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A COMPARISON OF THE OXYTETRACYCLINE
PREPARATIONS AQUACYCLINE® AND
TERRAMYCIN®—100 WITH REGARD TO
ABSORPTION CHARACTERISTICS, LOCAL
TISSUE REACTIONS AND RESIDUES
FOLLOWING DEWLAP INJECTIONS IN CALVES

By

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MARITIM, C. ALICE, SIDSEL SOHLBERG, KÅRE LINDQVIST and PER LØKKEN: *A comparison of the oxytetracycline preparations Aquacycline® and Terramycin®-100 with regard to absorption characteristics, local tissue reactions and residues following dewlap injections in calves.* Acta vet. scand. 1986, 27, 361—368. — In an experiment with 12 calves, Aquacycline® in a 5 % (OTC-A5) and a 10 % (OTC-A10) solution, was compared with Terramycin®-100 (OTC-C) by injecting 20 mg OTC/kg bwt. of these preparations in the dewlap and monitoring serum concentrations as well as tissue reactions and residues at the site of injection. All 3 preparations resulted in oxytetracycline (OTC) serum concentrations above 0.5 µg/ml of approximately 60 h. During this period, OTC-A5 resulted in a 39 % and OTC-A10 in a 20 % larger area under the serum concentration-time curve, as compared to OTC-C ($P < 0.05$). The recorded tissue reaction in the form of swelling during the first week following injection of OTC-A5 averaged 72 % of that after OTC-C ($P < 0.01$), while the mean swelling after OTC-A10 was 81 % of the corresponding value after OTC-C ($P < 0.05$). The OTC residue levels at the sites of injection were lower after OTC-A5, but none of the preparations resulted in OTC residues exceeding 0.3 mg at 28 days and about 0.15 mg at 42 days after injection. The pathological changes at the site of injection were somewhat more pronounced in those calves which received OTC-C. Accordingly, these results give some support to the claims that Aquacycline® offers advantages with respect to absorption characteristics and tissue tolerance.

bioavailability.

Large variations have been reported among injectable oxytetracycline (OTC) products with respect to bioavailability, serum drug levels and the degree of tissue irritation at the injection sites (Ziv 1980, Nouws 1982, Xia *et al.* 1983).

Aquacycline® (Rosco A/S, Taastrup, Denmark) is an OTC preparation which has recently been introduced in a 5 % (OTC-A5) and 10 % (OTC-A10) solution, with the claim that it offers several advantages. According to the manufacturers, the principle of Aquacycline® is that the OTC in the form of a magnesium complex is dissolved in a minor amount of propylene glycol and polyvidon. The final products are largely aqueous solutions with a pH of approximately 8. The stable solution of low viscosity should make it easy to inject with negligible pain and tissue irritation. It is further claimed to possess major advantages such as a large margin of safety with regard to toxicity and with absorption characteristics which maximise the antibacterial activity.

The aim of the present study was to examine some of the postulated advantages of the 2 Aquacycline® formulations by comparing them with Terramycin®-100 (Pfizer, Inc., New York, USA), a 10 % (OTC-C) preparation which has been widely used in veterinary medicine. Following dewlap injection, the 3 preparations were compared with regard to OTC bioavailability and serum concentrations, as well as tissue reactions and residues at the site of injection.

MATERIALS AND METHODS

Drugs

The 3 oxytetracycline formulations were: OTC-A5: Aquacycline®-5 injectable solution containing 50 mg/ml, and OTC-A10: Aquacycline®-100 injectable solution containing 100 mg/ml (Rosco, A/S, Taastrup, Denmark) and OTC-C: Terramycin®-100 injectable solution containing 100 mg/ml (Pfizer, Inc., New York, USA).

Animals and drug administration

Twelve mixed breed steers with a mean age of 10 months (range 8—13 months) and an average body weight of 146 kg (range 100—170 kg) were used. The animals were randomly divided into 3 groups of 4 calves. They received 20 mg OTC/kg

body weight of either OTC-C, OTC-A10 or OTC-A5 in the dewlap. The injections were introduced deeply towards the centre of the dewlap.

Blood samples

Ten ml of blood samples were drawn from the jugular vein into non-heparinised vacutainers just before and at 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120 and 144 h after drug administration. The blood samples were allowed to clot and centrifuged to obtain sera which were kept at -20°C until assayed for OTC.

Registration of swelling

The degree of swelling of the dewlap was taken as an indication of the extent of tissue reaction and was estimated by simple subtraction of measurements of the dewlap thickness at the site of injection, made before and at the stated intervals after injection.

