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EFFECT OF FEVER ON PHARMACOKINETICS OF OXYTETRACYCLINE IN CAMELS

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ABSTRACT
In this study, the effect of fever on the pharmacokinetics of long acting preparation of oxytetracycline (OTC) after intramuscular administration was investigated in camels. Injection of endotoxin lipopolysaccharide at a dose of 0.1 µg/kg in camels produced fever. Administration of long acting oxytetracycline at a dose of 10 mg/kg body weight intramuscularly to camels resulted in significantly higher concentration of antibiotic in febrile compared to normal camels. A higher mean plasma level, longer half-life and higher area under curve were observed in febrile compared to normal camels, suggesting favorable pharmacokinetic of oxytetracycline in febrile conditions. A high concentration of antibiotic in healthy and febrile condition 72 hours post-dosing would suggest persistent protection and efficacy for several days after a single intramuscular dose in camels.

KEYWORD: Camel, fever, Pharmacokinetics, intramuscular, oxytetracycline.

INTRODUCTION

Tetracyclines are one of the most extensively used antibiotics in the veterinary practice owing to its favourable pharmacokinetics and broad spectrum of antimicrobial efficacy. Tetracyclines are effective on gram-positive, gram-negative bacteria, Chlamydia, spirochetes and some protozoa (Prescott and Baggot, 1993). Oxytetracycline is a tetracycline with broad-spectrum antibacterial therapy, which normally requires some daily parenteral treatment (Roncada *et al.*, 2000). It has been demonstrated that a long-acting formulation of OTC is the drug of choice for treatment of some acute and chronic diseases (Cornwell, 1980). Oxytetracycline is a valuable choice in both of systemic and localized or tissue infections due to its balanced distribution between the blood and tissues (MERCER *et al.*, 1978; Grondel *et al.*, 1987). The pharmacokinetics of long-acting preparations of OTC have been extensively studied in various animal species, including cattle (Craigmill *et al.*, 2000), sheep (Nouws *et al.*, 1990), goat (Escudero *et al.*, 1996), pigs (Escudero *et al.*, 1996), fallow deer (Haigh *et al.*, 1997) and camel (Al-Nazawi and Homeida, 2002). However, information on the pharmacokinetics of most of antibacterial in camel is limited. The objective of the present investigation is to determine the pharmacokinetic properties of long acting oxytetracycline in normal and febrile camels after intramuscular administration.

MATERIALS & METHODS

Animals

Eight clinically healthy males and females one humped camels (*Camelus dromedarius*) 3-6 years old and ranging in body weight from 220-320kg were used. They were kept in separate pens and allowed free access to hay and water.

Drug administration

Animals were divided into two equal groups. Group 1, animals were given long acting oxytetracycline dihydrate (200mg/ml, Alamycin LA, Norbrook, UK) as a bolus i.m. injection at a dose of 10mg/kg body weight. The drug was also given to group 2 animals after induction of fever by endotoxin.

Induction of febrile state

Fever was induced by injecting lipopolysaccharide of *E. coli* (055: B) of (Difco Laboratories, Detroit, MI, USA) at a dose rate of 0.1µg/kg body weight intravenously (i.v.). A rise of rectal temperature of 1ºC 1/2 to 1 hour post injection is considered as febrile animals.

Collection of blood samples

Jugular blood samples were taken prior to and at 10, 20-, 30 minutes, 1, 2, 4, 6, 8, 16, 24, 72, 96 and 120 hours after administration of the drug. The blood samples were allowed to clot; serum is separated by centrifuged at 1200g for 5 minutes and stored at -20 ºC until analysis.

Analysis of oxytetracycline

Quantitation of oxytetracycline (OTC) in serum samples was accomplished using modification of the microbial inhibition assay (Nouws *et al.*, 1990; Al-Nazawi and Homeida, 2002). Bioassay plates were prepared by placing 9.5g Mueller Hinton Medium (Difco Laboratories, Detroit, MI, USA) and 250ml H_2O into 500ml Erlenmeyer flask which was autoclaved for 20 min solution then cooled to 50 ºC in a water-bath. One milliliter of a commercially available *Bacillus cereus* spore suspension (Difco Laboratories) was diluted in 50 ml of sterile saline and 0.4 ml of the diluted suspension is added to the media. After pouring and solidification of the media, 500 µl wells were cut into the solidified bioassay plates. Serum samples (500 µl) were placed directly into the wells without a cleanup step. Standards prepared using control serum was also added to each plate, and the plates are incubated overnight

at room temperature (23 ºC). Zones of inhibition were measured using micrometers and the results from the standards used to calculate the OTC concentration in each sample.

