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Comparative pharmacokinetics of an injectable cephalexin suspension in beef cattle

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Abstract

This study describes and compares the pharmacokinetics of a single 7.5 mg/kg dose of cephalexin monohydrate oil-based 20% suspension after its administrations to six cows by the intramuscular (i.m.) and subcutaneous (s.c.) routes, and to five calves by the i.m. route. Significantly ($P < 0.05$) higher peak plasma concentrations (5.6 ± 0.79 μg/ml *versus* 3.93 ± 1.24 μg/ml) and lower half-life (1.81 ± 0.56 h *versus* 4.21 ± 0.82 h) and mean residence time (4.12 ± 1.07 h *versus* 6.63 ± 0.85 h) were obtained after i.m. administration when compared to the s.c. administration to cows. No differences were found between pharmacokinetic parameters calculated for cows and calves. Cephalexin plasma concentrations remained above 0.5–0.75 μg/ml for 11–14 h and 8–9 h after the s.c. and i.m. administrations, respectively. Thus, route of administration may be an important issue to be considered when calculating dosage schedules for successful treatments and safe withdrawal times for veterinary medicines.

Keywords: Comparative pharmacokinetics; Cattle; Age; Route of administration; Cephalexin

1. Introduction

Cephalosporins are antimicrobial agents frequently used in cattle because of their bactericidal activity, scarce occurrence of adverse effects, and low cost. Many cephalosporins, i.e., ceftiofur, cephalothin and cephalexin, are commercially available as injectable formulations. The intramuscular (i.m.) and subcutaneous (s.c.) administrations offer a convenient option for antimicrobial treatments in cattle raised in intensive systems, and sustained release formulations, by producing a slow liberation of the active ingredient, are advantageous for maintaining drug concentrations for prolonged periods of time. Occasionally, i.m. and s.c. routes are considered interchangeable by the veterinary practitioner. However, it is known that several factors, including route of administration, age, and formulation may alter the rate and extent of drug absorption and disposition. Modifications in the pharmacokinetics of antimicrobial agents raise two major concerns when these drugs are administered to food-producing animals. First, successful antimicrobial treatment depends on appropriate plasma and tissue antibiotic concentrations. Penicillin and cephalosporin bactericidal activity is time dependent, thus, drug plasma concentrations must remain above the minimum inhibitory concentration (MIC) for the target microorganism for a certain period of time (Craig, 1998; Fridmodt-Møller, 2002; Drusano, 2004; McKellar et al., 2004). Second, the withdrawal time for veterinary products that provides assurance that the food or milk can be safely consumed is closely related to the rate of depletion of the active principle and/or its metabolites (Concordet and Toutain, 1997). Hence, variations in the disposition of drugs may impair clinical outcome, and may pose a risk to the health of consumers.

The purposes of the study reported here were to describe and compare the pharmacokinetics of a slow-release cephalexin suspension after its administration to cows by the i.m. and s.c. routes, and to calves by the i.m. route.

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2. Materials and methods

2.1. Animals

Six healthy adult Aberdeen Angus cows, weighing 519.5 ± 33.26 kg and five Aberdeen Angus calves, 29–38 days old and weighing 67.4 ± 16.8 kg, were used. Animals were determined to be clinically healthy by physical examination and hematological analyses. During the study all animals grazed alfalfa pasture *ad libitum* and calves had free access to maternal milk. This study was approved by the Institutional Animal Care and Use Committee, School of Veterinary Sciences, University of Buenos Aires.

2.2. Experimental procedures

A single dose of cephalexin (7.5 mg/kg) was administered intramuscularly and subcutaneously in a parallel design with a 15 day washout period between treatments to adult cows, and intramuscularly to calves. A slow-release formulation of 20% cephalexin monohydrate in coconut oil was used (Cefalexina 20%, Laboratorio Burnet, Buenos Aires, Argentina). Intramuscular administration was performed in the right side of the neck, halfway between the upper and lower middle third. Subcutaneous injection was applied under a skin fold on the lateral midline of the right side of the neck.

