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Research Article

PHARMACOKINETICS OF AMIKACIN IN HEALTHY GOATS AFTER REPETITIVE INTRAMUSCULAR ADMINISTRATION

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ABSTRACT

Pharmacokinetic study was carried out after repetitive intramuscular (I/M) administration of amikacin at the dose rate of 10 mg/Kg b.wt. for five days. Amikacin concentrations in plasma and pharmacokinetics parameters were analyzed by using microbiological assay technique. The minimum therapeutic concentration (C_p^{ss}min = MIC) ≥ 1.0 mg/ml was maintained in the plasma from 0.083 to 12 h on both 1st and 5th day of drug administration. Significantly higher plasma concentrations of the drug appeared from 0.083 to 12 h in 5th day as compared to 1st day. The kinetic parameters like absorption rate constant (A'), area under curve (AUC), area under first moment curve (AUMC), maximum plasma concentration (C_{max}) and total body clearance (ClB) were significantly higher on 5th day as compared to 1st day. All the other kinetic parameters differed non-significantly between 1st and 5th day of drug administration. The loading (D*) and maintenance (D^0) doses were 3.96 ± 0.17 and 3.57 ± 0.189 mg/kg b.wt., respectively to maintain the minimum therapeutic concentration of 1.0 µg/ml at the dosage interval of 12 h.

Keywords: Amikacin, Dose, Goat, Pharmacokinetics

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Amikacin is an aminoglycoside antibiotic primarily used for the treatment of infections caused by aerobic gram negative bacilli when first-line antibiotic treatment is ineffective (Boehr *et al.*, 2003). Due to its property of being refractory to most aminoglycoside modifying enzymes, amikacin has been successfully used to treat aminoglycoside resistant infections, and it is the most widely used semi-synthetic aminoglycoside (Ristuccia and Cunha, 1985). Amikacin alone or in combination with other antibiotics is used to treat a variety of serious infections caused by aerobic gram-negative bacteria, as well as mycobacteria and Nocardia (Tamma *et al.*, 2012). Amikacin is mainly administered intravenously, intramuscularly and through nebulization (Quon *et al.*, 2014). Other routes of administration for specific infections are intrathecal or intraventricular (Berning *et al.*, 2001). Since, amikacin exhibits the toxic effects common to aminoglycosides, i.e. ototoxicity and nephrotoxicity, the dose regime to maximize therapeutic outcomes and minimize adverse consequences is of great importance. Calculation of dosage regimen in most of the pharmacokinetic studies is based on the pharmacokinetic parameters derived from single intramuscular (I/M) administrations (Agrawal *et al.*, 2002); however, dosage regimen after repetitive dosing is not available. Hence, the present study was undertaken to investigate whether the dosage regimen calculated from I/M administration of amikacin in goats actually maintains the minimum inhibitory concentration (MIC) at the end of every dosage interval during repetitive administration.

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MATERIALS AND METHODS

Experimental animals: The experiment was performed in four clinically healthy female goats of Sirohi breed between 1 to 2 years of age and 15 to 25 kg body weight. The experimental protocol for general procedure and use of animals for conducting the present study has been reviewed and approved by the Institutional Animal Ethics Committee (No:873/IAEC/Vety/Rewa/2018; Dated: 28/06/2018), College of Veterinary Science & A.H., Rewa, Madhya Pradesh, India.

Test organism and chemicals: *Escherichia coli* (ATCC 25922) as test organism was used for estimation of concentration of the drugs in plasma by microbiological assay technique obtained from the National Collection of Industrial Micro-Organism (NCIM), Division of Bio-chemical sciences, National Chemical Laboratory, Pune. The injectable commercial preparation containing amikacin equivalent to 250 mg/ml, marketed by Amidac, India was used in the present investigation. The drug was administered at the dose rate of 10 mg/kg bwt I/M route (Agrawal *et al.*, 2001) once daily for five days (Saini and Srivastava, 1998).

