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DISPOSITION KINETICS AND DOSAGE REGIMEN OF CEFTRIAXONE IN CROSSBRED CALVES (SHORT COMMUNICATION)

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Disposition kinetics and urinary excretion of ceftriaxone were investigated in healthy crossbred calves after its single intravenous administration (10 mg kg^{-1}). Based on kinetic parameters, an appropriate dosage regimen of ceftriaxone in calves was calculated. The peak plasma level of ceftriaxone at 1 min was 84.0 ± 1.55 µg ml^{-1} which declined to 0.43 ± 0.05 µg ml^{-1} at 8 h. The value of elimination half-life ($t_{1/2\beta}$), volume of distribution $V_{d\ (area)}$ and total body clearance (Cl_B) were 4.39 ± 0.63 h, 1.91 ± 0.19 L kg^{-1} and 0.31 ± 0.01 L kg^{-1} h^{-1}, respectively. Approximately 41 per cent of total administered drug was recovered in the urine within 24 h of its administration. The plasma protein binding of ceftriaxone was found to be concentration dependent with an overall mean of 38.55 per cent. The binding capacity of ceftriaxone to plasma proteins and the dissociation rate constant of protein-drug complex were $20.1 \times 10^{-8} \pm 18.4 \times 10^{-8}$ mole g^{-1} and $1.07 \times 10^{-6} \pm 0.52 \times 10^{-6}$ mole, respectively. An appropriate intravenous dosage regimen of ceftriaxone in cattle would be 12 mg kg^{-1} repeated at 24 h.

Key words: Ceftriaxone, disposition kinetics, urinary excretion, dosage regimen, calf

Cephalosporin antibiotics are being increasingly employed in veterinary medicine for the treatment of mild to severe bacterial infections. Ceftriaxone, a third-generation cephalosporin is characterised by its excellent antibacterial activity against Gram-negative microorganisms in addition to a wide range of Gram-positive bacteria. For the judicious use of an antibiotic, a rational dosage regimen based on its pharmacokinetic investigation is a prerequisite. The disposition of ceftriaxone has been extensively investigated in man (Benet and Williams, 1991), rats (Hakim et al., 1989), mares (Gardner and Aucoin, 1994) and chickens (Junge et al., 1994) but such data are lacking in cattle except for one report in neonatal calves (Soback and Ziv, 1988). The purpose of this study was to investigate the disposition kinetics, urinary excretion and *in vitro* plasma protein binding of ceftri-

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axone in crossbred calves. From the disposition kinetic data, recommendations were made for the optimal dosage regimen of ceftriaxone in cattle.

The experiments were performed on ten healthy male crossbred calves (1–1½ years of age) weighing 60–175 kg. The animal were kept under the usual conditions. The study was conducted in two phases. In Phase I six calves were used for the evaluation of disposition kinetics of ceftriaxone. Ceftriaxone (Zieta Pharmaceuticals, Ahmedabad) was injected as 10 per cent solution in sterilised distilled water at the dose rate of 10 mg kg^{-1} into the left jugular vein. Blood samples were withdrawn from the contralateral jugular vein into heparinized glass tubes at different time intervals, viz. 1, 2.5, 5, 7.5, 10, 15, 20, 30, 45, 60 and 90 min and 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h after drug administration. Samples were centrifuged at room temperature and plasma was kept at –20 °C until the analysis, which usually took place on the day after collection.

In Phase II, urinary excretion of ceftriaxone was investigated in 4 calves. The dose and route of administration of the drug were the same as employed in Phase I of the study. The animals were placed into metabolic stalls prior to the start of the experiment. The metabolic stalls are designed in such a way that the whole amount of urine voided by the animals is collected without contamination and spillage. The urine samples were collected at predetermined time intervals, viz. 1, 2, 3, 6, 9, 12, 18 and 24 h after drug administration. The whole volume of urine was measured and after filtration 10 ml urine samples were taken for analysis.

The protein binding of ceftriaxone was determined by employing the standard equilibrium dialysing technique (Kunin et al., 1966), and the binding capacity of plasma proteins to ceftriaxone and the dissociation rate constant of protein-drug complex were determined as described by Pilloud (1973).

The concentration of ceftriaxone in plasma and urine was determined by the standard microbiological cylinder cup plate bioassay technique using *Sarcina lutea* (ATCC 9341) as test organism (Simon and Yin, 1970; Arret et al., 1971). The assay could detect 0.10 µg ml^{-1} of ceftriaxone.

The plasma concentration – time data for each calf were best fitted in a three-compartment open model and the pharmacokinetic parameters were calculated using the general formulas (Baggot, 1977; Gibaldi and Perrier, 1982).

