



## Pharmacokinetics of lincomycin following intravenous administration in febrile goats

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### ABSTRACT

Disposition of antimicrobials is known to be altered during disease conditions and fever is one of the common manifestations of bacterial infections in animals. The disposition of lincomycin (10 mg/kg, IV) during *Echerichia coli* endotoxin-induced fever in goats followed two compartment open model and drug was detected in plasma up to 8 h. The high AUC (39.5±6.21 µg.h/mL) indicated good antibacterial activity of lincomycin in goats. The volume of distribution and total body clearance were 3.35±0.45 L/kg and 0.28±0.03 L/h/kg, respectively. The long elimination half life 9.93± 2.83 h indicated persistence of drug for longer period in body. Lincomycin, is suggested to be repeated at 24 h interval for organisms sensitive to lincomycin having MIC up to 0.6 µg/mL for the treatment of bacterial infections manifested with fever in goats.

**Key words:** Fever, Goats, Lincomycin, Pharmacokinetics.

### INTRODUCTION

Lincosamides is a group of monoglycoside antibiotics containing amino-acid like side chain. It is a miscellaneous group of protein inhibiting antimicrobials with activities similar to members of the macrolide group of antibiotics (El-Sayed *et al.* 2015). Lincomycin is a member of the lincosamide antibiotics, with long duration in the body owing to its lipid solubility and wide tissue distribution. It has potent activity against gram positive aerobic and anaerobic bacteria, especially against penicillin-resistant strains of *Staphylococcus* spp. and *Streptococcus* spp. (Giguere, 2006; Papich and Riviere, 2009). Because of these features, lincomycin is recommended for the treatment of a variety of skin, respiratory, gastrointestinal, soft-tissue and bone infections (Greene and Boothe 2012; Patel 2006). It has been used for the treatment of respiratory tract infections in sheep, goats and calves (Papich and Riviere 2009). Successful treatment of arthritis and pedal osteomyelitis usually associated with *Trueperella pyogens* (*Arcanobacterium pyogens*) has been reported with lincomycin in sheep (Giguere, 2013). Pharmacokinetics of lincomycin has been conducted in dairy cattle (Weber *et al.* 1981), calves (Burrows *et al.* 1983, 1986), buffalo calves (Gouri *et al.* 2014), pigs (Chaleva and Nquyen 1987; Nielsen and Gyrd-Hansen 1998), cats (Albarellos *et al.* 2012, 2013) and chickens (El-Sayed *et al.* 2015). Further, disease conditions are known to alter the disposition of antimicrobials (Kumar *et al.* 2010; Burrows 1986). Fever is most common manifestations of infectious diseases and is reported to induce biochemical and physiological alterations in the cells (Van Miert 1987). Alterations in the

pharmacokinetics of various antimicrobial agents has been reported during experimentally-induced fever in ruminants (Rajput *et al.* 2008; Dumka and Singh 2013; Dumka and Srivastava 2013). However, there is paucity of information on the influence of fever on pharmacokinetics of lincomycin in goats. Therefore, the present study was undertaken to determine the pharmacokinetics of lincomycin in febrile goats.

### MATERIALS AND METHODS

**Experimental animals:** The experiments were performed on six healthy female non pregnant, non-lactating goats, 1–1.5 years of age and weighing between 35–50 kg, procured from University dairy farm and housed in an animal shed with a concrete floor and adequate ventilation. The animals were acclimatized to the animal shed under proper management conditions and were maintained on green fodder of the season and commercial pellet goat feed (Ashirwad Feed Mills, Chandigarh) @ 250 g per goat per day. A constant supply of water was maintained in the shed. The animals were determined to be healthy during the experimental period by regular clinical examination. However examination of blood, plasma biochemical examination and urine analysis were not conducted. The experimental protocol followed ethical guidelines on the proper care and use of animals and was approved by the Institutional Animal Ethics Committee (Vide Ref No. VMC/2014/IAEC/1046-73 dated 07-04-2014).

