Certificate of the Major Advisor and endorsement of the Head of the Department

Department of Veterinary Pharmacology & Toxicology Faculty of Veterinary Science & Animal Husbandry, Birsa Agricultural University, Ranchi-834006

CERTIFICATE

This is to certify that the thesis entitled **"PHARMACOKINETIC STUDIES OF LEVOFLOXACIN IN HEALTHY AND FEBRILE CALVES"** submitted in partial fulfilment of the requirements for the Degree of **Master of Veterinary Science (Veterinary Pharmacology & Toxicology)** of the Faculty of Post-Graduate Studies, Birsa Agricultural Universities, Kanke, Ranchi (Jharkhand) is the record of the bonafide research carried out by **Dr. Santosh Kumar** under my supervision and guidance. No part of the thesis has been submitted for any Degree or Diploma.

It is further certified that such help or information received during the course of this investigation and preparation of the thesis have been duly acknowledged.

ENDORSED

(B.K. Roy)	***(B. K. Roy)***
University Professor and Head	Major Advisor

Certificate of the Advisory Committee Members

CERTIFICATE

We, the undersigned members of the Advisory committee of Dr. **Santosh Kumar,** a candidate for the degree of **Master of Veterinary Science** with major in Veterinary Pharmacology & Toxicology have gone thought the Manuscript of the thesis and agree that the thesis entitled **"PHARMACOKINETIC STUDIES OF LEVOFLOXACIN IN HEALTHY AND FEBRILE CALVES"** may be submitted by **Dr. Santosh Kumar,** in partial fulfilment of the requirements of the degree.

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(B.K. Tiwary)

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Place……

Date …… **(Santosh Kumar)**

ABSTRACT

The pharmacokinetic studies of LVX after oral (20 mg/kg) and i.v. (5 mg/kg) administration were conducted in six healthy and febrile calves.

The mean value of Cp_{max} of LVX (4.50 ± 0.22 µg/ml) after single dose oral administration in healthy calves was significantly lower as compared to that in febrile calves (5.28 ± 0.32 µg/ml).

The Cp_{ther} of LVX was maintained for longer period in febrile calves (till 10 h) as compared to healthy calves (till 8 h).

The mean value of Cu_{max} in febrile (40.86 ± 2.19 µg/ml) was similar to that in healthy calves (39.38 ± 2.43 µg/ml).

The non-significant difference in various pharmacokinetic parameters of plasma viz. β, $t_{½}\beta$, and MRT was observed after oral administration of LVX in healthy and febrile calves.

The non-significant difference in various pharmacokinetic parameters of urine viz. $Cu_{max,}$ β, $t_{½}\beta$ observed after oral administration of LVX in healthy and febrile calves.

The mean value of Cp_{max} of LVX after single dose i.v. (5 mg/kg) in febrile calves (6.16 ± 0.15µg/ml) was significantly higher as compared to that in healthy calves (5.13 ± 0.13 µg/ml).

The Cp_{ther} of LVX was prolonged in febrile calves (till 8 h) in febrile calves as compared to healthy (till 6h) after i.v. administration.

The value of Cu_{max} of LVX in healthy calves (53.70 ± 2.37µg/ml) was significantly lower than as compared to 63.15 ± 3.44µg/ml in febrile calves.

The mean values of $t_{½}$ β, MRT, Cl_B, Vd_{area} and T/P differed significantly between healthy and febrile calves after i.v. administration.

The results indicated that levofloxacin was readily absorbed after oral administration and diffused thoroughly in body fluids, after both oral and i.v. administration. LVX may be clinically used to combat sensitive microbial infections of urinary tract after oral as well as i.v. administration.

LVX may be given orally @ 1.49 – 2.23 mg/kg (1.5 – 2 mg/kg) b.w. in febrile calves every 8 hourly. The i.v. dose of LVX in febrile calves may be 0.58 – 0.87 mg/kg (0.5 – 1 mg/kg) b.w. 6 hr interval.

CONTENTS

INTRODUCTION

In this modern scientific era both human and animals are equally important for ecological balance. Antimicrobial are the greatest contribution of present century and has become one of the most misused agent available to the clinicians, due to its widespread and indiscriminate use resulting in emergence of resistance among a number of pathogenic organisms, which in turn has created on ever increasing demand for newer drugs. Newer quinolones are choice of drug due to its low resistance, fewer side effects and better coverage of gram negative and gram-positive bacteria.

The history of newer quinolones began with discovery of nalidixic acid, which was discovered in 1963 as an accidental by-product during synthesis of antimalarial compound chloroquine. Nalidixic acid has been used for the treatment of urinary tract infection for many years. The therapeutic utility of nalidixic acid is limited due to its low serum concentration, toxicity and development of resistance. In early 1980s, a great achievement occurred in the field of antimicrobials with the development of Fluorinated 4-quinolones such as ciprofloxacin, norfloxacin and ofloxacin etc. These are very effective in different types of microbial infections and are effective orally as wall as parenterally.

Levofloxacin is the L-isomer of ofloxacin, a broad spectrum antimicrobial agent active against most gram-positive and gram-negative bacteria. It has improved pharmacokinetic and pharmacodynamic properties. It inhibits rickettsial growth at concentration equal to or half of those necessary for growth inhibition of ofloxacin (Maurin and Raoult, 1997).

Levofloxacin is the third generation fluoroquinolone (Owens and Ambrose, 2000) and acts by selective inhibition of bacterial DNA gyrase enzyme. It shows a enhanced activity against penicillin resistant *streptococcus pneumoniae* infection, acute sinusitis and acute bronchitis.

The safety and efficacy of levofloxacin are well documented in lower respiratory tract, urinary tract, skin and soft tissue infections. It has a long plasma half-life which allows once daily administration. It is more safer than other fluroquinolones and the risk of phototoxicity, liver toxicity and CNS toxicity are very low (Norrby, 1999).

Levofloxacine is currently abundantly used in humans. However, it is not being used in animals especially cattle because there is paucity in regard to dosage regimen which is generally calculated with the help of pharmacokinetic parameters.

Fever is the main cardinal manifestation of almost all infectious diseases and can change the kinetic variables of antimicrobial agents. Therefore, the present experiment was conducted to study the pharmacokinetics of levofloxacin in healthy and febrile calves with following objectives.

OBJECTIVES

1. To determine the plasma and urine levels of levofloxacin at different time intervals after single dose administration in healthy calves.
    a. After oral Administration
    b. After i.v. Administration
2. To determine the plasma and urine levels of levofloxacin at different time intervals after single dose administration in febrile calves.
    a. After oral Administration
    b. After i.v. Administration

3. Estimation of in-vitro plasma protein binding of levofloxacin in calves.
4. To calculate different pharmacokinetic profile of levofloxacin in healthy and febrile calves after single dose oral and i.v. administration
5. Calculation of dosage regimen of levofloxacin in febrile calves after single dose oral and i.v. administrations

REVIEW OF LITERATURE

A drastic change occurred in field of quinolones group of antimicrobial by introduction of fluorine atom into the basic structure of quinolone carboxylic acid. Fluoroquinolones is a group of antimicrobial agent that has changed the scenario of clinical therapeutics. The first member, nalidixic acid was introduced in 1960 (Lesher *et al*., 1962). Nalidixic acid possesses narrow spectrum activity and low resistance. The break through was achieved in early 1980, with the fluorination of position-6 and introduction of a piperazine substitution at position-7 in the quinolone nuclear structure (Domagala *et al*., 1988). Structure related changes increased the activity, altered pharmacokinetic characteristics and reduced toxicity of fluoroquinolones. Numerous chemical modifications of the quinolones molecules could produce a number of new quinolones having improved pharmacokinetic parameters in comparison to previous derivatives (Hosaka *et al*., 1992).

Levofloxacin is the L-isomer of ofloxacin has extended antibacterial activity than older fluoroquinolones such as ciprofloxacin, ofloxacin and less toxic than trovafloxacin (Norrby, 1990).

CHEMISTRY

The fluoroquinalones have a basic structure of quinolone carboxylic acid (Goueffon, *et al.*, 1981). The general structure for fluoroquinolone (4-quinolone ring) is as below:

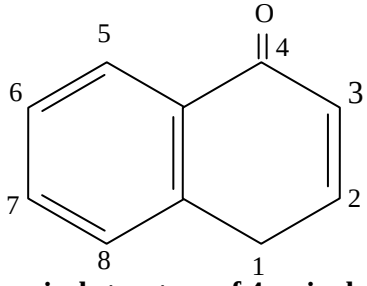

Fig 1: Chemical structure of 4-quinolone ring.

The modification of basic molecules at N_1 and C_6, C_7 and C_8 positions results in major changes in pharmacokinetic and pharmacodynamic properties with the changes in basic structure has been reported.

i. Addition of F atom at C_6 enhances DNA gyrase inhibitory activity and extends activity against *staphylococcus* and *pseudomonas*.

ii. Addition of piperazine group at C_7 extends antibacterial activity against *staphylococcus* and *pseudomonas*.

iii. Addition of cyclopropyl group at N_1, amino group at C_5 and F at C_6 extends spectrum against *Mycoplasma* and *Chlamydia*.

iv. Addition of methoxy group at C_8 position enhances activity and lowers selection of resistance against gram positive mutants.

Levofloxacin [(-) (s) – 9-fluoro – 2, 3 – dihydro – 3 methyl – 10 (4 – methyl – 1 – piperazinyl) – 7 – oxo – 7H – pyrido (1,2,3-de) – 1, 4 benzoxazine – 6 carboxylic acid hemihydrate] has the following structural formula.

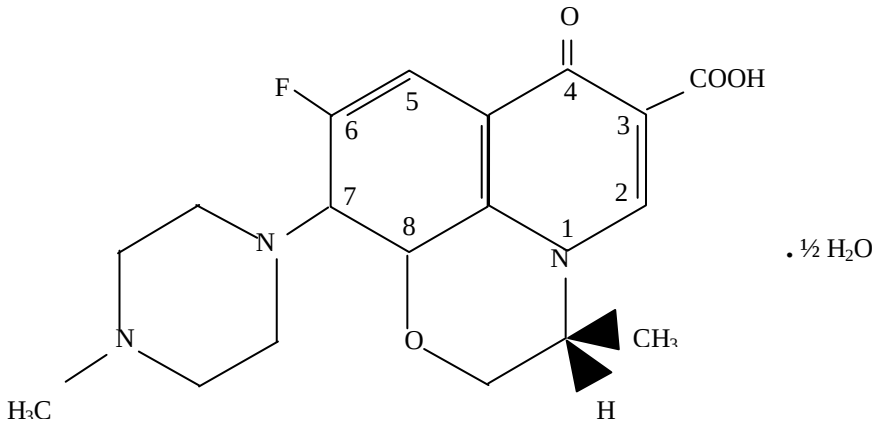

Fig. 2: Chemical structure of Levofloxacin

PHYSIO–CHEMICAL PROPERTIES

Levofloxacin is crystalline, slightly yellowish powder, molecular weight is 370.38, it is amphoteric and the molecule exist as a zwitter ion at the pH conditions in the small intestine. Its empirical formula is $C_{18}H_{20}FN_3O_4$. ½ H_2O.

ANTIMICROBIAL ACTIVITY

Levofloxacin has an excellent antibacterial activity against gram-positive and gram-negative micro-organism including anaerobes, *Mycoplasma*, *Chlamydia* species and *Toxoplasma gondii* (Yarsan, *et al*., 2003). Aerobic gram-positive micro-organism such as *Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis*. *Streptococcus pyogenes* and aerobic gram-negative micro-organism such as *E. coli, H. influenzae, Klebsiella pneumoniae, Ligonella pneumophila, Pseudomonas aeruginosa*, *Moraxella spp*. and *Proteus spp*. (Hooper, 2001).

MECHANISM OF ACTION

Levofloxacin acts through the selective inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an enzyme involved in replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a Key role in partioning of the chromosomal DNA during bacterial cell division (Perry, *et al*., 1999). The two strands of double helical DNA must be separated to permit DNA replication or transcription, results in over winding or excessive positive supercoiling of the DNA in front of the point of separation (Hooper, 2001). To combat this mechanical obstacle the bacterial enzyme DNA gyrase is responsible for continuous introduction of negative supercoils into DNA. This is an ATP dependent reaction requiring that both strands of the DNA be cut to permit passage of a segment of DNA through the break and the break is then resealed.

The DNA gyrase of *E. coli* is composed of two A subunits and two B Subunits encoded by gyr. A and gyr. B genes, respectively. The A subunits which carry out the strand cutting function of the gyrase are the site of action of quinolones.

Topoisomerase IV also is composed of four subunits encoded by the par 'C' and par 'E' genes in *E. coli*. Topoisomerase IV separates interlinked (catenated) daughter DNA molecules that are the product of DNA replication.

MINIMUM INHIBITORY CONCENTRATION (MIC)

The MIC value of levofloxacin is less than 2 µg/ml for all susceptible mico-organism MIC 0.5-2 µg/ml and 0.06-0.5 µg/ml for *S. pneumonia and S. aureus* respectively. The MIC for *Enterococcus faecalis, E. coli, H. influenzae and P. aeruginosa* is 0.25-2, 0.08-0.6, 0.008-0.03 and 0.5-4 µg/ml respectively.

PHARMACOKINETIC STUDIES

The aim of pharmacokinetics is to study the time concentration course of drugs and their metabolites in various body fluids, tissues and excreta and interpretation of such data based or suitable pharmacokinetic model (Wanger,1968). To study the pharmacokinetics of a drug, the body is subjected to different compartments. These compartments are mathematical entities having no physiological meaning. The disposition kinetics of a drug is described either by one compartment or multi-compartment open model depending on plasma level time profile curve. An open compartment model indicates free movement of drugs from one compartment to another compartment (i.e. blood to tissue and vice-versa).

i. One compartment open model

The one compartment open model describes the time course of most drugs in plasma or urine after i.m. or oral administration. In this model distribution of drugs from central to peripheral compartment is very rapid. Any change in drug concentration in the blood

reflects directly the quantitative change in its tissue level. The rate of drug elimination from the body is proportional to the concentration of drug in blood (Baggot, 1974). The plasma concentration time profiles if plotted on semilogarithmic scale, shows a straight line (Sams, 1978). The plasma drug level is described by the following equation:

$$Cp = Be - \beta t \quad \text{..... equation – (1)}$$

Where,

Cp = concentration of drug in plasma.

B = extrapolated zero time intercept of monoexponential curve.

β = overall elimination rate constant.

t = time elapsed after drug administration.

e = base of natural logarithm.

ii. Two compartment open model:

The two compartment open model describes the time course of most drugs after i.v administration. In this model the drug administered intravenously first distribute into the highly perfused tissues like liver, kidney and heart (central compartment) and thereafter more slowly to less perfused tissues like skin, bone, muscles and fat (peripheral compartment). The distribution and elimination process in this model are assumed to follow first order kinetics and elimination of drug is assumed to take place exclusively from central compartment. The drug concentration in plasma versus time profiles after i.v. administration is expressed by biexponential expression given in the equation – (2).

$$Cp = Ae^{-\alpha t} + Be^{-\beta t} \quad \text{..... equation – (2).}$$

Where as,

Cp = plasma concentration of the drug.

A = Zero time intercept of distribution phase.

B = Zero time intercept of elimination phase.

α= distribution rate constant.

β = elimination rate constant.

e = base of natural logarithm

t = time elapsed following drug administration.

The values of A, B, α and β are essential in calculating other kinetic rate constants indicate the relative contribution in respect of distribution and elimination process of a drug concentration time data (Baggot, 1977).

iii. Multi-Compartment open model:

In this model initial sharp decline in plasma concentration against time is due to distribution of drug from blood to highly perfused tissues. The gradual decline is because of distribution of drug from central to moderately perfused organs (Sharma, *et al*., 1995).

