Comparative Pharmacokinetics and Bioavailability of Ceftiofur in Horses After Intravenous, Intramuscular, and Subcutaneous Administration

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Ceftiofur sodium administered as a single dose (2.2 mg/kg, IV and SC) resulted in plasma concentrations of active drug similar to those achieved with the approved IM route. By varying dosing intervals after appropriate concentrations are achieved by IV, SC or IM administration should be effective for treatment of bacterial infections caused by susceptible organisms. Therefore, dosage intervals may have to be increased to q 12 h or q 24 h for less susceptible bacteria. Authors' addresses: Hagyard-Davidson-Mcgee, 4250 Iron Works Pike, Lexington KY 40511 (Slovis); Departments of Medicine and Epidemiology, School of Veterinary Medicine, University of California at Davis, Davis, CA 95616 (Wilson and Mihalyi); K.L. Maddy Equine Analytical Chemistry Laboratory, School of Veterinary Medicine, University of California at Davis, Davis, CA 95616 (Stanley) IDEXX Pharmaceuticals, 4249 Piedmont Parkway, Greensboro, NC 27410 (Kollias-Baker); and Department of Veterinary Medicine and Surgery, College of Veterinary Medicine, University of Missouri-Columbia, Columbia MO 65211 (Lakritz); e-mail: nmslovis@yahoo.com (Slovis). © 2006 AAEP.

1. Introduction

Ceftiofur is a broad-spectrum, third-generation cephalosporin that is approved for use in horses by IM injection only. Clinicians, however, frequently administer this antibiotic by IV or SC. After IM administration, ceftiofur rapidly undergoes hydrolysis to the microbiologically active and highly protein-bound metabolite called desfuroylceftiofur that has a much longer elimination half-life than parent ceftiofur. It has been speculated that rapid IV administration may overwhelm the ability of enzyme systems to convert ceftiofur to desfuroylceftiofur and may result in rapid renal elimination of a substantial fraction of the less highly protein-bound parent drug. The objective of this study was to determine if IV and SC administration of ceftiofur resulted in plasma concentrations of active drug comparable with those achieved with the approved IM route.

2. Materials and Methods

Six adult mares were used in this study. The horses were determined to be in good health based on results of physical examination, complete blood
count (CBC), plasma protein, fibrinogen determinations, serum biochemistry profiles, and urinalysis. Three doses of ceftiofur sodium\(^a\) (2.2 mg/kg) were administered to each horse by the IM, IV, and SC routes using a three-way crossover design with a 2-wk washout period between doses. The order of routes of administration for horses in group 1 was IV, IM, and SC. For group 2, the order was SC, IV, and IM. The order for group 3 was IM, SC, and IV. Before dosing (time 0) and at 3, 6, 12, 18, 30, 45 min, and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, and 24 h after dosing, blood sample were collected into heparinized-evacuated tubes through an indwelling venous catheter. Within 1 h of collection, blood samples were centrifuged at 600 \(g\) for 10 min at 20°C. The plasma was pipetted into duplicate plastic tubes, which were sealed and stored at −20°C until assayed for ceftiofur and desfuroylceftiofur.

All samples were analyzed for ceftiofur and desfuroylceftiofur concentrations using the liquid chromatography mass spectrometry (LC/MS) assay with a lower limit of quantitation of 0.1 \(\mu g/ml\).

Plasma concentration-time profiles were analyzed using a commercial pharmacokinetic software program, and values for pharmacokinetic parameters and plasma concentrations at specific time points were compared statistically.

3. Results
No adverse effects were observed in any of the horses treated in this study; feces remained normal throughout and beyond the study period. The mean peak plasma concentrations of ceftiofur were 1.279, 0.61, and 10.43 \(\mu g/ml\) at 17, 35, and 3 min for IM, SC, and IV, respectively. The mean peak concentrations of total serum ceftiofur and desfuroylceftiofur were 5.29, 3.65, and 13.90 \(\mu g/ml\) at 72, 120, and 3 min for IM, SC, and IV, respectively. The mean total serum concentrations of ceftiofur and its metabolite at 6, 12, and 24 h after injection were 1.92, 0.79, and 0.41 \(\mu g/ml\) for IM, 2.16, 0.91, and 0.45 \(\mu g/ml\) for SC, and 1.08, 0.55, and 0.31 \(\mu g/ml\) for IV.

4. Discussion
Ceftiofur is an antibiotic that is approved for use in horses by IM injection only. Anecdotal reports, however, indicate that ceftiofur is also administered to horses through the IV and SC routes. Most horses referred to a tertiary-care facility for treatment of a bacterial infection have an IV catheter placed for administration of antibiotics and other medications such as non-steroidal anti-inflammatory drugs and fluids. In these patients, ceftiofur is commonly administered through the IV catheter for the sake of convenience and safety. In addition, if animals are cachexic with poor muscle mass, some practitioners have opted to give ceftiofur SC to reduce muscle soreness. The results of this study indicate that IV and SC administration of ceftiofur sodium results in concentrations of ceftiofur and metabolites similar to those achieved after administration by the approved IM route, and it suggests that the concentrations achieved should be effective for treatment of infections caused by susceptible organisms.\(^1,4,5\) Reviewing the mean plasma concentrations at 6, 12, and 24 h, these dosing intervals should be adequate for the following susceptible bacteria:

* E. coli* (minimal inhibitory concentration [MIC] \(90 \leq 0.5 \mu g/ml\)) IV route should be q 24 h, but IM and SC will be adequate at q 12 h.
* Streptococci* (MIC \(90 \leq 0.03 \mu g/ml\)) and *Pasteurella* (MIC \(90 \leq 0.015 \mu g/ml\)) can be administered q 24 h by any route.

Different dosages have been commonly used in foals (5–10 mg/kg, q 8 h to q 6 h IV, IM or SC). Rationale for higher doses in foals is based on the fact that the bacteria typically isolated from foals (i.e., gram-negative enterics) typically have higher MICs than the beta-hemolytic Streptococci that are targeted in the label approval.\(^1,6\) Potential complications associated with the use of ceftiofur include diarrhea, muscle soreness, depression, and colic. An experimental perioperative use of ceftiofur in ponies undergoing laparotomies resulted in an increased prevalence of post-operative diarrhea.\(^7\)

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References and Footnotes

\(^a\)Naxcel, The Upjohn Co., Kalamazoo, MI 49001.
\(^b\)TOPFIT, VCH Publishers, Inc., Deerfield, FL 33442.