

PLASMA CONCENTRATIONS OF OXYTETRACYCLINE IN ELEPHANTS FOLLOWING INTRAVENOUS AND INTRAMUSCULAR ADMINISTRATION OF TERRAMYCIN/LA INJECTABLE SOLUTION

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Abstract

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S. R a t t a n a m o n t h i a n c h a i,
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The blood concentrations of oxytetracycline were studied in Asian elephants following the intravenous and intramuscular administration of Terramycin/LA solution. The drug was administered as 200 mg oxytetracycline base/ml in aqueous 2 - pyrrolidone at a dosage of 20 mg/kg body mass. The blood samples were collected from the ear veins of each animal. Plasma concentrations of oxytetracycline were analysed by microbiological method and high pressure liquid chromatography.

An average peak plasma concentration of 6.2 µg/ml was obtained in one hour following intravenous administration in elephants. No oxytetracycline was detected in plasma after the 60th post dosing hour. The average peak plasma concentration of 2.87 µg/ml was found in two hours following intramuscular injection of the drug. Concentrations exceeding 1 µg/ml were maintained for 48 hours after intramuscular dose. The drug was shown to result in sustained oxytetracycline blood concentrations over a three-day period following a single intramuscular administration of the drug to elephants.

Administration route, post-injection time, OTC, elephants.

Asian elephants are susceptible to a number of diseases for which antimicrobial drugs are recommended. The correct drugs prescribed, proper dosage and proper interval in elephants are still questions. Too often, failure to treat an illness in elephants is caused by the inability of the

veterinarian to administer adequate doses and appropriate intervals of the drugs. Schmidt (1978) proposed that elephants weighing the same as cattle and horses can be given the same dosage per unit of body mass, and 0.5 or 0.75 the recommended dose can be given to adult elephants.

In this study, blood concentrations of oxytetracycline were investigated in Asian elephants following intravenous and intramuscular administration of 200 mg oxytetracycline base/ml in aqueous 2 - pyrrolidone at a dosage of 20 mg/kg body mass. Results obtained could be used as a guideline for recommended dosage regimen for clinical use of this antibiotic in elephants.

Materials and Methods

Animals

Six healthy Asian elephants¹ weighing 2.030 - 3.475 kg were used in this study. The animals were acclimatized for 2 weeks around the experimental area². The cannula³ was placed in the right ear vein of each animal prior to drug administration. The animals were randomly assigned to two groups.

Drug administration and blood collection

The drug used in this study was Terramycin/LA injectable solution⁴ at the concentration of 200 mg of oxytetracycline base (OTC)/ml. The first three elephants received 10 ml of the drug/100 kg body mass intravenously via the cannula. The three remaining elephants received the same dosage of Terramycin/LA solution intramuscularly. The deep muscular injection was distributed bilaterally in the hind quarters. No more than 30 ml of Terramycin/LA solution was injected into individual site. Disposable 3 in, 16 ga needles were used to inject the drug. No tranquilizer was given prior to drug administration or the collection of blood samples. The elephants were chained by one front leg to a fixed point only to obtain the blood samples.

Following drug administration, blood samples were collected in heparinized syringes at 0, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, 84, 108, 132 hours post dosing. The blood samples were collected from the veins located on the posterior surface of the ears. After collection, the blood was centrifuged and the plasma was immediately frozen until assay.

Analytical method

Plasma samples were analysed for OTC by a microbiological method. The microbiological assays were carried out in 150 x 20 mm petri dishes, with reference organism *Bacillus cereus* ATCC No. 11785 (Bennett et al. 1966). The limit of sensitivity of the method is 0.25 µg/ml.

Selected plasma samples were also analysed by high pressure liquid chromatography⁶ (HPLC) (Sharma and Bevil 1978). The concentrations of OTC in plasma determined by microbiological assay were

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³ Intrademic^R Polyethylene tubing, Medical Formulation, CAT. No. PE 90 (7421), I.D. .043"

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⁶ The Varian's 5.000 Series liquid chromatographs with the CDS 401 Data system (VARIAN, VISTA 54), equipped with MicroPak CH - 10 and UV - 5 Selectable Wavelength detector

Table 1
Concentrations of oxytetracycline in elephant plasma following the intravenous administration of 20 mg Terracyclin/LA solution/kilogram of body mass.

