DISPOSITION KINETICS AND DOSAGE REGIMEN OF INTRAVENOUSLY INJECTED KANAMYCIN IN BUFFALOES

T. Saeed, R. Ahmad, M. Nawaz[1] and T. Iqbal
Department of Chemistry, University of Agriculture, Faisalabad
[1]Department of Physiology and Pharmacology, University of Agriculture, Faisalabad-38040

ABSTRACT

Genetical variations in the local population apprise of the need for describing biodisposition and fate of drug in indigenous species and environments. Kanamycin is one of the extensively used antibiotics in veterinary clinics. Its disposition kinetics was investigated in local female buffaloes following intravenous dose of 5 mg/Kg body weight. The blood samples collected at different time intervals were analyzed for kanamycin concentration by a microbiological assay. Two compartment model kinetics analysis of plasma kanamycin concentration versus time data revealed its rapid distribution and elimination with half life (t ½) 5.42±0.39 hours (Mean ± SE). Total body clearance of Kanamycin in buffaloes were 2.59±0.17 ml/min./Kg body weight. To maintain the minimum inhibitory concentration (MIC) of 2 µg/ml of plasma, optimal dosage regimen of 11.8 mg/kg body weight for primary and 9.4 mg/kg body weight for maintenance to be repeated after 12 hours interval has been suggested in buffaloes.

Keywords: Disposition kinetics,kahamycin, dosage regimen, buffaloes, optimal dosage regimen

INTRODUCTION

The environmental influences on the genetics, manifested through characteristic biochemical and physiological parameters ultimately affecting biodisposition and fate of drugs in a population have been explained by an original term Geonetic (Nawaz *et al.*, 1988). Such geonetical influences have been reported for blood and urine pH, haemochemisry, drug metabolism and kidney function in ruminants (Nawaz, 1994).

Kanamycin is a valuable member of amino glycosides antibiotics. It is extensively used in veterinary clinics to treat sensitive infections. Several studies have shown that biodisposition kinetics, renal clearance and urinary excretion of investigated drugs were different under indigenous conditions when compared with the values given in the literature (Nawaz, 1982; Nawaz and Shah, 1984; Muhammad, 1997). In continuation of these studies, disposition kinetics of kanamycin was investigated in buffaloes.

MATERIALS AND METHODS

Experiments were performed on 7 healthy Nili Ravi buffaloes during summer season at Livestock Production Research Institute (LPRI) Bahadarnagar, Okara. Animals were kept under similar environmental managemental conditions. The average body weight of the buffaloes was 600 kg ranging from 550 to 700 kg. In each experiment an intravenous canula was placed in one of the jugular veins. Control blood samples were collected before the drug administration. Each animal was given a single intravenous dose of kanamycin (Kanachron ® 10% Star Laboratories Ltd.) at dosage rate of 5mg kg-1 body weight. Blood samples were collected in sterilized, heparinized centrifuge tubes at 5, 10 and 30 minutes and then half an hour interval until 3 hours. Thereafter, at hourly interval upto six hours followed by samples collected at 8 and 10 hours post medication. Plasma was separated after centrifugation and kept at –20°C until analysis. Concentration of kanamycin in plasma was determined by a microbiological assay according to the disc agar diffusion method described by Arret *et al.* (1971) using Bacillussubtilis as test organism. In each animal plasma kanamycin concentration time data were analyzed and disposition kinetic parameters were calculated following two compartment open model by a computer program MW/PHARM version 3.02 by Rombowt, optimal dosage regimen for buffaloes was calculated (Baggot, 1977).

RESULTS AND DISCUSSION

Disposition kinetics

Mean ± SE values of kanamycin plasma concentration at different intervals following intravenous injection in 7 buffaloes are given Fig. 1 while mean ± SE results of pharmacokinetics parameters are shown in Table 1.

The elimination half life t ½ (5.42 hours) of buffaloes of present studies was longer than reported values; 2.21 hours in buffaloes (Fuhua *et al.*, 1989), 1.94 hours in buffaloes calves (Rampal *et al.*, 1993), 2.8 hours in cows (Zuyin *et al.*, 1989), 1.81 hours in sheep (Lashev *et al.*, 1992) and 2.16 hours in goats (Jianyuan *et al.*, 1989). Since the glomerular filtration is the principal excretion mechanism for kanamycin (Baggot, 1977), the lower glomerular filtration rate of local ruminants in comparison to their foreign counter parts (Akhtar, 1977; Hassan, 1998) may be attributed to the lower elimination and longer half life.

