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# Disposition kinetics of kanamycin in mules

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**ABSTRACT**

The disposition kinetics of kanamycin was investigated following an injection of a single intravenous dose 5 mg/kg body mass in healthy adult female mules. Blood samples collected at various time intervals post-medication were analyzed for kanamycin by microbiological assay. The plasma drug concentration versus time data was best fitted by a biexponential expression. Macro-kinetic parameters were computed for a two-compartment open model. Values for distribution half-life ($t_{1/2\hat{a}}$) and elimination half-life ($t_{1/2\,\beta}$) were 0.18 ± 0.26 and 4.39 ± 0.68 h, respectively. The apparent volume of distribution ($V_d$) was 0.64 ± 0.17 L/kg. Total body clearance ($Cl_B$) of the drug was 1.66 ± 0.22 ml/min.kg. Existing dosage of 5 mg/kg body mass at 24 h intervals does not maintain the desired minimum inhibitory concentration (MIC) at the end of proposed dosing intervals. Calculated optimal dosage regimen for kanamycin in mules was 8.73 and 7.45 mg/kg body mass for priming and maintenance, respectively, for a dosage interval of 12 h to maintain the concentration of 2 μg/ml in blood.

**Key words:** kanamycin, disposition kinetics, mule

## Introduction

Most developing countries are importing either raw active substance or finished drugs for human and veterinary use. Dosage regimens for these drugs are often based on studies carried out in foreign environments and species of animals. Generally speaking, in drug-importing countries

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environmental conditions and the genetic make-up of indigenous animals which affect the biodisposition and fate of drugs are different from their foreign counterparts. These differences are described by the original term "geonetics" (NAWAZ and SHAH, 1985; NAWAZ et al., 1988; NAWAZ, 1994). As a consequence of geonetical variations the optimal therapeutic usage of imported drugs should be determined in both the target species and their environments.

Kanamycin is an extensively used antibiotic for susceptible infections in animals. Mules are important draught animals. Therefore, the disposition kinetics of kanamycin was investigated in order to propose an optimal intravenous dosage regimen of the drug.

## Materials and methods

The disposition kinetics of kanamycin was investigated during the month of April in 8 healthy adult female mules maintained on a farm at Sargodha, Pakistan. Average body mass of the mules was 386 kg (range 375–410 kg). Animals were kept under similar management conditions. Prior to drug administration a control blood sample was drawn from the jugular vein and each animal was given kanamycin in a single intravenous dose of 5 mg/kg. b.m. (Kanachron® 10%, Batch No. VD 124, Star Laboratories, Lahore, Pakistan Ltd.). Blood samples were collected in heparinized centrifuge tubes at 5, 10, 15, 30, 60 minutes and then at 1.5, 2, 2.5, 3, 4, 6, 8, and 10 hours after drug administration. Blood samples were centrifuged at 500 × g for 10 minutes and plasma was separated and stored at freezing point until analysis.

Concentration of kanamycin in plasma was determined by microbiological assay (ARRET et al., 1971) using *Staphylococcus aureus* as a test organism. Standard curves of kanamycin 1, 2, 4, 6, 8 mg/ml in plasma and distilled water when plotted against the zone of inhibition revealed regression equation $y = 0.5395^{e0.2482}x$ and a value of $R^2 = 0.9754$. The plasma concentration versus time data was used to calculate several pharmacokinetics parameters using a PC program, MWPHARM version 3.02, a MEDIWARE product, Holland. This program calculates area under curve (AUC) from time t to a by polyexponential and trapezoidal rule

methods and the regression coefficient of best-fit to depict the compartmental analysis for pharmacokinetic parameters (BAGGOT, 1977). The pharmacokinetic parameters were used to calculate the optimal dosage regimen for kanamycin in mules.

**Results and discussion**

Plasma concentration of kanamycin versus time data plotted on a semilog scale depicted a biexponential decline (Fig. 1). This is similar to that noted in other species, such as the horse, dog and sheep (BAGGOT, 1978), sheep, goat, rabbit, chicken and pigeon (LASHEV et al., 1992) and cattle (GHAFFAR et al., 1996). Average ± SD values of the pharmacokinetic parameters calculated for a two compartment model are shown in Table 1.

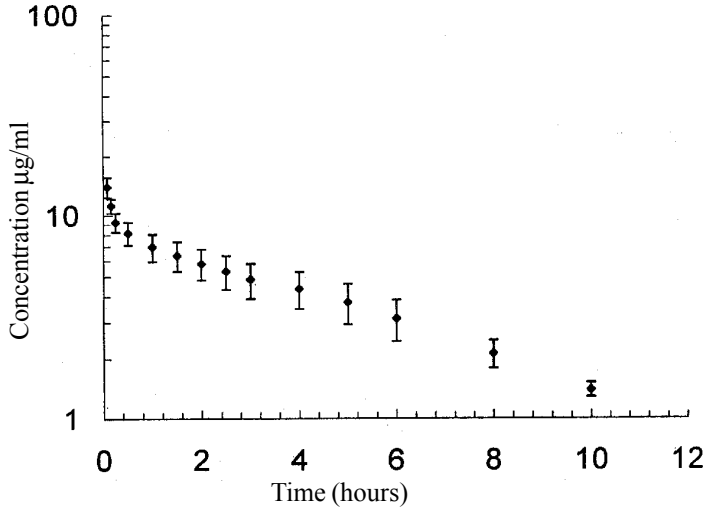


Fig. 1. Average plasma concentration (µg/ml) of kanamycin in mules against time after single (i/v) injection of 5 mg/kg body mass

