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SOME PHARMACOKINETICS AND BIOAVAILABILITY OF PAROMOMYCIN IN COWS

(With 5 Tables & 2 Figs.)

By

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مسار ومدى الإستفادة من عقار الباروموميسين

فى الأبقار

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إستهدفت الدراسة تتبع مسار عقار الباروموميسين وتحديد مدى الإستفادة عند حقنه عن طريق الوريد والعضل ، وقد إستخدم فى هذه الدراسة خمسة أبقار موضعه فى حالة صحية جيدة . ثم حقن العقار بمعدل ١٠ مجم/كجم من وزن الجسم وقد تم أخذ العينات (دم ، بول ، لبن) على فترات مختلفة لتحديد تركيز العقار فيها وقد تم ذلك بإستخدام ـ الطريقة الميكروبيولوجية وقد أظهرت دراسة تتبع المسار الدوائى لعقار الباروموميسين بعد حقنه فى العضل ولوحظ أن معدل نصف الحياه الامتصاصية (٥٦ وساعة) ونصف الحياه الافرازية (٤٧ر٥ ساعة) بينما عندما حقن العقار عن طريق الوريد كانت فترة نصف الحياه الافرازية (٥٥ر٢ ساعة) وكان حجم الإنتشار الظاهرى للعقار عند حسابه بطرق مختلفة أكثر من واحد لتر لكل كيلو جرام من وزن الجسم وهذا يدل على أن إنتشار العقار يتركز فى الأنسجة أكثر من البلازما، وكانت معدل الإستفادة من عقار الباروموميسين عند حقنه عن طريق العضل مابين (٠٩ر٧٤ ـ ٠١ر٨٨٪) وأن أعلى مستوى للعقار فى الدم (٤٤ر٧ ميكروجرام/ملليلتر) يصل بعد حوالى ساعة وربع من إعطاء العقار .

SUMMARY

Five clinically-healthy non-pregnant, lactating cows were each given paromomycin in dose of 10 mg/kg body weight, by the intravenous and intramuscular routes. The serial serum samples collected after each treatment were analysed for paromomycin concentration by the microbiological assay method using B.subltis (ATCC 6633) as test organism. A two compartment pharmacokinetic model was developed to describe the disposition of this drug. The elimination half-lifes were 5.47±0.57 and 2.55±0.12 hours for intramuscular and intravenous administration, respectively.

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The apparent specific volume of distribution were more than 1 litre/kg (1.418 litre/kg) which indicates a relatively higher distribution of paromomycin to tissues than in plasma in cows. The bioavailability of paromomycin after intramuscular injection amounted to 79.93±2.53% with a maximum serum concentration (C_{max}) of 7.44±0.23 ug/ml. about 1.5 hours after administration.

INTRODUCTION

Paromomycin, is an aminoglycoside antibiotic, used against sensitive Gram-positive and Gram-negative microorganisms (PIGNATELLI and SILVESTRI, 1963). It is used in treatment of many intestinal infections in cattle, calves, lambs, swine, chicken and monkeys, and of value in amaebiasis of dogs (ROSSOFF, 1974). Intramuscular administration of paromomycin (10 mg/kg b.wt.) in cows showed the highest concentration (6.6 ug/ml) after two hours, in swines administration of 10.20 and 40 mg/kg showed the highest blood level (12.7, 24.8 and 56.8 ug/ml. respectively) after one hour of injection. ZIV and SULMAN (1974) demonstrated that the distribution equilibrium of paromomycin in sheep was reached within one hour.

The aim of this work is to elucidate absorption, distribution, elimination and bioavailability of paromomycin in Frezian cows in Egypt.

MATERIAL and METHODS

Animals:

Five clinically, healthy, lactating and non-pregnant cows, weighing 850-950 kg were used. The animals were maintained on a normal commercial diet, although food was withheld for 2 hours before and after injection with 6 hours. No drug were administered, two weeks before the experiments.

