Pharmacokinetics of ceftiofur and metabolites after single intravenous and intramuscular administration and multiple intramuscular administrations of ceftiofur sodium to dairy goats

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Twelve (12) lactating dairy goats (46–71 kg body wt at study initiation) were divided into four treatment groups and dosed with ceftiofur sodium at 1.1 mg ceftiofur free acid equivalents (CFAE)/kg or 2.2 CFAE/kg using a complete two route (intravenous, i.v.; intramuscular, i.m.), two-period crossover design, with a 2-week washout between injections. After another 2-week washout period, the goats were dosed with ceftiofur sodium i.m. for 5 consecutive days at either 1.1 or 2.2 mg CFAE/kg. The goats from the 2.2 mg/kg multiple dose group were dried off and the i.v. kinetic study repeated. After all injections, blood samples were obtained serially for determination of combined serum concentrations of ceftiofur and metabolites. After intravenous doses of 1.1 and 2.2 mg/kg, the harmonic means of the terminal phase half-lives were 171.8 and 233 min, respectively, for lactating does. The harmonic mean of the terminal phase half-life after an i.v. dose of 2.2 mg/kg in non-lactating does was 254 min. The $AUC_{0-\infty}$ was significantly less and the clearance significantly greater during lactation. After i.m. doses of 1.1 and 2.2 mg/kg, the harmonic mean terminal phase half-lives were 163 and 156 min, respectively. The i.m. bioavailability of ceftiofur sodium in goats was 100%, and the $AUC_{0-\infty}$ was dose-proportional from 1.1–2.2 mg CFAE/kg body weight. After five daily i.m. doses of ceftiofur sodium at either 1.1 or 2.2 mg CFAE, there was minimal accumulation of drug in serum as assessed by C_{max}, and serum concentrations were dose-proportional after the multiple dosing regimen.

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INTRODUCTION

Ceftiofur sodium is a late generation cephalosporin which is approved for use in the United States in cattle, pigs, poultry, horses and dogs (Crosier *et al.*, 1996). The pharmacokinetics of ceftiofur in various species was reviewed by Brown *et al.* (1991). Since that time, additional reports have appeared for cattle (Soback *et al.*, 1991; Halstead *et al.*, 1992; Erskine *et al.*, 1995; Whittem *et al.*, 1995; Brown *et al.*, 1996), horses (Meyer *et al.*, 1992; Jaglan *et al.*, 1994), dogs (Brown *et al.*, 1995) and sheep (Craigmill *et al.*, 1997). A preliminary report on the pharmacokinetics of ceftiofur in sheep (Craigmill *et al.*, 1991) showed that the pharmacokinetics in sheep were very similar to those seen in cattle. Another preliminary report (Courtin *et al.*, 1994) showed the pharmacokinetic parameters in goats to be similar to sheep. The purpose of this study was to determine the single dose pharmacokinetics of ceftiofur sodium (as measured by combined ceftiofur and metabolite concentrations in serum) in goats after single i.v. and i.m. doses of 1.1 and 2.2 mg ceftiofur free acid equivalents (CFAE) per kg body weight, and after five daily i.m. injections of 1.1 and 2.2 mg CFAE/kg body weight, and to determine if lactation status affects the pharmacokinetic parameters of ceftiofur in dairy goats.

MATERIALS AND METHODS

Animals

Twelve lactating (mid to late lactation) dairy goats of various breeds were obtained from the dairy goat herd of the University of California, Dairy Goat Facility, Davis, CA, USA. The goats

ranged in age from 2 to 6 years and weighed 46.0–71.0 kg at the time of initial injection. All goats were in good health at the start of the study and observations on general health were made each day throughout the study. The goats were fed with a standard ration of oat hay, alfalfa pellets and a lactation ration consisting of 30% rolled corn, 30% rolled barley, 15% rolled wheat, 15% whole cottonseed, 2% soybean meal and 3% molasses. Feed consumption was monitored and recorded daily. Water was available *ad libitum* via an automatic watering system. The study protocols were approved by the Animal Use and Care Administrative Advisory Committee of the University of California, Davis.

