DISPOSITION KINETICS AND DOSAGE REGIMEN OF INTRAVENOUSLY INJECTED KANAMYCIN IN BUFFALOES

T. Saeed, R. Ahmad, M. Nawaz\textsuperscript{1} and T. Iqbal

\textit{Department of Chemistry, University of Agriculture, Faisalabad}

\textit{\textsuperscript{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\textsubscript{1/2}) 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, kanamycin, 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 Geometric (Nawaz et al., 1988). Such geometrical influences have been reported for blood and urine pH, haemochemistry, 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 managerial 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\textsuperscript{-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 up to 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 Bacillus subtilis 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 Rombout, 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 intravenous injection of 5 mg/kg body weight in 7 buffaloes.

<table>
<thead>
<tr>
<th>Kinetic parameter</th>
<th>Unit</th>
<th>Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>C ½P</td>
<td>µg/ml</td>
<td>7.41 ± 0.25</td>
</tr>
<tr>
<td>A</td>
<td>µg/ml</td>
<td>3.86 ± 0.42</td>
</tr>
<tr>
<td>B</td>
<td>µg/ml</td>
<td>3.55 ± 0.49</td>
</tr>
<tr>
<td>A</td>
<td>hr⁻¹</td>
<td>0.886 ± 0.247</td>
</tr>
<tr>
<td>B</td>
<td>hr⁻¹</td>
<td>0.132 ± 0.01</td>
</tr>
<tr>
<td>t ½ a</td>
<td>hr</td>
<td>1.16 ± 0.26</td>
</tr>
<tr>
<td>t ½ B</td>
<td>hr</td>
<td>5.42 ± 0.39</td>
</tr>
<tr>
<td>K1</td>
<td>hr⁻¹</td>
<td>0.23 ± 0.014</td>
</tr>
<tr>
<td>K12</td>
<td>hr⁻¹</td>
<td>0.304 ± 0.133</td>
</tr>
<tr>
<td>K21</td>
<td>hr⁻¹</td>
<td>0.492 ± 0.136</td>
</tr>
<tr>
<td>Vd</td>
<td>L/Kg</td>
<td>1.21 ± 0.20</td>
</tr>
<tr>
<td>Vc</td>
<td>L/Kg</td>
<td>0.68 ± 0.02</td>
</tr>
<tr>
<td>TBC</td>
<td>ml/min/kg</td>
<td>2.59 ± 0.17</td>
</tr>
</tbody>
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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, Fuhua 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. Fuhua 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.

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.

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


