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DISPOSITION KINETICS AND URINARY EXCRETION OF OXYTETRACYCLINE IN GOATS

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Pharmacokinetic parameters which describe the distribution and elimination of oxytetracycline were investigated in 6 normal beetal goats following intravenous administration of a single dose (25 mg/kg). The disposition kinetics of the drug was described in terms of bi-exponential expression $C_p = A_e^{-\alpha t} + B_e^{-\beta t}$. Based on the oxytetracycline levels in plasma, the elimination half-life was 11.94 ± 2.84 hours (mean ± SEM). Total body clearance which is the sum of all clearance processes, was 3.15 ± 0.38 l/kg. Based on these kinetic parameters, priming and maintenance doses at different time intervals were suggested. The influence of disease conditions on the predicted plasma levels remains to be verified.

INTRODUCTION

Among tetracyclines, the oxytetracycline is most widely used antibiotic in veterinary practice. The purpose of a dosage calculation is to provide an estimate of the amount of the drug which must be administered to produce an effective concentration in the body fluids for a certain period of time. With bacteriostatic agents like oxytetracycline, the plasma levels of free drug should not fall below the minimum effective concentration during the course of treatment. Previous studies have shown that kinetics and optimal therapeutic regimen of a drug are best determined in the animals and environments in which the drug is to be employed clinically (Nawaz, 1983). In this study, the pharmacokinetics, dosage and urinary excretion of oxytetracycline were determined in goats to develop a rational dosage regimen.

MATERIALS AND METHODS

For the investigation of disposition kinetics of oxytetracycline, the experiments were performed on six healthy female beetal goats during the month of March. The average body weight of the goats was 34 kg (28-43 kg). After withdrawing a control blood sample in each experiment, Oxytetracycline (Terramycin Injection, Pfizer Laboratories Ltd.) was injected through venous cannula at the dosage level of 25 mg/kg body weight. Blood samples were collected in heparinized centrifuge tubes at 5, 10, 15 minutes and then at 30 minutes intervals for 6 hours and at 12 and 24 hours after drug administration, plasma was separated after centrifugation and stored at 4°C until the next day for analysis. For the determination of urinary excretion of oxytetracycline, a balloon catheter (Foly No. 18, 30 ml) was aseptically inserted into the urinary bladder through urethra. The external opening of the catheter was connected to a collection flask and in this way, all the urine voided by the animals was collected continuously. Urine samples were collected at 120, 360, 480, 720 and 1440 minutes after the administration of oxytetracycline. The activity expressed in unit concentration (μg/ml) of oxytetracycline in plasma and urine samples was mea-

sured by the microbiological assay method of Arret *et al.* (1971). The plasma oxytetracycline concentration time data were analysed separately for each animal. The pharmacokinetic analysis and optimal dosage were calculated by the methods described by Baggot (1977). The pharmacokinetic parameters were calculated with the help of programmable calculator (TI-59 Texas Instruments) using a programme for two-compartment open model (Nawaz and Nawaz, 1982). The mean value and standard error of mean (SEM) for each pharmacokinetic term were calculated. The urinary excretion of oxytetracycline was expressed as the percentage (Average ± SD) of dose excreted.

Half-life is associated with the terminal exponential phase of the plasma concentration-time curve and is inversely related to the overall elimination rate constant (β). The half-life for elimination was 11.94 ± 2.84 (Mean ± SEM) is plotted against time on semi-logarithmic paper and is presented in Fig. 1. It is obvious that the concentration-time profile is multiphasic, so that at least a bi-exponential expression will be needed to describe disposition kinetics of the drug.

