate choice for the treatment of calves with respiratory tract infections caused by *P. haemolytica, P. multocida* and *H. somnus*. Also, such dosage regimen can be used for treatment of other infections in calves caused by the susceptible microorganisms.

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دراسة مقارنه للمسار الحركي للسيفتيوفور في عجول الأبقار والجاموس

أجريت هذه الدراسة على عدد خمسة إناث من عجول الأبقار وخمسة إناث من عجول الجاموس يتراوح الوزن من ١٦٣-٢٠٩ و ١٤٤-٣٥١ كجم ومن ٦-٩ شهور في العمر على التوالي. حيث تم إعطائهم عقار سيفتيوفور الصوديوم ٢,٢ مجم/كجم جرعة واحدة عن طريق الحقن الوريدي وبعد أسبوعين تم إعطائهم جرعة عضلية أخرى من نفس العقار. تم تجميع عينات من الدم في أوقات مختلفة من ٠,٠٨٣-٢٤ ساعة من بداية الحقن. وقد أظهرت الدراسة انه بعد الحقن الوريدي قد سلك العقار منحنى التركيز بالدم مقابل الزمن مسلك ثنائي الحجرات في عجول الأبقار و الجاموس، وفترة عمر النصف للتوزيع ((t0.5(α) ٠,١٧٦ و ٠,٣٨٤ ساعة وفترة عمر النصف للإخراج ((t0.5(β ٥,٠٤٧ و ١,٦٠٧ ساعة بعد حقن الحيوانات بجرعة ٢,٢ مجم/كجم على التوالي . وقد كان حجم توزيع العقار للأنسجة صغيرا (Vdss) ٠,٢٠٦ و ٠,١٣٤ لتر/ كجم على التوالي. ووجد أن معدل طرح سيفتيوفور الصوديوم (ClB) ٠,٠٣٠ و ٠,٠٦٥ لتر/كجم/ساعة على التوالي. أما بعد الحقن العضلي فقد كان أقصى تركيز للدواء (Cmax) ٥,٥٣٩ و ٩,٦٦٣ ميكروجرام / مللي وبعد (tmax) ٣,١٤٧ و ٠,٨٢٥ ساعة من الحقن على التوالي . وقد كانت فترة عمر النصف للامتصاص ((t0.5(ab ١,٠١٠ و ٠,٢١٧ ساعة وفترة عمر النصف للإخراج ((t0.5(el ٥,٢٣٩ و ١,٧٥٠ ساعة على التوالي. وقد وجد أن معدل الإتاحة الحيوية بعد الحقن العضلي ٨٩,٨٢ و ٩٩,٧ % على التوالي. أما نسبة الارتباط ببروتين المصل فكانت ٣٩,٦٨ و ١٤,١٤% على التوالي. وكانت تركيزات العقار في الدم تزيد عن أقل تركيز (MIC90) مثبط للبكتيريا على مدى ١٢ ساعة من بداية الحقن في عجول البقر و ٨ ساعات في عجول الجاموس . وقد خلصت الدراسة إلى إمكانية استخدام عقار سيفتيوفور الصوديوم بجرعة ٢,٢ مجم / كجم من وزن الجسم كل ١٢ ساعة في عجول البقر و كل ٨ ساعات في عجول الجاموس لعلاج أمراض الجهاز التنفسي المسببة بالبكتريا الحساسة لهذا العقار.