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THE PHARMACOKINETICS OF CEFTAZIDIME IN LACTATING AND NON-LACTATING COWS

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ABSTRACT

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The pharmacokinetics of ceftazidime (CAZ) were studied in lactating (LTG) and non-lactating (NLTG) cows. Two groups (LTG and NLTG) of 5 healthy dairy cows were given ceftazidime (10 mg/kg body weight) intravenously (i.v.) and intramuscularly (i.m.). Serum and milk (LTG) and serum samples (NLTG) were collected over a 24-h period post-administration. CAZ concentrations in serum and milk were determined by high-performance liquid chromatography, and an interactive and weighted-non-linear least-squares regression analysis was used to perform the pharmacokinetic analysis. The pharmacokinetic profiles in LTG and NLTG cows which had received CAZ i.v. fitted a three-compartment model and a two-compartment model, respectively. The CAZ concentration–time curves in serum and the area under the curve were greater and more sustained ($p < 0.05$) in the LTG cows by both routes, while the serum clearance ($Cl_s = 72.5 \pm 18.1$ ml/h per kg) was lower ($p < 0.05$) than that in the NLTG cows ($Cl_s = 185.9 \pm 44.2$ ml/h per kg). CAZ given i.v. exhibited a relatively long half-life of elimination ($t_{\frac{1}{2}\beta}$ (LTG) $= 1.1 \pm 0.2$ h; $t_{\frac{1}{2}\beta}$ (NLTG) $= 1.4 \pm 0.3$ h). Compared with other cephalosporins, CAZ had good penetration into the mammary gland ($47.7 \pm 38.2\%$ for CAZ i.v.; $51.1 \pm 39.0\%$ for CAZ i.m.). Finally, the bioavailability of CAZ (F(LTG) $= 98.9 \pm 36.8\%$; F(NLTG) $= 77.1 \pm 25.3\%$) was suitable for its use by the i.m. route in lactating and non-lactating cows.

Keywords: ceftazidime, cephalosporin, cattle, lactation, kinetics, milk

Abbreviations: AIC, Akaike information criterion; AUC, area under the curve; b.w., body weight; CAZ, ceftazidime; Cl_s, total serum clearance; C_{max}, peak serum concentration; COM, compartment open model; i.m., intramuscular(ly); i.v., intravenous(ly); LTG, lactating; K, rate constant (1, central compartment; 2, peripheral compartment; 3, deep compartment); NLTG, nonlactating; t_{max}, time of peak serum concentration; $t_{\frac{1}{2}}$, half-life

INTRODUCTION

Ceftazidime (CAZ) is a third-generation cephalosporin stable to β-lactamases produced by bacteria and characterized by its activity against many Gram-negative bacteria (O'Callaghan *et al.*, 1980; Jones *et al.*, 1981; Balant *et al.*, 1985; Soback and

Ziv, 1989; Thornsberry, 1985).

The pharmacokinetics of CAZ have been described using a two-compartment open model in human beings (Harding *et al.*, 1981; Ryan *et al.*, 1981; Wise *et al.*, 1981; Saito, 1983), dogs (Matsui *et al.*, 1984) and sheep (Rule *et al.*, 1991). Although there is little information on the effects of lactation on the pharmacokinetics of CAZ, it has been reported that it has good penetration into the mammary gland (Blanco *et al.*, 1983) and tissue fluid (Walstad *et al.*, 1983) of humans, exhibits low binding to plasma proteins (O'Callaghan *et al.*, 1980; Harding *et al.*, 1981; Rule *et al.*, 1991), and has no nephrotoxic effects (Capel and Pratt, 1981).

The purpose of the present investigation was to study the pharmacokinetics of CAZ in cows and evaluate the effect of lactation on its pharmacokinetic behaviour.

MATERIALS AND METHODS

Lactating (LTG) ($n = 5$) and non-lactating (NLTG) ($n = 5$) Holstein cows weighing 450 ± 50 kg were used to perform two different trials. Cows in the LTG group were clinically healthy and had a somatic cell count in their milk below 350 000 cells/ml in a pooled-milk sample. The NLTG cows were only required to be clinically normal.

