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DISPOSITION KINETICS AND DOSAGE OF KANAMYCIN IN BUFFALO HEIFERS

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ABSTRACT

Kanamycin is an extensively used antibiotic in veterinary practice. Therefore, its disposition kinetics and dosage were investigated in healthy buffalo heifers following a single intramuscular dose of 5 mg/kg body weight. The blood samples collected at proposed time intervals were analyzed for kanamycin concentration by a microbiological assay. Two-compartment model kinetic analysis revealed that the elimination half life ($t_{½}$ ß) was 4.58 ± 0.75 hours (Mean ± SD). The mean ± SD value of apparent volume of distribution (Vd) was 0.63 ± 0.10 L/kg. Total body clearance (TBC) was 1.67 ± 0.16 ml/min. kg (Mean ± SD). To maintain minimum inhibitory concentration (MIC) of 1.5 µg/ml, the optimum priming and maintenance doses of 6.45 and 5.50 mg/kg body weight, respectively, to be repeated with the dosing interval of 12 hours have been suggested.

INTRODUCTION

The pharmacokinetic behaviour of drugs is affected by genetics and environment indicating the need for describing disposition kinetics and dosage of various drugs under indigenous conditions (Nawaz *et al.*, 1988 Nawaz, 1994). In above cited studies the differences have been shown in pH of blood and urine, plasma protein binding, kidney functions, biotransformation and overall elimination of drugs in local versus foreign species of animals. In continuation of these studies the disposition kinetics and dosage of kanamycin were investigated in buffalo heifers.

MATERIALS AND METHODS

Experiments were conducted in six healthy Nili-Ravi buffalo heifers during the month of April, 1998. The average body weight of heifers was 222 kg. Animals were maintained under similar environmental and managemental conditions. In all animals one of the jugular veins was cannulated for the collection of blood samples. Prior to drug administration, a control blood sample was collected. Each animal was given a single intramuscular dose of kanamycin (Kanafer Batch No. 6960, Prix Pharmaceutica (Pvt.) Ltd., Lahore) at the dose rate of 5 mg/kg body weight in neck muscles. Blood samples were collected in sterilized heparinized centrifuge tubes at 15, 30, 45, 60 minutes and then half hourly intervals until 3 hours. Thereafter, at hourly intervals upto 6 hours followed by the samples collected at 8 hours post medication. Blood samples were centrifuged and plasma was separated and stored at -20 ^{0}C until analysis.

The plasma concentration of kanamycin was measured by microbiological assay according to disk agar diffusion method described by (Arret *et al.*, 1971) by using *Bacillus subtilus* as a test organism. The plasma kanamycin versus time data was analyzed separately for each animal and the disposition kinetic parameters were determined by two compartment model analysis (Baggot, 1977).

RESULTS AND DISCUSSION

The average ± SD values for the plasma kanamycin concentration against time in 6 buffalo heifers have been shown in Fig. 1. The plasma concentration of kanamycin when plotted on a semilogarithmic scale against time after I/M injection exhibitd a two compartment open model. The average ± SD values of the disposition kinetic parameters are presented in Table 1. It is seen that the distribution half life ($t_{½}$ α) was only 0.42 hour (25.2 minutes) in buffalo heifers which is longer than 4.09 minutes in dogs, 5.39 minutes in sheep and 5.42 minutes in horses (Baggot, 1977) and similar to 0.5 hour in cows (Ghaffar *et al.*, 1996). The elimination half life ($t_{½}$ ß) of kanamycin in this study was 4.58 hours which is longer than 1.65 hours in sheep, 1.4 hours in horses and 0.74 hour in dogs (Baggot, 1977). The half life of kanamycin in buffalo heifers is longer than 2.36 hours in buffaloes

(Fuhua *et al.*, 1989), 1.94 hours in buffalo calves (Rampal *et al.*, 1993), 2.81 hours in cows (Zuyin *et al.*, 1989), 1.81 hours in sheep and 1.95 hours in goats (Lashev *et al.*, 1992). Kanamycin is mainly excreted through glomerular filteration. Lower glomerular filteration rate (GFR) have been reported in local ruminants as compared to their foreign counterparts (Hassan, 1998). Therefore, lower GFR in local buffalo heifers may be responsible for longer half life. The shorter half life reported in dogs seems to be due to rapid urinary excretion of organic base kanamycin in acidic urine of dogs.

Table 1: Average ± SD values for the disposition kinetic parameters of kanamycin following a single intramuscular injection of 5 mg/kg body weight in 6 buffalo heifers.

