

## RENAL CLEARANCE AND URINARY EXCRETION OF KANAMYCIN IN DOMESTIC RUMINANT SPECIES

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### ABSTRACT

Species dependent geonetical differences in renal clearance and urinary excretion of kanamycin were investigated in adult female buffaloes, cows, sheep and goats. The drug was administered as a single intravenous dose (5 mg/kg b.wt). Blood and urine samples were collected at various time intervals after drug administration. The plasma and urine concentrations of the drug were determined using the microbiological assay. The mean ( $\pm$  SE) values for endogenous creatinine clearance (an index of glomerular filtration rate) were  $0.77 \pm 0.05$ ,  $0.49 \pm 0.07$ ,  $0.81 \pm 0.07$  and  $0.98 \pm 0.13$  ml/min.kg in buffaloes, cows, sheep and goats, respectively. Experiments regarding kidney handling of kanamycin in these ruminant species revealed respective values of renal clearance as  $0.08 \pm 0.01$ ,  $0.07 \pm 0.01$ ,  $0.19 \pm 0.02$  and  $0.23 \pm 0.04$  ml/min.kg. Besides glomerular filtration, kanamycin was reabsorbed from the renal tubules of all ruminant species and actively secreted into the renal tubules of buffaloes and goats. The cumulative percentages of intravenous dose of kanamycin excreted through urine during 12 hours in buffaloes, cows, sheep and goats were  $4.31 \pm 0.37$ ,  $2.53 \pm 0.30$ ,  $11.0 \pm 1.04$  and  $15.8 \pm 2.22$ , respectively. This species variation in the percentage of urinary excretion in these domestic ruminants coincides with their respective glomerular filtration rates, being the highest in goats, lowest in cows and intermediate in sheep and buffaloes.

**Key words:** Kanamycin, renal clearance, urinary excretion, domestic ruminants.

### INTRODUCTION

Antibiotics play an important role in the treatment of various infectious diseases in man and animals. Most of the developing countries like Pakistan are importing raw or finished drugs for human and veterinary health management. Drug developments supported by extensive preclinical and clinical investigations, are carried out in the drug exporting countries. In most cases, the genetic make up of man and animals and environmental conditions are different amongst the drug importing and exporting countries. Several studies have shown that the pharmacokinetic behavior, optimal dosage, renal clearance and urinary excretion of the investigated drugs were different under indigenous conditions when compared with the values given in the literature or in the product inserts supplied by the manufacturers (Muhammad *et al.*, 2003; Javed *et al.*, 2003). Therefore, it is imperative 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 used clinically.

Kanamycin is an important member of aminoglycoside group of antibiotics. It is a broad spectrum antibiotic being used to combat various infectious diseases in human and animals. Information regarding renal handling of kanamycin has not been studied in native ruminant species in Pakistan. Thus, the present project was planned to investigate renal

clearance and urinary excretion of kanamycin in female buffaloes, cows, sheep and goats kept under climatic conditions of Pakistan.

### MATERIALS AND METHODS

#### Experimental animals

Renal clearance and urinary excretion of kanamycin were investigated in normal adult Nili Ravi buffaloes, Sahiwal cows, Lohi sheep and Teddy goats weighing  $600 \pm 16.6$ ,  $416 \pm 7.26$ ,  $47 \pm 1.44$  and  $49 \pm 1.63$  Kg, respectively. For this purpose, 32 clinically healthy adult female animals, with 8 animals of each species were used. All the animals were maintained under similar environmental and managerial conditions at the Livestock Experimental Station, Bahadarnagar, Okara, Pakistan. These animals were stall fed with dry wheat straw and green fodder of the season. The animals had free access to drinking water. Experiments were performed during the months of September and October.

#### Methodology

Each animal was weighed before the start of each experiment. With animals restrained in standing position, both jugular veins were cannulated with plastic cannula No. 90 (Protex Ltd., England) for the administration of drug on the right side and collection of blood samples on the left side. A sterilized

disposable balloon catheter (Rush No. 14, 30 ml) was inserted into the urinary bladder through urethra of each animal. The external opening of the catheter was connected through rubber tubing to a urine collecting reservoir in which all the voided urine was quantitatively collected.