Time (hours)	Animal number			Mean ^a	S.D. ^b
	1	2	3		
1.0	7.09	5.64	5.84	6.19	0.64
2.0	5.64	3.61	3.61	4.28	0.95
3.0	3.61	2.51	--	3.06	0.55
4.0	2.68	1.87	2.44	2.33	0.33
6.0	2.16	1.17	1.52	1.62	0.40
8.0	1.28	0.71	1.28	1.09	0.26
12.0	1.03	0.35	1.17	0.85	0.35
18.0	<0.25	<0.25	0.35	0.28	0.03
24.0	<0.25	<0.25	<0.25	<0.25	--
36.0	<0.25	<0.25	--	<0.25	--
48.0	<0.25	<0.25	-	<0.25	--
60.0	0	0	0	0	--

a Expressed as $\mu\text{g/ml}$

b Standard deviation

Table 2
Plasma concentrations of oxytetracycline in one elephant following intravenous administration, determined by HPLC and microbiological assay

Time (hours)	Elephant No. 3	
	Microbiological	HPLC
1.0	5.84	5.13
2.0	3.60	2.95
4.0	2.44	2.11
8.0	1.28	1.92
12.0	1.17	1.63
24.0	<0.25	0.95
36.0	<0.25	0.56

Table 3
Concentrations of oxytetracycline in elephant plasma following the intramuscular administration of 20 mg Terramycin/LA solution/kilogram of body mass

Time (hours)	Animal number			Mean ^a	S.D. ^b
	4	5	6		
1.0	2.21	2.68	2.91	2.6	0.29
2.0	2.44	3.60	2.96	2.87	0.52
3.0	2.21	3.00	1.75	2.32	0.51
4.0	2.44	2.44	1.98	2.28	0.21
6.0	2.44	1.40	1.86	1.90	0.42
8.0	1.86	1.28	1.05	1.39	0.34
12.0	1.86	1.17	1.05	1.36	0.35
18.0	1.86	1.75	1.86	1.82	0.05
24.0	1.63	1.28	2.44	1.78	0.48
36.0	1.28	0.93	2.44	1.55	0.64
48.0	0.72	0.82	1.75	1.09	0.46
60.0	<0.25	0.36	1.40	0.67	0.52
84.0	<0.25	0.70	0.70	0.55	0.21
108.0	<0.25	<0.25	<0.25	<0.25	--
132.0	<0.25	<0.25	<0.25	<0.25	--

a Expressed as $\mu\text{g/ml}$

b Standard deviation

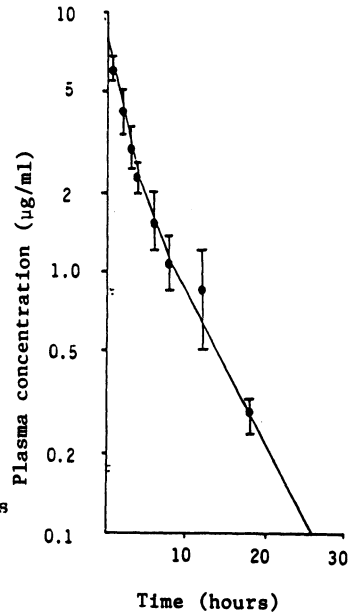


Fig. 1: The average plasma concentrations of oxytetracycline following the intravenous administration of 20 mg Terramycin/LA solution/kg body mass to 3 elephants.

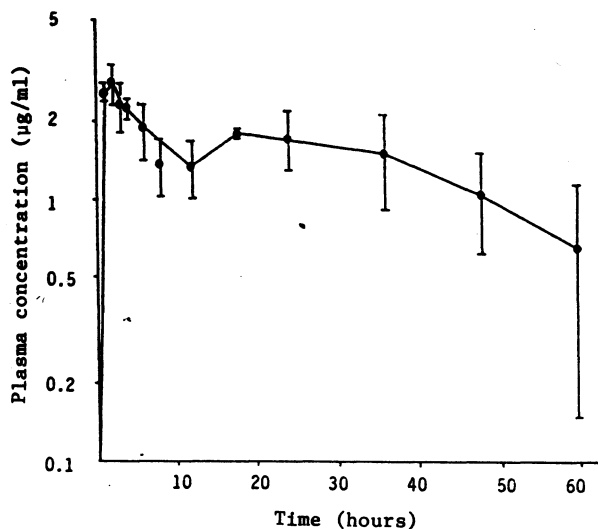


Fig. 2: The average plasma concentrations of oxytetracycline following the i.m. administration of 20 mg Terramycin/LA solution/kg body mass to 3 elephants.

used in data analysis. Good correlation was found between the 2 assay methods.

The data was calculated on a SHARP PC - 1500 with plotter/ Cassette Interface and CE - 502 A Statistics Library.

Results and Discussion

The average plasma concentrations for intravenous injection of Terramycin/LA at 20 mg/kg body mass to elephants are shown in Table 1. One hour following drug administration an average plasma concentration of oxytetracycline was 6.19 $\mu\text{g/ml}$. The drug in plasma decreased with time and reached 0.28 $\mu\text{g/ml}$ (approximate limit of detection) about 18 hours after dosing. Concentrations exceeding 1 $\mu\text{g/ml}$ were maintained for at least 8 hours following intravenous administration. A semilogarithmic plot of the average plasma concentrations at specific times following intravenous drug administration is illustrated in Figure 1.