**Induction of fever, drug administration and blood sampling:** Fever was induced by two repeated intravenous (IV) injections of *E. coli* endotoxin (Sigma Chemicals Co.,

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USA) at 1 h interval at the dose rate of  $1 \mu\text{g} \cdot \text{kg}^{-1}$  body weight. Rise in body temperature was monitored by frequent recording of rectal temperatures and animals were considered to be febrile when there was a 2 F rise in the rectal temperature. Once fever was induced, lincomycin was administered as single IV injection into jugular vein of all febrile animals at the dose rate  $10 \text{ mg/kg}$  body weight. Animals were considered to be febrile when there was  $2^\circ\text{F}$  rise in the rectal temperature. The rise in temperature after lincomycin treatment was in the range of  $2\text{-}3^\circ$  Fahrenheit above normal ( $101.5 - 103^\circ\text{F}$ ). The temperature was recorded upto 12 h and by this time the body temperature of all animals returned to normal. The dose of lincomycin used in the present study was comparable to the dosage used by previous workers in buffalo calves (Gouri *et al.*, 2014). Blood samples (3-5 ml) were drawn by venepuncture from the contralateral jugular vein at 0, 1, 2.5, 5, 10, 15, 30 min and 1, 2, 4, 8, 12 and 24 h using a vacutaner which collects blood by suction under vacuum causing minimum discomfort to the animal. Blood samples were collected into heparinized test tubes and plasma from the samples were separated by centrifugation at 2500 rpm for 15 min for drug assay.

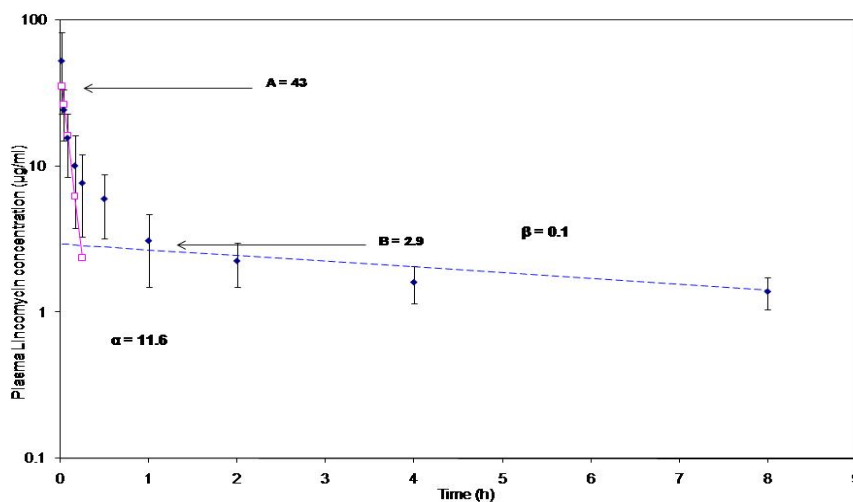
**Sample processing and drug assay:** The plasma samples (2000  $\mu\text{l}$ ) were added to centrifuge tubes. Subsequently, 2.3 ml of acetonitrile was added to all samples and mixed for 10 seconds and centrifuged at 1300 g for 10 min. After centrifugation, 3600  $\mu\text{l}$  of clear supernatant was pipetted into fresh test tube and kept for evaporation. Then evaporated samples were reconstituted in 400  $\mu\text{l}$  distilled water and mixed for 10 seconds. The mixed clear supernatant (200  $\mu\text{l}$ ) was pipetted into an autosampler vial for injected into the HPLC system. Lincomycin standard (Lincomycin hydrochloride, CDH, Delhi) was procured commercially. The

drug was estimated using HPLC (Perkin Elmer, series 200) by reverse-phase chromatography (Nielsen and Gyrd-Hansen 1998). The system conditions included analytical C18 column (particle size  $5 \mu$ ,  $4.6 \times 250 \text{ mm}$ , Waters, USA), acetonitrile as mobile phase A (25%), phosphate buffer as mobile phase B (75%), flow rate of 1 ml/ min, UV/VIS detector set at 210 nm as per the details mentioned in the published report of Nielsen and Gyrd-Hansen, (1998) for estimation of drug and Total Chrome software (version 6.1) for instrument control and data analysis. The method was validated in our laboratory. Retention time of lincomycin was 7 min and limits of detection and quantification were 0.1 and  $0.5 \mu\text{g}/\text{mL}$ , respectively. Extraction recoveries of lincomycin from plasma were  $84.0 \pm 4.56$ ,  $90.7 \pm 4.12$ , and  $94.9 \pm 3.29\%$  for low, medium and high QC samples, respectively. Intra and inter-day assay precision levels were lower than 5 and 6%, respectively.

