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PHARMACOKINETIC PROFILE AND TISSUE DISTRIBUTION OF APRAMYCIN IN CHICKENS

BY

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SUMMARY

Apramycin (20 mg/kg b. wt.) was administered by intravenous, oral and intramuscular routes in healthy chickens. Following intravenous injection the blood concentration curve was biexponential. The kinetic parameters showed an elimination half-life of 5.97 ±0.07 hours apparent volume of distribution 13.33±0.25 L. / kg. and clearance rate of 1.55±0.04 ml/kg/min. Following oral and intramuscular administration of apramycin reached its maximum concentration 4.46±0.07 and 5.67±0.14 ug/ml at maximum time. 41.77±2.89 and 42.81±5.89 minutes, with interval between doses 5.12±0.04 and 13.55±0.40 respectively. Apramycin was distributed in all tissues with withdrawal time of 3 days following oral and intramuscular administration for 5 days.

INTRODUCTION

Apramycin is one of the commonly used antibiotics in treatment of many bacterial diseases in animals and chickens (Ryden and Moore, 1977, Walton, 1978 and Theys et al., 1983). Pharmacok inetic profile of apramycin has been studied in animals by many investigators. (Ziv et al., 1985, Shikha 1987 and Pashov et al., 1988).

The aim of the present experiment was to describe the kinetic disposition, bioavailability, tissue distribution and withdrawal time of apramycin in chickens following oral, intramuscular and intravenous administration.

MATERIALS AND METHODS

Drug

Apramycin sulphate, was obtained as a pure powdered drug from Egyptian Co. for Chemicals and pharmaceuticals (Adwia), Cairo Egypt.

Birds

28 clinically healthy chickens of both sex with body weight of 1.5-2.0 kg and age of 45 days were used. The chickens were housed in groups of 5 birds in each cage and fed on balanced antibacterials free ration.

Experiment

1- Pharmacokinetic studies
Ten chickens were injected intravenously with apramycin in a single dose 20 mg/kg b. wt. (Pashov, 1988). Two weeks later (To insure complete clearance of their bodies form the drug). The 1st. 5 chickens were given the same dose orally (using stomach tube) and the laters (5 chickens) were given the same dose intramuscularly. Blood samples were collected from wing vein at 5, 10, 15, 30 minutes, 1, 2, 4, 6, 8 and 10 hours post-administration for determination of drug concentration in blood.

2- Tissue distribution

This experiment was performed on two groups of 9 chickens each. The 1st. group were given the

drug orally and those of the 2nd given the drug intramuscularly for 5 successive days in doses of 20 mg/kg b. wt. 3 chickens were slaughtered at 1, 3 and 5 days after stoping of drug administration. Samples of liver, kidneys lungs spleen, brain, intestine and muscles were taken for determination of tissue concentrations and withdrawal time of apramycin.

Analytical procedure:

Estimation of apramycin in blood and tissue samples was carried out by microbiological assay as described by Levetzow, (1971). The serum protein binding of the drug was determined in vitro according to the method described by Lorian (1975).

Statistical assay:

The pharmacokinetic data were calculated acording to the method described by Ritchel (1973) and Snedecor, (1964).

RESULTS

Following intravenous injection of apramycin in chickens in a dose of 20 mg/kg b. wt. Concentrations of the drug in blood revealed a biexponential decline that could be described by two compartments model (Fig. 1), Apramycin was detected in blood till 10 hours (Table 1). The pharmacokinetic data (Table 2) showed that apramycin was rapidly distributed t 0.5 (α) 5.29 ± 0.30) and slowly eliminated $t_{0.5B}$ 5.97 ± 0.07 apramycin was highly distributed in chicken (V_c 4.36 ± 0.11 L/kg). V_{dB}(13.35 ± 0.25 L/kg) and V_d (area) (12.08 ± 0.07). Delayed total body