If the plot of plasma concentration time profile is tri-phasic for three compartment open model the plasma concentration open model the plasma concentration is expressed by the following equation.

$Cp = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{\gamma t}$ ..... equation (3)

The residual methods are employed to estimate the additional constant γ and can be used to calculate K_{13} and K_{31} (Gibaldi and Perrier, 1975).

Clinical importance of pharmacokinetic studies

1. To correlate the drug concentrations with pharmacological activities.
2. To evaluate differences in the rate or extent of availability between formulations.
3. To estimate the drug elimination from the body.
4. To describe the effect of diseases on various pharmacokinetic parameters.
5. To calculate the drug dosage regimen in a given species of animal.
6. To determine the drug withdrawal period for drug residue in different edible tissues of food producing animal.
7. To identify the drug interaction.

RELEVANCE OF KINETIC PARAMETERS TO CLINICAL PRACTICE

The clinical application of pharmacokinetic studies comprise of determination of different kinetic parameters of a drug following different routes of administration, calculation of dosage regimen of a drug in a particular species and estimation of drug withdrawal period for drug residue in milk and tissues of food producing animals.

The distribution constant (α) and distribution half life ($t_{½\alpha}$) indicate the rate of distribution of a drug from plasma to body fluids and tissue following i.v. administration. The absorption constant (Ka) and absorption half life ($t_{½Ka}$) denotes the rate of absorption of a drug from its site after extravascular (i.m./s.c or oral) administration.

The overall elimination rate constant (β) is the most important kinetic parameter and is used to calculate the half life ($t_{½\beta}$), volume of distribution by area method (Vd_{area}) and total body clearance (Cl_B) (Baggot, 1977). It is also used to predict the withdrawal period for drug residue in milk and tissue of food producing animal Gibaldi and Weintraub (1971) and Mercer *et al*. (1977) described the elimination half life as time required to reduce the drug concentration to its half during the elimination phase of the

drug concentration time profile. The half life is inversely proportional to the overall elimination rate constant. Half life is of prime importance in determining the duration of a drug in the body. The half life of first order process is independent of route of administration and the dose. Knowledge of the half life of drug is extremely useful in predicting the *design of rational dosage regimen*.

The apparent volume of distribution (V_d) is a parameter in the pharmacokinetic characterization of drugs. The apparent Volume of distribution is a hypothetical volume of the body fluid that would be required to dissolve the total amount of drug to attain the same concentration as that found in the blood. Baggot (1977) stated that apparent volume of distribution of a drug without providing any clue whether the drug is uniformly distributed or restricted to certain tissues. A large volume of distribution indicates wide distribution throughout the body or extensive tissue binding or rapid excretion of a drug or combination of all the above. The small volume of distribution means that the drug is restricted to certain fluid compartments, mainly plasma and extracellular fluids due to the low lipid solubility or high protein binding of a drug.

Total body clearance (Cl_B) indicates the sum of the clearance of each eliminating organ, mainly liver and kidney. For most of the drugs, the half life is a complex function which depends upon the process of drug distribution, biotransformation and renal excretion. The parameter, body clearance on the other hand is independent of these processes and gives a proper expression of the rate of drug removal from the body. Unlike β and $t_{½\beta}$ which are hybrid constants and depend upon K_{12}, K_{21} and K_{el}, the body clearance changes exactly in proportion to K_{el} (Jusko and Gibaldi, 1972; Rowland *et al.*, 1973).

Jusko and Gibaldi (1972) noted that various constants α,β, A, B, $t_{½\alpha}$, $t_{½\beta}$, Vd_{area} are changed disproportionally with the magnitude of the elimination rate constant (K_{el})

and therefore, should not be used individually as a direct or safe measure of a change in drug elimination distribution.

Dose is a quantitative term estimating the amount of drug which must be administered to produce a particular biological response, is to establish a certain effective concentration of drug in the body requires the administration of maintenance dose at a particular dose interval after administration the priming or loading dose, so that concentration must be above a maximum effective time and below a level producing excessive side effect and toxicity. Thus, the objective of multiple dosage regimen is to maintain the plasma concentration of the drug within the limits of the maximum safe concentration and the minimum effective levels.

The dose of minimum effective levels is not constant but has to be adjusted to the microbiological pattern and to other factor like altered pathophysiological status of the body. The dosage recommended by manufacturers is often based on a relatively high bacterial sensitivity and the variation in minimum inhibitory concentration (Ziv, 1980). Also they are based on the in-vitro test while as different conditions prevail in-vivo where in natural defense works synergistically with an antimicrobial agent (Ziv, 1980b). Thus, in force of all these uncertainties in the body scientific approach to recommend a suitable dose of the drug is based on its pharmacokinetic parameters.

AFEBRILE CONDITION

Su-Chean *et al*. (1997) reported pharmacokinetics of levofloxacin following once daily 500 mg oral and intravenous administration in healthy humans by HPLC. Following oral administration, the peak plasma concentration (5.19 µg/ml) reached at

1.3h, the $t_{½}\beta$ was 7.4 h, AUC – 47.7 µg.h/ml and Cl_R – 125.5 ml/min following intravenous administration.

Albarellos *et al*. (2005) reported that pharmacokinetics of levofloxacin after single intravenous and repeat oral administration to cat. Following intravenous administration the $t_{½\beta}$ - 0.26 ± 0.18 h, Vd_{area} – 1.75 ± 0.42 L/kg, Cl_B – 0.14 ± 0.04L/h.kg and MRT was 12.99 ± 2.12 h. After repeat oral administration $t_{½\beta}$ - 0.18 ± 0.12 h, T_{max} - 1.62 ± 0.84 h, Cp_{max} - 4.70 ± 0.91 µg/ml and bioavailability was 86.27 ± 2.12 h.

Sci. Finder scholar (2004) reported that the pka values of the protonable function of the four quinolones are 8.76 ± 0.25 (Ciprofloxain), 6.8 ± 0.3 (Levofloxacin) and 10.8 ± 0.4 (Moxifloxacin) under a zwitterionic form at neutral pH.

Walfson and Hopper (1989) reported that only ofloxacin and levofloxacin are exclusively eliminated by the kidney where as trovafloxacin is eliminated primarily by hepatic mechanism.

The fluoroquinolones have a large volume of distribution and concentration in tissue at level that often exceed serum drug concentration. Penetration is particularly high in renal, lung, prostate, bronchial, nasal, gall bladder, bile and genital tract tissues (Goodman and Gilman, 1996).

Dumka and Srivastava (2006) reported pharmacokinetics and urinary excretion of levofloxacin following single intramuscular dose in cross bred calves. The peak plasma concentration Cp_{max} was 3.07 ± 0.08 µg/ml at 1 h, $t_{½}\alpha$ -2.14±0.24h, $t_{½}\beta$ - 3.67 ± 0.08 h, AUC – 7.66 ± 0.72 mg/L.h . The volume of distribution (Vd_{area}) was 1.02 ± 0.05 L/kg, MRT - 5.57 ± 0.51 h, Cl_B – 204.5 ± 22.6 ml/kg/h and bioavailability was 56.6 ± 12.4 % respectively. On the basis of pharmacokinetic parameter a suitable i.m. dose regimen of levofloxacin in cross bred calve was 1.5 mg/kg; repeated at 12 h interval.

Sharma *et al*. (1995) reported that fluoroquinolones are well absorbed after oral administration and bioavailability ranges from 35-100%. The peak concentrations of different fluoroquinolones are obtained at T_{max} between 1 to 3h after oral administration.

Perry *et al*. (1999) reported the pharmacokinetics of gatifloxacin after single oral dose (400 mg) administration in healthy humans. The maximum plasma concentration (Cp_{max}) 4.21 mg/L, time for maximum plasma concentration (T_{max}) 2 h, mean volume of distribution ($V\ d_{ss}$) 1.5 to 2.0 L/kg and elimination half life ($t_{½\beta}$) 7 to 14 h were reported.

Verma (2004) conducted in-vitro plasma protein binding of gatifloxacin in plasma of healthy goats which ranged between 49.17 to 69.27% with an overall mean of 67.27 ± 6.47%.

Norrby (1999) studied the pharmacokinetics of levofloxacin both after oral and i.v. administration and was characterized by a very high bioavailability, low (30-40%) protein binding, high tissues concentrations and elimination via the Kidney with minimal liver metabolism.

FEBRILE CONDITION

Riffat *et al*. (1982) reported the pharmacokinetics of sulfadimidine in afebrile and febrile dogs following single i.v dose administration @100 mg/kg b.w. They found that $t_{½\alpha}$ was 1.52 h in afebrile and 0.81 h in febrile dogs. No significant variation was found in the $t_{½\alpha}$ value, but the apparent volume of distribution (Vd) and volume of central compartment (Vc) differ significantly under febrile condition as compared to that in afebrile dogs.

Naber *et al.* (2001) screened a number of fluoroquinolones for treatment of UTI in human by comparing their antimicrobial activity. The dosage regimen of 500 mg ciprofloxacin twice daily, 500 mg levofloxacin once daily or 400 mg gatifloxacin once

daily, were comparable in the treatment of severe complicated UTI. In UTI by less susceptible uropathogens, such as *Pseudomonas aeruginosa*, the dose could be increased upto 750 mg twice daily (ciprofloxacin) and 500 mg twice daily (levofloxacin).

Sinha (2001) reported that the febrile condition decreased ofloxacin plasma levels and duration of Cp_{ther} after i.v. administration in goats. The values of $t_{½\beta}$, AUC and Cl_B after single dose (20mg/kg b.w.) oral administration were 3.69 ± 0.10 h, 129.85 ± 2.57 mg/L.h and 235 ± 0.04 ml/kg/min in febrile goats and 5.91 ± 0.50 h, 54.29 ± 1.30 mg/L.h and 4.53 ± 0.12 ml/kg/min in healthy goats respectively.

INTERACTION PHARMACOKINETICS

Dutta, (1988) inrestigated the pharmacokinetics of sulfadimidine in afebrile and febrile goats after singles i.v. dose (100 mg/kg). He found that C^0p. $t_{½\alpha}$, $t_{½\beta}$, AUC, Vd_{area} and Cl_B in febrile goats were 33.08 ± 1.81 mg/ 100ml, 0.86 ± 0.11 h, 5.44 ± 0.44 h, 1391 ± 81.61 mg/L.h, 0.57 ± 0.002 L/kg and 0.07 ± 0.004 L/kg/h, respectively. The above value in healthy goats were 29.69 ± 2.01 mg/100ml, 0.41 ± 0.04 h, 3.80 ± 0.13 h, 735.90 ± 68.98 mg/L.h, 0.72 ± 0.03 L/kg and 0.14 ± 0.01ml/kg/min. The study revealed that the kinetic parameters were significantly lower in afebrile goats.

Roy (1991) investigated the biokinetics of cephazolin in normal and febrile goats after single i.m. dose (20mg/kg) administration. The value of α, $t_{½\beta}$, Vd_{ss}, AUC ,Cl_B, K_{12} and K_{21} in febrile goats were 11.96 ± 1.18 h^{-1}, 1.424 ± 0.14 h, 1.22 ± 0.13 L/kg, 47.2 ± 2.61 mg/L.h, 10.662 ± 0.65 ml/kg/min, 6.638 ± 0.90 h^{-1} and 4.47 ± 0.15 h^{-1}, respectively. The above values in healthy goats were 4.91 ± 0.52 h^{-1}, 1.00 ± 0.04 h, 0.60 ± 0.05 L/kg, 62.88 ± 4.20 mg/L.h, 8.14 ± 0.56 ml/kg/min, 1.59 ± 0.25h^{-1} and 2.76 ± 0.18 h^{-1}, respectively. The α, $t_{½\beta}$ and Vd_{ss} values were significantly higher in febrile goats.

Patel (1992) studied the biokinetics of nalidixic acid in goats and found that the Cp_{max} of nalidixic acid after singles i.v. dose (10 mg/kg) was higher in febrile goats 101.05 ± 3.25 µg/ml than that in afebrile goats 49.91 ± 0.29µg/ml.

Lee-Lingiar *et al.* (1997) studied the effects of food and sucralfate on pharmacokinetics of a 500 mg single oral dose of LVX in healthy human subjects under fasting, fed and fasting with sucralfate given 2 h after levofloxacin. With a high fat meal the levofloxacin absorption was delayed and C_{max} was slightly lower. T_{max} was 1 h in (fasting) and 2 h (fed), C_{max} was 5.9 ± 1.3 (fasting) and 5.1 ± 0.9 µg/ml (fed). After sucralfate, the values of C_{max} and AUC 0 to ∞ were 6.7 ± 3.2 µg/ml and 47.9 ± 8.4 µg/ml and 50.5 ± 8.1 µg/ml under fasting conditions.

Prasad (2002) studied the pharmacokinetics of pefloxacin and its interaction with paracetamol in febrile goats. The C^0p was found to be 35.20 ± 3.28 µg/ml without paracetamol and 33.86 ± 3.04 µg/ml with paracetamol at 2.5 min in febrile goats after i.v. administration. The Cl_B did not differ significantly after single i.v. administration in febrile goats with and without paracetamol.

Singh (2002) investigated the pharmacokinetics of enrofloxacin in febrile goats after singles dose (5 mg/kg). i.v. and i.m administration. The C^0p of 24.42 ± 0.91 µg/ml at 2.5 min after i.v. administration and Cp_{max} of 10.76 ± 0.04 µg/ml at 15 min after i.m administration was reported. The mean value of Cl_B after i.v and i.m administration were 2.82 ± 0.27 and 2.27 ± 0.03 ml/kg/min, respectively. The $t_{½\beta}$ was 1.34 ± 0.09 h after i.v. and 2.25 ± 0.02 h after i.m. administration. The mean value of β in urine was 0.44 h^{-1} after i.v and 0.27 h^{-1} after i.m. administration.

Yarsan *et al.* (2003) studied the pharmacokinetics of levofloxacin in *Toxoplasma gondii* infected and control mice groups after single dose administration (10 mg/kg b.w.)

and found significant reduction in distribution half-life ($t_{½\beta}$) and an increase in the peak drug concentration (C_{max}) when compared with control group.

Kujur (2004) investigated the pharmacokinetics of sparfloxacin after single oral dose (20 mg/kg b.w.) administration with and without paracetamol in healthy and febrile goats. The mean value of plasma concentration (µg/ml) of SPX when administered without PAC was lower 20.86 ± 0.80 µg/ml than with PAC 40.93 ± 0.62 µg/ml. It was also found that the values of $t_{½\beta}$ and Cl_B were 7.03 ± 1.10 h and 1.87 ± 0.06 ml/kg/min (with PAC) and 4.65 ± 0.53 h and 2.40 ± 0.11 ml/kg/min (without PAC) in febrile goats, respectively.

Mishra (2006) studied the pharmacokinetics of levofloxacin in healthy and febrile goats. The mean value of peak plasma concentration (µg/ml) of LVX after oral and i.v. administration were 15.81 ± 1.71µg/ml and 18.21 ± 0.85µg/ml, respectively. The $t_{½\beta}$ was 3.84 ± 0.32 h and 2.92 ± 0.29 h after oral and i.v. administration in febrile goats. The Cl_B was 3.85 ± 0.31ml/kg/min and 2.49 ± 0.13 ml/kg/min after oral and i.v. administration in febrile goats, respectively.

MATERIALS AND METHODS

EXPERIMENTAL ANIMALS

The present study was conducted on a group of six clinically healthy cross bred female calves of R.V.C. dairy farm (4 to 6 months) weighing between 40-80 kg. The animals were maintained on balanced ration and partial grazing. Drinking water was given *ad. lib* throughout the period of investigation.

