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Pharmacokinetics of Oxytetracycline in Sheep After Various Intravenous Doses

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Abstract: Pharmacokinetics of oxytetracycline were investigated in 20 sheep following intravenous injection of 40, 80 and 160 mg/kg doses. An increase in concentration of oxytetracycline was found with increasing dose at all the sampling times in each animal. The peak plasma concentration of oxytetracycline attained after intravenous administration of 40, 80 and 160 mg/kg of the drug was 18.67±0.09, 40.63±0.16 and 86.51±0.10 μg/ml, respectively. These plasma concentrations decreased with plasma half lives of 10.88 ± 0.29, 5.87 ± 0.08 and 7.35 ± 0.08 hours respectively. Oxytetracycyine resided, as indicated by MRT for 11.23±0.25, 5.78±0.08, 6.73±0.05 hours post dosing of 40, 80 and 160 μg/kg body weight of drug. After administration of the drug the Clt was observed to be 8.71±0.08, 9.73±0.06 and 9.74±0.03 ml/h. The Vd in the present study was concluded to be 8.19±0.2, 5.09±0.16 and 6.22±0.06 liters after three exponential doses. It was, therefore, concluded that the plasma concentration of oxytetracycline is dose related according to the present investigation.

Koyunlarda Çeşitli Damariçi Dozlarından Sonra Oksitetrasiklin'in Pharmakokinetiği

Özet: Oksitetrasiklin'in farmakokinetiği 20 koyun üzerinde araştırıldı. Araştırmada koyunlara, 40, 80 ve 160 mg/kg'lık oksitetrasiklin, damardan enjekte edildi. Her örnek alımda, artan dozlarla birlikte, hayvanların hepsinde oksitetrasiklin konsantrasyonunun yükseldiği gözlendi. 40, 80 ve 160 mg/kg'lik damariçi ulaç uygulamasından sonra, oksitetrasiklinin plazma konsantrasyonlarındaki en yüksek değerleri sırasıyla 18.67 ± 0.09, 40.63 + 0.16 ve 86.51 ± 0.10 μg/ml oldu. Bu plazma konsantrasiyonları sırasıyla 10.88 ± 0.29, 5.87 ± 0.08 ve 7.35 ± 0.08 saatlik yarılanma süreleriyle azalmıştır. MRT değerlerine göre oksitetrasiklin 40, 80 ve 160 mg/kg'lık dozlardan sonra 11.23 ± 0.25, 5.78 ± 0.08 ve 6.73 ± 0.05 saat koyunlarda kalmıştır. İlacın verilmesinden sonra Clt'nin 8.71 ± 0.08, 9.73 ± 0.06 ve 9.74 ± 0.03 ml/saat olduğu bulunmuştur. Bu çalışmada üç üstel dozdan sora Vd'nin 8.19 ± 0.2, 5.09 ± 0.16 ve 6.22 + 0.06 litre olduğu sonucuna varıldı. Böylece oksitetrasiklinin plazma konsantrasyonunun doza bağlı olduğu sonucuna varıldı.

Introduction

Oxytetracycline is a broad spectrum antibiotic which has been used widely in human and veterinary practice (1). The disposition of oxytetracycline is reported to be influenced by dosage form, route of administration, absorption characteristics, diseased states and age of the animals (2). Research in the local environment on imported drugs is important because most of the work on these drugs is carried out in the countries where the genetic make up of humans and animals, environmental conditions and nutritional status are different from local ones. These variations may affect the disposition kinetics and dosage requirements of drugs (3) thus, warranting the determination of bioavailability and pharmacokinetics of drugs particularly those with low therapeutic indices. Unfortunately, much of this class of specific information is not readily available for clinical application in veterinary medicine. The present subject was, therefore, designed to study the pharmacokinetics of injectable veterinary formulation of oxytetracycline in various dosage regimens in normal sheep.

Materials and Methods

Drug Administration

After withdrawing a control blood sample in each experiment, oxytetracycline (Terramycin, pfizer Lab. Limited, Karachi, Pakistan) was injected through venous cannula at dosages of 40, 80 and 160 mg/kg body weight in each animal.

Animals

The experiments were performed on 20 clinically healthy female sheep weighing 15 to 20 kg. The animals were put out to graze and green fodder was provided in the afternoon while water was provided freely. The same animals were used for the three doses of oxytetracycline, given after a wash-out period of one week following each experimentation.

Study Design

The pharmacokinetics of oxytetracycline were investigated by a single dose triple cross over method in sheep following intravenous administration of three different doses.

