Pharmacokinetics of ceftiofur sodium in exotic and domestic avian species

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The pharmacokinetics of ceftiofur sodium were determined in domestic chicks, turkey poults, adult cockatiels (*Nymphicus hollandicus*), and adult orange-winged Amazon parrots (*Amazona amazonica*) after subcutaneous (chicks and turkey poults) and intramuscular (i.m.) dosing (cockatiels and Amazon parrots). Turkey poult data were best fit to a single exponential model with disappearance half-lives ($t_{1/2}$) of 8.6, 7.4 and 5.6 h after doses of 0.12, 0.24 and 0.48 mg ceftiofur free acid equivalents (CFAE)/poult, respectively. Data from chicks were best fit to a biexponential model with primary and secondary half-lives of 2.2 and 7.5, 3.7 and 6.8, and 3.8 and 5.3 h after doses of 0.04, 0.08 and 0.16 mg CFAE/chick, respectively. Cockatiel and Amazon parrot data were best fit to a biexponential model with primary and secondary half-lives of 0.28 and 2.5, and 0.93 and 7.9 h, respectively, after doses of 10 mg CFAE/kg body weight. The maximum concentration (C_{max}) and area under the concentration time curve (AUC) in chicks and poults were dose-proportional. The C_{max} for cockatiels was 5.2 µg/mL and for Amazon parrots was 11 µg/mL. Clearance in cockatiels and Amazon parrots were 11.3 and 3.8 mL/min/kg, respectively, and reflected the much greater AUC seen in Amazon parrots. Clearance values of ceftiofur were similar in chicks and Amazon parrots, slightly greater in turkey poults and greatest in cockatiels. These results indicate that pharmacokinetic differences must be considered when establishing dosage regimens for different avian species.

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INTRODUCTION

Gram positive, gram negative and anaerobic bacteria are potential microbial pathogens of birds (Gerlach, 1994). Several studies have been published regarding the use of aminoglycosides (Gronwall *et al.*, 1989; Flammer *et al.*, 1990c; Ramsay & Vulliet, 1993; Itoh *et al.*, 1996; Kollias *et al.*, 1996), penicillins (Ensley & Janssen, 1981; Kaukas *et al.*, 1987; Jacobs-Reitsma *et al.*, 1994), chloramphenicol (Clark *et al.*, 1982), fluoroquinolones (Flammer *et al.*, 1990a, 1991; Raemdonck *et al.*, 1992; Ortiz*et al.*, 1995), and tetracyclines (Williams, 1985; Flammer *et al.*, 1989, 1990b; Prus *et al.*, 1992; Moreno *et al.*, 1996) to treat bacterial infections in psittacine and domestic avian species; however, there is a paucity in the literature regarding the use of cephalosporins. Ceftiofur, a third generation, semi synthetic cephalosporin has excellent bactericidal efficacy against a variety of gram positive, gram negative and anaerobic pathogens, including many species of *Pasteurella spp., Streptococcus spp., Staphylococcus spp., Salmonella spp.,* and *Escherichia coli* (Brown *et al.*, 1991b). In mammals, ceftiofur has been shown to have a relatively long half-life (horse 3.2 h, Jaglan *et al.*, 1994; sheep 6.2 h, Craigmill *et al.*, 1997; cattle 6.6 h, Soback *et al.*, 1991; goat 3.7 h, Courtin *et al.*, 1997; dog 3.9 h, Brown *et al.*, 1995)

which offers the advantage of once daily drug administration. Ceftiofur sodium is approved for use in the United States in cattle, pigs, horses, dogs and poultry (Crosier *et al.*, 1996).

