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OXYTETRACYCLINES IN CATTLE

A COMPARISON BETWEEN A CONVENTIONAL AND A LONG-ACTING PREPARATION

By

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XIA, WENJIANG, POUL NIELSEN and N. GYRD-HANSEN: *Oxytetracyclines in cattle — A comparison between a conventional and a long-acting preparation.* Acta vet. scand. 1983, *24*, 120—128. — Pharmacokinetics of oxytetracycline (OTC) were studied in 4 cows after administration of either a conventional (OTC-C) or a long-acting (OTC-LA) preparation. After intravenous administration of OTC-C the elimination half-life for OTC was found to be 6 h. Intramuscular injection of OTC-C and OTC-LA resulted in almost identical plasma concentrations of OTC with peak values after 6—8 h. For both preparations the bioavailability after i.m. administration was 100 % and about 60 % of the dose was excreted in the urine during the first week. Plasma concentrations above 0.5 μg/ml were with both preparations maintained for approximately 60 h, indicating no retard effect of OTC-LA as compared to OTC-C.

oxytetracycline; pharmacokinetics; cattle.

In veterinary practice the broad-spectrum antibiotic oxytetracycline (OTC) is widely used, e.g. for treatment of respiratory diseases in cattle. In order to avoid repeated administration and thereby reducing the cost of treatments a long-acting preparation of oxytetracycline has been introduced on the market. The prolonged effect of this new preparation is claimed to be due to the use of an aqueous 2-pyrrolidone-based formulation which should lead to a controlled precipitation of oxytetracycline at the injection site without significant tissue damage (*Simpson* 1978, *Cornwell* 1980). It has been the purpose of the present investigation

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to determine and compare the pharmacokinetics for OTC after administration of the conventional (OTC-C) and the long-acting preparation (OTC-LA) to cows.

MATERIALS AND METHODS

Twelve experiments were performed in 4 dry, clinically healthy cows weighing 240—400 kg. The animals were fed hay, straw and a commercial concentrate twice daily and had free access to water.

The cows were treated as described in Table 1. Intravenous injections were given in a jugular vein and the dosage used was 10 mg per kg b.wt. in order to avoid too strong cardiovascular reactions (*Gyrd-Hansen et al.* 1981). The intramuscular injections were given in the shoulders and a maximum of 20 ml was administered at one injection site.

Table 1. Treatment with OTC in 4 cows.

Cow No.	Preparation	Route of administration	Dosage (mg/kg)
1—4	OTC-C[1]	i.v.	10
1—4	OTC-C	i.m.	20
1—4	OTC-LA[2]	i.m.	20

[1] Terramycin® vet. — 10 % OTC
[2] Terramycin® prolongatum — 20 % OTC

Blood samples were drawn through a cannula placed in the jugular vein on the opposite side of where the injection was performed. Samples were taken just before and at 2, 5, 10, 15, 20, 30, 45, 60 and 90 min, and 2, 3, 4, 5, 6, 8, 10, 12, 24, 30, 48, 72 and 96 h after administration of the drug. A balloon catheter (Rüsch No. 28) was inserted into the bladder and the bladder was emptied every second hour during the first 12 h of the experiment. Thereafter urine samples were collected at 24, 30, 48, 72, 96 and 168 h after administration of the drug.

An approximate estimate of OTC excreted in the urine during the first week was obtained as follows: In the first 6 urine samples from each cow the concentration of creatinine was measured and the amount of creatinine excreted per hour then calculated. In the following urine samples both OTC and creatinine were determined, and using the amount of creatinine

excreted per hour for the cow in question and the OTC-creatinine ratio for each urine sample, a rough estimate of the OTC excreted with the urine during the observation period could be calculated.

Analysis

The concentration of oxytetracycline (OTC) in plasma and urine samples was determined spectrofluorometrically by the method of *Poiger & Schlatter* (1976). The sensitivity of the method was: plasma 0.1 μg/ml and urine 0.2 μg/ml. The concentration of OTC in samples was calculated from standard curves based on analyses of blank samples to which OTC had been added. Creatinine was measured according to *Bonsnes & Taussky* (1945).

Calculation

The experimental data were analysed by a non-linear iterative curve-fitting program AUTOAN (*Sedman & Wagner* 1976). Pharmacokinetic parameters were calculated from the computerized curves according to *Baggot* (1977). Standard methods were used for statistical calculations.