A commercial preparation of kanamycin (Kanachron injection 10%, batch No. VD 120, Star Laboratories Ltd., Pakistan) was used in these studies. A single dose of kanamycin was injected intravenously through cannulated jugular vein at the dose rate of 5 mg Kg<sup>-1</sup> body weight.

Blood samples were collected in heparinized plastic centrifuge tubes. Prior to drug administration, a control blood sample was collected from each animal. Following drug administration, blood samples were drawn at 30, 60, 90, 120 and 150 minutes. After recording the pH, blood samples were centrifuged, plasma was separated and stored at -20°C until analysis.

In all animals, a blank urine sample was collected before administration of kanamycin. For renal clearance studies, 45 minutes after drug administration the urinary bladder was emptied completely and washed with distilled water through the catheter. Urine samples were collected at 75, 105, 135 and 165 minutes after washing. The volume of each urine sample was measured. For the study of urinary excretion, the urine voided until 4, 6, 8, 10 and 12 hours after drug administration was collected quantitatively. The pH of all urine samples was also recorded.

### Analytical procedure

Kanamycin concentrations in plasma and urine were determined by microbiological assay according to the disk agar diffusion method (Arret *et al.*, 1971), using *Bacillus subtilis* as test organism. The test organism (ATCC-6633) was obtained from Drug Testing Laboratory, Lahore. The concentrations of creatinine in plasma and urine were determined by using spectrophotometer (Spectronic 21, Bausch & Lomb, Germany) by Jaffe-reaction (Bonsnes and Taussky, 1945).

### Statistical analysis

The renal clearance of endogenous creatinine was used for the estimation of glomerular filtration rate (GFR). Renal clearance of kanamycin and endogenous creatinine was calculated as described previously (Swenson, 1985). Influences of diuresis, urine pH and plasma drug concentration on the renal clearance of drug were examined by regression/correlation analysis using Microsoft Excel version of computer programme.

The mean ( $\pm$  SE) values for kanamycin in the urine samples of experimental animals at different time intervals after intravenous injection were calculated. The concentrations versus time data were used to determine cumulative percent dose excreted until 12

hours after intravenous drug administration.

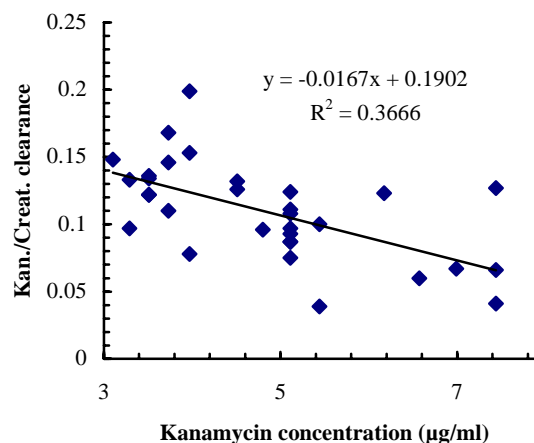
## RESULTS

### Renal clearance

#### Buffaloes

Mean ( $\pm$  SE) values for renal clearance of endogenous creatinine and kanamycin, diuresis, pH of blood and urine, plasma and urine concentrations of kanamycin and creatinine in 8 buffaloes are presented in Table 1. The rate of urine flow in buffaloes was  $0.023 \pm 0.002$  ml/min.kg. The pH of blood was  $7.58 \pm 0.02$  and of urine was  $8.20 \pm 0.03$ . The mean concentrations of endogenous creatinine in plasma and urine were  $19 \pm 0.59$  and  $633 \pm 25$   $\mu$ g/ml, respectively. The renal clearance of endogenous creatinine was  $0.77 \pm 0.05$  ml/min.kg.

Plasma and urine concentrations of kanamycin were  $4.83 \pm 0.39$  and  $16.1 \pm 0.57$   $\mu$ g/ml, respectively. The renal clearance of kanamycin was  $0.08 \pm 0.01$  ml/min.kg. The ratio between the clearance of kanamycin and the clearance of endogenous creatinine was  $0.11 \pm 0.01$ . The regression correlation analysis revealed a negative correlation ( $r = -0.605$ ) between plasma concentration of kanamycin and its renal clearance (Fig 1). However, diuresis and urine pH did not depict any significant correlation with the renal clearance of the drug.