Despite the availability of pharmacokinetic data for various antibiotics, the majority of the avian investigations have utilized only one model species and the representative animals were always of one body size and age. The pharmacokinetics of ceftiofur in various mammalian species have been reviewed by Brown *et al.* (1991a). To date, limited work has been published regarding the use of ceftiofur in domestic avian species (Schriemer *et al.*, 1992; Watts *et al.*, 1993; Devriese *et al.*, 1995) and there are no reports regarding the use of this drug in psittacines. The objective of this paper is to describe and compare the pharmacokinetics of ceftiofur sodium in exotic and domestic avian species (small and medium sized psittacines and chicken and turkey poults).

MATERIALS AND METHODS

Animals

Sixty adult (30 females, 30 males) cockatiels (*Nymphicus hollandicus*) were obtained from the University of California,

Davis Avian Sciences cockatiel colony. The average age of the birds was 1.1 years ($\pm$ 0.3 SD) with a range of 1–2 years and the average body weight was 91.3 g ($\pm$ 8.1 SD) with a range of 75.0–111.2 g. All birds were in good health which was determined by physical examination and body weight. The birds were maintained according to university approved animal care and use guidelines and were provided a pelleted diet (Roudybush maintenance crumbles, Sacramento, CA) and water *ad libitum*.

Twenty-seven (11 females, 14 males, and 2 birds of unknown gender) orange-winged Amazon parrots (*Amazona amazonica*) from the University of California, Davis Avian Sciences Amazon parrot colony were used for this study. The average bird age was 3.7 years ($\pm$ 1.4 SD) with a range of 2–6 years and the average body weight was 393 g ($\pm$ 31.7 SD) with a range of 328–455 g. All birds were in good health based on physical examination and normal complete blood counts and blood chemistries which had been run within the past 6 months. The birds were maintained according to university approved animal care and use guidelines and were provided with a continuous source of pelleted diet (Roudybush maintenance pellets) and water *ad libitum*.

Four-hundred and eighty Vantress/Cross chicks (240 females, 240 males), 30–40 g of body weight were purchased from a commercial hatchery (Zeeland Hatchery, Zeeland, MI). Upon arrival the birds were 24–36 h of age, whereas at the time of dosing they were between 48 and 60 h old. The birds were checked for appearance and vigour, wing banded and placed (five birds to a cage) in a standard heated commercial brooder. Water and diet (chicken starter P-607, Upjohn Feed Mill, Kalamazoo, MI) was provided *ad libitum*.

Four-hundred and thirty-two Kent Broad-Breasted White turkey poults (216 females, 216 males) between 42 and 83 g of body weight were purchased from a commercial hatchery (Zeeland Hatchery). Upon arrival the birds were 24–36 h of age, whereas at the time of dosing they were between 48 and 60 h old. The poults were checked for appearance and vigour, wing banded and placed three birds to a cage in a standard heated commercial brooder. Water and diet (chicken starter P-607, Upjohn Feed Mill) were provided *ad libitum*.

Drug

Ceftiofur sodium (Naxcel®, Pharmacia-Upjohn, Kalamazoo, MI) sterile powder was reconstituted with sterile water for injection USP immediately prior to injection. The ceftiofur sodium was reconstituted to 50 mg/mL and 25 mg/mL CFAE for the Amazon parrot and cockatiel injections, respectively. The differing concentrations were made so that a comparable and reasonable volume of drug could be administered with confidence. For the chicks and turkey poults, the dose solutions were prepared just prior to injection by dissolving purified ^{14}C-ceftiofur sodium (28.8 mg CFAE) in 12 mL of water for injection giving a stock solution of 2.4 mg ^{14}C-CFAE per mL. For the chicks, a 10 mL aliquot of the 2.4 ^{14}C-CFAE mg/mL stock solution was diluted to 30 mL with sterile water to give an 0.8 mg/mL solution, a 15 mL aliquot of the 0.8 mg/mL solution was diluted to 30 mL with sterile water to give a 0.4 mg/mL solution, and 15 mL of the

0.4 mg/mL solution was diluted to 30 mL with sterile water to give a 0.2 mg/mL solution. For the turkey poults, aliquots of the 2.4 ^{14}C-CFAE mg/mL stock solution were utilized in a similar fashion to create 1.20 mg and 0.60 mg ^{14}C-CFAE mg/mL dose solutions. To insure homogeneity, all dose solutions were prepared fresh on the day of administration and were filtered through a 0.2 μm sterile filter. The residual dosing solutions for the chicks and turkey poults were assayed to confirm that the administered drug dilutions were within the expected concentrations.