Pharmacokinetic analysis

The data from serum concentration of OTC in camels were analyzed using PKSolver (Zhang *et al.*, 2010). Different models were used assuming noncomartmental, one compartment or two compartments kinetic model. Filtering and selection of the appropriate model was analyzed by examination of diagnostic parameters, taking r2 as a measure of fitting accuracy. The Parameters calculated included area under the curve (AUC), distribution rate constants (a, b), y intercepts (A, B), Mean residence time (MRT), volume of distribution at steady state (Vss), halflife (t½), maximum concentration (C_{max}) and time of maximum concentration (t_{max}). The area under curve was calculated by a linear trapezoid method.

RESULTS

Administration of endotoxin to camels at a dose of 0.1µg/kg body weight produced a consistent increase in rectal temperature with peak (41.6ºC) at 3hours after its injection. The comparison of oxytetracycline in serum of normal and febrile camels at various time intervals is represented graphically in Fig. 1. The drug appeared in serum at the same time. The maximum concentration was 1.7 µg/ml in febrile animals significantly higher than 0.8 µg/ml in normal animals. Interestingly, the time required to achieve the maximal plasma concentration was smaller in febrile than in normal animals (2.25 and 1.8 hours, respectively). The concentration of antibiotic was 0.22 µg/ml in normal and 0.42 µg/ml in febrile camels at 72 hours post antibiotic injection. The pharmacokinetic parameters of oxytetracycline in normal and febrile animals are given in Table 1. The values for elimination half-life ($t_{1/2}$), area under curve (AUC), and mean residential time (MRT) were significantly higher in febrile camels as compare to normal camels.

TABLE 1: Pharmacokinetic parameters of oxytetracycline (10 mg/kg) given as a single intramuscular dose in normal or febrile camels.

Parameter	Unit	Normal	Febrile
A	µg/ml	0.43	33.94
Alpha	1/h	0.027	0.69
B	µg/ml	0.51	1.00
Beta	1/h	0.017	0.012
ka	1/h	2.023	0.75
Parameter	Unit	Value	Value
k10	1/h	0.020	0.045
k12	1/h	0.0012	0.468
k21	1/h	0.022	0.198
Tmax	h	2.25	1.83
Cmax	µg/ml	0.89	1.7
AUC 0-t	µg/ml*h	34.34	49.5
AUC 0-inf	µg/ml*h	45.14	80.3
t1/2	h	33*	49*
MRT	h	46	71
Diagnostics	Normal	Febrile	
r obs-pre	0.977	0.95	
R^2	0.99	0.97	

*Based on noncopmartmental analysis

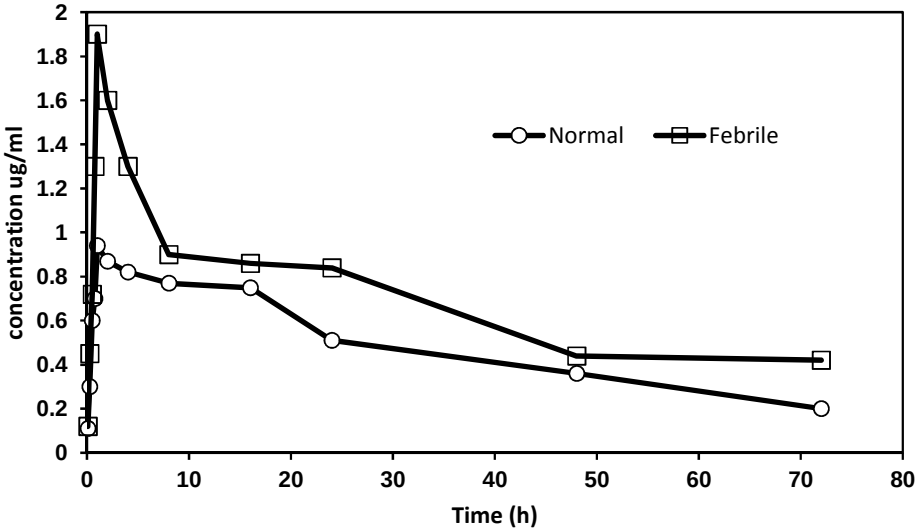
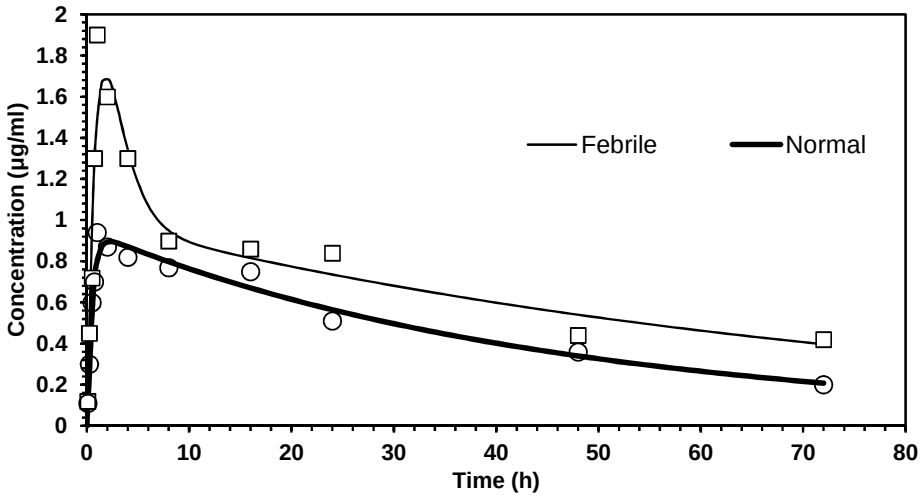


