Many types of bacteria cause primary or secondary infections in birds. In birds, gram-negative bacteria commonly infect the respiratory or alimentary tract and gram-positive bacteria commonly infect the skin and upper respiratory or gastrointestinal tracts. Consequently, antimicrobials are commonly administered to birds for treatment of infections. Pharmacokinetic and pharmacodynamic properties of many antimicrobials, including fluoroquinolones, β-lactams, tetracyclines, and macrolides, have been determined for several species of birds. Many antimicrobials have a short half-life, which necessitates frequent treatment and potentially causes an increase in handling-related stress for patients, veterinary staff, and owners.

Third-generation cephalosporins, such as ceftiofur, are bactericidal, have a broad spectrum of activity against bacteria, and have low toxicity. Cephalosporins inhibit bacterial cell wall synthesis and are typically more resistant to deactivation by β-lactamases than are penicillins. Third-generation cephalosporins have fair

**Objective**—To determine the pharmacokinetic properties of 1 IM injection of ceftiofur crystalline-free acid (CCFA) in American black ducks (Anas rubripes).

**Animals**—20 adult American black ducks (6 in a preliminary experiment and 14 in a primary experiment).

** Procedures**—Dose and route of administration of CCFA for the primary experiment were determined in a preliminary experiment. In the primary experiment, CCFA (10 mg/kg, IM) was administered to ducks. Ducks were allocated into 2 groups, and blood samples were obtained 0.25, 0.5, 1, 2, 4, 8, 12, 48, 96, 144, 192, and 240 hours or 0.25, 0.5, 1, 2, 4, 8, 24, 72, 120, 168, and 216 hours after administration of CCFA. Plasma concentrations of ceftiofur free acid equivalents (CFAEs) were determined by use of high-performance liquid chromatography. Data were evaluated by use of a naive pooled-data approach.

** Results**—The area under the plasma concentration versus time curve from 0 hours to infinity was 783 h·µg/mL, maximum plasma concentration observed was 13.1 µg/mL, time to maximum plasma concentration observed was 24 hours, terminal phase half-life was 32.0 hours, time that concentrations of CFAEs were higher than the minimum inhibitory concentration (1.0 µg/mL) for many pathogens of birds was 123 hours, and time that concentrations of CFAEs were higher than the target plasma concentration (4.0 µg/mL) was 73.3 hours.

** Conclusions and Clinical Relevance**—On the basis of the time that CFAE concentrations were higher than the target plasma concentration, a dosing interval of 3 days can be recommended for future multidose CCFA studies. (Am J Vet Res 2012;73:620–627)
to good activity against gram-positive bacteria, excellent activity against gram-negative bacteria, and activity against some anaerobic bacteria. Studies have revealed that the MIC of ceftiofur for many bacteria (eg, Escherichia coli, Salmonella spp, Proteus spp, Klebsiella spp, and Staphylococcus intermedius) isolated from poultry is ≤ 1.0 µg/mL. Toxicoses and adverse reactions attributable to ceftiofur are rare but include gastrointestinal tract and hypersensitivity reactions. Anaemia and thrombocytopenia have been detected in dogs that received an overdose or had a prolonged duration of administration of cephalosporins.

The interval during which the concentration of a cephalosporin is higher than the MIC of that drug for a pathogen is considered the most accurate predictor of its efficacy against that pathogen. A β-lactam antimicrobial is typically efficacious against a pathogen when the serum or plasma concentration of that drug is higher than the MIC for 50% to 60% of the dosage interval, provided the β-lactam has a postantibiotic effect for that pathogen. Maintenance of an effective circulating concentration of a cephalosporin in birds often requires more frequent administration and a higher dose than those required for mammals. Cephalosporin dosage regimens that are effective against bacteria may differ among species of bird. In birds, cephalosporins typically have elimination half-lives < 2 hours, and higher doses of ceftiofur are required for birds than for mammals to achieve the same Cmax. Additionally, the size and species of bird affect the pharmacokinetics of cephalosporins. Therefore, it may be necessary to include several species of bird in studies of cephalosporins to properly characterize the efficacy of those antimicrobials. An effective, long-acting, third-generation cephalosporin could be a useful addition to the antimicrobials that are currently available for use in birds. Such an antimicrobial would provide broad-spectrum activity against bacteria and allow a substantially longer dosing interval than that required for other types of antimicrobial.

Ceftiofur crystalline-free acid is a suspension of ceftiofur in sterile oil, which substantially increases the terminal half-life of the drug versus other formulations of ceftiofur. It is approved by the US FDA for treatment of gram-negative, gram-positive, and anaerobic bacterial infections in cattle and swine and for treatment of Streptococcus equi subsp zooepidemicus infections in horses. Because it is a bactericidal, broad-spectrum, and long-acting antimicrobial, CCFA could be a useful antimicrobial for treatment of bacterial diseases in birds. The objective of the study reported here was to determine the pharmacokinetic properties of CCFA following a single IM injection in American black ducks (Anas rubripes).

