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Pharmacokinetics of Tylosin in Desert Sheep after Intramuscular Injection

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Abstract: The pharmacokinetics of tylosin after intramuscular administration at a dose of 1g kg^{-1} body weight was studied in eleven healthy desert sheep. A peak level of tylosin C_{max} of 198±0.95 μg mL^{-1} was achieved after t_{max} of 0,9±0.13 h and the mean distribution half-life ($t_{1/2}\beta$) was 2±0.3 h and the apparent elimination half-life ($t_{1/2}\beta$) was 72.2±9.3 h. The volume of distribution (V_d) was found to be 53.299±3.907 L. The area under the curve ($AUC°_{240}$) of tylosin was calculated as being 1947.8±177.8 μg mL^{-1} and the Area Under Maximum Concentration Curve (AUMC) was 74285.4±5420.75 μg/mL/h^2. The total clearance (cl_β) was 511.7±207 μl h^{-1} and the mean resident time was 30±9.83 h.

Key words: Pharmacokinetic, intramuscular, tylosin, sheep, AUMC

INTRODUCTION

Tylosin, an antibiotic of the macrolides group, is widely used in veterinary medicine either for prophylaxis or for treatment of a wide range of anaerobic bacteria. Gram-positive bacteria and mycoplasma (Duthu 1985; Prescott and Baggot, 1988). Tylosin could be administered in feed, drinking water, or injected intramuscularly mainly for prevention and treatment of Chonic Respiratory Disease (CRD). The pharmacokinetic characteristics and tissues disposition profiles for macrolide antibiotics are influenced by structural and physiochemical properties (Baggot and Gingerich, 1976; Carlier *et al.*, 1987; Ziv *et al.*, 1995). The pharmacokinetic aspects of tylosin have been evaluated in different species (Ziv *et al.*, 1995; Kowalski *et al.*, 2002; Parts *et al.*, 2002; Saurit *et al.*, 2002), goats (Atef *et al.*, 1991) and camels (Ziv *et al.*, 1995). The purpose of the present research is to study the pharmacokinetic parameters of tylosin after intramuscular administration in healthy sheep.

MATERIALS AND METHODS

Animals: Twelve male's desert sheep, aged 9-12 month, weighing between 30-35 kg were used. Sheep were put in pens (3×3 m) and fed with balanced ratio of concentrate and forageand water was available *ad libitum*. After clinical examination and liver and kidney tests, all animals were apparently healthy and allowed to acclimatize for two weeks before the start of the experiment.

Drug administration and sample collection: A single dose of 1g kg^{-1} body weight of tylosin ((Macrolan-200, Interchemie, Holland) was injected intramuscularly in the cervical muscle. Blood samples were collected from the jugular vein, in heparinized tubes from each sheep at 0 (pre-treatment), 0.25, 0.05, 0.75, 1, 6, 24, 96, 168 and 240 h after drug administration. Plasma samples were separated by centrifugation (1200×g for 5 min) and stored at -20°C until analysis.

Plasma assay: Tylosin plasma concentration (μg mL^{-1}) were estimated microbiologically by the modification one-plate test method described elsewhere (Koenen *et al.*, 1995; Koenen and DeBeer, 1998).

Pharmacokinetic analysis: Following Intramuscular (IM) administration, the tylosin plasma concentration versus time data were best fitted by a biexponential equation, $C_p=A_e^{-\alpha t}+B^{-\beta t}$. Consequently a two-compartment open

