
Comparative Pharmacokinetic Studies of Kanamycin in Camels, Sheep and Goats

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Abstract :

Pharmacokinetics of kanamycin in camels, sheep and goats were determined following a single IV dose of 5µg/kg body weight of kanamycin. Plasma concentrations of kanamycin versus time were best fitted to a two-compartment open model with a $t_{1/2}$ of 6.2, 3.5 and 2.9 hours and volume of distribution of 0.6, 0.28 and 0.18 L/kg for camels, sheep and goats, respectively. In the camel, an increase of kanamycin plasma concentration reoccurred after 7 hours post injection producing a trough-like pattern of $t_{1/2}$ of 26.3 hours, suggesting that kanamycin is extensively reabsorbed from urinary tract of camel. Due to significant differences in pharmacokinetic parameters of kanamycin between the 3 animals species, extrapolation of doses of drugs from one species to the other should be avoided.

Key Words : Camel, sheep, goats, kanamycin, pharmacokinetics

Introduction :

Aminoglycoside antibiotics constitute a very important weapon in the veterinarians armamentarium against Gram-negative infections (Nordstrom *et al.*, 1993; Rivere and Jerry, 2002; Haritove *et al.*, 2004). As a group, they are the drugs of choice for the treatment of serious Gram-negative infections in animals (Matti *et al.*, 1989; Toutain 2003; Chambers 2006). Aminoglycosides are a therapeutically essential class of antibiotics whose usefulness is often restricted by their nephrotoxic and ototoxic potential (Parker and Davey 1993; Rivere and Jerry, 2002). However, they are still considered to be the drug of choice for treating serious aerobic Gram-negative infections in veterinary medicine (Staneva *et al.*, 1994; Agrawal *et al.*, 2001). Kanamycin, first introduced in the late 1950, has a primarily Gram-negative spectrum of antimicrobial activity (Prescott *et al.*, 2000; Chambers 2006). It is a polybasic water soluble antibiotic synthesized by *Streptomyces kanamyceticus*. It is an important member of aminoglycoside group (Prescott *et al.*, 2000; Chamber 2006). The pharmacokinetics of

kanamycin and amikacin are very similar, because of the structural similarities between them (Lashev *et al.*, 1992; Prescott *et al.*, 2000; Chamber 2006). The pharmacokinetics of the kanamycin is different across species lines and the variability within each animal population is large, indicating a significant amount of heterogeneity in kanamycin disposition in both diseased and normal animals (Lashev *et al.*, 1992; Uppal *et al.*, 1997; Errecalde *et al.*, 2001; Lashev and Lasarova, 2001; Haritova and Lashev, 2004). A similarly large variability in kanamycin pharmacokinetics has also been reported in human (Powell *et al.*, 1983; Lees and Aliabadi, 2002; Chamber 2006). In addition, the inherent variability caused by many different disease states necessitates close monitoring of serum or plasma concentrations to optimize efficiency and minimize toxicosis (Powell *et al.*, 1983; Firth *et al.*, 1993; Rampal *et al.*, 1993; Ziv *et al.*, 1995). Information regarding to pharmacokinetics of kanamycin have not been studied in local ruminant species. This study was planned to investigate pharmacokinetics of kanamycin in camels, sheep and goats.

Materials and Methods :

Animals and preparations:

For the study of the pharmacokinetic of kanamycin, eight animals of each of the following species camels (*Camelus dromedarius*), goats (Ardi) and sheep (Neimi) were used. The animals had free access to food and drinking water. Each animal was weighed before the start of each experiment. Animals were cannulated under strict aseptic conditions with plastic canulla No. 90 (Portex Ltd, England) for administration of drugs and collection of blood samples.

Drug administration:

A single dose of kanamycin sulphate (5µg/kg, Sigma, UK.) was injected intravenously (i/v).

Collection of blood:

Blood samples were collected in heparinized tubes prior to drug administration and at 5, 10, 15, 30 minutes and then at half-hourly intervals until 3 hours. Thereafter, at hourly interval up to 10 hours, and 1 and 2 days post-treatment.

Kanamycin analysis:

The blood samples were allowed to clot, serum was separated by centrifugation (1200 × g for 5 min) and was stored at -20 °C until analysis. Kanamycin was estimated by the method of Ali (1981). Trichloroacetic acid

was used for deproteinization and acidification of samples. Fluorescence was measured in spectrophotometer (Pyunicam, England) at wavelength of 406 nm. The sensitivity of the assay was 0.1 $\mu\text{g/ml}$.

