Plasma levels, pharmacokinetics and dosage regimen of intravenously administered gatifloxacin in buffalo calves (*Bubalus bubalis)* on coadministration with meloxicam

Os níveis plasmáticos, farmacocinética e regime de dosagem de gatifloxacina administrado por via intravenosa em bezerros búfalos (Bubalus bubalis) na administração concomitante com meloxicam

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Abstract

The pharmacokinetics of intravenously administered gatifloxacin, upon concomitant administration with meloxicam was investigated in buffalo calves. Meloxicam was administered subcutaneously (0.5 mg.kg^{-1}) immediately followed by intravenous administration of Gatifloxacin (4 mg.kg^{-1}). The concentration of gatifloxacin was estimated in plasma by microbiological assay. Pharmacokinetic parameters were calculated and appropriate dosage schedule was computed. The therapeutic plasma drug concentration was maintained up to 12 h. Gatifloxacin was rapidly distributed from blood to tissue compartment, which was evident from the high values of distribution rate constant, α_1 (11.9 ± 0.52 h^{-1}) and the ratio of rate constant of transfer of drug from central to peripheral compartments and vice versa, K_{12}/K_{21} (3.05 ± 0.36) and K_{13}/K_{31} (2.04 ± 0.12). The area under the plasma drug concentration-time curve and apparent volume of distribution were 12.0 ± 0.68 μg.ml^{-1}.h and 2.69 ± 0.14 L.kg^{-1}, respectively. The elimination half-life ($t_{1/2\beta}$), total body clearance (Cl_B) and the ratio of drug present in peripheral to central compartment (P/C) were 5.59 ± 0.40 h, 337.6 ± 19.9 ml.kg^{-1}.h^{-1} and 8.04 ± 0.50, respectively. The present study revealed that the most suitable dosage regimen of gatifloxacin when concomitantly administered with meloxicam in buffalo calves would be 2.5 mg.kg^{-1} followed by 2.0 mg.kg^{-1} at 12 h intervals.

Keywords: Buffalo calves. Gatifloxacin. Meloxicam. Pharmacokinetics.

Resumo

Investigou-se a farmacocinética da gatifloxacina, administrada por via intravenosa, concomitante à aplicação de meloxicam em bezerros búfalos. O meloxicam foi administrado por via subcutânea (0,5 mg.kg^{-1}), imediatamente seguido pela administração intravenosa de gatifloxacina (4 mg.kg^{-1}). A concentração plasmática de gatifloxacina foi estimada por ensaio microbiológico. Os parâmetros farmacocinéticos foram calculados e a posologia adequada foi computada. A concentração plasmática do fármaco-terapêutico foi mantida por 12 h. A gatifloxacina foi rapidamente distribuída a partir de sangue para o compartimento de tecido, o que ficou evidente a partir dos valores elevados da taxa constante de distribuição, α_1 (11.9 ± 0.52 h^{-1}) e a proporção de velocidade constante de transferência de droga a partir de centrais para os compartimentos periféricos e vice-versa, K_{12}/K_{21} (3.05 ± 0.36) e K_{13}/K_{31} (2.04 ± 0.12). A área sob a curva plasmática de concentração-tempo da droga e o volume aparente de distribuição foi de 12.0 ± 0.68 μg.ml^{-1}.h e 2.69 ± 0.14 L.kg^{-1}, respectivamente. A meia-vida ($t_{1/2\beta}$), a depuração corporal total (Cl_B) e relação da droga presente no sangue periférico para o compartimento central (P/C) foram 5.59 ± 0.40 h, 337.6 ± 19.9 ml.kg^{-1}.h^{-1} e 8.04 ± 0.50, respectivamente. O presente estudo revelou que o regime de dosagem mais adequado de gatifloxacina quando administrada concomitantemente com meloxicam em bezerros búfalos seria 2,5 mg.kg^{-1} seguida de 2,0 mg.kg^{-1} em intervalos de 12 h.

