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Pharmacokinetics of Ceftiofur Crystalline Free Acid in Sheep Following Single-Dose Subcutaneous Administration

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ABSTRACT

Objective: To determine the pharmacokinetic parameters for a single dose subcutaneous administration of ceftiofur crystalline free acid (CCFA) in sheep at a dose of 6.6 mg/kg body weight.

Animals: Nine adult apparently healthy female Suffolk-crossbred sheep.

Procedures: Serial blood samples were collected by venipuncture after single subcutaneous administration of CCFA at 6.6 mg/kg body weight. Concentrations of ceftiofur free acid equivalents (CFAE) in serum were measured by high performance liquid chromatography at regular intervals for 14 days following drug administration. Pharmacokinetic data was analyzed using compartmental and non-compartmental methods.

Results: Pharmacokinetics of subcutaneous CCFA in sheep were best described using a single compartment model with the following average (± SD) parameters: area under the concentration time curve $_{0\rightarrow\infty}$ (206.6 hr*ug/ml ± 24.8), observed maximum serum concentration (2.4 ug/ml ± 0.5), and observed time of maximum serum concentration (23.1 hrs ±10.1). No significant adverse drug reactions were observed. Serum CFAE concentrations above *Mannheimia haemolytica* and *Pasteurella multocida* target serum concentration $\geq$ 1µg/ml were maintained from a range of 2.6 to 4.9 days.

Conclusions and Clinical Relevance: CCFA achieved adequate therapeutic serum concentrations against *Mannheimia haemolytica* and *Pasteurella multocida*. This drug could be an effective treatment against common ovine respiratory pathogens.

ABBREVIATIONS

$AUC_{0\rightarrow\infty}$	Area Under the Serum Concentration vs Time Curve from time 0 to infinity
CCFA	Ceftiofur Crystalline Free Acid
CFAE	Ceftiofur Free Acid Equivalents
C_{max}	Maximum Concentration
DFC	Desfuroylceftiofur
FDA	Food and Drug Administration
HPLC	High Performance Liquid Chromatography
K_{01}	Absorption Rate Constant
K_{01}_HL	Absorption Half-life
K_{10}	Elimination Rate Constant
K_{10}_HL	Elimination Half-life
λz	Terminal Phase Rate Constant
λz_HL	Terminal Phase Elimination Half-life
LOD	Limit of Detection
LOQ	Limit of Quantification

MIC	Minimum Inhibitory Concentration
RSD	Residual Standard Deviation
SD	Standard Deviation
T_{max}	Time of Maximum Concentration
V_d	Volume of Distribution

Bacterial pneumonia affects sheep of all ages and results in mortality and decreased weight gain leading to economic losses.[1, 2] Death losses in sheep in the U.S. caused by respiratory disease accounted for 9.4% of total death losses from non-predators in the year 2009 and resulted in 2.9 million dollars lost by the sheep industry.[3] Two of the most common bacterial agents causing pneumonia in sheep include *Mannheimia haemolytica* and *Pasteurella multocida,* with *M. haemolytica* being more common.[1,4,5] Typical outbreaks of pneumonic pasteurellosis in sheep start with sudden deaths in the lamb population followed by signs of lower respiratory disease in the ewe population.[2] The use of effective antibiotic drugs for the treatment and control of bacterial pneumonia in sheep is crucial to prevent losses in the face of an outbreak. An antibiotic effective against *M. haemolytica* and *P. multocida* and labeled for both treatment and control of respiratory disease can help reduce morbidity and mortality in the sheep population.

