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Pharmacokinetics of Long-Acting Oxytetracycline Formulation Following Intramuscular Administration in Desert Sheep

[1]Samia A.A. Hassan, [2]Sana A.I. Shaddad, [2]A.K. Muddathir, [3]I.B. El-Tayeb,
[4]A.O.M. Nour, [5]M.H. Al-Nazawi and [5]A.M. Homeida
[1]Department of Biochemistry, Nutrition and Toxicology,
Central Veterinary Research Laboratory, Alamarat, P.O. Box 8067, Khartoum, Sudan
[2]Department of Pharmacology, [3]Department of Pharmacognosy,
[4]Department of Pharmaceutics, Faculty of Pharmacy, University of Khartoum,
P. O. Box 1996, Khartoum, Sudan
[5]College of Veterinary Medicine and Animal Resources, King Faisal University,
P.O. Box 3498, Al-Ahsa 31982, Saudi Arabia

Abstract: The pharmacokinetics of long-acting Oxytetracycline (OTC) formulation (Alamycin-LA) was studied after intramuscular (IM) route at a dose of 1 mg kg^{-1} body weight to fifteen healthy desert sheep. The mean C_{max} values of 74.8±13.22 μg mL^{-1} was after 0.9±0.13 h, the mean distribution phase was 2.0±0.4 h and the apparent elimination half-life was 126±23 h. The volume of distribution (V_d) was found to be 67.933±4.88 L. The area under the curve (AUC^0_{240}) and the area under concentration-time curve (AUMC) were 2530.26±203.3, 242522.2±48504.5 μg/ml/h^2, respectively. The total body clearance (cl_β) was 373.63±18.9 mL h^{-1} while the mean resident time (MRT) was 90.61±13.8 h.

Key words: Pharmacokinetic, intramuscular, long-acting oxytetracycline, sheep

INTRODUCTION

Oxytetracycline is a highly active, broad-spectrum antibiotic which is extensively used in veterinary practice. It is active against aerobic Gram-positive and Gram-negative bacteria, Rickettsia, Mycoplasma and Chlamydia (Riviere and Spoo, 2001). Oxytetracycline is produced by a fermentation process by Actinomycete.

It has been demonstrated that long acting formulation of OTC is the drug of choice for the treatment of some acute as well as for chronic diseases (Cornwell, 1980). The muscle damage of OTC long acting formulation have been criticized by De Banting and Baggot (1996) who reported that local tolerance at I. M. injection site was similar for both long-acting and ordinary formulations.

The pharmacokinetic parameters of different long-acting formulation of OTC has been studied in various animal species including cattle (Xia *et al*., 1983; Fourtivan *et al*., 1989; Meijer *et al*., 1993) and pigs (Elkorchi *et al*., 2001). Ziv and Sulman (1974) published the first report on serum pharmacokinetics of OTC in sheep and cattle. In addition, information on OTC pharmacokinetic in sheep (Nouws *et al*., 1990) and goat is limited (Escder *et al*., 1994).

The objective of the present study, was to determine the pharmacokinetics of OTC in desert sheep after I.M. administration of long-acting formulation at a single dose of 1g kg^{-1} and to evaluate the withdrawal time of the drug.

MATERIALS AND METHODS

Animals: Fifteen healthy males desert sheep, aged 9-12 month and weighing between 35-37 kg were used in this study. The animals were put in pens and fed with balanced feed (concentrate and forage) and water was available ad libitum. All animals passed clinical examination and liver and kidney function tests.

Drug administration and sample collection: After 2 weeks adaptation period, a single dose of 1 mg kg^{-1} body weight of oxytetracycline (Alamycin LA, Norbrook Laboratories Limited Station Work, Ewry, North Ireland) was injected intramuscularly in the cervical muscle and massaged after drug administration. Blood samples were collected from

Corresponding Author: M.H. Al-Nazawi, College of Veterinary Medicine and Animal Resources, King Faisal University, P.O. Box 3498, Al-Ahsa 31982, Saudi Arabia

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.

Drug assay: Oxytetracycline concentration in plasma were measured by using a modification of one-plate test method (Koenen-Dierick *et al.*, 1995 and Koenen-Dierick and DeBeer, 1998), using *Bacillus subtitilis* BGA spores (DSM618) as the test organism.