Collection of blood samples and estimation of amikacin: Blood samples (approx. 1 ml) were drawn from

jugular vein into heparinized glass centrifuge tubes for plasma collection on 1st and 5th day of drug administration at 0, 2.5, 5, 10, 15, 20, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h. The concentration of amikacin in plasma was estimated by a rapid, specific microbiological assay technique using *Escherichia coli* as the test organism (Paul *et al.*, 1971).

Bioassay technique and pharmacokinetic analysis: Punch bioassay technique was used to estimate the concentration of amikacin in plasma (Arret *et al.*, 1971). The plasma concentration-time profile of amikacin for each animal was used to determine the pharmacokinetics parameters on the basis of Gibaldi and Perrier (1982).

Calculation of dosage regimen and statistical analysis: The dosage regimen for maintaining minimal therapeutic concentration in plasma at the desired dosage intervals (t) was calculated using the equations as reported by Baggot (1977). Statistical analysis was done by using paired 't' test (Snedecor and Cochran, 1994).

RESULTS AND DISCUSSION

The comparative plasma concentrations of amikacin in healthy goats after I/M administration are shown in table 1. The mean plasma concentration of amikacin was 0.24 ± 0.02 µg/ml and 0.33 ± 0.02 µg/ml at 0.42 h while, the drug was detected with plasma concentration 0.27 ± 0.02 mg/ml and 0.33 ± 0.02 µg/ml till 24h on 1st and 5th day, respectively. The mean peak plasma concentration (C_{max}) was 18.15 ± 0.69 µg/ml and 19.84 ± 0.60 µg/ml on 1st and 5th day at 4 h. The MIC (≥ 1.0 µg/ml) of amikacin was maintained from 0.083 to 12 h on both 1st and 5th day. Significantly higher plasma concentrations of the drug appeared from 0.083 to 12 h on 5th day as compared to 1st day of amikacin administration.

For kinetic analysis, plasma concentrations of amikacin were plotted on a semi-logarithmic scale as a function of time and the data was analyzed using a one compartment open model (Gibaldi and Perrier, 1982). The comparative kinetic parameters of amikacin in healthy goat after repetitive I/M administration have been shown in table 2. Significantly higher values of the absorption rate constant (A), area under curve (AUC), area under first moment curve (AUMC), and maximum plasma concentration (C_{max}) and total body clearance (ClB) were observed on 5th day as compared to 1st day. All other kinetic parameters differed non significantly between 1st and 5th day of amikacin administration.

The $t_{1/2}$Ka of amikacin was 1.21 ± 0.11 h and 1.06 ± 0.03 h on 1st and 5th day, respectively. However, findings contrary to the present findings have been reported by Uppal *et al.* (1997) in goat (0.24 h), Brown *et al.* (1984) in mare (0.385 h), Uppal *et al.* (1998) in buffalo calf (0.214 h), Carli *et al.* (1990) in calves (0.36 h) and sheep (0.43 h). The $t_{1/2}$b of amikacin was 3.57 ± 0.13 h and 3.80 ± 0.10 h on 1st and 5th day, respectively. This might have contributed to less excretion of amikacin leading to the longer half-life and persistence of higher concentration in plasma for most of the time intervals. These findings are in concordance with the findings of Saini and Shrivastava (1998) and Brown *et al.* (1986), who reported 3.09 h in bovine calves and 3 h in foal. However, contrary to the present findings, $t_{1/2}$b observed earlier 1.64 h in lactating sheep (Haritova, 2004), 2.05 h in lactating goats (Abo-el sooud, 1999), 2.02 h in red tailed hawks (Bloomfield *et al.*, 1997), 1.408 h in goats (Uppal *et al.*, 1997) and 2.3 h in mare (Brown *et al.*, 1984). The difference in observed half-life value in the present study as compared to other species may be due to differences in metabolism, process of excretion, species and intra-species variation.