Currently, there are four antibiotics approved by the FDA for the treatment of respiratory disease in sheep; these include ceftiofur sodium, tilmicosin, procaine penicillin G, and oxytetracycline hydrochloride.[6,7,8,9] Tilmicosin, procaine penicillin G, and oxytetracycline hydrochloride offer limited coverage against pneumonic pathogens because each of these drugs

is labeled against either *M. haemolytica* or *P. multocida*; none of these drugs carries a label claim against both pathogens.[7,8,9] Ceftiofur sodium[a], one of three currently available ceftiofur preparations, offers broader coverage as it is labeled for the treatment of both *M. haemolytica* and *P. multocida.*[6] Ceftiofur sodium, however, requires daily intramuscular administration requiring multiple injections per course of treatment; such frequent dosing reduces its practicality for use when treating multiple animals in production settings. In addition, ceftiofur sodium is not labeled for control and/or prevention of disease in high-risk ovine populations.

Ceftiofur crystalline free acid[b] is a long-acting formulation of ceftiofur approved by the FDA for the treatment of respiratory disease in cattle, horses, and swine.[10,11,12] As a third-generation cephalosporin, ceftiofur is bactericidal and functions by inhibiting bacterial cell wall synthesis. It is distinguished for its excellent activity against Gram-negative bacteria and resistance to β-lactamases.[13,14] Desfuroylceftiofur, its primary metabolite, results from hydrolytic cleavage of the thioester bond of ceftiofur and forms conjugates with additional molecules through disulfide bonds.[14] Despite its complex metabolism, all components (ceftiofur, DFC, and DFC-conjugates) preserve their β-lactam ring and antibiotic properties.[14,15] Ceftiofur crystalline free acid is widely used in cattle for treatment and control of bovine respiratory disease due to its proven efficacy and duration of action.

In cattle, CCFA is labeled for single subcutaneous injection at a dose of 6.6 mg/kg of bodyweight in the base of the ear or posterior pinna. Plasma concentrations are maintained at therapeutic concentrations for at least 7.1 days in this species.[10] Currently, CCFA does not have an FDA approved label claim for any small ruminants. Effective April 5, 2012 the FDA prohibited the extralabel use of cephalosporins in major food-producing animals including cattle, swine, chickens, and turkeys.[16] The new regulation limits the use of cephalosporins to the

approved dose level, frequency, duration, and route of administration. Use of these drugs for disease prevention is also prohibited. However, sheep, in addition to goats, rabbits, and ducks, are considered a minor food-producing species and therefore are exempt from this regulation.

Even though there is an FDA-approved short acting ceftiofur product (ceftiofur sodium) for sheep, CCFA could offer therapeutic advantages over ceftiofur sodium. Administration of CCFA would reduce the number of injections per treatment course and minimize patient handling and stress, which is desirable in commercial sheep operations due to the strong flocking instincts of sheep.[17] Repeated restraint and isolation stress in sheep have been shown to compromise lymphocyte function and cell-mediated immunity.[18,19] Therefore the use of a single dose long-acting antibiotic could result in improved immune responses against pathogens and offer a therapeutic advantage over antibiotics requiring multiple doses.

The objective of this study was to determine the pharmacokinetic parameters for a single dose subcutaneous administration of CCFA in sheep at a dose of 6.6 mg/kg body weight. The specific hypothesis was that adequate serum concentrations of CCFA equivalents would be attained after a subcutaneous single dose administration of CCFA at 6.6 mg/kg body weight.

MATERIALS AND METHODS

This study was approved by the Institutional Animal Care and Use Committee of the University of California-Davis (Protocol #15947).

Animals

Nine adult female Suffolk-crossbred sheep, determined to be healthy based on physical examination, were used for this study. The sheep were less than 2 years of age and weighed

from 62 to 82 kg. No drug treatments had been administered for 60 days prior to the start of the study. All animals were housed together at the University of California-Davis Sheep Facility, Davis, CA. Sheep had *ad libitum* access to water and were fed alfalfa hay once per day. Throughout the course of the study sheep were monitored daily for feed/water consumption and general health.

