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Comparison of the Pharmacokinetics of Conventional and Long-Acting Formulations of Oxytetracycline in Sheep*

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Abstract: The pharmacokinetics of conventional and long-acting oxytetracycline (OTC) formulation were evaluated in sheep at a single dosage of 20 mg-kg^{-1} body weight (bw). Conventional formulation was injected by intravenous (IV) route and long-acting formulation of oxytetracycline was administered by intramuscular (IM) route. Then blood samples were taken at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84 and 96 hours. Oxytetracycline analysis was performed by HPLC in plasma. The plasma drug concentration-time profile was characteristic of a two-compartment open model. Following IM administration, time to reach maximal plasma drug concentration was 2 hours and maximal plasma drug concentration was 5.13±0.31 µg/ml. After IV and IM administration of oxytetracycline, the elimination times were 1.14±1.13 and 18.92±1.86 hours, respectively. Intramuscular bioavailability was found to be 73%. Also, AUC was found to be 106.24±8.92 and 78.92±5.07 µg- ml^{-1} hours^{-1}, respectively, IV and IM.

Key Words: Oxytetracycline, long acting, pharmacokinetic.

Oksitetrasiklinin Koyunlarda Geleneksel ve Uzun Etkili Formülasyonlarının Farmakokinetiğinin Karşılaştırılması

Özet: Bu çalışmada, koyunlarda oksitetrasiklinin geleneksel ve uzun etkili formülasyonlarının farmakokinetiği, 20 mg/kg canlı ağırlığa olacak şekilde tek doz verilerek değerlendirildi. Geleneksel formülasyon damar içi yolla enjekte edildi, uzun etkili formülasyon ise kas içi yolla verildi. Daha sonra 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84 ve 96. saatlerde kan örnekleri toplandı. Plazmada oksitetrasiklin analiz HPLC ile gerçekleştirildi. Plazma ilaç yoğunluğu zaman eğrisi 2 bölmeli açık modele uygun olarak bulundu. Kas içi uygulamayı takiben doruk değere ulaşma süresi 2 saat ve doruk ilaç yoğunluğu da 5.13±0.31 µg/ml olarak tespit edildi. Damar içi ve kas içi yolla oksitetrasiklin uygulamasından sonra atılma yarı ömrü sırasıyla, 1.14±1.13 ve 18.92±1.86 saat olarak bulundu. Kas içi biyoyararlanım, %73 olarak tespit edildi. Diğer taraftan AUC, damar içi ve kas içi uygulamalar için sırasıyla, 106.24±8.92 ve 78.92±5.07 µg/ml/saat olarak belirlendi.

Anahtar Sözcükler: Oksitetrasiklin, uzun etki, farmakokinetik.

Introduction

Oxytetracycline (OTC), obtained from *Streptomyces rimosus*, a broad-spectrum antibiotic of the tetracycline group, is widely used in the treatment of bacterial diseases in animals (1,2,3). A treatment regimen which requires repeated injection is time consuming and expensive, and can be stressful and hazardous, particularly, but not only, to the patient (4). At present, parenteral OTC therapy involves daily administrations over several days. Research has been directed toward obtaining a depot formulation that would allow a reduction in the frequency of administration. A long-acting formulation of OTC may provide sustained OTC blood concentration 3 to 5 days after a single IM injection

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(5). There have been many studies on the pharmacokinetics of OTC in different species (6). Also, Moreno et al (4) investigated the pharmacokinetics of OTC with lidocaine after IM administration in sheep.

The objective of this study was to compare, in terms of pharmacokinetic parameters, a single IM administration of the long-acting formulation with a conventional formulation of OTC in sheep.

Materials and Methods

Animals

A total of eight healthy adult Akkaraman sheep weighing 55-70 kg bw were used. All of the animals were female and in good health and were housed and fed an antibiotic-free diet (alfalfa hay and straw) during the study period. Water was available ad libitum. Animals were divided into two groups, A and B. Group A (n: 3) was used for IV studies of conventional formulation of OTC, and Group B (n:5) was used for IM studies of long-acting formulation of OTC.

Drug administration

Conventional formulation of OTC was prepared just before IV administration. Oxytetracycline standard was supplied from ICN Biomedicals Inc. Intravenous injections were given via the right jugular vein in order to determine disposition parameters of OTC at a normal injection rate (<10 s).

The long-acting formulation contained 200 mg of OTC hydrochloride/ml. This formulation was supplied from Pfizer Inc. (Primamycin/LA). Intramuscular injections were given deep into the gluteal muscles with 6 cm x 2 mm needles.

Both Group A and Group B sheep were given 20 mg of OTC/kg of body weight (IM or IV). The IM dose volume was divided into two parts and 3.5 to 4 ml was injected per site.

Collection and treatment of samples

Blood samples (a volume of 3 ml) from both groups were collected from the jugular vein via an injector and put into heparinized tubes. Collection times for IV and IM routes were at postinjection hours 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84 and 96. Plasma was separated by centrifugation at 3000 rpm for 3 minutes, and stored at –20 °C until assayed.