**Pharmacokinetic analysis:** Appropriate pharmacokinetic model was determined by application of Akaike's Information Criterion (AIC) on individual concentration-time curves. The pharmacokinetic parameters were calculated according to classical equation (Gibaldi and Perrier 1982). The mean pharmacokinetic variables were obtained by averaging the variables calculated for drug disposition after IV drug administration to each animal.

## RESULTS AND DISCUSSION

The disposition curve of lincomycin in febrile animals revealed that pharmacokinetics of lincomycin followed two-compartment open model (Fig.1). Various kinetic determinants that describe the disposition of lincomycin, after its intravenous injection in febrile goats are presented in Table 1. At one minute, the peak plasma level of lincomycin was  $52.7 \pm 10.4 \mu\text{g}/\text{mL}$ . The plasma levels declined rapidly to  $3.09 \pm 0.54 \mu\text{g}/\text{mL}$  at 1 h and were



**Fig 1:** Plasma concentration time profile of lincomycin in febrile goats following single IV dose of  $10 \text{ mg} \cdot \text{kg}^{-1}$ . Distribution (—○—) and elimination (—) phases are represented by least square regression lines. Plasma concentration at different time intervals are represented by dots (◆)

**Table 1:** Pharmacokinetic parameters of lincomycin following its single intravenous injection (10 mg.kg<sup>-1</sup>) in febrile goats

Parameter	Unit	Animal Number						Mean ± E
		1	2	3	4	5	6	
AUC	µg.ml <sup>-1</sup> .h	44.9	32	28.9	26.7	36.9	67.9	39.5±6.21
AUMC	µg.ml <sup>-1</sup> .h <sup>2</sup>	739.1	260.0	254.4	107.3	375.1	2113.0	641.6±21.6
Vd	L.kg <sup>-1</sup>	4.33	2.77	3.47	1.78	2.99	4.78	3.35±0.45
Vd <sub>(area)</sub>	L.kg <sup>-1</sup>	3.67	2.53	3.03	1.5	2.75	4.61	3.01±0.43
Cp <sup>0</sup>	µg.ml <sup>-1</sup>	79.0	46.5	44.2	41.8	30.7	33.8	46.0±7.06
P/C	Ratio	33.2	11.9	17.3	8.44	8.2	15.2	14.8±3.93
A	µg.ml <sup>-1</sup>	77.2	43.1	41.7	37.1	27.6	31.8	43.1±7.21
α	h <sup>-1</sup>	11.3	15.9	11.2	8.74	9.3	13.3	11.6±1.09
t <sub>1/2α</sub>	h	0.06	0.04	0.06	0.07	0.07	0.05	0.06±0.01
K <sub>12</sub> /K <sub>21</sub>	Ratio	28.03	10.8	12.4	5.39	7.47	14.6	13.1±3.39
B	µg.ml <sup>-1</sup>	1.96	3.31	2.51	4.73	3.06	2.02	2.93±0.42
α	h <sup>-1</sup>	0.05	0.11	0.09	0.21	0.09	0.03	0.09±0.03
t <sub>1/2β</sub>	h	13.5	6.14	6.97	3.29	7.66	22.4	9.99±2.83
Cl <sub>B</sub>	L.kg <sup>-1</sup> .h <sup>-1</sup>	0.223	0.312	0.344	0.374	0.271	0.148	0.28±0.03
Ke1	h <sup>-1</sup>	1.76	1.45	1.52	1.57	0.83	0.49	1.27±0.20
MRT	h	16.48	8.12	8.77	4.02	10.17	31.22	13.1±3.97

AUC, area under concentration-time curve; AUMC, area under the first moment of the plasma concentration-time-curve; Vd<sub>(area)</sub>, apparent volume of distribution; Vd<sub>(ss)</sub>, volume of distribution at steady state; Cp<sup>0</sup>, plasma drug concentration at zero time; P/C, ratio of the drug present in the peripheral to central compartment; A and B, zero-time plasma concentration intercepts of regression lines of distribution and elimination phases, respectively; α and β, distribution and elimination coefficients, respectively, in the biexponential equation that describes the plasma concentration-versus-time data; t<sub>1/2α</sub>, distribution half life; K<sub>12</sub>/K<sub>21</sub>, ratio of rate constant for central to peripheral compartment and peripheral to central compartment; t<sub>1/2β</sub>, elimination half life; Cl<sub>B</sub>, total body clearance; K<sub>el</sub>, elimination rate constant from the central compartment; MRT mean residence time of drug in the body.

