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Pharmacokinetics and optimal dosage of kanamycin in domestic ruminant species

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ABSTRACT

Pharmacokinetics and optimal dosage of kanamycin were investigated in domestic ruminant species. In indigenous female adult Nili/Ravi buffaloes, Sahiwal cattle, Lohi sheep and Teddy goats, values of elimination half-life ($t_{1/2\beta}$), volume of distribution (V_d) and total body clearance (Cl_B) have been found to be greater than most respective values in their foreign counterparts. Elimination half-life values in domestic ruminants correspond to their respective glomerular filtration rate (GFR) values: the higher the GFR, the shorter the half-life. Comparison of half-life values in domestic ruminants with corresponding total body clearance values showed that shorter half-life should not be equated with higher clearance. To maintain the minimum inhibitory concentration (MIC) of 2 μg/ml of plasma, an optimal dosage regimen of 10.9, 10.2, 12.7 and 15.4 mg/kg body mass for priming and 9.31, 7.79, 11.7 and 14.7 mg/kg body mass for maintenance to be repeated at 12 hour interval have been suggested in buffaloes, cattle, sheep and goats, respectively.

Key words: kanamycin, pharmacokinetics, dosage, domestic ruminants

Introduction

Kanamycin is an important member of the aminoglycoside antibiotics group and is being used mainly to combat gram-negative bacilli infections in the veterinary clinics of Pakistan. Several studies have shown that the

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pharmacokinetics, optimal dosage, renal clearance and urinary excretion of the investigated drugs were different under indigenous conditions when compared with the values given in the literature (NAWAZ, 1982; NAWAZ and SHAH, 1985; NAWAZ, 1994; JAVED et al., 1984; MUHAMMAD et al., 1999). In continuation of the studies, pharmacokinetics and optimal dosage of kanamycin were investigated in domestic ruminant species.

Materials and methods

For the study of pharmacokinetics of kanamycin, 32 experiments were conducted, 8 each in healthy female Nili/Ravi buffaloes, Sahiwal cattle, Lohi sheep and Teddy goats. All the ruminant animals were kept under similar environmental and management conditions at the Livestock Experimental Station, Bahadarnagar, Okara, Pakistan.

In all experiments, an intravenous cannula was placed in one of the jugular veins. Control blood samples were collected before drug administration. Kanamycin sulfate (Kanachron® injection 10%, Star Laboratories Ltd, Lahore, Pakistan.) was injected as a single dose (5 mg/kg body mass) through the opposite jugular vein. Blood samples were collected at 5, 10, 15 and 30 minutes and then at half hourly intervals until 3 hours. Thereafter, at an hourly interval up to 6 hours, followed by the samples collected at 8 and 10 hours post medication. The blood was collected in heparinized glass centrifuge tubes. After centrifugation, plasma was separated and stored at -20 °C until analysis. Concentration of kanamycin in plasma was determined by microbiological assay according to the disk agar diffusion method described by ARRET et al. (1971), using *Bacillus subtilis* as test organism.

In each animal, plasma kanamycin concentration time data were analyzed and pharmacokinetic parameters were calculated following the two-compartment open model by computer programme MW/PHARM Version 3.02 by F. Rombowt. Optimal dosage regimen for each ruminant species was calculated (BAGGOT, 1977).

Statistical analysis. The mean values and standard error of mean ± (SE) for each concentration and parameter were calculated. Analysis of variance (ANOVA) was performed with species as treatment. When a

significant F value was obtained, Duncan's Multiple Range Test (DMR) was used to determine which species was different from another.

Results

Pharmacokinetics. Mean values of plasma concentration at different time intervals in buffaloes, cattle, sheep and goats are given in Fig. 1, while mean ± SE results of pharmacokinetic parameters in eight animals of each species with inter-species statistical comparison are shown in Table 1.