Assay

Plasma OTC concentrations were determined by HPLC with a UV detector (Cecil-UK) (7). The column was ODSC8. 20 µl of filtered fluid was injected into the HPLC system and scanned at 280 nm. The mobile phase was composed of 10% acetonitrile (Merck LİChrosolv) and 90% water containing KH_2PO_4 (0.04 M) with the pH adjusted to 2.5 with a flow rate of 1.0 ml min^{-1}. The plasma concentration of OTC was calculated by comparison of the total areas under the chromatographic peak of experimental plasma samples and standard calibration curves.

Pharmacokinetic and statistical analysis

The pharmacokinetic parameters were calculated with the PKCALC computer program (8) on the basis of two compartment pharmacokinetic models for each animal. Data obtained from the pharmacokinetic calculations were analysed statistically by the Mann-Whitney U test ($p<0.05$), for which the SPSS Release 8.00 computer program was used.

Pharmacokinetic constants and parameters

AUC	(µg- $ml^{-1}hours^{-1}$)	Area under the plasma concentrationtime curve
MRT	(hours)	Mean residence time of drug
Alfa	($hours^{-1}$)	Slope of distribution phase
Beta	($hours^{-1}$)	Slope of elimination phase
$t_{1/2\ alfa}$	(hours)	Half-life of drug distribution
$t_{1/2\ beta}$	(hours)	Half-life of drug elimination
A_1	(µg/ml)	Drug quantity in the central compartment
A_2	(µg/ml)	Drug quantity in the peripheral compartment
C max	(µg/ml)	Maximum concentration of drug
T max	(hours)	Time to reach the maximum concentration of drug
F	(%)	The ratio fraction of the absobed drug

Results

Oxytetracycline plasma concentrations obtained at different times after IV administration of conventional formulation were homogeneous and are plotted in Figures 1 and 2. The oxytetracycline plasma concentration-time profile was best fitted in all the animals to the biexponential equation corresponding to the two-compartment open model.

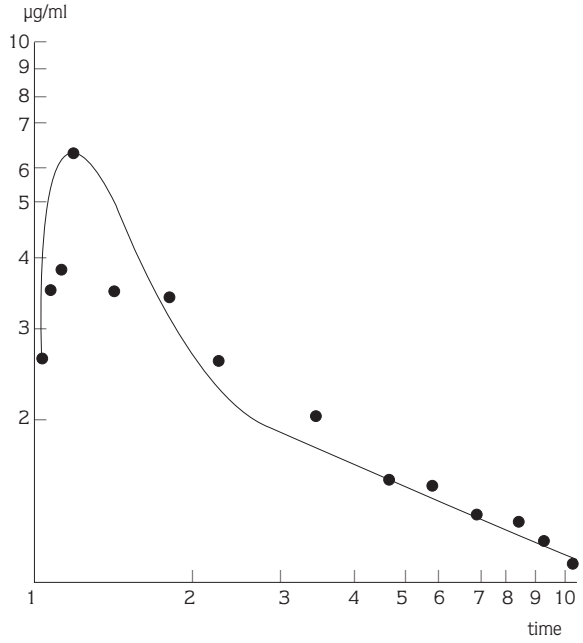

Figure 1. Logarithmic plot of average plasma concentrations of OTC (mean±SEM) in sheep following the IV administration of conventional formulation at a single dose of 20 mg kg^{-1} body weight.

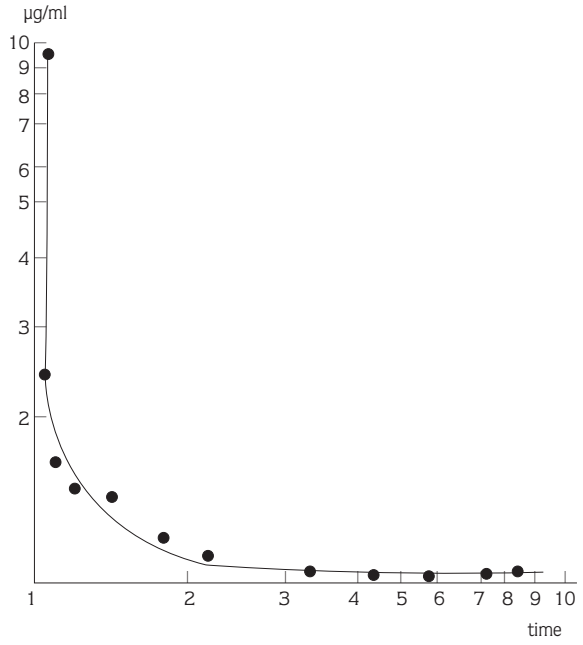

Figure 2. Logarithmic plot of average plasma concentrations of OTC (mean±SEM) in sheep following the IM administration of long-acting formulation at a single dose of 20 mg kg^{-1} body weight.