detected up to 8 h (1.39 ± 0.08 µg/mL). The time for which the plasma drug levels remained above or equal to minimal inhibitory concentration (MIC) value were calculated using the formula:

$$\%T>MIC = 1 - \left[ \frac{D}{I(\text{area}) \times MI} \right] \times \left[ \frac{t_{1/2}}{\ln(2)} \right] \times \left[ \frac{10}{D} \right]$$

Where, T>MIC is the time interval (in per cent) during which the plasma concentration is above or equal to the MIC values, ln is the natural logarithm, D is the proposed dose, V<sub>d(area)</sub> is the volume of distribution, t<sub>1/2β</sub> is the terminal elimination half-life, and DI is the dose interval (Turnidge 1998). Table 2 shows the calculated % T>MIC for lincomycin based on the estimated pharmacokinetic parameters obtained following IV injection in goats for 8, 12 and 24 h dosing interval.

In support of the present observation, the elimination pattern of lincomycin fitted two-compartment open model in buffalo calves (Gouri *et al.* 2014) and broiler chickens (El-Sayed *et al.* 2015). Since there are no reports

**Table 2:** Calculated %T>MIC for lincomycin based on the estimated pharmacokinetic parameters obtained following IV injection (10 mg/kg) in febrile goats for 8, 12 and 24 h dosing interval

MIC(µg/ml)	T>MIC		
	24	12	8
0.06	169	338	507
0.1	138	277	415
0.6	31	61	92

on the pharmacokinetic data of lincomycin in febrile condition in any animal species, the results of the present study are compared with the pharmacokinetic data of other animal species reported in healthy condition and also with the disposition of other drugs, ceftriaxone and florfenicol, commonly used in domestic animals to combat bacterial infections manifested with fever. The high AUC of lincomycin in febrile goats was consistent to the high value reported for AUC of lincomycin as 41.6 µg.ml<sup>-1</sup>.h in buffalo calves after single IV administration (Gouri *et al.* 2014) and in cats 39.76 ± 13.49 µg.ml<sup>-1</sup>.h. (Alberallos *et al.* 2012). The value of AUC, observed in present study, was also consistent with high AUC (40.3 ± 1.70 µg.h/mL) after administration of florfenicol in febrile calves. (Dumka and Singh, 2013). High distribution of lincomycin to various tissues and body fluids were reflected by large Vd<sub>area</sub> which was higher than the Vd<sub>area</sub> in calves with induced *Pasteurella haemolytica* pneumonia (1.2 L/kg), buffalo calves (1.15 L.kg<sup>-1</sup>), pigs (1.1 L.kg<sup>-1</sup>) cats (0.97-1.24 L.kg<sup>-1</sup>) and chicken (1.76 L.kg<sup>-1</sup>) for lincomycin (Burrows *et al.* 1986; Nielsen and Gyrd-Hansen 1998; Albarellos *et al.* 2012, 2013; Gouri *et al.* 2014; El-Sayed *et al.* 2015). In support of present result, Vd<sub>area</sub> of florfenicol in febrile calves (2.11 ± 0.18 L/kg) was reported by Dumka and Singh, (2013). The excellent tissue penetration of lincomycin was also reflected by high P/C ratio. However, this value was higher than the P/C ratio of 1.55±0.19 following IV administration of florfenicol in febrile calves (Dumka and Singh, 2013). Lincomycin was rapidly distributed from central to peripheral compartment in febrile goats as is evident from the high value of distribution rate