Tissue samples

From each of the 3 groups, 1 calf was slaughtered 28 days and another 42 days after drug administration. Large portions of the dewlap were excised around the sites of injection.

The injection sites were exposed by cutting partially through the midline of the dewlaps for gross examination and photography. The sites of injection were further illuminated with UV-light for the detection and localization of OTC. The areas showing tetracycline fluorescence and tissue damage were excised and weighed, and from these, representative sections were excised for OTC assays and for histological examination. The samples for OTC analyses were kept at -20°C until analysed, and those for histology were preserved in 10 % buffered formalin until processed.

OTC analyses

The concentration of OTC in serum and tissue samples was determined by the microbiological agar diffusion method using *Staphylococcus aureus* NCTC 6571 as the test organism (*Dornbush & Abbey 1972*).

Histology

The dewlap specimens for histology were embedded in paraffin wax and sections were cut and stained with haematoxylin and eosin for light microscopic examination.

Calculations

The concentrations of OTC in serum and tissue samples were calculated from the standard curves. The areas under the OTC serum concentration time-curves (AUCs) were calculated by the trapezoidal method (Baggot 1977). Student's t-test was used for statistical comparison between the mean values of the calculated AUCs (Durant 1977).

The concentrations of OTC residues in the selected representative samples showing fluorescence and the total weight of this part served as basis for obtaining a rough estimate of OTC residues at the injection sites.

The areas under the dewlap swelling-time curves were calculated by the trapezoidal method.

RESULTS

OTC serum concentrations

Individual and mean OTC serum concentration curves for the 3 OTC preparations are presented in Fig. 1. Compared to a mean peak concentration of 1.8 μg OTC/ml after the administration of OTC-C, somewhat higher peak concentrations were obtained with OTC-A10 (2.1 $\mu\text{g}/\text{ml}$) and OTC-A5 (2.6 $\mu\text{g}/\text{ml}$). Serum concentrations above 0.5 μg OTC/ml were reached within 2 to 3 h for all 3 preparations and maintained for about 60 h

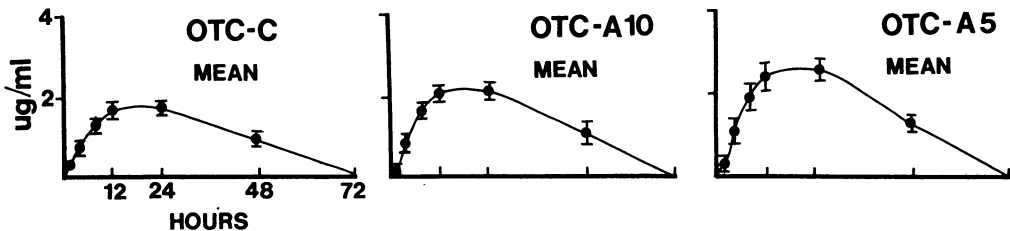


Figure 1. Mean and individual OTC serum concentrations ($\mu\text{g}/\text{ml}$) in 3 groups of 4 calves following dewlap injections of 20 mg OTC/kg bwt. of OTC-C, OTC-A10 and OTC-A5.

(range 53—63 h) after OTC-C, 60 h (range 56—65 h) after OTC-A10 and with OTC-A5 for 61 h (range 60—64 h). During this period, the AUCs (areas under the curves) for both Aquacycline® preparations were found to be significantly larger than the corresponding AUC for OTC-C ($P < 0.05$), while there was no significant difference between the AUCs for OTC-A5 and OTC-A10 ($P > 0.05$).

Swelling

Between the calves there were rather large variations in the swelling at the site of injection, especially when injected with OTC-A5 (Fig. 2). The mean recorded swelling during the first week following injection of OTC-A5 was 72 % of the corresponding value after OTC-C ($P < 0.01$) while the swelling after OTC-A10 averaged 81 % of that after OTC-C ($P < 0.05$). Thereafter there were no significant differences in the recorded swellings.