Palavras-chave: Bezerros búfalos. Gatifloxacina. Farmacocinética. Meloxicam.

Introduction

Gatifloxacin, a recently introduced fluoroquinolone, possesses good activity against a wide range of gram-positive and gram-negative pathogens, atypical organisms and some anaerobes[1]. It is commonly indicated for the treatment of acute bacterial sinusitis, chronic bronchitis, pneumonia, urinary tract infec-

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tions, acute pyelonephritis and gonorrhea[2]. Fluoroquinolone resistance relates directly to human and veterinary usage and emerging bacterial resistance poses the single greatest threat to the future survival of the fluoroquinolone drugs as an antibiotic class[3]. As a member of respiratory quinolones, gatifloxacin possesses enhanced activity against *S. pneumoniae, H. influenza* and *M. catarrhalis*[4]. Under field conditions, in the management of bacterial infections, administration of an analgesic agent with an antibacterial is a regular feature. Meloxicam, a novel NSAID of the oxicam class, is one of the most potent inhibitors of cyclooxygenase-2 currently available. Fluoroquinolones have been known to interact with non-steroidal anti inflammatory drugs at pharmacokinetic and pharmacodynamic level[5]. The pharmacokinetic study of gatifloxacin has been investigated in rabbits[6], mice[7], humans[8] and buffalo calves[9,10]. Concurrent administration of gatifloxacin has been found to alter the pharmacokinetics of meloxicam in buffalo calves[11]. Further, concomitant administration of meloxicam[12] and paracetamol[13] have been shown to influence the disposition of levofloxacin in calves. However, there is no information available on the effect of meloxicam on the pharmacokinetics of gatifloxacin. In view of the paucity of such data on alterations in pharmacokinetic behavior of simultaneously administered drugs, the present study was planned to determine the plasma levels, pharmacokinetics and an optimal dosage regimen of gatifloxacin in buffalo calves (*Bubalus bubalis*) after its single intravenous administration along with subcutaneous administration of meloxicam.

Material and Method

Five healthy male buffalo calves of non-descript breed, ranging between six months to one year of age and 116-168 kg body weight were used for the study. The animals were kept in the departmental animal shed under standard conditions of management for two weeks prior to the commencement of the study and were provided green fodder and water *ad libitum.*

Gatifloxacin (Gatiquin, Cipla Ltd., India) was administered at the dose rate of 4 $mg.kg^{-1}$ body weight into the left jugular vein immediately after subcutaneous injection of meloxicam (Metacam, Intas Pharmaceuticals Ltd., India) at the dose rate of 0.5 $mg.kg^{-1}$ into the neck region. The experimental protocol followed the ethical guidelines on the proper care and use of animals and has been approved by the institutional animal ethics committee (Protocol Reg. no. 497/01/a/CPCSEA). The doses of gatifloxacin and meloxicam employed in the present study were similar to the doses of these drugs in buffalo calves and calves in previous disposition studies[10,12].

Heparinized blood samples (5 ml) were collected from the contralateral jugular vein into at 1, 2.5, 5, 7.5, 10, 15, 30 min and 1, 2, 4, 6, 8, 10, 12, 14 and 24 h post drug administration, as performed by previous workers[10]. Plasma was separated by centrifugation at 1300 g for 15 min at room temperature and stored at -20 ^{0}C until analysis, which was performed next day.

The concentration of gatifloxacin in plasma samples was estimated by a standard microbiological assay technique[14] using *Escherichia coli* (MTCC 739) as the test organism as per the method described by previous workers[10]. Assay plates were incubated at 34 ^{0}C for 12 h. At the end of incubation, the diameter of zone of inhibition of each well was measured with a Fisher Lilly Antibiotic Zone Reader (Fisher Scientific Company USA). The punching device used to create wells of uniform size was fabricated with six stainless steel columns having an inner diameter of 6 mm fixed at equal distance to a heavy metal base which could be sterilized in oven. Three alternate wells were filled with one plasma sample and the remaining three wells with a reference drug solution. This method estimated the level of parent

drug and its active metabolites having antibacterial activity. The assay could detect a minimum of 0.05 μg.ml^{-1} of gatifloxacin. For each sample, nine replicates were analyzed and correlated with the zone of inhibition of standard reference solution of gatifloxacin (0.2 μg.ml^{-1}). The concentration of drug in the samples was calculated as μg.ml^{-1} of plasma.