### Materials and Methods

**Animals**—Three male and 3 female adult American black ducks (mean ± SD weight, 1.14 ± 0.09 kg [range, 1.02 to 1.26 kg]; age range, 3 to 8 years) were included in a preliminary experiment to determine the dose and route of administration of CCFA that would be used in the primary experiment. Seven male and 7 female adult American black ducks (mean ± SD weight, 1.60 ± 0.21 kg [range, 1.15 to 2.0 kg]; age range, 3 to 8 years) were included in the primary experiment. Ducks were housed in outdoor pens at the Smithsonian Conservation Biology Institute in Front Royal, Va. Each duck was determined to be healthy on the basis of results of a physical examination. All experiments were approved by the Smithsonian National Zoological Park Animal Care and Use Committee.

**Preliminary experiment**—Six ducks were injected SC with 10, 15, or 20 mg of CCFA/kg (2 ducks [1 male and 1 female]/dose). Blood samples (0.75 to 1.4 mL) were collected ≤ 1 week prior to dosing (0 hours) and 0.25, 0.5, 1, 4, 8, 24, 72, 120, and 168 hours after SC administration of CCFA to the ducks. After a washout period of 3 months, 4 of those same ducks were injected IM with 10 or 20 mg of CCFA/kg (2 ducks [1 male and 1 female]/dose). Blood samples (0.8 to 1.3 mL) were collected ≤ 1 week prior to dosing (0 hours) and 0.25, 0.5, 1, 2, 4, 8, 12, 24, 72, and 120 hours after IM administration of CCFA to the ducks. Blood samples were collected from a jugular or cutaneous ulnar vein. Blood samples were centrifuged (2,500 × g for 20 minutes), and plasma supernatant was placed in 500-µL vials; plasma samples were stored at −70°C until they were shipped frozen on dry ice for sample analysis at the University of California-Davis School of Veterinary Medicine Veterinary Drug Residue Laboratory. To monitor for adverse effects of administration of CCFA or repeated handling of ducks, a physical examination (including inspection of the injection site) was performed for each duck each time it was handled. For each duck, a plasma biochemical analysis was performed ≤ 1 week before and 3 to 5 weeks after SC and IM administrations of CCFA and a CBC was performed ≤ 1 week before and 3 to 5 weeks after IM administration of CCFA to detect adverse effects of administration of that drug. Results of plasma biochemical analyses and CBCs were interpreted by comparison of results with those for blood samples that had been collected from healthy ducks and evaluated at the National Zoological Park Clinical Pathology Laboratory. Plasma samples were analyzed to determine noncompartmental pharmacokinetic variables (t1/2, λz, Cmax, Tmax, time that concentrations of CFAEs were higher than MIC, AUC0–∞, and AU C0–∞/dose of CCFA) of CCFA for each duck in the preliminary experiment. Time that concentrations of CFAEs were higher than MIC was defined as the time during which the concentration (1.0 µg/mL) of CFAEs was higher than that required to exceed the MIC for many pathogens of birds.

**Primary experiment**—On the basis of results of the preliminary experiment, a dose (10 mg/kg) and route of administration (IM) of CCFA were selected for use in the primary experiment. Ducks were weighed ≤ 24 hours before the start of the primary experiment. The CCFA was mixed thoroughly and aspirated into a syringe ≤ 1 minute before administration to each duck to prevent precipitate from blocking the needle bore during injection. Each duck was injected with 10 mg of CCFA/kg in a pectoral muscle (0 hours). Injections were performed with 1-mL syringes and 22-gauge needles. To ensure that a sufficient number of blood samples were obtained at each time point for analysis and to
minimize the total volume of blood obtained from each duck within a 7-day period after injection of CCFA, ducks were randomly allocated into 2 groups. Blood samples (0.9 to 1.3 mL) were collected into tubes containing lithium heparin from 4 male and 4 female ducks (weight range, 1.3 to 2.0 kg) at ≤2 weeks prior to dosing (0 hours) and 0.25, 0.5, 1, 2, 4, 8, 24, 72, 120, 168, and 216 hours after administration of CCFA. Blood samples were collected from a jugular or cutaneous ulnar vein. The total volume of blood collected from each duck within a 7-day period after administration of CCFA was <10% of its estimated total volume of blood. Blood samples were centrifuged (2,500 × g for 20 minutes), and plasma supernatant was transferred to 500-μL vials; plasma samples were stored at −70°C until they were shipped frozen on dry ice for analysis at the University of California-Davis School of Veterinary Medicine Veterinary Drug Residue Laboratory. Ducks were examined to detect injection site reactions by visual inspection every day and by palpation every time they were handled for blood sample collection for 10 days after administration of CCFA. Activity, appetite, and fecal output of the ducks were monitored daily by keeper staff.