RESULTS AND DISCUSSION

The elimination of OTC from plasma after intravenous injection (Fig. 1) is best described by a three-compartment open model corresponding to the formula:

$$C_t = P \cdot e^{-\pi t} + A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

where C_t is the plasma concentration at time t.

In experiments on cows and ewes *Ziv & Sulman* (1974) found that the elimination of OTC was best described by the two-compartment open model and this model was also used by *Bretzlaff et al.* (1982) in their experiments on cows. The reason for this difference may however be explained by the more frequent blood sampling during the initial phase of the present study, which made it possible to distinguish between 2 distribution processes.

The distribution of OTC may thus be described as the sum of two exponential functions ($P \cdot e^{-\pi t} + A. \cdot e^{-\alpha t}$) reflecting differences in the rate of distribution. The half-lives calculated from these 2 functions were on an average 4 ± 1 min and 34 ± 9 min (Table 2). The volume of the central compartment (V_c) was found to be as small as 0.08 l/kg (Table 2) i.e. less than the

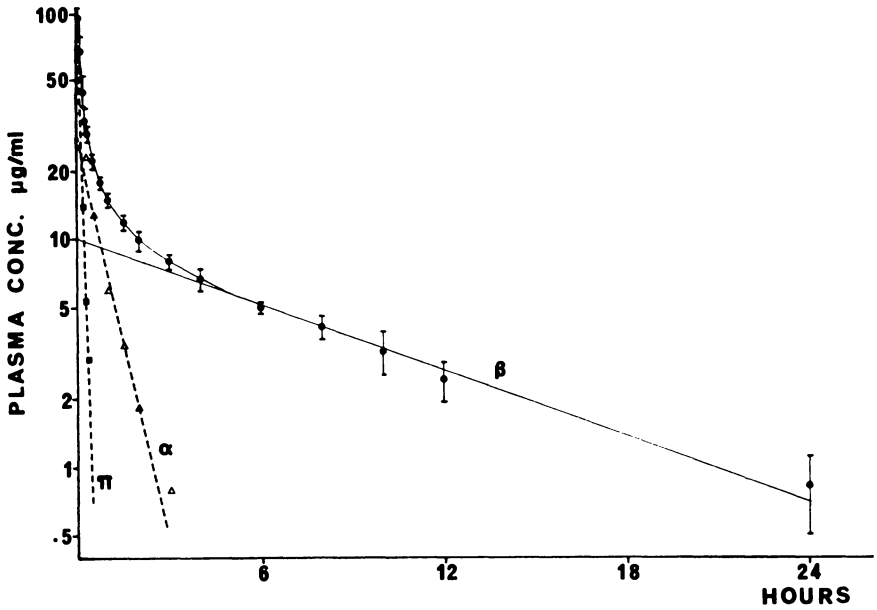

Figure 1. Plasma concentration of OTC after intravenous administration of OTC-C to cows. Dosage: 10 mg/kg. π and α represent distribution of OTC in the organism while β illustrates the elimination. Average of 4 cows. The bars indicate 1 s.

Table 2. Pharmacokinetic parameters describing disposition of OTC in cows after intravenous injection of 10 mg/kg.

Parameters[1]	Units	Mean ± s (n = 4)
C_o	µg/ml	124 ± 15
V_c	l/kg	0.08 ± 0.01
$V_{d(area)}$	l/kg	0.75 ± 0.04
Cl_B	ml/min/kg	1.42 ± 0.21
AUC_∞	µg · min/ml	7100± 1200
K_{12}	min^{-1}	0.09 ± 0.05
K_{21}	min^{-1}	0.06 ± 0.03
K_{13}	min^{-1}	0.035 ± 0.010
K_{31}	min^{-1}	0.007 ± 0.001
K_{el}	min^{-1}	0.018 ± 0.003
$t_{½\beta}$	min	366 ± 64
$t_{½\alpha}$	min	34 ± 9
$t_{½\pi}$	min	4.3 ± 1.3

[1] For explanation of symbols, see e.g. *Baggot* (1977).

extracellular fluid volume. *Bretzlaff et al.* (1982) in their experiments on cows, where the first blood sample was not collected until 1 h after the injection, found V_c to be 0.37 l/kg.