**Fig. 1: Effect of plasma concentration of kanamycin on its renal clearance in buffaloes.**

#### Cows

The results of renal clearance in 8 cows are shown in Table 2. The rate of urine flow in cows was  $0.018 \pm 0.001$  ml/min.kg. The values for the pH of blood and urine were  $7.67 \pm 0.03$  and  $8.15 \pm 0.06$ , respectively. The concentrations of endogenous creatinine in plasma and urine were  $12.0 \pm 1.52$  and  $300 \pm 46.4$ , respectively. The renal clearance of endogenous creatinine was  $0.49 \pm 0.07$  ml/min.kg.

In cows, mean level of kanamycin in plasma was

$4.03 \pm 0.36$   $\mu\text{g/ml}$ , while in urine it was  $15.5 \pm 1.41$   $\mu\text{g/ml}$ . The



renal clearance of kanamycin was  $0.07 \pm 0.01$  and its ratio with that of endogenous creatinine was  $0.20 \pm 0.04$ . The regression/correlation analysis did not show any influence of diuresis, pH of urine and plasma concentration of kanamycin on the renal clearance of the drug.

### Sheep

In sheep, the results of diuresis, pH of blood and urine and renal clearance are presented in Table 3. The rate of urine flow was  $0.04 \pm 0.01$  ml/min.kg. The pH of blood was  $7.48 \pm 0.02$  and that of urine was  $7.91 \pm 0.06$ . The mean concentrations of endogenous creatinine in plasma and urine were  $15.4 \pm 0.79$  and  $538 \pm 85.4$   $\mu\text{g/ml}$ , respectively. The renal clearance of endogenous creatinine was  $0.81 \pm 0.07$  ml/min.kg.

The mean plasma level of kanamycin was  $7.52 \pm 0.49$   $\mu\text{g/ml}$ , while in urine its level was  $46.4 \pm 7.25$   $\mu\text{g/ml}$ . The renal clearance of kanamycin was  $0.19 \pm 0.02$  ml/min.kg. The ratio of clearance of kanamycin to that of endogenous creatinine remained as  $0.26 \pm 0.03$ . By regression correlation analysis, a significant positive correlation ( $r = 0.534$ ,  $p < 0.05$ ) was observed between diuresis and renal clearance of drug (Fig 2), while plasma concentration and urine pH did not reveal any significant effect on the renal clearance of kanamycin.

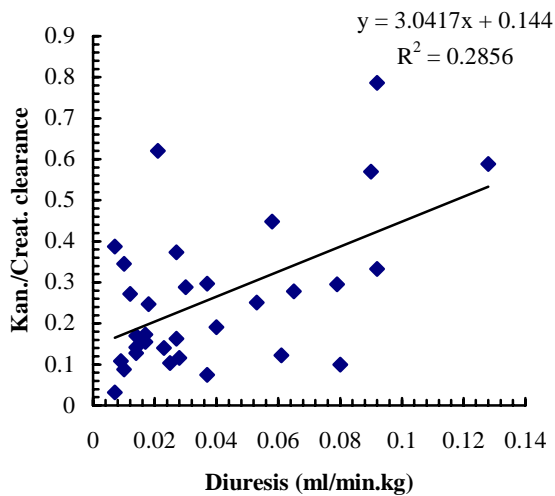


Fig. 2: Effect of diuresis of kanamycin on its renal clearance in sheep.

### Goats

In goats, value of diuresis was  $0.07 \pm 0.02$  ml/min.kg. The pH values of blood and urine were  $7.42 \pm 0.02$  and  $8.01 \pm 0.06$ , respectively. The concentration of endogenous creatinine in plasma was  $10.4 \pm 0.56$   $\mu\text{g/ml}$  and in urine it was  $217 \pm 30.8$   $\mu\text{g/ml}$ . The renal clearance of endogenous creatinine was  $0.98 \pm 0.13$  ml/min.kg (Table 4).