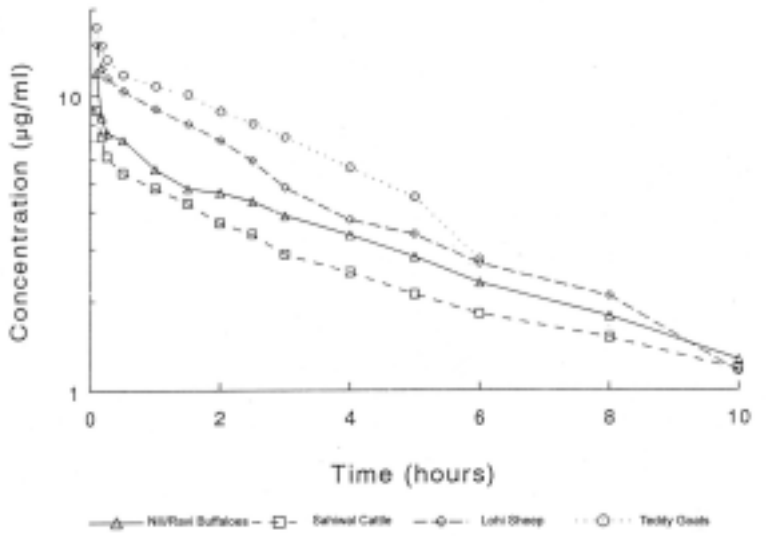

Fig. 1. Mean plasma concentration of kanamycin on a semilogarithmic scale versus time after a single intravenous dose (5 mg/kg) to ruminants (n = 8)

The mean ± SE value of $t_{1/2\beta}$ in sheep (3.42 ± 0.11 hours) and goats (2.81 ± 0.20 hours) were statistically equal but significantly (P>0.05) shorter than 4.35 ± 0.24 hours in buffaloes and 6.00 ± 0.50 hours in cattle.

Table 1. Mean ± SEM values for the disposition kinetics of kanamycin following intravenous administration of 5 mg/kg body mass in each of the 8 adult female Nili/ Ravi buffaloes, Sahiwal cattle, Lohi sheep and Teddy goats

Parameters	Units	Buffaloes (n = 8)	Cows (n = 8)	Sheep (n = 8)	Goats (n = 8)
C°_{p}	µg/ml	20.2 ± 3.75^{B}	12.9 ± 4.12^{B}	19.3 ± 1.90^{B}	33.6 ± 5.50^{A}
A	µg/ml	13.8 ± 3.78^{A}	8.82 ± 3.59^{A}	9.80 ± 1.65^{A}	19.1 ± 5.26^{A}
α	hr^{-1}	8.82 ± 1.99^{B}	5.10 ± 2.70^{B}	7.22 ± 2.46^{B}	17.8 ± 2.44^{A}
$t_{½\alpha}$	hr	0.13 ± 0.03^{B}	0.64 ± 0.19^{A}	0.32 ± 0.11^{B}	0.05 ± 0.01^{B}
B	µg/ml	6.40 ± 0.61^{C}	4.10 ± 0.62^{D}	9.46 ± 0.75^{B}	14.5 ± 0.55^{A}
β	hr^{-1}	0.16 ± 0.01^{C}	0.12 ± 0.01^{D}	0.21 ± 0.01^{B}	0.26 ± 0.02^{A}
$t_{1/2\beta}$	hr	4.35 ± 0.24^{B}	6.00 ± 0.50^{A}	3.42 ± 0.11^{C}	2.81 ± 0.20^{C}
K_{12}	hr^{-1}	5.59 ± 1.75^{A}	3.35 ± 2.14^{A}	3.76 ± 1.59^{A}	9.47 ± 2.36^{A}
K_{21}	hr^{-1}	2.88 ± 0.50^{B}	1.53 ± 0.58^{B}	3.29 ± 0.93^{B}	8.01 ± 0.43^{A}
K_{el}	hr^{-1}	0.52 ± 0.11^{A}	0.34 ± 0.10^{A}	0.39 ± 0.04^{A}	0.58 ± 0.10^{A}
V_c	1/kg	0.36 ± 0.09^{B}	0.60 ± 0.09^{A}	0.28 ± 0.02^{B}	0.18 ± 0.03^{B}
$V_{d\,area}$	1/kg	0.80 ± 0.07^{B}	1.21 ± 0.12^{A}	0.51 ± 0.04^{C}	0.34 ± 0.01^{C}
Cl_B	ml/min.kg	2.13 ± 0.14^{A}	2.37 ± 0.13^{A}	1.72 ± 0.08^{B}	1.47 ± 0.10^{B}