Drug treatment/subject sampling

Amazon Parrots and Cockatiels

All birds were weighed the day prior to drug administration. The administered dose of ceftiofur sodium was based on a 10 mg CFAE/kg body weight dosage. The average doses of ceftiofur sodium administered were 0.91 mg ($\pm$ 0.08 SD, 0.75–1.11 mg range) and 3.93 mg ($\pm$ 0.32 SD, 3.28–4.55 mg range) for the cockatiels and Amazon parrots, respectively. The ceftiofur was injected into the birds' pectoral musculature following application of negative pressure to ensure that the drug was not being administered directly into a blood vessel. The injections were performed using insulin syringes (unit-100; 0.3 mL) with integral 27 gauge 9 mm needles (Monoject, Sherwood Medical, St. Louis, MO) to ensure accurate and consistent delivery of small drug volumes.

The birds were randomly divided into groups based on bleeding times. Six cockatiels were bled at 0, 8 and 12 h post-antibiotic injection, whereas 10 cockatiels were bled at 0.5, 1, 2 and 4 h post-injection. A total volume of 1.0 mL of blood was drawn from each cockatiel and each bird was bled only once. The cockatiels were bled from the right jugular vein with a 1.0 mL tuberculin syringe with a 26 gauge 9 mm needle. Nine of the Amazon parrots were bled at 0 and 8 h post-ceftiofur administration, eight of the Amazon parrots were bled at 12 and 24 h post-ceftiofur administration, and 18 Amazon parrots were bled at 0.5, 1, 2, and 4 h post injection. A volume of 1.0 mL of blood was drawn from each bird at each bleeding time and the total blood volume sampled per Amazon parrot was 4.0 mL. The birds were bled from the right and left medial metatarsal veins and the right jugular vein utilizing a 1.0 mL tuberculin syringe with a 26 gauge 9 mm needle or a 3.0 mL syringe with a 25 gauge 16 mm needle. Blood samples were directly deposited into microtainer tubes containing lithium heparin (Sarstedt Inc., Newton, NC) and allowed to sit for no longer than 15 min before being centrifuged. Separation of the red blood cells from the plasma was achieved by centrifugation at $3000 \times \boldsymbol{g}$ for 10 min. The plasma was separated from the red blood cell pellet, distributed into cryogenic storage vials, and stored at $-80°C$ until assayed.

Chicks

A complete series of sample collections for pharmacokinetic analysis was performed four times over 4 weeks using 120 birds

each week. All birds were weighed on the day of drug administration and randomly assigned to one of three treatment groups. Each bird was manually restrained and injected subcutaneously in the neck with a single 0.2 mL aliquot of either a 0.2, 0.4 or 0.8 mg CFAE/mL dosing solution. The drug was administered utilizing a 1.0 mL syringe fitted with a 26 gauge × 13 mm needle. Five chicks from each cage were killed at 0.05, 0.1, 0.2, 0.5, 1, 2 4 and 8 h post-treatment according to a randomized schedule. All birds were killed by decapitation according to animal care and use guidelines. Blood samples were collected into heparinized containers as composite samples (five birds within each cage) and processed into plasma within 2 h after collection (ceftiofur and metabolites are stable in plasma and serum for several hours following collection of samples). The plasma was immediately frozen in a dry ice/alcohol bath and stored at −20°C until assayed by HPLC.