Study design

Blood samples to be used as control samples were obtained from the jugular vein of each study subject (n=9) before drug administration. On *Day 1* each study subject received a single subcutaneous injection of CCFA at a dose of 6.6 mg/kg of body weight in the right cervical region. The cervical region was selected as the preferred injection site due to its high frequency of use in sheep production and minimal impact on meat quality. Jugular vein blood samples (two 10 ml samples) were collected into sterile vacutainer tubes with no additive by venipuncture of the left jugular vein prior to drug administration and at 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 240, 288, 336 hours following drug administration. Samples were allowed to clot for for 30 minutes at room temperature and were then centrifuged at 2000 X g for 15 minutes before serum extraction and storage. Serum was stored in individual aliquots at -80^{o}C.

Injection sites were monitored daily for the first two weeks of the study and every 48 hours for the remaining two weeks by the same evaluator for 4 weeks post-injection. Injection site reactions were evaluated subjectively for presence/progression of swelling which was assessed by palpation and visual assessment. The presence of heat, redness, and pain at the injection site were recorded if evident.

Minimum inhibitory concentration data

Minimum inhibitory concentration data was gathered through a search of the University of California-Davis VMTH Clinical Microbiology Laboratory database from January 1st 1998 to October 11th, 2012. The search included ovine bacteria isolated from the respiratory tract including the nasal cavity, trachea, and lung for which a MIC for ceftiofur had been determined by the broth microdilution technique[c], in accordance with procedures described by the Clinical Laboratory Standards Institute.[20] The MIC required to inhibit 50% of organisms (MIC_{50}) and 90% of organisms (MIC_{90}) were determined for three concentration cut-off values included in the pharmacokinetic analysis: 0.5, 1.0, and 2.0 μg/ml. A target plasma ceftiofur concentration of 1.0 μg/ml was selected based on the MIC data for *M. haemolytica* and *P. multocida* as these are common ovine pneumonic pathogens.

Drug analysis

The drug analytical method was modified from that previously published by *Jaglan, et al.*[21] Samples were analyzed within 30 days of collection using HPLC for ceftiofur and desfuroylceftiofur-metabolites. In brief, dithioerythritol solution was first added to serum samples (1 ml) in order to cleave any macromolecules attached to ceftiofur or DFC metabolites. A C-18 solid phase extraction column[d] was used to extract DFC, which was then derivatized with iodoacetamide to form DFC acetamide. A strong cation exchange cartridge[e] was utilized for additional cleanup. With UV detection at 240 nm, the composition of the mobile and stationary phases for HPLC analysis were kept constant at 7% acetonitrile, 1% acetic acid, with 90 mg heptane sulfonic acid/L, and pH 4.0 with a C18, 4μm, 3.9 x 150 mm column[f]. DFC had a limit of quantification and detection of 0.1μg/ ml and 0.05 μg/ml, respectively for serum. All

data with values of <0.1μg/ml were excluded from the pharmacokinetic analysis. The standard curve was generated with serum collected from study sheep pre-treatment at concentrations of 0.1 to 10 μg/ml (R^2=0.9990). Quality control samples were run concurrently with each set of study samples and the average recoveries were 97.8, 90.8 and 89.6 respectively for 0.2, 1.0 and 5.0 ug/ml. The RSDs were 11.8, 7.7 and 9.0 respectively for 0.2, 1.0 and 5.0 ug/ml.

Pharmacokinetic analysis

A commercial software program[g] was used to analyze all data using compartmental and non-compartmental methods. For the compartmental approach, the following pharmacokinetic parameters were analyzed: apparent V_d, K_{01}, K_{01}_HL, K_{10}, and K_{10}_HL. Parameters calculated for the non-compartmental method included the $AUC_{0\rightarrow\infty}$ and the λ_z and λ_z_HL. The observed C_{max} and the T_{max} were obtained directly from the reported data. Studies investigating MICs of ceftiofur sodium in sheep have reported the MIC_{90} for *M. haemolytica* and *P. multocida* to be 0.13 μg/ml and ≤0.031 μg/ml, respectively.[6] Previous studies performed in cattle and goats reported a target MIC of 0.2 μg/ml.[22,23] In this study, a target serum concentration of 1.0 μg/ml was used based on MIC values for *Mannheimia haemolytica* and *Pasteurella multocida* isolated at the University of California-Davis VMTH Clinical Microbiology Laboratory. Two additional target serum concentrations of 0.5 and 2.0 μg/ml were included in the analysis. Time that drug concentrations remained below and above the target serum concentration were calculated using the above mentioned commercial software program.