Drug

NAXCEL® Sterile Powder (ceftiofur sodium; Lot no. 375-JY; 1 gram vial Pharmacia & Upjohn, Kalamazoo, MI, USA) with Sterile Water for Injection USP (Lot no. 154-KH, Diamond Scientific, Des Moines, IA, USA).

Drug treatment

Intravenous (i.v.) and intramuscular (i.m.) kinetics.
Goats were randomized by weight into four treatment groups. Randomization was checked by Bartlett's and Analysis of Variance tests. Using a two-way crossover design, the i.v. and i.m. kinetics of ceftiofur in goats were determined at two dose levels: 1.1 mg/kg and 2.2 mg/kg. Groups 1 and 3 received the 1.1 mg/kg dose and groups 2 and 4 received 2.2 mg/kg. Groups 1 and 2 received the drug i.v. first, and after a 2-week washout received the same dose i.m. Groups 3 and 4 received the drug i.m. first, and after a 2-week washout received the same dose i.v. All animals remained drug free for 17–25 days, at which time the multiple i.m. dose study occurred. For the multiple dose study, groups 1 and 3 were combined and received the 1.1 mg/kg dose, and groups 2 and 4 were combined and received the 2.2 mg/kg dose. Blood samples were taken daily from the six animals at each dose level prior to drug administration and at 1, 2, 4, 8, and 12 h after dosing.

Following the conclusion of the multiple i.m. dose kinetics portion of the study, the goats in the combined 2.2 mg/kg group (groups 2 and 4) were taken off feed for 3 days to stop lactation. After a 6-week washout from the end of the multiple dose portion, these goats received the drug i.v. at a single dose of 2.2 mg/kg.

In the pharmacokinetic portion of the study, i.v. blood samples were taken just prior to drug administration, and at 10, 15, 20, 30, 45 and 60 min; and at 1.5, 2, 3, 4, 6, 8, 12, and 24 h after dosing. For the goats given the drug i.m., blood samples were taken just prior to administration and at 10, 20, 30, 45, and 60 min; and 1.5, 2, 3, 4, 6, 8, 12, and 24 h after dosing.

Assay

Blood samples were allowed to clot for at least 1 h at room temperature, then refrigerated if necessary until processed. Samples were centrifuged and the serum separated and frozen immediately as one aliquot at -20°C. All samples were kept frozen at -20°C until assay. Standards were made up in goat serum and frozen to control for stability. Serum samples were analysed for ceftiofur and desfuroylceftiofur-related metabolites using a modification of the method published by Jaglan *et al.* (1990). Different chromatographic conditions were used as required for routine analysis of a large quantity of samples. These conditions are described by Banting *et al.* (1989). Briefly, the method uses dithioerythritol to cleave any macromolecule bound to desfuroylceftiofur in the serum. The sample is then run through a C18 solid phase extraction (SPE) column and further derivatized with iodoacetamide to create desfuroylceftiofur acetamide. After elution from the C18 SPE, further clean-up was done on a SCX SPE. The HPLC analysis was done isocratically (the mobile phase was 7% acetonitrile, 1% acetic acid, with 90 mg heptane sulphonic acid/litre, and pH = 4.0) on a Nova-pak C18, 4 μm, 3.9 × 150 mm (Waters Corporation, Milford, MA, USA) with UV detection at 240 nm. Six standards were run in goat serum each day, and three spiked quality control samples were included in each batch. The mean accuracy of more than 64 spikes of three different concentrations was 0.99 with a relative standard deviation of 11%. The limit of quantitation (LOQ) of the assay was 0.1 μg CFAE/mL of serum. All results below the LOQ for the assay were not used in the calculations or pharmacokinetic modelling.