Administration of the drug and collection of samples:

Paromomycin was used as 17.5% solution (Ammino farma, Vetem S.P.A. Milano. Italy). The same animals were used as control before injectionof the drug. Each animal was administered by two does (10 mg/kg body weight) with one week interval by intraveuous and intramuscular routes; the drug was administered at 37°C (semilar to body temperature). Blood, urine and milk samples were collected before and at 15, 30 mins., 1,2,4,6,12 and 24 hours after drug administration. Blood samples were taken from right jugular vein, collected in two parts, the 1st portion was drawn into centrifuge tubes for obtaining serum for determination of paromomycin concentration, urea, creatinine concentration, SGOT, SGPT and alkaline phosphatase activities. While the 2nd one was collected directly into sterile test tubes containing sodium fluride (10 mg/ml blood) as anticoagulant for determination of blood glucose level. Urine was allowed to drain via a sterile rubber ballon catheter (Foltex No. 28) fixed inside the bladder at the time of sampling, whereas samples were collected by hand milking.

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Analytical methods:

The concentration of paromomycin in serum, urine and milk was estimated by microbiological assay method described by GROVE and RANDALL (1955) using Bacillus subtlis (ATCC 6633) as a test organism. Creatinine and urea concentration in both serum and urine were estimated according to the method described by HUSDAN and RAPOPORT (1963) COULOMBE and FAVREAUS (1963) respectively. Glucose, SGOT and SGPT in serum were estimated by using Monotes-Kits of Boehringer, Mannheim Gmbh, Diagnostica, West Germany. Serum total lipids were estimated according to FRINGS and DUMM (1970).

Pharmacokinetic analysis:

For estimation of the disposition kinetics of paromomycin, a two-compartment open model was applied (BAGGOT, 1978). From the serum concentration at different times of sampling, the distribution and elimination half-life (t 1/2 and t 1/2 B, respectively) for paromomycin were calculated using a semilogarithmic system. The apparent volume of distribution (Vd') was calculated by the area [$Vd_{(area)}$], extrapolation [$Vd_{(B)}$] and the pseudoequilibrium [$Vd_{(B)}$] methods (BAGGOT, 1977). The half-life (t 1/2 or B) was calculated according to the following equation:

$$t\ 1/2 \quad or\ B = \frac{\ln 2}{or\ B}$$

The extent of absorption was obtained by compating the area under the serum concentration-time curve following intramuscular dosage (A.U.C. i.m) with that obtained when the same dose was given intravenously (A.U.C. i.v) to the same animals.

$$\text{Bioavalability } \% = \frac{\text{A.U.C. (i.m)}}{\text{A.U.C. (i.v)}} \times 100$$

The apparent volume of central compartment Vc was obtained from the equation:

$$Vc = \frac{\text{Dose (ug/ml)}}{\text{cp (ug/ml)}} \text{ ml/kg}$$

Where:

Cp° is the drug concentration in the serum immediately following intravenous dosage.

The obtained data were statistically analysed according to SNEDECOR (1964) and the results were given as mean ± standard error (X ± S.E.).

RESULTS

The average concentration of paromomycin in serum, urine and milk after a single intramuscular and intravenous injection of 10 mg/kg b.wt. were datermined at different intervals (Table 1&2). The serum level reached its maximum concentration after intram-

uscular injection (7.44±0.23 ug/ml) after one hour. The concentration of paromoycin was higher in urine than that in serum or milk and the maximum concentration in urine was reached after 2 hours.

The disposition kinetics:

The values of disposition kinetics of paromomycin after a single intramusclar injection of 10 mg/kg b.wt. in cows are shown in Table (1) and Fig. (1). The absorption half-life ($t_{1/2\ ab}$ 0.56±0.005 h) and elimination half-life ($t_{1/2\ B}$ 5.47±0.57 h) indicated that paromomycin was rapidly absorbed and rapidly eliminated. Inspection of the serum concentration-time curve which followed drug administration by intramuscular route, demonstrated that the absorption rate constant (K_{ab}) was 1.26±0.03 h^{-1} and the elimination rate constant (K_{el}) was 0.128±02 h^{-1}. The blood concentration of paromomycin following intravenous injection revealed a biexponential decline that can be interpreted as conferring two-compartment model characteristics. In this aspect the distribution half-life ($t_{1/2}$ 1.24±0.07 h) and the elimination half-life ($t_{1/2\ B}$ 2.55±0.12 h). The apparent volume of distribution by the area, extrapolation and pseudoequilibrium were 1089. 34±15.65; 1418.79±11.25 and 1085.84±28.24 ml/kg, respectively (Table 3 & Fig. 1). The systemic bioavallability of paromomycin in cows after a single intramuscular injection of 10 mg/kg b.wt. was illustrated in Table (4). Clearence of paromomycin, creatinine and urea as well as their relations are illustrated in Table (5).

