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DISPOSITION KINETICS OF APRAMYCIN IN GOATS

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SUMMARY

The disposition kinetics and milk and urine concentration of apramycin were estimated in six goats. Following intramuscular and intravenous injection of 20 mg/kg b.wt., blood milk and urine samples were collected at 5, 15, 30 min., 1, 2, 4,6, 8,10,12 hours post injection.

The collected samples were used for determination of apramycin concentration using the microbiological assay method.

Following intramuscular injection of apramycin, the highest concentration in serum was recorded at 1 hour with $t_{0.5}$(ab) value f 47.78 min. and $t_{0.5}$ (β) f 1.53 h. The peak milk and urine concentration was reached at 4 hours. Following intravenous injection of apramycin it follows two-compartment model with to $t_{0.5}(\alpha)$ 14.11 min. and $t_{0.5}$ (β) 3.22 h., V_C 0.97 L/kg. The Cl(B)) was 1.668 ml/kg. The mean systemic bioavailability was 78.25%.

The protein binding percent of apramycin of serum and milk was 8.5% and 39.25% respectively.

INTRODUCTION

Apramycin is a member of aminoglycosides antibiotics which is produced by *streptomyces lenebravius*. The antibacterial spectrum of apramycin includes streptomycin and neomycin resistant *E. coli* and *Salmonella* (Ryden and Moore, 1977; Walton, 1978 and Theys et al., 1983).

Apramycin was commonly used in treatment of Gram negative bacterial infection in Veterinary Medicine (Ryden and Moore, 1977 and Walton, 1978). Few data are available on the absorption, distribution and elimination of apramycin in goats. The present work was designed to describe the pharmacokinetic profil of apramycin in lactating goats and residue in milk which may affect the consumers.

MATERIAL AND METHODS

Drug:

Apramycin sulphate R was (obtained as a pure (100%) water soluble powder form Egyptian Co. for Chemicals and Pharmaceuticals (ADWIA),

Cairo, Egypt.

Animals:

Six lactating female (Baladi) normal goats were used with body weight 18 to 20 kg and aged from 30 to 36 months, they were fed on balanced ration and water ad libitum.

Experiment:

Goats were given a single intravenous dose of 20 mg/kg. b.wt. and after two weeks the same animals were given the same dose intramuscularly. Blood samples were collected immediately before medication and 5, 15, 30 minutes, 1, 2, 4, 6, 8, 10, 12 and 24 hours post-administration. Urine and milk samples were collected at the same time intervals as in blood samples.

Analytical procedure:

Apramycin concentrations in serum, milk and urine samples were assayed using microbiological assay method as described by Arret et al. (1971) and Walton (1978), protein binding to serum and milk proteins was assayed according to Lorian (1975).

The pharmacokinetic data were calculated according to the method described by Baggot (1978).

RESULTS

Following intramuscular injection of apramycin (20 mg/kg.b.wt.) it was detected in serum after 5 minutes and increased gradually to a maximum concentration 2.20±0.05µg/ml at hour, 7.0±0.63µg/ml and 131.70 ±4.01 µg.ml at 4hours, in serum, milk and urine, respectively. The concentration decreased gradually to lower level at 6, 16 and 12 hours post-injection in serum, milk and urine samples, respectively Table (1).

The kinetic parameters following intramuscular injection showed that $t_{0.5}$ (ab) 47.7±6.82 min. with maximum concentration C_{max} 1.78±0.06 µg/ml maximum time t_{max} 1.46±0.105 hr. and it is highly eliminated with $t_{0.5}$ (β) 1.53±0.05 0.06hr. Table (2) and Fig. (1 and 2).

Following intravenous injection of 20 mg/kg. b.wt. apramycin was detected in serum, milk and urine at 5 minutes follwing injection and decreased gradually to its lowest concentration at 12 hours Table (1). The drug obayed two-compartment model with $t_{0.5}$ (α)14.11 min., $t_{0.5}$ (β) 3.21 ±0.21 rs. and K_{el} 1.7132±0.02 h^{-1}. Apramycin was highly distributed with V_d (area) 7.07±0.29 L/kg.

It appears from the obtained results that the bioavailatility of apramycin in lactating goats following intramuscular injection was 78.25% (Table 2). Apramycin binds to protein of serum and milk at 8.51% and 39.25% respectively.

Table 1 : Concentrations of apramycin (ug/ml) in serum , milk and urine of goats following intramuscular and intravenous injection of 20 mg/kg b.wt. (n = 6).

IM : Intramuscular
IV : Intravenous.