All the calves were acclimatized and dewormed (Albendazole 5 mg/kg b.w.) before the onset of experiment. The pharmacokinetic studies of levofloxacin were carried out in each of six calves with 15 days washout interval.

EXPERIMENTAL DRUGS

1. Levoday® infusion (5mg/ml): Marketed by Recon Health Care Ltd; Bangalore was injected i.v. at the dose of 5 mg/kg b.w. to each of six healthy and febrile calves.
2. L-Cin ® (500mg) tablet: Marketed by Lupin Ltd; Mumbai was given orally at the dose rate of 20 mg/kg b.w. to each of the six healthy and febrile calves.

CONSTRUCTION OF FEBRILE MODEL

The febrile condition was produced as per standardized fever model (Groothuis *et al*., 1980, Ladefoged, 1977; Miert, 1980) in each of the six calves by i.v. administration of lipopolysaccharide (LPS) of E. coli serotype O126 : B_8 (Sigma Chemical Company, St Louis, Mo U.S.A) LPS (100ug) was dissolved in sterile distilled water (100 ml) to make a solution of 1 μg/ml. LPS initially was injected i.v. (0.2 μg/kg) and the half dose was repeated at 5^{th} hour for prolongation of fever. Temperature of each calve was recorded before and administration of LPS at predetermined time intervals.

COLLECTION OF EXPERIMENTAL SAMPLES

The samples of blood and urine were collected post i.v. and oral administration of levofloxacin in healthy and febrile calves at 0,2.5,5,10,20,30,45 min and 1,2,3,4,6,8,10,12 and 24 h respectively.

Blood

Hairs around the jugular vein on either side of neck of the calves were shaved and the area was cleaned with ether. The blood samples were collected in sterilized test tubes containing appropriate amount of sodium citrate from jugular vein by vein puncture at predetermined time intervals following drug administration. Plasma was separated by centrifugation at 4000 rpm for 15 min and was kept in refrigerator at 4^0C till analysis. The analysis was always done within 24 h of sample collection.

Urine

For the collection of urine samples a sterile. Foley's balloon catheter (No. 24) was lubricated with glycerine and was introduced through urethra to the urinary bladder of the experimental calves with the help of flexible metal probe. The balooning of the catheter was done by injecting 80 ml of sterile water through syringe to keep the catheter in proper position. Prior to drug administration urine samples were collected for preparation of standards and after drug administration at predetermined time intervals. The collected samples were kept in refrigerator and were analyzed on next days.

EXPERIMENTAL DESIGN

Levofloxacin was administered intravenously and orally in each of six healthy and febrile calves. An interval of 15 days was allowed as washout period before the administration of next dose.

Intravenous administration

A) Plasma and urine levels of levofloxacin after single dose (5 mg/kg) i.v. administration in healthy calves:

Before administration of drug the blood and urine samples were collected for control as well as preparation of standards. Levofloxacin was administered @ 5 mg/kg, i.v. in left jugular vein to each of calf. Blood and urine sample were collected in fresh test tubes at predetermined time intervals.

B) Plasma and Urine levels of levofloxacin after single dose (20 mg/kg) oral administration in febrile calves:

The normal rectal temperature of each calve was recorded. LPS (0.2µg/kg b.w.) was injected to each of six calves and rise in temperature was maintained by repeating half dose of LPS (0.1µg/kg) at 5^{th} h. Levofloxacin was administrated (5 mg/kg) to each of the calves after one hour of LPS injection. Blood and urine samples were collected for control as well as for preparation of standards before drug administration. The rectal temperature was recorded throughout the investigation.

Oral Administration

A. Plasma and urine levels of levofloxacin after single oral dose (20 mg/kg) administration in healthy calves:

The blood and urine samples were collected for control as well as preparation of standards before administration of drug. Levofloxacin was administered @ 20 mg/kg b.w. orally to each of the six calves. Blood and urine samples were collected in test tube at predetermined time intervals.

B. Plasma and Urine levels of levofloxacin after single oral dose (20 mg/kg) administration in febrile calves:

The rectal temperature of each calf was recorded before fever production. Febrile condition was produced in each calf after the i.v. injection of LPS (0.2 µg/kg). Half dose of LPS (0.1 µg/kg) was injected at 5^{th} hour to maintain the rise of temperature. Levofloxacin was administered @ 20 mg/kg b.w. orally to each of the six calves after 1 h of LPS injection. Blood and Urine samples were collected prior and after drug administration. Rectal temperature was recorded the throughout experiment.

IN-VITRO PLASMA PROTEIN BINDING

The plasma protein binding of levofloxacin was determined by the "equilibrium dialysis" technique as described by Davis (1943) and Sisodia *et al.* (1965). Dialysis tubes of appropriate size (Size 22/32″) were used. The cut piece of dialysis tubes were washed with distilled water and soaked in phosphate buffer (pH-7.4) overnight at 37^0C in incubator. Glass tubes (2-3″ Size) with both ends open were taken and at one end a piece of dialysis tube was securely tied in order to make a closed dialysis bag. Leakage was tested by inflating the dialysis bag and placing it in a beaker containing phosphate buffer.

Plasma standard solutions of levofloxacin were prepared in the concentrations of 6.25, 12.5, 25 and 50 µg/ml. The pH of the plasma was measured and adjusted to 7.4 with the help of pH meter. 5 ml of each plasma standard was placed into separate dialysis bag prepared previously. All the dialysis bags were suspended separately in larger test tube containing 5 ml of phosphate buffer solution and all were kept in an incubator at 37^0C overnight.

Plasma and buffer standard solutions of levofloxacin were prepared and concentration of drug in plasma and buffer was read with the help of PC based U.V

spectrophotometer. Plasma protein binding of drug was calculated by following formula given by Linkenheinmer *et al.* (1965).

$$\% \text{ plasma protein binding} = \frac{\text{Conc. of drug in plasma} - \text{Conc. of drug in buffer}}{\text{Conc. of drug in plasma}} \times 100$$

PREPARATION OF LEVOFLOXACIN STANDARDS

1 mg levofloxacin (0.2 ml of 0.5 % Levoday® inj.) was diluted in distilled water (10 ml) to make a concentration of 100 µg /ml. It was further serially diluted to make different concentrations viz., 50, 25, 12.5, 6.25, 3.125 and 1.562 µg /ml. The respective standard curve was plotted with O.D. obtained versus standard concentrations of levofloxcin in plasma and urine with the help of P.C. based U.V. spectrophotometer.

ANALYTICAL METHOD

The standardized analytical method was used for the estimation of levofloxacin in plasma and urine. The peak absorbance of levofloxacin was observed at 286 nm. The sensitivity of the method for detection of LVX was 0.62 µg/ml.

Plasma

To each ml of plasma, 4 ml of 0.02% formic acid in isopropyl alcohol (IPA) was added and the mixture was shaken vigorously for complete deproteinization. The sample was centrifuged for 15 min at 4000 rpm and clear supernatant was transferred to another test tube. The standard solution of levofloxacin was prepared in plasma always before analysis and standard curve was plotted on computer and concentration (µg /ml) of each plasma sample was recorded.

Urine

0.1 ml of urine was taken in a clean test tube and was diluted with 0.9 ml distilled water. 4 ml of 0.02% formic acid in IPA was added in each test tube and shaked vigorously. The sample was centrifuged at 4000 rpm for 15 minutes and supernatant separated. The standard solution of levofloxacin was prepared in control urine and standard curve was plotted each time before analysis. The concentrations of levofloxacin in experimental samples were determined by comparing the standard curve plotted on P.C. based U.V. spectrophotometer.

CALCULATION OF PHARMACOKINETIC PARMETERS

The different pharmacokinetic parameters of levofloxacin after single oral and i.v. administration in healthy and febrile calves were determined by computer programming (Pharmkit) which are listed below:

1. A (μg/ml) - Zero time plasma concentration of drug at distribution phase.
2. B (μg/ml) - Zero time plasma concentration for elimination phase.
3. Ka (h^{-1}) - The regression co-efficient for absorption phase of the curve after oral administration and calculated by the method of residual yields.
4. α(h^{-1}) - Regression co-efficient for distribution phase (distribution rate constant).
5. β (h^{-1}) - Regression co-efficient for elimination phase (elimination rate constant).
6. C^0p (μg/ml) - The theoretical zero time plasma drug concentration.
7. $t_{½\ Ka}$, $t_{½\alpha}$ and $t_{½\beta}$(h) - The respective half life of absorption ,distribution and elimination phase. The values were calculated by standard formula (Baggot, 1977).

8. AUC (mg/L.h) - The area under the plasma concentration curve was calculated as below

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta}$$

9. MRT (h) - The mean residual time (MRT) of levofloxacin was calculated by the following formula:

$$MRT = \frac{AUMC}{AUC}$$ (Raoff and Sams, 1985)

10. Cl_B (ml/kg/min) - The total body clearance of the drug representing the sum of all clearance processes in the body was calculated as below:

$$Cl_B = Vd_{area} \times \beta$$

11. Vd_{area} (L Kg^{-1}) - The volume of distribution in total area under curve

$$Vd_{area} = \frac{D}{AUC.\beta} \quad \text{or} \quad \frac{D}{(A/\alpha+B/\beta).\beta}$$

12. K_{21} (h^{-1}) - Rate of diffusion of the drug from peripheral compartment to central compartment.

$$K_{21} = \frac{A.\beta + B.\alpha}{A + B}$$ (Notari, 1980)

13. K_{12} (h^{-1}) - Rate of diffusion of drug from central to peripheral compartment.

$K_{12} = \alpha + \beta - K_{21} - K_2$ (Notari, 1980)

14. K_2 or Kel (h^{-1}) - The elimination rate constant of drug from central compartment.

$$Kel \text{ or } K_2 = \frac{\alpha.\beta}{K_{21}}$$ (Notari, 1980)

15. T/P ratio = $\frac{K_{12}}{K_{21}-\beta}$

CALCULATION OF DOSAGE REGIMEN

The dose of levofloxocin (mg/kg b.w.) was calculated by standard method described by Richard (1980).

$$D(mg/kg) = C_{ther}. Vd_{area}/F$$

Where, $$F= \frac{AUC\ (oral)}{AUC\ (i.v.)}$$

Dosage interval of levofloxacin was calculated based on the method described by Shargel and Andrew (1985) :

$$Cp_{max}/Cp_{min} = 1- e^{-\beta.r}$$

r = interval for dose report

β = overall elimination rate constant

STATISTICAL ANALYSIS

The statistical comparison of important pharmacokinetic parameters was done by statistical method (Snodecor and Cochran, 1989). Quantitative data were analyzed, using the paired 't' test. A value $p<0.05$ and $p<0.01$ were considered significant.

Concentrations of levofloxacin (LVX) after single oral dose (20 mg/kg) administration in healthy calves

Plasma

The plasma concentrations of LVX after oral administration in healthy calves have been presented in table 1. This table showed that the mean Cp_{max} and Cp_{min} were 4.50±0.24 and 0.92±0.06 µg/ml at 1 h and 8 h, respectively. The mean Cp_{ther} was maintained between 15 min to 8 h. The Cp_{max} in individual calf ranged between 3.96 to 5.17 µg/ml and was found at 1 h. The Cp_{min} in individual calf varied between 0.69 to 1.12 µg/ml.

Urine

Table 5 shows the urine concentrations of LVX after oral administration in healthy calves. The mean Cu_{max} 39.38±2.43 µg/ml was observed at 2 h and gradually declined to 0.99±0.03 µg/ml at 10 h. The Cu_{max} in individual calf ranged between 32.06 to 48.23µg/ml. The Cu_{max} 48.23 µg/ml was higher. The table 5 shows that beyond 10 h the drug was not detected in experimental calves.

Concentrations of LVX after single oral dose (20mg/kg) administration in febrile calves

Plasma

Table 2 shows the mean peak plasma concentration of LVX 5.28±0.32 µg/ml was observed at 2 h. The mean Cp_{min} 0.89 ± 0.07 µg/ml was observed at 10 h.

Table 1: Plasma concentrations (μg/ml) of levofloxacin after single oral dose (20 mg/kg) administration in healthy calves (n=6).

Time	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
15 min	3.72	2.94	3.30	2.39	2.15	2.26	2.79±0.23
30 min	4.06	3.46	3.84	3.07	2.75	2.98	3.36±0.21
45 min	4.58	3.82	4.56	3.39	3.13	3.38	3.81±0.25
1 h	5.08	4.02	5.17	3.93	4.88	3.96	4.50±0.24
2 h	4.73	3.67	4.82	3.54	4.10	3.17	4.00±0.27
3 h	4.70	2.56	4.16	2.67	3.54	2.50	3.35±0.37
4 h	3.52	2.43	3.65	2.39	3.00	2.33	2.88±0.24
6 h	2.58	1.68	2.45	1.81	2.02	1.94	2.08±0.14
8 h	1.04	0.89	1.12	0.69	1.00	0.83	0.92±0.06
10 h	BDL	BDL	BDL	BDL	BDL	BDL	BDL

BDL = Below Detection Level

Table 2: Plasma concentrations (μg/ml) of levofloxacin after single oral dose (20mg/kg) administration in febrile calves (n=6).

Time	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
15 min	4.78	3.21	4.54	2.31	3.11	2.19	3.35±0.40
30 min	5.16	3.99	4.92	2.89	3.64	2.98	3.93±0.35
45 min	5.83	4.15	5.86	3.17	4.04	3.02	4.34±0.46
1 h	6.02	4.91	5.98	3.98	4.86	3.78	4.92±0.35
2 h	6.25	5.13	6.26	4.30	5.46	4.27	5.28±0.32
3 h	5.50	4.26	5.62	4.11	5.00	3.68	4.69±0.29
4 h	4.97	3.46	4.89	3.96	4.78	3.39	4.24±0.27
6 h	3.23	2.78	3.60	2.95	3.12	2.88	3.09±0.11
8 h	2.15	1.94	2.24	1.01	2.38	1.13	1.80±0.22
10 h	1.06	0.79	1.00	0.72	1.12	0.66	0.89±0.07
12 h	BDL	BDL	BDL	BDL	BDL	BDL	BDL

BDL = Below Detection Level

Table 3: Plasma concentrations (μg/ml) of levofloxacin after single dose intravenous (5mg/kg) administration in healthy calves (n=6).

Time	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
2.5 min	5.08	4.97	5.02	4.94	5.89	4.92	5.13±0.13
5 min	4.56	3.68	4.39	3.66	4.69	3.69	4.11±0.18
10 min	3.93	5.73	3.68	2.92	3.31	2.94	3.23±0.16
20 min	3.07	2.18	3.26	2.12	3.00	2.10	2.62±0.20
30 min	2.89	2.04	2.69	2.00	2.40	1.97	2.33±0.14
45 min	2.50	1.98	2.15	1.83	2.13	1.73	2.05±0.10
1 h	2.23	1.54	1.78	1.42	1.90	1.52	1.73±0.11
2 h	1.97	1.28	1.34	1.26	1.48	1.32	1.44±0.10
3 h	1.26	1.07	1.12	1.09	1.16	1.13	1.13±0.02
4 h	1.12	0.92	0.89	0.97	0.87	0.98	0.95±0.03
6 h	0.93	0.77	0.69	0.99	0.66	0.69	0.78±0.04
8 h	BDL	BDL	BDL	BDL	BDL	BDL	BDL

BDL = Below Detection Level

Table 4: Plasma concentrations (μg/ml) of levofloxacin after single dose intravenous (5mg/kg) administration in febrile calves (n=6).