Pharmacokinetic analysis: Following intramuscular (IM) administration, peak plasma drug concentrations were read directly from the data for each sheep. The OTC plasma concentration versus time data were best fitted by a biexponential equation, $C_p = A_e^{-\alpha t} + B^{-\beta t}$. Consequently a 2 compartment open model was used to describe the plasma disposition of OTC. The relevant pharmacokinetic parameters were calculated following I.M. injection of a single dose of 1 mg kg^{-1} where, C_{max} is the maximum attained drug concentration in the plasma and was featured from the drug plasma-time 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 2 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 αβ (A+B)/ (αA+βB); k_{12} is the rate constant for drug distribution from central to peripheral compartment and calculated by AB $(\beta-\alpha)^2$/ (A+B)/(Aβ+Bα); k_{21} is the rate constant for drug distribution from peripheral to central compartment and calculated by (Aβ+Bα)/(A+B). $V_{d\ (area)}$ is the apparent volume of drug distribution calculated by dose/ ($AUC^0\alpha\times\beta$). AUC^0_{240} is the area under log-transformed drug plasma concentration-time curve from time curve from time zero to infinity and calculated as AUC^0_{240} + (detected drug plasma concentration at 240 h/k_{cl}). Cl_β is the total body clearance of the drug based on the total elimination phase β and was calculated using the formula $V_{d\ (area)} \times \beta$. AUC^0_α is the area under momentum of drug plasma-time curve from time zero to infinity and calculated by trapezoidal rule where it equals AUC^0_{240} + (concentration of the drug at time 240 h ×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 $AUMC^0\ \alpha$/ $AUC^0\ \alpha$.

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

RESULTS

Following intramuscular injection of long-acting tetracycline in a single dose of 1 mg kg^{-1} body weight. The plasma concentration was declined by time (Fig. 1). The pre dose plasma samples were free from any antibiotics. The highest concentration was found to be 74.8±13.22 μg mL^{-1} while minimum concentration was noted to be 4.4±0.18 μg μL^{-1} after 0.75 and 240 h, respectively (Table 1).

The peak plasma concentration C_{max} 74.8±51.2 μg mL^{-1} was evaluated at t_{max} 0.90±0.13 h and the mean distribution phase half[life ($t_{1/2}\alpha$) was noted to be 2±0.4h and the average apparent elimination half-life ($t_{1/2}\beta$) was 126±23 h, k_{cl}, k_{12} and k_{21} values were calculated as being 0.030±0.007, 0.2583±0.06 and 0.0631±0.0027h^{-1}, respectively.

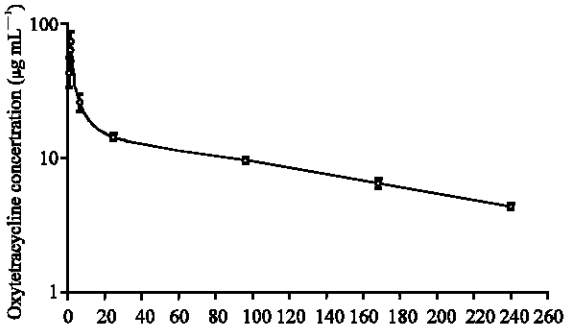

Fig. 1: Mean semi-log plasma concentrations of long-acting oxytetracycline versus time following intramuscular administration of a single dose of 1 mg kg^{-1} body weight to healthy sheep (n = 15)

Table 1: Mean values ± SEM of long-acting oxytetracycline plasma concentrations following intramuscular of 1mg kg^{-1} body weight to healthy sheep (n = 15)

Time (h)	Tylosin concentration (μg mL^{-1})
0	0
0.25	43.4±9.20
0.5	64.6±12.20
0.75	74.8±13.22
1	73.9±13.59
6	26.2±3.81
24	14.5±1.8
96	4±0.65
168	6.67±0.53
240	4.4±0.18

Table 2: Pharmacokinetic parameters (mean±SEM) of long-acting oxytetracycline after single intramuscular administration of 1mg kg^{-1} body weight to healthy sheep (n = 15)

Pharmacokinetic value	Pharmacokinetic parameters
C_{max} (μg mL^{-1})	74.8±51
T_{max} (h)	0.90±0.13
A (μg mL^{-1})	81.2±18
B (μg mL^{-1})	16.51±3.3
α (h^{-1})	0.346±0.0821
β (h^{-1})	0.0055±0.0009
$t_{1/2\alpha}$ (h)	2.00±0.4
$t_{1/2\beta}$ (h)	126±23
K_{el} (h^{-1})	0.0301±0.007
K_{12} (h^{-1})	0.2583±0.063
K_{21} (h^{-1})	0.0631±0.0027
$V_{d(area)}$ (L)	67.933±4.88
AUC^0_{240} (μg/mL/h)	2530.26±203.33
AUC^0_{α} (μg/mL/h)	2676.44±231.86
$AUMC^0_{\alpha}$ (μg/mL/h)	242522.2±48504.5
Cl_{β} (ml h^{-1})	373.63±18.9
MRT (h)	90.61±13.87