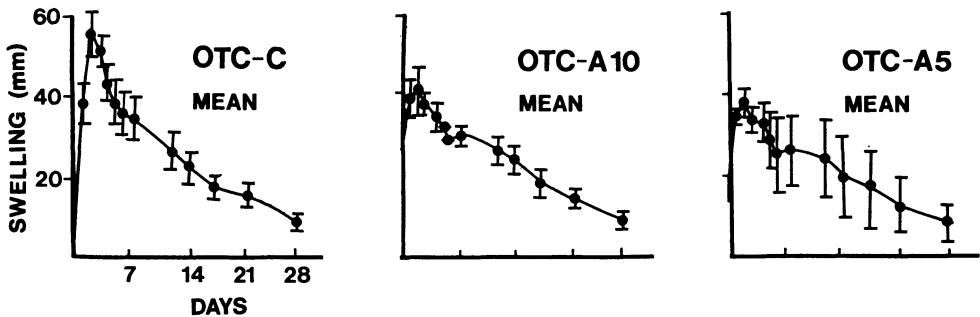


Figure 2. Mean and individual swellings in the dewlaps of 3 groups of 4 calves following dewlap injections of 20 mg OTC/kg bwt. of OTC-C, OTC-A10 and OTC-A5.

Necropsy

At post mortem examination of the animals slaughtered 28 and 42 days after dewlap injection, the injection sites showed somewhat more tissue damage after OTC-C than after the Aquacycline® preparations (Fig. 3). Microscopic examination of the dewlap injection sites revealed areas of chronic inflammatory reaction after all 3 OTC preparations.

OTC residues at the injection sites

Illumination of the dewlap injection sites with UV-light revealed yellow tetracycline fluorescence.

The total amounts of OTC residues were estimated to be 0.22 mg 28 days after and 0.05 mg 42 days after injection of OTC-C in the dewlap. The corresponding values for OTC-A10 were 0.32 and 0.03 mg, and for OTC-A5, 0.15 and 0.01 mg.

DISCUSSION

The present findings give some support to the claims that the Aquacycline® preparations offer advantages with regard to absorption characteristics, since OTC-A5 gave a 39 % and OTC-A10 a 20 % increase in the areas under the serum concentration-time curves compared to OTC-C.

At the injection site, detectable OTC residues out-lasting a pre-slaughter time limit of 4 weeks, but they were low for all the 3 OTC preparations, and did not exceed 0.3 mg at 28 days and about 0.15 mg at 42 days.

The larger injected volume of the less concentrated OTC-A5 resulted in less swelling as well as less pronounced histopathological changes. Since the randomisation resulted in a lower mean body weight in the animals receiving OTC-A5, and the OTC was administered according to body weight, this may partly account for the smaller residues after OTC-A5.

While injection in the dewlap of aqueous penicillin was found to be a valid alternative to the intramuscular route (*Bergsjø 1976*), this did not prove to be the case with OTC (*Maritim 1985*). Comparison of the areas under the serum concentration curves, indicated that the bioavailability of OTC after dewlap injection was only about half of that obtained after intramuscular injection. The dewlap might, nevertheless, represent a suitable test site for studies on absorption characteristics and tissue tolerance of various drug formulations (*Maritim 1985*).

We have been unable to find any published data on the pharmacokinetics and the postulated advantages of Aquacycline®, except for the information provided by the manufacturer in their product description.

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Alice C. Maritim, Sidsel Sohlberg, Kåre Lindqvist and Per Løkken: A Comparison of the Oxytetracycline Preparations.