Kinetic parameters	Units	Average ± SD
A	µg/ml	15.32 ± 4.72
B	µg/ml	3.63 ± 1.13
Cmax	µg/ml	9.94 ± 1.59
α	$hour^{-1}$	1.75 ± 0.51
ß	$hour^{-1}$	0.16 ± 0.23
$t_{1/2}\alpha$	hour	0.42 ± 0.09
$t_{1/2}ß$	hour	4.58 ± 0.75
K_{el}	$hour^{-1}$	0.42 ± 0.07
K12	$hour^{-1}$	0.79 ± 0.21
K21	$hour^{-1}$	0.69 ± 0.36
Vc	L/kg	0.24 ± 0.05
Vd(area)	L/kg	0.63 ± 0.10
Vd(ss)	L/kg	0.50 ± 0.09
TBC	ml/min.kg	1.67 ± 0.16

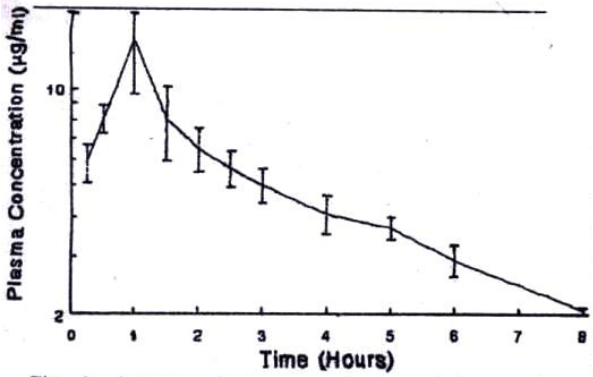

Fig. 1: Average plasma concentration of kanamycin following a single intramuscular dose of 5 mg/kg body weight to buffalo heifers.

The apparent volume of distribution (Vd) calculated by area method and the steady state volume of distribution revealed values of 0.63 and 0.50 L/kg, respectively, which are closer to each other and indicate the restriction of drug to the central compartment. The value of Vd in present investigation is higher as compared to values 0.17 L/kg in horses, 0.22 L/kg in sheep, 0.23 L/kg in dogs (Baggot, 1977), 0.2 L/kg in buffalo calves (Rampal *et al.*, 1993), 0.18 L/kg in cows (Zuyin *et al.*, 1989), 0.26 L/kg in sheep and 0.26 L/kg in goats (Lashev *et al.*, 1992).

Total body clearance (TBC) is the sum of all processes which contribute towards the elimination of drug from the body and is the volume of blood completely cleared of a drug per unit time. The total body clearance of kanamycin in buffalo heifers was 1.67 ± 0.16 ml/min. kg. This value is similar to that reported in sheep 1.52 and 1.43 ml/min.kg in horse (Baggot, 1977), 1.55 ml/min.kg in buffalo calves (Rampal *et al.*, 1993), 1.5 ml/min. kg in goats (Lashev *et al.*, 1992) and 1.48 ml/min.kg in horse (Baggot *et. al.*, 1981).

Based on the kinetic behaviour of kanamycin in present study, its dosage regimen has been calculated on viewing the differences in the disposition kinetics parameters amongst different species. There is wide variation in the accepted values of kanamycin MIC for different microbial infections. However, the lowest value of (MIC) has been reported 1.5 µg/ml for the most sensitive organisms (Ghafar *et al.*, 1996). The apparent volume of distribution is necessory for computing priming and maintenance doses. When a fixed amount of drug is administered at a constant dosage interval, a steady state will be established eventually in which the plasma concentration time curve will be the same during the successive dosage intervals (Wagner and Northam, 1967). The maintenance dose is calculated by the following relationship.

$$D = Cp(min)\ V'd(e^{ßt}-1)$$

Where Cp(min) is the minimum inhibitory concentration, Vd is the apparent volume of distribution, ß is the elimination rate constant and t is the dosage interval. The Priming dose is obtained by omitting -1 from the above equation. Considering 12 hours a convenient and suitable dosage interval, with an adequate MIC or Cp(min) 1.5 µg/ml and using the values of V'd and ß from Table 1, the priming and maintenance doses are calculated as 6.45 and 5.50 mg/kg/12 hours. This is in accordance with the recommended doses of 5-12 mg kanamycin/kg body weight at 12 hours intervals in cattle, sheep, dogs and pigs (Booth and McDonald, 1988). The dose 5 mg/kg body weight/24 hours recommended by the

manufacturers failed to maintain the MIC of 1.5 µg/ml at the end of dosing interval. The suggested dosage interval of 12 hours has been strongly supported by the veterinary practitioners in order to get the desired therapeutic response.

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