The semi-logarithmic plot of plasma concentration of ceftriaxone against time was best fitted in three compartments and hence the disposition kinetics of ceftriaxone was calculated by a triexponential equation. However, the disposition kinetics of ceftriaxone in neonatal calves was described by a biexponential equation (Soback and Ziv, 1988).

At 1 min of injection, the peak plasma concentration was 84.0 ± 1.55 µg ml^{-1}, which rapidly declined to 17.9 ± 0.95 µg ml^{-1} at 20 min and then gradually declined to 2.61 ± 0.38 µg ml^{-1} at 2 h. The drug was not detected in plasma after 8 h of administration. The pharmacokinetic parameters are summarised in Table 1.

Table 1

Disposition kinetic parameters of ceftriaxone in calves following a single intravenous dose of 10 mg kg^{-1} body weight

Pharmacokinetic parameter	Unit	Calf number						Mean ± SEM
		1	2	3	4	5	6	
C_p°	$\mu g\,ml^{-1}$	108.2	112.6	119.2	150.7	113.1	124.2	121.3 ± 6.30
A_1	$\mu g\,ml^{-1}$	89.5	96.5	87.2	126.2	77	91.5	94.7 ± 6.83
A_2	$\mu g\,ml^{-1}$	17	13.6	30.5	23.1	34.8	31	25.0 ± 3.45
B	$\mu g\,ml^{-1}$	1.59	2.51	1.48	1.39	1.25	1.73	1.66 ± 0.18
α_1	h^{-1}	11.82	13.66	16.34	17.94	15.29	19.66	15.78 ± 1.16
α_2	h^{-1}	1.113	0.971	2.033	1.244	1.744	1.819	1.491 ± 0.18
β	h^{-1}	0.182	0.232	0.183	0.133	0.097	0.203	0.172 ± 0.02
$t_{1/2}\alpha_1$	h	0.059	0.051	0.042	0.039	0.045	0.035	0.045 ± 0.003
$t_{1/2}\alpha_2$	h	0.611	0.714	0.341	0.557	0.398	0.381	0.500 ± 0.06
$t_{1/2\beta}$	h	3.8	2.99	3.79	5.2	7.17	3.42	4.39 ± 0.63
AUC	$\mu g\,ml^{-1}h$	31.35	31.89	28.44	36	37.91	30.18	32.63 ± 1.47
AUMC	$\mu g\,ml^{-1}h^2$	61.93	60.39	52.02	93.28	145.39	51.58	77.43 ± 14.9
V_C	$L\,kg^{-1}$	0.09	0.09	0.08	0.07	0.09	0.08	0.08 ± 0.003
V_T	$L\,kg^{-1}$	0.91	0.91	0.92	0.93	0.91	0.92	0.92 ± 0.003
$V_{d\,(area)}$	$L\,kg^{-1}$	1.75	1.35	1.92	2.08	2.73	1.63	1.91 ± 0.19
$V_{d\,(ss)}$	$L\,kg^{-1}$	0.63	0.59	0.64	0.72	0.01	0.57	0.69 ± 0.07
$C1_B$	$L\,kg^{-1}h^{-1}$	0.32	0.31	0.35	0.28	0.26	0.33	0.31 ± 0.01
T/P	ratio	17.9	14.2	21.9	30.4	29.8	19.3	22.3 ± 2.68
MRT	h	1.98	1.89	1.83	2.59	3.84	1.71	2.31 ± 0.33
t_d	h	21.5	16.8	21.4	29.4	40.3	19.2	24.8 ± 3.6

C_p° = plasma drug concentration at zero time; A_1, A_2 and B = zero time plasma drug concentration intercepts of regression lines of distribution phases I, II, and elimination phase, respectively; α_1, α_2 = rate constants of distribution phases I and II, respectively; β = elimination rate constant; $t_{1/2}\alpha_1$, $t_{1/2}\alpha_2$= half lives of distribution phases I and II, respectively; $t_{1/2\beta}$ = elimination half-life; AUC = area under the plasma concentration - time curve; AUMC = area under the first moment of plasma concentration - time curve; V_c = volume of central compartment; V_T = volume of tissue compartment; $V_{d\,(area)}$ = apparent volume of distribution; $V_{d\,(SS)}$ = steady-state volume of distribution; $C1_B$ = total body clearance; T/P = tissue/plasma ratio; MRT = mean residence time; t_d = total duration of pharmacological effect

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The high value of the distribution rate constant α_1 (15.78 h^{-1}) indicates rapid transfer of drug from central to peripheral compartment I. The low value of α_2 (1.49 h^{-1}) indicates gradual transfer of drug to peripheral compartment II. The calculated volume of distribution (1.91 ± 0.19 L kg^{-1}) indicates an extensive penetration of the drug into various body tissues and fluids. The high value of the T/P ratio further confirmed the extensive penetration of ceftriaxone into body tissues and fluids.

