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Studies on Biodisposition Kinetics and Urinary Excretion of Kanamycin in Goats

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Abstract: The biodisposition kinetics and urinary excretion of kanamycin was investigated in eight normal adult female goats of beetle breed after intravenous dose of 5 mg/kg to each goat. After single intravenous administration of kanamycin in goats, the distribution half-life and biological half-life had average of 8.1 ± 0.893 min and 2.87 ± 0.12 hrs and ranged between 4.28 to 11.61 minutes and 2.44 to 3.37 hrs respectively. The apparent volume of distribution of kanamycin in goat calculated by area method was 584.6 ± 34.21 ml/kg. The rate constants for Lanamycin transfer across compartment 1 to 2, K_{12} and 2 to 1, K_{21} were 1.846 ± 0.316 hr⁻¹ and 3.800 ± 0.434 hr and ranged between 1.016 to 3.713 hr⁻¹ and 2.45 to 5.77 hr⁻¹, respectively. Total body clearance of kanamycin calculated on per kg basis ranged 1.79 to 3.59 ml/min/kg with an average value 2.389 ± 0.194 ml/min/kg, Cumulative urinary excretion as percent of total dose excreted at 12 hours was 10.266 ± 1.233 . The studies showed variation in pharmacokinetic behaviour of kanamycin in indigenous goats as compared to earlier studies.

Key Words: Drug metabolism, kanamycin, pharmacokinetics, urinary excretion

Introduction

The feasibility of using antibacterial substance *in vivo* as chemotherapeutic agents is dependent primarily upon the specificity of such substances. Serious toxicity is the major limitation to the usefulness of the aminoglycosides and the same spectrum of toxicity is shared by all members of the group. Kanamycin has the potential to produce reversible and irreversible vestibular, cochlear and renal toxicity and nephrotoxicity. However kanamycin is ten times less toxic than neomycin (Treppenhauer, 1973). Due to its effectiveness, kanamycin is used most often for the therapy of infections due to gram negative microorganisms such as *Klebsiella*, *Enterobacter*, *Proteus*, *E. coli*/etc.

The validity and utility of bioavailability measurement of drug depends upon its pharmacokinetics behaviour in the body. Pharmacokinetics of kanamycin has been discussed previously in ruminants (George *et al.*, 1986; Rule *et al.*, 1988; Lashev *et al.*, 1992) and in non-ruminants (Fox and Russell, 1987; Feodorov *et al.*, 1987; Firth *et al.*, 1988; Gast and Stephens, 1988). Depending on the ionization constant of drugs, the biodisposition is determined in different body fluid compartments by the value of pH. Studies have shown that amongst geometrical factors affecting biodisposition and fate of drugs, pH is an important parameter which differs amongst local and foreign species (Nawaz and Shah, 1985; Nawaz *et al.*, 1988). Besides, the other factors which can affect biodisposition and fate of drugs under indigenous conditions include blood protein, drug metabolism and excretion. Due to these differences, it is important that imported drugs be evaluated under local environment. In view of the geometrical variations and importance of kanamycin as broad spectrum antibiotic, the kinetics of kanamycin was determined in goats and reported in this paper.

Materials and Methods

Eight healthy female goats of beetle breed were randomly selected and maintained under similar conditions of management. Mean body weight of each animal was 49.25 kg (SD ± 1.63). Animals were cannulated at Juglar vein on neck region using plastic cannula. For urine collection, a balloon catheter (Foley No. 18, 30 ml) was aseptically inserted through urethra into urinary bladder of goats.

Each animal was given single intravenous dose of 5 mg kanamycin/kg body weight. The blood samples were collected in heparinized glass tubes at 5, 10, 15, 30, 60, 90, 120, 150, 180 minutes and then at 4, 5, 6, 8, 10 and 12 hours after the administration. Blood pH was determined through pH meter at 37°C. Blood samples were centrifuged at 3000 rpm for 15 minutes and stored at -20°C until analyses. Urine samples were collected upto 120 minutes at the interval of 30 minutes and then at 4, 6, 8, 10 and 12 hours after drug administration and stored at -20°C until further analysis.

