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PHARMACOKINETIC DATA ON DOXYCYCLINE AND ITS DISTRIBUTION IN DIFFERENT BIOLOGICAL FLUIDS IN FEMALE GOATS

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ABSTRACT

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A pharmacokinetic study of doxycycline after intravenous administration at 5 mg/kg body weight in goats revealed that a concentration of ≥ 0.5 μg/ml was maintained for 5 min–2 h, 4–12 h, 2–12 h and 5 min–>48 h in plasma, interstitial fluid, milk and urine respectively. The low $t_{1/2\alpha}$ of 0.73 ± 0.11 h and high $t_{1/2\beta}$ of 16.63 ± 1.58 h show that the drug is rapidly distributed but slowly eliminated from the body. The tissue:plasma concentration of 4.86 ± 1.06 during the elimination phase [$K_{12}/(K_{21}-\beta)$] indicates a high expected tissue concentration, which is supported by similarly increased drug concentration in interstitial fluid and milk. The high Vd_{area} of 9.78 ± 0.86 L/kg observed denotes that, apart from its wide distribution, the drug may be stored in fat depots as it is known to be highly lipophilic. As the drug maintained a therapeutic concentration for a shorter time in plasma, and the calculated dose rate for maintaining a minimal plasma concentration of 0.5–1.5 μg/ml is relatively high, it may not be of much use in treating septicaemia in this species. Since the observed tissue:plasma concentration was higher and a therapeutic concentration was maintained in interstitial fluid and milk for longer, the drug can be used for other systemic infections at a lower dose rate than that required for treating septicaemia. As the drug maintained a very high concentration in urine, it may be of particular value in treating urinary tract infections caused by sensitive micro-organisms.

INTRODUCTION

Tetracycline and oxytetracycline are the most widely and routinely used tetracyclines in the treatment of various microbial infections in veterinary practice. Doxycycline, another member of the tetracycline series, is now widely employed in human practice for its high bioavailability, prolonged maintenance of therapeutic concentration and greater efficacy against many infective organisms (Sande and Mandell, 1980). Doxycycline has been introduced very recently into veterinary practice in India and only a few reports are available on the pharmacokinetics of this drug in animals, particularly goats. To be effective in a particular infection, the drug should be present at a therapeutic concentration in the target organ throughout its course of action. This can be achieved judiciously if the dosage regimen is derived from a pharmacokinetic study of the concentration of the drug in plasma and tissues or tissue fluids. The present study was carried out to obtain such data.

MATERIALS AND METHODS

The experiments were conducted on six apparently healthy lactating goats weighing 25–30 kg. For collection of interstitial fluids, two multiperforated (each perforation of 6 mm diameter) table tennis balls were aseptically implanted subcutaneously in the neck and flank region of each animal using the technique of Kozak *et al.* (1977). After 4–5 weeks it was possible to aspirate interstitial fluid with the help of a sterile syringe and hypodermic needle. Urine was collected by introducing a Foley's balloon catheter (No.14) into the bladder through the urethra, and holding it in position by inflating the balloon by injecting 20 ml of air. Milk was collected manually.

A doxycycline hydrochloride capsule (Duracycline, Unichem Laboratories Ltd., India) equivalent to 100 mg of doxycycline base, was dissolved in sterile distilled water and the solution (5 mg/ml) was injected intravenously (i.v.) at 5 mg/kg body weight into each animal. Samples of plasma, interstitial fluid, milk and urine were collected at 5, 15, 30 and 45 min and at 1, 2, 4, 8, 12, 24, 30, 36 and 48 h after administration of the drug. Assays of doxycycline in these body fluids were carried out by a cylinder plate diffusion method using *Bacillus cereus* (ATCC 111778) as the test micro-organism (British Pharmacopoeia, 1980).

Since the profile of the log plasma drug concentration versus time showed a biphasic curve, kinetic parameters were calculated from formulae derived for a 2-compartment open model (Gibaldi and Perrier, 1975; Baggot, 1977; Notari, 1980). The dosage regimen for maintaining minimal plasma concentrations of 0.5, 1.0 and 1.5 μg/ml at the dosage intervals (γ) of 12 and 24 h was calculated by the method described by Notari (1980).