Trial 1 was conducted by giving a single dose of 10 mg/kg body weight of CAZ by the intravenous (i.v.) route. Following CAZ administration, blood samples were collected from the jugular vein of the cows at 5, 10, 15, and 30 min and at 1, 2, 3, 4, 5, 6, 8, 12, and 24 h. In the LTG group, composite 5-ml milk samples were also collected starting at 15 min and then at the same times as the blood samples.

Trial 2 was performed 15 days after trial 1 was concluded with the cows being given an intramuscular (i.m.) injection of the same dose of CAZ and following the same sampling procedure as in trial 1.

The blood samples were allowed to clot and were centrifuged at 1000*g* for 5 min to separate the serum. The milk and serum samples were stored at –70°C for at least 14 days before the CAZ concentration was determined.

The ceftazidime concentrations in the serum and milk samples were measured by high-performance liquid chromatography. Briefly, the samples were allowed to thaw and were mixed in 250-µl aliquots with 100 µl of 0.02 mol/L H_3PO_4/KH_2PO_4 buffer (pH 2.6), 20 µl of 30% (v/v) perchloric acid solution in 0.02 mol/L H_3PO_4/KH_2PO_4 buffer and 250 µl of methanol. The specimens were then centrifuged at 1000*g* for 5 min and the supernatants were recovered. Finally, 10 µl of each supernatant was injected into a µBondapak alkyl phenyl C-1B column (Waters, Milford, MA, USA) with 16% (v/v) acetonitrile solution in 0.02 mol/L H_3PO_4/KH_2PO_4 buffer as the mobile phase of a high-performance liquid chromatography system (System Gold-Network, USA) equipped with a UV absorbance detector at 254 nm wavelength to analyse the CAZ concentrations. The method had an intra-run coefficient of variation of 3.1% and a minimum limit of detection of 0.2 µg/ml.

The ceftazidime concentration data were used for pharmacokinetic analysis by an interactive and weighted-non-linear least-squares regression analysis (Metzler and Tong, 1981). The Akaike information criterion (AIC) (Akaike, 1978) was used to

determine the compartmental model best adapted to the data set. Hybrid constants P, A and B (extrapolations at zero time of the experimental terms), the slope of the rapid phase of distribution (α), the slope of the slower phase of distribution (π), and the slope of elimination phase (β) were used to calculate the rate constants from the central to peripheral compartment (K_{12}) and vice versa (K_{21}), the rate constants from the central to a deep compartment (K_{13}) and vice versa (K_{31}), and the rate constants of elimination (K_{10}) (Gibaldi and Perrier, 1982).

The bioavailability (F) of CAZ was assessed using the following equation (Baggot, 1977):

$$F = \mathrm{AUC}_{0\text{-}\infty}\ (\mathrm{i.m.})/\mathrm{AUC}_{0\text{-}\infty}\ (\mathrm{i.v})$$

where $\mathrm{AUC}_{0\text{-}\infty}$ (i.m.) = the area under the curve (AUC) after i.m. administration and $\mathrm{AUC}_{0\text{-}\infty}$ (i.v.) = AUC after i.v. administration for the same animal. The AUC was calculated by the trapezoidal method (Gibaldi and Perrier, 1982), with extrapolation to infinite time.

The apparent volume of the central compartment (V_c) was calculated from the following equation:

$$V_c = \mathrm{Dose}\ (\mu\mathrm{g/ml})/C_0$$

where the concentration at zero time (C_0) = $P+A+B$ in a three-compartment open model (3-COM) and $C_0 = A+B$ in a two-compartment open model (2-COM).

The distribution volume at steady state (V_{dss}) was calculated as follows (Baggot, 1977):

$$V_{dss} = [(K_{21}K_{31} + K_{12}K_{13} + K_{21}K_{13})/K_{21}K_{31}]V_c\ (\text{3-COM})$$

and

$$V_{dss} = [(K_{12} + K_{21})/K_{21}]V_c\ (\text{2-COM})$$

The total serum clearance (Cl_s) was calculated using the following equation (Baggot, 1977):

$$Cl_s = K_{el}V_c$$

The rapid distribution ($t_{\frac{1}{2}} = 1\mathrm{n}\ 2/\alpha$), the slower distribution ($t_{\frac{1}{2}} = 1\mathrm{n}\ 2/\pi$), and the elimination ($t_{\frac{1}{2}} = 1\mathrm{n}\ 2/\beta$) half-lives were calculated using equations given by Baggot (1977).

