

COMPARATIVE PHARMACOKINETIC STUDIES ON OXYTETRACYCLINE IN CAMELS, SHEEP AND GOATS

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ABSTRACT

Kinetics of long-acting oxytetracycline (OTC) injected intravenously (IV) at a dose of 5 mg/kg was determined in each of eight camels, sheep and goats. The disposition of OTC was described by two-compartment open model. Two elimination half-lives were recorded for the camel (81 min and 46.1 h), whereas in sheep and goats these were 3.2 and 3.4 h, respectively. The peak plasma concentration was 10.2, 850 and 780 µg/ml at 5 minutes in camel, sheep and goats, respectively. The values of volume of distribution were 1.4, 13.4 and 12.1 litre/kg for the camels, sheep and goats, respectively. In sheep and goats, values of $t_{1/2}$, V_d and clearance were found similar but different from camel, indicating exclusive distribution and substantial storage which were consistent with oxytetracycline lipophilicity and the large fat content of camel body.

Key words: Camel, goat, sheep, pharmacokinetics, oxytetracycline

INTRODUCTION

Oxytetracycline (OTC) is a broad-spectrum antibiotic that inhibits the growth of many pathogenic organisms, including bacteria, mycoplasma and some protozoa (Prescott and Baggot, 1993). It is widely used in veterinary medicine for the treatment of respiratory and gastrointestinal infections (Payne *et al.*, 2002). It has been demonstrated that a long-acting formulation of OTC is the drug of choice for treatment of some acute, as well as for protracted, diseases (Cornwell, 1980). There have been numerous studies carried out on the pharmacokinetics of OTC in various animal species, including cattle (Mawhinney *et al.*, 1996; Craigmill *et al.*, 2000; Roncada *et al.*, 2000), Sheep (Craigmill *et al.*, 2000), goat (Escudero *et al.*, 1996; Payne *et al.*, 2002), pigs (Nielsen and Gyrd-Hansen, 1996) and fallow deer (Haigh *et al.*, 1997). However, information on the pharmacokinetics of most of antibacterials in camel is limited. Moreover, an original term "geonetic" has been coined to describe environmental influences on the genetics which are manifested by characteristics biochemical and physiological parameters which ultimately affect the biodisposition and fate of drugs in population (Nawaz *et al.*, 1988; Nouws *et al.*, 1986; 1990). Such geonetical influences have been reported for blood and urine pH, blood proteins, drug metabolism and kidney function in buffaloes, cows, sheep, goats and camels (Nawaz *et al.*, 1988; Al-Dughaym *et al.*, 1998). From these studies it may be

concluded that biochemical and physiological parameters are influenced by geonetical conditions which ultimately affect the disposition kinetic, fate and response to drugs. For example, sulphonamides and antibiotics under indigenous geonetical conditions are different from disposition recorded elsewhere (Nawaz and Khan, 1979; Homeida *et al.*, 1981; Homeida, 1999). Therefore, it is imperative that an optimal dosage regimen should be based on the pharmacokinetics data determined in the species and environment in which a drug is to be employed clinically. This study was planned to investigate pharmacokinetics of oxytetracycline in camels, sheep and goats following IV injections of a single dose (5 mg/kg).

MATERIALS AND METHODS

Experimental animals

For the comparative pharmacokinetic studies of oxytetracycline in camels, sheep and goats, 24 animals were used, eight each of camels, sheep and goats including four male and four females in each species. The animals were allowed to rest for certain time to make sure none of them had received any medication for at least 8 weeks prior to OTC administration. Water, hay and concentrate supplements were provided *ad libitum*. Description of experimental animals is given in Table 1.

Table 1: Description of experimental animals

Animals	Breed	No. of animals		Age (years)	Weight (kg)
		Male	Female		
Camel	----	4	4	3-6	200-320
Sheep	Neimi	4	4	2-3	60-65
Goat	Ardi	4	4	3-4	45-55

Drug administration and blood sampling

Oxytetracycline hydrochloride (Oxtra, Fatro, Italy) solution was administered as intravenous (IV) bolus injection at a dose of 5 mg/kg body weight to experimental animals. Prior to drug administration, a control blood sample was collected from each animal from the jugular vein in heparinized tubes. Following drug administration the blood sample were drawn at 5, 10, 15, 30, 45 and 60 minutes and then at hourly intervals upto 8 hours, followed by samples collected at 10, 24, 48, 72, 96 and 120 hours postmedication. The blood samples were allowed to clot, serum was separated by centrifugation ($1200 \times g$ for 5 min) and was stored at -20°C until analysis. Oxytetracycline was estimated by the method of Pilloud (1973). Trichloroacetic acid was used for deproteinization and acidification of samples. Fluorescence was measured in spectrophotometer (Pyunicam, England) at wavelength of 436 nm.