Time	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
2.5 min	6.52	6.71	5.97	5.89	6.30	5.56	6.16±0.15
5 min	6.04	6.09	5.23	5.41	5.00	5.10	5.47±0.17
10 min	5.67	5.64	5.01	5.18	5.78	4.97	5.36±0.13
20 min	5.13	5.08	4.88	4.71	5.04	4.47	4.88±0.09
30 min	4.35	4.78	4.58	4.64	4.83	4.00	4.52±0.11
45 min	4.09	4.18	4.26	4.04	4.37	3.59	4.08±0.10
1 h	3.72	3.67	4.00	3.64	4.02	3.24	3.71±0.10
2 h	3.45	3.28	3.57	3.26	3.68	2.90	3.35±0.10
3 h	3.10	2.85	3.06	3.00	3.16	2.27	2.91±0.11
4 h	2.80	2.47	2.74	2.74	2.84	2.07	2.61±0.11
6 h	1.71	1.44	1.39	1.42	1.21	1.68	1.47±0.07
8 h	0.92	0.86	1.02	0.88	0.67	0.79	0.85±0.04
10 h	BDL	BDL	BDL	BDL	BDL	BDL	BDL

BDL = Below Detection Level

Table 5: Urine concentrations (μg/ml) of levofloxacin after single oral dose (20 mg/kg) administration in healthy calves (n=6).

Time	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
15 min	15.46	12.25	18.60	13.87	16.47	18.36	15.89±0.93
30 min	24.45	18.39	28.21	18.20	23.05	25.46	22.96±1.48
45 min	28.90	24.06	34.25	26.08	32.14	30.30	29.28±1.40
1 h	32.74	30.71	40.34	30.78	42.93	35.01	35.41±1.91
2 h	36.04	34.63	46.34	32.06	48.23	39.01	39.38±2.43
3 h	22.06	26.34	32.80	24.18	34.68	26.80	27.81±1.83
4 h	16.80	18.92	20.04	15.23	21.46	16.50	18.15±0.88
6 h	8.41	6.04	11.57	7.57	12.15	9.08	9.09±0.88
8 h	3.02	2.16	4.68	3.48	5.70	4.16	3.86±0.46
10 h	0.92	0.87	1.06	0.98	1.12	1.02	0.99±0.03
12 h	BDL	BDL	BDL	BDL	BDL	BDL	BDL

BDL = Below Detection Level

Table 6: Urine concentrations (μg/ml) of levofloxacin after single oral dose (20 mg/kg) administration in febrile calves (n=6).

Time	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
15 min	17.06	14.08	18.85	12.30	16.21	14.34	15.47±0.87
30 min	23.45	18.73	25.82	16.15	26.05	18.37	21.42±1.57
45 min	26.06	24.18	32.14	20.50	34.25	28.40	27.58±1.89
1 h	30.62	28.70	36.55	25.06	38.10	32.60	31.93±1.81
2 h	33.46	32.05	40.45	30.10	42.32	36.05	35.73±1.79
3 h	38.20	36.50	47.04	34.25	48.94	40.25	40.86±2.19
4 h	24.22	22.38	32.62	28.01	30.36	26.80	27.39±1.41
6 h	12.06	10.81	18.10	16.45	21.20	18.38	16.16±1.48
8 h	6.95	5.01	8.25	6.80	11.86	7.25	7.68±0.85
10 h	2.20	1.50	2.62	1.32	4.02	3.08	2.46±0.37
12 h	0.87	0.66	1.04	1.70	1.08	0.98	0.88±0.06
24 h	BDL	BDL	BDL	BDL	BDL	BDL	BDL

BDL = Below Detection Level

Table 7: Urine concentrations (μg/ml) of levofloxacin after single dose intravenous (5 mg/kg) administration in healthy calves (n=6).

Time	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
2.5 min	-	-	-	-	-	-	-
5 min	34.66	45.25	30.62	42.04	43.00	38.50	39.01±2.06
10 min	45.54	56.39	48.08	68.51	57.97	56.20	55.44±3.03
20 min	62.40	68.64	56.50	72.25	66.52	70.10	66.06±2.14
30 min	42.50	48.16	38.42	58.53	36.05	43.26	44.48±3.00
45 min	28.09	26.82	22.68	36.39	24.10	32.78	28.47±1.94
1 h	18.76	14.20	10.75	25.96	15.30	18.80	17.29±1.94
2 h	12.27	8.32	6.00	12.80	8.80	10.36	9.75±0.95
3 h	7.06	6.84	3.46	6.25	4.15	5.95	5.61±0.55
4 h	4.15	3.53	1.06	2.58	1.65	2.04	2.50±0.43
6 h	1.02	0.66	0.78	0.82	0.78	0.94	0.83±0.04
8 h	BDL	BDL	BDL	BDL	BDL	BDL	BDL

BDL = Below Detection Level

Table 8: Urine concentrations (μg/ml) of levofloxacin after single dose intravenous (5 mg/kg) administration in febrile calves (n=6).

Time	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
2.5 min	-	-	-	-	-	-	-
5 min	45.86	48.97	32.83	52.49	47.49	54.01	46.94±2.81
10 min	52.05	56.17	44.01	64.96	55.90	62.78	55.98±2.81
20 min	60.20	64.44	52.30	69.16	60.31	68.20	62.43±2.32
30 min	67.70	70.50	58.24	74.02	68.12	72.00	68.42±2.05
45 min	38.25	46.58	34.58	48.95	32.24	42.44	40.50±2.47
1 h	26.14	32.65	24.52	30.46	20.80	25.06	26.60±1.59
2 h	18.20	20.49	16.18	18.02	16.47	14.10	17.24±0.81
3 h	10.25	8.02	12.00	7.87	10.75	8.93	9.63±0.61
4 h	5.13	4.50	8.32	3.25	4.40	4.45	5.00±0.64
6 h	2.94	1.18	3.50	1.76	2.46	1.37	2.20±0.34
8 h	1.00	0.25	1.06	0.86	1.16	0.65	0.83±0.12
10 h	BDL	BDL	BDL	BDL	BDL	BDL	BDL

BDL = Below Detection Level

The mean Cp_{ther} of LVX was maintained between 15 min to 10 h after single dose oral administration. The Cp_{max} in individual febrile calves ranged between 4.27 to 6.26 µg/ml at 2 h. The plasma samples collected at 12 h could not show the presence of LVX.

Urine

The individual and mean urine concentrations of LVX after single oral dose in febrile calves have been presented in table 6. The mean Cu_{max} was observed to be 40.86±2.19 µg/ml at 3 h post drug administration that declined gradually to 0.88±0.06 µg/ml till 12 h. The tCu_{ther} of LVX after single oral dose administration maintained between 15 min to 12 h.

Concentrations of LVX after single i.v. dose (5 mg/kg) administration in healthy calves

Plasma

The individual and mean plasma concentrations of LVX at different time intervals are depicted in table 3. The mean Cp_{max} was found to be 5.13±0.13µg/ml at 2.5 min and declined gradually to 0.78±0.04 µg/ml at 6 h. The Cp_{ther} was maintained in all experimental calves between 2.5 min to 4 h after single i.v. dose LVX administration in healthy calves. The individual Cp_{max} 5.89 µg/ml of LVX was observed in calf no. 5. The experimental plasma samples collected at 8 h post i.v. administration could not show presence of drug in any healthy calves.

Urine

Table 7 shows urine concentrations of LVX at different time intervals after single dose (5 mg/kg) i.v. administration in healthy calves. The mean Cu_{max} of LVX was obtained to be 66.06±2.14 µg/ml at 20 min and therefore declined slowly to 0.83±0.04

µg/ml at 6 h. The therapeutic urine concentration of LVX was observed to be maintained between 2.5 min to 6 h after i.v. administration in healthy calves.

Concentrations of LVX after single i.v. dose (5 mg/kg) administration in febrile calves

Plasma

Table 4 shows individual and mean plasma concentrations of LVX at different time interval after single dose (5 mg/kg) i.v. administraion in febrile calves. The mean Cp_{max} was observed to be 6.16±0.15 µg/ml at 2.5 min and declined to 0.85±0.04 µg/ml at 8 h. The mean Cp_{ther} was maintained between 2.5 min to 8 h post i.v. LVX administration. The individual plasma concentration of LVX ranged between 5.56 to 6.71 µg/ml.

Urine

The individual and mean urine concentrations of LVX after i.v. administration in febrile calves is depicted in table 8. The mean Cu_{max} was obtained to be 68.42±2.05 µg/ml at 30 min and thereafter declined to 0.83±0.12 µg/ml at 8 h. The tCu_{ther} was maintained between 5 min to 8 h after i.v. administration.

Pharmacokinetic profile of levofloxacin (LVX) after single oral dose (20 mg/kg) administration in healthy claves.

Plasma kinetics

The mean pharmacokinetic profile of levofloxacin after single dose (20 mg/kg) oral administration in individual healthy calves has been depicted in table 9. The mean

values of A and B were 5.73±0.57 and 7.09±0.68µg/ml, respectively. It is also evident from table 9 that the mean value of β, $t_{½\beta}$ and Cl_B were 0.25±0.01 h^{-1}, 2.99±0.15 h and 13.06±0.78 ml/kg/min, respectively. The mean value of MRT and Vd_{area} in healthy calves were 4.66±0.13 h and 3.40±0.30 L, respectively.

Urine kinetics

Table 13 depicts the urine kinetics of LVX after single dose oral administration in healthy calves. The mean value of Cu_{max} was observed to be 31.68±1.90 µg/ml at T_{max} of 1.27±0.03 h. The mean values of β, $t_{½\beta}$ and Cl_B were 0.38±1.90 h^{-1}, 1.75±0.02 h and 2.08±0.11 ml/kg/min, respectively after single dose oral administration in healthy calves.

Pharmacokinetic profile of LVX after single oral dose (20 mg/kg) administration in febrile calves

Plasma

The mean pharmacokinetic profile of LVX after single dose oral administration in febrile calves has been depicted in table 10. The mean value of A, B and C^o_P were 8.16±0.40, 10.15±0.37 and 18.32±0.63 µg/ml, respectively in healthy calves. It may also be observed from the table that the mean value of Ka and β were 0.95±0.05 h^{-1} and 0.23±0.01 h^{-1}, respectively. The value of $t_{½Ka}$, $t_{½\beta}$ and Cl_B were 0.72±0.03 h, 6.04±0.14 h and 9.27±0.66 ml/kg/min, respectively. It may also be evident from table 10 that the mean value of MRT and Vd_{area} in febrile calves was 5.03±0.12 h and 2.40±0.10 L, respectively after single oral dose (20mg/kg) administration in febrile calves.

Table 9: Pharmacokinetic profile of levofloxacin in plasma after single oral dose (20 mg/kg) administration in healthy calves (n=6).

Kinetic parameters	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
A (µg/ml)	6.88	4.30	7.37	5.19	6.97	3.70	5.73±0.57
B (µg/ml)	9.22	5.55	8.60	6.67	8.00	4.51	7.09±0.68
C^0p (µg/ml)	16.10	6.85	15.97	11.86	14.97	8.21	12.80±1.25
Ka (h^{-1})	1.14	2.20	1.45	1.30	1.17	2.35	1.60±0.19
β(h^{-1})	0.25	0.21	0.23	0.26	0.25	0.18	0.25±0.01
$t_{½Ka}$ (h)	0.60	0.31	0.47	0.53	0.58	0.29	0.46±0.05
$t_{½β}$ (h)	2.76	3.16	2.92	2.63	2.77	3.75	2.99±0.15
AUC (mg/L.h)	27.19	19.19	26.63	18.77	22.24	18.50	22.08±1.47
Cl_B (ml/kg/min)	10.64	14.34	10.63	15.58	12.71	14.49	13.06±0.78
Vd_{area}(L)	2.55	3.92	2.69	3.56	3.05	4.71	3.40±0.30
T_{max}(h)	1.38	1.04	1.36	1.30	1.52	1.09	1.28±0.06
MRT (h)	4.42	4.80	4.61	4.26	4.61	5.28	4.66±0.13
Cp_{max}(µg/ml)	5.10	3.98	5.21	3.78	4.30	3.41	4.29±0.27

Table 10: Pharmacokinetic profile of levofloxacin in plasma after single oral dose (20 mg/kg) administration in febrile calves (n=6).

Kinetic parameters	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
A (µg/ml)	7.14	7.73	7.91	10.11	7.39	8.69	8.16±0.40
B (µg/ml)	10.85	9.11	11.21	11.14	9.15	9.49	10.15±0.37
C^0p (µg/ml)	17.99	16.84	19.12	21.25	16.54	18.18	18.32±0.63
Ka (h^{-1})	0.96	1.18	0.97	0.78	0.95	0.90	0.95±0.05
β(h^{-1})	0.21	0.22	0.22	0.27	0.19	0.25	0.23±0.01
$t_{½Ka}$ (h)	0.71	0.58	0.71	0.87	0.72	0.77	0.72±0.03
$t_{½β}$ (h)	3.19	3.10	3.14	2.52	3.63	2.69	6.04±0.14
AUC (mg/L.h)	38.73	30.71	39.46	27.63	35.48	26.12	33.02±2.12
Cl_B (ml/kg/min)	7.64	9.75	7.58	11.02	8.06	11.62	9.27±0.66
Vd_{area} (L)	2.11	2.62	2.06	2.41	2.63	2.71	2.40±0.10
T_{max} (h)	1.44	1.56	1.50	1.86	1.86	1.82	1.67±0.07
Cp_{max} (µg/ml)	6.16	5.21	6.22	4.35	5.16	4.25	5.22±0.31
MRT (h)	5.03	5.00	4.98	4.72	5.68	4.81	5.03±0.12

Table 11: Pharmacokinetic profile of levofloxacin in plasma after single dose intravenous (5 mg/kg) administration in healthy calves (n=6).

Kinetic parameters	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
A (µg/ml)	2.58	5.85	2.82	3.64	4.43	3.83	3.86±0.44
B (µg/ml)	1.68	1.69	2.21	1.67	2.61	2.02	2.01±0.14
$C^{o}p$ (µg/ml)	4.26	7.54	5.03	5.31	7.04	5.85	5.83±0.46
α (h^{-1})	3.456	15.87	2.79	10.94	16.25	8.81	9.68±2.17
β (h^{-1})	0.10	0.13	0.20	0.11	0.24	0.18	0.16±0.02
$t_{½\,\alpha}$ (h)	0.20	0.04	0.24	0.06	0.04	0.07	0.10±0.03
$t_{½\,\beta}$ (h)	6.92	5.02	3.31	6.06	2.86	3.74	4.65±0.60
AUC (mg/L.h)	10.05	7.70	8.28	7.77	8.93	7.67	8.40±0.35
MRT (h)	8.84	6.91	4.59	8.76	3.97	5.28	6.39±0.78
Cl_B (ml/kg/min)	4.31	6.28	7.19	5.21	7.15	7.31	6.24±0.46
Vd_{area} (L)	2.58	2.73	2.07	2.74	1.77	2.37	2.37±0.14
K_{21} (h^{-1})	1.42	3.65	1.33	3.51	6.17	3.16	3.20±0.66
K_2 (h^{-1})	0.24	0.56	0.41	0.34	0.63	0.50	0.44±0.05
K_{12} (h^{-1})	1.9	11.79	1.25	7.2	9.68	5.33	6.19±1.56
T/P	1.43	3.65	1.10	2.11	1.62	1.78	1.94±0.33

Table 12: Pharmacokinetic profile of levofloxacin in plasma after single dose intravenous (5 mg/kg) administration in febrile calves (n=6).