Turkey poults

A complete series of sample collections for pharmacokinetic analysis was performed six times over 6 weeks using 72 birds each week. All birds were weighed on the day of drug administration and randomly assigned to one of three treatment groups. Each bird was manually restrained and injected subcutaneously in the neck with a single 0.2 mL aliquot of either a 0.12, 0.24 or 0.48 mg CFAE/mL dosing solution. The drug was administered utilizing a 1.0 mL syringe fitted with a 22 gauge × 13 mm needle. Three turkey poults from each cage were killed at 0.1, 0.2, 0.5, 1, 2, 4, 8 and 12 h post-treatment according to a randomized schedule. All birds were killed by decapitation according to animal care and use guidelines. Blood samples were collected into heparinized containers as composite samples (three turkey poults within each cage) and were processed as described previously for the chicks.

High Performance Liquid Chromatography

Amazon Parrots and Cockatiels

Ceftiofur, desfuroylceftiofur and desfuroylceftiofur conjugates all have microbiological activity, and are easily converted to desfuroylceftiofur for analysis (Salmon *et al.*, 1996). Plasma samples were analysed for ceftiofur and desfuroylceftiofur related metabolites using a modification of the method published by Jaglan *et al.* (1990). Briefly, the method uses dithioerythritol to cleave any macromolecule bound desfuroylceftiofur also dimer, glutathione and cysteine conjugates in the serum. The sample is then run through a C18 solid phase extraction (SPE) column and further derivatized with iodoacetamide to create desfuroylceftiofur acetamide. After elution from the C18 SPE, further cleanup is done on a SCX SPE. The HPLC analysis was done isocratically (the mobile phase was 7% acetonitrile, 1% acetic acid, with 90 mg heptane sulfonic acid/litre and pH = 4.0) on a Nova-pak C18, 4 μm, 3.9 × 150 mm (Waters Corporation, Milford, MA) with ultraviolet detection at 240 nm. The limit of quantification of the assay was 0.1 μg CFAE/mL of serum. All

results below the limit of quantification were not used in the calculations or pharmacokinetic modelling.

Chick/turkey poult samples

The plasma samples were processed as described above, according to the method published by Jaglan *et al.* (1990) with modifications to account for radioactivity detection.

Pharmacokinetic analysis

Amazon Parrots and Cockatiels

The data for each time point were utilized for the pharmacokinetic analysis according to the 'naive pooled data approach' (Martin *et al.*, 1984) which provides average parameter estimates for the data. Pharmacokinetic data including area under the concentration time curve (*AUC*), mean residence time (*MRT*), maximum concentration (*C*$_{max}$), and appropriate half-lives (*t*$_{1/2}$) were calculated from the mean plasma concentrations using the commercial software program, PK Analyst (Micromath, Salt Lake City, UT). Single intramuscular (i.m.) dose data were model led using the following pharmacokinetic equation:

$$C_p = \left[\sum_{i=1}^{z} C_i \exp(-\lambda_i t) \right] - \left(\sum_{i=1}^{z} C_i \right) \exp(-k_a t)$$

where C_i is the intercept and λ_i is the slope of the z terms in the equation, t is time, and k_a is the rate constant of absorption. The pharmacokinetic equation was fitted to the data using a weighing factor of $1/\text{concentration}^2$ unless otherwise noted.

Chicks and turkey poults

The data obtained from each pharmacokinetic run were analysed using the SAS NLIN procedure (SAS/STAT Version 6, SAS Institute, Cary, NC), and trapezoidal integration to calculate the *AUC* and *MRT* parameters. The half-lives were calculated from the calculated rate constants without weighting of the data.

Statistical analysis

For the chicks and turkey poults, the individual pharmacokinetic parameters calculated from the replicate trials were summarized as mean $\pm$ standard deviation. An analysis of variance was done on the half-lives, *MRT*s and time of observed maximum plasma concentration (*t*$_{max}$) parameters for each dose for each species to determine if there were any dose-related differences.