The elimination half-life ($t_{\frac{1}{2}\beta}$) varied from 308 to 454 min and was on an average 366 ± 64 min. This value is comparable to data reported by other research workers (6.5 h: *Bretzlaff et al.* 1982, 6.5 h: *Hjerpe* 1975, 6.7 h: *Yoder & Packer* 1954, 8 h: *Schipper & Petersen* 1952, 4.1 h: *Ziv & Sulman* 1974). The apparent volume of distribution $V_{d(area)}$ for OTC was on an average 0.75 ± 0.04 l/kg (Table 2) and thus of the same order of magnitude as reported by *Bretzlaff et al.* (1982) from their experiments with cows ($V_{d(area)} = 0.53$ l/kg). The apparent volume of distribution in cows is lower than in pigs (1.26 l/kg: *Mercer et al.* 1978, 1.38 l/kg: *Xia et al.* 1983), dogs (2.1 l/kg: *Baggot* 1977) and man (1.89 l/kg: *Kunin et al.* 1959).

Intramuscular injection of OTC-C resulted in plasma concentrations (Fig. 2) with a maximum of about 7 µg/ml obtained 6—8 h after administration of the drug. Calculation of the apparent elimination half-life after intramuscular administration (∼ 12—14 h) shows that this is considerably longer than after intravenous administration. This difference indicates that during the elimination phase continued absorption of OTC from the injection site is still going on. The absorption rate thus becomes the limiting factor for clearing of the drug from plasma.

Absorption of OTC from the injection site after intramuscular injection of OTC-LA took initially place at a somewhat faster rate than after administration of OTC-C, but the resulting plasma concentrations were not significantly different from each other (Fig. 2). The maximum concentration of OTC in plasma was also for OTC-LA obtained 6—8 h after administration of the drug. Calculation of the area under the curve (AUC) after intravenous (OTC-C) and intramuscular (OTC-C and OTC-LA) injections, and taking the difference in doses into consideration, showed AUC to be the same in all 3 cases. This means that the bioavailability was about 100 % after intramuscular administration of both preparations.

In experiments on calves *Nouws* (1982) reported a slight retard-effect of OCT-LA whereas such effect was not seen in the present study (Fig. 2). *Nouws* (1982) stated that this retard-effect of OTC-LA depends on the tissue damage produced at the injection site. A similar weak retard-effect of OTC-LA has been

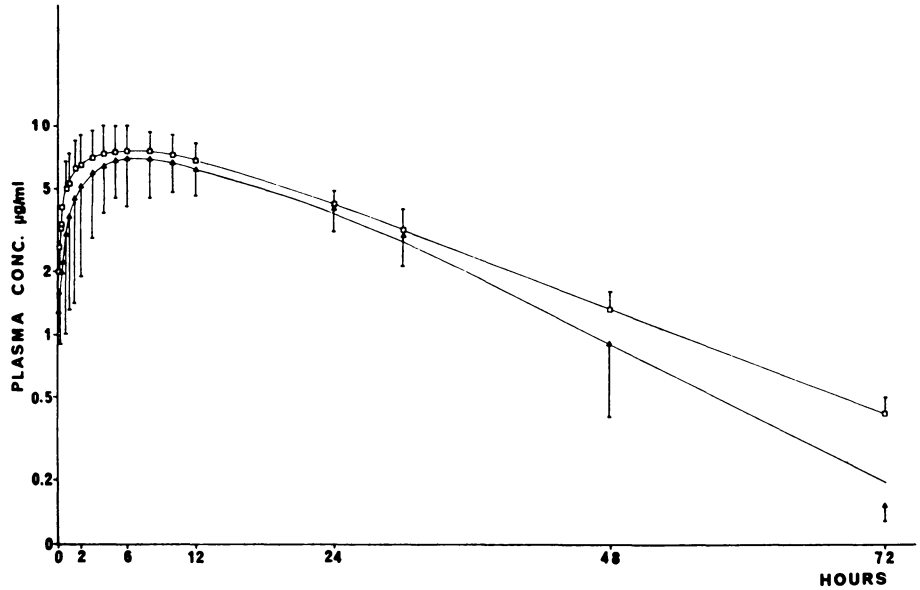

Figure 2. Plasma concentrations of OTC after intramuscular injection of OTC-C (▲) and OTC-LA (□). Dosage: 20 mg/kg. Average of 4 cows. The bars indicate 1 s.

reported from experiments with intramuscular injections of the 2 preparations in pigs (*Xia et al.* 1983). Also in this case the retard-effect of OTC-LA was connected with tissue damage whereas no tissue damage was observed after treatment with OTC-C. Good clinical results have been reported (vide *Luthman & Jacobsson* 1982) after treatment with 20 mg OTC-LA per kg b.wt., but the authors ascribed these good results to the high dose administered and not to a sustained action af the preparation.