C_{max} = is the maximum attained drug concentration in the plasma, T_{max} = is the time at which maximum attained drug concentration in the plasma, A and B = A and B are intercepts of slopes of the initial distribution phase and the terminal elimination phase, α and , β = are the rate constants associated with distribution and elimination phases, $t_{1/2\alpha}$ and $t_{1/2\beta}$ = are the distribution and total body elimination half-lives of the drug, K_{el} = is the rate constant for the drug elimination from the central compartment, K_{12} = is the rate constant for the drug elimination from the central compartment, K_{21} = is the rate constant for drug distribution from central to peripheral compartment, $V_{d(area)}$ = is the apparent volume of drug distribution, AUC^0_{240} = is the area under log-transformed drug plasma concentration-time curve from time zero to infinity, AUC^0_{α} = is the area under momentum of drug plasma-time curve from time zero to infinity, $AUMC^0_{\alpha}$ = area under concentration-time curve from time zero to infinity, Cl_{β} = is the total body clearance of the drug, MRT = is the mean resident time for the drug in the body

DISCUSSION

Maximum concentration (C_{max}) and time to reach this concentration (t_{peak}) are represented in Table 2. The observed C_{max} (74.8 μg mL^{-1}) of oxytetracycline long-acting (OTC-LA) preparation in sheep was similar to that reported in hens (75.76 μg mL^{-1}) (Moreno *et al.*, 1996) but higher than those reported in calves (5.20 μg mL^{-1}) and sheep (6.09 μg mL^{-1}) by Craigmill *et al.* (2000). This could be due to the difference in dose level and method of evaluation.

The t_{max} was nearly similar to those reported in sheep (1.7 h) and in fallow deer (0.7 h) by Escder *et al.* (1996) and Haigh *et al.* (1997) but lower than that obtained in sheep (3.5 h) and calves (2.83 h) by Craigmill *et al.* (2002). The difference in values could be due to difference in breed.

Following intramuscular administration, the absorption half-life ($t_{1/2\alpha}$ 2 h) and the time to maximum concentration (t_{max} 0.9 h) indicated that OTC-LA is rapidly absorbed in sheep at the beginning, but afterwards, absorption extends over along period of time (MRT 90.6 h). However, $t_{1/2\alpha}$ was similar to that reported in hens (121.65 min), after intravenous administration (Serrano *et al.*, 1999) and that (Escder *et al.*, 1996) in goat (1.4 h) after intramuscular injection.

The observed elimination half-life ($t_{1/2\beta}$ 126 h) in sheep was higher than those reported before (58.2 h) by Moreno *et al.* (1996) and (20.6 h) Craigmill *et al.* (2000), the variation could be due to the difference in elimination process, body size, temperature and age.

As shown in Table 2 k_{el}, k_{12}, k_{21} ratio were nearly similar to those reported in hens (k_{el}, 2.90, k_{12} 0.94, k_{21} 0.78 h^{-1}) (Moreno *et al.* (1996) and lower than that reported in calves (k_{el}, 1.23, k_{12} 0.033, k_{21} 0.031 h^{-1}) by Craigmill *et al.* (2000). This indicated that the drug was slowly eliminated from the body, a similar conclusion was observed from OTC-LA in cattle (FAO, 1995).

The apparent volume of distribution ($V_{d\ (area)}$) was much higher than that reported in sheep (3.08 L), calves (3.30 L) (Craigmill *et al.*, 2000) and goat (7.69 L) (Escder *et al.*, 1996). The variations found may be due to the difference in species, plasma protein binding and pharmacokinetic model. While higher values were reported in turkeys (360 μL kg^{-1}) (Dyer, 1989), suggesting extensive penetration of the drug into tissue and this could be due to high solubility of the drug.

As shown in Table 2 the mean values of AUC^0_{240}, AUC^0_{α} and $AUMC^0_{\alpha}$ were higher than those reported in sheep (209 μg/h/ml), calves (168 μg/h/ml) (Craigmill *et al.*, 2000). This variations could be due to species difference, dose level and pharmacokinetic model.

The observed Cl_{β} value in this study was higher than those reported previously in goat 3.1 mL h^{-1} and 4.7 mL h^{-1} (Escder *et al.*, 1996; Elsheikh *et al.*, 1997), respectively.

The MRT value observed was high (90.61 h) and nearly similar to that reported in pigs (85 h) (Elkorchi *et al.*, 2001). But contrasted with the MRT observed by (Escder *et al.*, 1996) in sheep (35.90 h) and goats (37.52 h). In conclusion the different in pharmacokinetics in this study may be attributed to a different compartmental modeling.