FIGURE 1: The plasma concentrations versus time of oxytetracycline (10 mg/kg) given as a single intramuscular dose in normal or febrile camels. The data were analyzed by noncompartmental analysis (A) and 2 compartments model (B).



DISCUSSION

In this study, the pharmacokinetics of long acting preparation of oxytetracycline was estimated in normal and febrile camels. Fever was induced in camels by by administration of endotoxins as previously described (Al-Dughaym, 2004). The serum oxytetracycline concentrations were constantly higher in febrile than in normal camels (Al-Nazawi and Homeida, 2002) and probably as a result of significant slower elimination and total body clearance observed in febrile camels. Significant increase in $t_{1/2}$ obtained in febrile camels over that of normal camels suggests that oxytetracycline is removed from the body at slower rate in febrile condition compared to normal state. Endotoxin induced fever can result in various haemodynamic changes (Bradley, 1979; Al-Dughaym, 2004) including decrease in blood pressure, cardiac output, glomeular filteration, renal blood flow and decreased hepatic drug metabolism (Roth *et al.*, 1997), all contributing to lower clearance rate and longer $t_{1/2}$. The observed Cmax in this study indicates that the maximal plasma concentration is lower in camels compared with other animals. Cmax was 6.09 µg/ml in sheep (Craigmill *et al.*, 2000), 5.7µg/ml in calves (Kumar and Malik, 1998) and 4.4 µg/ml in dogs (Kikuvi *et al.*, 2001). This is due to the differences in the pharmaceutical formulation and slower absorption of the drug from the injection site. The present profile of long acting formulation in camels indicated lower Cmax compared with the non-long acting formulations; however, highly persistent plasma concentrations were detectable for about 3 days. Moreover, the plasma-drug concentration was higher in febrile camels. The higher AUC observed in febrile compared to normal camels would suggest a better clinical benefits of fever as it enhances the capacity of drug to penetrate cellular barriers (Booth and McDonald, 1988). Significantly, longer MRT in febrile condition compared to normal state may be due to cardiovascular changes associated with fever during which peripheral circulation increases (Pennington *et al.*, 1975; El Korchi *et al.*, 2001). Higher MRT indicated more residence of the drug in camels tissues and fluids, giving a clinical advantage of prolonged drug effect in feverish conditions. Rikihisa and Jiang have shown that *invitro* concentrations of oxytetracycline above 0.01 µg/ml effectively suppress bacterial growth (Rikihisa and Jiang, 1988). In this study a mean concentration of 0.22 µg/ml and 0.42 µg/ml was maintained in normal and febrile states at 72 hours post antibiotic dosing, suggesting that dosing regimen of long acting oxytetracycline perform a sufficiently high and prolonged plasma concentrations in camels that may be effective in controlling chronic diseases and long standing infections.

REFERENCES

Al-Dughaym, A.M. (2004) Some endotoxin-induced clinical and biochemical changes in plasma of camels (camelus dromedarius). Vet Res Commun, 28(8): 711-718.