The plasma concentration of OTC exceeded 0.5 µg/ml therapeutically active concentration: *Luthman & Jacobsson* 1982) for about 60 h. This period is comparable to the 70 h reported by *Fourtillan & Dubourg* (1982) in cows and the 60 h found by *Nouws* (1982) in his study on calves. After administration of the same dose to pigs the plasma concentration of OTC exceeded 0.5 µg/ml for only 28—35 h (*Xia et al.* 1983), which is in agreement with the shorter half-life for OTC in this species.

Almost 50 % of the administered dose was excreted in urine within 12 h after intravenous injection of the drug (Fig. 3). The urinary excretion of OTC proceeded more slowly after intra-

muscular administration with only 25—30 % of the dose excreted in 12 h.

There was, however, no difference in the rate of excretion between OTC-C and OTC-LA. By calculating the excretion of OTC on the basis of the renal excretion of creatinine it was shown (Fig. 3) that the total urinary excretion was almost the same (50—60 %) after intravenous injection of OTC-C as after intramuscular injection of OTC-C and OTC-LA. It seems reasonable to assume that the remaining part may be excreted with faeces as the molecular weight of OTC ($\sim$ 460) is high enough to permit biliary excretion (*Mercer et al.* 1978).

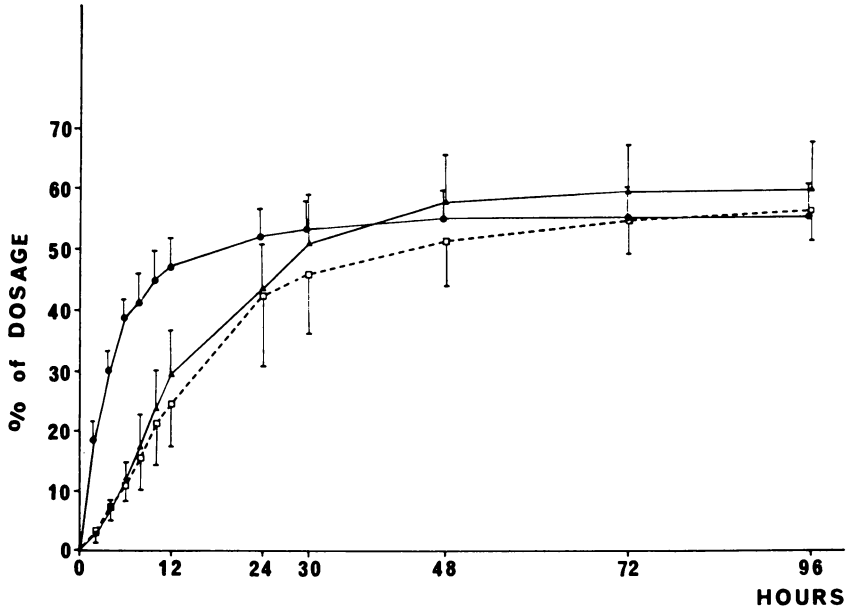

Figure 3. Cumulative excretion of OTC in urine from cows after intravenous injection of OTC-C (●) and intramuscular injection of OTC-C (▲) and OTC-LA (□). Average of 4 cows. The bars indicate 1 s.

In conclusion it may be stated that no retard-effect of the OTC-LA preparation as compared with OTC-C could be demonstrated in the present study on cows. Using the same dosage therapeutically active plasma concentrations of OTC were present for approximately 60 h with both preparations. From experimens in pigs (*Xia et al.* 1983) and calves (*Nouws* 1982) it is known that OTC-LA causes far more tissue damage than OTC-C. Together with the results from the present study this indicates that in cows OTC-LA has no advantages over OTC-C.

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REFERENCES

Baggot, J. D.: Principles of Drug Disposition in Domestic Animals: The Basis of Veterinary Clinical Pharmacology. W. B. Saunders & Co., Philadelphia 1977, pp. 155—158.

Bonsnes, R. N. & H. H. Taussky: On the colorimetric determination of creatinine by the Jaffe reaction. J. biol. Chem. 1945, *158*, 581—591.

Bretzlaff, K. N., R. S. Ott, G. D. Koritz, T. F. Lock, R. F. Bevill, R. V. Shawley, B. K. Gustafsson & L. E. Davis: Distribution of oxytetracycline in the genital tract of cows. Amer. J. vet. Res. 1982, *43*, 12—16.

Cornwell, R. L.: Evaluation of a long-acting injectable oxytetracycline. Mod. vet. Pract. 1980, *61*, 945—947.