Statistical analysis

All pharmacokinetic data was reviewed as mean ± standard deviation. Harmonic means and pseudo standard deviations were calculated for the K_{01}_HL, K_{10}_HL, and λ_z_HL.

RESULTS

The MICs of ovine respiratory tract bacteria isolated at the UCD-VMTH Clinical Microbiology Laboratory during a 15-year period are summarized in Table 1. During this timeframe there were 13 identified bacteria including 3 *M. haemolytica* and 2 *P. multocida*. The MIC for the 3 *M. haemolytica isolates* was ≤ 0.06 with all isolates being susceptible at a ceftiofur concentration of ≥ 0.5 μg/ml. Two *P. multocida* were isolated; the MIC range for *P. multocida* was from ≤ 0.06 to ≤ 0.25 and both isolates were susceptible to ceftiofur at a concentration of ≥ 0.5 μg/ml.

No adverse clinical reactions were observed during this study. All animals maintained a normal appetite and behavior and remained healthy throughout the course of the study. No systemic adverse reactions were observed following drug administration or blood collection. Injection site reactions were present at 24 hrs. post-injection in all sheep. These were fairly localized and firm on palpation, and visually evident in only 1 sheep (sheep #6). No signs of redness, heat, or pain were noted. By 8 days post-injection, all 9 sheep had visible and palpable injection reactions that decreased over time. In sheep #1 a raised elliptical swelling measuring approximately 12.7 cm long on day 8, decreased significantly over the course of the study, and measured <0.5 cm in diameter at 30 days post-injection. Sheep #3 had a flat vertical swelling measuring 12.1 cm long on day 8 that decreased to <0.5 cm one month post-injection. By the end of the study (4 weeks post-injection) 4 sheep (# 1, 3, 6, 8) had non-painful, soft, <1cm diameter, flat subcutaneous swellings, which were palpable but not visible. Sheep #2 had a flat,

soft, and <1cm diameter swelling by day 28 post-injection. This animal had to be euthanized on day 29 for causes unrelated to the study. The remaining 4 sheep (# 4,5,7,9) had no evidence of an injection reaction at 30 days post-injection.

A one-compartment model resulted in the best fit for the majority of the study data points. The serum concentration averages for the study animals are shown in Figure 1 as a function of time. All samples collected prior to drug administration had no detectable concentrations of CFAE. The earliest sampling time that serum CFAE concentrations were non-detectable was 192 hr. Three of the study animals still had CFAE concentrations below the LOQ (0.1μg/ml) but still above the LOD (0.05 μg/ml) at the 336 hr sampling time. Noncompartmental and compartmental pharmacokinetic parameters for all study subjects are summarized in Table 2. The mean K_{01}_HL was 1.85 h and the mean K_{10}_HL was 52.58 h. The mean observed area under the concentration-time curve from time 0 to infinity was 206.63±24.85 μg*h/ml. The mean observed C_{max} was 2.45±0.59 μg/ml and the mean observed T_{max} was 23.11±10.15 h. The mean λ_z and λ_z_HL were 0.02±0.01 1/h and 44.95 h, respectively. The time interval for which drug concentrations remained above target serum concentrations are depicted in Table 2. Serum drug concentrations remained below the target serum concentration (1 μg/ml) for an average time of 145.94±43.59 h and above this target MIC for an average time of 80.73±19.15 h.