**Plasma sample analysis**—Preliminary and primary experiment plasma samples were analyzed to determine concentrations of CFAEs (including ceftiofur and desfuroylceftiofur-related metabolites) by use of high-performance liquid chromatography. Dithioerythritol (100 mg/0.5 mL of plasma) was added to plasma samples to cleave macromolecule-bound desfuroylceftiofur metabolites. Plasma samples were passed through a C18 solid-phase extraction column and derivatized with iodoacetamide to yield desfuroylceftiofur acetamide. High-performance liquid chromatography analysis was performed isocratically (mobile phase solvent, 7% acetonitrile and 1% acetic acid with 90 mg of heparin) for 4 to 5 hours. The broth culture was then added dropwise to saline (0.9% NaCl) solution to achieve a McFarland standard of 0.5 as determined by a nephelometer. Ten microliters of this suspension was diluted in 11 mL of cation-adjusted Mueller-Hinton broth that contained N-Tris(hydroxymethyl) methyl-2-aminoethane sulfonic acid; plates for the determination of antimicrobial resistance were inoculated with 50 μL of this broth/well. The plates were incubated at 35°C without CO2 overnight (16 hours). The MIC of ceftiofur for each bacterial isolate was determined.

**Pharmacokinetic analysis**—Pharmacokinetic analysis of time versus plasma concentration data was performed with commercial software. Data were analyzed by use of a naive pooled-data approach. The model that best fit the data was determined by visual examination of line fits and by residual plots of Akaike information criteria. Uniform weighting of data was used for the analysis. Because the analytic method that was used to measure plasma ceftiofur concentrations also measures concentrations of other active ceftiofur metabolites, the time that concentrations of CFAEs were higher than the MIC (1.0 μg/mL) and the time that concentrations of CFAEs were higher than the target plasma concentration (4.0 μg/mL) were determined.

Pharmacokinetic variables determined for compartmental analysis included the initial-phase rate constant and the terminal-phase rate constant. For noncompartmental analysis, the following pharmacokinetic variables were determined: terminal-phase rate constant, t1/2, AUC, and C∞. The model that best fit the data was determined by visual examination of line fits and by residual plots of Akaike information criteria. Uniform weighting of data was used for the analysis. Because the analytic method that was used to measure plasma ceftiofur concentrations also measures concentrations of other active ceftiofur metabolites, the time that concentrations of CFAEs were higher than the MIC (1.0 μg/mL) and the time that concentrations of CFAEs were higher than the target plasma concentration (4.0 μg/mL) were determined.

**Results**

**Preliminary experiment**—During the preliminary experiment, ducks were healthy and no injection site reactions were observed. Results of CBCs...
and plasma biochemical analyses did not indicate any clinically important findings in ducks after administration of CCFA. Results of plasma biochemical analyses and CBCs were interpreted by comparison of results with those for blood samples that had been collected from healthy ducks and evaluated at the National Zoological Park Clinical Pathology Laboratory.

Plasma concentrations of CFAEs and the pharmacokinetic parameters determined during the preliminary experiment (Table 1) suggested that CCFA seemed to have a longer terminal half-life and the concentration of CFAEs seemed to be higher than the MIC for a longer period after IM administration versus after SC administration in the ducks, although these data were not examined via statistical analysis. A CCFA dose of 10 mg/kg and an IM route of administration were selected for use in the primary experiment because this dose and route of administration resulted in plasma concentrations of CFAEs in ducks of the preliminary experiment that were higher than the plasma concentration of ceftiofur (1.0 µg/mL) required to exceed the MIC for many pathogens of birds.

Primary experiment—During the primary experiment, ducks were healthy and adverse effects of CCFA administration were not detected. No injection site reactions were observed, and no adverse effects to the gastrointestinal tract were detected in the ducks.

The pharmacokinetic parameters were calculated via a naïve pooled-data approach (Table 2). Terminal-phase rate constants were similar (terminal-phase rate constant for compartmental analysis, 0.020 hours⁻¹; terminal-phase rate constant for noncompartmental analysis, 0.022 hours⁻¹), initial rate constant was 0.22 hours⁻¹, $t_{1/2,\lambda_z}$ was 32.0 hours, $T_{\text{max}}$ (h) = 24, $C_{\text{max}}$ (µg/mL) = 13.07, $\text{AUC}_{0-\infty}$ (h•µg/mL) = 782.9, time concentrations of CFAEs $\geq$ MIC (h) = 123.3, time concentrations of CFAEs $\geq$ target plasma concentration (h)* = 73.3.

*Target plasma concentration was defined as 4.0 µg/mL. $K_{\text{in}}$ = Initial-phase rate constant (compartmental analysis), $K_{\text{el}}$ = Terminal-phase rate constant (compartmental analysis), $\lambda_z$ = Terminal-phase rate constant (noncompartmental analysis). See Table 1 for remainder of key.