In goats, the plasma concentration of kanamycin was  $9.43 \pm 0.37$ , while in urine it was  $39.7 \pm 4.35$   $\mu\text{g/ml}$ . The renal clearance of kanamycin was  $0.23 \pm 0.04$  ml/min.kg. The ratio of the kanamycin clearance to that of endogenous creatinine was  $0.23 \pm 0.02$ . The regression analysis showed a negative correlation between the plasma concentration of kanamycin and its renal clearance (Fig 3). The diuresis and urine pH failed to influence the renal clearance of the drug.

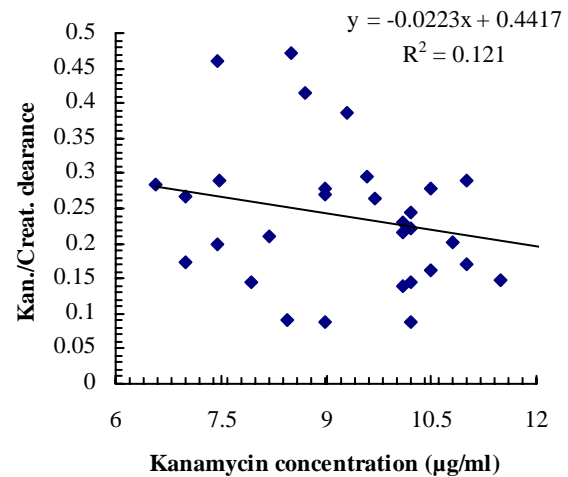


Fig. 3: Effect of plasma concentrations of kanamycin on its renal clearance in goats.

### Urinary excretion

Mean ( $\pm$  SE) values of cumulative percent of dose excreted for each species are presented in Fig. 4. It is evident in this figure that cumulative percent of dose excreted at 12 hours in the urine of goats was 15.8, followed by 11.0 in sheep, 4.31 in buffaloes and 2.53 in cows.

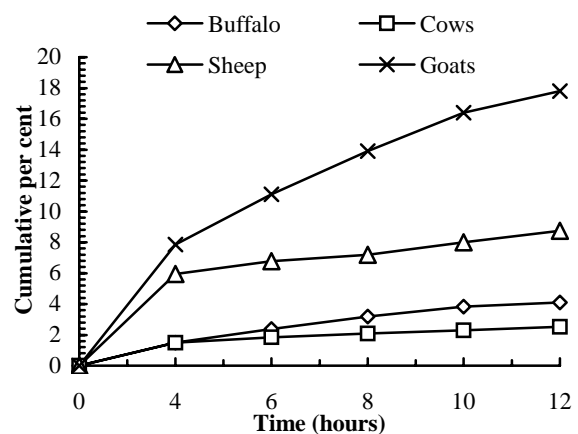


Fig. 4: Mean cumulative percent of kanamycin intravenous dose (5 mg/kg) excreted in urine of ruminant species.



## DISCUSSION

### Renal clearance

#### Buffaloes

The diureses of  $0.023 \pm 0.002$  ml/min.kg recorded in buffaloes in the present studies is lower than the values of urine flow reported as  $0.120 \pm 0.016$  ml/min.kg (Iqbal, 1994) but is in agreement with  $0.029$  ml/min.kg (Akhtar, 1987). The rate of urine flow depends upon several factors including water intake, metabolic status of the animal and environmental conditions. The pH of blood was  $7.58 \pm 0.02$  and that of urine it was  $8.20 \pm 0.03$ . During summer and winter seasons mean blood pH in buffaloes was recorded as 7.68 and 7.90, respectively by Nawaz *et al.* (1992) and 7.76 and 7.90, respectively by Chaudhary (1989). The variation observed in the blood pH of the buffaloes indicates a better adoption to the environmental conditions.