Biochemical effects:

Administration of paromomycin in a dose of 10 mg/kg b.wt. showed no singificant alterations in creatinine, urea, glucose and total lipid concentrations and SGOT, SGPT and alkaline phosphatase activities.

DISCUSSION

The extensive use fo amino-glycoside antibiotic for treatment of various infections in animals and man, beside the problems caused by its residues in food-producing animals, have necessitate the study of pharmacokinetic, models to reveal the disposition of each individual antibiotic in each individual species. Breed and species differences were observed in the rate of absorption, distribution and elimination of different aminoglycosides. In our study, the absorption half-life of paromomycin is 0.56 hour which confirm the rapid abserption from the site of injection. As recorded with other aminoglycosides, gentamicin showed rapid absorption after intramuscular administration in cattle (30 mins) (VANGELOV, 1974; 16.54 mins in buffaloes (EL-BAUOMY, et al. 1985). It was evident from the obtained results that the serum concentration of paromomycion in cows following an intravenous of intramuscular injection of 10 mg/kg body weight wer higher than the minimum inhibitory concentration of many bacterial strains including those resistant to penicillin (GHIONE, et al. 1960 and PIGNATELLI and SILVESTRI, 1965).

PAROMOMYCIN IN COWS

Paromomycin showed a relative not short elimination half-life (5.47 h), while, ZIV and SULMAN (1974) reported that the half-life of paromomycin in sheep was 4.6 hours, this slight variation may be considered as species variation. Some investigators studied the elimination half-life value of aminoglycosides, in cows as 1.9 hour for kanamycin (BAGGOT, 1978); 111 minutes in cattle for gentamicin (ZIV and SULMAN, 1974). Moreover, in other species there is more variation recorded in the elimination half-life of gentamicin as 30-40 minsin rats (BARAZA, et al. 1980); 75 mins in dog (BAGGOT, 1977); 152 mins in horses (PEDERSOLI, 1980); 26 hours in hydrated leopard frogs (RIVIERI, 1979) and 82 hours in gopher snakes (BUSH, et al. 1978).

The high value of apparent volume of distribution (1418.79-1085.84 ml/kg) observed in our investigations denoted more distribution of paromomycin in tissues than in plasma. This result showed great variation of paromomycin than kanamycin and gentamicin in dogs which showed low volume of distribution (0.236-0.278 L/Kg and 0.260-0.448 L/K) respectively (BAGGOT, 1977). Also in cow and goat kanamycin showed low volume of distribution (0.22 L/K); horse (0.20 L/Kg) (BAGGOT, 1977) which could be attributed to its molecular size and minimal binding affinity to plasma proteins which resemble other aminoglycoside antibiotics which freely diffusable in the interstitial tissue water (CYSLYNCK, et al. 1971; RIGAMY, et al. 1973 and GORDON, et al. 1972).

The bioavailability of paromomycin in cows, in the present study, which expresses the portion of the dose entering the systemic circulation after intramuscular injection, ranged from 74.09-88.01%. These values indicate better absorption of paromomycin from its site of int-ramuscular injection than some other autibiotics i.e. Kanamycin, erythromycin, tylosin and ampicillin (BAGGOT, 1977).

Body clearence of paromomycin (4.89±0.15 ml/kg/min). which can be attributed almost entirely to renal clearence evidenced by the highest concentration in urine (12.15 ug/ml for intramuscular and 15.68 ug/ml for intravenous) detected after two hours post-injection, proved the kidney as main channel of paromomycin excretion. This result were observed in some other antibiotics as kanamycin (BAGGOT, 1978; ORME and CUTLER, 1969); chloramphenical (GOODMAN and GILMAN, 1975; BRANDER and PUGH, 1977). Also, the calculated urine/serum concentration ratio was 0.66-3.84 for intreamuscular and 0.23-5.19 for intravenous which indicate the higher urinary excretion of paromomycin.