Following IM administration, the time to reach maximal plasma drug concentration was found to be 2 hours, and maximal drug concentration 5.13(0.31 µg/ml. The elimination half-life was 18.92±1.86 hours, MRT was 27.69±1.23 hours and AUC_{0-96} was 78.92±5.07 µg- $ml^{-1}hours^{-1}$. Intramuscular bioavailability was found to be 73%. Following IV administration the elimination half-life was 1.14±1.13 hours, MRT was 12.04±1.13 hours and AUC_{0-96} was 106.24±8.92 µg-$ml^{-1}hours^{-1}$ (Table 1).

The long-acting formulation gave a peak value and a significantly lengthened blood concentration tail. There was also evidence of a moderate plateau effect in the long-acting formulation between 4 and 8 hours in that the mean OTC plasma concentrations remained between 2.480 µg/ml and 2.380 µg/ml. During that period (Table 1) the differences between the mean elimination half-life, MRT and AUC values of the two groups were highly significant ($p<0.05$). A concentration of 0.5 µg/ml was taken as typical of values which have been used in various studies, to represent a minimum blood therapeutic concentration of OTC. The mean values for the conventional formulation exceeded this concentration for 28 hours, and those for the long-acting formulation for 48 hours. The difference between these two values was statistically significant ($p<0.05$).

Discussion

When bacteriostatic drugs such as OTC are administered, the serum values of the drug should not decrease below the effective concentrations at any time during the period of treatment. Because repeated dosage of OTC is not always practical, a long-acting formulation was developed to achieve rapid high blood values and to provide a greater effective serum value over several days (5). In the present study, the peak plasma concentration was 5.13±0.31 µg/ml 2 hours after IM administration of the long acting formulation, decreasing rapidly for 2-4 hours but exceeding 0.20 µg/ml for 96 hours. The duration of the effective plasma concentration (0.5 µg/ml) in the long-acting formulations was from 36 to 48 hours after IM injections. In other investigations, peak plasma concentrations of 4.6 µg/ml were obtained at 3 hours (4), 5 µg/ml at 2 hours (9) and 4.30 µg/ml at 4.4 hours after IM injections in sheep. The peak plasma concentrations and time profile appeared to be similar to

Parameters	Units	Primamycin-LA (IM)	Conventional (IV)
$AUC_{(0\text{-}96\ hours)}$	$\mu g\text{-}ml^{-1}hours^{-1}$	78.92±5.07	106.24±8.92*
A_1	µg/ml	3.10±0.17	89.60±40.39
A_2	µg/ml	-3.10±0.17	-89.60±40.39
MRT	hours	27.69±1.23	12.04±1.13*
Alfa	$hours^{-1}$	2.77±0.25	0.46±4.14
Beta	$hours^{-1}$	0.037±0.16	0.60±0.78
$T_{1/2\ alfa}$	hours	0.25±0.14	1.48±0.69
$T_{1/2\ beta}$	hours	18.92±1.86	1.14±1.13*
C max	µg/ml	5.13±0.31	-
T max	hours	2.0	-
F	%	0.73	

Table 1. Pharmacokinetic parameters (mean±SEM) of OTC in sheep following administration of conventional (IV) and long-acting (IM) formulation at a single dose of 20 mg kg^{-1} body weight.

* $p<0.05$

those reported by Moreno et al. (4) and Pfizer Ref. No 8306 (9). However in the former study, an OTC formulation with lidocaine was used. T_{max} and C_{max} have been reported in different species (6.26 hours and 5.92 $\mu g\text{-}ml^{-1}$ respectively in cows, according to Meijer et al., taken from Moreno et al. (4); 4.62 hours, in goats, according to Escodero et al., taken from Moreno et.al. (4). The AUC was lower than the values reported by Moreno et al (4). Also, the AUC was lower than the values found in other species (86.2 $\mu g\text{-}ml^{-1}hours^{-1}$ in goats and 153.11 $\mu g\text{-}ml^{-1}hours^{-1}$ in cows, according to Escudero et al. taken from Moreno et.al. (4) and according to Meijer et al. taken from Moreno et.al. (4), respectively). The half-life ($t_{1/2\beta}$) obtained for long-acting formulation of OTC in the present study was found to be shorter than in other studies on the same species (58.24 hours, Moreno et al., (4). After IV administration of the conventional formulation of OTC, the values of AUC, $t_{1/2\beta}$ and MRT were 106.24±8.92 $\mu g\text{-}ml^{-1}hours^{-1}$, 1.14±1.13 hours and 12.04±1.13 hours, respectively. The values of AUC, $t_{1/2\beta}$ and MRT of both formulations were different statistically. The value of AUC for the conventional formulation was higher than that of the long acting-formulation, but, the values of MRT and $t_{1/2\beta}$ were shorter. These differences between both formulations were statistically significant ($p<0.05$). Also, the duration of effective plasma concentrations was from 18 to 28 hours. In another study (10), after IV administration of OTC in sheep, the value of $t_{1/2\beta}$ was found to be 3.68 hours, which was longer than in the present study.

The data presented for OTC indicate that after IM and IV administration of equal doses of long-acting and conventional formulation, an equivalent OTC blood profile is not produced. The IM administration of long-acting formulation of OTC provided therapeutic concentrations for a longer period of time, up to 48 hours. Therefore, this formulation can be administered every two days.

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