Time	Serum		Milk		Urine	
	IM	IV	IM	IV	IM	IV
5 min	0.48 ± 0.007	18.00 ± 0.26	0.18 ± 0.040	0.50 ± 0.080	12.80 ± 1.390	28.50 ± 1.56
15 min	0.79 ± 0.040	10.07 ± 0.27	0.32 ± 0.060	12.00 ± 2.50	45.50 ± 2.50	43.30 ± 1.05
30 min	1.40 ± 0.080	6.10 ± 0.150	0.70 ± 0.060	25.50 ± 1.670	75.80 ± 6.25	81.67 ± 1.67
1 h.	2.20 ± 0.05	1.90 ± 0.075	1.50 ± 0.060	14.83 ± 1.64	100.00 ± 4.47	233.30 ± 10.50
2 h.	1.50 ± 0.050	0.82 ± 0.030	3.80 ± 0.380	8.33 ± 1.28	120.00 ± 3.65	160.00 ± 4.47
4 h.	0.55 ± 0.190	0.52 ± 0.02	7.00 ± 0.630	3.37 ± 0.56	131.70 ± 4.01	141.70 ± 8.33
6 h.	0.22 ± 0.008	0.32 ± 0.015	1.40 ± 0.370	2.80 ± 0.23	74.17 ± 5.80	44.17 ± 0.800
8 h.	—	0.28 ± 0.003	0.30 ± 0.060	1.20 ± 0.194	39.00 ± 4.020	24.17 ± 0.80
10 h.	—	0.12 ± 0.003	0.15 ± 0.016	0.90 ± 0.17	13.80 ± 1.170	11.70 ± 0.33
12 h.	—	—	—	0.30 ± 0.06	3.16 ± 0.42	9.33 ± 0.33

Table 2 : Kinetic parameters of apramycin after intravenous and intramuscular injection of 20 mg/kg b.wt. in goats (n = 6).

Route	Intravenous			Intramuscular	
Parameter	Unit	$\bar{X} \pm SE.$	Parameter	Unit	$\bar{X} \pm SE.$
B.Wt.	kg	19.00 ± 0.45	B.Wt.	kg	19.00 ± 0.45
C_p^o	ug/ml	20.70 ± 0.80			
A	ug/ml	19.41 ± 1.13	A	ug/ml	3.34 ± 0.07
	h^{-1}	2.96 ± 0.079	$K_{(ab)}$	h^{-1}	1.0015 ± 0.18
$t_{0.5(\alpha)}$	min	14.11 ± 0.38	$t_{0.5(ab)}$	min	47.78 ± 6.82
B	ug/ml	1.3401± 0.036	B	ug/ml	3.49 ± 0.13
B	h^{-1}	0.2301± 0.0004	K_{el}	h^{-1}	0.4507± 0.53
$t_{0.5(B)}$	h.	3.2165± 0.075	$t_{0.5(B)}$	h.	1.53 ± 0.053
K_{12}	h^{-1}	1.0779± 0.075	cal	ug/ml	1.785 ± 0.069
K_{21}	h^{-1}	0.3966± 0.0007	C_{max}		
K_{el}	h^{-1}	1.7132± 0.02	obs.	ug/ml	2.25 ± 0.06
V_c	L/kg	0.9700± 0.04	cal.	h.	1.4639± 0.105
V_B	L/kg	16.61 ± 1.78	t_{max}		
V_{dss}	L/kg	3.59 ± 0.29	obs.	h.	1.500 ± 0.19
$V_{d(area)}$	L/kg	7.068± 0.29			
$Cl_{(13)}$	ml/kg/min	1.6680± 0.06	Interval between doses	h.	4.95 ± 0.0.79
A.U.C.	ug/ml/min	12.39 ± 0.36	A.U.C.	ug/ml/min	11.39 ± 0.82
			Bioavai-lability	%	78.25 ± 3.5

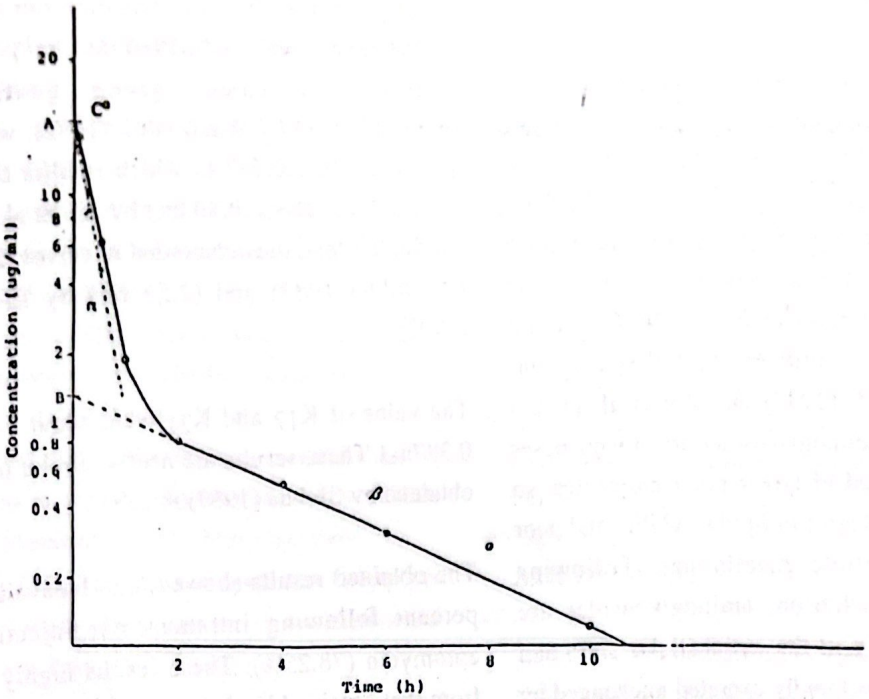

Fig. (1): Semilogarithmic graf depecting the time concentration course of apramycin in serum of goats after a single intravenous injection of 20 mg/kg b. wt. (n = 6)