The low concentration of Paromomycin in cow milk, in the present investigation, indicated the limited extent of penetration of thedrug through mammary gland epithelium which behaves as a lipoidal membrance separating blood of pH 7.4 from milk of PH ranging from 6.5 to 6.8. According to RASMUSSEN (1966), aminoglycoside antibiotics (including paromomycin) attain a limited extent of penetration into milk which can be related to their extremely poor solubility in non-polar solvents and to their low lipid-to-water partition caeffecient (BAGGOT, 1977).

In conclusion, the intramuscular injection of paromomycin prolong the therapeutic concentrations of the drug and theraby reduce the costs of using this amtibiotic in appropriate animal species.

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Table (1)

Mean serum, urine and milk concentration of paromomycin and their relations after intramuscular administration of 10 mg/kg body weight (n = 5)

Time after injectino (H)	Serum conc. (ug/ml)	Urine conc. ug/ml	Urine ratio serum	Milk conc. ug/ml	Milk ratio serum
0.00 (control)	0.0 ±0.0	0.0 ±0.0	0.0 ±0.0	0.0 ±0.0	0.0 ±0.0
0.15	2.62±0.06	--	--	--	--
0.30	6.07±0.16	4.38±0.12	0.66±0.004	--	--
1.00	7.44±0.23	9.23±0.23	0.82±0.03	2.55±0.16	0.23±0.02
2.00	4.90±0.26	12.15±0.09	2.61±0.14	2.83±0.16	0.57±0.005
4.00	2.82±0.15	10.35±0.23	3.84±0.16	1.60±0.06	0.60±0.03
6.00	1.98±0.11	4.68±0.18	2.49±0.24	--	--
12.00	1.22±0.07	3.38±0.18	2.87±0.25	--	--
24.00	0.0 ±0.0	1.48±0.13	--	--	--

Table (2)
Mean serum, urine and milk concentrations of paromomycin (10 mg/kg) body weight and their relations after intravenous injection (n = 5)

Time after injectino (H)	Serum conc. (ug/ml)	Urine conc. ug/ml	Urine ratio serum	Milk conc. ug/ml	Milk ratio serum
0.0 (control)	0.0 ±0.0	0.0 ±0.0	0.0 ±0.0	--	--
0.T5	10.57±0.022	2.45±0.13	0.23±0.01	--	--
0.30	9.54±0.22	4.14±0.04	0.44±0.01	--	--
1.0	6.48±0.12	9.63±0.16	1.49±0.02	4.55±0.11	0.71±0.02
2.0	4.40±0.09	15.68±0.16	3.57±0.11	2.67±0.08	0.61±0.03
4.0	3.3 ±0.21	10.63±0.10	3.24±0.13	1.93±0.60	0.59±0.02
6.0	1.55±0.04	8.03±0.07	5.19±0.13	1.02±0.02	0.66±0.04
12.0	--	6.40±0.15	--	--	--
24.0	--	5.26±0.11	--	--	--

Table (3)

Disposition kinetics of paromomycin in cows after a single intramuscular and intravenous dose of 10 mg/kg body weight (n = 5)

Parameter	i.m. Unit	i.m. Mean ± S.E.	Parameter	i.v. Unit	i.v. Mean ± S.E.
A	ug/ml	10.75±0.06	Cpo	ug/ml	11.29± 0.08
Kab	h^{-1}	1.26±0.03	A	ug/ml	4.25± 0.57
t 1/2	h	0.56±0.05		h^{-1}	0.56± 0.003
B	ug/ml	12.18±0.04	t 1/2	h	1.24± 0.007
Kel	h^{-1}	0.128±0.02	B	ug/ml	7.05± 0.06
t 1/2B	h	5.47±0.57	B	h^{-1}	0.27± 0.01
C_{max}	ug/ml	7.44±0.23	t 1/2B	h	2.55± 0.12
T_{max}	h	1.25±0.05	K_{12}	h^{-1}	0.04± 0.005
			K_{21}	h^{-1}	0.39± 0.07
			Kel	h^{-1}	0.33± 0.01
			V_c	ml/kg	885.33± 6.32
			V_d (area)	L/kg	1089.34±15.65
			V_d (B)	L/kd	1085.84±28.24
			V_d (B)	L/kg	1418.79±11.25
			Cl_B	ml/kg. min.	4.89± 0.15
			Total excretion time	h	5.85±0.21
Body Weight	kg	372.5±7.39	Body wt	kg	372.5 ± 7.39