The high pressure liquid chromatographic procedure was used to confirm the quantitation of oxytetracycline in plasma and to detect the presence of any metabolites. The concentrations of oxytetracycline in plasma of elephant no. 3, determined by both HPLC and the microbiological assay, are shown in Table 2. No metabolites were found in plasma of elephants receiving Terramycin/LA solution.

The individual and average concentrations of oxytetracycline in plasma following intramuscular administration of 20 mg Terramycin/LA/kg body mass to elephants are presented in Table 2. The average peak concentration of oxytetracycline in plasma was 2.87 $\mu\text{g/ml}$. This maximum value occurred two hours following drug administration. As shown in Table 3, the oxytetracycline concentration in plasma varied from 2.4 - 3.6 $\mu\text{g/ml}$ among individual animals

at two hours. The concentrations exceeding $1 \mu\text{g/ml}$ were maintained at least for 48 hours following intramuscular dosing. A semilogarithmic plot of an average plasma concentration vs time is presented in Figure 2.

After intramuscular injection of 20 mg/kg of the Terramycin/LA solution to elephants, peak plasma levels were achieved between 1 and 48 hours and ranged from 1.09 - 2.87 $\mu\text{g/ml}$ (Table 3). Plasma concentrations were higher than the minimal inhibitory concentrations (MIC) reported for most susceptible pathogens (0.5 $\mu\text{g/ml}$ OTC) for approximately 84 hours, except for *E. coli*. The MIC values for *E. coli* have been reported to be 4 $\mu\text{g/ml}$ for OTC in a calf (Garrrod et al. 1973; Atkinson 1983; Barry and Thornberry 1980; Rosenblatt 1980), and this organism would probably be little affected on the i.m. dose employed.

It appears that the drug was rapidly absorbed and was shown to result in sustained OTC blood concentrations over a three-day period in elephants following a single intramuscular injection of 20 mg/kg body mass. It is possible to compare the results in elephants with those reported elsewhere in cattle, sheep and swine (Technical Information, Agricultural Development Division, Pfizer Ltd. 1978 - 1981).

Koncentrace oxytetracyklinu v krvi slonů po intravenozní aplikaci Terramycinu/LA

U 6 asijských slonů (o živé hmotnosti 2030 - 3475 kg) byla sledována koncentrace oxytetracyklinu (OTC) v krvi po intravenózní a intramuskulární aplikaci roztoku Terramycinu/LA. Léčivo bylo podáváno v dávce 20 mg.kg⁻¹ živé hmotnosti ve vodném 2-pyrrolidonu (200 mg oxytetracyklinu/ml). Vzor-ky krve byly u všech zvířat odebírány z ušních žil. Koncentrace oxytetracyklinu v krevní plazmě byly stanoveny metodou mikrobiologickou a vysokotlakou kapalinovou chromatografií.

Po iv. aplikaci byla průměrná nejvyšší koncentrace v plazmě slonů za 1 h, po 60 h OTC v plazmě již prokázán nebyl. Po im. podání byla zjištěna nejvyšší koncentrace OTC, 2,87 $\mu\text{g.ml}^{-1}$ za 2 h po podání léčiva. Koncentrace přesahující 1 $\mu\text{g.ml}^{-1}$ se udržovala 48 h po aplikaci OTC. Jediná im. aplikace léčiva tedy byla dostatečná k udržení účinné koncentrace OTC v krvi slonů.

Концентрация окситетрациклина в крови слонов после внутривенной дачи тетрацицина/ла

У 6 азиатских слонов (живой массы 2030 - 3475 кг) проводились исследования концентрации окситетрациклина (ОТЦ) в крови после внутривенного и внутримышечного введения раствора тетрацицина/ла. Медикамент давали дозой 20 мг.кг⁻¹ живой массы в водном 2-пирролидоне (200 мг окситетрациклина/мл). Образцы крови у всех животных из ушных вен. Определение концентрации окситетрациклина в кровяной плазме проводили микробиологическим методом и жидкостной хроматографией высокого давления.

Средняя максимальная концентрация после ввода внутривенно наблюдалась в плазме слонов спустя 1 час, после 60 часов ОТЦ в плазме не был уже установлен. После интрамукулчурной дачи была установлена максимальная концентрация ОТЦ 2,87 мг.мл⁻¹ через 2 часа после приема лекарства. Концентрация, превышающая 1 мг.мл⁻¹ достигала одинакового уровня Двое суток после ввода ОТЦ. Следовательно, одного внутримышечного применения было

достаточно для поддержки эффективной концентрации ОТС в крови слонов.

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