Table 1—Noncompartmental pharmacokinetic parameters for American black ducks (Anas rubripes) that received CCFA (10, 15, or 20 mg/kg, SC; and 10 or 20 mg/kg, IM) at 0 hours during a preliminary experiment.

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Route of administration</th>
<th>$t_{1/2,\lambda_z}$ (h)</th>
<th>$C_{\text{max}}$ (µg/mL)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>Time concentrations of CFAEs $\geq$ MIC (h)</th>
<th>$\text{AUC}_{0-\infty}$ (h•µg/mL)</th>
<th>$\text{AUC}_{0-\infty}/\text{CCFA}$ dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>SC</td>
<td>12.2</td>
<td>16.9</td>
<td>4</td>
<td>67.8</td>
<td>485.0</td>
<td>48.5</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>10.6</td>
<td>22.6</td>
<td>8</td>
<td>66.7</td>
<td>543.3</td>
<td>54.3</td>
</tr>
<tr>
<td>15</td>
<td>SC</td>
<td>10.7</td>
<td>21.6</td>
<td>4</td>
<td>65.7</td>
<td>476.8</td>
<td>31.8</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>10.1</td>
<td>20.4</td>
<td>8</td>
<td>67.7</td>
<td>579.1</td>
<td>38.8</td>
</tr>
<tr>
<td>20</td>
<td>SC</td>
<td>17.8</td>
<td>18.2</td>
<td>8</td>
<td>71.6</td>
<td>830.3</td>
<td>41.5</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>13.4</td>
<td>26.3</td>
<td>8</td>
<td>71.8</td>
<td>867.5</td>
<td>43.4</td>
</tr>
<tr>
<td>10</td>
<td>IM</td>
<td>29.1</td>
<td>15.5</td>
<td>24</td>
<td>120.0</td>
<td>1,114.4</td>
<td>111.4</td>
</tr>
<tr>
<td>20</td>
<td>IM</td>
<td>25.8</td>
<td>17.1</td>
<td>24</td>
<td>144.4</td>
<td>1,109.3</td>
<td>110.9</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>17.4</td>
<td>19.2</td>
<td>12</td>
<td>116.1</td>
<td>1,550.4</td>
<td>77.5</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>28.6</td>
<td>32.5</td>
<td>12</td>
<td>119.9</td>
<td>1,119.4</td>
<td>56.0</td>
</tr>
</tbody>
</table>

The MIC was defined as 1.0 µg/mL. Results represent data for 2 ducks for each combination of dose and route of administration.

Figure 1—Concentrations of CFAEs in plasma samples obtained from 14 American black ducks (Anas rubripes) that received a single dose of CCFA (10 mg/kg, IM) at 0 hours. Each symbol represents data for a particular duck, and the values of the predicted model are represented by the line.

Table 2—Compartmental and noncompartmental pharmacokinetic parameters of CCFA (10 mg/kg, IM) in 14 American black ducks.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{\text{in}}$ (h⁻¹)</td>
<td>0.22</td>
</tr>
<tr>
<td>$K_{\text{el}}$ (h⁻¹)</td>
<td>0.020</td>
</tr>
<tr>
<td>$\lambda_z$ (h⁻¹)</td>
<td>0.022</td>
</tr>
<tr>
<td>$t_{1/2,\lambda_z}$ (h)</td>
<td>32.0</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>24</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>13.07</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (h•µg/mL)</td>
<td>782.9</td>
</tr>
<tr>
<td>Time concentrations of CFAEs $\geq$ MIC (h)</td>
<td>123.3</td>
</tr>
<tr>
<td>Time concentrations of CFAEs $\geq$ target plasma concentration (h)*</td>
<td>73.3</td>
</tr>
</tbody>
</table>

*Target plasma concentration was defined as 4.0 µg/mL. $K_{\text{in}}$ = Initial-phase rate constant (compartmental analysis), $K_{\text{el}}$ = Terminal-phase rate constant (compartmental analysis), $\lambda_z$ = Terminal-phase rate constant (noncompartmental analysis). See Table 1 for remainder of key.
that a 1-compartment model best fit the plasma concentration versus time data (Figure 1).

MICs—The MICs of ceftiofur for bacteria isolated from various samples obtained from birds were determined (Table 3). Bacterial isolates for which the ceftiofur MIC50 was ≤ 1.0 µg/mL included Enterobacter spp, Klebsiella spp, Pasteurella spp, Proteus spp, Serratia spp, Staphylococcus aureus, and nonfermentative group 3 bacteria. Additional bacterial isolates for which the ceftiofur MIC50 was ≤ 1.0 µg/mL included E coli, S intermedius, coagulase-negative Staphylococcus spp, and Streptococcus spp. Bacterial isolates for which the ceftiofur MIC50 and MIC90 were ≥ 4.0 µg/mL included Acinetobacter spp, Enterococcus spp, and Pseudomonas spp, which indicated that these bacteria were not susceptible to ceftiofur. The MIC data were compared with values of MICs of ceftiofur that have been reported in other studies for bacteria isolated from various samples obtained from birds (Appendix). Among bacteria isolated from Anseriformes or Galliformes in those studies, MIC50 values of ceftiofur for E coli, Klebsiella spp, Proteus spp, Salmonella spp, and S intermedius were 0.5 to 1.0 µg/mL, and MIC90 values of ceftiofur for Citrobacter spp, Enterobacter spp, Enterococcus spp, Pseudomonas spp, coagulase-negative Staphylococcus spp, and Streptococcus spp were > 4.0 µg/mL.