RESULTS

All animals in the study were normal following treatment and no adverse effects were observed in any of the birds after drug administration. The mean plasma concentrations of ceftiofur and metabolites (CAM) measured as ceftiofur free acid equivalents in

plasma in cockatiels and Amazon parrots, chicks, and turkey poults are shown in Tables 1, 2, and 3, respectively. These data are also presented graphically in Fig. 1a–d for visual comparison.

Following intramuscular administration, ceftiofur and metabolites rapidly appeared in the plasma of cockatiels by 30 min post treatment (5.25 ± 1.03 µg CFAE/mL) and declined to 0.09 ± 0.19 µg CFAE/mL by 12 h post drug administration (Fig. 1a). In the orange-winged Amazon parrots, ceftiofur and metabolites were also evident by 30 min post intramuscular drug administration (10.99 ± 2.13 µg CFAE/mL) and declined to 0.27 ± 0.13 µg CFAE/mL by 24 h post-treatment (Fig. 1b).

Following subcutaneous administration, ceftiofur and metabolites rapidly appear in the plasma of chicks and turkey poults. While the t_{max} values within each dose range for and between the species are highly variable, they are all close to 1 h post

Table 1. Mean plasma concentrations $\pm$ standard deviations of ceftiofur free acid equivalents (µg/mL) per sampling time for cockatiels and orange-winged Amazon parrots

Sampling time (h)	Cockatiels	Amazon Parrots
0.5	5.25 ± 1.03 ($n = 10$)	10.99 ± 2.13 ($n = 18$)
1	3.07 ± 0.81 ($n = 10$)	8.92 ± 2.11 ($n = 18$)
2	1.82 ± 0.67 ($n = 10$)	5.19 ± 1.29 ($n = 18$)
4	1.03 ± 0.38 ($n = 10$)	2.32 ± 0.83 ($n = 18$)
8	0.31 ± 0.11 ($n = 6$)	1.92 ± 0.52 ($n = 9$)
12	0.09 ± 0.19 ($n = 6$)	0.75 ± 0.25 ($n = 8$)
24	——	0.27 ± 0.13 ($n = 8$)

Table 2. Mean plasma concentrations $\pm$ standard deviations of ceftiofur free acid equivalents (µg/mL) per sampling time for three dosages (mg/chick) for chicks. Each mean and standard deviation was derived from 4 samples and each sample represents pooled blood from 5 chicks

Sampling Time (h)	0.04 mg/chick	0.08 mg/chick	0.16 mg/chick
0.05	0.64 ± 0.34	1.17 ± 0.23	2.56 ± 0.60
0.1	0.47 ± 0.11	0.78 ± 0.39	1.66 ± 0.65
0.2	0.38 ± 0.26	0.98 ± 0.34	1.54 ± 1.11
0.5	0.53 ± 0.05	1.15 ± 0.51	2.16 ± 0.82
1	0.64 ± 0.31	1.09 ± 0.75	2.47 ± 0.76
2	0.57 ± 0.25	0.95 ± 0.33	2.05 ± 0.28
4	0.33 ± 0.16	0.78 ± 0.32	1.49 ± 0.42
8	0.30 ± 0.30	0.42 ± 0.23	0.58 ± 0.46

Table 3. Mean plasma concentrations $\pm$ standard deviations of ceftiofur free acid equivalents (µg/mL) per sampling time for three dosages (mg/poult) for turkey poults. Each mean and standard deviation was derived from 6 samples and each sample represents pooled blood from 3 poults

Sampling Time (h)	0.12 mg/poult	0.24 mg/poult	0.48 mg/poult
0.1	1.72 ± 0.84	2.77 ± 1.46	8.00 ± 2.94
0.2	1.85 ± 0.59	3.62 ± 1.70	6.24 ± 2.78
0.5	1.43 ± 0.39	3.88 ± 0.84	6.02 ± 1.87
1.0	1.70 ± 0.70	2.91 ± 0.85	6.86 ± 2.14
2.0	1.91 ± 0.69	2.92 ± 1.07	5.56 ± 2.13
4.0	1.09 ± 0.36	2.01 ± 0.57	3.53 ± 1.93
8.0	1.09 ± 0.54	1.51 ± 0.59	3.03 ± 2.22
12.0	0.68 ± 0.47	0.99 ± 0.62	1.54 ± 0.60

dosing. The C_{max} are dose proportional within each dose range for both species, and the C_{max} (2.10 ± 0.73 µg/mL) for the lowest turkey poult dose (0.12 mg/poult) lies between the C_{max} values for the 0.08 and 0.16 mg/chick doses.