The elimination half-life of ceftriaxone in healthy calves calculated in the present study was 4.39 ± 0.63 h which is considerably longer than that found in mares (Gardner and Aucoin, 1994), rats (Hakim et al., 1989) and neonatal calves (Soback and Ziv, 1988). The $t_{1/2\beta}$ value of ceftriaxone after intravenous administration in mares, rats and neonatal calves was calculated to be 0.81 ± 0.16 h, 0.48 h and 1.4 ± 0.6 h, respectively. Ceftriaxone has a very long elimination half-life of 7.3 ± 1.6 h in human beings (Benet and Williams, 1991).

Table 2 summarises the data on urinary excretion of ceftriaxone after its single intravenous administration. The highest drug concentration was obtained within 2 h and about 41 per cent of the total administered drug was recovered in the urine within 24 h. A rapid urinary excretion has also been reported in neonatal calves (Soback and Ziv, 1988) and in man (Benet and Williams, 1991).

Table 2

Urinary excretion of ceftriaxone in calves following a single intravenous dose of 10 mg kg^{-1} body weight

Time interval (h)	Urinary drug concentrations (μg ml^{-1})	Extent of excretion (% of total dose)
0–1	422.2 ± 164.4	14.3 ± 7.8
1–2	711.7 ± 135.2	14.4 ± 3.34
2–3	305.6[a]	7.92
3–6	427.6 ± 122.5	14.8 ± 2.74
6–9	126.1 ± 29.2	2.27 ± 0.64
9–12	14.7 ± 5.43	0.34 ± 0.11
12–18	28.8 ± 6.71	0.91 ± 0.35
18–24	0.95 ± 0.16	0.07 ± 0.03
Total		41.4 ± 1.69

[a]value of a single animal

Table 3 shows the *in vitro* plasma protein binding of ceftriaxone at different concentrations. The extent of protein binding varied from 11.9 to 71.1 per cent with a mean of 38.6 per cent. The results on plasma protein binding of ceftriaxone revealed that the extent of binding is inversely proportional to the plasma concen-

tration. The results of the present investigation agree with those of Popick et al. (1987) and Hakim et al. (1989) who reported that the protein binding of ceftriaxone was concentration dependent in rats, baboons, human beings and rabbits. In rats, ceftriaxone was highly bound (approximately 90–95%) at low plasma concentrations (< 10 μg ml^{-1}) but considerably less binding (approximately 60%) was obtained at high plasma concentrations (> 400 μg ml^{-1}).

Table 3

In vitro binding of ceftriaxone to plasma proteins of calves

Exp. no.	Extent of binding (%)						β_i	K_β
	Concentration of ceftriaxone (μg ml^{-1})							
	2	5	10	25	50	75	(mole g^{-1})	(mole)
1	53.0	68.2	42.9	30.4	16.2	8.72	1.95×10^{-8}	1.06×10^{-6}
2	56.5	73.8	34.5	45.96	23.8	11.6	1.42×10^{-8}	1.97×10^{-6}
3	51.0	71.4	32.2	38.88	19.5	15.3	57.0×10^{-8}	0.17×10^{-6}
Mean	53.5	71.1	36.5	38.4	19.8	11.9	20.1×10^{-8}	1.07×10^{-6}
± SEM	± 1.61	± 0.58	± 3.25	± 4.50	± 2.21	± 1.90	$\pm 18.4 \times 10^{-8}$	$\pm 0.52 \times 10^{-6}$

The capacity of calf plasma proteins to bind ceftriaxone (β_i) and the dissociation rate constant of protein-drug complex (K_β) were also determined. In three different experiments the value of β_i and K_β of ceftriaxone were calculated to be $20.1 \times 10^{-8} \pm 18.4 \times 10^{-8}$ mole g^{-1} and $1.07 \times 10^{-6} \pm 0.52 \times 10^{-6}$ mole, respectively.

Based on these results, to maintain the minimum therapeutic plasma concentration of 0.1 μg/ml (Soback and Ziv, 1988), the most appropriate dosage regimen of ceftriaxone in cattle was calculated to be 12 mg kg^{-1} repeated at 24 h intervals. Since cephalosporins are primarily excreted by the kidney, the dosage should be reduced in cases of renal insufficiency.

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