Statistical analysis was performed by unpaired t-test comparisons to determine the effects of lactation within the same route of administration (serum) and of the route of administration within same lactation status.

TABLE I
Pharmacokinetic variables[a] for ceftazidime after single intravenous (i.v.) and intramuscular (i.m.) doses (10 mg/kg) in lactating (LTG) (n= 5) and non-lactating (NLTG) (n= 5) dairy cows

Pharmacokinetic variable	Group of cows (route of administration)			
	LTG (i.v.)	NLTG (i.v.)	LTG (i.m.)	NLTG (i.m.)
A (μg/ml)	50.2±10.5	58.4±33.4	–	–
B (μg/ml)	44.9±13.8	24.7±11.8	–	–
C (μg/ml)	4.1±1.4	–	–	–
α (h^{-1})	15.3±15.9	5.6±2.0	–	–
β (h^{-1})	0.7±0.1	0.5±0.1	–	–
π (h^{-1})	0.04±0.03	–	–	–
$AUC_{0-\infty}$ (μg/ml/h)	261.3±124.2[b]	55.3±12.2	233.2±71.6[b]	38.3±5.9
C_{max} (μg/ml)	103.8±11.2	83.1±36.6	35.7±2.6	11.6±2.3
V_{dss} (ml/kg)	489.8±136.9	390.2±212.9	–	–
Cl_s ((ml/h)/kg)	72.5±18.1	185.9±44.2[b]	–	–
V_c (ml/kg)	139.5±98.1	158.8±68.7	–	–
K_{10} ((h^{-1})	0.5±0.2	1.5±0.6	0.3±0.02	0.5±0.1
K_{12} (h^{-1})	4.5±5.9	1.5±1.2	–	–
K_{21} (h^{-1})	4.8±3.8	1.1±0.8	–	–
K_{13} (h^{-1})	0.8±0.5	–	–	–
K_{31} (h^{-1})	0.09±0.07	–	–	–
$t_{\frac{1}{2}K(10)}$ (h)	1.2±0.9	0.5±0.2	2.6±0.2	1.7±0.7
$t_{\frac{1}{2}\alpha}$ (h)	0.08±0.05	0.14±0.06	–	–
$t_{\frac{1}{2}\beta}$ (h)	1.1±0.2	1.4±0.3	2.2±0.6	3.6±1.7
$t_{\frac{1}{2}\pi}$ (h)	28.1±19.2	–	–	–
K_{01} (h^{-1})	–	–	5.4±2.4	4.7±3.6
$t_{\frac{1}{2}K(01)}$ (h)	–	–	0.1±0.1	0.2±0.1
t_{max} (h)	–	–	0.7±0.3	0.7±0.2
F (%)	–	–	98.9±36.8	77.1±25.3
$AUC_{0-\infty}$ (milk) (μg/ml/h)	115.3±74.5	–	150.7±63.9	–
Penetration (milk) (%)	47.7±38.2	–	51.1=39.0	–
t_{max} (h) (milk)	1.0±0.8	–	1.3±1.3	–
C_{max} (milk) (μg/ml)	2.2±1.2	–	3.7±1.4	–

[a]Values are presented as mean±(SD)

[b]Significantly higher ($p<0.05$) than in the other group of cows receiving CAZ by the same route of administration

RESULTS

The pharmacokinetic variables are presented in Table I. The concentration values for CAZ in serum and milk (LTG cows) and in serum (NLTG cows) over time following i.v. and i.m. administration are plotted in Figures 1 and 2, respectively.

