Plasma Disposition of Ceftiofur and Metabolites After Intravenous and Intramuscular Administration of Ceftiofur Sodium to Calves of Various Ages

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Abstract

Find out what happens to ceftiofur (NAXCEL® Sterile Powder) after you leave the barn when the drug, the bug and the calf take over. Just as that wet naveled little cutey grows up to be that cantankerous black baldy, some of its metabolic machinery matures as well. This study reviews the pharmacokinetics of ceftiofur sodium in calves as they mature from 7 days to 9 months of age.

The approved dosage regimes for ceftiofur sodium, 1.1-2.2 mg/kg (0.5-1.0 mg/pound) bodyweight administered intramuscularly once daily for up to five consecutive days, provides plasma concentrations of ceftiofur and metabolites above the minimum inhibitory concentration ($MIC_{90} \leq 0.06 \mu g/mL$) for the bovine bacterial respiratory disease pathogens *Pasteurella hemolytica, Pasteurella multocida* and *Haemophilus somnus*. In this study plasma concentrations are maintained for a longer period of time in neonatal calves than in older calves. This update will review the absorption, distribution, metabolism and excretion of ceftiofur in calves from 7 days to 9 months of age providing useful information for bovine practitioners.

Introduction

The absorption, distribution, metabolism and excretion of a compound in an animal or population of animals may be affected by a variety of factors including age. Ceftiofur sodium (NAXEL® Sterile Powder) is approved for use in cattle, regardless of age, for the treatment of the bacterial component of bovine respiratory disease. This study was designed to compare the plasma disposition of ceftiofur and metabolites after ceftiofur sodium was administered intravenously (IV) or intramuscularly (IM) as a single dose of 2.2 mg ceftiofur equivalents/kg (the upper end of the approved U.S. dosage range of 0.5-1.0 mg/pound) to 7-day old, 1-month old, 3-month old, 6-month old, and 9-month old calves.

Experimental Design

Sixteen one-day-old Holstein bull calves (initial weight 30-50 kg: Group 1) and 14 six-month-old Holstein steers (initial weight 250-300 kg: Group 2) were acquired from a single source and acclimated in Tulare, California. Group 1 calves were fed unmedicated milk replacer through 30 days of age and then converted to the same roughage/concentrate diet as Group 2. Group 1 calves and Group 2 calves were then randomly assigned by weight to one of two treatment groups, with Groups 1-IV and 2-IV receiving ceftiofur sodium IV by jugular venipuncture, and Groups 1-IM and 2-IM receiving ceftiofur sodium IM in the semimembranosus/semitendinosus region. Group 1 calves were dosed at 7 days of age, 1 month of age, and 3 months of age; Group 2 calves were dosed at 6 months and 9 months of age. Blood samples were obtained by jugular venipuncture from each calf before drug administration and at 0.33, 0.67, 1.0, 1.5, 2, 4, 8, 12, 24, 30, 36, 48, 60, and 72 hours after dosing. Plasma samples were analyzed using an HPLC assay that converts ceftiofur and all desfuroylceftiofur metabolites to desfuroylceftiofur acetamide. The limit of quantitation of the assay is 0.150 µg ceftiofur equivalents/mL of plasma. The area under the curve (AUC), terminal phase half-life ($t_{1/2\text{-}\beta}$ or $t_{1/2\text{-}K}$), systemic clearance (Cl_B), and steady-state volume of distribution (Vd_{ss}) were estimated. Analysis of variance was used for statistical comparison of route and age, using a significance level of 0.05. All data are reported as $X \pm SD$.