The AUC values of amikacin were significantly lower (131.75 ± 3.39 µg/ml.h) on 1st day as compared to 154.28 ± 4.63 µg/ml.h on 5th day. However, contrary to these findings, Agrawal *et al.*, 2001 have reported lower AUC in goats (73.18 µg/ml.h), in lactating sheep (94.09 ± 6.95 µg/ml.h) (Haritova, 2004) and in Greyhounds dogs

Table 1

Comparative plasma concentrations (Mean±SE) of amikacin on 1st and 5th day following I/M administration in healthy goat

	Plasma concentration of amikacin ($mg.ml^{-1}$)	
Time (h)	1st Day	5th Day
0.042	00.24±0.02	00.33±0.03
0.083	01.10±0.28	01.37±0.28*
0.166	02.05±0.42	02.50±0.43*
0.25	04.05±0.19	04.95±0.25*
0.50	06.75±0.32	07.95±0.44*
0.75	08.45±0.20	09.42±0.22*
1	10.05±0.19	11.03±0.17*
1.5	11.46±0.46	12.96±0.73*
2	12.89±0.73	18.15±0.69*
4	18.15±0.69	19.78±0.65*
6	13.10±0.60	14.35±0.94*
8	05.43±0.29	06.33±0.22*
12	02.25±0.12	02.88±0.15*
24	00.27±0.02	00.33±0.02

*Significant ($p<0.05$) difference following I/M administration in healthy goat on 1st and 5th day

Table 2

Comparative pharmacokinetic parameters (Mean±SE) of amikacin on 1st and 5th day following I/M administration in healthy goats

Parameter (Unit)	1st day	5th day
A' (µg/ml)	36.91±1.79	40.01±1.95*
B (µg/ml)	27.66±2.83	26.62±1.98
Ka (h^{-1})	0.62±0.09	0.66±0.02
$t_{1/2}$Ka (h)	1.21±0.11	1.06±0.03
β (h^{-1})	0.19±0.01	0.18±0.00
$t_{1/2}$β (h)	3.57±0.13	3.80±0.10
AUC (µg/ml.h)	131.75±3.39	154.28±4.63*
AUMC (µg/ml.h^2)	626.30±155.39	920.55±23.94*
MRT (h)	5.90±0.15	5.98±0.09
Vd_{area} (L/kg)	0.39±0.22	0.36±0.19
Cl_B (ml/kg/h)	76.06 ±1.90	64.98±1.86*
C_{max} (µg/ml)	18.15±0.69	19.78±0.65*
T_{max} (h)	4.00±0.00	4.00±0.00

*Significant difference ($p<0.05$); Zero-time concentration during absorption (A'); Zero-time concentration during elimination phases (B); Absorption rate constant (Ka); Absorption half-life ($t_{1/2}$ ka); Elimination rate constant (β); Elimination half-life ($t_{1/2}$β); Area under curve (AUC); Area under first moment curve (AUMC); Mean residence time (MRT); Volume of distribution (Vd_{area}); Total body clearance (Cl_B); Maximum plasma concentration (C_{max}); Time required to attain peak plasma level (T_{max}).

Table 3

Comparative dosage regimens (Mean±SE) for amikacin following I/M administration in healthy goats

C_p^{∞}min (µg/ml)	τ (h)	Dose	Amikacin (mg/kg bwt)
1	12	D*	3.96±0.17
		D^0	3.57±0.19
2	12	D*	7.95±0.36
		D^0	7.15±0.38

C_P^{∞}min= Minimum therapeutic concentration in plasma (MIC); τ(h)=Dosage interval; D*=Loading or priming dose; D^0= Maintenance dose