**Discussion**

American black ducks did not develop any adverse clinical signs attributable to CCFA administration (10 mg/kg, IM) during the study reported here. Additionally, none of the previously reported adverse effects (eg, gastrointestinal tract disturbances, anaphylactic reactions, or anemia) of ceftiofur administration were detected in the ducks during 2 years after completion of the present study.

Results of the preliminary experiment in the present study indicated that administration of 10 or 20 mg of CCFA/kg resulted in plasma concentrations of CFAEs > 1 µg/mL. Intramuscular administration of CCFA resulted in plasma concentrations of CFAEs > 1.0 µg/mL for a longer period than did SC administration of CCFA. Additionally, CCFA seemed to have greater apparent bioavailability after IM administration than after SC administration, as indicated by the higher AUC0–∞, although these data were not tested via statistical analysis, nor was the IV route of administration included in the study. The doses of CCFA administered IM in the preliminary experiment were chosen on the basis of the dose of CCFA recommended for cattle (6.6 mg/kg). The cattle dose was rounded up (10 mg/kg) for ease of CCFA dose calculation in the present study, and a higher dose of CCFA (20 mg/kg) was also administered to the ducks because ducks likely have a higher metabolic rate than that of cattle. Results of the preliminary experiment indicated that 10 mg of CCFA/kg administered IM was sufficient to achieve plasma concentrations of CFAEs that were expected to be active against bacteria. Because IM administration of 10 mg of CCFA/kg was investigated in the primary experiment in the present study, another study would be required.

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Table 3—Minimum inhibitory concentrations of ceftiofur for bacteria isolated from various samples that had been obtained from 175 birds and submitted to the William R. Pritchard Veterinary Medical Teaching Hospital Microbiology Laboratory at the University of California-Davis from January 2000 through September 2010.

<table>
<thead>
<tr>
<th>Bacterial isolate</th>
<th>Source</th>
<th>No. of isolates</th>
<th>MIC50 (µg/mL)</th>
<th>MIC90 (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter spp</td>
<td>Anseriforme, Psittaciforme, and NR</td>
<td>5</td>
<td>4.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Anseriforme, Galliforme, Psittaciforme, and NR</td>
<td>51</td>
<td>&lt; 0.5</td>
<td>&gt; 4.0</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>Anseriforme, Columbiiforme, Coraciiforme, Psittaciforme, and NR</td>
<td>21</td>
<td>&lt; 0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Enterococcus spp</td>
<td>Anseriforme, Galliforme, Psittaciforme, and NR</td>
<td>32</td>
<td>&gt; 4.0</td>
<td>&gt; 8.0</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>Anseriforme, Galliforme, Psittaciforme, and NR</td>
<td>31</td>
<td>&lt; 0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Nonfermentative group 3</td>
<td>Anseriforme, Galliforme</td>
<td>4</td>
<td>&lt; 0.25</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>Pasturella spp</td>
<td>Anseriforme, Galliforme, Psittaciforme, and NR</td>
<td>21</td>
<td>&lt; 0.5</td>
<td>&lt; 0.06 to 1.0</td>
</tr>
<tr>
<td>Proteus spp</td>
<td>Anseriforme, Psittaciforme, and NR</td>
<td>10</td>
<td>&lt; 0.5</td>
<td>&lt; 0.5 to 1.0</td>
</tr>
<tr>
<td>Pseudomonas spp</td>
<td>Anseriforme, Galliforme, Psittaciforme, and NR</td>
<td>26</td>
<td>&lt; 4.0</td>
<td>&lt; 8.0</td>
</tr>
<tr>
<td>Serratia spp</td>
<td>Psittaciforme and NR</td>
<td>4</td>
<td>&lt; 0.5</td>
<td>&lt; 0.5 to 1.0</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Galliforme, Psittaciforme, and NR</td>
<td>16</td>
<td>&lt; 0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Staphylococcus intermedius</td>
<td>Galliforme, Psittaciforme, and NR</td>
<td>6</td>
<td>&lt; 0.5</td>
<td>&lt; 0.5 to 1.0</td>
</tr>
<tr>
<td>Staphylococcus spp [coagulase negative]</td>
<td>Galliforme, Psittaciforme, and NR</td>
<td>41</td>
<td>&lt; 0.5</td>
<td>&lt; 0.06 to 1.0</td>
</tr>
<tr>
<td>Streptococcus spp</td>
<td>Psittaciforme and NR</td>
<td>7</td>
<td>0.5</td>
<td>&lt; 0.5 to 4.0</td>
</tr>
</tbody>
</table>