Pharmacokinetic analysis

Kinetic parameter were calculated according to Baggot (1977). Mean values and variables were calculated.

Statistical analysis

Analysis of variance was performed with species as treatments. When a significant "F" value was obtained, Duncan's Multiple Range Test was used to determine which species was different from the other (Steel and Torrie, 1984).

RESULTS

The mean peripheral plasma concentrations of OTC in camels, sheep and goats were best described by a two-compartment open model (Fig. 1). Values of the kinetic parameters are presented in Table-2. Two elimination half-lives were recorded for the camel ($t_{1/2\beta_1} = 81$ minutes and $t_{1/2\beta_2} = 46.1$ h). Elimination half-lives in sheep and goats were 3.2 and 3.4 h, respectively. The values of distribution half life ($t_{1/2\alpha}$) were 8.1 minutes in camels, 7.0 minutes in sheep and 7.6 minutes in goats.

In camel, after a decline there was an increase of OTC plasma concentration about 6 h post-injection, reaching a maximum of $3.1 \mu\text{g/ml}$ at 7 hour post-injection and then declined thereafter producing a trough-like pattern. The new half-life of this elimination phase was 46.1 h. Such pattern was absent in plasma of sheep and goats. The volume of distribution was 1.4 L/kg in camels, 13.4 L/kg in sheep and 12.1 L/kg in goats.

Statistical comparisons were made between different kinetic parameters of the three animals species and are presented in Table 2.

DISCUSSION

The curve describing the pharmacokinetic behavior of OTC in the camel looks, at least in the first part, similar to sheep and goats and other species (Oukessou *et al.*, 1992; Ali, *et al.*, 1996). The distribution half-life ($t_{1/2\alpha}$) is shorter than that reported for dogs, cows, ewes, swines and horses (Pilloud, 1973; Ziv and Sulman, 1974; Schifferlin *et al.*, 1982). The drug has been reported to follow a 2-compartment open model in the three animal species (Oukessou *et al.*, 1992). In camel during the first 5 hours after injection, the drug followed a similar pattern as in other ruminant species (Pilloud, 1973). The first elimination half-life ($t_{1/2\beta_1}$) in the present study is similar in the 3 animal species but is less than the values reported for horses and cows (Teske *et al.*, 1973; Pilloud, 1973). The elimination of second phase ($t_{1/2\beta_2}$) of the curve was also longer than reported in horses and cows (Toutain and Raynaud, 1983). The estimated values for elimination constants (K_{12} & K_{21}) were similar to those in buffalo (Varma and Paul, 1983). Volume of distribution (V_d) of the drug in the camel was similar to V_d in cows and swines (Pilloud, 1973; Mercer *et al.*, 1978) but was smaller than that of sheep and goat. The V_d of oxytetracycline in camel is larger than the volume of its body water indicating excellent penetration of the drug in all of the body fluids (Gilman *et al.*, 1991). Such property is highly recommended since an antibiotic efficacy depends on its penetration into tissue (Ibrahim, 1988; Mercer *et al.*, 1978).