The plasma concentration-time profile of gatifloxacin after its concomitant administration with meloxicam in each animal was used to establish various disposition kinetic determinants and the mean kinetic variables were obtained by averaging the variables calculated for individual animal. Disposition kinetic parameters were calculated manually by the computed least-squares linear regression technique[15].

Results

The plasma levels of gatifloxacin at different time intervals following its single intravenous injection of 4 mg.kg^{-1} after subcutaneous administration of meloxicam (0.5 mg.kg^{-1}) are presented in figure 1. At 1 min, the mean plasma drug concentration was 11.3 ± 0.45 μg.ml^{-1} and the drug was detected in plasma up to 24 h. The pharmacokinetic parameters that describe the distribution and elimination pattern of gatifloxacin were calculated and presented in table 1. Using convenient dosage interval, the priming (D) and mainte-

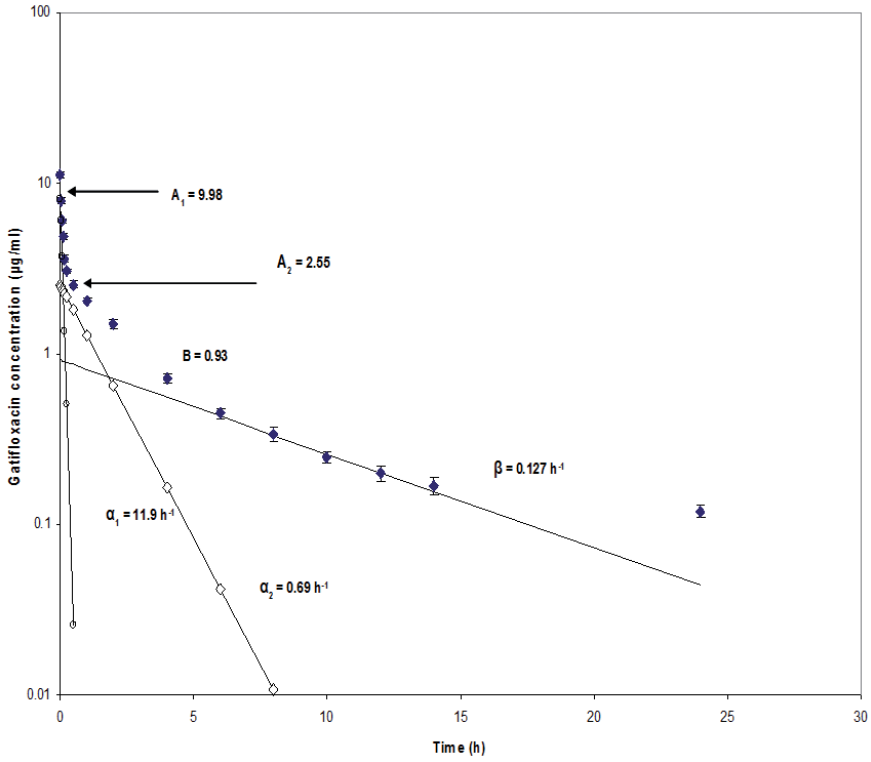

Figura 1 - Semilogarithmic plot of plasma concentration-time profile of gatifloxacin following its single intravenous injection of 4 mg.kg^{-1} body weight after subcutaneous administration of meloxicam (0.5 mg.kg^{-1}) in buffalo calves. Values are presented as mean ± SE of five animals. The data was analyzed according to three-compartment open model. Distribution (α_1 and α_2) and elimination (β) phases are represented by least square regression lines. The calculated points of distribution phase were obtained by the feathering technique. Constants A_1, A_2 and B are the zero-time intercepts of distribution and elimination phases, respectively