Kinetic parameters	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
A (µg/ml)	0.80	1.80	0.45	0.30	3.71	1.90	1.49±0.47
B (µg/ml)	5.27	5.09	5.19	5.16	9.23	4.17	5.68±0.66
C^0p (µg/ml)	6.07	6.89	5.64	5.46	12.94	6.07	7.17±1.06
α (h^{-1})	1.32	5.31	11.56	1.88	0.53	4.89	4.24±1.51
β (h^{-1})	0.20	0.21	0.20	0.21	0.32	0.18	0.22±0.01
$t_{½\alpha}$ (h)	0.52	0.13	0.05	0.36	1.30	0.14	0.41±0.17
$t_{½\beta}$ (h)	3.46	3.25	3.44	3.29	2.10	3.69	3.20±0.20
AUC (mg/L.h)	21.68	20.30	21.19	20.50	20.94	18.22	20.47±0.45
MRT (h)	4.74	4.50	4.89	4.59	3.50	4.95	4.52±0.19
Cl_B (ml/kg/min)	3.17	3.42	3.178	3.38	3.63	3.72	3.41±0.08
Vd_{area} (L)	0.95	0.97	0.95	0.96	0.66	1.19	0.94±0.06
K_{21} (h^{-1})	1.17	3.97	10.65	1.78	0.46	3.41	3.57±1.38
K_2 (h^{-1})	0.22	0.28	0.21	0.22	0.36	0.25	0.25±0.02
K_{12} (h^{-1})	0.13	1.27	0.9	0.09	0.03	1.41	0.63±0.23
T/P	0.13	0.33	0.08	0.05	0.21	0.43	0.20±0.05

Urine

Table 14 shows the mean pharmacokinetic profile of LVX in urine after oral single dose administration in febrile calves. The value of Cu_{max} and T_{max} were 3.95±2.17 µg/ml and 1.40±0.04 h, respectively. The mean value of $t_{½\beta}$ and Cl_B after single dose oral administration in febrile calves were 1.85±0.06 h and 1.64±0.08 ml/kg/min, respectively.

Pharmacokinetic profile of LVX after single i.v. dose (5 mg/kg) administration in healthy calves

Plasma

The mean pharmacokinetic profile of LVX after i.v. administration in healthy calves has been depicted in table 11. The mean value of A, B and C^o_P were 3.86±0.44, 2.01±0.14 and 5.83±0.46 µg/ml, respectively in healthy calves. It may also be observed from the table that the mean value of α and β were 9.68±2.17 h^{-1} and 0.16± 0.02 h^{-1}. The value of $t_{½\alpha}$, $t_{½\beta}$ and Cl_B were 0.41±0.03 h, 4.65±0.60 h and 6.24±0.46 ml/kg/min, respectively. It may also be evident from table 11 that the mean value of rate of drug transfer from central to peripheral (K_{12}), peripheral to central (K_{21}) and elimination from the central compartment (K_2) after i.v. administration in healthy calves were 6.19±1.56 , 3.20±0.66 and 0.44±0.05 h^{-1}, respectively.

Urine

Table 15 shows the mean pharmacokinetic profile of LVX in urine after i.v. administration in healthy calves. The values of Cu_{max} and T_{max} were 53.70±2.37 µg/ml and 0.10±0.01 h, respectively. The mean value of $t_{½\beta}$, Cl_B and MRT after i.v. administration in healthy calves were 0.87±0.03 h, 1.2±0.09 ml/kg/min and 1.26±0.04 h, respectively.

Pharmacokinetic profile of LVX after single i.v. dose (5 mg/kg) administration in febrile calves:

Plasma

The mean and individual kinetic profile of LVX in plasma after i.v. administration has been presented in table 12. The mean value of A, B and C^{o}_{P} were 1.49±0.47, 5.68±0.66 and 7.17±1.06 µg/ml, respectively in febrile calves. It may also be observed from the table that the mean values of α and β were 4.24±1.51 and 0.22±0.01 h^{-1}, respectively. The value of $t_{½\alpha}$, $t_{½\ \beta}$ and Cl_B were 0.41±0.17 h, 3.20±0.20 h and 3.41±0.08 ml/kg/min, respectively. Table 12 also shows that the mean value of rate of drug transfer from central to peripheral (K_{12}), peripheral to central (K_{21}) and elimination from central compartment (K_2) after i.v. administration in febrile calves were 0.63±0.23 h^{-1}, 3.57±1.38 h^{-1} and 0.25±0.02 h^{-1}, respectively.

Urine

Table 16 shows the mean and individual profile of LVX in urine after i.v. administration in febrile calves. The values of Cu_{max} and T_{max} were 63.15±3.44 µg/ml and 0.46±0.02 h, respectively. The mean value of $t_{½\beta}$, Cl_B and MRT after i.v. administration in febrile calves were 1.31±0.08 h, 0.79±0.01 ml/kg/min and 1.70±0.10 h, respectively.

Total urine execretion of levofloxacin (LVX) after single oral dose (20 mg/kg) administration in healthy calves:

Table 17 shows total urine concentrations (mg/ml) of LVX at different time intervals after single oral dose (20 mg/ kg) administration in urine of healthy calves. The maximum urine excretion was observed to be 174.25±10.50 mg/ml. at 2 h which declined to 6.48±0.26 mg/ml at 10 h. The minimum urinary excretion of LVX after oral

Table 13: Pharmacokinetic profile of levofloxacin in urine after single oral dose (20mg/kg) administration in healthy calves (n=6).

Kinetic parameters	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
Cu_{max} (μg /ml)	31.58	24.31	38.09	28.45	36.66	31.00	31.68±1.90
β (h^{-1})	0.40	0.39	0.40	0.38	0.39	0.36	0.38±1.90
$t_{½\beta}$ (h)	1.70	1.74	1.70	1.78	1.73	1.89	1.75±0.02
MRT (h)	3.08	3.04	3.16	3.20	3.25	3.16	3.14±0.03
Cl_B (ml/kg/min)	2.28	2.35	1.75	2.41	1.67	2.07	2.08±0.11
$t_{½\alpha}$ (h)	0.34	0.36	0.26	0.37	0.258	0.34	0.32±0.02
T_{max} (h)	1.20	1.28	1.30	1.29	1.42	1.16	1.27±0.03
tCu_{ther} (h)	10	8	10	10	10	10	9.66±0.30

Table 14: Pharmacokinetic profile of levofloxacin in urine after single oral dose (20 mg/kg) administration in febrile calves (n=6).

Kinetic parameters	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
Cu_{max} (μg/ml)	29.55	30.32	39.33	27.02	41.40	36.11	33.95±2.17
β (h^{-1})	0.34	0.41	0.38	0.41	0.33	0.36	0.37±0.01
$t_{½\,\beta}$ (h)	2.02	1.67	1.79	1.68	2.05	1.88	1.85±0.06
MRT (h)	3.70	3.53	3.76	3.86	4.00	3.90	3.79±0.06
Cl_B (ml/kg/min)	1.76	1.95	1.38	1.79	1.43	1.56	1.64±0.08
T_{max} (h)	1.44	1.56	1.61	1.70	1.56	1.70	1.40±0.04
tCu_{ther} (h)	10	10	12	10	12	12	11.00±0.40

Table 15 Pharmacokinetic profile of levofloxacin in urine after single dose intravenous (5 mg/kg) administration in healthy calves (n=6).

Kinetic parameters	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
Cu_{max} (μg/ml)	48.73	53.61	51.14	65.97	49.12	53.92	53.70±2.37
β (h^{-1})	0.64	0.73	0.63	0.76	0.76	0.72	0.72±0.02
$t_{½β}$ (h)	1.07	0.94	1.09	0.90	0.90	0.95	0.87±0.03
MRT (h)	1.49	1.29	1.21	1.20	1.20	1.25	1.26±0.04
Cl_B (ml/kg/min)	1.08	1.15	1.63	0.93	0.93	1.11	1.20±0.09
T_{max} (h)	0.33	0.44	0.33	0.34	0.34	0.44	0.36±0.02
tCu_{ther} (h)	6	6	4	6	4	4	5.00±0.40

Table 16 Pharmacokinetic profile of levofloxacin in urine after single dose intravenous (5 mg/kg) administration in febrile calves (n=6).

Kinetic parameters	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
Cu_{max} (μg/ml)	56.07	72.36	48.51	70.21	68.41	63.39	63.15±3.44
β (h^{-1})	0.51	0.69	0.46	0.51	0.43	0.61	0.53±0.03
$t_{½\beta}$ (h)	1.33	0.99	1.46	1.34	1.60	1.13	1.31±0.08
MRT (h)	1.81	1.39	2.10	1.53	1.92	1.47	1.70±0.10
Cl_B (ml/kg/min)	0.77	0.76	0.78	0.77	0.85	0.82	0.79±0.01
T_{max} (h)	0.50	0.50	0.40	0.50	0.40	0.50	0.46±0.02
tCu_{ther} (h)	8	6	8	6	8	6	7.00±0.40

administration ranged between 6.07 to 7.28 mg/ml. It may be observed that at 15 min the urinary excretion was 36.39 mg/ml.

Total urine excretion (mg/ml) of levofloxacin (LVX) after single oral dose (20 mg/kg) administration in febrile calves:

The total urine concentration (mg/ml) of LVX at different time intervals is depicted in table 18. The mean maximum excretion was obtained to be 195.34±14.94 mg/ml at 3 h which declined to 5.55±0.48 mg/ml. at 12 h. The individual excretion of LVX ranged between 33.21 to 44.45 mg/ml. at 15 min in febrile calves.

Total urine excretion (mg/ml) to LVX after single intravenous dose (5 mg/kg) administration in healthy calves:

Table 19 shows total urine excretion of LVX at different time intervals after single i.v. dose (5mg/kg) administration in healthy calves. The maximum excretion was observed to be 34.00±3.03 mg/ml at 20 min which declined to 3.66±0.24 mg/ml at 6 h. The therapeutic concentration of LVX was maintained between 5 min to 6 h after single i.v. dose administration in healthy calves.

Total urine excretion (mg/ml) of LVX after single i.v. dose (5 mg/kg) administration in febrile calves:

The total urine excretion of LVX at different time intervals in febrile calves is depicted in table 20. The mean maximum urinary excretion of LVX was obtained to be 35.04±2.45 mg/ml. at 30 min which declined to 4.36±0.37 mg/ml. at 8 h. The urinary excretion at 15 min ranged between 19.69 to 32.10 mg/ml. in febrile calves.

Table 17: Total urine concentrations (mg/ml) of levofloxacin after single oral dose (20 mg/kg) administration in healthy calves (n=6).

Time	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
15 min	34.01	24.50	46.5	23.57	49.41	41.37	36.39±4.07
30 min	61.12	40.45	62.06	36.4	57.62	76.38	55.67±5.54
45 min	57.8	60.06	68.5	65.2	64.28	106.05	70.31±6.67
1 h	08.22	73.70	100.8	92.39	128.7	87.52	96.88±6.82
2 h	169.38	155.83	185.36	134.6	217.03	183.34	174.25±10.50
3 h	88.06	10.62	147.6	99.13	142.18	134.00	120.26±9.11
4 h	70.56	141.98	86.04	56.25	85.72	69.3	84.99±11.21
6 h	48.84	33.82	69.42	49.20	74.54	59.92	56.29±5.78
8 h	16.91	12.96	25.74	20.88	34.2	25.37	22.67±2.79
10 h	5.70	5.82	6.89	6.07	7.28	7.14	6.48±0.26
12 h	BDL	BDL	BDL	BDL	BDL	BDL	BDL

BDL = Below Detection Level

Table 18: Total urine concentrations (mg/ml) of levofloxacin after single oral dose (20 mg/kg) administration in febrile calves (n=6).

Time	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
15 min	39.23	28.16	47.12	33.21	48.63	44.45	40.13±3.03
30 min	46.9	46.82	43.07	48.15	70.33	51.43	51.11±3.64
45 min	78.18	65.28	89.99	51.25	95.9	85.2	77.63±6.21
1 h	76.55	86.10	98.68	75.18	95.25	88.02	86.63±3.55
2 h	157.26	163.45	194.16	135.45	198.90	173.04	170.37±8.86
3 h	160.44	171.55	235.2	154.12	249.50	201.25	195.34±14.94
4 h	108.99	111.9	146.79	140.05	145.72	139.36	132.12±6.37
6 h	74.77	70.26	115.84	98.7	122.96	113.83	99.39±8.31
8 h	38.22	31.06	49.5	39.44	72.34	42.05	45.43±5.39
10 h	13.2	8.85	15.19	8.58	24.12	18.78	14.78±2.23
12 h	5.65	3.96	6.76	4.06	7.02	5.88	5.55±0.48
24 h	BDL	BDL	BDL	BDL	BDL	BDL	BDL

BDL = Below Detection Level

Table 19: Total urine concentrations (mg/ml) of levofloxacin after single dose intravenous (5 mg/kg) administration in healthy calves (n=6).

Time	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
2.5 min	-	-	-	-	-	-	-
5 min	17.33	16.90	18.37	16.81	21.5	15.40	17.71±0.77
10 min	18.21	28.19	24.04	34.25	34.78	28.10	27.92±2.33
20 min	31.2	27.45	28.25	28.90	46.56	42.06	34.00±3.03
30 min	21.25	24.08	15.35	23.41	14.42	21.63	20.02±1.53
45 min	16.85	18.77	15.87	18.19	14.46	13.11	16.20±0.81
1 h	13.13	11.36	6.45	18.17	7.65	15.04	11.96±1.65
2 h	24.54	12.48	10.20	19.20	14.96	20.72	17.01±2.01
3 h	17.65	13.68	7.61	12.50	7.05	14.87	12.22±1.55
4 h	15.73	8.82	2.12	5.67	4.12	4.08	6.75±1.83
6 h	4.59	2.64	3.27	3.85	3.58	4.04	3.66±0.24
8 h	BDL	BDL	BDL	BDL	BDL	BDL	BDL

BDL = Below Detection Level

Table 20: Total urine concentrations (mg/ml) of levofloxacin after single dose intravenous (5 mg/kg) administration in febrile calves (n=6).

Time	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
2.5 min	-	-	-	-	-	-	-
5 min	32.10	24.48	19.69	20.99	23.74	21.60	23.76±1.65
10 min	20.82	39.32	17.60	25.98	33.54	25.11	27.06±3.00
20 min	36.12	25.77	26.15	27.66	24.12	27.28	27.85±1.58
30 min	27.08	42.30	40.76	37.01	27.12	35.00	35.04±2.45
45 min	19.12	37.26	24.20	19.58	19.34	25.46	24.16±2.59
1 h	20.91	16.32	14.71	21.32	12.48	12.53	16.37±1.46
2 h	30.94	40.98	24.27	36.04	27.99	31.02	31.87±2.20
3 h	22.61	20.05	20.40	17.31	21.50	22.32	20.69±0.72
4 h	13.33	9.00	20.80	5.57	11.00	12.01	11.95±1.90
6 h	12.64	18.00	16.45	7.39	9.84	6.25	12.86±1.61
8 h	4.70	5.31	4.24	3.95	5.33	2.66	4.36±0.37
10 h	BDL	BDL	BDL	BDL	BDL	BDL	BDL

BDL = Below Detection Level

Table 21: Percent urinary excretion of levofloxacin after (oral, 20 mg/kg and intravenous, 5 mg/kg) administration in healthy and febrile calves (n=6).

Route of administration	CALF NO.						Mean±S.E.
	1	2	3	4	5	6	
ORAL (Healthy)	46.14	43.51	55.47	37.12	53.67	51.39	47.88±2.58
ORAL (Febrile)	56.63	51.93	72.38	50.13	70.31	62.71	60.69±3.48
I.V Healthy	51.20	46.43	36.53	46.04	42.05	46.62	44.81±1.85
I.V. Febrile	68.19	78.75	63.68	56.69	53.73	57.87	63.15±3.44

Comparative mean plasma and urine concentrations (µg/ml) of LVX (oral, 20 mg/kg and i.v., 5 mg/kg) in healthy and febrile calves:

Plasma

Table 22 shows the comparative mean plasma concentrations of LVX after single dose oral and i.v. administration in healthy and febrile calves. It may be evident that the mean Cp_{max} of LVX (oral) in healthy calves 4.50±0.22 µg/ml was found at 1 h was less as compared with febrile calves 5.28±0.32 µg/ml at 2 h.