Values with different superscripts in each row indicate statistically significant difference ($P<0.05$)

C°_{p} = plasma drug concentration immediately following intravenous administration of single dose of a drug

A = extrapolated zero time plasma drug concentration of $\propto$ phase

B = extrapolated zero time plasma drug concentration of β phase

$\propto$ = distribution rate constant

t_{α} = distribution half-life

β = overall elimination rate constant

$t_{1/2_{\beta}}$ = biological or Elimination half-life

K_{12} = first order transfer rate constant for distribution between central and peripheral compartments

K_{21} = first order transfer rate constant for distribution between peripheral and central compartments

K_{el} = first order rate constant for elimination of a drug from central compartment.

V_c = apparent volume of central compartment

$V_{d\,area}$ = apparent volume of drug distribution calculated by area method

Cl_B = total body clearance

However, the longest half-life was recorded in cattle (6.00 ± 0.50 hours) and the shortest in goats (2.81 ± 0.20 hours). Mean values for the V_d were significantly ($P>0.05$) lower in buffaloes (0.80 ± 0.07 l/kg) than in cattle

Table 2. Intravenous dosage regimens of kanamycin (mg/kg) for different dosing intervals in adult female Nili/Ravi buffaloes, Sahiwal cattle, Lohi sheep and Teddy goats

Animal		Dosing interval (hours)														
		8					10					12				
		MIC (μg/ml)														
		1	1.5	2	3	4	1	1.5	2	3	4	1	1.5	2	3	4
Buffaloes	P	2.88	4.32	5.75	8.63	11.5	3.96	5.94	7.92	11.9	15.8	5.46	8.19	10.9	16.4	21.8
	M	2.08	3.12	4.15	6.23	8.31	3.16	4.74	6.32	9.49	12.6	4.66	7.00	9.31	13.9	18.6
Cattle	P	3.16	4.74	6.32	9.48	12.6	4.02	6.03	8.03	12.1	16.1	5.11	7.76	10.2	15.3	20.4
	M	1.95	2.93	3.90	5.85	7.80	2.81	4.22	5.61	8.42	11.2	3.89	5.85	7.79	11.7	15.6
Sheep	P	2.74	4.10	5.47	8.21	10.9	4.16	6.24	8.33	12.5	16.7	6.34	9.50	12.7	19.0	25.4
	M	2.23	3.34	4.45	6.68	8.91	3.65	5.48	7.31	10.9	14.6	5.83	8.75	11.7	17.5	23.3
Goats	P	2.72	4.08	5.44	8.16	10.9	4.58	6.87	9.16	13.7	18.3	7.69	11.6	15.4	23.1	30.8
	M	2.38	3.57	4.76	7.14	9.53	4.24	6.36	8.48	12.7	16.9	7.36	11.0	14.7	22.1	29.4

P = priming dose; M = maintenance dose

(1.21 ± 0.12 l/kg). Both these values were significantly ($P<0.05$) higher than the statistically equal values found in sheep (0.51 ± 0.04 l/kg) and in goats (0.34 ± 0.01 l/kg). The mean ± SE value of Cl_B 2.13 ± 0.14 ml/min. kg in buffaloes was statistically equal to the value 2.37 ± 0.13 ml/min. kg in cattle. These values were significantly ($P<0.05$) higher than those of statistically equal 1.72 ± 0.08 ml/min. kg in sheep and 1.47 ± 0.10 ml/min. kg in goats.