The pharmacokinetic parameters calculated from the plasma data are shown in Table 4. The secondary half-lives measured in chicks and turkey poults are similar at each dose tested, and the AUC values within each species are dose-proportional. The secondary phase half-life in Amazon parrots (7.9 h) is similar to that seen in chicks (5.3–7.5 h) and turkey poults (5.6–8.6 h). The secondary phase half-life in cockatiels (2.5 h) is less than one-half that measured for the other birds. The total body clearance range calculated from the mean AUC at each dose suggests a slower clearance from turkey poults (1.6–4.4 mL/kg/min)
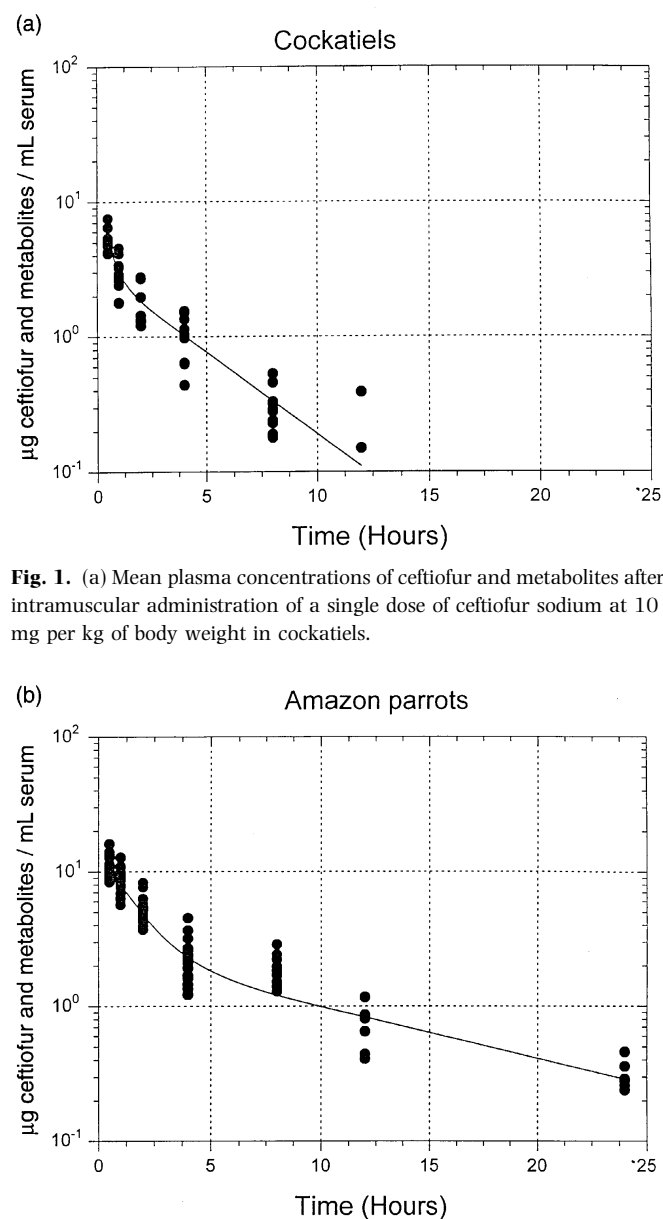
(a)

Fig. 1. (a) Mean plasma concentrations of ceftiofur and metabolites after intramuscular administration of a single dose of ceftiofur sodium at 10 mg per kg of body weight in cockatiels.