*Source is the order of the birds from which samples for bacterial culture and determination of MICs were obtained. NR = Not reported.*
to determine whether IM administration of CCFA doses < 10 mg/kg would achieve plasma concentrations of CFAEs in ducks that are effective against bacteria. Ceftriaxone crystalline-free acid administered IM at a dose of 10 mg/kg had a longer duration of action in American black ducks in the present study than has been reported for other third-generation cephalosporins administered to other species of birds. Results of another study indicated that the mean $t_{1/2}$ of cefovecin in psittacines and domestic birds ranges from 2.5 to 8.7 hours. In comparison, the $t_{1/2}$ of CCFA in ducks in the present study was 32 hours. Ceftriaxone administered IM at a dose of 100 mg/kg has an elimination half-life of 5.1 hours in chickens. Cefovecin, a recently developed antimicrobial that has a long terminal half-life in dogs and cats allowing a dosing interval of 14 days, has a mean ± SD plasma half-life of 0.9 ± 0.3 hours in domestic hens after SC administration of a dose of 10 mg/kg. Therefore, CCFA appears to have a longer terminal half-life than other third-generation cephalosporins in birds, which suggests that effective circulating antimicrobial concentrations may be maintained for a longer time after CCFA administration than after administration of other cefiotur formulations. Ceftriaxone crystalline-free acid seemed to have different pharmacokinetic properties in American black ducks in the present study, compared with findings for other cephalosporin formulations evaluated in other species of birds. For example, $T_{\text{max}}$ of ceftriaxone sodium (1 to 11.6 mg/kg, SC) in domestic birds ranges from 0.4 to 2.7 hours, and mean ± SD $T_{\text{max}}$ of cefovecin (10 mg/kg, SC) in hens is 17 ± 3 minutes. In contrast, $T_{\text{max}}$ of CCFA in ducks in the present study was 24 hours. The $C_{\text{max}}$ of ceftriaxone sodium in psittacines and domestic birds ranges from 0.86 to 10.99 $\mu$g/mL, and mean ± SD $C_{\text{max}}$ of cefovecin in hens is 6 ± 2 $\mu$g/mL, whereas $C_{\text{max}}$ of CCFA in ducks in the present study was 13.1 $\mu$g/mL. The AUC$_{\text{0-}\infty}$ of ceftriaxone sodium in psittacines and domestic birds ranges from 3.4 to 43.8 $\mu$g/mL, and mean ± SD AUC$_{\text{0-}\infty}$ of cefovecin in hens is 8 ± 1 $\mu$g/mL, whereas AUC$_{\text{0-}\infty}$ of CCFA in ducks in the present study was 783 $\mu$g/mL. The pharmacokinetic properties of CCFA in American black ducks in the present study were comparable to pharmacokinetic properties of CCFA in mammals and other species of birds. Other pharmacokinetic studies have indicated the mean ± SD $T_{\text{max}}$ of CCFA (5 mg/kg, IM) in swine is 22.0 ± 12.2 hours, and the mean ± SD $T_{\text{max}}$ of CCFA (6.6 mg/kg, administered SC in the middle third of the ear) in beef cattle is 12.0 ± 6.2 hours. These results were similar to those for ducks in the present study ($T_{\text{max}}$ 24 hours). Results of those other studies reveal that values of $t_{1/2}$ for CCFA in swine (49.6 ± 11.8 hours) and beef cattle (62.3 ± 13.5 hours) were longer than the $t_{1/2}$ (32.0 hours) detected after administration of CCFA (10 mg/kg, IM) to ducks in the present study. However, in swine and beef cattle, mean ± SD values of $C_{\text{max}}$ (4.17 ± 0.92 $\mu$g/mL and 6.90 ± 2.68 $\mu$g/mL, respectively) and AUC$_{\text{0-}\infty}$ (373.0 ± 56.1 $\mu$g/mL and 376 ± 66.1 $\mu$g/mL, respectively) differ from the values of $C_{\text{max}}$ (13.1 $\mu$g/mL) and AUC$_{\text{0-}\infty}$ (783 $\mu$g/mL) in ducks in the primary experiment of the present study. This difference in the values of pharmacokinetic variables of CCFA may be attributable to the higher dose of CCFA that was administered to ducks in the present study, compared with the doses administered to swine and beef cattle in the other studies, or to physiologic differences among these species. Interestingly, a study in which CCFA (6.6 mg/kg, SC) was administered to nonlactating goats revealed higher mean ± SD $T_{\text{max}}$ (26.7 ± 16.5 hours), lower mean ± SD $C_{\text{max}}$ (2.25 ± 1.13 $\mu$g/mL), and lower mean ± SD AUC$_{\text{0-}\infty}$ (159.35 ± 19.4 $\mu$g/mL) of CCFA than the corresponding values for swine, beef cattle, and ducks (present study).