Dosage regimen. Based on pharmacokinetic data, the priming and maintenance doses of kanamycin in each species for 8, 10 and 12 hours dosing intervals taking MIC of kanamycin in blood as 1, 1.5, 2, 3 and 4 μg/ml is shown in Table 2.

Values with different superscripts in each row indicate a statistically significant difference ($P<0.05$)

Discussion

Pharmacokinetics. Species difference among ruminants indicated that after a single intravenous 5mg/kg administration, the highest plasma kanamycin concentration was observed in goats, intermediate in sheep and buffaloes and the lowest in cattle (Fig. 1). Such differences in plasma concentration among animals of different species after an intravenous injection of an equal dose of the same kanamycin preparation are due to

species-dependent variations in biodisposition of kanamycin in these animals.

The values of $t_{1/2\beta}$, V_d and Cl_B investigated in present study were found to be higher than the most respective values of kanamycin and other aminoglycosides reported in the literature (Table 3). Aminoglycosides are mainly excreted through glomerular filtration (PRESCOTT and BAGGOT, 1988). HASAN (1998) reported lower GFR in indigenous domestic ruminants as compared to their foreign counterparts; in female buffaloes 0.77 ml/min. kg, in cattle 0.49 ml/min. kg, in sheep 0.81 ml/min. kg and in goats 0.98 ml/min. kg. In the present study, longer values for elimination half-life in cattle, followed by intermediate values in buffaloes and sheep and shorter values in goats, correspond to the above mentioned lower values of GFR in cattle, intermediate in buffaloes and sheep and higher GFR in goats. This reflects that the higher the GFR, the lower is the half-life value. The lower GFR in indigenous domestic ruminant species appears to be responsible for longer half-life. Less than unity comparable values of V_d in buffaloes, sheep and goats were lower than the greater than unity values in cattle, which signified extensive tissue localization of kanamycin in cattle. The total body clearance of kanamycin expressed in ml/min. kg was minimum in goats, followed by medium values in sheep and buffaloes, and maximum in cattle, does not coincide with the 1.5-5 times lower GFR, as kanamycin was expected to be excreted mainly through filtration. This indicates an involvement of active tubular secretion and/or extra renal elimination of the drug in the ruminant species. Comparison of body clearance values with the respective half-life values (Table 1) evidenced that the higher clearance of a drug should not be equated with shorter half-life, since the clearance parameter comprises a volume as well as a rate component (BAGGOT, 1977).

Dosage regimen. In veterinary medicine 1-4 μg/ml plasma levels of kanamycin may be accepted as MIC (2 μg/ml as an optimal one) against the majority of the susceptible organisms (LEORY et al., 1976). During the course of therapy, plasma level of an antibiotic should not fall below a minimum inhibitory concentration at the end of a certain dosing interval (BAGGOT, 1977). The dose recommended by manufacturers of the pharmaceutical preparation of kanamycin (5 mg/kg/24 hours) failed to

maintain therapeutic concentrations for 24 hours in buffaloes, cattle, sheep and goats in the present study. BOOTH and MCDONALD (1988) recommended doses of 5-12 mg kanamycin/kg body mass at 12-hour intervals in cattle, sheep, dogs and pigs.

Table 3. Reported values of some pharmacokinetic parameters of aminoglycosides in domestic ruminants