Table 1 - Pharmacokinetic parameters of intravenously administered gatifloxacin @ 4 mg.kg^{-1} on concomitant administration of meloxicam (0.5 mg.kg^{-1}, sc) in buffalo calves (n = 5)

Parameter	Unit	Mean±SE
Cp^o	μg.ml^{-1}	13.5 ± 0.44
A_1	μg.ml^{-1}	9.98 ± 0.39
α_1	h^{-1}	11.9 ± 0.52
$t_{½\alpha1}$	h	0.059 ± 0.003
A_2	μg.ml^{-1}	2.55 ± 0.19
α_2	h^{-1}	0.684 ± 0.05
$t_{½\alpha2}$	h	1.03 ± 0.07
B	μg.ml^{-1}	0.924 ± 0.06
β	h^{-1}	0.127 ± 0.01
$t_{½\beta}$	h	5.59 ± 0.40
AUC	μg.ml^{-1}.h	12.0 ± 0.68
AUMC	μg.ml^{-1}.h^2	75.9 ± 7.50
Vd_{area}	L.kg^{-1}	2.69 ± 0.14
Cl_B	ml.kg^{-1}.h^{-1}	337.6 ± 19.9
MRT	h	6.26 ± 0.34
K_{el}	h^{-1}	1.13 ± 0.03
K_{12}/K_{21}	ratio	3.05 ± 0.36
K_{13}/K_{31}	ratio	2.04 ± 0.12
P/C	ratio	8.04 ± 0.50
t_d	h	24.2 ± 1.73

A_1 and A_2 = zero-time plasma drug concentration intercepts of the regression lines of distribution phases 1 and 2, respectively; α_1 and α_2 = rate constants of distribution phases 1 and 2, respectively; B and β = zero-time plasma drug concentration intercept of elimination phase and elimination rate constant, respectively; $t½\alpha_1$ and $t½\alpha_2$ = half-lives of distribution phases 1 and 2, respectively; t½β= elimination half-life; AUC = area under the plasma concentration-time curve; AUMC = area under the first moment curve; Vd_{area} = apparent volume of distribution; Cl_B = total body clearance; MRT = mean residence time; td = duration of therapeutic effect; K_{12} and K_{21} = micro-rate constants from central to peripheral compartment 1 and vice versa, respectively; K_{13} and K_{31} = micro-rate constants from central to peripheral compartment 2 and vice versa, respectively; K_{el} = elimination rate constant from central compartment; P/C = ratio of drug present in the peripheral to central compartment

nance (D') doses of gatifloxacin were calculated according to the equations:

$D = C_p (min)^{\propto}.Vd\ (e^{\beta\tau})$ $\quad D' = C_p (min)^{\propto}.Vd\ (e^{\beta\tau} - 1)$

Where, Cp $(min)^{\propto}$ is the minimum inhibitory concentration of gatifloxacin, β is the elimination rate constant and τ is the dosage interval[16]. Taking various dosage intervals for maintaining the different MICs ranging from 0.05 to 0.5 μg.ml^{-1}, the priming and maintenance doses of gatifloxacin were calculated and are presented in table 2.

Discussion and Conclusions

Evaluation of the results on observed plasma levels revealed that the disposition pattern of gatifloxacin was best fitted to three-compartment open model and adequately described by the tri-exponential equation $Cp = A_1e^{-\alpha1t} + A_2e^{-\alpha2t} + Be^{-\beta t}$, where Cp is the gatifloxacin concentration at time t, A_1, A_2 and B are zero-time intercepts of distribution and elimination phases, respectively, α_1 and α_2 are the rate constants of distribution phases 1 and 2, respectively, β is the