In the present study, the renal clearance of endogenous creatinine in buffaloes was  $0.77 \pm 0.05$  ml/min.kg. This value is lower than 1.74 ml/min.kg (Boehncke, 1980) but higher than 0.44 and 0.34 ml/min.kg in summer and winter seasons, respectively (Nawaz *et al.*, 1988). A significant negative correlation between plasma concentration of kanamycin and ratio of renal clearance of kanamycin and that of endogenous creatinine can be attributed to the saturation of excretory mechanism at higher drug plasma levels which is indicative of involvement of active tubular secretion. There was no significant correlation between diuresis and urine pH and the renal clearance of drug. Thus, the renal handling of kanamycin in buffaloes besides glomerular filtration also involves active tubular secretion.

#### Cows

The urine flow rate in cows was  $0.018 \pm 0.001$  ml/min.kg, which is comparable to 0.019 ml/min.kg during summer (Akhtar, 1987). The values for the pH of blood and urine were  $7.67 \pm 0.03$  and  $8.15 \pm 0.06$ . In earlier studies, the values of blood pH during summer and winter were recorded as 7.69 and 8.07 (Nawaz and Shah, 1985), while the urine pH has been recorded as 8.45 and 8.47 during the two seasons, respectively (Akhtar, 1987).

The renal clearance of endogenous creatinine was  $0.49 \pm 0.07$  ml/min.kg, which is comparable to 0.54 ml/min.kg recorded earlier during summer (Nawaz *et al.*, 1988). However, this value is lower than  $1.17 \pm 1.11$  ml/min.kg (Iqbal, 1994). Analysis of the data revealed that the rate of urine flow, urine pH and the plasma concentration of kanamycin did not influence the renal clearance of the drug in cows. This indicates that the renal handling of kanamycin in cows mainly involves the glomerular filtration.

#### Sheep

The rate of urine flow in sheep was recorded to be

$0.040 \pm 0.008$  ml/min.kg. In previous studies, the rate of urine flow was reported as 0.019 and 0.037 ml/min.kg during summer and winter seasons, respectively (Akhtar, 1987) and  $0.065 \pm 0.01$  ml/min.kg (Iqbal *et al.*, 1990). The respective values for the pH of blood and urine were  $7.48 \pm 0.02$  and  $7.91 \pm 0.06$ . The values of blood pH during summer and winter were recorded as 7.60 and 7.74 (Nawaz and Shah, 1985). The urine pH has been noted as 8.45 and 8.47 during summer and winter seasons, respectively (Akhtar, 1987).

The renal clearance of endogenous creatinine showed a mean value of  $0.81 \pm 0.07$  ml/min.kg. This is comparable to previously reported values (Alvi *et al.*, 1985; Afzal *et al.*, 1982) being 1.0 and 1.19 ml/min.kg, respectively.

In sheep, regression/correlation analysis revealed a significant ( $P < 0.05$ ) positive correlation between diuresis ( $r = 0.534$ ) and renal clearance of kanamycin. This indicates that at lower diuresis, the drug had more time to stay in the tubules from where it would be reabsorbed. There was no significant correlation between plasma concentration of kanamycin and urine pH with the renal clearance of drug. Thus, the renal excretion of kanamycin in sheep, besides glomerular filtration, also involves back diffusion.

#### Goats

The diuresis in goats was  $0.067 \pm 0.019$  ml/min.kg. In previous studies, the values of diuresis were 0.049 ml/min.kg (Nawaz *et al.*, 1988), 0.130 ml/min.kg (Iqbal *et al.*, 1986), 0.052 ml/min.kg (Nawaz *et al.*, 1990) and  $0.121 \pm 0.015$  ml/min.kg (Iqbal, 1994). The mean value for the pH of blood was  $7.42 \pm 0.02$ , while that of the urine it was  $8.01 \pm 0.06$ . The value of blood pH is within the range of values recorded in domestic ruminants including goats (Nawaz *et al.*, 1990).