DISCUSSION

The bacteriological data gathered for ovine respiratory tract isolates included 13 isolates with 6 (46.2%), 8 (61.5%) and 8 (61.5%) isolates susceptible to ceftiofur at serum concentrations of 0.5, 1, and 2 μg/ml, respectively. There was an increase in susceptibility as the serum ceftiofur concentration doubled from 0.5 to 1 μg/ml, but remained similar as it doubled from 1 to

2 μg/ml. All of the isolates of *M. haemolytica* ($MIC_{90} \leq 0.06$ μg/ml) and *P. multocida* ($MIC_{90} \leq$ 0.25 μg/ml) were susceptible to ceftiofur at a serum threshold of ≥ 0.5 μg/ml. This microbiological data suggests that a target serum ceftiofur concentration threshold of 1 μg/ml is appropriate to treat *M. haemolytica* and *P. multocida* as well as other bacteria isolated from the ovine respiratory tract. Five of the 13 isolates were not susceptible to ceftiofur at a serum concentration of 1 μg/ml (*Escherichia coli, Providencia stuartii, Pseudomonas aeruginosa)*; however, these isolates reflected a $MIC_{90} \geq 8$ μg/ml and would likely have been resistant to ceftiofur. The target serum concentration of 1 μg/ml used in this study is significantly higher than target serum/plasma concentrations selected for other species in previous studies.[22, 23, 26] It is also much higher than the MIC_{90} for *P. multocida* (0.031 μg/ml) and *M. haemolytica* (0.125 μg/ml) provided by the FDA when ceftiofur sodium was approved for treatment of pneumonia in sheep.[6] Taking into consideration that both active and inactive ceftiofur metabolites are measured in experimental assays and that a variety of factors such as tissue perfusion, drug protein binding, and tissue injury can affect drug concentrations in target tissues, it is appropriate to select a relatively high serum target drug concentration.[15]

The results of this study demonstrate that when CCFA is administered subcutaneously in sheep at 6.6 mg/kg of body weight, serum concentrations remain above the targeted serum concentration (≥ 1 μg/ml) for an average of 3.4 days. From a clinical standpoint, it should be noted that the time above the targeted serum concentration was highly variable in individual animals, with a minimum of 2.6 days and a maximum of 4.9 days. Individual variability in this parameter has been previously described in other species such as the goat and foal; however, as expected, species specific MICs were used for these studies.[23,27] High individual variability was also evident in other pharmacokinetic parameters in this study including K_{01}_HL, K_{10}_HL, T_{max},

λ_z_HL. This could be attributed to individual physiologic variability, differences in fat deposition, and variations in gastrointestinal, hepatic, and renal function. The use of a single drug administration site in this study could have also resulted in variable drug absorption among individual animals. This can occur when there is a limited surface area of absorption that leads to drug pooling. An alternative administration protocol utilizing multiple injection sites per dose could improve drug absorption and yield more uniform pharmacokinetic parameters among individual study subjects. In addition, given that CCFA is an extended release formulation, terminal half-lives following subcutaneous administration could be impacted by "flip-flop" kinetics where the slower and extended absorption process complicates the estimation of the terminal elimination rates. For example, sheep #7 had an exceptionally high K_{01}_HL (6.87 h) in comparison to the other study sheep. This prolonged absorption time could have been attributed to accidental intradermal injection during drug administration, however this animal did not have an injection site reaction that could be palpated for an extended period of time compared to the other sheep and this animal's injection site swelling disappeared shortly after injection. Thus, it is more likely that the long half-life was a reflection of the extended release formulation.

In a preliminary report, the C_{max} of ceftiofur sodium in sheep was 4.33 and 7.13 μg/ml[28], when administered intramuscularly at 1.1 and 2.2 mg/kg respectively, which was much higher than that of CCFA in the current study. The T_{max} of ceftiofur sodium when administered at 1.1 and 2.2 mg/kg IM (32 min and 49 min, respectively) [28] are understandably very different from that of CCFA (23.1 hr) considering that ceftiofur sodium is designed for rapid absorption while CCFA is formulated as a slow-release drug. Ceftiofur sodium is a water-based sodium salt and is absorbed much faster than CCFA, which is a suspension of caprylic/capric triglyceride and