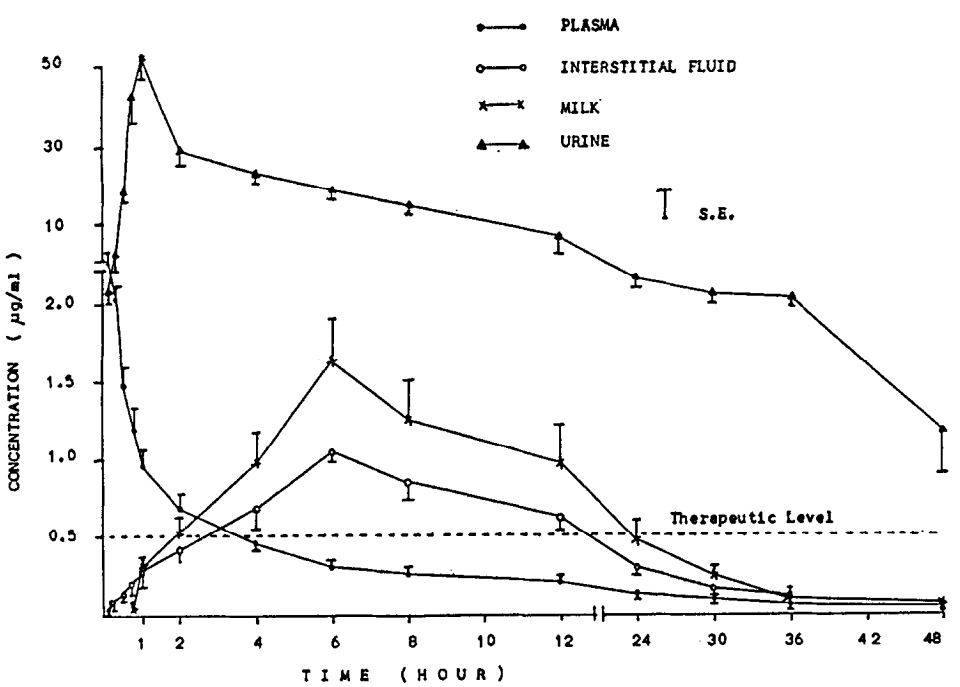

Figure 1. The concentration of doxycycline in different body fluids of female goats after a single intravenous injection of 5 mg/kg body weight

RESULTS

The mean concentrations of doxycycline in various body fluids at different time intervals after a single injection of 5 mg/kg (i.v.) are presented in Figure 1. The drug appeared by 5 min in all the body fluids except milk, in which it was detected at 45 min. Peak concentrations of 6.04 ± 0.81, 1.06 ± 0.06, 1.64 ± 0.25 and 52.90 ± 6.11 μg/ml were attained at 5 min, 6 h, 6 h and 1 h in plasma, interstitial fluid, milk and urine respectively. Concentrations of $\geqslant$0.5 μg/ml in plasma, interstitial fluid, milk and urine were maintained for periods of 5 min–2 h, 4–12 h, 2–12 h, and 5 min–>48 h respectively. The drug was still detectable in all the body fluids after 48 h.

Table I shows the values of different kinetic parameters calculated by the 2-compartment open model. Table II presents the values of appropriate loading and maintenance doses for maintaining concentrations of 0.5, 1.0 and 1.5 μg/ml at the selected dosage intervals of 12 and 24 h. Table II also shows the values of the attainable maximum plasma concentration during repetitive administration.

DISCUSSION

Although doxycycline appeared within 5 min in various body fluids, its appearance in milk was delayed, possibly due to the milk barrier, since it is known that penetration of a drug into body tissues and fluids may vary due to the specialised nature of the membrane at the site (Verwey *et al.*, 1965).

The calculated value for the distribution half life ($t_{1/2}\alpha$) of 0.73 ± 0.11 h shows that the drug is rapidly distributed in different body fluids and tissues. This is supported by the appearance of the drug in interstitial fluid after 5 min. A similar value for $t_{1/2}\alpha$ of 0.56 h in cows and ewes was reported by Ziv and Sulman (1974). The reported $t_{1/2}\alpha$ of 0.87 ± 0.293 h in humans (Raghuram and Krishnaswamy, 1982) is also of a similar order. The above data therefore suggest a similar rate of distribution of doxycycline in goats, cows, ewes and humans.

The mean elimination half life ($t_{1/2}\beta$) of 16.63 ± 1.58 h observed in goats in the present investigation is intermediate between that reported by Michael *et al.* (1979) in dogs (11.5 h) and that noted by Ziv and Sulman (1974) in cows and ewes (24.75 h). In man, a wide variation in $t_{1/2}\beta$ values has been reported, from 8.3 h (Doluisio and Dittert, 1969) to 15 h (Migliardi and Wittenau, 1967) and 20 h (Merier *et al.*, 1969/70). The high values for α and low values for β obtained in the present study indicate rapid distribution and slow elimination of doxycycline, suggesting that the drug is a long-acting antibiotic in goats.