After i.v. administration, the mean Cp_{max} in healthy 5.13±0.13µg/ml was also less as compared with febrile calves 6.16±0.15 µg/ml at 2.5 min It may be evident from the above table that mean plasma concentrations differed significantly($P<0.01$) between healthy and febrile calves after oral as well as i.v. administration.

Urine

The comparative mean urine concentrations (table 23) of LVX after oral administration shows that in febrile calves the urine excretion was apparently higher 40.86±2.19µg/ml as compared to healthy 30.38±2.43 µg/ml. After i.v. administration the Cu_{max} in febrile calves was 68.43±2.05µg/ml was also higher as compared to healthy 66.06±2.14µg/ml . It may be observed from the table that after oral administration in healthy and febrile calves the Cu_{ther} was prolonged as compared with i.v. administration.

Comparative mean plasma and urine concentrations (µg/ml) of levofloxacin after (oral, 20 mg/kg and i.v., 5 mg/kg) administration in healthy and febrile calves:

Healthy

Table 24 shows the comparative mean plasma and urine concentrations of LVX after oral and i.v. administration in healthy calves. It may be evident that the mean Cp_{max}

Table 22: Comparative mean plasma concentrations (μg/ml) of levofloxacin after (oral, 20mg/kg and intravenous, 5mg/kg) administration in healthy and febrile calves (n=6).

Time	LVX, Oral		t-value	LVX, I.V.		t-value
	Healthy	Febrile		Healthy	Febrile	
2.5 min	-	-	-	5.13±0.13	6.16±0.15	5.13**
5 min	-	-	-	4.11±0.18	5.47±0.17	4.60**
10 min	-	-	-	3.23±0.16	5.36±0.13	9.70**
15 min	2.79±0.23	3.35±0.40	2.32*	-	-	-
20 min	-	-	-	2.62±0.20	4.88±0.09	12.22**
30 min	3.36±0.19	3.93±0.35	2.52*	2.33±0.14	4.52±0.11	10.94**
45 min	3.81±0.23	4.35±0.46	1.80^{NS}	2.05±0.10	4.08±0.10	19.28**
1 h	4.50±0.22	4.92±0.35	1.96^{NS}	1.73±0.11	3.71±0.10	15.93**
2 h	4.00±0.24	5.28±0.32	11.61**	1.44±0.10	3.35±0.10	14.88**
3 h	3.35±0.34	4.69±0.29	9.84**	1.13±0.02	2.91±0.12	13.67**
4 h	2.88±0.22	4.24±0.27	11.16**	0.95±0.03	2.61±0.11	12.99**
6 h	2.08±0.13	3.09±0.11	12.83**	0.78±0.04	1.47±0.07	9.45**
8 h	0.92±0.05	1.80±0.22	4.72**	-	0.85±0.04	-
10 h	0.89±0.07	-	-	-	-	-

*p<0.05; **p<0.01, NS=Non significant

Table 23: Comparative mean urine concentrations (μg/ml) of levofloxacin after (oral, 20 mg/kg and intravenous, 5 mg/kg) administration in healthy and febrile calves.

Time	LVX, Oral		t-value	LVX, I.V.		t-value
	Healthy	Febrile		Healthy	Febrile	
2.5 min	-	-	-	-	-	-
5 min	-	-	-	39.01±2.06	46.94±2.81	3.71**
10 min	-	-	-	55.44±3.03	5.98±2.81	0.26^{NS}
15 min	15.83±0.93	15.47±0.87	0.40^{NS}	-	-	-
20 min	-	-	-	66.06±2.14	62.43±2.32	5.59**
30 min	22.96±1.48	21.42±1.57	1.11^{NS}	44.48±3.00	68.43±2.05	9.73**
45 min	29.28±1.40	27.580±1.89	1.58^{NS}	28.47±1.94	0.50±2.47	7.20**
1 h	35.41±1.91	31.93±1.81	5.45**	17.29±1.94	26.60±1.59	4.10**
2 h	39.38±2.43	35.73±1.79	5.03**	9.75±0.95	17.24±.81	5.75**
3 h	27.81±1.83	40.86±2.19	13.09**	5.61±0.55	9.63±0.61	3.36**
4 h	18.15±0.88	27.39±1.41	6.44**	2.50±0.43	5.00±0.6	2.47*
6 h	9.09±0.88	16.16±1.48	7.36**	0.83±0.04	2.20±0.34	3.76**
8 h	3.86±0.46	7.68±0.85	7.75**	-	0.83±0.12	-
10 h	0.99±0.03	2.46±0.37	3.80**	-	-	-
12 h	-	0.88±0.06	-	-	-	-

*p<0.05; **p<0.01, NS=Non significant

Table 24: Comparative mean plasma and urine concentrations (μg/ml) of levofloxacin after (oral, 20 mg/kg and intravenous, 5 mg/kg) administration in healthy calves.

Time	LVX, Oral		t-value	LVX, I.V.		t-value
	PLASMA	URINE		PLASMA	URINE	
2.5 min	-	-	-	5.13±0.13	-	-
5 min	-	-	-	4.11±0.18	39.01±2.06	14.81**
10 min	-	-	-	3.23±0.16	55.44±3.03	15.08**
15 min	2.79±0.23	15.83±0.93	12.22**	-	-	-
20 min	-	-	-	2.62±0.20	66.06±2.14	24.84**
30 min	3.36±0.19	22.96±1.48	12.48**	2.33±0.14	44.48±3.00	12.46**
45 min	3.81±0.23	29.28±1.40	16.81**	2.05±0.10	28.47±1.94	11.99**
1 h	4.50±0.22	35.41±1.91	15.85**	1.73±0.11	17.29±1.94	7.17**
2 h	4.00±0.24	39.38±2.43	13.78**	1.44±0.11	9.75±0.95	8.20**
3 h	3.35±0.34	27.81±1.83	12.14**	1.13±0.02	5.61±0.55	7.47**
4 h	2.88±0.22	18.15±0.88	17.07**	0.95±0.03	2.50±0.43	3.43**
6 h	2.08±0.13	9.09±0.88	7.69**	0.78±0.04	.83±0.04	0.91^{NS}
8 h	0.92±0.05	3.86±0.46	5.92**	-	-	-

*p<0.05; **p<0.01, NS=Non significant

and Cu_{max} of LVX oral in healthy calves were 4.50±0.22 µg/ml at 1 h and 39.38±2.43µg/ml at 2 h, respectively. After i.v. administration, the mean Cp_{max} and Cu_{max} in healthy calves were 5.13±0.13 µg/ml at 2.5 min and 66.06±2.14µg/ml at 20 min, respectively. It may also be evident from the above table that mean plasma and urine concentrations significantly higher (P<0.01) in healthy calves after oral as well as i.v. administration.

Febrile

Table 25 depicts the comparative mean plasma and urine concentration of LVX after oral and i.v. administration in febrile calves. The Cp_{max} was observed to be 5.28±0.32 µg/ml at 2 h where as Cu_{max} of 40.86±2.19 µg/ml was found at 3 h, respectively. After i.v administration the mean Cp_{max} and Cu_{max} in febrile calves were 6.16 ± 0.15 µg/ml at 2.5 min and 68.43±2.05 µg/ml at 30 min, respectively. It may also be evident from the above table that mean plasma and urine concentration significantly higher (P<0.01) in febrile calves after oral as well as i.v. administration.

Comparative mean pharmacokinetic profile of levofloxacin in plasma and urine after (oral, 20 mg/kg and i.v., 5 mg/kg) administration in healthy and febrile calves:

Plasma

The kinetic profile of LVX in plasma after oral and i.v. administration of LVX in healthy and febrile calves has been depicted in table 26. The mean value of A, B and C^{o}_{P} were 5.73±0.57, 7.09±0.68 and 12.82±1.25µg/ml after oral administration in healthy calves, whereas the same parameters were 8.16±0.40, 10.15±0.37 and 18.32±0.63 µg/ml in febrile calves. It may be evident from the table 26 that the mean values of β, $t_{½\beta}$ and Cl_B were 0.25±0.01 h^{-1}, 2.99±0.15 h and 13.06±0.78 ml/kg/min in healthy calves and the same were 0.2 ± 0.01 h^{-1}, 3.04±0.14 h and 9.29±0.66 ml/kg/min in febrile calves.

Table 25: Comparative mean plasma and urine concentrations (μg/ml) of levofloxacin after (oral, 20 mg/kg and intravenous, 5 mg/kg) administration in febrile calves.

Time	LVX, Oral		t-value	LVX, I.V.		t-value
	PLASMA	URINE		PLASMA	URINE	
2.5 min	-	-	-	6.16±0.15	-	-
5 min	-	-	-	5.47±0.17	46.94±2.81	13.45**
10 min	-	-	-	5.36±0.13	55.98±2.81	16.31**
15 min	3.35±0.40	15.47±0.87	19.25**	-	-	-
20 min	-	-	-	2.62±0.20	62.43±2.32	22.12**
30 min	3.93±0.35	21.42±1.57	11.76**	2.33±0.14	68.43±2.05	28.05**
45 min	4.35±0.46	27.58±1.89	11.78**	2.05±0.10	40.50±2.47	13.17**
1 h	4.92±0.35	31.93±1.81	14.33**	1.73±0.11	26.60±1.59	12.73**
2 h	5.28±0.32	35.73±1.79	16.51**	1.44±0.10	17.24±0.81	15.99**
3 h	4.69±0.29	40.86±2.19	15.89**	1.13±0.02	9.63±0.61	10.71**
4 h	4.24±0.27	27.39±1.41	16.25**	0.95±0.03	5.00±0.64	3.43**
6 h	3.09±0.11	16.16±1.48	8.18**	0.78±0.04	2.20±0.34	1.86^{NS}
8 h	1.80±0.22	7.68±0.85	6.84**	0.85±0.05	0.83±0.12	0.18^{NS}
10 h	0.89±0.07	2.46±0.37	4.11**	-	-	-
12 h	-	0.88±0.06	-	-	-	-

*p<0.05; **p<0.01, NS=Non significant

Table 26: Comparative mean pharmacokinetic profile of levofloxacin in plasma after (oral, 20mg/kg and intravenous, 5 mg/kg) administration in healthy and febrile calves.

Kinetic parameters	LVX, ORAL		t-value	LVX, I.V.		t-value
	Healthy	Febrile		Healthy	Febrile	
A (µg/ml)	5.73±0.57	8.16±0.40	2.60**	3.86±0.44	1.49±0.47	4.88**
B (µg/ml)	7.09±0.668	10.15±0.37	4.88**	2.01±0.14	5.68±0.66	5.96**
C^0p (µg/ml)	12.82±1.25	18.32±0.63	3.56**	5.83±0.46	7.17±1.06	1.38^{NS}
Cp_{max} (µg/ml)	4.29±0.27	5.22±0.31	10.05**	6.16±0.13	6.16±0.15	5.13**
Ka /α (h^{-1})	1.60±0.16	0.95±0.05	3.18**	9.68±2.17	4.24±1.51	1.57^{NS}
β(h^{-1})	0.25±0.01	0.23±0.01	0.18^{NS}	0.16±0.02	0.22±0.01	1.72^{NS}
$t_{½\ Ka}$ /$t_{½\ \alpha}$ (h)	0.46±0.05	0.72±0.03	4.75**	0.10±0.03	0.41±0.17	1.50^{NS}
$t_{½\beta}$ (h)	2.99±0.15	3.04±0.14	0.17^{NS}	4.65±0.60	3.20±0.20	2.41*
T_{max}(h)	1.28±0.06	1.67±0.07	3.70**	-	-	-
AUC (mg/L.h)	22.08±0.06	1.67±0.07	3.70**	-	-	-
MRT(h)	4.66±0.13	5.03±0.12	1.8^{NS}	6.39±0.78	4.52±0.19	2.32*
Cl_B (ml/kg/min)	13.06±0.78	9.29±0.66	10.44**	6.24±0.46	3.41±0.08	6.15**
Vd_{area} (L)	3.41±0.30	2.40±0.10	4.11**	2.37±0.14	0.94±0.06	10.73**
K_{21} (h^{-1})	-	-	-	3.20±0.66	3.57 ± 1.38	0.18^{NS}
K_2 (h^{-1})	-	-	-	0.44±0.05	0.25±0.02	4.56**
K_{12} (h^{-1})	-	-	-	6.19±1.56	0.63±0.23	3.24**
T/P	-	-	-	1.94±0.33	0.20±0.05	5.05**

*p<0.05; **p<0.01, NS=Non significant

The mean value of MRT and Vd_{area} in healthy calves were 4.66±0.13 h and 3.41±0.30 L where as in febrile calves the values of above parameters were 5.03±0.12 h and 2.40±0.10 L.

The mean value of A, B and C^{o}_{P} after i.v. administration were observed to be 3.86±0.44, 2.01±0.14 and 5.83±0.46 µg/ml in healthy calves where as1.4±0.47, 5.68±0.66 and 7.17±1.06µg/ml in febrile calves, respectively. It may also be observed from table 26 that the mean value of α and β after i.v. administration of LVX were 9.68±2.17 h^{-1} and 0.16±0.02 h^{-1} in healthy calves and 4.24±1.51 h^{-1} and 0.22±0.01 h^{-1} in febrile calves, respectively. The value of $t_{½\alpha}$ and $t_{½\beta}$ were 0.10±0.03 h and 4.65±0.60 h in healthy calves, whereas 0.40±0.17 h and 3.20±0.20 h in febrile calves, respectively. The mean values of MRT, Cl_B and Vd_{area} were 6.39±0.78 h, 6.24±0.46 ml/kg/min and 2.37±0.14 L (healthy) and 4.52±0.19 h, 3.41±0.08 ml/kg/min and 0.94±0.06 L (febrile), respectively.

It may also be evident from table 26 that the mean value of rate of drug transfer from central to peripheral (K_{12}), peripheral to central (K_{21}) and elimination from central compartment (K_2) after i.v. administration of LVX in healthy calves were 6.19±1.56 h^{-1}, 3.20±0.66 h^{-1} and 0.44±0.05 h^{-1}, respectively. The above data in febrile calves were 0.63±0.23 h^{-1}, 3.57±1.38 h^{-1} and 0.25±0.02 h^{-1}, respectively.

Urine

Table 27 shows the comparative mean pharmacokinetic profile of LVX calculated from urine after oral and i.v. administration in healthy and febrile calves. The value of Cu_{max} and T_{max} after oral administration in healthy and febrile calves were 31.68±1.90µg/ml at 1.27 ±0.03 h and 33.95±2.17 µg/ml at 1.60±0.04 h, respectively. The above values after i.v administration were 53.70±2.37 µg/ml at 0.36±0.02 h in healthy and 63.15±3.44 µg/ml at 0.46±0.02 h in febrile experimental calves.

Table 27: Comparative mean pharmacokinetic profile of levofloxacin in urine after (oral, 20mg/kg and intravenous, 5 mg/kg) administration in healthy and febrile calves.