297 cottonseed oil.[25] The terminal phase rate constant and half-life of ceftiofur sodium, (0.0018-
298 0.0015/min and 6.48-7.65 h)[28] are also quite different from that of CCFA. This difference might
299 be unexpected considering that the metabolism and elimination of ceftiofur should be the same
300 regardless of the preparation. However, the terminal phase for CCFA pharmacokinetics might
301 not be completely dependent on elimination kinetics but rather on a combination of absorption
302 and elimination.
303 Comparing the pharmacokinetics of CCFA in sheep in this study with that of cattle, goats,
304 alpacas, and horses documented in previous studies[23,24,26], the overall pharmacokinetic profile
305 appears most similar to goats and alpacas. The $AUC_{0\rightarrow\infty}$ is very similar to that in alpacas
306 (199.22±42.13 μg*h/ml) and observed C_{max} is quite similar among all three species (alpacas:
307 2.65, goats: 2.25 μg/ml).[23,26] The observed T_{max} was very similar to that in the caprine species
308 following subcutaneous administration (26.7 h) and that in the adult equine following
309 intramuscular administration (22 h), but was lower than that of the alpaca (36 h).[23,24,26] The
310 K_{01}_HL of CCFA in sheep in our study was comparable to that in alpacas (K_{01}_HL: 1.37 h),
311 however the K_{10}_HL was substantially longer than both alpacas (K_{10}_HL: 31.38 h) and goats
312 (K_{10}_HL: 36.9 h).[23,26] The λz_HL in the ovine species was comparable to that in alpacas (44.70
313 h) and higher than that in goats (36.9 h).[23,26] Similarities in pharmacokinetic parameters among
314 these species could be due to comparable drug doses (6.6 mg/kg), intervals (single injection),
315 sites of drug administration (subcutaneously in cervical or axillary area), and blood sampling
316 times.[23,26] Physiological resemblances among these species, such as age, weight, fat distribution,
317 and gastrointestinal function could also result in similar pharmacokinetic profiles for
318 subcutaneously administered CCFA.

In this study no adverse drug reactions were observed in sheep following subcutaneous administration of CCFA at a dose of 6.6 mg/kg of body weight. Injection site reactions were noted one day post-injection in all subjects and persisted in 4 subjects to 4 weeks, however these reactions diminished markedly over the course of the study. These reactions did not negatively affect the study sheep and were not considered to be clinically significant. Injection reactions following CCFA administration have also been noted in other species including goats, adult equids, and cattle[23,24,25]; however, the incidence and duration of injection reactions observed in this study exceeded that seen in other species. The site of injection selected for this study (cervical) is appropriate from a production standpoint as it is commonly used in the sheep industry for administration of medications. However, it differs from the FDA approved injection site in cattle, which is the posterior base of the ear in lactating dairy cattle and the posterior aspect of the middle third or posterior base of the ear in beef and non-lactating dairy cattle.[10] The ear is considered a novel site for antibiotic injections in cattle; however the subcutaneous cervical region is not an approved injection site for the administration of CCFA in cattle due to the presence of violative drug residue levels for extended periods of time following single administration[29]. Administration of CCFA in the ear of cattle allows for considerably shorter residue withdrawal times because this tissue is deemed inedible by the U.S. Department of Agriculture[25,30]. Even though the amount of subcutaneous tissue at the posterior base of the ear is limited in sheep compared to cattle, it could be a superior alternative injection site from a meat quality and tissue residue standpoint and should be further investigated.

From a human food safety/meat withdrawal standpoint, this study provided scientific data that an extended withdrawal interval needs to be observed if CCFA is used in an extra-label manner and is administered subcutaneously in sheep. Even though meat samples were not