Table 2 - Calculated intravenous dosage regimen of gatifloxacin at various dosage intervals, to maintain different therapeutic plasma drug concentrations when prescribed with meloxicam in buffalo calves

Therapeutic plasma concentration (µg. ml^{-1})	Dosage interval (h)				
	8	10	12	16	24
0.05	0.37 (0.24)	0.48 (0.35)	0.62 (0.49)	1.05 (0.92)	3.06 (2.93)
0.1	0.74 (0.47)	0.96 (0.69)	1.25 (0.98)	2.11 (1.84)	6.13 (5.86)
0.2	1.49 (0.95)	1.92 (1.39)	**2.49 (1.96)**	4.21 (3.67)	12.3 (11.7)
0.3	2.23 (1.42)	2.89 (2.08)	3.74 (2.93)	6.32 (5.51)	18.4 (17.6)
0.5	3.72 (2.37)	4.81 (3.46)	6.23 (4.89)	10.5 (9.18)	30.7 (29.3)

Values given are expressed as mg.kg^{-1} body weight; Maintenance doses are given in parentheses

elimination rate constant and e represents the base of natural logarithm. The minimum inhibitory concentration (MIC_{90}) of gatifloxacin was maintained from 1 min to 12 h of administration. The MIC_{90} of gatifloxacin against various organisms has been reported to be ranging from 0.015 to 8 µg.ml^{-1}.[7] In view of the influences of different factors *in vivo* and to cover majority of the susceptible microorganisms the MIC of gatifloxacin has been considered to be 0.2 µg.ml^{-1} in this discussion. At 1 min of injection, the peak plasma level was approximately 56 fold higher than the MIC of gatifloxacin. Gatifloxacin has been shown to attain plasma levels of 4.53 to 6.07 µg.ml^{-1} following single intravenous injection in human beings[4,17,18].

Gatifloxacin was rapidly transferred from the central to peripheral compartment 1 in buffalo calves as is evident from the high value of distribution rate constant, α_1 (11.9 ± 0.52 h^{-1}). The high ratios of K_{12}/K_{21} (3.05 ± 0.36) and K_{13}/K_{31} (2.04 ± 0.12) also indicated rapid transfer of the drug from central to peripheral compartments. Similar trend was observed for the distribution of gatifloxacin into various tissues and body fluids after its intravenous administration alone in buffalo calves[10]. The large Vd_{area} (2.69 ± 0.14 L.kg^{-1}) and P/C ratio (8.04 ± 0.50) further suggested extensive penetration of gatifloxacin into the body fluids and tissues of buffalo calves. In accordance to our findings, high values of volume of distribution have been reported after intravenous administration of gatifloxacin alone in buffalo calves (3.56 L.kg^{-1})[10] and after single or multiple administrations of oral and intravenous doses of gatifloxacin in man (1.45 to 2.01 L.kg^{-1})[8]. High value of AUC (12.0 ± 0.68 µg.ml^{-1}.h^{-1}) reflected a vast area covered under drug concentration. In agreement to our findings, high value of AUC (17.1 µg.ml^{-1}.h^{-1}) was observed after intravenous administration of gatifloxacin alone in buffalo calves[10]. High values of AUC have also been reported after intravenous administration of marbofloxacin (7.7 µg.ml^{-1}.h) in cattle and enrofloxacin (17.8 µg.ml^{-1}.h) in calves[19,20].

The elimination half-life of gatifloxacin (5.59 ± 0.4 h) calculated in the present study was shorter than the half life of 10.4 h obtained after administration of the same dose of gatifloxacin alone in buffalo calves[10], however it was comparable to half-life reported for gatifloxacin (6.24 ± 9.4 h) in human beings[4,17,18]. Similar values have also been reported for the half-life of other fluoroquinolones, marbofloxacin (5.7 h) in cattle[20] and pefloxacin (6.88 h) in sheep[21]. The total body clearance of gatifloxacin in buffalo calves in the present study (337.6 ± 19.9 ml.kg^{-1}.h^{-1}) was higher than the values of Cl_B reported after single intravenous injection of gatifloxacin in human beings (182-206 ml.kg^{-1}.h^{-1}) and buffalo calves (235.1 ml.kg^{-1}.h^{-1})[10,17,22]. This finding is supported by the earlier reports where-

in meloxicam was reported to increase the total body clearance of levofloxacin two fold upon simultaneous administration in calves[12].