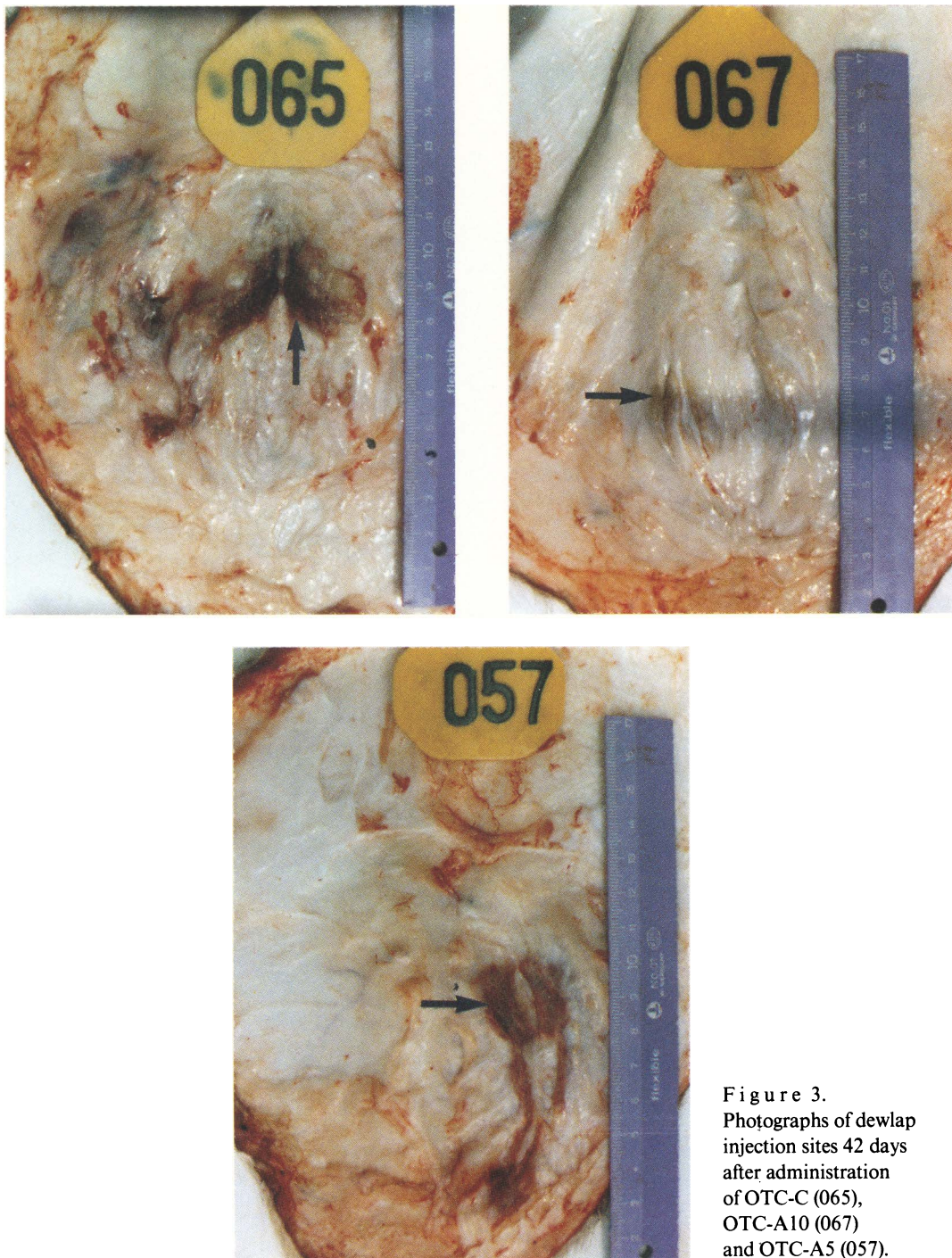


Figure 3.
Photographs of dewlap
injection sites 42 days
after administration
of OTC-C (065),
OTC-A10 (067)
and OTC-A5 (057).

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SAMMENDRAG

En sammenligning av oksytetracyklinpreparatene Aquacycline® og Terramycin®-100 med hensyn på absorpsjonskarakteristika, lokale vevsreaksjoner og rester på injeksjonsstedet etter administrasjon i dogglappen på kalv.

Aquacycline® i 5 % (OTC-A5) og 10 % (OTC-A10) oppløsning ble sammenlignet med Terramycin®-100 (OTC-C) i et forsøk med 12 kalver. Preparatene ble injisert i dogglappen i en dose av 20 mg oksy-

tetracyklin (OTC)/kg kroppsvekt. Serumkonsentrasjoner, vevsreaksjoner og rester på injeksjonsstedet ble registrert.

Etter injeksjon av alle tre preparatene var OTC-serumkonsentrasjonen høyere enn 0.5 µg/ml i ca. 60 timer. I denne perioden var arealet under serumkonsentrasjonskurven 39 % større for OTC-A5 og 20 % større for OTC-A10 enn for OTC-C ($P < 0.05$).

I den første uken etter injeksjonen av OTC-A5 var hevelsen på injeksjonsstedet gjennomsnittlig 72 % av den etter OTC-C ($P < 0.01$), mens den tilsvarende verdi etter OTC-A10 var 81 % ($P < 0.05$).

OTC-restene på injeksjonsstedet var lavest etter OTC-A5, men for ingen av preparatene oversteg restene 0.3 mg 28 dager og 0.15 mg 42 dager etter administrasjonen. Vevsforandringene på injeksjonsstedet var noe mer uttalte etter OTC-C.

Resultatene viser at Aquacycline® under disse forsøksbetingelser byr på fordeler i forhold til Terramycin® når det gjelder absorpsjonskarakteristika og vevstoleranse.

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