342 evaluated in this study, serum concentrations reflected circulating systemic drug concentrations.
343 In order to establish a regulatory approved withdrawal time, tissue sample data is necessary but
344 was not within the scope of this study. The data from this study supports an extended
345 withdrawal interval, because at the last sampling time point (336 hr), three of the eight animals
346 had CFAE serum concentrations above the limit of detection. Even though ceftiofur sodium is
347 approved in the US, a tolerance was not established at the time of approval. Therefore if CCFA
348 is used in an extra-label manner, since there is no established tolerance, any detectable ceftiofur
349 or ceftiofur metabolite residues would be considered violative. Therefore, based on the results of
350 this study, withdrawal intervals of at least 336 hours should be considered when sheep are
351 administered a single dose of CCFA at 6.6. mg/kg subcutaneously. Further studies evaluating
352 ceftiofur and ceftiofur metabolite residues in tissues are necessary to establish a more accurate
353 withdrawal interval.
354 In conclusion, data from this study suggests that CCFA, when administered in sheep at
355 6.6 mg/kg of body weight subcutaneously, will achieve adequate serum concentrations that could
356 treat and control respiratory disease caused by *M. haemolytica* and *P. multocida*. Considering
357 that serum concentrations remained above the targeted drug concentration for 2.5-5 days in the
358 study subjects, a suggested therapeutic dosage for CCFA administration for sheep is 6.6 mg/kg
359 administered subcutaneously every 48-72 hours. Further studies evaluating the safety, efficacy,
360 pharmacokinetics, and drug residues of multi-dose administration are necessary. In addition,
361 prospective studies integrating clinical cases, in vitro procedures, and pharmacokinetic analysis
362 would also provide a better understanding of the metabolism and efficacy of CCFA in sick
363 animals.
364

FOOTNOTES

[a] Naxcel, Pfizer Inc., New York, NY

[b] Excede, Pfizer, Inc., New York, NY

[c] Sensititre, Thermo Scientific Trek Diagnostic Systems, Cleveland, OH

[d] Varian, Inc., Walnut Creek, CA, USA

[e] Varian, Inc., Walnut Creek, CA, USA

[f] Nova-pak column, Waters Corporation, Milford, MA, USA

[g] WinNonLin version 5.2; Pharsight Corporation, Mountain View, CA, USA

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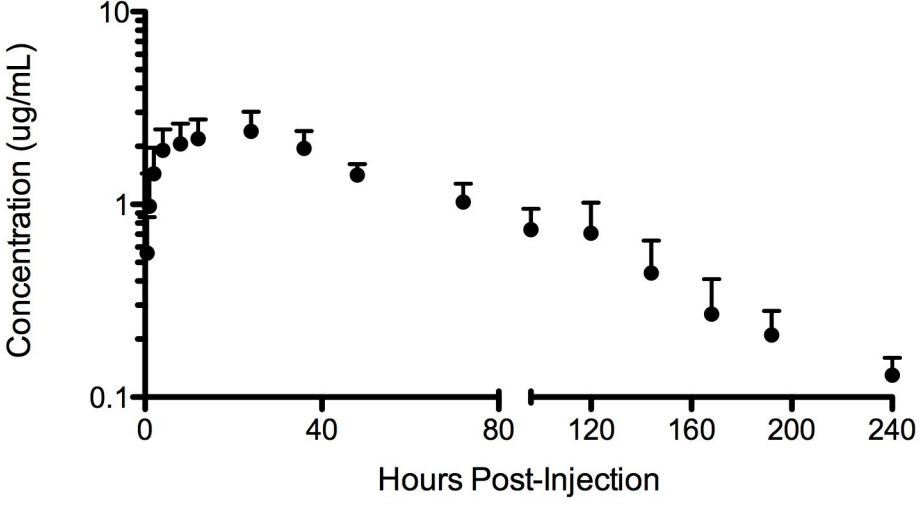
FIGURE LEGEND

Figure 1. Time following treatment versus mean concentrations of ceftiofur crystalline free acid equivalents (ceftiofur and desfuroylceftiofur-related metabolites) in serum samples from adult sheep (n=9) after a single subcutaneous injection of ceftiofur crystalline free acid at 6.6 mg/kg body weight. Concentration values below the limit of quantitation of the assay were not included in calculating the means.


Concentration (ug/mL)
10
1
0.1
0
40
80
120
160
200
240
Hours Post-Injection