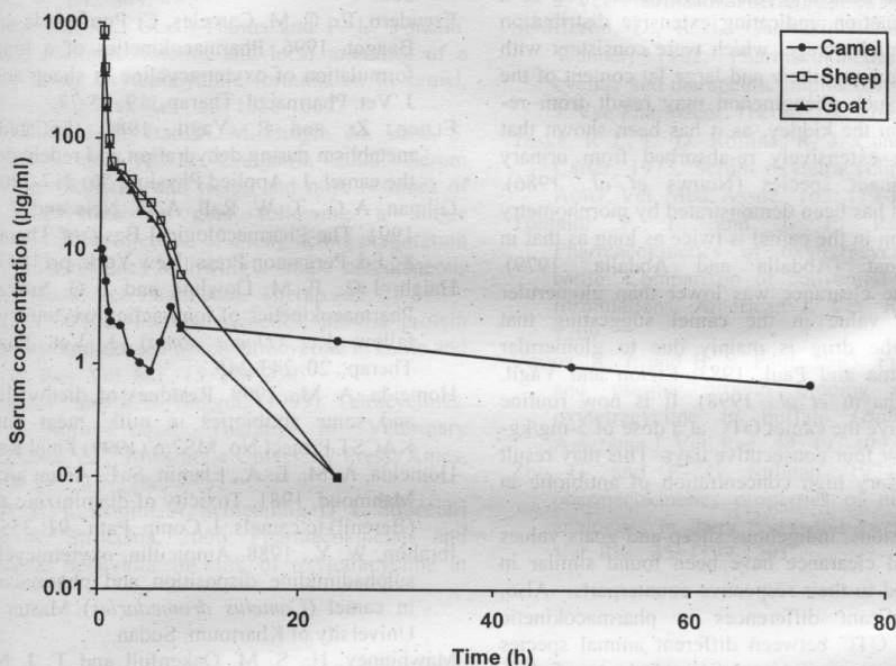


Fig. 1: The semilogarithmic plot of oxytetracycline concentration in plasma versus time follow in IV administration of a single dose of 5 mg/kg to camel, sheep and goats (n=8).

Table 2: Pharmacokinetic parameters of oxytetracycline in camels, sheep and goats after a single IV bolus of 5 mg/kg body weight (n=8)

Disposition Parameters	Camel	Sheep	Goat
C_{max} (µg/ml)	10.2	850	780
T_{max} (min)	5.0	2.0	2.0
A (µg/ml)	7.5	720	690
B (µg/ml)	3.3	250	320
C_p^0 (µg/ml)	10.8	7.0	8.2
$T_{1/2}(\alpha)$ (min)	8.1	7.0	7.6
$T_{1/2}(\beta_1)$ (h)	2.8	3.2	3.4
$T_{1/2}(\beta_2)$ (h)	46.1	-	-
K_{12} (min ⁻¹)	0.0491	0.0325	0.031
K_{21} (min ⁻¹)	0.0293	0.0158	0.0144
K_{el} (min ⁻¹)	0.01321	0.0126	0.012
V_d (area) (l/kg)	1.4112	13.4	12.1
Cl_B (ml/min/kg)	0.0072	0.0014	0.0012

C_{max} = peak concentration; T_{max} = time of peak; A = zero-time intercept of distribution phase; B = zero-time intercept of elimination phase; C_p^0 = plasma drug concentration at time zero after drug administration; $t_{1/2}(\alpha)$ = half-life of distribution phase; $t_{1/2}(\beta_1)$, $t_{1/2}(\beta_2)$ = elimination half-lives of phase I & II, respectively; K_{12} = rate of transfer of drug from central to peripheral compartments; K_{21} = rate of transfer of drug from peripheral to central compartments; K_{el} = elimination rate constant from central compartment; V_d (area) = volume of drug distribution; Cl_B = total body clearance of the drug.

* indicate statistically significant difference ($P < 0.05$).

After 5 hours post-injection, the drug level showed a characteristic peak and trough profile, as well as a biphasic elimination, indicating extensive distribution and/or substantial storage, which were consistent with oxytetracycline lipophilicity and large fat content of the camel body. Such phenomenon may result from re-absorption from the kidney, as it has been shown that antibiotics are extensively re-absorbed from urinary tract in ruminant species (Nouws *et al.*, 1986). Furthermore, it has been demonstrated by morphometry that the nephron in the camel is twice as long as that in cow and goat (Abdalla and Abdalla, 1979). Oxytetracycline clearance was lower than glomerular filtration rate value in the camel suggesting that excretion of the drug is mainly due to glomerular filtration (Varma and Paul, 1983; Etzion and Yagil, 1985; Al-Dughaym *et al.*, 1998). It is now routine procedure to give the camel OTC at a dose of 5-mg/kg-body weight for four consecutive days. This may result in an unnecessary high concentration of antibiotic in camel.

In conclusions, indigenous sheep and goats values of $t_{1/2}$, V_d and clearance have been found similar in OTC compared to their respective counterparts. Also, due to significant differences in pharmacokinetic parameters of OTC between different animal species (camel, sheep, goat), extrapolation of doses of drug from one species to another should be avoided.

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