Kanamycin concentration in plasma and urine was determined by microbiological assay according to disk agar diffusion method (Arret *et al.*, 1971) using *Bacillus subtilis* as test organism. Discs were impregnated with standard or sample solution (0.1 ml) and placed on nutrient agar petri dishes containing 0.1% spore suspension of the test organism. After incubation at 37°C for 14 hours, zones of inhibition due to Kanamycin activity were measured in diameter with the help of vernier caliper. Kanamycin concentration in samples was determined by comparing the zones of inhibition of samples with standards.

Results and Discussion

Plasma concentration and Pharmacokinetics: Peak plasma kanamycin concentration (11.15 ± 0.669 µg/ml) was found after 0.083 hour injection. The concentration decreased with time and reached to 2.013 ± 0.128 µg/ml after six hours injection. No Kanamycin was detected eight hours after injection of the drug. Mean plasma concentration of Kanamycin was plotted against time (Fig. 1). Plasma concentration-time data were used to determine the various pharmacokinetic parameters using two compartment open model (Baggot, 1977) as opposed to non-compartmental model (Gibaldi, 1984). The non-compartmental model was considered unsuitable because monoexponential equation showed a poor correlation coefficient. Two compartment model was also used in previous studies in dogs, sheep and horses (Baggot, 1977) and in sheep, goats, rabbits, chickens and pigeons (Lashev *et al.*, 1992).

The disposition curve showed a biexponential fall (Fig. 1). The initial steep decline in plasma drug concentration may be due mainly to distribution of the drug from the central to the

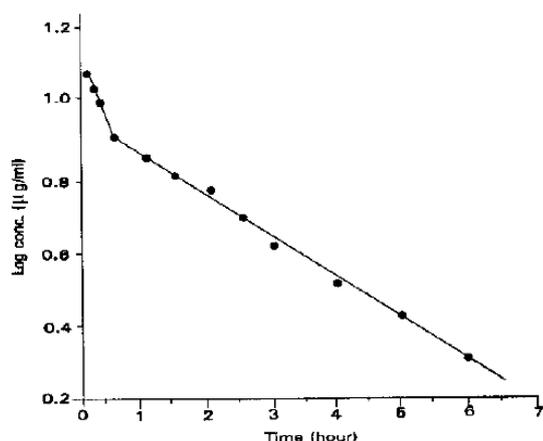


Fig. 1: Average Plasma conc. of Kanamycin against time after single 1/v injection

peripheral compartment. Once apparent distribution equilibrium is established, the rate of decline in plasma drug concentration is reduced and determined mainly by irreversible elimination of drug from the central compartment (β or elimination phase). Biexponential expression for two compartment model follows following relationship:

$$CP = Ae^{-\alpha t} + Be^{-\beta t}$$

where A and B are intercept terms with dimensions of concentration ($\mu\text{g/ml}$), α and β are distribution and elimination rate constants respectively (expressed in units of reciprocal time) and e represents the base of natural logarithm.

The pharmacokinetic parameters determined under two compartment open model are presented in Table 1.

Table 1: Disposition kinetic parameters of kanamycin after intravenous administration of single dose (5 mg/kg)

Parameter	Mean \pm SEM
t ₂ α min ⁻¹	8.1 \pm 0.893
t ₂ β hr ⁻¹	2.87 \pm 0.121
Vd ml/kg	584.6 \pm 34.21
K ₁₂ h ⁻¹	1.846 \pm 0.316
K ₂₁ h ⁻¹	3.80 \pm 0.0434
ClB ml/kg/min	2.389 \pm 0.194

The distribution half-life ($t_{\alpha/2}$) of kanamycin after intravenous administration in eight adult goats ranged between 4.26 to 11.4 minutes with an average of 8.1 \pm 0.893 minutes. The

value is comparable to the one in dogs (4.09 minutes), sheep (5.09 min) and horse (5.42 min) as shown by Baggot (1977). From these observations it may be concluded that $t_{\alpha/2}$ of kanamycin is similar in the indigenous goat.

The biological half life ($t_{\beta/2}$) represents the elimination of the drug from the body; shorter half-life showing rapid elimination. ten was found to be 2.872 \pm 0.121 horse in the present study, longer than reported in literature. In man, it was found to be 2.00 hours (Kirby *et al.*, 1976) and 1.5 hours (Yamasaku *et al.*, 1986). The half-life of Kanamycin after i/m administration in horse was reported to be 1.8 \pm 0.24 (Baggot *et al.*, 1981). The difference observed seems to be due to physiological variation in different species. Kanamycin is mainly eliminated from the body through urinary excretion. Shorter half-life reported in dog and human beings seems to be due to acidic urine pH in these species. On the other hand, longer half-life of Kanamycin in goat is in line with lower GFR in the local goat (Akhtar, 1987).

