The Food and Agriculture Organization of the United Nations estimates that approximately 90% of the world’s 1.044 billion domestic ducks are in Asia. China and Vietnam account for approximately 75%, and most are distributed in China.1 Historically, Enterobacteriaceae infections are common in waterfowl, including ducks. The Enterobacteriaceae is a large family of bacteria that includes many familiar pathogens, such as Salmonella spp, Escherichia coli, and Campylobacter spp,2,3 which are not only potential microbial pathogens of waterfowl, but also an important threat to human health.4–6

β-Lactam antimicrobials are used in treatment and prevention programs for bacterial diseases of waterfowl. Several studies have been published regarding the use of amoxicillin,7–10 ampicillin,9,11,12 and ceftiofur13–15 to treat Enterobacteriaceae infections in waterfowl; however, there is a paucity of literature regarding the use of cefquinome.

**Pharmacokinetics and bioavailability of cefquinome in healthy ducks**

**Objective**—To determine pharmacokinetics and bioavailability of cefquinome administered IV, IM, or PO to healthy ducks.

**Animals**—Thirty-six 2-month-old Muscovy ducks.

**Procedures**—Ducks were randomly assigned to 3 groups of 12 birds each for a single IV, IM, or PO administration at a dose of 5 mg/kg. Blood samples were collected before and at various intervals after each administration. Cefquinome concentration was determined by use of high-performance liquid chromatography at 268 nm with a UV detector, and pharmacokinetics were analyzed.

**Results**—The disposition of cefquinome following IV or IM administration was best described by a 2-compartment model. After IV administration, mean ± SD elimination half-life was 1.57 ± 0.06 hours, clearance value was 0.22 ± 0.02 L/kg•h, and apparent volume of distribution at steady state was 0.41 ± 0.04 L/kg. After IM administration, elimination half-life was 1.79 ± 0.13 hours, peak concentration time was 0.38 ± 0.06 hours, peak drug concentration was 9.38 ± 1.61 µg/mL, and absolute mean ± SD bioavailability was 93.28 ± 13.89%. No cefquinome was detected in plasma after PO administration.

**Conclusions and Clinical Relevance**—Results indicated that cefquinome was absorbed quickly and had excellent bioavailability after IM administration, but absorption after PO administration was poor. (Am J Vet Res 2011;72:122–126)

Cefquinome is a broad-spectrum cephalosporin antimicrobial that has been approved solely for veterinary use. It is highly stable when exposed to β-lactamases that are produced by most clinically important bacteria.16 The pharmacokinetics of cefquinome in mice, dogs, pigs, and calves have been reviewed by Limbert et al,17 and additional studies18–22,a,b on the pharmacokinetics of cefquinome in cattle, goats, horses, neonatal pigs, and fishes have been published. Favorable pharmacokinetic features of cefquinome, such as good absorption, high bioavailability, low protein binding, and primary elimination unchanged via the kidneys, are documented. Absorption of orally administered cefquinome is poor in laboratory species and cattle.16 However, no study on the pharmacokinetics of cefquinome in poul-

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**ABBREVIATIONS**

| AUC | Total area under the concentration versus time curve |
| AUMC | Area under the first moment concentration versus time curve |
| Cl | Total body clearance of drug from plasma |
| Cmax | Maximum drug concentration |
| HPLC | High-performance liquid chromatography |
| MIC | Minimum inhibitory concentration |
| t1/2α | Distribution half-life |
| t1/2β | Elimination half-life |
| t1/2ka | Absorption half-life |
| tmax | Time of maximum drug concentration |
| Vss | Apparent volume of distribution at steady state |

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try or waterfowl has been reported yet, to the authors’ knowledge. Thus, to explore the possibilities of using cefquinome in the treatment of bacterial infections in waterfowl and developing a rational individual dosage regimen, the purpose of the study reported here was to investigate the pharmacokinetics and bioavailability of cefquinome (5 mg/kg) following IV, IM, or PO administration in healthy Muscovy ducks.

**Materials and Methods**

**Animals**—Thirty-six 2-month-old healthy Muscovy ducks (18 males and 18 females) with a mean ± SD weight of 2.20 ± 0.60 kg were used for the study. The ducks were purchased from a duck farm and housed under controlled conditions at 25°C according to the requirements for this species. They were fed an antimicrobial-free balanced diet ad libitum with free access to fresh water. During the testing period, the ducks’ health was closely monitored by use of daily physical examination. All animal procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the US National Institutes of Health.