Fourtillan, J. B. & D. Dubourg: Pharmacocinétiques sanguine et tissulaire de l'oxytetracycline après administration de la terramycine longue action chez la vache. (Pharmacokinetics of long-acting terramycin in cattle). Pharmacologie et Toxicologie Vétérinaires, INRA Publ. Paris 1982. Les colloques de l'I.N.R.A., *8*, 133—134.

Gyrd-Hansen, N., F. Rasmussen & M. Smith: Cardiovascular effects of intravenous administration of tetracycline in cattle. J. vet. Pharmacol. Therap. 1981, *4*, 15—25.

Hjerpe, C. A.: Treatment of bacterial pneumonia in feedlot cattle. Proc. Annu. Meet. Amer. Ass. Bovine Pract. 1975, *8*, 33—47.

Kunin, C. M., A. C. Dornbusch & M. Finland: Distribution and excretion of four tetracycline analogues in normal young men. J. clin. Invest. 1959, *38*, 1950—1963.

Luthman, J. & S.-O. Jacobsson: A comparison of two oxytetracycline formulations in cattle. Acta vet. scand. 1982, *23*, 147—149.

Mercer, H. D., R. H. Teske, P. E. Long & D. H. Showalter: Drug residues in food animals. II. Plasma and tissue kinetics of oxytetracycline in young cross-bred swine. J. vet. Pharmacol. Therap. 1978, *1*, 119—128.

Nouws, J. F. M.: Comparative plasma oxytetracycline levels of a "long acting" and a normal oxytetracycline formulation in ruminant calves. Pharmacologie et Toxicologie Vétérinaires, INRA Publ. Paris 1982. Les collogues de l'I.N.R.A., *8*, 195—198.

Poiger, H. & C. Schlatter: Fluorimetric determination of tetracyclines in biological materials. Analyst 1976, *101*, 808—814.

Schipper, I. A. & W. E. Petersen: Milk, blood and urine concentrations of aureomycin after intramammary infusions and intravenous administration. Vet. Med. 1952, *47*, 367—371.

Sedman, A. J. & J. G. Wagner: AUTOAN. A decision-making computer program. Publication Distribution Service. Ann Arbor, Michigan 1976.

Simpson, J. E.: Sustained oxytetracycline blood concentrations in swine due to a unique long-acting formulation. Proc. Internat. Pig Vet. Soc., 5th World Congress, Zagreb 1978, M 46.

Xia, W., N. Gyrd-Hansen & P. Nielsen: Comparison of pharmacokinetic parameters for two oxytetracycline preparations in pigs. In press.

Yoder, H. W. & R. A. Packer: Bovine blood serum concentrations of terramycin (oxytetracycline) following intravenous and intramuscular administration. Amer. J. vet. Res. 1954, *15*, 412—416.

Ziv, G. & F. G. Sulman: Analysis of pharmacokinetic properties of nine tetracycline analoques in dairy cows and ewes. Amer. J. vet. Res. 1974, *35*, 1197—1201.

SAMMENDRAG

Oxytetracyklin til kvæg — Sammenligning mellem et konventionelt og et prolongeret præparat.

Oxytetracyklin (OTC) findes som injektionsvæske til veterinær brug i en konventionel (OTC-C) og en „long-acting" (OTC-LA) præparation. I den foreliggende undersøgelse er de to præparater sammenlignet i 12 forsøg på 4 køer.

Efter intravenøs injektion of OTC-C fandtes eliminationshalveringstiden for OTC til 6 timer og 55—60 % af den injicerede dosis blev udskilt med urinen i løbet af den første uge.

Intramuskulær injektion af ens doser af OTC-C og OTC-LA resulterede i næsten identiske plasmakoncentrationskurver med højeste koncentration efter 6—8 timer. Sammenlignet med de plasmaværdier, der opnåedes ved intravenøs injektion, fandtes biotilgængeligheden for begge præparater efter intramuskulær administration at være ca. 100 %, og ca. 60 % af dosis kunne genfindes i urinen.

Plasmakoncentrationer over 0.5 μg/ml kunne for så vel OTC-C som OTC-LA opretholdes i ca. 60 timer efter en intramuskulær injektion af 20 mg/kg lgv.

Da der således ikke kunne påvises en forlænget virkningstid for OTC-LA sammenlignet med OTC-C, og da det i andre undersøgelser er vist, at OTC-LA fremkalder betydelig mere vævsbeskadigelse på injektionsstedet end OTC-C, må det konkluderes, at hos kvæg frembyder OTC-LA ingen fordele i forhold til OTC-C.

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