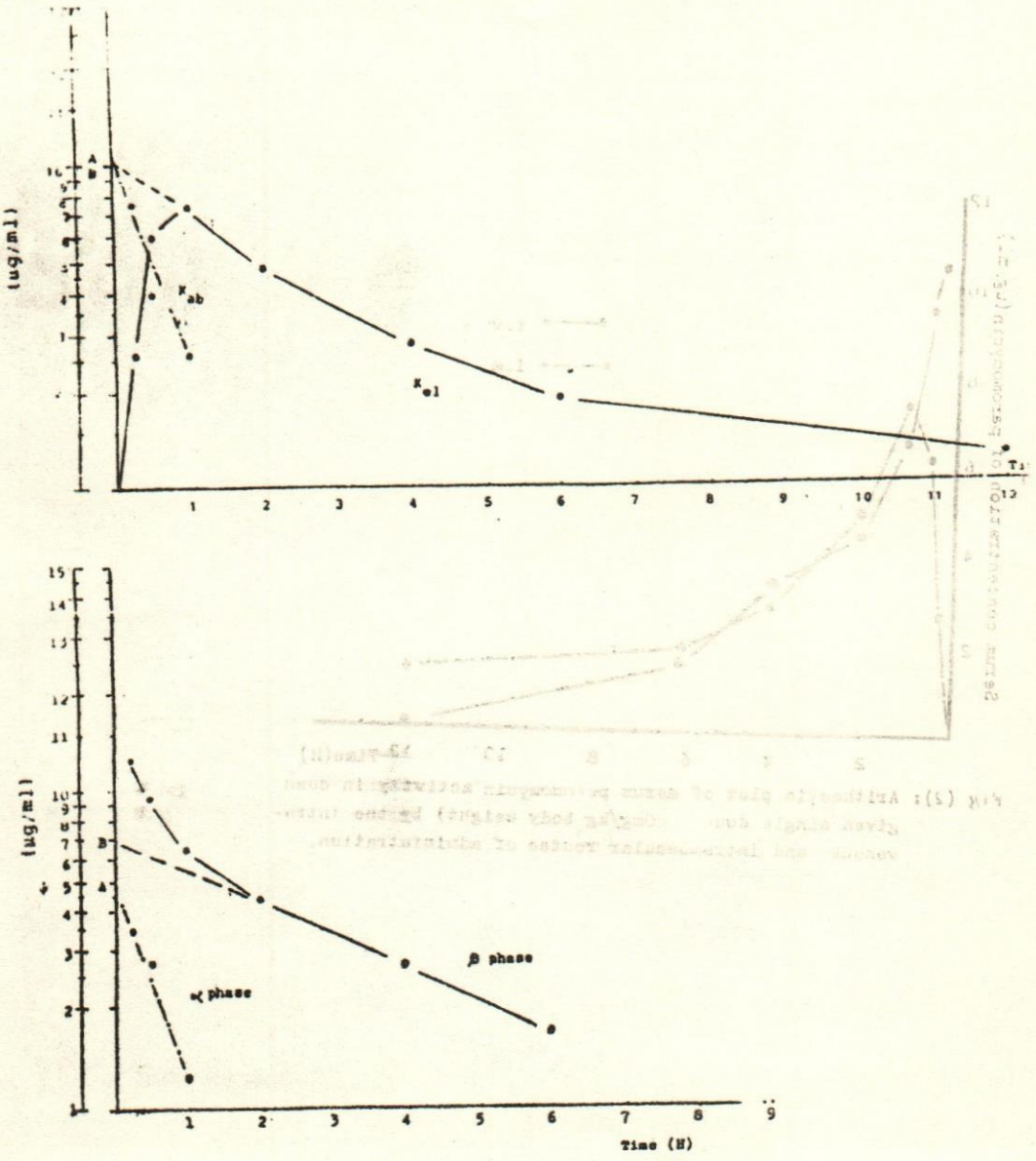

Fig. (1): Semilogarithmic graf depicing the time course of paromomycin in serum of cows after a single intramuscular (A) and intravenous (B) injection in a dose of 10 mg/kg body weight.

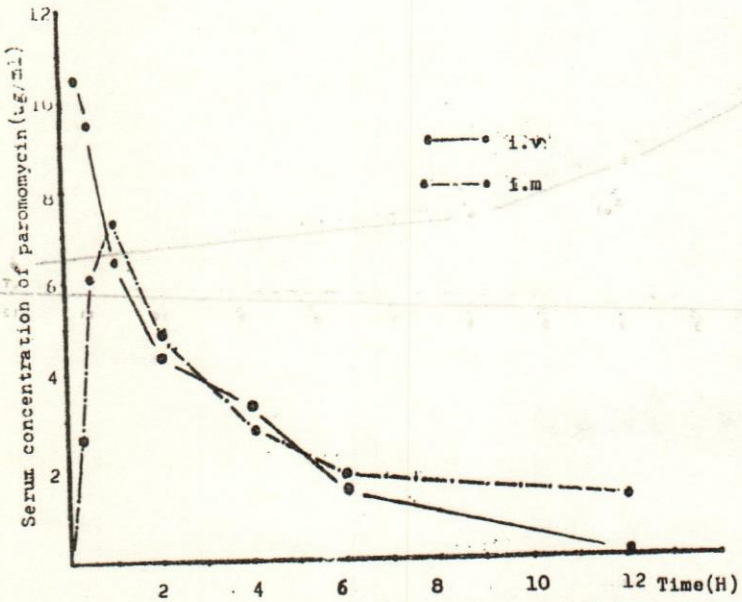

Fig (2): Arithmetic plot of serum paromomycin activity in cows given single dose (Omg/kg body weight) by the intravenous and intramuscular routes of administration.

Table (4)

Systemic bioavailability of paromomycin in cows after a single intramuscular injection of 10 mg/kg body weight (n = 5)

Cow's number	A.U.C. intravanous ug/ml/h	A.U.C. intramuscular ug/ml/h	Bioavailability %
1	44.22	35.175	79.55
2	46.75	34.64	74.09
3	44.567	35.592	79.86
4	45.54	40.08	88.01
5	45.54	35.58	78.13
Mean±S.E.	45.27±0.49	36.21±1.19	79.93±2.53

Table (5)

Clearance of paromomycin (10 mg/kg body weight), creatinine, urea and their relations (n = 5)

Time after injection (H)	Paromomycin clearance (ml/min/10 kg)	Creatinine clearance (ml/min/10 kg)	Paromomycin creatinine clearance	urea clearance (ml/min/10 kg)	Paromomycin urea clearance
0.0 (control)	--	0.84±0.13	-	1.44±0.14	--
0.15	0.06±0.002	0.55±0.03	0.103±0.005	1.17±0.07	0.0525±0.004
0.30	0.10±0.004	0.39±0.09	0.32 ±0.06	0.84±0.08	0.1225±0.0197
1.00	0.28±0.007	0.50±0.11	0.64 ±0.11	0.78±0.08	0.375 ±0.0603
2.00	0.44±0.02	0.24±0.04	1.76 ±0.06	0.63±0.06	0.735 ±0.1184
4.0	0.34±0.03	0.23±0.03	1.53 ±0.21	0.52±0.06	0.6925±0.1596
6.0	0.36±0.03	0.25±0.06	1.62 ±0.26	0.29±0.04	1.2725±0.1472
12.0	--	0.27±0.06	-	0.31±0.05	--
24.0	--	0.23±0.05	-	0.37±0.04	--