Heparinized blood samples were collected from the left jugular vein of adult cows (4 ml) and calves (1.5 ml) at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 13, 17, 24, 27, 30 and 36 h after drug administration. Plasma was separated by centrifugation and frozen (−20 °C) until analyzed within one month after sample collection, as one-month cephalexin stability in blood plasma has been previously determined (Zendelovska et al., 2002). Samples were collected up to 36 h after cephalexin administration, because 36 h was the dosing interval recommended by the manufacturer.

2.3. Analytical method

Concentrations of cephalexin in plasma were determined in triplicate by an agar diffusion microbiological assay previously described (Bennet et al., 1966) using *Micrococcus luteus* ATCC 9341 as test organism. Standard curves of cephalexin were prepared in pooled bovine plasma and run simultaneously with test samples. Pure cephalexin standard was generously provided by Laboratories Holliday-Scott, Buenos Aires, Argentina. The quantification and detection limits were 0.20 μg/ml. The correlation coefficient for the regression line of the standard solution (from 50.00 μg/ml to 0.20 μg/ml) was 0.989. The within and between-day coefficients of variation and the accuracy of the assay were less than 10%.

2.4. Pharmacokinetic calculations

The drug concentration–time data in plasma for each animal and each route of administration were analyzed by non-compartmental techniques using the PCNONLIN 4.0 Software (SCI Software, Lexington, KY, USA). For peak concentration in plasma (C_{max}) and time to peak concentration in plasma (t_{max}) observed values were taken. The apparent terminal rate constant, λ_z, was determined by linear regression of the last 4–5 points on the terminal phase of the logarithmic plasma concentration–time curve. The terminal half-life, $t_{½\lambda}$, was calculated as ln $2/\lambda_z$. The area under the plasma concentration–time curve (AUC) for the time (t) at which the final measurable concentration was obtained (AUC_{0-t}) was calculated by the linear trapezoidal rule. The $AUC_{t-\infty}$ from the final time point to time infinity was estimated as the ratio of the final observed concentration/λ_z. The total area under the concentration–time curve ($AUC_{0-\infty}$) was calculated by addition of AUC_{0-t} and $AUC_{t-\infty}$. The mean residence time (MRT) was calculated as AUMC/AUC, where AUMC is the area under the curve of the product of time and the plasma drug concentration–time from time zero to infinity. All values are reported as mean ± standard deviation (SD).

2.5. Statistical analysis

The non-parametric Wilcoxon Matched Pairs Test was used to compare relevant pharmacokinetic parameters obtained after the i.m and s.c. administrations in cows, whereas the non-parametric Mann–Whitney test was applied to compare the results obtained in cows and calves after cephalexin i.m. administration. A value of $P < 0.05$ was considered significant.

3. Results

No adverse reactions that could be related to treatment were observed in either cows or calves. Mean ± standard deviation (SD) cephalexin plasma concentration–time curves obtained for each administration are shown in Fig. 1. The pharmacokinetic parameters are given in Table 1.

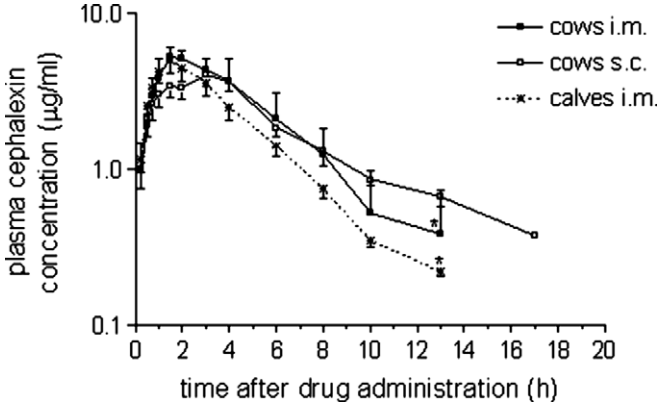

Fig. 1. Mean cephalexin plasma concentration–time curves after intramuscular (i.m.) and subcutaneous (s.c.) administrations in cows ($n = 6$) and after i.m. administration in calves ($n = 5$). Bars represent the standard deviation. * = Mean of two cows and three calves.