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PHARMACOKINETICS AND DOSAGE OF OXYTETRACYCLINE IN BUFFALOES

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ABSTRACT

Plasma concentrations of oxytetracycline have been measured in adult normal buffaloes after a single dose of 7.5 mg/kg and pharmacokinetic analysis was done by one compartment open model. The volume of distribution was 2.12 ± .01 l/kg indicating the maximum penetration and tissue localization. The longer half-life for elimination (28.2 ± 5.2 h) in buffaloes than in other species was found to be due to lower glomerular filtration rate. Body clearance, the sum of all clearance processes, was 54 ± 17 ml/kg/h. Based on these studies, priming and maintenance doses were suggested as 5 and 2.2 mg/kg at 24 h interval and 9 and 6.3 mg/kg at 48 h dosing interval, respectively. The influence of diseased conditions on the predicted plasma levels of drug remains to be verified experimentally.

INTRODUCTION

The environmental and genetic variations can influence the physiological, biochemical and pharmacological parameters of a population. Such variations have been observed in the renal glomerular filtration rate (GFR), blood and urine pH and renal excretion of urea in sheep (Nawaz and Shah, 1984). Similarly, the glomerular filtration rate was of lower magnitude in buffaloes when compared with other species of animals (Hassan *et al.*, 1979) and the drugs such as oxytetracycline, which are excreted mainly through glomerular filtration, may persist in the body for longer periods of time, thus having different dosage requirements. Therefore, an optimal dosage schedule should be based on the pharmacokinetic parameters determined in the species and environments in which the drug is to be used clinically.

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Oxytetracycline is a broad spectrum antibiotic which is commonly used in veterinary clinics and very few studies have been carried out on its disposition kinetics in buffaloes. In view of this, the pharmacokinetics of oxytetracycline was performed to establish the optimal dosage regimen in the adult buffaloes.

MATERIALS AND METHODS

The pharmacokinetics of oxytetracycline was investigated in eight female buffaloes. All the animals were clinically healthy and maintained under similar managemental conditions at the Livestock Production Research Institute, Bahadarnagar, Okara. The average weight of the animals was 628 kg (range : 568-688 kg).

A control venous blood sample was drawn from each animal before drug administration. Oxytetracycline (Oxytetracycline-100 PVP injection, Pfizer Labs. Ltd., Pakistan) was injected intravenously at the dosage rate of 7.5 mg/kg body weight. Following drug administration, blood samples were collected in heparinized centrifuge tubes through plastic venous cannula placed in the left jugular vein of each animal The blood samples were drawn at 5, 10, 15, and 30 minutes post-injection, then at hourly intervals until 9 hours followed by the samples collected at 12, 15, 18, 24, 36 and 48 hours. The blood samples were centrifuged and plasma was separated for the determination of oxytetracycline by microbiological assay described by Arret *et al.* (1971).

The plasma concentration of oxytetracycline versus time data for each animal were analysed separately and the rate of decline in plasma drug concentration was calculated by least square regression analysis. The pharmacokinetic parameters of one compartment model were determined by the methods described by Baggot (1977).

Renal GFR was determined by measuring the renal clearance of endogenous creatinine. The endogenous creatinine in the plasma and urine samples was measured by the method of Bonsnes and Taussky (1945). The renal clearance of endogenous creatinine and exogenous inulin have shown similar values in ruminants (Nawaz and Shah, 1984), therefore, the renal clearance of endogenous creatinine is a satisfactory index of the GFR.

RESULTS

The oxytetracycline plasma concentration (mean ± SD) against time after intravenous administration in buffaloes (n=8) is shown in Fig 1. The plasma concentration of the drug revealed a distribution phase which passed during the first hour post-injection, therefore, in all experiments pharmacokinetic analysis has been performed by one-compartment model. The pharmacokinetic parameters of oxytetracycline following a single dose have been presented in Table 1. The half-life of the drug ranged between 23 to 33 hours. There was a slow decline in the plasma concentration of drug and the therapeutic level in most cases persisted in the body for about 48 hours after drug administration, and the average plasma concentration at that time was 1.03 μg/ml. The apparent volume of distribution (V_d) relates the drug concentration in plasma