Kinetic parameters	LVX, ORAL		t-value	LVX, I.V.		t-value
	Healthy	Febrile		Healthy	Febrile	
Cu_{max} (µg/ml)	31.68±1.90	33.95±2.17	1.58^{NS}	53.70±2.37	63.15±3.44	2.71**
β (h^{-1})	0.38±5.61	0.37±0.01	0.54^{NS}	0.72±0.02	0.53±0.03	4.04**
$t_{½\ \beta}$ (h)	1.75±0.02	1.85±0.06	1.37^{NS}	0.97±0.03	1.31±0.08	3.63**
T_{max} (h)	1.27±0.03	1.60±0.04	5.62**	0.36±0.02	0.46±0.02	4.63**
MRT (h)	3.14±0.03	3.79±0.06	16.26**	1.26±0.04	1.70±0.10	3.39**
Cl_B (mg/kg/min)	2.08±0.11	1.64±0.08	7.99**	1.20±0.09	0.79±0.01	4.20**
tCu_{ther} (h)	9.66±0.33	11.00±0.40	3.16**	5.00±0.40	7.00±0.40	2.73**

***p<0.05, **p<0.01, NS=Non Significant**

The above table also shows that the values of $t_{½\beta}$, Cl_B and MRT after oral administration of LVX were 1.75±0.02 h, 2.08±0.11 ml/kg/min and 3.14±0.03 h (healthy) and 1.85±0.06 h, 1.64±0.08 ml/kg/min and 3.79±0.06 h in febrile calves. The above values after i.v administration were 0.97±0.03 h, 1.20±0.09 ml/kg/min and 1.26±0.04 h healthy and 1.31±0.08 h, 0.79±0.01 ml/kg/min and 1.70±0.10 h in febrile calves.

Comparative mean pharmacokinetic profile of plasma and urine concentrations (µg/ml) of levofloxacin after (oral, 20mg/kg and i.v., 5 mg/kg) administration in healthy and febrile calves:

Healthy

Table 28 shows the comparative mean pharmacokinetic profile of plasma and urine concentration of LVX in healthy calves. It may be evident that the mean Cp_{max} and Cu_{max} of LVX oral in healthy calves were 4.29±0.27 µg/ml and 31.68±1.90 µg/ml, respectively. After i.v. administration the mean Cp_{max} and Cu_{max} in healthy calves were 6.16±0.13 and 53.70±2.37 µg/ml, respectively. The table shows that the Cu_{max} 6.16±0.13 µg/ml found after i.v. was higher to that after oral 4.28±0.27 µg/ml. Similarly the Cu_{max} observed after i.v. was also higher as compared to that in healthy calves. In plasma after oral administration in healthy calves the mean value of β, $t_{½\beta}$, MRT and Cl_B were 0.25±0.01 h^{-1}, 2.99±0.15 h, 4.66±0.13 h and 13.06±0.78 ml/kg/min and in urine after oral administration the mean value of β, $t_{½\beta}$, MRT and Cl_B were 0.38±5.61 h^{-1}, 1.75±0.02 h, 3.14±0.03 h and 2.08±0.11 ml/kg/min, respectively. After i.v. administration in healthy calves the plasma mean value of β, $t_{½\beta}$, MRT and Cl_B were 0.16±0.02 h^{-1}, 4.65±0.60h, 6.39±0.78 h and 6.24±0.46 ml/kg/min after i.v. administration in healthy calves whereas, the urine mean value of β, $t_{½\beta}$, MRT and Cl_B were 0.72±0.02 h^{-1} 0.97±0.03 h,

Table 28 Comparative mean pharmacokinetic profiles of plasma and urine concentrations (µg/ml) of levofloxacin after (oral, 20 mg/kg and intravenous, 5 ml/kg) administration in healthy calves.

Kinetic parameters	Oral		t-value	I.V		t-value
	Plasma	Urine		Plasma	Urine	
A (µg/ml)	5.73±0.57	-	-	3.86±0.44	-	-
B (µg/ml)	7.09±0.68	-	-	2.01±0.14	-	-
Cp_{max}/Cu_{max} (µg/ml)	4.28±0.27	31.68±1.9	13.84**	6.16±0.13	53.70±2.37	25.69**
Ka/α (h^{-1})	1.60±0.19	-	-	9.68±2.17	-	-
β (h^{-1})	0.25±0.01	0.38±5.61	15.84**	0.16±0.02	0.72±0.02	17.91**
$t_{½\ Ka}/t_{½\alpha}$ (h)	0.46±0.05	-	-	0.10±0.03	-	-
$t_{½\ \beta}$ (h)	2.99±0.15	1.75±0.02	3.67**	1.65±0.60	0.97±0.03	5.59**
T_{max}(h)	1.28±0.06	1.27±0.03	0.11 ^{NS}	-	0.36±0.02	-
AUC (mg/L.h)	22.08±1.47	-	-	8.04±0.35	-	-
MRT (h)	4.66±0.13	3.14±0.03	9.97**	6.39±0.78	1.26±0.04	6.16**
Cl_B (ml/kg/min)	13.00±0.78	2.08±0.11	13.78**	6.24±0.46	1.20±0.09	11.14**
Vd_{area} (L)	3.41±0.30	-	-	2.37±0.14	-	-
C^0_P (µg/ml)	12.82±1.25	-	-	5.83±0.46	-	-

*p<0.05, **p<0.01, NS=Non Significant

Tables 29 Comparative mean pharmacokinetic profile of plasma and urine concentrations (µg/ml) of levofloxacin after (oral, 20 mg/kg and intravenous, 5 mg/kg) administration in febrile calves.

Kinetic parameters	LVX,ORAL		t-value	LVX,I.V		t-value
	Plasma	Urine		Plasma	Urine	
A (µg/ml)	8.16±0.40	-	-	1.49±0.47	-	-
B (µg/ml)	10.15±0.37	-	-	5.65±0.66	-	-
Cp_{max}/ Cu_{max} (µg/ml)	5.22±0.31	33.95±2.17	15.75**	6.16±0.15	6.16±0.15	27.37**
Ka/α (h^{-1})	0.95±0.05	-	-	4.24±1.51	-	-
β (h^{-1})	0.23±0.01	0.37±0.01	12.56**	0.22±0.01	0.53±0.03	5.49**
$t_{½\ Ka}$/$t_{½α}$ (h)	0.72±0.03	-	-	0.41±0.17	-	-
$t_{½\ β}$ (h)	3.04±0.14	1.85±0.06	9.24**	3.20±0.20	1.31±0.08	6.44**
T_{max} (h)	1.67±0.07	1.60±0.04	1.32 ^{NS}	-	0.46±0.02	-
AUC (mg/L.h)	33.02±2.12	-	-	20.47±0.45	-	-
MRT(h)	5.03±0.12	3.79±0.06	9.56**	4.52±0.19	1.70±0.10	10.57**
Cl_B (ml/kg/min)	9.27±0.66	1.64±0.08	10.92**	3.41±0.08	0.79±0.01	31.58**
Vd_{area} (L)	2.40±0.10	-	-	0.94±0.06	-	-
C^0p (µg/ml)	18.32±0.63	-	-	7.17±1.06	-	-

*p<0.05, **p<0.01, NS=Non Significant

Tables 30 Comparative mean percent excretion of levofloxacin after (oral, 20 mg/kg and intravenous, 5 mg/kg) administration in healthy and febrile calves (n=6).

LVX, ORAL		t value	LVX, I.V.		t value
Healthy	**Febrile**		**Healthy**	**Febrile**	
47.88±2.58	60.69±3.48	9.20**	44.81±1.85	63.15±3.44	4.85**

*p<0.05, **p<0.01, NS=Non Significant

1.26±0.04 h and 1.20±0.09 ml/kg/min, respectively. It may also evident from the above table that the mean pharmacokinetic profile of plasma and urine concentration were higher significantly (P<0.01) in healthy calves after oral as well as i.v. administration.

Febrile

Table 29 shows that the comparative mean pharmacokinetic profile in plasma and urine of LVX in febrile calves. It may be evident that the mean Cp_{max} and Cu_{max} of LVX and in febrile calves were 5.22±0.31 and 33.95±2.17 µg/ml, respectively. After i.v administration the mean Cp_{max} and Cu_{max} in febrile calves were 6.16±0.15 and 63.15±3.44 µg/ml, respectively. In plasma after oral administration in febrile calves the mean value of β, $t_{½\beta}$, MRT and Cl_B were 0.23±0.01 h^{-1}, 3.04±0.14 h, 5.03±0.12 h and 9.27±0.66 ml/kg/min whereas in urine after oral administration the mean value of β, $t_{½\beta}$, MRT and Cl_B were 0.37±0.01 h^{-1}, 1.85±0.06 h, 3.79±0.06 h and 1.64±0.08 ml/kg/min, respectively.

After i.v. administration in febrile calves the plasma mean value of β, $t_{½\beta}$, MRT and Cl_B were 0.22±0.01 h^{-1}, 3.20±0.20 h, 4.52±0.19 h and 3.41±0.08 ml/kg/min after i.v. administration in febrile calves. However, the urine mean value of β, $t_{½\beta}$, MRT and Cl_B were 0.53±0.03 h^{-1}, 1.31±0.08 h, 1.70±0.10 h and 0.79±0.01 ml/kg/min, respectively. It may also evident from the table 29 that the mean pharmacokinetic profile of plasma and urine concentrations significantly higher (P<0.01) in febrile calves after oral as well as i.v. administration.

Plasma protein binding

Table 31 sows the in-vitro plasma protein binding of levofloxacin in calves. It is evident from the table that plasma protein binding of LVX varied between 47.42±0.36 to 27.91±0.16 percent with an overall mean of 38.78±3.60 percent.

Table 31: In- vitro percent plasma protein binding of levofloxacin in calves (n=6).

Concentrations (µg/ml)	CALF No.						
	1	2	3	4	5	6	Mean±S.E.
6.25	47.80	47.60	46.00	47.70	48.80	46.64	47.42±0.36
12.50	42.50	42.80	43.50	42.10	42.35	41.40	42.44±0.26
25	36.10	36.80	38.15	36.80	38.00	38.25	37.35±0.33
50	27.40	28.00	27.50	27.80	28.54	28.36	27.91±0.16

Overall mean 38.78±3.60 percent

Table 32 Mean rectal temperature (^{0}F) after LPS injection @ 0.2 µg/ml in calves (n=6)

Group	Mean rectal temperature (^{0}F) at h											
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**24**
I	101.53±0.05	104.53±0.09	104.70±0.07	105.36±0.56	106.50±0.78	105.23±0.05	106.63±0.01	106.63±0.01	105.05±0.07	104.45±0.08	103.46±0.09	102.50±0.07
II	101.55±0.08	103.43±0.05	104.36±0.05	105.36±0.05	106.41±0.04	106.6±0.04	106.78±0.03	106.28±0.04	105.53±0.06	104.41±0.06	103.40±0.08	102.00±0.18

Group I = Treated with LVX orally.

Group II = Treated with LVX I.V.

At 0 h and 5 h LPS was injected intravenously.

Table 33 Suggested dosage regimen (mg/kg) of levofloxacin for oral and intravenous administration in febrile calves.

ORAL	INTRAVENOUS
1.49 – 2.23 mg/kg (1.5 – 2 mg/kg)* every 8 h	0.58 – 0.87 mg/kg (0.5 – 1 mg/kg)* every 6 h

* Dosage in parentheses is recommended for clinical use.

Effect of LPS on the rectal temperature of calves

Table 32 shows the mean rectal temperature (^{0}F) by endotoxin (LPS) injection (0.2 µg/kg) i.v. in calves. The table reveals that the temperature raised within an hour of LPS injection in both groups and was maintained till 24 h after repetition of half dose (0.1 µg/kg) i.v. at 5th h.

DISCUSSION

Most pharmacokinetic models are deterministic in nature. They assume that results are decided by antecedent causes, which may be inherited or environmental. There is no particular emphasis on discrete events, and transformations are followed only in bulk. Such models give the expectation of a smooth concentration or amount time course. Deviations and fluctuations are usually attributed to experimental error. Parameters, such as rate constants and volumes are assumed to remain constant.

The relationship between the dose of a drug given to a patient and utility in the treatment of the disease is described both of pharmacokinetics and pharmacodynamics. It also contributes in product designing of a drug and drug interaction. Clinical pharmacokinetics details the effects of disease and other factors on the various pharmacokinetic parameters in animals.

PLASMA LEVEL

The comparative mean plasma levels time profile of LVX after single dose (20mg/kg) oral administration (table 22) in healthy and febrile calves evidenced significantly higher mean peak plasma concentration in febrile 5.28±0.32 µg/ml than healthy calves 4.50±0.22 µg/ml. It may be evident from table 22 that tCp_{max} in febrile calve 2 h was delayed as compare to healthy calves 1 h. It is obvious that absorption of LVX in febrile animals was delayed as compared to healthy animals 1 h. However, the plasma levels between 15 min to 2 h were higher in febrile calves as compared to healthy. The Cp_{max} in febrile calves 6.16±1.15 µg/ml was marginally higher as compared with healthy calves 5.13±0.13µg/ml after single dose i.v. administration.

It has been reported that a variety of drugs are absorbed directly from the stomach especially in monogastric animals, by simple diffusion of the nonionized drugs moiety. Quick absorption is generally observed from all of acidic drugs except the highly ionized sulfonic acids. In contrast, none of the basic compounds are absorbed except those so weakly basic that they are partially nonionized in gastric contents.

In contrast to the findings obtained in this study, the Cp_{max} of ofloxacin and duration of Cp_{ther} after i.v. administration decreased in febrile goats relationship between the intensity of a pharmacologic effect and the post distributive concentration of drug in plasma or serum. In studies of individual differences in the effect of drugs in relation to drug concentration in tissue of rats, it has been found that the duration of narcosis produced by a constant dose of pentobarbital sodium differed widely in different rats.

Following oral administration of LVX to calves, attainment of Cp_{max} at 1 h in healthy and 2 h in febrile, indicated rapid absorption of the drug from the G.I. tract

The results incorporated in table 23 could evidence similar Cu_{max} in febrile 40.86±2.19 µg/ml and healthy calves (39.38±2.43 µg/ml). The attainment of Cu_{max} in febrile was observed latter at 3 h as compared to healthy calves 2 h. However, it is suspiring to note that similar excretion of LVX after single dose oral administration in healthy calves could show higher Cp_{max} as compared to febrile calves. However, in both cases, plasma and urine in febrile animals the T_{max} after oral drug administration was latter in febrile condition. In febrile condition after LVX i.v. administration in which the Cu_{max} was higher in febrile (46.94±2.81 µg/ml) as compared to healthy calves (39.01±2.06 µg/ml). However, after i.v. administration the T_{max} was similar 1 h both in healthy and febrile calves.

The perusal of table 23 also shows that tCp_{ther} of LVX in febrile calves was longer both after oral 12 h and i.v. 8 h administration. Similar trend was also maintained for tCp_{ther} in which the tCp_{ther} was prolonged after i.v. administration in febrile 8 h as well as healthy 6 h.

Similar to the results obtained in this experiment, increased Cp_{ther} in febrile subject has also been reported for different chemotherapeutic agents i.e. gentamicin in rabbits (Halkin *et al*., 1981), sulfadimidin in goats (Dutta, 1988), cefazolin in goats (Roy, 1991), nalidixic acid in goats (Patel, 1992), gatifoxacin in goats (Verma, 2004) and LVX in goats (Mishra, 2006). It may be mentioned here, that claves and goats although, being different species are ruminant in which the absorption of drug follows the similar pattern. Similar to the result obtaind in this study, high plasma levels of pefloxacin has also been observed in febrile goats (Prasad, 2002). It is obvious to mention that febrile condition, may raise the plasma levels of antimicrobial agents in animals especially ruminants.

It may be mentioned that only free drug is available for glomerular filtration; therefore the persistence of drug that is excreted in this way can be influenced by the fractional binding of LVX. Moreover, the rate of disappearance from the body tends to be self limiting, at least through the range in which fractional binding increases with falling drug concentration; the lower the drug concentration, the smaller the fraction subject to filtration at the glomeruli.