Pharmacokinetic and statistical calculations:

Kinetic parameter were calculated according to Baggot (1977). Mean values and variables were calculated. Analysis of variance (ANOVA) was performed and when a significant F value was obtained, Duncan's Multiple Range Test was used to determine which species is different from the other. Table (1) gives the definitions and formulae of kinetic parameters derived from two compartment open model.

Results :

The mean peripheral plasma concentration of kanamycin in camels, sheep and goat receiving a single IV dose of 5 $\mu\text{g/kg}$ body weight of kanamycin versus time are summerized in Figure 1. These data are best filled to a two-compartment open model. Values of the kinetic parameters which describe the disposition of kanamycin in the 3 species of animals are presented in Table 1. Two elemination half-lives were recorded for the camel ($t_{1/2} \beta_1 = 6.2$ hours and $t_{1/2} \beta_2 = 26.3$ hours). Elimination half-lives in sheep and goat were 3.5 and 2.9 hours, respectively. The disappearance of kanamycin from plasma in the 3 species was steep and reflects the processes involved in the distribution of the drug from central to peripheral compartment with a $t_{1/2} \alpha$ of 36, 18 and 3 minutes in camels, sheep and goat, respectively.

In camel there was an increase of kanamycin plasma concentration about 7 hours post-injection reaching a maximum of 3.4 $\mu\text{g/ml}$ at 8 hour post-injection and then declined thereafter producing a trough-like pattern. The new half-life of this elemination phase was 26.3 hours. Such pattern was absent in plasma of sheep and goat. The volume of distribution was 0.6 in camels, 0.28 in sheep and 0.18 L/kg in goat.

Statistical comparison were made between different kinetic parameters of the 3 animals species and presented in Table 1.

Table (1)

Pharmacokinetic parameters of kanamycin in camels, sheep and goat after a single IV bolus of 5 $\mu\text{g}/\text{kg}$ body weight.

Disposition Parameters	Camel	Sheep	Goat
C_{\max} ($\mu\text{g}/\text{ml}$)	9.2*	11.1	17.2
T_{\max} (min)	2	2	2
A ($\mu\text{g}/\text{ml}$)	8.02*	10.1	15.3
B ($\mu\text{g}/\text{ml}$)	4.6*	9.1	12.1
$C^{\circ}P$ ($\mu\text{g}/\text{ml}$)	12.9	14.2	19.3
$T_{1/2}(\alpha)$ (min)	3.6	18*	3
$T_{1/2}(\beta_1)$ (hours)	6.2*	3.5	2.9
$T_{1/2}(\beta_2)$ (hours)	26*	-	-
K_{12} (min^{-1})	0.005	0.06	0.156*
K_{21} (min^{-1})	0.025	0.052	0.086
K_{cl} (min^{-1})	0.0056	0.0053	0.0096
$V_{d(\text{area})}$ (L/kg)	0.60*	0.28	0.18
Cl_B (ml/kg/min)	2.1	1.7	1.4

C_{\max} = Maximum attainable plasma concentration, T_{\max} = Time at maximum plasma concentration, A = Extrapolated zero time plasma drug concentration of the α phase, obtained by the method of residuals, B = Extrapolated zero time plasma drug concentration of the β phase, α , β = Hybrid rate constants associated with biexponential expression that mathematically described the disposition curve. $C^{\circ}P$ = Plasma drug concentration immediately following intravenous administration of single dose of adrug, $T_{1/2} \alpha$ = Distribution half-life, $T_{1/2} \beta$ = Biological half-life, K_{12} = First order transfer rate constant for distribution between the central and peripheral compartment, K_{21} = First order transfer rate constant for distribution between the peripheral and central compartment, K_{cl} = First order transfer rate constant for elimination of a drug from the central compartment, V_c = Apparent volume of central compartment, $V_{d(\text{area})}$ = Apparent volume of drug distribution calculated by area method, Cl_B = Total body clearance.

* Values followed by different letters indicate statistically significant difference ($P < 0.05$).

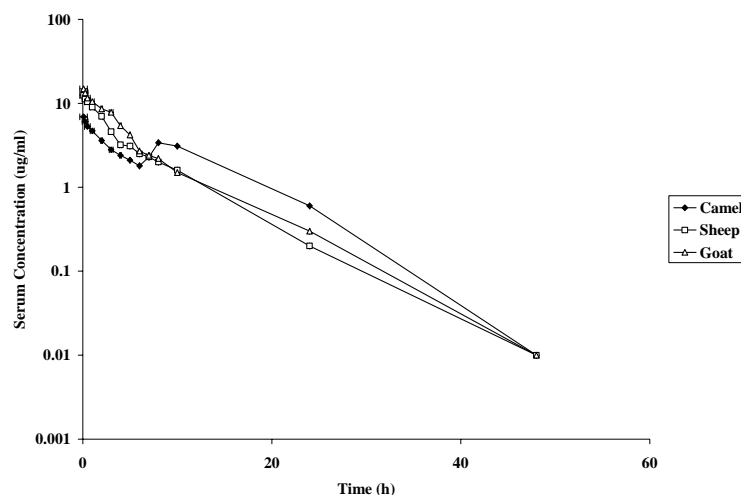


Figure (1) : The semilogarithmic plot of mean kanamycin concentration in plasma versus time following IV administration of a single dose of 5 µg/kg to camel, sheep and goat.