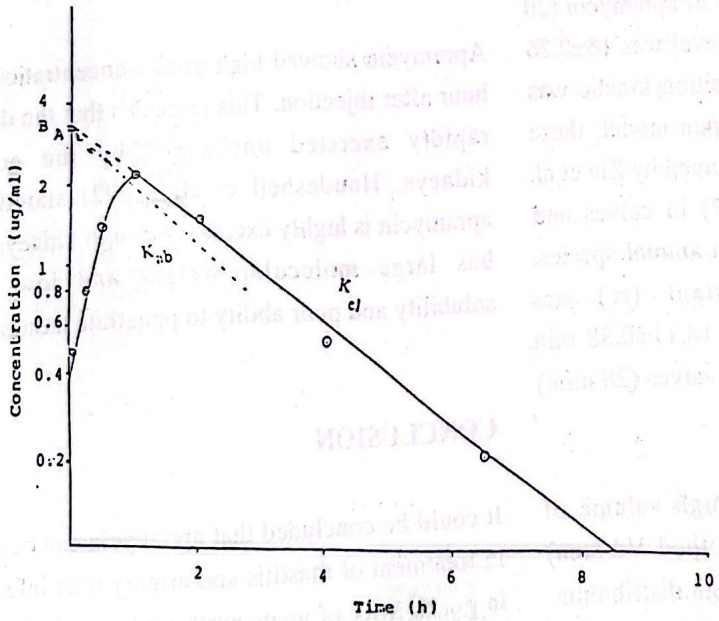

Fig. (2): Semilogarithmic graf depecting the time concentration course of apramycin in serum of goats after a single intramuscular injection of 20 mg/kg b. wt. (n = 6).

DISCUSSION

The present study showed that intramuscular injection of apramycin (20 mg/kg.b.wt.) is rapidly absorbed with a peak level (2.20 ug/ml) at 1 hour with short $t_{0.5}$ (β), the rapid excretion of the drug is confirmed by high urine and milk concentrations for a long time. Apramycin persisted in urine at higher level (3.16±0.42 µg/ml for 12h. than in milk (0.15±0.016) for 10hr Houdeshell et al. (1982) and Ziv et al. (1985) mentioned that aminoglycosides are organic bases and are composed of larger polar molecules, so they have a low degree of lipid solubility and poor ability to penetrate membranes. Following parentral administration, aminoglycosides are distributed mainly in the extracellular fluid and most of the dose is rapidly excreted unchanged by the normal kidney.

Following intravenous injection of apramycin (20 mg/kg b.wt) in goats the peak level was 18±0.26 µg/ml at 5 minutes. The disposition kinetic was conferring two compartment open model, these results were similar to those obtained by Ziv et al. (1985) in calves Shikha (1987) in calves and Lashev et al. (1992) in different animal species. The distribution rate constant (α) was (2.95±0.079h^{-1}). The $t_{0.5}$ (ab) 14.11±0.38 min. was smaller than that recorded in calves (28 min.) by Ziv et al. (1985).

The obtained results showed a high volume of distribution given by the area method Vd(area) (7.068±0.29 L/kg) that suggests high distribution. In contrary apramycin in calves showed lower volume of distribution 0.71 L/kg. by ziv et al. (1985) and 0.153 L/kg. by El-Gamal (1992).

In the present work, the elimination rate constant of apramycin was (0.2328±0.004 h^{-1}) as those recorded in camel given gentamycin (0.24±0.01h^{-1}) by Wasfi et al. (1992), with long $t_{0.5}$ (β) 3.2165±0.717 h. which smaller than that recorded in calves (4.40 hr.) by Ziv et al. (1985) and higher than those recorded in calves (2.31hr.) by Shikha 1987) and (2.53 hr.) by El-Gamal (1992).

The value of K_{12} and K_{21} were about 1.08 and 0.397h-1 These results are nearly similar to those obtained by Shikha (1987) in calves.

The obtained results showed high bioavailability percent following intramuscular injection of apramycin (78.25%). These results highly differ from that obtained by Aziz et al. (1988) (96.2% in buffalo) and by El-Gamal (1992) (61.98±in calves).

Apramycin showed high urine concentration at 1 hour after injection. This indicates that the drug is rapidly excreted unchanged by the normal kidneys. Houdeshell et al. (1992) stated that apramycin is highly excreted through kidneys as it has large molecular weight and low lipid solubility and poor ability to penetrate tissues.

CONCLUSION

It could be concluded that apramycin can be used in treatment of mastitis and urinary tract infection in goats. Milk of goats must not be used 10 hours post-drug administration to avoid the harmful effect of the drug on consumer health.

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