Species	Aminoglycosides	Dose (mg/kg)	Route	$t_{1/2\beta}$ (hour)	V_d (L/kg)	Cl_B (ml/min. kg)	References
Buffaloes	Kanamycin	10	i. m.	2.21*	0.34*	1.78*	Fuhua et al. (1989)
	Streptomycin	10	i. m.	3.94*	0.38*	1.12*	Fuhua et al. (1989)
	Gentamycin	2	i. m.	2.24*	0.22*	1.13*	Fuhua et al. (1989)
Buffalo calves	Kanamycin	10	i. v.	1.94	0.20	1.55	Rampal et al. (1993)
	Kanamycin	5	i. v.	4.35	0.80	2.13	Present study
Cattle	Kanamycin	-	-	3.5	-	-	Ziv and Sulman (1974)
	Kanamycin	15	i. m.	2.81	0.18	0.79	Zuyin et al. (1989)
	Streptomycin	10	i. m.	4.07	0.21	0.61	Zuyin et al. (1989)
	Gentamycin	10	i. m.	3.17	0.13	0.51	Zuyin et al. (1989)
	Kanamycin	5	i. v.	6.0	1.21	2.37	Present study
Sheep	Kanamycin	10	i. v.	1.65	0.22	1.52	Baggot (1977)
	Kanamycin	10	i. v.	1.81	0.26	1.67	Lashev et al. (1992)
	Kanamycin	5	i. v.	3.42	0.51	1.72	Present study
Goats	Kanamycin	10	i. m.	2.16*	0.37*	1.97*	Jianyuan et al. (1989)
	Streptomycin	10	i. m.	4.81*	0.57*	1.37*	Jianyuan et al. (1989)
	Gentamycin	2	i. v.	2.32*	0.22*	1.07*	Jianyuan et al. (1989)
	Kanamycin	10	i. v.	1.95	0.26	1.50	Lashev et al. (1992)
	Kanamycin	5	i. v.	2.81	0.34	1.47	Present study

i. m. = intramuscular; i. v. = intravenous * = calculated from data

Based on 2 µg/ml MIC plasma level of kanamycin, the pharmacokinetic data of present study demonstrate that the optimal dosage regimen for a 12-hour dosing interval in adult buffaloes, cows, sheep and goats should be:

1. In buffaloes, priming dose 10.9 mg/kg body mass, and maintenance 9.31 mg/kg.
2. In cattle priming and maintenance dose, 10.2 mg/kg body mass and 7.79 mg/kg, respectively.
3. Priming dose 12.7 mg/kg body mass in sheep, and maintenance 11.7 mg/kg.

4. For goats priming dose 15.4 mg/kg body mass, maintenance dose 14.7 mg/kg.

This suggests that an optimal dosage regimen should be based on the pharmacokinetic data determined in the species, and the environment in which a drug is to be employed clinically.

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SAŽETAK

Istražena je farmakokinetika i optimalno doziranje kanamicina u domaćih preživača. Poluvrijeme eliminacije lijeka iz plazme ($t_{1/2\hat{a}}$), prividni volumen raspodjele (V_d) i ukupni klirens lijeka iz organizma (Cl_B) bio je veći u odraslih ženki bivola Nili/Ravi, goveda Sahiwal, ovaca Lohi i koza Teddy od odgovarajućih vrijednosti drugih autora. Vrijednosti poluvremena eliminacije lijeka u domaćih preživača odgovarale su vrijednostima stupnja glomerularne filtracije. Što je bio veći stupanj glomerularne filtracije to je bilo kraće poluvrijeme izlučivanja. Usporedba vrijednosti poluvremena izlučivanja s odgovarajućim ukupnim klirensom pokazala je da kraće poluvrijeme izlučivanja ne bi trebalo izjednačiti s većim klirensom. Za održavanje minimalne inhibicijske koncentracije od 2 μg/ml plazme kao optimalna početna doza preporučuje se za bivola 10,9 mg/kg, za govedo 10,2 mg/kg, za ovcu 12,7 mg/kg te za kozu 15,4 mg/kg tjelesne mase. Za održavanje koncentracije lijeka preporučuje se ponovno davanje u razmaku od 12 sati za bivola 9,31 mg/kg, za govedo 7,79 mg/kg, za ovcu 11,7 mg/kg te za kozu 14,7 mg/kg tjelesne mase.

Ključne riječi: kanamicin, farmakokinetika, doziranje, domaći preživači