Discussion :

During the course of antimicrobial therapy an antibiotic must maintain a certain therapeutic level or minimum inhibitory concentration (MIC) in plasma or serum. The recommended MIC of kanamycin that is effective against most pathogenic bacteria is in the range of 1-4 µg/ml (Prescott *et al.*, 2000; Rivere and Jerry, 2002). The mean plasma concentration of kanamycin remained above the lower limit of MIC was 10 hours for all the 3 species. Similar levels were observed in sheep and goat (Jianyuan 1989; Khan *et al.*, 1994). Species difference amongst ruminant indicated that after a single intravenous 5 mg/kg administration, the highest plasma kanamycin was observed in goat followed by sheep and the lowest in camels.

The pharmacokinetic behavior of parentally administered kanamycin has been described in terms of two compartment open model in the 3 species studied here and elsewhere as in the case of cows (Rampal *et al.*, 1993; Ziv *et al.*, 1995; Errecalde *et al.*, 2001), sheep (Lashev *et al.*, 1992; Lashev and Lasarova, 2001; Haritova and Lashev, 2004), horses (Baggot *et al.*, 1981; Firth *et al.*, 1993) and goat (Khan *et al.*, 1994; Uppal *et al.*, 1997; Agrawal *et al.*, 2001).

The distribution and elimination half-life values, of 18 min and 3.5 hours in sheep were longer than the respective values of 8 min and 1.8 hours as reported in sheep by lashev *et al.* (1992). In contrast to these studies, slower distribution and rapid elimination were investigated in sheep by Haritova and Lashev. (2004). Khan *et al.* (1994) related longer half-life of kanamycin to slower glomerular filtration rate.

The volume of distribution recorded in local sheep of present study, 0.51 L/kg has been found higher than values reported in foreign counterparts, 0.22 L/kg (Baggot 1977) and 0.26 L/kg (Lashev *et al.*, 1992).

The total body clearance in local sheep, 1.70 ml/kg/min is lower than the value 4.12 ml/kg/min reported by Khan *et al.* (1994). The value of clearance in the present study is comparable to 1.67 and 1.52ml/kg/min investigated by lashev *et al.* (1992) and Baggot (1977), respectively.

Distribution and elimination half-life of kanamycin (3 minutes and 2.9 hours, respectively), in present study compared to the respective values 8.2 and 4.7 hours of streptomycin in goat by Jianyuan *et al.* (1989), revealed rapid distribution and elimination of drug in local goat. Following 10 mg/kg intravenous injection of kanamycin Lashev *et al.* (1992) reported similar distribution but shorter elimination half-lives as 0.09 and 1.95 hours, respectively. It is recommended that due to significant differences in pharmacokinetic parameters of kanamycin in the three animal species, extrapolation of dosage from one species to the other should be avoided.

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دراسة مقارنة الحرائك الدوائية للكنمايسين في الجمال والأغنام و الماعز

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الملخص :

تم دراسة الحرائك الدوائية لعقار الكنمايسين بحقنه بجرعة مقدارها ٥ميكروغرام للكيلوجرام في الوريد في الجمال والأغنام و الماعز. تم رسم تركيز الكنمايسين وملائمته للموديل ذو الفرقتين الحرائكي وكان عمر النصف ٢,٦ و ٣,٥ و ٩,٢ ساعة في الجمال والأغنام و الماعز على التوالي وكان حجم توزيع الدواء هو ٠,٦ و ٠,٢٨ و ٠,١٨ ساعة في الجمال والأغنام و الماعز على التوالي. لقد ارتفع تركيز الكنمايسين في بلازما الجمال بعد ٧ ساعات من حقنه بعد اختفائه وتم الحصول على عمر نصف جديد مقداره ٢٦,٣ ساعة. حيث تم استنتاج أن العقار قد تم امتصاصه من الجهاز البولي. وينسب للاختلاف الظاهر في الحرائك الدوائية بين الحيوانات فإنه يمنع استنتاج الجرعات من حيوانات إلى أخرى.