Table 1: Mean ± SE values for the disposition kinetic parameters of kanamycin following a single interavenous injection of 5 mg/kg body weight in 7 buffaloes.

Kinetic parameter	Unit	Mean ± SE
C°P	µg/ml	7.41 ± 0.25
A	µg/ml	3.86 ± 0.42
B	µg/ml	3.55 ± 0.49
A	Hr^{-1}	0.898 ± 0.247
ß	hr^{-1}	0.132 ± 0.01
t ½ a	hr	1.16 ± 0.26
t ½ ß	hr	5.42 ± 0.39
K el	hr^{-1}	0.23 ± 0.014
K_{12}	hr^{-1}	0.304 ± 0.133
K_{21}	hr^{-1}	0.492 ± 0.136
Vd	L/Kg	1.21 ± 0.20
Vc	L/Kg	0.68 ± 0.02
TBC	ml/min.kg	2.59 ± 0.17

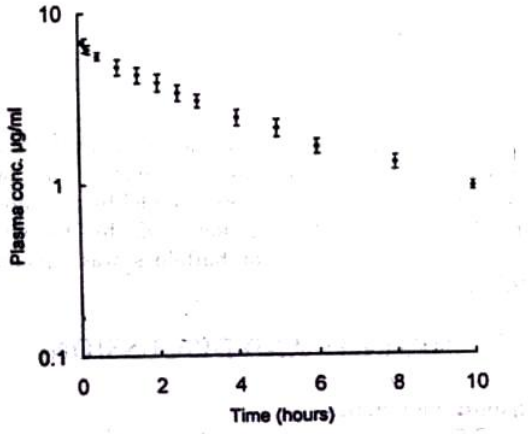

Fig. 1: Mean ± SE plasma concentration of kanamycin against time after a single i.v. injection of kanamycin (5 mg/kg body weight) in buffaloes.

Apparent volume of distribution (Vd) relates drug concentration in plasma to the total amount of the drug in the body after distribution equilibrium has been attained. The value of Vd in buffalo (1.21 L/Kg) in agreement with that investigated in local cows, 1.28 L/Kg (Ghaffar *et al.*, 1996) indicated an excellent penetration of the drug in the tissues of local buffaloes and cows. However, Fahua *et al.* (1989) reported lower Vd of 0.34 L/Kg in buffaloes. Further lower values than that of local buffaloes have been reported in buffalo calves (0.01 L/Kg) Rampal *et al.* (1993), in mules (0.64 L/Kg) Muhammad (1997), in horses (2.23 L/Kg), Baggot *et al.* (1981) and rabbits (2.25 L/Kg) Lashev *et al.* (1992). Besides inter and intra species biological variation, a possible explanation for the higher values of Vd in present study may be linked to the lower extrapolated zero time drug concentration (B) as compared to its high values in above cited studies. Earlier investigations of sulphadimidine in sheep have shown that 29.6% increase in zero time drug concentration was primarily responsible for 24.5 lower Vd in summer than in winter (Nawaz and Nawaz, 1983). Total body clearance (TBC) represent sum of metabolic and excretory processes and is the volume of blood cleared of a drug in a unit time. The mean value of TBC was 2.59 ml/min./kg. A similar value of TBC 2.50 ml/min./kg has been reported in cows by Ghaffar *et al.* (1996). However, lower values of TBC were investigated in buffaloes 1.7 ml/min./kg. Fahua *et al.* (1989), in sheep 1.52 ml/min./kg (Baggot, 1977) and in goats 1.50 ml/min./kg (Lashev *et al.* 1992). Higher value of TBC in present study may be attributed to the higher value of Vd (1.21 L/Kg) as compared to the above referred studies 0.34 L/Kg in buffaloes, 0.22 L/Kg in sheep and 0.26 L/Kg in goats.

Dosage regimen

In veterinary medicine 1-4 µg/ml plasma level may be accepted as optimal MIC (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 the manufactures of the pharmaceutical preparation of kanamycin (5 mg/kg for 24 hours) failed to maintain the therapeutic concentration for 24 hours in buffaloes. Booth and McDonald (1988) recommended the dose of 5-12 mg kanamycin/kg body weight at 12 hours intervals in cattle, sheep, dogs and pigs.