Pharmacokinetic and statistical analysis

All pharmacokinetic analyses were done using a weighted nonlinear least-squares regression program (RSTRIP, Version 5, MicroMath Scientific Software, Salt Lake City, UT, USA) to fit the pharmacokinetic equation to the individual animal data sets. Single intravenous dose serum concentration vs. time data were modelled using the following general pharmacokinetic equation for single doses:

$$C_p = \sum_{i=1}^{z} C_i \exp(-\lambda_i t)$$

where C_p is the drug concentration in serum, C_i is the intercept and λ_i is the slope of the z terms in the equation, and t is time. Single intramuscular dose data were modelled using the following pharmacokinetic equation:

$$C_p = \left[\sum_{i=1}^{z} C_i \exp(-\lambda_i t)\right] - \left(\sum_{i=1}^{z} C_i\right) \exp(-k_a t)$$

In this equation, k_a is the rate constant for the primary disposition phase, which includes absorption and distribution processes. The first and last doses of the multiple dose study were modelled using the equation for single doses presented above. All pharmacokinetic equations were fitted to the data using a weighting factor of $1/\text{concentration}^2$ unless otherwise noted. Goodness of fit of biexponential and triexponential models was determined using the RSTRIP Model Selection Criterion (MSC) which is similar to Akaike's Information Criterion. The biexponential model provided excellent fits for all the i.v. and i.m. data.

Statistical analysis

All data are summarized as $\overline{X} \pm$ SD unless otherwise noted. Area under the concentration–time curve per dose (*AUC*/Dose), mean residence time (*MRT*), maximum concentration C_{max}, clearance (*Cl*), volume of distribution ($V_{d(ss)}$) and appropriate half-lives ($t_{1/2}$) were analysed using an analysis of variance and two-tail Student's *t* test.

RESULTS

Single dose crossover study

The pharmacokinetic parameters obtained from the combined serum concentrations of ceftiofur and metabolites (CAM) after single i.v. doses 1.1 and 2.2 mg CFAE per kilogram are shown in Table 1. Calculated peak concentrations of CAM after intravenous doses of 1.1 and 2.2 mg/kg were 8.0 ± 1.1 μg/mL and 14.0 ± 2.5 μg/mL, respectively. The peak concentration of CAM in non-lactating dairy goats following doses of 2.2 mg CFAE/kg was 16.1 ± 1.6 μg/mL, and was not significantly different from the lactating state ($P = 0.059$). The pharmacokinetic parameters obtained from serum concentrations of ceftiofur and metabolites (CAM) after single i.m. doses 1.1 and 2.2 mg CFAE per kilogram are shown in Table 2. The C_{max} after i.m. doses of 1.1 and 2.2 mg CFAE/kg were 2.7 ± 1.2, and 4.57 ± 0.96 μg/mL, respectively. The t_{max} after i.m. doses of 1.1 and 2.2 mg CFAE/kg were 69.9 ± 49.1 min and 70.4 ± 26.6 min, respectively. The C_{max}/dose after 1.1 mg/kg was not different than that after 2.2 mg/kg ($P = 0.50$). Twenty-four h after dosing, serum concentrations were below the limit of quantitation after i.v. and i.m. doses of 1.1 or 2.2 mg/kg, except in one animal at the i.m. 2.2 mg/kg dose (0.2 μg/mL at 24 h).

After intravenous doses of 1.1 and 2.2 mg/kg to lactating does and 2.2 mg/kg to non-lactating does, the harmonic mean primary disposition phase (distribution) half-lives ($t_{1/2a}$) were 28.0, 41.6, and 48.0 min, respectively. The terminal disposition phase half-lives ($t_{1/2b}$) were 171.8, 233, and 254 min after intravenous doses of 1.1 and 2.2 mg/kg to lactating does and 2.2 mg/kg to non-lactating does, respectively. After intramuscular doses of 1.1 and 2.2 mg/kg, the harmonic mean primary disposition phase (which includes absorption and distribution processes) half-lives ($t_{1/2a}$) were 12.0 and 16.0, respectively. The terminal disposition phase half-lives ($t_{1/2b}$) were 163 and 156 min after intramuscular doses of 1.1 and 2.2 mg/kg, respectively. The mean residence times after i.v. dosing were not significantly different for lactating and non-lactating goats, or at the 1.2 and 2.2 mg/kg doses for lactating goats.