The goats used in the present study showed a mean renal clearance of endogenous creatinine as  $0.98 \pm 0.13$  ml/min.kg. This value is lower than 21.5 ml/min.10 kg (Nawaz and Rasmussen, 1979). The renal clearance of endogenous creatinine recorded earlier in local goats averaged 1.43 and 1.86 ml/min.kg during summer and winter, respectively (Nawaz *et al.*, 1988), 1.62 ml/min.kg (Nawaz *et al.*, 1990) and 1.29 ml/min.kg (Iqbal, 1994). The analysis of data on diuresis, urine pH, plasma concentration of kanamycin and renal clearance of endogenous creatinine and kanamycin showed a significant ( $P < 0.05$ ) negative correlation ( $r = -0.348$ ) between plasma concentration of the drug and its renal clearance. This is indicative of involvement of active secretion of the drug at the kidney tubular level. However, diuresis and urine pH did not influence the renal excretion of the drug. Hence, renal handling of kanamycin in goats involves glomerular filtration and active tubular secretion.

The indigenous buffaloes, cows, sheep and goats showed blood pH range in agreement with a pH range (7.00 to 7.80) that has been stated as compatible with life (Pitts, 1966). However, GFR is lower under subtropical environment in the local ruminants when compared with

the dwellers of temperate environments, as has been explained by an original term "geonetics" (Nawaz *et al.*, 1988).

In all ruminant species included in the present study, the ratio of renal clearance of kanamycin and renal clearance of endogenous creatinine was less than one. This reflects the lower renal clearance of drug than respective GFR in individual species (almost 9 times in buffaloes, 7 times in cows, 5 times in sheep and 4 times in goats), which is indicative of back diffusion of the drug during its renal handling. It shows that during renal clearance of kanamycin, almost 89, 80, 74 and 77% of the drug is being reabsorbed at the kidney tubular level in buffaloes, cows, sheep and goats, respectively. Hence, on the basis of these observations it is evident that besides glomerular filtration, back diffusion is involved in all ruminant species during their renal excretion of drug. Regression/correlation analysis also evidenced the involvement of active tubular secretion in buffaloes and goats. Thus, renal clearance of kanamycin in buffaloes and goats involves glomerular filtration, back diffusion and active tubular secretion. In cows and sheep it involves glomerular filtration and back diffusion. Although the primary mechanism of renal excretion of kanamycin is by glomerular filtration (Prescott and Baggot, 1988; Gilman *et al.*, 1990), yet tubular reabsorption in man (Cabana and Taggart, 1973) and tubular reabsorption and to some extent active tubular secretion in dogs (Baggot *et al.*, 1985) and tubular resorption of gentamycin in juvenile dogs have also been reported (Riviere and Coppoc, 1981).

#### Urinary excretion

The cumulative percent of dose of kanamycin excreted at 12 hours in the urine was maximum in goats (15.8%) and minimum in cows (2.53%), with intermediate values in sheep (11.00%) and buffaloes (4.31%). This species variation in urinary excretion coincides with their respective GFR values, being the highest in goats, lowest in cows and intermediate in sheep and buffaloes.

Higher urinary excretion of kanamycin (74 % of the administered dose) in 24 hours in buffalo calves has been reported. Further, 96 and 74-94 % of total dose of amikacin and arbekacin were excreted in the urine of dogs and human volunteers, respectively (Baggot *et al.*, 1985; Yamasku *et al.*, 1986).

Lower urinary excretion of kanamycin in domestic ruminants under current investigation is evidenced by the results regarding its renal handling. These results show that regardless the involvement of active tubular secretion in buffaloes and goats, 74-89% of the administered dose of the drug was absorbed at kidney tubular level. Lower urinary excretion of kanamycin and its back diffusion has been reported in local mules (Muhammad, 1997).

Moreover, kanamycin is an organic base with a pKa value of 7.8, which means that the drug is 50%

unionized at pH 7.8. When the pH of urine in domestic ruminants increases, the drug would be more unionized. A high degree of unionization provides more of the drug available for reabsorption and therefore, high clearance values may not be observed when the pH is high.

#### Conclusions

Based on the findings of the present study it can be concluded that renal clearance of endogenous creatinine in indigenous domestic ruminant species was lower than their foreign counterparts. Renal handling of kanamycin, besides glomerular filtration, involved back diffusion. Active tubular secretion was observed in buffaloes and goats. Urinary excretion of kanamycin in domestic ruminant species was found to be lower than the literature values

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