The volume of central compartment was 2.42 ± 0.32 (Mean ± SEM). The mean ± SEM value for the apparent specific volume of distribution was 3.15 ± 0.46 l/kg. Body clearance, unlike β (2nd $t^{\frac{1}{2}}$) which are

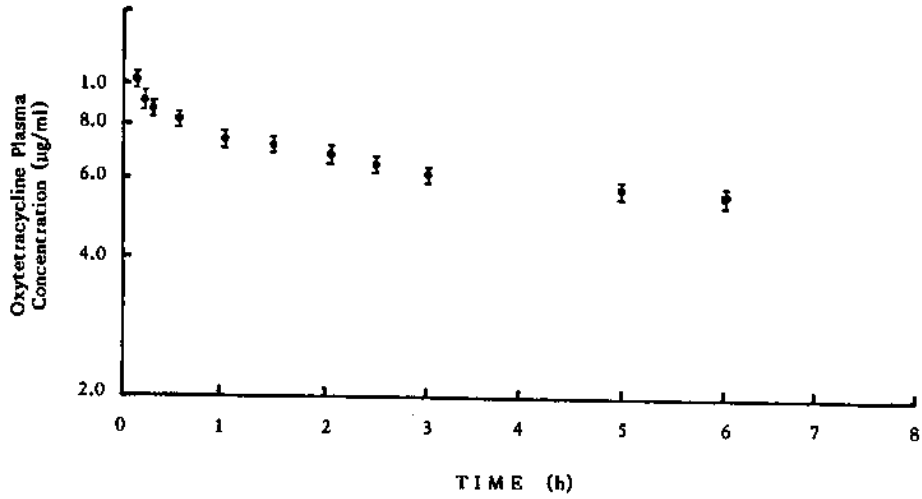

Fig. 1. Log plasma concentration (mean±SEM) of oxytetracycline against time after intravenous administration of a single dose (25 mg/kg) to goats (n = 6).

RESULTS

Disposition kinetics: The pharmacokinetic parameters which describe distribution and elimination of oxytetracycline in normal goats are given in Table 1. The mean value for the distribution half-life was 0.31 hour.

hybrid parameters, changes exactly in proportion to K_{el} (Jusko and Gibaldi, 1972), clearance of oxytetracycline was 3.05 ± 0.88 ml/h/kg (Mean ± SEM). The hybrid parameters should not be used individually as a sole measure of a change in drug distribution or elimination.

Table 1. Pharmacokinetic parameters (Mean ± SEM) of oxytetracycline in goats following intravenous injection of a single dose (25 mg/kg)

Kinetic parameters and units	Mean ± SEM
A (μg/ml)	2.41 ± 0.69
B (μg/ml)	7.94 ± 0.83
$t_{1/2}$ (h)	0.31 ± 0.18
$t_{1/2}$ B (h)	11.94 ± 2.84
V_d (l/kg)	3.15 ± 0.46
V_c (l/kg)	2.42 ± 0.32
Cl_B (ml/h/kg)	3.05 ± 0.88
K_{12} (h^{-1})	0.49 ± 0.41
K_{21} (h^{-1})	1.73 ± 0.53
K_{el} (h^{-1})	0.88 ± 0.03

Urinary excretion: The urinary excretion of oxytetracycline in goats in terms of cumulative percentage (average ± SD) of administered dose excreted in urine is presented in Fig. 2. A 2 hours post-oxytetracycline administration 0.59% (± 0.12), at 6 hours 1.24% (±0.15), at 8 hours 1.45% (± 0.15) and at 12 hours 1.85% (±0.26) of the dose was excreted in the urine of goats.

DISCUSSION

Disposition kinetics: The disposition kinetics of oxytetracycline has been described by the two-compartment open model in goats. After an intravenous injection of 25 mg/kg dose, the drug maintained therapeutic plasma levels of 1.446 μg/ml for about 18 hours which is longer than 6 hours in dogs at 5 mg/kg dose (Baggot *et al.*, 1977).

The mean ± SEM value for the half-life in our intravenous experiments on goats is 11.94 ± 2.84 hour which is comparable with the results of other workers in the ruminants. Pilloud (1973) calculated a biological half-life of 9.12 hours in cow and 10.5 hours in horses, Ziv and Sulman (1974) 9.24 hours in cows and goats and Singh *et al.* (1989) 12.14 hours in buffaloes.