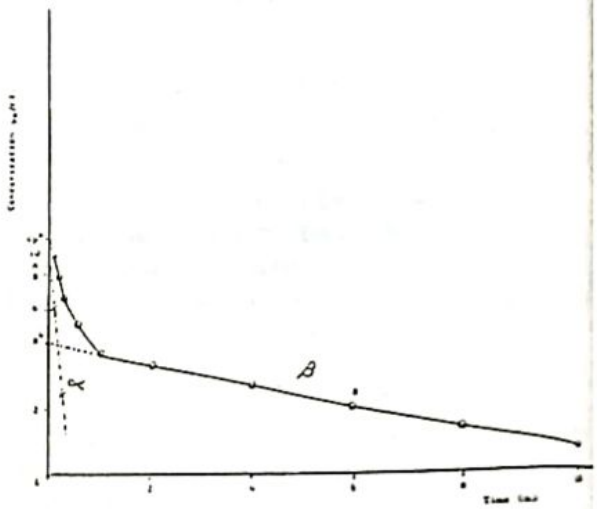

Fig. (1): Semilogarithmic graph depecting the time concentration course of apramycin in serum of chickens after a single intravenous injection of 10 mg/kg b. wt. (n=10).

Table (1): Serum concentrations of apramycin (µg/ml) in chickens after a single oral intramuscular and intravenous administration of 20 mg/kg b. wt. (x ± S. E.) (n = 10).

Time (h)	Oral	Concentration (ug/ml)	
		Intramuscular	Intravenous
5 min	2.42 ± 0.02	3.40 ± 0.10	9.60 ± 0.22
10 min	3.04 ± 0.04	4.54 ± 0.02	7.80 ± 0.33
15 min	3.92 ± 0.05	5.04 ± 0.04	6.30 ± 0.15
30 min	4.52 ± 0.02	6.12 ± 0.05	4.61 ± 0.07
1 h.	3.08 ± 0.05	5.22 ± 0.18	3.55 ± 0.02
2 h.	1.52 ± 0.02	4.02 ± 0.02	3.21 ± 0.02
4 h.	0.31 ± 0.004	2.30 ± 0.03	2.49 ± 0.023
6 h.	- -	1.28 ± 0.45	1.95 ± 0.016
8 h.	- -	0.71 ± 0.009	1.58 ± 0.025
10 h.	- -	0.35 ± 0.002	1.25 ± 0.017

Table (2): Pharmacokinetic values of apramycin in chickens after a single intravenous injection of 20 mg/kg b. wt. (n=10).

Parameter	Unit	x ± S. E.
B. wt.	kg	1.85 ± 0.25
C°p	µg/ml	11.55 ± 0.32
A	µg/ml	8.88 ± 0.46
α	h-1	5.29 ± 0.30
t0.5 (α)	min	8.14 ± 0.32
B	µg/ml	3.96 ± 0.01
B	h^{-1}	0.1162 ± 0.0016
t0.5 (β)	h.	5.97 ± 0.07
K_{12}	h^{-1}	3.28 ± 0.20
K_{21}	h^{-1}	1.7076 ± 0.088
k_{el}	h^{-1}	0.3585 ± 0.01
V_c	L/kg	4.36 ± 0.11
$V_{d\beta}$	L/kg	13.35 ± 0.25
V_{darea}	Ll/kg	12.08 ± 0.07
Cl (β)	Kl/kg/min	1.552 ± 0.04
A. U. C	µg/ml/min	35.71 ± 0.397

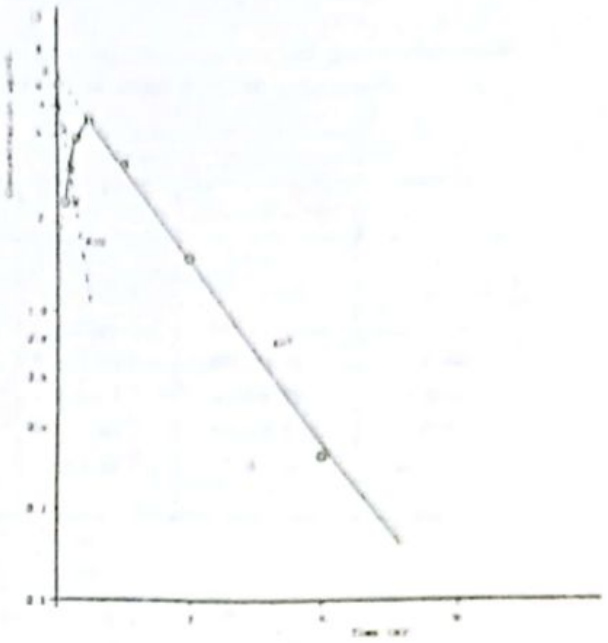

Fig. (2): Semilogarithmic graph depecting the time concentration course of apramycin in serum of chickens after a single oral administration of 20 mg/kg b. wt. (n=5)