**Reagents and chemicals**—Cefquinome sulfate powder (84.1%) was dissolved in sterile double-distilled water to obtain a cefquinome solution. A cefquinome standard (80.9%) was used for quality control. Acetonitrile and methanol were HPLC grade, and other chemicals including acetic acid, sodium acetate, and sodium hydroxide were analytical reagent grade. Double-distilled water was used in preparing all solutions.

**Experimental design**—At the beginning of the experiments, the birds were weighed and randomly assigned to 3 groups of 12 birds each for single IV, IM, or PO administration at a dose of 5 mg/kg. Cefquinome was administered IV into the left brachial vein and IM into the pectoral muscle. For PO administration, the drug was given by installation of the cefquinome solution into the crop via a plastic tube. Feed was made available 6 hours after drug administration.

Blood samples were collected before (0 hours) and 0.083, 0.167, 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, and 24 hours following IV, IM, and PO drug administration. Each blood sample (1.5 mL) was collected from the right wing vein into a syringe containing heparin. Plasma was isolated by centrifugation (3,500 × g for 10 minutes) at 4°C. Plasma samples were stored at –80°C until analysis was performed.

**Analytic method**—The extraction procedure was modified from a published method. Frozen plasma samples were thawed at 21°C, and an aliquot of 500 µL of plasma was transferred into a capped 1.5-mL polystyrene centrifuge tube. To all plasma samples, 500 µL of HPLC-grade acetonitrile was added. After vortex mixing for 15 seconds, the samples were centrifuged at 12,000 × g for 10 minutes. The supernatant was filtered through a 0.22-µm nylon filter and transferred to an autosampler vial.

A modified HPLC method was used to determine cefquinome concentration. The HPLC system was equipped with a quaternary pump, online degasser, autosampler, column heater, and UV detector. Chromatographic separation of cefquinome was achieved on a reverse-phase column with an injection volume of 5 µL. Column temperature was maintained at 25°C. The mobile phase consisted of acetonitrile-aqueous (vol/vol, 13:87) provided as an isocratic form with a flow rate of 1.0 mL/min. The aqueous solution contained 100 mM acetic acid and 100 mM sodium acetate, adjusted to pH 4.0 with sodium hydroxide. The UV detection wavelength was 268 nm.

**Method validation**—A stock solution of cefquinome (1 mg/mL) was prepared by dissolving 12.40 mg of cefquinome standard (80.9%) in 10 mL of deionized water. Standard working solutions of 0.02, 0.05, 0.1, 0.5, 1, 2.5, 10, and 25 µg/mL were prepared by diluting the stock solution. All stock and working solutions were stored at 4°C. Standard curves were plotted by use of the peak area versus the corresponding concentration of cefquinome. Each point was established from the mean of 5 determinations. Correlation coefficients were > 0.99 for standard curves. The recovery, intraday, and interday coefficients of variability were validated via repetitive analysis of the plasma samples spiked with cefquinome (0.1, 1, and 10 µg/mL). Mean ± SD recoveries of cefquinome were 94.39 ± 2.41%, 93.79 ± 2.09%, and 96.09 ± 2.81% (n = 5); intraday coefficients of variation were 2.55%, 2.23%, and 2.93% (3); and interday coefficients of variation were 7.76%, 5.58%, and 4.28% (5), respectively. The limit of quantification of cefquinome in plasma was chosen as the concentration used for the lowest concentration on the calibration curves and for which the coefficient of variation of repeatability was < 20% (limit of quantification, 0.05 µg/mL).

**Pharmacokinetic analysis**—A nonlinear least-squares regression analysis program, 3P97; was used to fit the plasma concentration versus time data to a series of pharmacokinetic models with plasma cefquinome concentration data weighted by 1, 1/c, and 1/c², where c is the plasma cefquinome concentration. The concentration versus time data for cefquinome were obtained from each duck and were used to calculate kinetic disposition. The number of exponential terms was determined by application of the Akaikes information criterion.