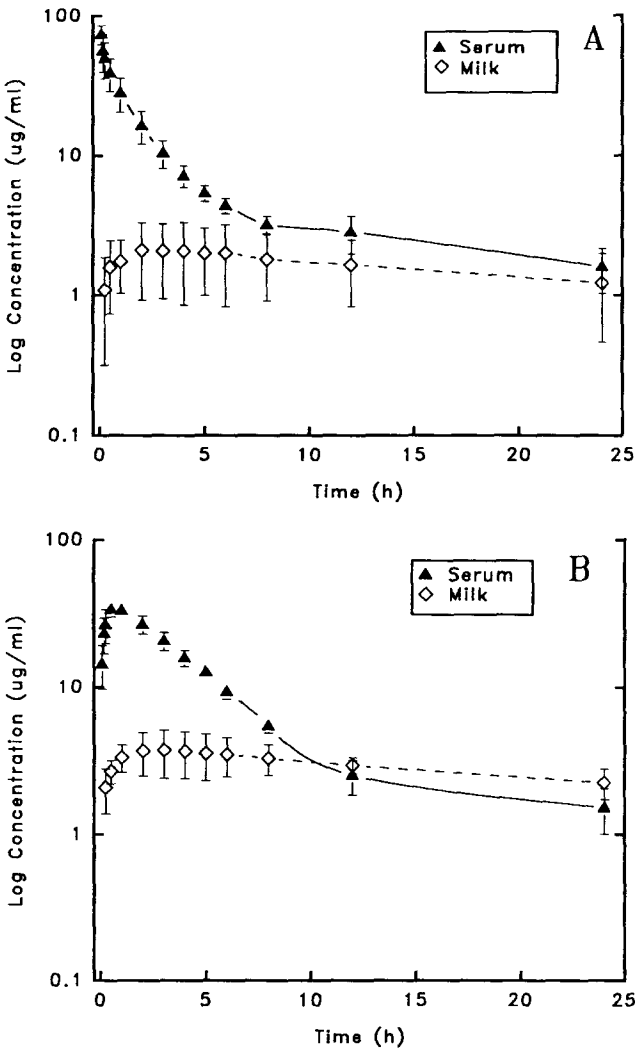

Figure 1. A semilogarithmic plot of the concentrations of ceftazidime in serum and milk versus time after intravenous (A) and intramuscular (B) administration (10 mg/kg) in 5 lactating dairy cows

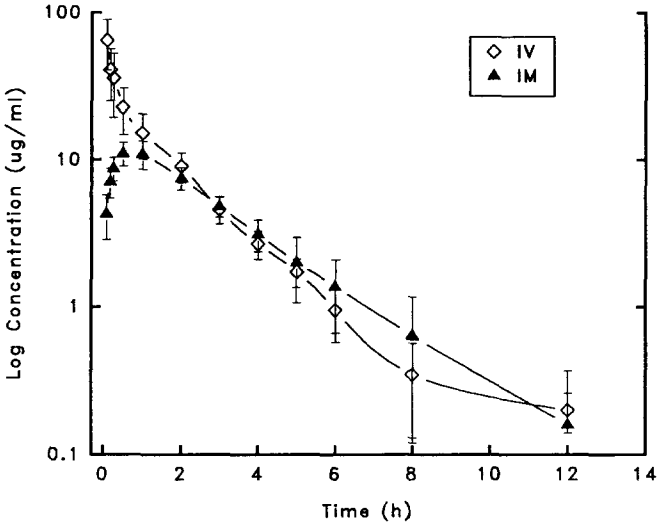

Figure 2. A semilogarithmic plot of the serum concentrations of ceftazidime versus time after intravenous (i.v.) and intramuscular (i.m.) administration (10 mg/kg) in 5 non-lactating dairy cows

In the LTG cows, the profiles of the concentration of CAZ in serum over time after i.v. administration appeared to show an unusual 'flip-flop' pattern, where the first slope corresponded to a rapid distribution (α) followed by slopes relating to elimination (β) and to a slower distribution (π) (Figure 1A). On the other hand, the NLTG cows exhibited only a rapid distribution phase (α). 3-COM gave the best fit for the data describing the pharmacokinetic profiles of CAZ after i.v. administration in LTG cows (AIC = 34.3). By contrast, 2-COM was most suitable to describe the pharmacokinetics in NLTG cows after i.v. administration (AIC = 25.4). A single-compartment model was used for the i.m. route for both LTG and NLTG cows.