Table (3): Pharmacokinetic values of apramycin in chickens after a single oral and itnramuscular administration of 20 mg/kg. b. wt. (n=5).

Parameter	Unit	Route of administration	
		Oral	Intramuscular
B. wt.	kg	1.89 ± 0.31	1.90 ± 0.29
A	µg/ml	4.996 ± 0.81	4.86 ± 0.22
K_{ab}	h-1	2.63 ± 0.25	3.95 ± 0.45
$t_{0.5\ (ab)}$	min	16.49 ± 1.76	12.00 ± 2.02
B	µg/ml	6.25 ± 0.11	7.11 ± 0.37
B	h-1	0.7074 ± 0.01	0.2999 ± 0.01
$t_{0.5\ (\beta)}$	h	0.9813 ± 0.02	2.33 ± 0.12
C_{max} obs	µg/ml	4.52 ± 0.02	6.12 ± 0.05
C_{max} calc.	µg/ml	4.46 ± 0.07	5.67 ± 0.14
t_{max} obs.	min	30.00 ± zero	30.00 ± zero
t_{max} calc.	min	41.77 ± 2.89	42.81 ± 5.89
Interval between doses.	h.	5.12 ± 0.04	13.55 ± 0.40
A. U. C.	µg/ml/min	10.54 ± 0.15	25.54 ±4.57
Bioavailability	%	29.76 ± 0.65	85.54 ± 4.57

Table (4): Tissue concentrations of apramycin (μg/g) after oral and intramuscular administration of 20 mg/kg b. wt. for 5 days. (n=3) (M ± S. E.) O=oral Im.=intramoscular.

Tissue	1st day		2nd day		3rd day	
	0	Im	0	Im	0	Im
Liver	2.30 ± 0.01	2.50 ± 0.02	1.20 ± 0.001	1.50 ± 0.002	-	-
Kidneys	4.50 ±0.11	5.20 ±0.16	1.50 ± 0.001	1.70 ± 0.01	-	-
Lungs	2.00 ±0.001	2.2 ± 0.002	0.8 ± 0.006	1.00 ± 0.007	-	-
Spleen	5.60 ±0.006	5.00 ± 1.10	2.00 ± 0.006	2.5 ±0.001	-	-
Brain	1.90 ± 0.01	1.8 ± 0.001	0.80 ± 0.001	0.60 ±0.002	-	-
Muscles	2.00 ± 0.05	3.50 ± 0.04	1.00 ± 0.001	1.80±0.005	-	-
Intestine	3.50 ± 0.01	3.00 ± 0.02	1.80 ± 0.002	1.00 ± 0.001	-	-

clearance of apramycin (1.55 ± 0.04 mg/kg/in) was correlated with the prolonged elimination half live time following oral and intramuscular administration of apramycin (20 mg/kg b. wt.) (Fig. 2 and 3) & (Table 3) it was highly absorbed form the site of administration K_{ab} (2.63 ± 0.25 and 3.95 ± 0.45 h^{-1}) and maximum concentrations C_{max} (4.52 ± 0.02 and 6.12 ± 0.05 ug/ml) at t_{max} 4.46±0.07 and 5.67—0.14 h. respectively.