constant and short distribution half-life. In support of the present findings, comparable values for high distribution rate constant of  $11.2 \text{ h}^{-1}$  and short distribution half-life of  $0.06 \text{ h}$  have been reported after intravenous injection of lincomycin in buffalo calves (Gouri *et al.* 2014). Further, in agreement with the present findings, short distribution half lives of  $0.37 \text{ h}$  and  $0.07 \text{ h}$  has been reported following IV, injection of florfenicol in sheep (Lane *et al.*, 2004). Rapid transfer of lincomycin from central to peripheral compartment was also evident by high  $K_{12}/K_{21}$  ratio which was greater than the corresponding ratio of  $4.40 \pm 0.1$  observed in buffalo calves (Gouri *et al.* 2014). The lipophilic nature and high  $pK_a$  values of  $7.6$  of this compound might be the major reasons for the good distribution of lincomycin to the tissues. Total body clearance of lincomycin in febrile goats was consistent to the value of  $Cl_{\beta}$  reported for lincomycin in buffalo calves ( $0.24 \text{ L.kg}^{-1}.\text{h}^{-1}$ ) and in cats ( $0.28 \text{ L.kg}^{-1}.\text{h}^{-1}$ ) but less than the corresponding value of  $0.46 \text{ L.kg}^{-1}.\text{h}^{-1}$  in pigs and chicken (Albarellos *et al.* 2012; Huimin *et al.* 2012; Gouri *et al.* 2014; El-Sayed *et al.* 2015). The  $Cl_{\beta}$  of lincomycin in present study was also lower than the  $Cl_{\beta}$  of ( $0.50 \pm 0.02 \text{ L/h/kg}$ ) in febrile calves and higher than  $Cl_{\beta}$  ( $0.26 \text{ L/h/kg}$ ) in sheep for florfenicol (Dumka and Singh, 2013; Jianzhong *et al.*, 2004). The high value of  $t_{1/2\alpha}$  in the present study ( $9.99 \pm 2.83 \text{ h}$ ), which was longer than the elimination half-life of  $3.3 \text{ h}$  in buffalo calves,  $3.38 \text{ h}$  in pigs,  $4.2 \text{ h}$  in cats and  $3 \text{ h}$  in calves for lincomycin (Gouri *et al.* 2014; Albarellos *et al.* 2012, 2013; Huimin *et al.* 2012), indicated slow elimination of lincomycin during febrile condition in goats. This finding was comparable to the prolonged  $t_{1/2\alpha}$  of florfenicol ( $3.08 \pm 0.07 \text{ h}$ ) in febrile cross bred calves than that in healthy ( $2.76 \pm 0.16 \text{ h}$ ) reported by Dumka and Singh, (2013). This was further shown by the long MRT which was longer than the MRT of  $4.32 \text{ h}$  in buffalo calves,  $5.5 \text{ h}$  in cats and in  $3.76 \text{ h}$  in chicken after IV administration of lincomycin (Albarellos *et al.* 2013; Gouri *et al.* 2014; El-Sayed *et al.* 2015). The MRT of lincomycin obtained in present study was also higher than the MRT of florfenicol ( $2.93 \pm 0.06 \text{ h}$ ) in febrile calves (Dumka and Singh, 2013). Minimum inhibitory concentration

( $MIC_{90}$ ) lincomycin has been reported in the range of  $0.06$ - $2.0 \mu\text{g.ml}^{-1}$  against *Streptococcus*, *Mycoplasma hyopneumoniae*, and *Staphylococcus* spp. (Petinaki *et al.* 2008; Albarellos *et al.* 2012; Giguere 2013). The  $T > MIC$  was calculated for  $MIC_s$  of  $0.06$ ,  $0.1$ , and  $0.6 \mu\text{g/mL}$ . Lincomycin acts as time dependant antibacterial drug and the most important pharmacodynamic/pharmacokinetic parameter for such types of drugs is the length of time during which drug remains above the MIC value. It is generally recommended that  $T > MIC$  should be at least  $50\%$  of the dosage interval to ensure an optimal antibacterial effect (Toutain and Lees 2004). The experiment data in present study, showed that lincomycin at dose rate  $10 \text{ mg/kg}$  body weight IV should be repeated at  $24 \text{ h}$  interval for organisms sensitive to lincomycin having MIC up to  $0.1 \mu\text{g/mL}$  and at  $12 \text{ h}$  interval for bacteria having MIC of  $0.6 \mu\text{g/mL}$ . The favourable pharmacokinetic profile of lincomycin with rapid distribution, high AUC, large  $V_{d_{area}}$ , prolonged elimination half-life and  $12 \text{ h}$  dosing interval suggested that lincomycin may be an appropriate antibacterial when prescribed in febrile goats.

## CONCLUSION

The dose regimen suggested in present study may serve as a guideline for clinical use in goats after establishing PD studies and potential clinical testing of lincomycin in this species. Since only six animals were used in the present study, the PK parameters need to be verified in a larger population of goats and variations in dosage regimens may be required.

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## CONFLICT OF INTEREST

None of the authors has any financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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