Results

The following table summarizes the results of the study:

		Age				
	Value	7 days	1 month	3 months	6 months	9 months
IV	C_0 (μg/mL)	10.6±1.69	10.6±1.88	13.2±1.50	16.8±8.85	12.9±6.52
	AUC (μg•h/mL)	127±21.1	135±21.6	74.0±10.7	61.0±17.7	68.5±12.8
	$t_{1/2\beta}$ (h)	16.1±1.54	17.2±3.08	8.22±2.84	5.95±1.15	7.00±2.26
	Cl_B (mL/h/kg)	17.8±3.25	16.7±3.10	30.3±4.60	39.8±14.9	33.0±5.52
	Vd_{ss} (mL/kg)	345±61.6	335±91.9	284±49.0	258±71.5	300±138
IM	C_{max} (μg/mL)	9.36±2.24	9.31±1.98	8.35±1.02	8.68±3.66	9.25±3.94
	AUC (μg•h/mL)	162±60.4	150±23.3	66.2±4.92	64.6±4.54	73.8±10.5
	$t_{1/2\text{-}K}$ (h)	12.3±1.87	11.4±0.914	5.20±0.73	4.15±0.614	4.42±0.674
	Cl_B/F (mL/h/kg)	14.9±4.15	14.9±2.36	33.4±2.52	34.2±2.41	30.4±4.42
	Vd_{ss}/F (mL/kg)	263±66.0	251±48.6	260±24.0	214±13.6	203±21.4

Discussion and Conclusions

The bioavailability of a drug is the extent of absorption from a non-intravenous dose compared to that from an intravenous dose. This is based on the comparison of the area under the plasma concentration vs. time curves (AUC) for both routes (I.V. and I.M.). Ceftiofur intramuscular bioavailability, at each age, appears to be complete. The AUC in 7-day old and one month old calves was significantly larger than in 3, 6, or 9 month old calves ($p<0.01$). Maximum plasma concentrations, C_0 for IV administration, C_{max} for IM administration, were similar in all age calves. Residue levels in tissues are associated with maximum drug concentrations, as maximum drug levels drive drug concentrations into tissues for ß-lactam antibiotics. For ceftiofur, C_{max} were no higher in younger calves than in older calves. Figure 1 illustrates the plasma concentrations vs. time for ceftiofur and metabolites for calves from 7 days to 9 months of age.

The depletion or elimination half-life ($t_{1/2}$) is the time it takes for the concentration in plasma or tissues to decrease by 50%. Half-life is calculated:

$$t_{1/2} = (0.693)(Vd_{ss})/Cl_B$$

The extent of distribution of drug from the vascular system into the extravascular tissues and fluids are evaluated by the term volume of distribution (Vd_{ss}). A larger value would indicate more distribution from the vascular system into the extravascular tissues and fluids and/or a larger intravascular volume. Smaller Vd_{ss} indicates that the drug is retained to a larger degree within the vascular system due to plasma protein binding or decreased extravascular fluid or tissue distribution. The Vd_{ss} was smaller in calves 3 months of age and older, compared with calves that were 7 days or 1 month of age, indicative of the decreasing extracellular fluid concentrations in maturing cattle. This effect has been observed with other water-soluble antibiotics such as gentamicin. Systemic clearance (or total body clearance); Cl_B is a measure of the volume of blood or plasma cleared of drug per unit of time. Systemic clearance of a drug is dependent on organ function and organ blood flow. The Cl_B was larger in calves 90 days and older, compared with calves that were 7 days and 1 month, perhaps indicative of maturation of the metabolism and/or excretion processes for ceftiofur and metabolites.

Implications

The approved dosage regimes for ceftiofur sodium, 1.1-2.2 mg/kg (0.5-1.0 mg/pound) bodyweight administered intramuscularly once daily for up to five consecutive days, provides plasma concentrations of ceftiofur and metabolites above the minimum inhibitory concentration ($MIC_{90} \leq 0.06$μg/mL) for the bovine bacterial respiratory disease pathogens *Pasteurella hemolytica, Pasteurella multocida* and *Haemophilus somnus*. In this study plasma concentrations are maintained for a longer period of time in neonatal calves than in older calves. Peak plasma concentrations are no higher in neonatal calves than in mature cattle, this suggests that tissue concentrations are no higher in neonatal calves than in mature cattle.

Figure 1. Plasma concentrations of ceftiofur and metabolites (measured as desfuroylceftiofur acetamide by HPLC) from ceftiofur sodium after a single IM injection in calves from 7 days to 9 months of age.