Authors of a recent study in which CCFA (10 mg/kg, IM) was administered to helmeted guineafowl (Numida meleagris) reported a mean ± SD terminal half-life of 29.0 ± 4.9 hours, mean ± SD $C_{\text{max}}$ of 5.26 ± 1.54 $\mu$g/mL, mean ± SD $T_{\text{max}}$ of 19.3 ± 9.71 hours, and mean ± SD area under the plasma concentration versus time curve of 300 ± 69.3 $\mu$g/mL. Compared with results for American black ducks in the present study (to which CCFA was administered at that same dose and by that same route of administration), $C_{\text{max}}$ and AUC$_{\text{0-}\infty}$ were lower for those guineafowl and $T_{\text{max}}$ and terminal half-life were similar for those guineafowl. Plasma concentrations of cefiotur were higher than the MIC (1 $\mu$g/mL) for many bacterial pathogens of poultry and domestic ducks for 72 hours in 12 of 14 guineafowl in that other study. In American black ducks in the present study, plasma concentrations of CFAEs were > 1 $\mu$g/mL for 123 hours. These results suggested that after IM administration of 10 mg of CCFA/kg, $C_{\text{max}}$ and AUC$_{\text{0-}\infty}$ were higher and the time during which the plasma concentration was > 1 $\mu$g/mL was longer for ducks in the present study than for guineafowl in the other study. Given that guineafowl in the other study and American black ducks in the present study were of similar size, this variation may be attributable to physiologic differences among Galliformes and Anseriformes.

In general, MICs of cefiotur for bacteria isolated from birds are higher than those for bacteria isolated from cattle, swine, or horses. For many bacteria isolated from cattle, swine, and horses, MIC$_{90}$ of cefiotur is < 0.03 $\mu$g/mL. Bacteria isolated from Anseriformes or Galliformes for which the MIC$_{90}$ value of cefiotur is 0.5 to 1.0 $\mu$g/mL include E coli, Klebsiella spp, Proteus spp, Salmonella spp, and S intermedium (Appendix). Those same studies revealed that MIC$_{90}$ values of cefiotur for Citrobacter spp, Enterobacter spp, Enterococcus spp, Pseudomonas spp, coagulase-negative Staphylococcus spp, and Streptococcus spp are > 4.0 $\mu$g/mL. On the basis of the results of the present study, it appears that Enterobacter spp, S aureus, coagulase-negative Staphylococcus spp, and Streptococcus spp isolated from birds may have higher susceptibility to cefiotur, and S intermedium and E coli isolated from birds may have lower susceptibility to cefiotur, compared with findings for bacteria isolated from cattle, swine, or horses. Results of the present study support results of the other studies, which indicate that Enterococcus spp and Pseudomonas spp are typically resistant to cefiotur. Considering these pharmacokinetic and MIC data, bacteria that would be most susceptible to CCFA may include Enterobacter spp, Klebsiella spp, Pasteurella.
spp, Proteus spp, Serratia spp, S. aureus, and nonfermentative group 3 bacteria; E. coli, S. intermedius, coagulase-negative Staphylococcus spp, and Streptococcus spp may have intermediate susceptibilities to CCFA. However, despite the broad spectrum of action of ceftiofur, antimicrobials should be chosen on the basis of results of culture and susceptibility testing whenever possible.

To compensate for inactive ceftiofur metabolites that are detected by use of high-performance liquid chromatography, some studies30,36 conducted to investigate pharmacokinetics of ceftiofur in cattle and swine have used a target MIC value of 0.2 µg/mL, despite the reported MIC of ceftiofur of 0.03 µg/mL for many species of bacteria commonly isolated from these animals.33 Results of a study33 in which the antimicrobial activities of ceftiofur and desfurolyceftiofur were investigated indicate that both of these metabolites have similar activities against gram-negative bacteria but that ceftiofur is 2 to 8 times more active than is desfurolyceftiofur against certain gram-positive bacteria. Because the ratio of circulating ceftiofur to its less active metabolites after administration in birds is unknown, and because the in vivo activities of these metabolites in birds are unknown, a target plasma concentration (4 µg/mL) that was 4 times higher than the MIC (1 µg/mL) was used in the present study. For many bacterial pathogens of birds, the MIC of ceftiofur is ≤ 1 µg/mL. Therefore, a target plasma concentration of 4 µg of ceftiofur/mL was used in the present study because that concentration was expected to be active against most of the bacterial isolates that were susceptible to this antimicrobial. On the basis of the finding in the present study that the time that concentrations of CFAEs were higher than the target plasma concentration was 73.3 hours, we suggest a dosing interval of 3 days should be used in future studies conducted to investigate administration of multiple doses of CCFA to ducks.