Neither the $t_{\frac{1}{2}\alpha}$ nor the $t_{\frac{1}{2}\beta}$ was significantly different after i.v. administration in LTG and NLTG cows ($p > 0.05$).

The concentration–time curves after both i.m. and i.v. administration showed the concentration of the antibiotic to be higher and more sustained in the serum of the LTG cows (Figures 1A and 1B) than in the NLTG cows (Figure 2). Consequently, $AUC_{0\text{-}\infty}$ (i.m.) and $AUC_{0\text{-}\infty}$ (i.v.) were greater in LTG cows ($p < 0.05$) than in NLTG cows (Table I).

The Cl_s in the NLTG cows after i.v. administration was greater ($p < 0.05$) than in the LTG cows.

In the LTG cows, the pharmacokinetic variables for CAZ in milk, such as $AUC_{0\text{-}\infty}$, penetration, t_{max} and C_{max}, did not exhibit significant differences ($p > 0.05$) after i.m. or i.v. administration (Table I).

DISCUSSION

The pharmacokinetic profiles of CAZ after i.v. administration in LTG and NLTG cows were described using 3-COM and 2-COM, respectively. In LTG animals, there is no comparable information on the pharmacokinetics of CAZ. However, the description of pharmacokinetic profiles by 2-COM in NLTG animals agrees with studies reported earlier in human beings (Harding *et al.*, 1981; Wise *et al.*, 1981; Ryan *et al.*, 1981) and sheep (Rule *et al.*, 1991).

The serum distribution half-lives (α phase) of CAZ administered i.v. in LTG and NLTG cows were similar to the half-life reported for dogs (0.12 ± 0.04 h) (Matsui *et al.*, 1984), but shorter than those in humans (0.62 ± 0.01 h) (Saito, 1983) and in sheep (0.22 ± 0.09 h) (Rule *et al.*, 1991).

The elimination half-lives for LTG and NLTG cows were longer than the half-life reported in dogs (0.8 ± 0.02 h) (Matsui *et al.*, 1984) but shorter than those reported in sheep (1.6 ± 0.2 h) (Rule *et al.*, 1991) and in humans (1.8 ± 0.2 h) (Wise *et al.*, 1981).

Although the clearance in NLTG cows was greater than in LTG cows, it was similar to that reported in sheep (212.8 ± 79.9 (ml/h)/kg) (Rule *et al.*, 1991), and also to the renal clearance (185.0 ± 9.0 (ml/h)/kg) and to the body clearance (215.0 ± 3.0 (ml/h)/kg) reported in dogs (Matsui *et al.*, 1984).

Blanco and colleagues (1983) reported sustained concentrations of CAZ in milk following a multiple-dose administration to human beings, similar to the results observed after i.v. and i.m. bolus administration in the present study. These latter results, along with the difference between the volume of distribution at steady-state and the volume of the central compartment ($p < 0.05$) in both LTG and NLTG cows, a long elimination half-life, a low degree of binding to plasma protein (O'Callaghan *et al.*, 1980; Harding *et al.*, 1981; Rule *et al.*, 1991) and the low molecular weight of CAZ (Barza, 1981) are compatible with good extravascular distribution of CAZ. Consequently, and considering also the K_{13}/K_{31} ratio, it may be speculated that the mammary gland works as a deep compartment trapping antibiotic in the milk. The reduced serum clearance and the slower phase of distribution (Figure 1) in LTG cows may be complementary evidence for this trapping process.

The concentrations of CAZ during the experiment were higher than the minimal inhibitory concentrations reported earlier for many Gram-negative bacteria (Soback and Ziv, 1989).

In conclusion, CAZ is a third-generation cephalosporin that exhibits a relatively long elimination half-life compared to other cephalosporins in cows, a high degree of penetration into the mammary gland, and a bioavailability averaging 88% after i.m. administration.

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