The $AUC_{0-\infty}$ derived by the method of trapezoids after i.v. dosing was 774 ± 195 μg.min/mL, 1625 ± 270 μg.min/mL, and 2036 ± 383 μg.min/mL after doses of 1.1 and 2.2 mg/kg to lactating does and 2.2 mg/kg to non-lactating does, respectively. The $AUC_{0-\infty}$ during lactation was significantly less ($P < 0.05$) than that when the goats were dry and the clearance of ceftiofur was significantly greater ($P < 0.05$) in lactating goats than in non-lactating goats given 2.2 mg/kg i.v.. The $V_{d(ss)}$ of ceftiofur in goats given 2.2 mg/kg ceftiofur during lactation and after drying off were not significantly different ($P = 0.098$).

Table 1. Pharmacokinetic values obtained from serum concentrations of ceftiofur and metabolites after intravenous administrations of a single dose of ceftiofur sodium at doses of 1.1 and 2.2 mg ceftiofur free acid equivalents/kg in goats

	$t_{1/2a}$ (min)	$t_{1/2b}$ (min)	Cp_0 (μg/mL)	$AUC_{0-\infty}$ (μg.min/mL)	Clearance (mL/min/kg)	$V_{d(ss)}$ (L/kg)	*AUC*/Dose	*MRT* (min)
i.v., Lactating,								
1.1 mg/kg (Mean)	28.0	171.8	7.96	774	1.49	0.26	704.00	188
(Std. Dev.)	(harmonic)	(harmonic)	(1.1)	(195)	(0.33)	(0.03)	(177.00)	(62)
i.v., Lactating,								
2.2 mg/kg (Mean)	41.6	233.0	14.0	1625	1.38	0.31	739.00	230
(Std. Dev.)	(harmonic)	(harmonic)	(2.5)	(270)	(0.21)	(0.07)	(123.00)	(67)
i.v., Non-lactating,								
2.2 mg/kg (Mean)	48.0	254.0	16.1	2036[a]	1.11[a]	0.25	925.00	231
(Std. Dev.)	(harmonic)	(harmonic)	(1.6)	(383)	(0.21)	(0.03)	(174.00)	(54)

[a]Significantly different from the i.v., Lactating 2.2 mg/kg *AUC* value, $P < 0.05$.

Table 2. Mean pharmacokinetic values obtained from serum concentrations of ceftiofur and metabolites after intramuscular administration of a single dose of ceftiofur sodium at doses of 1.1 and 2.2 mg ceftiofur free acid equivalents/kg in goats

i.m. data summary									
	$t_{1/2a}$ (min)	$t_{1/2b}$ (min)	C_{max} (μg/mL)	C_{max}/Dose	t_{max} (min)	$AUC_{0-\infty}$ (μg.min/mL)	AUC/Dose	*MRT* (min)	Lag Time (min)
i.m., 1.1 mg/kg	12.0	163.0	2.7	2.4	69.9	695	632.00	269	8
(Std. Dev.)	(harmonic)	(harmonic)	(1.2)	(1.1)	(49.1)	(175)	(159.00)	(115)	(4.3)
i.m., 2.2 mg/kg	16.0	156.0	4.57	2.1	70.4	1447	658.00	287	5.0
(Std. Dev.)	(harmonic)	(harmonic)	(0.96)	(0.4)	(26.6)	(328)	(149.00)	(112)	(5.7)

The $AUC_{0-\infty}$ after i.m. dosing was 695 ± 175 μg.min/mL and 1447 ± 328 μg.min/mL after doses of 1.1 and 2.2 mg/kg, respectively. The i.m. bioavailability of ceftiofur sodium in goats was 100%, and the $AUC_{0-\infty}$ was dose-proportional from 1.1–2.2 mg CFAE/kg body weight in goats.

The serum concentration profiles for CAM after i.m. and i.v. dosing of non-lactating goats with 1.1 and 2.2 mg CFAE/kg are shown in Figs 1 and 2. The graphs show that 60 min after dosing, the i.v. and the i.m. curves converge and are superimposable for the rest of the samples assayed. Figure 3 shows the mean and standard deviations of the serum concentrations of CAM following single i.v. doses of 2.2 mg CFAE/kg given to the same six goats when lactating, and 6 weeks after drying off (non-lactating). The mean serum levels in the lactating goats were invariably, but not consistently significantly lower than those observed when the goats had been dried.