Although CCFA seems to be a promising long-acting broad-spectrum antimicrobial for use in birds, a study in which multiple doses are administered would be needed to confirm our recommended dosing interval of 3 days. Further studies could be conducted to determine whether administration of CCFA to birds at doses that are the same as those recommended for use in mammals results in half-life, AUC0–∞, and Cmax values that are comparable to those in ducks of the present study. Also, the pharmacokinetics of CCFA may differ among species of birds, and further studies are warrant-ed to characterize these differences.

References


Appendix

Summary of values of MICs of ceftiofur that have been reported in other studies[10,11,23] for bacteria isolated from various samples obtained from birds.

<table>
<thead>
<tr>
<th>Bacterial isolate</th>
<th>Source</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/mL)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
<th>MIC range (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter lwoffi</td>
<td>Duck</td>
<td>ND</td>
<td>ND</td>
<td>8.0 to 16.0</td>
</tr>
<tr>
<td>Aeromonas spp</td>
<td>Duck</td>
<td>ND</td>
<td>ND</td>
<td>0.13</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Turkey</td>
<td>ND</td>
<td>0.5–2.0</td>
<td>0.13 to 16.0</td>
</tr>
<tr>
<td>E coli</td>
<td>Chicken</td>
<td>ND</td>
<td>0.5–4.0</td>
<td>≤ 0.03 to 16.0</td>
</tr>
<tr>
<td>E coli</td>
<td>Duck</td>
<td>0.5</td>
<td>1.0</td>
<td>≤ 0.03 to 32.0</td>
</tr>
<tr>
<td>Citrobacter spp</td>
<td>Turkey</td>
<td>1.0</td>
<td>32.0</td>
<td>0.5 to &gt; 32.0</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>Turkey</td>
<td>0.5</td>
<td>&gt; 32.0</td>
<td>0.13 to &gt; 32.0</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>Duck</td>
<td>0.0</td>
<td>ND</td>
<td>4.0 to &gt; 32.0</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>Turkey</td>
<td>0.5</td>
<td>1.0</td>
<td>0.13 to 2.0</td>
</tr>
<tr>
<td>Pasteurella spp</td>
<td>Duck</td>
<td>ND</td>
<td>ND</td>
<td>≤ 0.03</td>
</tr>
<tr>
<td>Proteus spp</td>
<td>Turkey</td>
<td>0.13</td>
<td>1.0</td>
<td>0.06 to 32.0</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>Duck</td>
<td>0.06</td>
<td>0.5</td>
<td>0.06 to &gt; 32.0</td>
</tr>
<tr>
<td>Pseudomonas spp</td>
<td>Duck</td>
<td>ND</td>
<td>ND</td>
<td>32.0</td>
</tr>
<tr>
<td>Pseudomonas spp</td>
<td>Turkey</td>
<td>32.0</td>
<td>&gt; 32.0</td>
<td>0.06 to &gt; 32.0</td>
</tr>
<tr>
<td>Salmonella spp</td>
<td>Turkey</td>
<td>1.0</td>
<td>1.0</td>
<td>0.5 to 1.0</td>
</tr>
<tr>
<td>Salmonella spp</td>
<td>Duck</td>
<td>1.0</td>
<td>1.0</td>
<td>0.5 to 1.0</td>
</tr>
<tr>
<td>Staphylococcus spp</td>
<td>Turkey</td>
<td>1.0</td>
<td>2.0</td>
<td>1.0 to 2.0</td>
</tr>
<tr>
<td>Staphylococcus spp (coagulase negative)</td>
<td>Turkey</td>
<td>2.0</td>
<td>8.0</td>
<td>0.13–&gt; 32.0</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Duck</td>
<td>1.0</td>
<td>2.0</td>
<td>0.5 to 2.0</td>
</tr>
<tr>
<td>Staphylococcus intermedius</td>
<td>Duck</td>
<td>0.25</td>
<td>1.0</td>
<td>0.13 to 2.0</td>
</tr>
<tr>
<td>Staphylococcus xylosus</td>
<td>Duck</td>
<td>ND</td>
<td>ND</td>
<td>2.0 to 4.0</td>
</tr>
<tr>
<td>Streptococcus spp and Enterococcus spp</td>
<td>Turkey</td>
<td>&gt; 32.0</td>
<td>&gt; 32.0</td>
<td>≤ 0.03 to &gt; 32.0</td>
</tr>
<tr>
<td>Vibrio cholera</td>
<td>Duck</td>
<td>ND</td>
<td>ND</td>
<td>≤ 0.03</td>
</tr>
</tbody>
</table>

Source is the type of bird from which samples for bacterial culture and determination of MICs were obtained. ND = Not determined.