The apparent volume of distribution is equal to the dose of the drug divided by the zero time plasma concentration i.e. "B", the average value for the volume of distribution was found to be 3.15 ± 0.46 l/kg which is comparable with 2.09 l/kg in dogs (Baggot, 1977), 2.12 l/kg in buffaloes (Shah *et al.*, 1984), 3.71 l/kg in buffaloes (Singh *et al.*, 1989) and 2.83 l/kg in dogs (Shah and Nawaz, 1986). The smaller volume of distribution described by Pilloud (1973) is possibly due to the flourimetric method used.

The value for the body clearance is 3.05 ± 0.88 ml/kg/h which is higher than 0.16 l/kg/h in cows and goats (Ziv and Sulman, 1974), 0.185 l/kg/h of tetracycline hydrochloride in swine (Kniffen *et al.*, 1990) and 0.16 l/kg/h in veal calves (Schifferli *et al.*, 1982).

The dosage calculations proposed are based on the assumption that only the free drug is active against microorganisms. This hypothesis seems true because oxytetracycline acts on ribosomal protein synthesis and must, therefore, enter the bacterial cell. When designing a dosage regimen, it is essential to define the range of therapeutic plasma levels.

For majority of microorganisms that show susceptibility to oxytetracycline, 1.25 to 5 μg/ml plasma concentration range may be considered therapeutic. Based on the value of half-life equal to 11.94 hours and V_d of 3.15 l/kg, the priming and maintenance doses calculated at different dosage intervals are given in Table 2, with an adequate C_p (minimum) of 1.25 μg/ml.

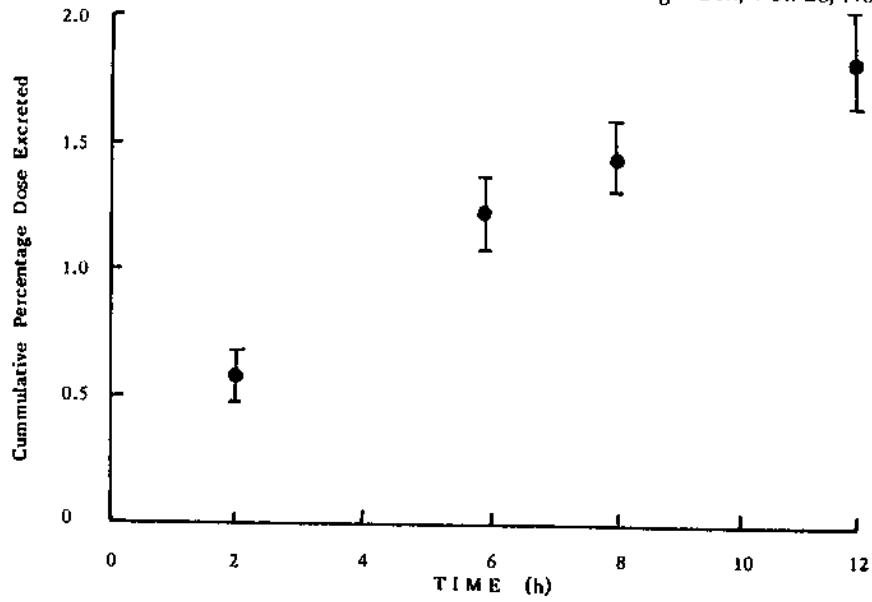

Fig. 2. Urinary excretion of total oxytetracycline expressed as cumulative percentage (mean ± SD) (n = 6) of dose against time after intravenous injection of a single dose (25 mg/kg) in goats.

Table 2. Calculated intravenous doses of oxytetracycline for goats at different dosage intervals at MIC 1.25 μg/ml

Dosing interval (hours)	Dose mg/kg	
	Priming	Maintenance
12	8	4
24	16	12
36	32	28

Urinary excretion: The urinary excretion of oxytetracycline in goats shows that only 1.85% of the dose was excreted in 12 hours after intravenous administration. The concentration of oxytetracycline in urine began to drop after 10 days of storage and declined to 34% of the original concentration after 28 days (Limpoka, 1980). The low value of percentage oxytetracycline excretion in urine is might be due to the fact that the urine samples of goats were stored for more than 28 days before analysis. The urinary excretion of a small fraction of the intravenous dose in goats also suggested that some of the drug was involved in the enterohepatic recycling or was sequestered in deep tissues.

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