Multiple dose administration study

The pharmacokinetic parameters obtained from serum concentrations of ceftiofur and metabolites (CAM) after the first and fifth of five daily i.m. doses 1.1 and 2.2 mg CFAE per kilogram are shown in Table 3. The C_{max} were observed after each dose at the 1 or 2 h sampling times, and were 2.7 ± 0.8 μg/mL and 3.6 ± 0.3 μg/mL after the first and fifth doses of 1.1 mg/kg, respectively. Similarly, C_{max} were observed at the 1 h sampling time, and were 4.9 ± 1.6 μg/mL and 5.8 ± 0.8 μg/mL after the first and fifth doses of 2.2 mg/kg, respectively. There was no accumulation of drug in serum, as assessed by C_{max}, upon five daily i.m. doses of ceftiofur sodium at either 1.1 or 2.2 mg CFAE/kg, and C_{max} was dose-proportional using that multiple dosing regimen. There were no differences in any of the parameters measured at either dose level. Figure 4 shows the serum levels measured during the 5 day multiple dose study, and shows that no accumulation of CAM in plasma was apparent.

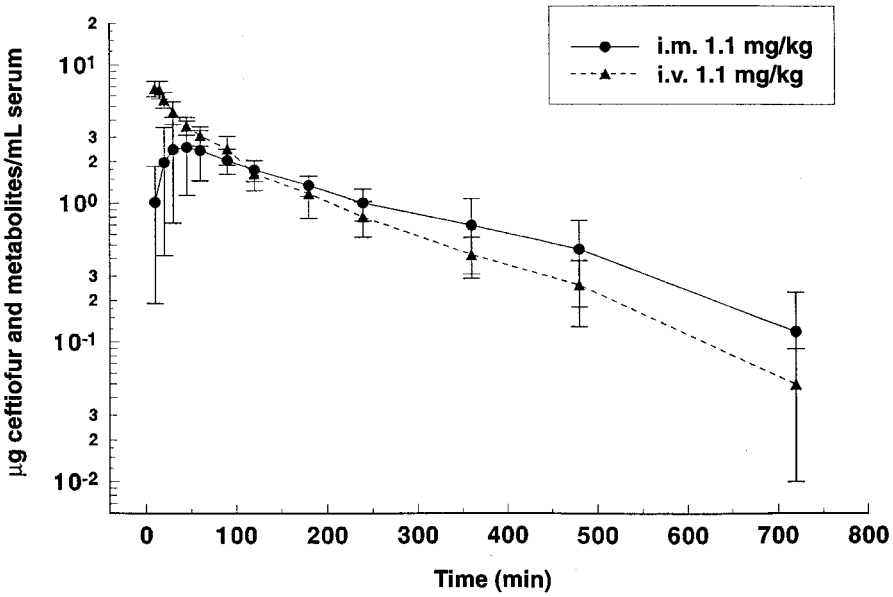

Fig. 1. Mean combined serum concentrations of ceftiofur and metabolites after intravenous and intramuscular administrations of a single dose of ceftiofur sodium of 1.1 mg ceftiofur free acid equivalents (per kg) in goats.