Experimentally induced fever has been observed to impair the hepatic metabolism (Sony *et al*., 1972; Elin *et al*., 1975 and Trenhalme *et al*., 1976). Contradictory to the above, many authors have reported decreased serum concentrations and a reduced half-life for gentamicin in febrile patients especially in humans (Sibs *et al*., 1975 and Pennington *et al*., 1975). The contradictory finding reported by above

authors is obvious due to differences in chemical class of the drug and species. However, it is true that if fever is decreasing the rates of metabolism of fluoroquinolones, it can raise the level of parent drug in plasma. This is also strengthened with the findings incorporated in regard to the urinary excretion of LVX where high urine concentration in febrile calves was noted. The method employed in this experiment for analysis of LVX, measured only the parent drug but not the metabolites and the observed level in urine was meant for parent drug only. The further investigation in regard to the measurement of LVX metabolites is required so that the extent of metabolism of LVX may be pin pointed in the febrile calves. If the metabolism of LVX is retarded it is advantageous in the sense that efficacy of this antimicrobial may be increased because the elimination may be delayed; because the elimination is combination of excretion and metabolism.

LPS of *E. coli* in an endotoxin and in used to cause sings and symptoms resembling septicemia (Tune and Hsu, 1985). The LPS administrated to experimental animals, interacts with various cellular components (neutrophils, basophil, eosinophils, monocytes and other mixed macrophages) and released the endogenous pyrogen producing febrile condition (Dinarella, 1979). LPS has been observed to produce fever after 1 mg to sheep (Wilson *et al*., 1984), 0.1 µg/kg to horses, rabbits and dogs (Pennington et al., 1975).

In the present experiment LPS was administered i.v. @ 0.2 µg/kg in calf that produced fever for 5 h and half dose (0.1 µg/kg) repeated at 5 h could prolonged the fever for 12 h (Table 32). The restlessness, shivering and abdominal discomfort was noticed following LPS administration. Similar symptoms, after LPS administration was also reported (Bennest and Benson, 1950; Pennington *et al*., 1975; Wilson et al., 1984 and Roy *et al*., 1984).

It may be observed from table 22 that the plasma levels of LVX after oral 4.50±0.22 µg/ml and i.v. 5.13±0.13 µg/ml were found to be similar. It is clear that after i.v. administration, the bioavailability is usually 100% and even after the four time less dose (5 mg/kg) could maintain a level similar to that after oral (20 mg/kg).

It may be mentioned here that LVX is a lipophilic drug (Kawakami et al., 2000; Christopher et al., 2001) and therefore due to high unionized moiety will diffuse faster through, the rumen (pH, 6.5) of calves. The attainment of delayed T_{max} in febrile calves seems to be due to shivering leading to vasoconstriction. However, the increased Cp_{max}, though the absorption was delayed in febrile calves could not be clearly understood. It is true that about 75% of the drug given orally is absorbed in 1 to 3 h especially in monogastric animals. There are established factors like G.I. motility, splanchnic blood flow, particle size of drug and physico-chemical properties of drug that may have an effect on the pattern of drug absorption after oral route administration. It is also true that the factors influencing absorption were similar both in healthy and febrile calves.

URINARY PROFILE

The kidney is a dynamic organ which receives about 25 per cent of the cardiac output and is responsible for excretion of water soluble non-protein bound substances. The perusal of urinary excretion (table 5,6,7 and 8) shows that LVX was fairly and rapidly excreted in urine after oral and i.v. administration in healthy and febrile calves. It may be observed from table 8 and 7 that Cu_{max} of LVX was marginally higher in febrile calves (68.42±2.05 µg/ml) as compared to that in healthy calves (66.06±2.14 µg/ml) after single dose i.v. administration. After single dose oral administration the Cu_{max} was approximately similar in febrile calves (40.86±2.19 µg/ml) as to that of healthy calves (39.38±2.43 µg/ml). The similar pattern of excretion of LVX in febrile calves could

produced higher Cp_{max} in febrile calves after single dose i.v. administration. It may be mentioned here that LVX is a lipophillic drug which is supposed to be eliminated sufficiently from kidney in calves (Morrby, 1999). The MIC of LVX is reported less than 2 µg/ml for all susceptible microorganisms (Hooper, 2000). Contradictory to i.v. administration, the higher Cu_{max} in febrile as compared to that in healthy calves after oral administration probably occurred due to lower value of Cl_B in febrile (9.29±0.66 ml/kg/min) as compared to healthy calves (13.06±0.78 ml/kg/min).

It may be observed form the above table 21 the per cent urinary excretion of LVX was higher in febrile calves 60.69±3.48 per cent as compared to that in healthy calves 47.88±2.58 per cent after single dose oral administration, similarly after single dose i.v. administration per cent urinary excretion was higher in febrile calves 63.15±3.44 per cent as compared to that in healthy calves 44.81±1.85 per cent. However, it may be pointed out here that 4 times higher oral dose of LVX was given to both healthy and febrile. It is well known that when the urine pH is high, basic drugs are excreted slowly and more extensive metabolism occurs. When the urine pH is low, basis drugs are excreted more rapidly and metabolism is less extensive. The tubular epithelium of the distal tubules is selectively permeable or more permeable to the unionized lipid soluble molecules than to poorly lipid soluble anion or cation. The pka of the compound and the pH and volume of tubular fluid determines the concentration of urine ionized molecules in the tubular fluid. Similar to the findings reported in this study, Sci. Finder scholar (2004) reported the pka values of the protonable function of the C_7 substituent of the four quinolones are 6.8±0.3 (LVX), 8.76±0.25 (ciprofloxacin) 8.4±0.4 (geranoxacin) and 10.8±0.4 (moxifloxacin) under a zwitter ionic form at neutral pH. The rate of re-absorption from tubular fluid in to the circulation depends on this concentration and on the partition-characteristics of the molecules. Water loading is an another important factors that can estimate volume

dependent fluctuations in urinary excretion rate of drug. The tCu_{max} was earlier in healthy calves (20 min) as compared to febrile calves (30 min). After oral administration of LVX, the Cu_{max} in febrile caves 40.86±2.19 µg/ml was similar to that in healthy calves 39.38±2.43 µg/ml. However after oral administrations tCu_{max} was earlier in healthy calves (2 h) as compared to febrile calves (3 h). The comparative urinry excretion (table 23) shows the Cu_{ther} was maintained between 15 min and 12 h after and administration and 5 min to 8 h in febrile calves after i.v. administration. Similar finding of decrease in tCu_{ther} in febrile goats have also been reported by other investigators (Prasad, 2002 and Singh, 2002). It is worthy to mention here that the rate of filtration of a drug depends on the volume of fluid which is filtered in the glomerulus and the unbound concentration of drug in plasma. Since, drug unbound to plasma proteins is not filtered due to its high molecular size. Therefore, the rate of secretion of a drug by kidney will be depend on the binding of drug of the proteins involved in active transport relative to that bound to plasma proteins and the rate of transfer of drug across the tubular membrane and the rate of delivery of the drug to the secretary site (Goodman and Gilman, 1980).

The plasma protein binding in this study for LVX was found to be in the range of 27.91±0.16 to 47.42±0.36 per cent (Table 31). Extended duration of action observed in this study has also been reported for highly bound sulfonamides in febrile calves (Notari, 1980).

PHARMACOKINETIC

There is a paucity of data available in the veterinary literature describing, absorption, distribution, metabolism and excretion of LVX. The plasma LVX concentrations after single dose oral (20 mg/kg) and i.v. (5 mg/kg) vs time data were analyzed by "pharmkit" computer programme. The disappearance of LVX from plasma

after i.v. administration was described by a bi-exponential equation with initial ($t_{½\alpha}$) and terminal half life ($t_{½\beta}$) of 0.40±0.17 and 3.20±0.20 h respectively in febrile calves. The above half life observed in febrile calves after i.v. administration were higher as compared with healthy calves $t_{½\alpha}$ -0.10±0.03 and $t_{½\beta}$- 4.65±0.60 h. The mean elimination rate constant observed in febrile calves 0.22±0.01 h was comparatively lower to that in healthy calves 0.16±0.02 h which probably showed lower $t_{½\beta}$ in febrile 3.20±0.20 h as compared to healthy calves 4.65±0.60 h. The $t_{½\beta}$ value is a rough estimate that gives an idea of drug repeatation schedule. Therefore, the $t_{½\beta}$ obtained in febrile calves indicates the earlier repetition of LVX in febrile calves as compared to healthy one. However, the plasma levels of (table 22) showed higher Cp_{max} in febrile calves as compared to healthy calves. It is obvious that even though the Cp_{max} was higher in febrile calves, need an earlier repetition after i.v. administration. After single dose oral administration, the $t_{½}$ ka in febrile 0.95±0.05 h^{-1} was lower as compared with healthy calves 1.60±0.16 h^{-1}. The $t_{½\beta}$ on the other hand was observed to be higher in febrile calves 3.04±0.14 h as compared to healthy calves 2.99±0.15 h. The occurrence of higher $t_{½\beta}$ value in febrile calves other oral administration seems to independent of β values, because in both healthy and febrile calves the value was similar. The above higher $t_{½\beta}$ value obtained in febrile calves was a result of lower Cl_B value in febrile calves 9.29 ± 0.66 ml/kg/min.

The value for Cl_B observed after oral administration in healthy 13.06±0.78 ml/kg/min and febrile calves 9.29±0.66 ml/kg/min as compared to that after i.v. administration in healthy 6.24±0.46 ml/kg/min and febrile calves 3.41±0.08 mg/kg/min were higher. Thus it obvious that the observed variation in the magnitude of Cl_B could have influenced the plasma levels of LVX after oral and i.v. administration in healthy and febrile calves. This is the reason of why Cp_{max} 4.92±0.35 µg/ml after oral

administration in febrile calves was very near to the Cp_{max} in febrile calves after 4 times lower dose after i.v. 6.16±6.15 µg/ml administration in febrile calves. However, higher plasma levels of fluorouinolones (ENR) after i.v. (15.98±0.34) and i.m. 20.26±0.76 µg/ml in febrile calves have been reported (Singh, 2001). The Cp_{max} after oral administration in healthy (15.81±1.71 µg/ml) was similar to that after i.m. administration in healthy calves.

The plasma levels of pefloxacin with paracetamol after i.v. 26.87±0.44 µg/ml and oral 39.33±0.40 µg/ml in febrile goats were also higher as compared to the observed plasma levels in this experiment (Prasad 2002).

PLASMA PROTEIN BINDING

The mean percent of plasma protein binding (Table 31) at plasma concentrations of 6.25 to 50 µg/ml ranged between 27.91±0.16 to 47.42±0.36 percent in calves. The overall plasma protein binding for other fluoroquinolones has been reported by Singh (2001) 36.38±7.5 per cent for enrofloxacin, Verma (2004) 67.27±6.47 per cent for gatifloxacin and Mishra (2006) 46.08±1.40 per cent for levofloxacin in goats. In human, the plasma protein binding of LVX in the range of 20 to 40 per cent has also been reported (Norrby, 1999; Trampuz et al., 2002 an Bergogne-Berezin, 2002).

DOSAGE REGIMEN

Based on kinetic profile LVX may be given orally @ 1.49 to 2.23 mg/kg b.w. in febrile calves every 8 hourly. The i.v. dose of LVX in febrile calves was calculated to be 0.58 to 0.87 mg/kg b.w. every 6 hourly.

SUMMARY AND CONCLUSION

The pharmacokinetic studies of LVX after oral (20 mg/kg) and i.v. (5 mg/kg) administration were conducted in six healthy and febrile calves.

Oral administration

The mean value of Cp_{max} of LVX (4.50 ± 0.22 µg/ml) after single dose oral administration in healthy calves was significantly lower as compared to that in febrile calves (5.28 ± 0.32 µg/ml).

The Cp_{ther} of LVX was maintained for longer period in febrile calves (till 10 h) as compared to healthy calves (till 8 h).

The mean value of Cu_{max} in febrile (40.86 ± 2.19 µg/ml) was similar to that in healthy calves (39.38 ± 2.43 µg/ml).

The non-significant difference in various pharmacokinetic parameters of plasma viz. β, $t_{½}\beta$, and MRT was observed after oral administration of LVX in healthy and febrile calves.

The non-significant difference in various pharmacokinetic parameters of urine viz. $Cu_{max,}$ β, $t_{½}\beta$ observed after oral administration of LVX in healthy and febrile calves.

Intravenous adminstration

The mean value of Cp_{max} of LVX after single dose i.v. (5 mg/kg) in febrile calves (6.16 ± 0.15µg/ml) was significantly higher as compared to that in healthy calves (5.13 ± 0.13 µg/ml).

The Cp_{ther} of LVX was prolonged in febrile calves (till 8 h) in febrile calves as compared to healthy (till 6h) after i.v. administration.

The value of Cu_{max} of LVX in healthy calves (53.70 ± 2.37µg/ml) was significantly lower than as compared to 63.15 ± 3.44µg/ml in febrile calves.

The mean values of $t_{½}$ β, MRT, Cl_B, Vd_{area} and T/P differed significantly between healthy and febrile calves after i.v. administration.

CONCLUSION

The results indicated that levofloxacin was readily absorbed after oral administration and diffused thoroughly in body fluids, after both oral and i.v. administration. LVX may be clinically used to combat sensitive microbial infections of urinary tract after oral as well as i.v. administration.

LVX may be given orally @ 1.49 – 2.23 mg/kg (1.5 – 2 mg/kg) b.w. in febrile calves every 8 hourly. The i.v. dose of LVX in febrile calves may be 0.58 – 0.87 mg/kg (0.5 – 1 mg/kg) b.w. 6 hr interval.

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APPENDIX

ABBREVIATIONS :

@	:	at the rate of
®	:	Registered trade mark
µg	:	Microgram
A	:	Zero time plasma concentration intercept of distribution phase.
Ad lib	:	Ad libitum
AUC	:	Area under curve
B	:	Zero time plasma concentration intercept of elimination phase.
b.w.	:	Body weight
Cl_B	:	Total body clearance
C^0p	:	Zero time plasma concentration.
Cp_{max}	:	Maximum plasma concentration
Cp_{min}	:	Minimum plasma concentration
Cp_{ther}	:	Therapeutically effective plasma concentration
Cu_{max}	:	Maximum urine concentration
Cu_{min}	:	Minimum urine concentration
Cu_{ther}	:	Therapeutically effective urine concentration
D	:	Dose
e	:	Base of natural logarithm
h	:	Hour
h^{-1}	:	Per hour
i.m.	:	Intramuscular
i.v.	:	Intravenous
K_{12}	:	First order rate constant for transfer of drug from central compartment to peripheral compartment

K_2	:	First order rate constant for elimination from central compartment
K_{21}	:	First order rate constant for transfer of drug from peripheral compartment to central compartment
kg	:	Kilogram
L	:	Litre
LPS	:	Lipopolysaccharide
mg	:	Milligram
min	:	Minute
ml	:	Millilitre
nm	:	Nanometer
P.C.	:	Personal computer
PAC	:	Paracetamol
PFX	:	Pefloxacin
r	:	Repeat interval
rpm	:	revolution per minute
s.c.	:	Subcutaneous
T/P	:	Tissue plasma ratio
$t_{½}Ka$	:	Absorption half life
$t_{½\alpha}$	:	Biological half life (Distribution phase)
$t_{½\beta}$	:	Biological half life (Elimination phase)
U.V.	:	Ultravoilet
Vd_{area}	:	Apparent volume of distribution by area
α	:	Distribution rate constant
β	:	Elimination rate constant