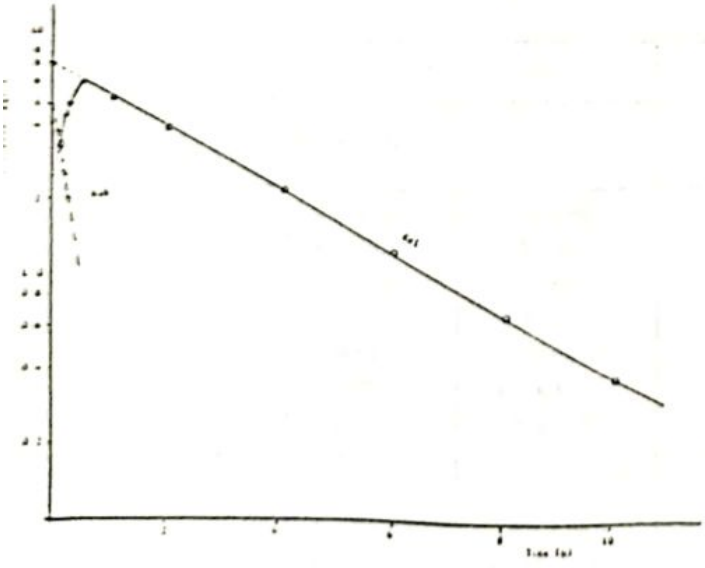

Fig. (3): Semilogarithmic graph depecting the time concentration course of apramycin in serum of chickens after a single intramuscular injection of 20 mg/kg b. wt. (n=10).

Apramycin was rapidly eliminated following oral administration with $^{t}0.5(\beta)$ (9.98 ± 0.02 h.) and interval between doses (5.12 ± 0.04 h). The drug was slowly eliminated following intramuscular injection with $^{t}0.5$ (β) (2.33 ± 0.12 h) and prolonged interval between doses (13.55 ± 0.40 h). The bioavailability of the drug was 29.76% adn 85.54 ± 4.57% following oral and intramuscular administration respectively. Protein binding was 14.8% after in vitra detection.

Apramycin was highly distributed in all tissues (Table 4) with more concentrations in kidneys, spleen and lungs following oral and intramuscular administration for 5 days. The withdrawal time was 3 days.

DISCUSSION

Apramycin is a member of *Streptomyces tenebrarius* producing antibiotic. It is one of aminoglycosides used in treatment of Gram-negative bacterial infections in poultry (freidlin et al., 1985).

Following i.v. injection of apramyci in a single dose (20 mg/kg b. wt.) in chickens. It opeyed two-compartment open model. Our findings are

similar to those obtained by Ziv et al., (1985) Shikha (1987) in calves. Aziza (1985) neomycin in chickins and Lasheu et al., (1992) in different animal species.

Apramycin showed higher distribution rate constant (α) 5.29±0.30, this result was supported by short $t_{0.5}$ (α) 8.14±0.30. The same results were obtained in calves by ziv et al. (1985). Apramycin showed very high volume of distribution V_d (area) (13.35 ± 0.25 L/kg) in chickens while it showed low volume of distribution in calves (ziv et al., 1985 and El-gamal, 1992). Apramycin showed higher K_{12}/K_{21} (more than one). This indicates that it is highly distributed from the 1st. compartment (blood) to the 2nd. compartment (tissues). This is supported by the higher volume of distribution (Shikha 1987). Apramycin was slowly eliminated with $Cl_{(\beta)}$ (1.55 ± 0.04 ml/min/kg) high $^{t}0.5_{(\beta)}$ 5.97±07. This is due to aminglycosids are organic bases and are compressed of larger polar molecules. They have a slow degree of lipid solubility and pore ability to penetrate membranes (Houdeshell et al., 1982 and ziv et al. 1985). Slow clearance rate in calves and sheep was recorded by Shikha (1987) Intramuscular administration of apramycin was highly absorbed and reached its maximum concentrations at 30 minutes, and slowly eliminated. This is supported by high bioavailability (85.54 ± 4.57%) and long I.b.d. 13.55 ±0.40 h. The same results were obtained by ziv et al. 1985) in calves Aziz et al., 1988 in buffalo valves and El-Gamal (1992) in calves. Oral administration of apramycin showed it is slowly absorbed and slowly eliminated and this supported by lower bioavailability % (29.76±0.65%) and short interval between dose 5.12 ± 0.04.

Apramycin was highly distributed in all tissues due to its higher volume of distribution with withdrawal time 3 days, it had withdrawal time in eggs 9 days (Romvary et al., 1991).

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