The calculated value for the tissue:plasma concentration during the elimination phase $[K_{12}/(K_{21}-\beta)]$ of 4.86 ± 1.06 indicates very good distribution of the drug in the peripheral compartments. This fact is supported by the very high drug concentration obtained in interstitial fluid and milk as compared to plasma during the elimination phase. Values for K_{12}, K_{21} and K_{el} were reported to be 0.734 ± 0.08, 0.468 ± 0.07 and 0.75 ± 0.008 h^{-1} respectively in cows and ewes (Ziv and Sulman, 1974) and 0.50 ± 0.140, 0.74 ± 0.163 and 0.074 ± 0.0083 h^{-1} respectively in humans (Raghuram and Krishnaswamy, 1982). These findings suggest that the tissue:plasma concentration

TABLE I
Kinetic parameters of doxycycline in the goat derived from a 2-compartment open model

Parameter	Value (mean ± SE)
Extrapolated zero time concentration (μg/ml)	
Distribution (A)	2.55 ± 0.41
Elimination (B)	0.41 ± 0.03
C_0^P (A + B)	2.96 ± 0.40
Rate constant (h^{-1})	
Distribution (α)	1.066 ± 0.158
Elimination (β)	0.044 ± 0.004
Half life (h)	
Distribution ($t_{1/2}\alpha$)	0.73 ± 0.11
Elimination ($t_{1/2}\beta$)	16.63 ± 1.58
Micro-rate constant of drug transfer (h^{-1})	
Central to peripheral compartment (K_{12})	0.669 ± 0.135
Peripheral to central compartment (K_{21})	0.197 ± 0.035
Elimination from central compartment (K_{el})	0.244 ± 0.036
Tissue:plasma concentration	
$K_{12}/(K_{21}-\beta)$	4.86 ± 1.06
Fraction of drug available for elimination from central compartment	
F_c	0.196 ± 0.030
Volume distribution (L/kg)	
Vd_{area}	9.78 ± 0.86
Total body clearance (ml kg^{-1} min^{-1})	
Cl_B	6.91 ± 0.43

will be higher in goats than in cows, ewes or humans. Doxycycline is highly lipophilic in nature and would be expected to be distributed more in fatty tissue depots (Schach Von Wittenau and Yeary, 1963; Schach Von Wittenau and Delahunt, 1966). Thus the higher tissue:plasma concentration obtained in goats compared with that in cattle may be due to the higher muscle fat content of goats (Baruah, 1984).

The volume distribution (Vd) of a drug can be calculated by different methods. Vd calculated by the area method (Vd_{area}) only correctly predicts the distribution of a

TABLE II
Dosage regimen of doxycycline for intravenous route in goat to maintain specified plasma concentrations

Desired plasma concentration	0.5 μg/ml		1.0 μg/ml		1.5 μg/ml	
Maintenance time	12 h	24 h	12 h	24 h	12 h	24 h
Loading dose (D*) (mg/kg)	10.57±0.70	17.83±1.56	21.14±1.39	35.67±3.11	31.70±2.09	53.50±4.67
Maintenance dose (D_0) (mg/kg)	4.29±0.45	11.59±1.45	8.58±0.90	23.19±2.90	12.86±1.34	34.79±4.35
Maximum concentration in plasma (μg/ml)	0.85±0.04	1.45±0.13	1.71±0.08	2.90±0.26	2.56±0.12	4.36±0.40

drug in the body during the longer elimination phase (Notari, 1980). The Vd_{area} of 9.78 ± 0.72 L/kg obtained in these goats was high as compared with the apparent volumes of distribution of the drug of 0.9–1.8 L/kg in children (Ceccarelli *et al.*, 1971) and 0.75 ± 0.089 L/kg in adult humans (Raghuram and Krishnaswamy, 1982). In other animals, values of Vd_{area} were also lower than in these goats, being 2.285 ± 0.31 L/kg in cows and ewes (Ziv and Sulman, 1974) and 3.25 L/kg in dogs (Michael *et al.*, 1979). The very high Vd_{area} obtained during the present study may be attributed to the wide distribution of the drug coupled with its storage in tissue depots, most likely in fat.

Dosage regimens calculated to maintain minimal plasma concentrations (C_p^{∞}min) of 0.5–1.5 μg/ml (for mild to severe infections) are shown in Table II. Since the drug maintained a concentration of ⩾0.5 μg/ml in plasma for only a short period, it may not be of much use in cases of septicaemia as multiple doses or high loading and maintenance doses would be required to maintain this concentration in the plasma. However, the drug is probably effective in systemic infections of body fluids and tissues at the recommended therapeutic dose rates because therapeutic concentrations (⩾0.5 μg/ml) are maintained for longer periods in interstitial fluid and milk. Furthermore, since it is eliminated at a very high concentration in urine (Table I), this drug should be extremely useful for treating suitable urinary tract infections.

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