Most pharmacokinetic parameters were calculated by use of classic equations associated with compartmental analysis. The distribution and t 1/2 were calculated as t 1/2 = 0.693/α and t 1/2 = 0.693/β, respectively. A noncompartmental approach was used to determine the AUC and AUMC by use of the linear trapezoidal rule with extrapolation to time infinity. The V and CI were calculated as V = dose × AUMC/(AUC)² and CI = dose/AUC, respectively. The t 1/2 and C 1/2 were observed from the plot of concentration versus time curve. Bioavailability (F) was calculated by use of the equation:

\[ F(\%) = \left(\frac{\text{AUC}_{\text{IV or IM}}}{\text{AUC}_{\text{PO}}}\right) \times 100 \]

Pharmacokinetic parameters are expressed as arithmetic mean ± SD values, except for half-lives, which are reported as harmonic mean ± pseudo-SD values. The mean for each pharmacokinetic variable was determined by calculating the mean of the calculated parameters for drug in each animal.
Results

No cefquinome was detected in plasma after PO administration. Plasma concentrations of cefquinome following IV and IM administration were determined (Table 1), and mean plasma concentration versus time curves were plotted (Figure 1). The plasma concentration of cefquinome in the first sampling time after IV administration was assumed to be the highest initial plasma concentration. At 12 hours after IV administration, the mean ± SD plasma concentration of cefquinome decreased from 19.23 ± 1.44 µg/mL to 0.04 ± 0.004 µg/mL. For IM administration, cefquinome was detectable at 5 minutes and the highest plasma concentration appeared at 30 minutes after administration. Subsequently, mean ± SD plasma concentration of cefquinome decreased from 9.87 ± 1.66 µg/mL to 0.06 ± 0.01 µg/mL at 12 hours after IM administration. No cefquinome was detected in any duck’s plasma 24 hours after IV or IM administration.

On the basis of the value of the Akaike information criterion, a 2-compartment open model and a 2-compartment open model with first-order absorption were determined to be the best models for the initial plasma concentration versus time data after IV and IM administration at a dose of 5 mg/kg. Mean pharmacokinetic parameters calculated for cefquinome after IV and IM administration on the basis of compartmental pharmacokinetic analysis were determined (Table 2).

The MIC values of cefquinome against most Enterobacteriaceae pathogens from ducks were unified as a fixed value of 0.1 on the basis of studies of bacteria from pigs, cattle, and horses. Subsequently, the duration of plasma concentration greater than the MIC was calculated from the plot of concentration versus time curve. This duration was 10 hours for IV administration and 11 hours for IM administration.

Discussion

Results of the present study indicated that cefquinome has favorable pharmacokinetic properties after administration in healthy Muscovy ducks. After IV administration of cefquinome at a single dose of 5 mg/kg, the concentration versus time curve was best fitted by use of a 2-compartment open model, which has also been reported in sows given cefquinome IV at a dose of 1 mg/kg and in young pigs given cefquinome IV at a dose of 2 mg/kg. The t1/2 and CI ranged from 1.30 to 2.30 hours and 0.19 to 0.26 L/kg/h, respectively, indicating rapid elimination of cefquinome following IV administration. According to the previous studies, the t1/2 and CI ranged from 1.30 to 2.30 hours and 0.19 to 0.26 L/kg/h, respectively, in various species, which are values similar to our data. Compared with other cephalosporins, the t1/2 of cefquinome in Muscovy ducks following IV administration was shorter than that of cefotaxime in healthy chickens (+2.23 ± 0.05 hours), but similar to that of ceftriaxone in young broilers (0.60 to 1.40 hours). The less hydrophobic nature and low pKa values of 2.51 or 2.91 of this compound might be the major reason for the limited distribution of cefquinome to the tissues as suggested by the low Vss of 0.41 ± 0.04 L/kg. Similar findings for cefquinome were also observed in young pigs, sows, calves, and dogs.

After IM administration of cefquinome at a single dose of 5 mg/kg, the concentration versus time curve was best fitted by a 2-compartment open model with first-order absorption, which has also been reported in young pigs given cefquinome IV at a dose of 2 mg/kg. The t1/2 and F were 0.12 ± 0.02 L/kg/h, respectively, indicating rapid elimination of cefquinome following IV administration. According to the previous studies, the t1/2 and CI ranged from 1.30 to 2.30 hours and 0.19 to 0.26 L/kg/h, respectively, in various species, which are values similar to our data. Compared with other cephalosporins, the t1/2 of cefquinome in Muscovy ducks following IV administration was shorter than that of cefotaxime in healthy chickens (+2.23 ± 0.05 hours), but similar to that of ceftriaxone in young broilers (0.60 to 1.40 hours).