The elimination half-life of kanamycin in mules of 4.39 hours was longer than the 1.4 hours in horse, 1.65 hrs in sheep, 0.74 hour in dog (BAGGOT, 1977); 1.8 hours in the horse (BAGGOT et al., 1981); 2.36 hours in buffaloes (FUHUA et al., 1989); 1.81 hours in sheep, and 1.95 hour in goats

(LASHEV et al., 1992). The apparent volume of distribution (Vd) calculated by the area method was 0.64 L/kg, which is higher than 0.17 L/kg in horse, 0.23 L/kg in dog and 0.22 L/kg in sheep (BAGGOT et al., 1977), and 0.23 L/kg in horse (BAGGOT et al., 1985). The difference was due to a lower value of "B", the extrapolated zero time plasma drug concentration of the elimination phase in mules. Total body clearance ($Cl_B$) of kanamycin in mules was 1.66 ml/min.kg, which is comparable with $Cl_B$ 1.43 ml/min.kg in the horse, 1.52 ml/min.kg in sheep (BAGGOT, 1977); 1.48 ml/min.kg in horse (BAGGOT et al., 1981), and 1.5 ml/min.kg in the dog (BAGGOT, 1977), and 1.67 ml/min.kg in buffalo heifers (MUHAMMAD et al., 1999).

Table 1. Pharmacokinetic parameters of kanamycin following a single intravenous injection of 5 mg/kg b. w. in 8 female mules

| Kinetic parameters | Units | Average ± SD |
|---|---|---|
| $C°_P$ | μg/ml | 22.1 ± 7.95 |
| A | μg/ml | 14.2 ± 6.65 |
| B | μg/ml | 7.91 ± 2.07 |
| α | $h^{-1}$ | 9.64 ± 5.98 |
| β | $h^{-1}$ | 0.16 ± 0.02 |
| $t_{1/2\alpha}$ | h | 0.18 ± 0.26 |
| $t_{1/2\beta}$ | h | 4.39 ± 0.68 |
| Ke1 | $h^{-1}$ | 0.76 ± 0.87 |
| $K_{12}$ | $h^{-1}$ | 5.83 ± 4.15 |
| $K_{21}$ | $h^{-1}$ | 3.49 ± 1.92 |
| Vc | L/kg | 0.25 ± 0.09 |
| $Vd_{(area)}$ | L/kg | 0.64 ± 0.17 |
| $Vd_{ss}$ | L/kg | 0.60 ± 0.13 |
| $Cl_B$ | m1/min.kg | 1.66 ± 0.22 |

Based on the pharmacokinetics of kanamycin, a dosage regimen was calculated considering 2 mg/ml as the optimum minimum inhibitory concentration (MIC) for most equine pathogens (BAGGOT et al., 1985). Priming and maintenance doses were calculated as 8.73 and 7.45 mg/kg b.m., respectively, with a dosing interval of 12 hours to maintain the target

trough MIC of 2 mg/ml. These doses are similar to 5 to 12 mg/kg/12 hours in cattle, sheep, dog and pigs (BOOTH and McDONALD, 1988) and 10.3 mg/kg/12 hours and 8.4 mg/kg/12 hours in cows for priming and maintenance doses, respectively, (GHAFFAR et al., 1996), but higher than the manufacturer's recommendation of 5 mg/kg/24 hours. Compared with the manufacturer's recommended dosage regimen of 5 mg/kg/d, the clinical appraisal of dose 7.5 to 10 mg/kg b.i.d. in the Faculty's Veterinary Hospital revealed improved therapeutic response in equines, with no indication of toxicity in the animals.

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**SAŽETAK**

Istražena je farmakokinetika raspodjele kanamicina u zdravih, odraslih mula nakon jednokratne intravenske primjene u dozi 5 mg/kg tjelesne mase (t.m.) u zdravih odraslih mula. Uzorci krvi uzeti u različitim vremenskim razmacima bili su pretraženi na količinu kanamicina mikrobiološkim testom. Koncentracija lijeka u plazmi u odnosu na vrijeme najviše je odgovarala bieksponencijalnoj krivulji. Za izračunavanje farmakokinetičkih pokazatelja rabljen je dvoprostorni otvoreni model. Rezultati su pokazali da je poluvrijeme raspodjele lijeka ($t_{1/2\alpha}$) iznosilo 0.18 ± 0.26, a poluvrijeme eliminacije ($t_{1/2\beta}$) 4.39 ± 0.68 sati. Prividni volumen raspodjele lijeka ($V_d$) bio je 0.64 ± 0.17 l/kg, a ukupni klirens ($Cl_B$) 1.66 ± 0.22 ml/min/kg. Dozom 5 mg/kg t.m. jedanput na dan nije postignuta željena minimalna inhibicijska koncentracija (MIC) na kraju doznog razmaka. Izračunato je da je optimalna udarna doza kanamicina za mule iznosila 8.73, a doza održavanja 7.45 mg/kg t.m. Pritom se lijek mora primjenjivati svakih 12 sati da bi se postigla koncentracija u krvi 2 mg/ml.

**Ključne riječi:** kanamicin, kinetika raspodjele, mula