(79.97 µg/ml.h) (Kukanich and Coetzee, 2007). The AUMC values of amikacin were 626.30 ± 15.39 µg/ml.h^2 on 1st day and 920.55 ± 23.94 µg/ml.h^2 on 5th day. Bhat and Kumar (2019) reported lower AUMC values (22.7 ± 0.266 µg/ml.h^2 on 1st day and 24.57 ± 0.229 µg/ml.h^2 on 5th day) following repetitive once daily I/V administration of amikacin in cow calves. The MRT values of amikacin was 5.90 ± 0.15 h on 1st day and 5.98 ± 0.09 h on 5th day. These findings are in close agreement with the results of Agrawal *et al.* (2001), who reported MRT 4.67 ± 0.19 h in goats. The higher values of AUC, AUMC and MRT in the present investigation reflect that the drug remains in the body for comparatively longer duration of time.

The Vd_{area} of amikacin was 0.39 ± 0.22 L/kg and 0.36 ± 0.19 L/kg on 1st and 5th day, respectively. The Vd_{area} obtained in the present investigation is in accordance with the findings of Agrawal *et al.* (2001), who reported 0.39 ± 0.03 L/kg in goats. However, contrary to the present findings, Vd_{area} were 0.26 ± 0.029 L/kg in mare (Brown *et al.*, 1984), 0.201 ± 0.005 L/kg in buffalo calf (Uppal *et al.*, 1998), 0.28 ± 0.03 L/kg in red tailed hawks (Bloomfield, 1997), 0.26 ± 0.029 L/kg in mare (Brown *et al.*, 1984) and 0.58 L/kg in foal (Brown, 1986). The higher values of Vd_{area} indicate greater distribution of amikacin in body of goat.

The total body clearance (Cl_B) of amikacin was 76.06 ± 1.90 and 64.98 ± 1.86 ml/kg/h on 1st and 5th day, respectively. Cl_B value reported earlier 2.34 ± 0.17 ml/kg/min in goats (Agrawal *et al.*, 2001), 0.97 ml/kg/min in camel (Wasfi *et al.*, 1999), 2.66 ml/kg/min in dogs (Baggot *et al.*, 1985), 1.33 ± 0.11 ml/kg/min in mare (Brown *et al.*, 1984) and 0.752 ± 0.012 ml/kg/min in buffalo calves (Uppal *et al.*, 1998). This difference in the values of Cl_B amongst various species of the animals indicated that difference in their glomerular filtration rates of amikacin which is polar organic base, hence weakly bound to serum proteins and is excreted as unchanged into the urine by glomerular filtration (Carli *et al.*, 1990). Variations among age, sex, species, breed and different methods for estimating the kinetic parameters may contribute to the wide discrepancies in kinetic parameters as reported by various researchers (Jayachandran *et al.*, 1990).

The ultimate objective of the study of disposition kinetics is to determine an appropriate dose regimen of drugs. For any antimicrobial agent, the dosage regimen is calculated to maintaining the minimum therapeutic concentration (C_p^{∞}min = MIC) throughout the course of infections. Based on these kinetic parameters, the dosage regimen for maintaining minimal therapeutic concentration of 1 and 2 µg/ml in plasma at the dosage intervals 12 hr have been shown in Table 3. The calculated dosage regimens of amikacin for C_p^{∞}min = 1.0 µg/ml were 3.96 ±0.17 mg/kg b.wt. (D*) and 3.57 ± 0.19 mg/kg b.wt. (D^0) and for C_p^{∞}min =2.0 µg/ml were 7.95 ± 0.36 mg/kg b.wt. (D*) and 7.15 ± 0.38 mg/kg b.wt. (D^0), respectively at 12 h dosage intervals (τ). These calculated doses at C_p^{o} min

(MIC) = 1.0 µg/ml, are lower than that for goats D* (7.4 mg/kg b.wt.) and D^0 (7.0 mg/kg b.wt.) at 8 h interval (Agrawal *et al.*, 2001) and in healthy cow calves was D* (13 mg/kg b.wt.) and D^0 (12 mg/kg b.wt.) at 12 h interval (Saini and Srivastava, 1998).

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