The ultimate objective of the pharmacokinetic study was to determine an optimum intravenous dosage regimen of gatifloxacin. Taking 12 h as a convenient dosage interval, with a minimum therapeutic plasma level (C_p (min)∞) of 0.2 μg.ml^{-1} and using the values of β and Vd_{area} from Table 1, the appropriate priming and maintenance dosage of gatifloxacin would be 2.49 mg.kg^{-1} followed by 1.96 mg.kg^{-1} at 12 h intervals or under field condition it would be 2.5 mg.kg^{-1} and 2.0 mg/kg^{-1} intravenously at 12 h intervals, when prescribed along with meloxicam in buffalo calves. This dose was quite different than the dose of 5 mg.kg^{-1} at 24 h intervals calculated for intravenous administration of gatifloxacin alone in buffalo calves[10].

Simultaneous administration of meloxicam in the present study decreased the Vd_{area}, P/C ratio, AUC and elimination half life and increased the total body clearance of gatifloxacin in buffalo calves in comparison to gatifloxacin administered alone in buffalo calves[10], indicating lesser distribution to peripheral tissues and body fluids and decreased duration of therapeutic effect of gatifloxacin when used with meloxicam. Thus gatifloxacin would require more frequent dosing at 12 h intervals when prescribed along with meloxicam than the 24 h dosing schedule recommended for gatifloxacin alone in buffalo calves[10].