(b)

Fig. 1. (b) Mean plasma concentrations of ceftiofur and metabolites after intramuscular administration of a single dose of ceftiofur sodium at 10 mg per kg of body weight in orange-winged Amazon parrots.
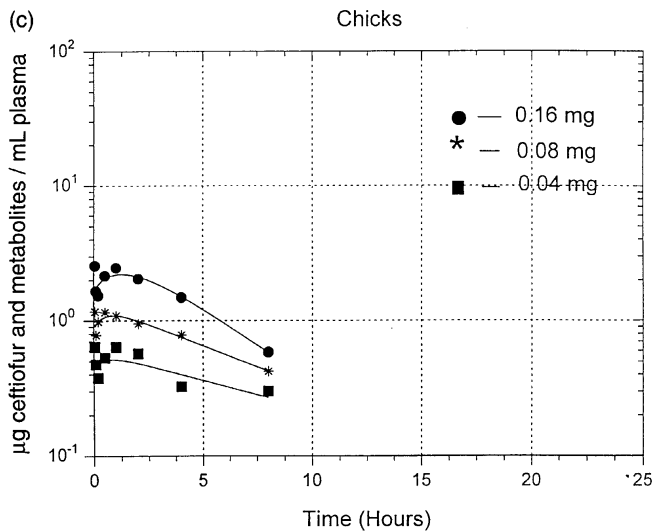
(c)

Chicks

Fig. 1. (c) Mean plasma concentrations of ceftiofur and metabolites after subcutaneous administrations of single dose of ceftiofur sodium at 0.04, 0.08 and 0.12 mg/chick.
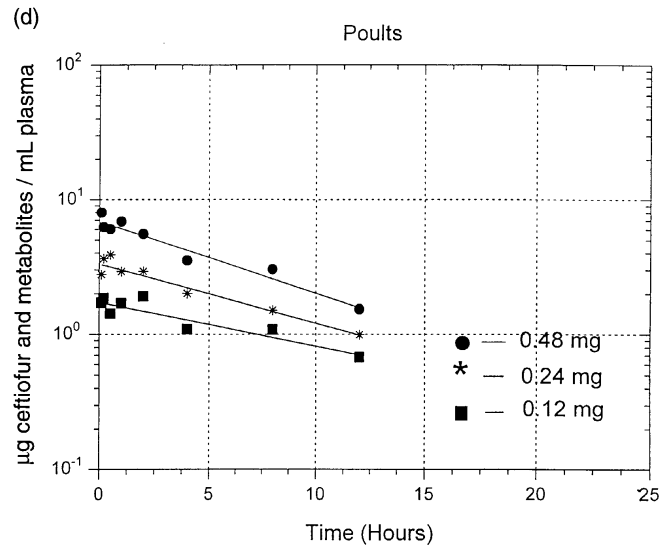
(d)

Poults

Fig. 1. (d) Mean plasma concentrations of ceftiofur and metabolites after subcutaneous administrations of single dose of ceftiofur sodium at 0.12, 0.24 and 0.48 mg/turkey poult.

Table 4. Mean pharmacokinetic values obtained from plasma concentrations of ceftiofur and metabolites after administration of a single dose of ceftiofur sodium in cockatiels, orange-winged Amazon parrots, chicks and turkey poults