Sampling Procedure

Blood samples were collected in heparinized centrifuge tubes 0.5, 1.0, 2.0, 4.0, 8.0, 12.0 and 24.0 hours after drug administration. Immediately after collection, the blood samples were centrifuged at 2000, rpm for 10 minutes plasma was separated and used fresh for the drug analysis.

Drug Analysis

The concentrations of oxytetracycline in plasma samples was measured by disc agar diffusion bioassay using *Bacillus subtilis* as the test organism as described by Arret et al. (4).

Data Analysis

The pharmacokinetic parameters were estimated using the nonlinear least square regression technique employed in PK II-, which is software for pharmacokinetics analysis (5). An appropriate model was selected on the basis of the least Akaike Information Criterion (AIC) values (6).

The parameters included the peak plasma concentration (Cmax), area under the plasma concentration-time curve ($AUC_{0-\infty}$), first moment of plasma concentration time curve ($AUMC_{0-\infty}$), mean residence time (MRT) and distribution half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2}$ elim), apparent volume of distribution (Vd) and total body clearance (Cl_t).

Statistical Analysis

The pharmacokinetics and disporition parameters determined in sheep for oxytetracycline were compared to evaluate the difference between the two sources of the drug. Mean value ($\bar{X}$) and the standard error of mean (±SEM) were calculated for each parameter using the computer program SPSS (7).

Results and Discussion

There was no dropout of animals during the study. The mean±SEM for the plasma concentration of oxytetracycline after intravenous administration of 40, 80 and 160 mg/kg in sheep are given in Table 1. The average plasma concentrations of the drug against time are plotted in Fig. 1. The data was best fitted by the two compartment open model as mentioned by the lowest AIK values in each case. The previous studies on the pharmacokinetics of oxytetracycline have also been described by the two compartment open model (8-9). The increase in the concentration of oxytetracycline was shown with increasing dosage at all the sampling times in sheep. This increase in concentration seems to be dose dependent.

The mean±SEM for the intravenous pharmacokinetic parameters based on the plasma level-time profile of the drug are presented in Table 2. After the administration of a single dose of oxytetracycline at the rate of 40, 80 and 160 mg/kg body weight, the drug attained the maximum plasma concentrations Cmax of 18.67±0.095, 40.63±0.16 and 85.51±0.10 μg/ml, respectively. In healthy pigs, George and coworkers (10) reported C_{max} values of 73 μg/ml after a single intramuscular dose of 20 mg/kg which is comparable with the C_{max} values originated after administration of 40 mg/kg dose in the present study. It is far higher than the reported C_{max} value of 4 μg/ml after the administration of 20 mg/kg dose in young cattle by Toutain and Raynaud (11). These variations are due to the differences in dose, routes of administration and species.

The $AUC_{0-\infty}$ values were noted to be 76.68±0.71, 137.21±0.89 and 237.97±0.80 μg.h/ml after the administration of intravenous dose of 40, 80 and 160 mg/kg. MRT values of 11.23±0.25 hours after 40 mg/kg dose reduced to 5.78±0.08 hours after 80 mg/kg dose while it was 6.73±0.05 hours after an administration of 160 mg/kg dose. Oukessou et al. (12) reported a value of MRT of 7.7±2.8 hours after an intravenous dose of 5 mg/kg in camels.

Time (hours)	Doses		
	40 mg/kg	80 mg/kg	160 mg/kg
0.5	18.67±0.09	40.63±0.16	86.51±0.10
1.0	10.19±0.67	15.21±0.53	35.26±0.11
2.0	5.14±0.05	9.20±0.10	16.14±0.07
4.0	2.75±0.06	4.64±0.04	9.51±0.09
8.0	1.84±0.02	3.06±0.03	6.37±0.07
12.0	1.32±0.03	2.04±0.02	4.17±0.04
24.0	0.80±0.02	0.94±0.02	2.01±0.01

Table 1. Mean±SEM (n=20) concentration of oxytetracycline after administration of various intravenous doses of 40, 80 & 160 mg/kg body weight.

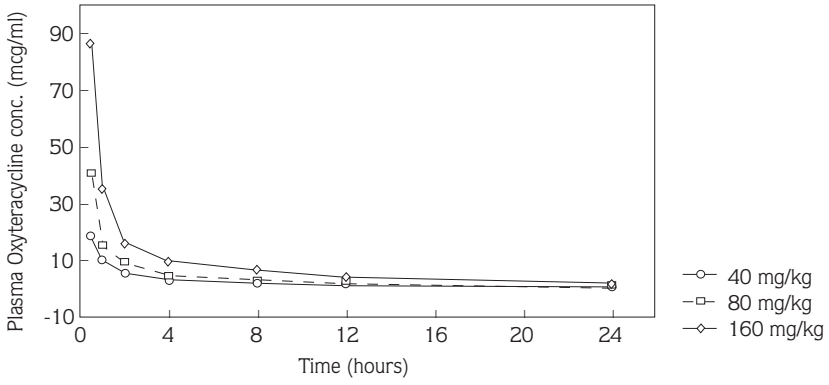

Figure 1. Mean plasma concentration of Oxytetracycline against time following intravenous administration in sheep (n=20).