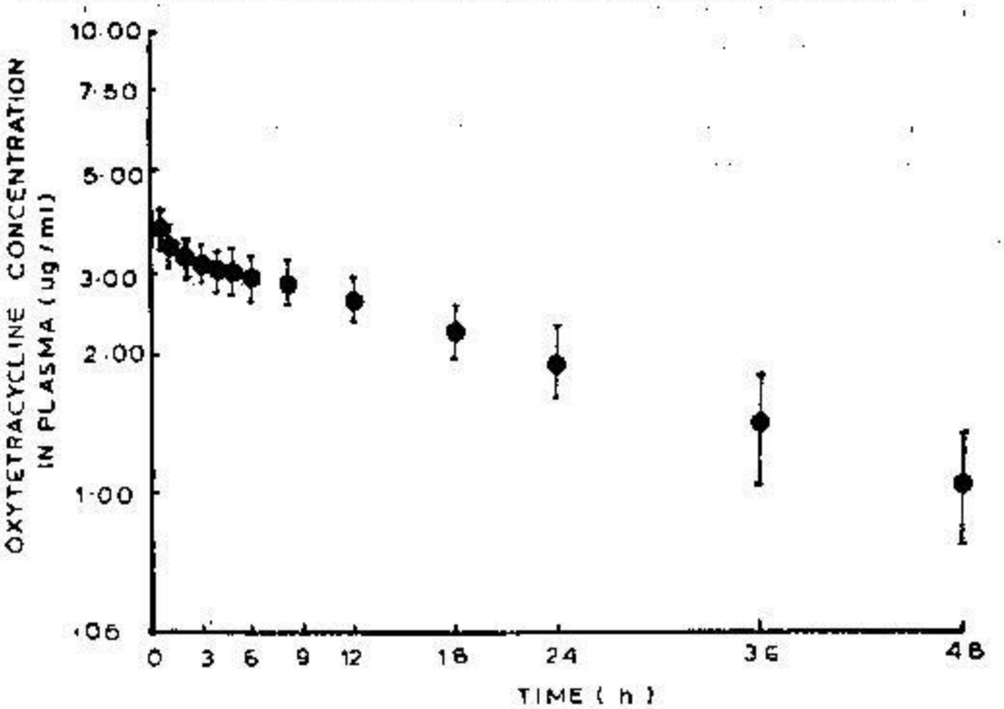

Fig. 1. Plasma concentration (mean ± SD) of oxytetracycline against time after intravenous administration of single dose (7·5 mg/kg) to buffaloes (n=8).

Table 1. *Pharmacokinetic parameters (mean ± SD) of oxytetracycline in buffaloes following an intravenous injection of a single dose (7.5 mg/kg).*

Kinetic parameters and units		Mean ± SD
B (μg/ml)	: Zero time drug concentration	3.53 ± 1.75
β (h^{-1})	: Elimination rate constant	0.0254 ± 0.009
$t_{\frac{1}{2}}$ (h)	: Elimination half-life	28.2 ± 5.2
V_d (l/kg)	: Apparent volume of distribution	2.12 ± 0.11
Cls (ml/h/kg)	: Body clearance	53.8 ± 17.3
C_p (48 h) (μg/ml)	: Plasma concentration at 48 hours	1.03 ± 0.36

to the total amount of drug in body after distribution equilibrium has been attained and its average value was 2.12 ± 0.11 l/kg. Body clearance (Cls) represents the sum of metabolic and excretory processes and is the volume of blood completely cleared of a drug in a unit time. The mean ± SD value of Cls was 53.8 ± 17.3 ml/h/kg. The renal GFR revealed average ± SD value of 3.99 ± 0.64 ml/min/10 kg.

DISCUSSION

Oxytetracycline showed rapid distribution phase as compared to that of elimination and the plasma concentration of the drug one hour after intravenous injection, showed a mono-exponential decline. In view of this, one compartment model adequately describes the pharmacokinetic behaviour of oxytetracycline in buffaloes. The average half-life of the drug was 28 h in buffaloes which is longer than 20 h in cows (Luthman and Jacobsson, 1982), 10.5 h in horses (Pilloud, 1973), 22 h in sheep (unpublished data) and 6 h in dogs (Baggot *et al.*, 1977). The principal elimination process for oxytetracycline is the glomerular filtration because the drug is not metabolised in the body. The GFR in buffaloes is quite less as compared to that in cows, sheep (Nawaz and Shah, 1984) and dogs (Baggot *et al.*, 1977) in which the values are 8.1, 12.9 and 44.2 ml/min/10 kg, respectively. The much lower GFR in buffaloes than in other species would explain the observed differences in half-life. Vari-

ations in the extent of distribution of drug in body fluids and tissues and, to a much lesser degree, in binding to plasma proteins may also influence the rate of elimination. Analysis of unsuccessful antibiotic treatment has shown that inadequate antibiotic concentration in tissues is the most frequent cause of drug ineffectiveness (Kiss *et al.*, 1976). It has been shown that oxytetracycline from polyvinylpyrrolidone (PVP) formulation is rapidly absorbed (Immelman and Dreyer, 1981) and has the maximum tissue penetration. So the higher antibiotic concentrations in tissue extravascular fluids are probably more important than in blood in determining the outcome of therapy of infections localized in tissues other than blood. But the susceptibility of bacteria to the action of oxytetracycline varies not only between species but also between strains within the same species. For majority of organisms that show susceptibility to oxytetracycline, the serum concentration range of 1.25 to 5.00 μg/ml may be considered therapeutic (Baggot *et al.*, 1977).

With a convenient dosage interval, calculation of the maintenance dose (D), as given below, is based on the minimum effective concentration (C_p min) and the volume of distribution (V_d) :

$$D = C_p^{\infty} (\text{min}).\ V_d\ (e^{\beta t} - 1)$$

The priming dose is calculated by omitting −1 in the above equation. Taking 48 hours as a convenient and suitable dosing interval, with an adequate C_p (min) of 1.25 μg/ml and using the values of V_d and β given in Table 1, the priming and maintenance doses were calculated as 9 and 6.3 mg/kg, respectively. At a reduced dosage interval of 24 hours, the priming and maintenance doses will be 5 and 2.2 mg/kg, respectively. The experimental varification of prediction and influence of diseased conditions needs to be investigated.

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