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Pharmacokinetics of Ceftiofur Crystalline Free Acid In Swine

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Introduction and Objectives

Ceftiofur crystalline free acid (CCFA) is metabolized *in vivo* to desfuroylceftiofur and related metabolites, as are ceftiofur sodium (NAXCELTM/EXCENELTM Sterile Powder) and ceftiofur hydrochloride (EXCENEL RTU Sterile Suspension). The dosage form is an extended release, ready-to-use sterile suspension of CCFA (CCFASS), with a single dose regimen to provide full course therapy to treat bacterial swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis* and *Streptococcus suis*. The unique extended-release properties of the formulation (patent pending) enable plasma concentrations of active ceftiofur metabolites to be maintained above the minimum inhibitory concentration of target SRD pathogens for at least 7-8 days after a single IM injection of 5 mg ceftiofur-equivalents (CE)/kg body weight.

The objective of this study was to evaluate the pharmacokinetic (PK) profile of ceftiofur and desfuroylceftiofurrelated metabolites in plasma after administration of a single IM injection of 5 mg ceftiofur-equivalents (CE)/kg body weight (BW) administered as CCFA-SS in pigs.

Materials and Methods

Five pigs (28.5 to 31.9 kg the day before dosing) were each administered a single dose of CCFA-SS, at 5 mg CE/kg BW, by intramuscular (IM) injection in the neck. Blood samples were collected before treatment administration and at 1, 2, 4, 6, 12, 24, 48, 72, 96, 168 and 240 hours after treatment administration. Plasma samples were assayed for ceftiofur and desfuroylceftiofur-related metabolites using the validated HPLC-DCA assay [1]. The limit of quantitation for this plasma assay method is 0.15 µg/ml. The plasma concentration data for ceftiofur and desfuroylceftiofur-related metabolites were analyzed sing the WinNonlinTM PK software package. The plasma data were analyzed using both non-compartmental and compartmental PK techniques. The parameters used to summarize PK behavior were: area under the concentration profile from zero to the limit of quantitation ($AUC_{0\text{-}LOQ}$), the time the concentration was greater than 0.2 µg/ml based on noncompartmental techniques ($t_{>0.2,\ nca}$), the maximum observed concentration ($C_{max,\ obs}$), the mean residence time from zero to the limit of quantitation ($MRT_{0\text{-}LOQ}$), and $C_{max,\ obs}/t_{>0.2,\ nca}$. Estimates of $t_{>0.2,\ nca}$ were calculated using the terminal portion of the depletion curve via linear extrapolation (non-compartmental). Estimates of the compartmental PK parameters were calculated but were not used for decision-making purposes.

Results and Discussion

The mean PK results (± SD) for each parameter are presented in the following table (Table 1).

Table 1. PK parameters for CCFA 5 mg CE/kg once IM

PK Parameter	Mean Value ± SD
$AUC_{0\text{-}LOQ}$ (µg•h/ml)	391 ± 48.6
$t_{>0.2,\ nca}$ (h)	195* ± 16.2
$MRT_{0\text{-}LOQ}$ (h)	49.7 ± 3.68
$C_{max,\ obs}$ (µg/ml)	5.63 ± 1.06
$C_{max,\ obs}/t_{>0.2,\ nca}$ (µg/ml•h)	0.0291 ± 0.00619

*median value, 189 h

The plasma profile is presented below in Figure 1, together with the profile for ceftiofur sodium (NAXCEL/EXCENEL Sterile Powder) after IM administrationat 3 mg CE/kg BW for three consecutive days [2].

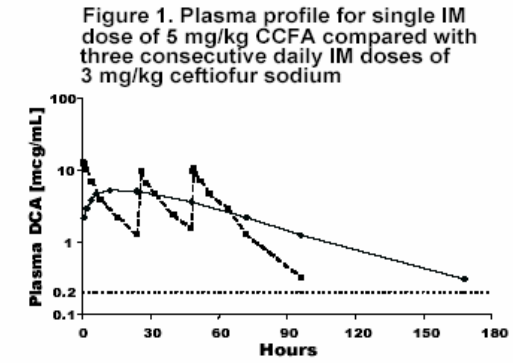

Figure 1. Plasma profile for single IM dose of 5 mg/kg CCFA compared with three consecutive daily IM doses of 3 mg/kg ceftiofur sodium

Therapeutic plasma levels of ceftiofur and desfuroylceftiofur-related metabolites were reached within one hour of CCFA treatment (2.23 ± 1.08 µg/ml) (earliest time point evaluated). Clinical efficacy of beta-lactam antibiotics is related to time above MIC (as compared with concentration above MIC). Plasma levels remained above 0.2 µg/ml (above the MICs for nearly 100% of target SRD pathogens isolated and tested over the past 12 years [3]) for 8 days. This is substantially longer than for a full 3-day dosing regimen for ceftiofur sodium at 3 mg/kg BW. This full course therapy in a single treatment provides benefits of improved convenience, dosing compliance and animal welfare.

References

1. Hamlow PJ, et al. Unpublished data on file.
2. Gilbertson TJ, et al. Unpublished data on file.
3. Salmon SA, et al. 2002. Proc.17th IPVS Congress. P78.