References

1. PERRY, C. M.; ORMROD, D.; HURST, M.; ONRUST, S. U. Gatifloxacin: a review of its use in the management of bacterial infections. **Drugs,** v. 62, n. 1, p. 169-207, 2002.
2. DANIEL, A. H. New drugs of 2000. **Journal of the American Pharmacists Association,** v. 41, n. 2, p. 229-272, 2001.
3. BAKKEN, J. S. The fluoroquinolones: How long will their utility last? **Scandinavian Journal of Infectious Diseases,** v. 36, n. 2, p. 85-92, 2004.
4. FISH, D. N.; NORTH, D. S. Gatifloxacin, an advanced 8-methoxy fluoroquinolone. **Pharmacotherapy,** v. 21, n. 1, p. 35-59, 2001.
5. LANGTRY, H. D.; LAMB, H. M. Levofloxacin: its use in infections of the respiratory tract, skin, soft tissues and urinary tract. **Drugs,** v. 56, p. 487-515, 1998.
6. LUTSAR, I.; FRIEDLAND, I. R.; WUBBEL, L.; MCCOIG, C. C.; JAFRI, H. S.; NG, W.; GHAFFAR, F.; MCCRACKEN JR., G. H. Pharmacodynamics of gatifloxacin in cerebrospinal fluid in experimental cephalosporin-resistant pneumococcal meningitis. **Antimicrobial Agents and Chemotherapy,** v. 42, n. 10, p. 2650-2655, 1998.
7. ANDES, D.; CRAIG, W. A. Pharmacodynamics of the new fluoroquinolone gatifloxacin in murine thigh and lung infection models. **Antimicrobial Agents and Chemotherapy,** v. 46, n. 6, p. 1665-1670, 2002.
8. NAKASHIMA, M.; UEMASTU, T.; KOSUGE, K.; KUSAJIMA, H.; OOIE, T.; MASUDA, Y.; ISHIDA, I.; UCHIDA, H. Single and multiple-dose pharmacokinetics of AM-1155, a new 6-fluoro-8-methoxy quinolone in humans. **Antimicrobial Agents and Chemotherapy,** v. 39, p. 2635-2640, 1995.
9. RAIPURIA, M.; DUMKA, V. K.; SANDHU, H. S.; RAM, D. Gatifloxacin pharmacokinetics in buffalo calves after single intramuscular administration. **Veterinarski Arhiv,** v. 76, n. 6, p. 471-478, 2006.
10. RAIPURIA, M.; DUMKA, V. K.; SANDHU, H. S. Plasma concentrations, pharmacokinetics and urinary excretion of gatifloxacin after single intravenous injection in buffalo calves. **Veterinary Research Communications,** v. 31, p. 1013-1020, 2007.
11. DUMKA, V. K.; SANDHU, H. S.; RAJPUT, N. Effect of gatifloxacin on the pharmacokinetics of meloxicam in buffalo calves. **Indian Journal of Animal Sciences,** v. 77, n. 12, p. 1270-1272, 2007.
12. DUMKA, V. K.; SINGH, H.; SRIVASTAVA, A. K. Disposition kinetics and urinary excretion of levofloxacin on concomitant administration with meloxicam in cross bred calves. **Environmental Toxicology and Pharmacology**, v. 26, p. 56-60, 2008.
13. DUMKA, V. K. Disposition kinetics and dosage regimen of levofloxacin on concomitant administration with paracetamol in cross bred calves. **Journal of Veterinary Science**, v. 8, n. 4, p. 357-360, 2007.
14. ARRET, B.; JOHNSON, D. P.; KIRSHBAUM, A. Outlines of details for microbiological assay of antibiotics: second revision. **Journal of Pharmaceutical Science**, v. 60, p. 1689-1694, 1971.
15. GIBALDI, M.; PERRIER, D. Methods of residuals. In: GIBALDI, M.; PERRIER, D. **Pharmacokinetics**. New York: Marcel Dekker, 1982. p. 433-444.
16. BAGGOT, J. D. Principles of pharmacokinetics In: BAGGOT, J.D. **Principles of drug disposition in domestic animals. The basis of veterinary clinical pharmacology**. Philadelphia: WB Saunders Inc, 1977. p. 144-189.
17. GAJJAR, D. A.; LACRETA, F. P.; UDERMAN, H. D. A dose escalation study of the safety, tolerability and pharmacokinetics of intravenous gatifloxacin in healthy adult men. **Pharmacotherapy,** v. 20, n. 6.2, p. 49-58, 2000.
18. LACRETA, F. P.; KAUL, S.; KOLLIA, G. D.; DUNCAN, G.; RANDALL, D. M. GRASELA, D. M. Interchangebility of 400 mg intravenous and oral gatifloxacin in healthy adults. **Pharmacotherapy,** v. 20, n. 6, p. 59-66, 2000. Pt. 2.

19. AHANGER, A. A.; SRIVASTAVA, A. K.; RAINA, R. Disposition kinetics of enrofloxacin in crossbred calves. **Journal of Veterinary Pharmacology and Toxicology,** v. 3, n. 1/2, p. 16-20, 2003.

20. THOMAS, V.; DELEFORGE, J.; BOISRAME, B. Pharmacokinetics of marbofloxacin in pre-ruminant and ruminant cattle. In: CONGRESS OF EUROPEAN ASSOCIATION FOR VETERINARY PHARMACOLOGY AND TOXICOLOGY, 6., 1994, Edinburgh, Scotland. **Proceedings…** 1994. p. 60-61.

21. MOUTAFCHIEVA, R.; DJOUVINOV, D. Pharmacokinetics of pefloxacin in sheep. **Journal of Veterinary Pharmacology and Therapeutics**, v. 20, p. 405-407, 1997.

22. LACRETA, F. P.; KOLLIA, G. D.; DUNCAN, G.; BEHR, D.; GRASELA, D. M. Age and gender effects on the pharmacokinetics of gatifloxacin. **Pharmacotherapy,** v. 20, n. 6, p. 67-75, 2000. Pt. 2.