Al-Nazawi, M. & Homeida, A. (2002) Disposition kinetics of oxytetracycline after a single intravenous injection in the arabian camel. JOURNAL OF CAMEL PRACTICE AND RESEARCH, 9(1): 5-8.

Booth, N. H. & McDonald, L. E. (1988) Veterinary pharmacology and therapeutics. Iowa State University Press.

Bradley, S. (1979) Cellular and molecular mechanisms of action of bacterial endotoxins. Annual Reviews in Microbiology, 33(1): 67-94.

Cornwell, R.L. (1980) Evaluation of a long-acting injectable oxytetracycline. Mod Vet Pract, 61(11): 945-947.

Craigmill, A.L., Holland, R.E., Robinson, D., Wetzlich S. & Arndt, T. (2000) Serum pharmacokinetics of oxytetracycline in sheep and calves and tissue residues in sheep following a single intramuscular injection of a long-acting preparation. J Vet Pharmacol Ther, 23(6): 345-352.

El Korchi, G., Prats, C., Arboix, M. and Perez, B. (2001) Disposition of oxytetracycline in pigs after im administration of two long-acting formulations. J Vet Pharmacol Ther, 24(4): 247- 250.

Escudero, E., Carceles, C. M., Ponferrada, C. and Baggot, J. D. (1996) The pharmacokinetics of a long-acting

formulation of oxytetracycline in sheep and goats. J Vet Pharmacol Ther, 19(1): 75-77.

Grondel, J., Nouws, J., Jong, M.D., Schutte, A. and Driessens, F. (1987) Pharmacokinetics and tissue distribution of oxytetracycline in carp, cyprinus carpio l., following different routes of administration. Journal of Fish Diseases, 10(3): 153-163.

Haigh, J.C., Dowling, P.M. and Smits, J.G. (1997) Pharmacokinetics of long-acting oxytetracycline in fallow deer (dama dama). J Vet Pharmacol Ther, 20(3): 243-245.

Kikuvi, G.M., Mitema, E. S. & Buoro, I. B. (2001) The pharmacokinetics of a long-acting oxytetracycline formulation in healthy dogs and in dogs infected with ehrlichia canis. Vet Res Commun, 25(5): 391-400.

Kumar, R. and Malik, J.K. (1998) Some pharmacokinetic parameters and dosage regimens for a long-acting formulation of oxytetracycline in 6- to 8-month-old male calves. Vet Res Commun, 22(8): 533-544.

Mercer, H.D., Teske, R.H., Long, P.E. & Showalter, D.H. (1978) Drug residues in food animals ii. Plasma and tissue kinetics of oxytetracycline in young cross-bred swine. J Vet Pharmacol Ther, 1(2): 119-128.

Nouws, J.F., Smulders, A. and Rappalini, M. (1990) A comparative study on irritation and residue aspects of five oxytetracycline formulations administered intramuscularly to calves, pigs and sheep. Vet Q, 12(3): 129-138.

Pennington, J.E., Dale, D.C., Reynolds, H.Y. and MacLowry, J. D. (1975) Gentamicin sulfate pharmacokinetics: Lower levels of gentamicin in blood during fever. J Infect Dis, 132(3): 270-275.

Prescott, J. F. and Baggot, J. D. (1993) Antimicrobial therapy in veterinary medicine. Iowa State University Press.

Rikihisa, Y. and Jiang, B.M. (1988) In vitro susceptibilities of ehrlichia risticii to eight antibiotics. Antimicrobial agents and chemotherapy, 32(7): 986-991.

Roncada, P., Ermini, L., Schleuning, A., Stracciari G.L. & Strocchia, A. (2000) Pharmacokinetics and residual behaviour in milk of oxytetracycline in cows following administration of uterine pessaries. J Vet Pharmacol Ther, 23(5): 281-285.

Roth, R.A., Harkema, J.R., Pestka, J.P. and Ganey, P.E. (1997) Is exposure to bacterial endotoxin a determinant of susceptibility to intoxication from xenobiotic agents? Toxicology and applied pharmacology, 147(2): 300-311.

Zhang, Y., Huo, M., Zhou, J. and Xie, S. (2010) Pksolver: An add-in program for pharmacokinetic and pharmacodynamic data analysis in microsoft excel. Comput Methods Programs Biomed, 99(3): 306-314.