Pharmacokinetic	INTRAVENOUS DOSES		
Parameters	40 mg/kg	80 mg/kg	160 mg/kg
$t_{1/2}\alpha$ (h)	0.52±0.01	0.25±0.00	0.31±0.00
$t_{1/2}$ elim (h)	10.88±0.29	5.87±0.08	7.35±0.06
$AUC_{0-\bullet}$ (µg, h/ml)	76.68±0.71	137.21±0.89	273.97±0.80
$AUMC_{0-\bullet}$ (µg, h^2/ml)	862.77±24.21	794.09±14.25	1843.09±12.9
MRT (h)	11.23±0.25	5.78±0.08	6.73±0.05
CLT (ml/h)	8.71±0.08	9.73±0.06	9.74±0.03
Vd (liters)	8.19±0.20	5.09±0.16	6.22±0.06
Cmax (µg/ml)	18.67±0.09	40.63±0.16	86.51±0.10

Table 2. Mean±SEM (n=20) pharmacokinetics parameters of oxytetracycline after administration of various intravenous doses of 40, 80 & 160 mg/kg body weight.

The $t_{1/2}\alpha$ was observed to be 0.52±0.01, 0.25±0.00 and 0.31±0.00 hours after a dose of 40, 80 & 160 mg/kg body weight. These values are far lower than the reported value of 2.0 to 2.5 hours after a dose of 20 mg/kg in cows and calves after an intramuscular injection (13). These differences may be attributed to the variation in the dosage form, species and route of drug administration.

The $t_{1/2}$ elim is the time required for 50% of the drug to be eliminated from the body after distribution equilibrium has been attained. The half-lives of oxytetracycline were found to be 10.88±0.29, 5.87±0.08 and 7.35±0.08 after intravenous administration of the drug at a dosage level of 40, 80 & 160 mg/kg body weight, respectively. In calves, after an administration of a test preparation of oxytetracycline, Black and coworkers (14) reported a range of t1/2 elim to be 8-14 hours. This range is in fair agreement with that of the present study. In sheep, the same parameter is reported to be 6.30 hours after an oxytetracycline

hydrochloride dose of 10 mg/kg (9) while Meijer et al. (8) reported a very slow terminal elimination phase of 95 hours in veal calves after intravenous administration. In cattle, after an administration of 20 mg/kg of oxytetracycline intramuscularly, a higher $t_{1/2}$ elim value of 21.83 hours was recorded by Toutain and Raynaud (11). The higher value of elimination half-life has been attributed to a combination of continued absorption and elimination of the drug. The elimination half-life after intravenous and intramuscular administration in buffalo calves at a dosage level of 22 mg/kg were reported to be 2.82-3.6 h and 10.5-16.5 h, respectively (15). The $t_{1/2}$ elim value after I/V administration in this previous study is less than these present values but unexpectedly the value after I/M administration is similar to those of the present study.

Total body clearance has been concluded in the present study to be 8.71±0.08, 9.73±0.06 & 9.74±0.03 ml/h after an administration of 40, 80 & 160 mg/kg respectively. Reported values of total body clearance after intravenous and intramuscular dose of 22 mg/kg in buffalo calves varied from 1.02-1.45 ml/h/kg and 1.17-1.49 ml/h/kg, respectively (15). There was higher Clt value of 75.3±23.2 ml/h/kg after 5 mg/kg in camels and 281 ml/h/kg in sheep after intravenous administration of 10 mg/kg of oxytetracycline hydrochloride (9, 12). In the present study, the volume of distribution was determined to be 8.19±0.20, 5.09±0.16 and 6.22±0.06 liters after administration of 40, 80 and 160 mg/kg body weight of oxytetracycline, respectively. Varma and Paul (15) reported a value of Vd to be 1.18-2.15 l/kg in buffalo calves after an intramuscular dose of 22 mg/kg body weight. An intravenous dose of 5 mg/kg body weight in camels generated a Vd value of 706.00±168.6 ml/kg (12).

In comparison with the different intravenous doses of oxytetracycline in the present study, the plasma levels of the drug seems to be dose dependent. The experimental validation and effect of diseased conditions must be analyzed.

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