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model was used to describe the plasma disposition of tylosin. The relevant pharmacokinetic parameters were calculated following I.M. injection of a single dose of 1mg kg^{-1} where C_{max} is the maximum attained drug concentration in the plasma and was featured from the drug plasma-tim plot, t_{max} is the time at which C_{max} was attained and also featured from the plot. A and B are intercepts of slopes of the initial distribution phase and the terminal elimination phase, respectively. αand β are the rate constants associated with distribution and elimination phases and obtained from the slopes of the two lines, respectively; $t_{1/2\alpha}$ and $t_{1/2\beta}$ are the distribution and total body elimination half-lives of the drug and were obtained as 0.693/α and 0.693/β, respectively; k_{cl} is the rate constant for the drug elimination from the central compartment and calculated by $\alpha\beta(A+B)/(\alpha A+\beta B)$; k_{12} is the rate constant for drug distribution from central to peripheral compartment and calculated by $AB(\beta-\alpha)^2/(A+B)/(A\beta+B\alpha)$; k_{21} is the rate constant for drug distribution from peripheral to central compartment and calculated by $(A\beta+B\alpha)/(A+B)$. $V_{d(area)}$ is the apparent volume of drug distribution calculated by dose/$(AUC°\alpha\times\beta)$. $AUC°_{240}$ is the area under log-transformed drug plasma concentration-time curve from time curve from time zero to infinity and calculated as $AUC°_{240}$ + (detected drug plasma concentration at 240h/k_{cl}). Cl_β is the total body clearance of the drug based on the total elimination phase βand was calculated using the formula $V_{d(area)}\times\beta$. $AUC°_\alpha$ is the area under momentum of drug plasma-time curve from time zero to infinity and calculated by trapezoidal rule where it equals $AUC°_{240}$ + (concentration of the drug at time 240h×240)/k_{cl} + (concentration of the drug at time 240h/ke_{12}. MRT is the mean resident time for the drug in the body and was given by $AUMC^0\ \alpha$/ $AUC°\ \alpha$.

Statistical analysis: Statistical analysis was performed using software Miercal Origin 8, 2002 (Miercal Inc., USA). Pharmacokinetic parameters were expressed as mean±SEM.

RESULTS

The plasma concentration of intramuscular injection of tylosin at a dose of 1g to eleven sheep at different times were represented in Table 1.

Tylosin pharmacokinetic parameters were recorded in Table 2. Intramuscular injection of tylosin induced a peak concentration C_{max} 198±0.95 mg mL^{-1} in plasma of sheep after t_{max} 0.93±0.1 while ($t_{1/2}\alpha$) was 2±0.3h and the biological half-life ($t_{1/2}\beta$) was 72.2±9.3h. The volume of distribution was found to be 53.299±3.907L.

Table 1: Mean values±SEM of tylosin plasma concentrations following intramuscular of 1g kg^{-1} body weight to healthy sheep. (n = each 11)

Time (h)	Tylosin concentration (μg mL^{-1})
0	0
0.25	88.3±18
0.5	153.5±25
0.75	180.5±29
1	198±34
6	43±13
24	8±1.8
96	4±0.6
168	2±0.5
240	1±0.07

Table 2: Pharmacokinetic parameters (mean±SEM) of tylosin after single intramuscular administration of 1g kg^{-1} body weight to healthy sheep. (n = each 11)

Pharmacokinetic value	Pharmacokinetic parameters
C_{max} (μg mL^{-1}).	198±95
T_{max} (h)	0.93±0.1
A (μg mL^{-1})	265.5±110
B (μg mL^{-1})	9.98±2.1
A (h^{-1})	0.3448±0.07
B (h^{-1})	0.0096±0.001
$t_{1/2\alpha}$ (h)	2.00±0.3
$t_{1/2\beta}$ (h)	72.2±9.3
K_{el} (h^{-1})	0.1522±0.083
K_{12} (h^{-1})	0.1804±0.052
K_{21} (h^{-1})	0.0217±0.0038
$V_{d(area)}$ (L)	53.299±3.907
$AUC°_{240}$ (μg/ml/h)	1947.8±177.8
$AUC°_\alpha$ (μg/ml/h)	1954.4±205.4
$AUMC^0_\alpha$ (μg/ml/h)	74285.4±5420.75
Cl_β (ml/h)	511.7±20.7
MRT (h)	38.01±9.83

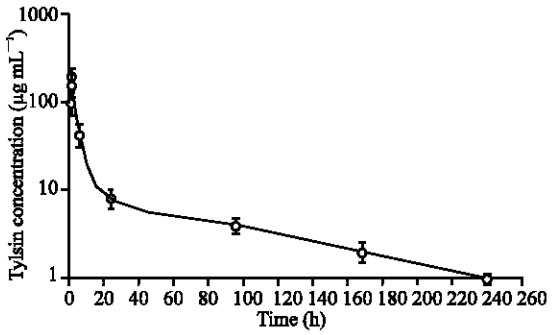

Fig. 1: Mean semi-log serum concentrations of tylosin versus time following intramuscular administration of a single dose 1g kg^{-1} body weights to healthy sheep (n = 11 each)

The actual rate constant k_{12}, k_{21} and k_{cl} were calculated as being 0.1511±0.083, 0.184±0.050 and 0.0217±0.0038h^{-1}, respectively. The area under concentration-time curve was determined as being 74285.4±5420.75 mg/ml/h^2 while the area under the curve was 194.8±177.8 mg/ml/h (Table 2).