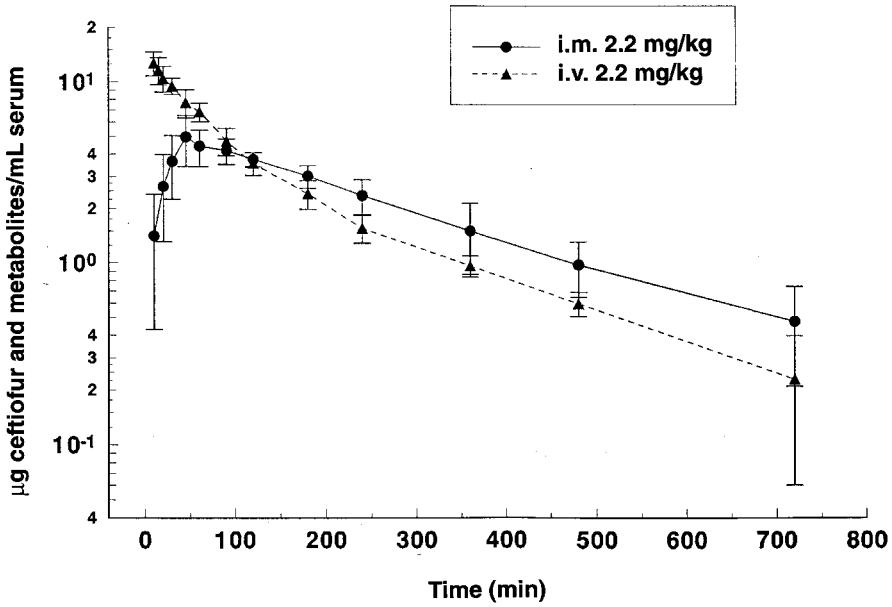

Fig. 2. Mean combined serum concentrations of ceftiofur and metabolites after intravenous and intramuscular administrations of a single dose of ceftiofur sodium of 2.2 mg ceftiofur free acid equivalents (per kg) in goats.

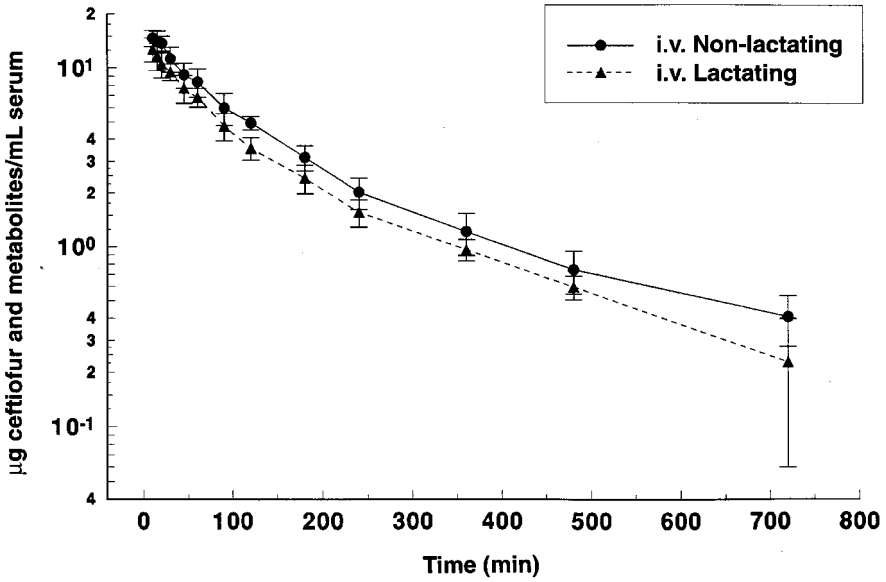

Fig. 3. Mean combined serum concentrations of ceftiofur and metabolites after intravenous administration of a single dose of ceftiofur sodium of 2.2 mg ceftiofur free acid equivalents (per kg) to six goats when lactating and 6 weeks after drying off (non-lactating).

Table 3. Pharmacokinetic values obtained from serum concentrations of ceftiofur and metabolites after intramuscular administration of multiple (once daily for 5 days) injections of ceftiofur sodium at doses of 1.1 and 2.2 mg ceftiofur free acid equivalents/kg in goats

	$t_{1/2a}$ (min)	$t_{1/2b}$ (min)	C_{max}* (µg/mL)	$AUC_{0-\infty}$ (µg.min/mL)	$AUMC_{0-\infty}$ (µg.min^2/mL)	*MRT* (min)
1.1 mg/kg						
First Dose						
Mean	31.7	113.2	2.7	841	196370	231
(Std. Dev.)	(harmonic)	(harmonic)	(0.8)	(252)	(119420)	(74)
Last Dose						
Mean	6.9	120.0	3.6	837	157504	188
(Std. Dev.)	(harmonic)	(harmonic)	(0.3)	(223)	(54331)	(38)
2.2 mg/kg						
First Dose						
Mean	12.5	156.2	4.9	1537	371759	254
(Std. Dev.)	(harmonic)	(harmonic)	(1.6)	(271)	(119777)	(71)
Last Dose						
Mean	8.6	115.5	5.8	1683	311564	203
(Std. Dev.)	(harmonic)	(harmonic)	(0.8)	(247)	(147956)	(56)

* Observed serum levels.