REFERENCES

Cornwell, R.L., 1980. Evaluation of long acting injectable oxytetracycline. Modern Veterinary Practice, 61: 954-957.

Craigmill, A.L., R.E. Holland, D. Robinson, S. Wetzlich and T. Arndt, 2000. Serum pharmacokinetics of oxytetracycline in sheep and calves and tissue residues in sheep following a single intramuscular injection of long-acting preparation. J. Vet. Pharmacol. Therap., 23: 345-352.

De Banting, A.I. and J.D. Baggot, 1996. Comparison of the pharmacokinetics and local tolerance of 3 injectable oxytetracycline formulation in pigs. J. Vet. Pharmacol. Therap., 19: 50-55.

Dyer, D.C., 1989. Pharmacokinetics of oxytetracycline in Turkey: Evaluation of biliary and urinary excretion. Am. J. Vet. Res., 50: 522-524.

Elkorchi, G., C. Prats, M. Arboix and B. Perez, 2001. Disposition of oxytetracycline in pigs after I.M. administration of 2 long-acting formulations. J. Vet. Pharmacol. Therap., 24: 247-250.

Elsheikh, H.A., I.A. Osman and B.H. Ali, 1997. Comparative pharmacokinetics of ampicillin trihydrate, gentamicin sulphate and oxytetracycline hydrochloride in Nubian goats and desert sheep. J. Vet. Pharmacol. Therap., 20: 262-266.

Escder, E., C.M. Carceles, C. Ponferrada and J.D. Baggot 1996. Pharmacokinetics of long-acting formulation of oxytetracycline in sheep and goats. J. Vet. Pharmacol. Therap., 19: 75-77.

Escder, E., C.M. Carceles and J.M. Serrano, 1994. Pharmacokinetics of oxytetracycline in goats: Modifications induced by long-acting formulation. Vet. Rec., 135: 548-552.

FAO, 1995. Residues of some veterinary drug in animals and food, Rome, F.A.O.

Fourtivan, J.B., I. Ingrand and J. Moreav, 1989. Biodisponibites de I oxytetracycline chez les bovines aprez administrations intramusculaire-Recueil. De Med. Vet., 165: 727-731.

Haigh, J.C., P.M. Dowling and J.G. Smits, 1997. Pharmacokinetics of long-acting oxytetracycline in fallow deer (Damadama). J. Vet. Pharmacol. Therap., 20: 243-245.

Koenen-Dierick, K. and O. De Berry, 1998. Optimization of antibiotic residue screening test, based on inhibitor of *Bacillus subtilis* BGA, with experimental design. Food Additive and Contamination, 15: 528-534.

Koenen-Dierick, K., L. Oker Man, L. Dezulter, J.M. Degroodlt, J. Vanltoof and S. Srebmik, 1995. A one-plate microbiological secreening test for antibiotic residues. Testing in kidey tissue and meat and alternative to ECC four-plate method. Food Additive and Contamination, 12: 77-82.

Meijer, L.A., K.G.F. Ceyssens, W.T.G. Dejong and B.I.J.A. Greve, 1993. Three phase elimination of oxytetracycline in veal calves: The presence of an extended terminal elimination phase. J. Vet. Pharmacol. Therap., 16: 214-222.

Moreno, L., J.M. Serrano, A. Reja, E. Guimero and E. Escudero, 1996. Pharmacokinetics of oxytetracycline after intravenous administration at 2 dose levels to hens. J. Vet. Pharmacol. Therap., 19: 495-497.

Nouws, J.F.M., A. Smulders and M. Rappalini, 1990. A comparative study on irritation and residues aspect of 5 oxytetracycline formulations administrated intramuscularly to calves, pigs and sheep. Vet. Q., 12: 129-138.

Riviere, J.E. and J.W. Spoo, 2001. Tetracycline Antibiotics. In: Veterinary Pharmacology and Therapeutic, Adams, R.H. (Ed.). 8th Edn. Iowa State University Press Ames, Iowa, pp: 828-841.

Serrano, J.M., L. Moreno, I. Rosado and E. Guimera, 1999. Biliary elimination kinetics and tissue concentrations of oxytetracycline after intravenous administration in hens. J. Vet. Pharmacol. Therap., 22: 148-152.

Xia, W., P. Neilsen and N. Gyrd-Hensen, 1983. Comparison of pharmacokinetic parameters for 2 oxytetracycline preparations in cows. Acta Vet. Scand., 24: 120-128.

Ziv, G. and F.G. Sulman, 1974. Analysis of pharmacokinetic properties of 9 tetracycline analogs in dairy cows and ewes. Am. Vet. Res., 35: 1197-1201.