The concentrations reached a level of 198±34 μg mL^{-1} after 1 h while the minimum concentrations were evaluated as 1±0.07 μg mL^{-1} after 240 h post dose. The

drug plasma concentrations revealed a biexponential decline which could be described by the open two-compartment model (Fig. 1).

The total body clearance of the drug was found to be 511.7±20.7 mL h^{-1} and the mean resident time was 30.01±9.83 h.

DISCUSSION

As shown in Fig. 1, the decline in plasma tylosin concentration following single intramuscular injection of 1g kg^{-1} in sheep could be described by the two compartment open model (Baggot 1977; Burrow 1980). The observed C_{max} (198 μg mL^{-1}) was much higher than those obtained after I. M. injection in goat C_{max} (2.38 μg mL^{-1}) (Atef *et al.*, 1991) and in camel C_{max} (1.16 μg mL^{-1}) following I. V. administration (Ziv *et al.*, 1995). The difference in C_{max} values could be attributed to difference in species and dosage level. The time to reach this concentration t_{max} (0.93h) was shorter than that reported in goat (4.19h) following I.M. injection (Atef *et al.*, 1991).

As shown in Table-2, the $t_{1/2\alpha}$ (2 h) value was higher than that achieved in goat (0.2 h), after I.V. injection (Atef *et al.*, 1991) but it was nearly similar to that of tylosin in camel (3 h) (Ziv *et al.*, 1995). The observe $t_{1/2\beta}$ (72.2 h) value was higher than that recorded following I.V. injection in goat (3.04 h) (Atef *et al.*, 1991) and camel (54.97 h) (Ziv *et al.*, 1995). The prolong elimination half-life following I.M. injection indicated continual release of the drug either from the injection site or from tissues which serve as reservoirs for the drug, a phenomenon characteristic of macrolide antibiotics (Burrows *et al.* 1983; 1986).

The value of k_{cl},(0.1522 h^{-1}), k_{12} (0.1804 h^{-1}) and k_{21} (0.0217 h^{-1}) were less than those reported in goat (k_{cl}, 0.02, k_{12} 2.5, k_{21} 2.5 min^{-1}) (Atef *et al.*, 1991) and in camel (k_{cl}, 4.58, k_{12} 3.66, k_{21} 4.91 min^{-1}) (Ziv *et al.*, 1995).

The low values indicate the slow distribution of tylosin between the body compartments. The V_d (53.299L) value was much higher than those reported after IV administration in goat (1.7L) (Atef *et al.*, 1991) and in pig (14.6L) (Parts *et al.*, 2002) but it was lower than that in cow (307L) (Duthu 1985) and another macrolide antibiotic tilmicosin; which in sheep (165L) (Modric *et al.*, 1998) and this indicated a wide distribution of the drug.

As shown in Table 2, the high values of $AUC°_{240}$ (1947.8 μg mL^{-1}/h), $AUC°_{\alpha}$ (1954.4 μg mL^{-1}/h) and AUMC°α (74285.4 μg mL^{-1}/h^2) following I.M. injection were different from those obtained in goat ($AUC°_{I.M.}$ 47.4 μg mL^{-1}/h, $AUC°_{I.V.}$ 65.3 μg mL^{-1}/h) (Atef *et al.*, 1991) which indicated more absorption of the drug, while the difference in values may be attributed to dosages. The observed Cl_{β} (511.7 mL^{-1}) was much higher than that in goat (6.8 mL min^{-1}) (Atef *et al.*, 1991) and in cow (4602 mL/mim^{-1}) (Duthu 1985) but less than those achieved in normal and water deprived camel (97156 mL/min^{-1}) and (13468 mL/min^{-1}), respectively, which indicates large clearance of the drug. MRT value (38.01 h) was within the range achieved in cattle (36.9 h) and sheep (40.6 h) following tilmiosin administration (Modric *et al.*, 1998). But lower than that obtained in normal camel (207.58 min) (Ziv *et al.*, 1995) which indicate that the extent of absorption was high. The different in pharmacokinetics in this study may be attributed to difference in species or dosage of drug.

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