Apparent volume of distribution (Vd) of Kanamycin was found to be 584.6 \pm 34.2 ml/kg. It was obtained by the terminal exponential phase of drug decline in plasma after intravenous injection of known amount of drug. The values in present study are higher than reported earlier by Baggot (1977) in sheep (217 mg/kg), dog (225 ml/kg) and horse (174 ml/kg). The difference may be due to extent of protein binding of Kanamycin in different species.

The rate constant for the Kanamycin transfer across central compartment (1) to peripheral compartment (2). K_{12} ranged between 1.16 to 3.78 per hour (1.846 \pm 0.3168). K_{21} rate of transfer of kanamycin from peripheral compartment to central compartment was found to be 3.82 \pm 0.434 and ranged between 0.3032 to 0.4684 hr⁻¹. Drug elimination takes place from central compartment. Keeping in view the rapid distribution of drug, establishment of equilibrium and homogenous distribution between central and tissue compartments, the rate of transfer from compartment 1 to 2 is lower than from compartment 2 to 1. It also indicates the restriction of drug to central compartment.

Total body clearance is the product of the apparent volume of distribution and overall elimination rate constant. The total body clearance of kanamycin was calculated on per kg basis and ranged between 1.79 to 3.59 ml/min/kg with average of 2.389 \pm 0.194 ml/min/kg. Total body clearance may be varied due to species variation and due to different environments conditions. Baggot (1978) reported this value to be 3.21 \pm 0.72 ml/min/kg in beagles. Much higher values (108.9 ml/min/kg.) are reported for man (Yamasaku *et al.*, 1986).

Urinary Excretion: For determination of urinary excretion of Kanamycin, urine samples were collected at different time intervals after intravenous injection of 5 mg/kg dose.

Table 2: Urinary dose excretion following administration of kanamycin (5 mg/kg)

Kanamycin excretion	Time in Hours									
	0.75	1.25	1.75	2.25	2.75	4.00	6.00	8.00	10.00	12.00
Total excretion (mg)	2.676 \pm 0.335	2.254 \pm 0.349	2.282 \pm 0.376	1.939 \pm 0.249	2.197 \pm 0.456	2.891 \pm 0.686	4.693 \pm 0.769	2.889 \pm 0.467	2.186 \pm 0.494	1.258 \pm 0.289
Cummulative excretion (mg)	2.687 \pm 0.335	4.930 \pm 0.640	7.213 \pm 0.837	9.153 \pm 0.893	11.35 \pm 1.080	14.243 \pm 1.711	18.936 \pm 2.413	21.826 \pm 2.733	24.012 \pm 3.089	25.271 \pm 3.267
Total excretion (%)	1.072 \pm 0.116	0.892 \pm 0.119	0.923 \pm 0.148	0.795 \pm 0.112	0.916 \pm 0.218	0.166 \pm 0.262	0.905 \pm 0.308	1.177 \pm 0.191	0.881 \pm 0.193	0.536 \pm 0.107
Cummulative excretion (%)	1.072 \pm 0.116	1.964 \pm 0.212	2.888 \pm 0.256	3.683 \pm 0.277	4.599 \pm 0.398	5.766 \pm 0.634	7.671 \pm 0.916	8.848 \pm 1.050	9.729 \pm 1.180	10.266 \pm 1.233

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Concentration of Kanamycin was determined by microbiological assay. Kanamycin excretion increased with time upto six hours and then decreased (Table 2). Cumulative excretion being 25.271 ± 3.267 mg. Table 2 also shows kanamycin excretion as percent of dose excreted. Cumulative urinary excretion as percent of dose excreted was found to be $10.266 \pm 1.233\%$ after 12 hrs. of Kanamycin administration. This is in contradiction with that of Yamasaku *et al.* (1986) who showed that 74-94% of dose was excreted in urine of volunteers after 8 hours. This contradiction may be due to chemical nature of Kanamycin.

Present study revealed considerable variation in the pharmacokinetic behaviour of Kanamycin in indigenous goats as compared to similar studies conducted under different environmental conditions and reported in literature. These differences in biodisposition of kanamycin may be attributable to the specific biochemical and physiological characters of indigenous goats.

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