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After IM administration of cefquinome at a single dose of 5 mg/kg, the concentration versus time curve was best fitted by a 2-compartment open model with first-order absorption, which has also been reported in young pigs given cefquinome IV at a dose of 2 mg/kg. The t1/2 and F were 0.12 ± 0.02 hours and 93.28 ± 13.89%, respectively, indicating the absorption of cefquinome following IM administration was rapid and nearly complete. Compared with cephalothin, a shorter t1/2 (0.12 ± 0.02 hours) was observed in Muscovy ducks following IM administration than that in other avian species including quail, pigeons, ducks, cranes, and emus (0.5 hours). The excellent bioavailability...
associated with the IM administration has been confirmed in different animal species such as young pigs (range, 83.7% to 107.0%)\(^2\) and horses (range, 89.2% to 103.70%).\(^3\) In the present study, the \(t_{\text{max}}\) and \(C_{\text{max}}\) were 0.38 ± 0.06 hours and 9.38 ± 1.61 µg/mL, respectively, indicating that with IM administration, these values are approximately equivalent to those obtained 20 minutes after IV administration at the same dose. This was further confirmed by the similarity of the plasma concentration curves for the 2 routes of administration in the terminal phase. The \(t_{\text{max}}\) of cefquinome following IM administration varied with animal species and dosage, as has been reported in young pigs (0.28 ± 0.07 hours),\(^2\) goats (0.51 ± 0.17 hours),\(^2\) and calves (0.85 ± 0.11 hours)\(^2\) or 2.00 hours,\(^2\), but this is consistent with one of the main pharmacokinetic characteristics of cefquinome; namely, rapid absorption. The \(t_{1/2}\) of 1.79 ± 0.13 hours following IM administration was comparable with that of IV administration (1.57 ± 0.06 hours) in Muscovy ducks, but less than the value (4.36 ± 2.35 hours) in young pigs.\(^2\)

The MICs of cefquinome for bacterial isolates from ducks have not yet been determined. Based on studies of bacteria from pigs, cattle, and horses, the MICs for \(E\) coli, \(Salmonella\) spp, and \(Enterobacteriaceae\) spp were 0.03 to 0.06, 0.098, and 0.098 µg/mL, respectively. The antibacterial effect of cefquinome was time dependent,\(^3\) which is a common feature of \(\beta\)-lactams, suggesting that the time for plasma concentrations to reach and exceed the MICs was a critical factor for determining its efficacy.\(^3\) However, cefquinome has substantial sub-MIC pharmacodynamic effects against most bacterial species tested.\(^3\) Gunderson et al\(^3\) suggested that exceeding MIC by 1 to 5 times for 40% to 100% of the interadministration interval is appropriate for most time-dependent agents. Craig and Andes\(^3\) determined that bacteriologic cure increased from approximately 40% to 80% as the time with the drug concentration greater than the MIC increased from 10% to 100% of the interadministration interval in humans with otitis media treated with \(\beta\)-lactam antibacterial drugs. For most pathogens of the Enterobacteriaceae, maximal efficacy for cefquinome in a neutropenic murine thigh- or lung-infection model is approached when serum concentrations are greater than the MIC for 60% to 70% of the interadministration interval.\(^3\) In the present study, the duration of plasma drug concentration greater than the MICs was > 10 hours. Therefore, a therapeutic plasma cefquinome concentration can be maintained for 14 to 18 hours if the cefquinome is given once a day at a dosage of 5 mg/kg.

Compared with cefotiofur, one of the third-generation cephalosporins approved for treatment of bacterial infections in poultry by the FDA, cefquinome had similar pharmacokinetic characteristics, such as rapid absorption, but the terminal half-life of cefquinome (1.57 ± 0.06 hours) was shorter than that of cefotiofur in healthy chickens (4.23 ± 0.05 hours).\(^2\) A shorter \(t_{1/2}\) and fast excretion might be major reasons for less use of cefquinome in waterfowl, compared with cefotiofur. In addition, absorption of cefquinome following PO administration via feed or drinking water is poor because of its instability when exposed to moisture. Therefore, it is problematic to administer cefquinome to ducks because PO administration via feed or drinking water is the most convenient route of drug administration in waterfowl. However, because of its excellent antibacterial effect, cefquinome might still be used in the treatment of bacterial infections in individual valuable waterfowl. Additional studies are needed to ascertain the actual blood concentrations of cefquinome associated with effectiveness against specific pathogens in waterfowl.

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