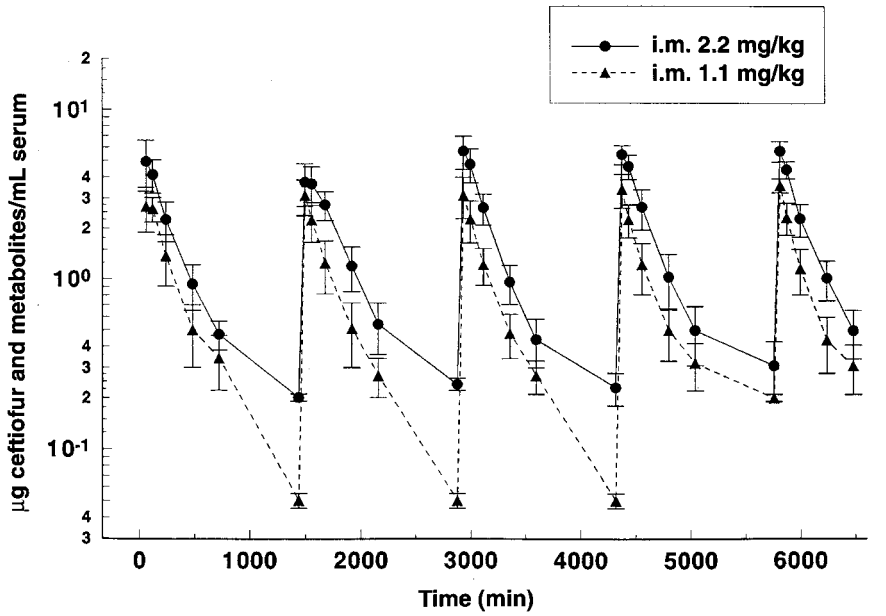

Fig. 4. Mean combined serum concentrations of ceftiofur and metabolites after intramuscular administration of ceftiofur sodium at a dose of 1.1 or 2.2 mg ceftiofur free acid equivalents (per kg) every 24 h for 5 consecutive days.

DISCUSSION

The pharmacokinetics of the combined concentrations of ceftiofur and metabolites after administration of ceftiofur sodium in goats do not appear to be different from that noted in cattle (Soback *et al.*, 1991; Halstead *et al.*, 1992; Whittem *et al.*, 1995; Erskine *et al.*, 1995), swine (Beconi-Barker *et al.* 1996), dogs (Brown *et al.*, 1995), or horses (Meyer *et al.*, 1992; Jaglan *et al.*, 1994). The longer half-lives noted in cattle and swine in previous studies, compared to goats in the present study, are probably a reflection of blood sampling not being obtained after 24 h in the present study. Similar results were observed in horses using a blood sampling schedule of similar duration to that used in the present goat study. (Jaglan *et al.*, 1994)

CONCLUSIONS

Intramuscular bioavailability of ceftiofur sodium was 100% after doses of 1.1 and 2.2 mg/kg, respectively; and the pharmacokinetics of ceftiofur sodium were dose-proportional by either the i.m. or i.v. route in goats from 1.1–2.2 mg ceftiofur free acid equivalents/kg. The pharmacokinetics of ceftiofur sodium were dose-proportional using dosage regimens of 1.1–2.2 mg ceftiofur equivalents/kg. Furthermore, there was minimal accumulation when the drug was administered i.m. once daily for up to 5 consecutive days. Single dose pharmacokinetics accurately predicted multiple dose data. The serum concentrations of CAM were consistently, but not significantly higher when the goats were dry, and the $AUC_{0-\infty}$ during lactation was significantly less ($P < 0.05$) than when the goats were dry. The primary and secondary distribution half-lives, and the *MRT*s were not different. There was a trend towards increased C_{p0} and decreased $V_{d(ss)}$ when the goats were dried. The significant increase in clearance would have blunted the difference in apparent volume of distribution of ceftiofur in lactating goats. An increased apparent volume of distribution for benzylpenicillin in lactating ewes has been reported previously (Oukessou & Benlamlih, 1990).

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