Based on 2 µg/ml MIC plasma level of kanamycin, the pharmacokinetics data of present study demonstrates that the optimal dosage regimen for 12 hours dosing interval in adult buffaloes should be 11.8 mg/kg body weight as primary and 9.4 mg/kg as

maintenance. It depicts that an optimal dosage regimen should be based on the pharmacokinetics data determined in the species and environment in which a drug is to be employed clinically.

REFERENCES

Akhtar, P., 1987. Renal clearance of endogenous and exogenous substances in domestic ruminants during summer and winter seasons. Ph.D. Thesis, Dept. Physio. Pharma. Univ. Agri., Faisalabad.

Arret, B., D.P. Johnson and A.Kirshbaum, 1971. Outline of details for microbiological assay of antibiotics. 2nd Ed. J. Pharm. Sci., 60: 1689-1694.

Baggot, J.D., 1977. Principles of drug disposition in domestic animals. W.B. Saunders Co., Philadelphia.

Baggot, J.D., N.D. Love, J.R. Rose and R. Raus, 1981. The pharmacokinetics of some aminoglycosides antibiotics in the horses. J. Vet. Pharm. Therap., 4(4): 277-284.

Booth, N.H. and L.E. McDonald, 198. Veterinary pharamcology and Therapeutics, 6th Ed. Iowa State Univ. Press Ames, Iowa, pp: 829-830.

Fuhua, Z., X. Zhen and Z. Xinru, 1989. Pharmacokinetics studies of aminoglycosides antibiotics in buffaloes. In: K.F. Fung Ed. Pharmacokinetic stuides of antibiotics in animals. Academic Press China, pp: 26-29.

Ghffar, T., T.Iqbal and M. Nawaz, 1996. Disposition kinetics and dosage of kanamycin in cows. Pakistan Vet. J., 16(3): 122-124.

Hassan, I.J., 1998. Pharmacokinetics, renal clearance and urinary excretion of kanamycin in domestic ruminant species. Ph.D. Thesis, Dept. Physio. Pharma., Univ. Agri., Faisalabad.

Jianyuan, W., L. Qingyr, H. Wenjie, L. Fue, G. Tianji and S. pofanf, 1989. Pharmacokinetic studies of three aminoglycosides antibiotics in milk goats. In: K.F Fung Ed. Pharmacokinetic studies of Antibiotics in Animals, Academic Press China, pp: 35-39.

Lashev, L.D., D.A. Pashov and T.N. Marinkov, 1992. Interspecies differences in the pharmacokinetic of kanamycin and aparamycin. Vet. Res. Commun., 18(4): 293-300.

Muhammad, F., 1997. Disposition kinetics, renal clearance and urinary excretion of kanamycin in mules. M.Sc. Thesis, Dept. Physio. Pharma., Univ. Agri., Faisalabad.

Nawaz, M. and R. Nawaz, 1983. Pharmacokinetics and urinary excretion of sulphdimidine in sheep during summer and winter. Vet. Rec., 112(16): 379-381.

Nawaz, M. T. Iqbal and R. Nawaz, 1988. Geonetical considerations in disposition kinetics evaluation of chemotherapeutic agents. Vet. Pharmacol. Toxicol. & Therapy in Food Producing Animals. Vol. 2. Proc. 4th Europ. Assoc. Vet. Pharmacol. Therap., 28th August-2nd September, Budapest, pp: 260.

Nawaz, M., 1994. Factors affecting disposition kinetics of sulfadimidine in animals. Proc. 2nd Cong. Europ. Assoc. Vet. Pharmacol. Toxicol., 13-17 September. Toulouse, Pharmacologie and Toxicologie, Veterinaires INRA Publication, Paris, France, pp: 193-194.

Nawaz, M. and B.H. Shah, 1984. Renal clearance of endogenous creatinine and urea in sheep during summer and winter. Res. Vet. Sci., 36: 220-224.

Rampal, S.A., A.K. Srivastava and R.K. Chaudhary, 1993. Disposition kinetics, urinary excretion and dosage regimen of kanamycin in buffalo calves following single intravenous administration. Vet. Res. Commun., 17(3): 219-225.

Zuyin, Z., W. Shufen, X. Huixin, C. Weiren, W. Daju and H. Yongsheng, 1989. Pharmacokinetic studies of three aminoglycosides in cattle following intramuscular administration. In: K.F. Fung Ed. Pharamcokinetic Studies of Antibiotics in nimals, Adacemic Press China, pp: 30-34.