Species/Dosage/Drug Administration Route	$t_{1/2a}$ Hours	$t_{1/2b}$ Hours	C_{max} µg/mL	t_{max} Hours	AUC µg·hr/mL	Clearance mL/kg/min	MRT Hours
Cockatiels: 10mg/kg i.m.	0.28	2.5	5.25	—	14.7	11.3	2.8
Amazon Parrots: 10 mg/kg i.m.	0.93	7.9	10.99	—	43.8	3.8	7.6
Chicks: 0.04 mg/poult s.c. (1–1.3 mg/kg)	2.20 ± 0.71	7.50 ± 0.28	0.86 ± 0.25	1.17 ± 0.76	3.40 ± 1.03	5–6.4	2.59 ± 0.24
Chicks: 0.08 mg/poult s.c. (2–2.6 mg/kg)	3.70 ± 1.51	6.77 ± 3.74	1.67 ± 0.12	0.83 ± 0.29	8.66 ± 4.45	3.8–5	2.93 ± 0.58
Chicks: 0.16 mg/poult s.c. (4–5.3 mg/kg)	3.80 ± 1.47	5.33 ± 4.21	2.74 ± 0.71	0.83 ± 0.29	14.81 ± 3.75	4.5–6	2.52 ± 0.73
Turkey Poults: 0.12 mg/poult s.c. (1.4–2.9 mg/kg)	—	8.65 ± 6.40	2.10 ± 0.73	2.67 ± 2.66	14.23 ± 4.46	1.6–3.4	4.91 ± 0.63
Turkey Poults: 0.24 mg/poult s.c. (2.8–5.8 mg/kg)	—	7.45 ± 4.60	4.36 ± 1.28	0.40 ± 0.15	23.15 ± 4.63	2–4.2	4.68 ± 0.31
Turkey Poults: 0.48 mg/poult s.c. (5.9–11.6 mg/kg)	—	5.58 ± 4.30	8.96 ± 2.08	0.48 ± 0.43	43.72 ± 15.59	2.2–4.4	4.49 ± 0.76

than from chicks (3.8–6.4 mL/kg/min). The clearance in orange-winged Amazon parrots (3.8 mL/kg/min) is similar to that seen in the chicks, while the clearance in cockatiels (11.3 mL/kg/min) is substantially greater. The half-lives, *MRTs* and t_{max} parameters calculated for each of the three doses for the chicks and poults did not differ significantly within each species.

DISCUSSION

Cephalosporins offer the advantages of low toxicity and a broad antimicrobial spectrum (Caprile, 1988). Ceftiofur, a new generation cephalosporin, is favoured due to less frequent administration when compared to other cephalosporins, its wide range of antimicrobial therapy, and its long storage stability after reconstitution (7 days when refrigerated, and frozen reconstituted solutions are stable for up to 8 weeks; Plumb, 1995).

The pharmacokinetics of beta-lactam antibiotics (cephalosporins) have been briefly described in a few avian species (Bush *et al.*, 1981; Junge *et al.*, 1994). In comparison, the half-lives of ceftiofur determined in the present study were longer than the half-lives of other cephalosporins reported for birds (Bush *et al.*, 1981; Junge *et al.*, 1994). An exception to this was in the cockatiel, which when injected intramuscularly with ceftiofur, exhibited a relatively short half-life of 2.3 h, which is consistent with the higher clearance seen in cockatiels compared to the other birds (Amazon parrots, chicks and turkey poults). This shorter half-life of ceftiofur in the cockatiels appeared to be relative to their small body size (cockatiels vs. Amazon parrots) and was consistent with work done by Bush *et al.* (1981) in which the biological half-life of cephalothin sodium (100 mg/kg, single intramuscular injection) varied depending on the species (quail, pigeons, cranes, emus) and body weight of the subjects which were being studied. In Bush's study (1981), the smaller species (quail

and pigeons) had a shorter biological half-life (16–41 min with continued measurable plasma concentrations for 2.5 h after the drug was injected), whereas the larger avian species (emus, cranes) had a longer biological half-life (54 min and measurable plasma values 5.5 h after injection). In our study, this trend was observed between the smaller (cockatiel) and larger (orange-winged Amazon parrot) psittacines, however, it was not demonstrated between the small domestic birds (chicks and turkey poults) and the larger parrot (orange-winged Amazon parrot). The ceftiofur half-lives and clearances of the chicks and turkey poults were very similar to the Amazon parrots despite differences in dosage, route of drug administration, age and body size. Therefore, these data support the concept that antibiotic pharmacokinetics in avian species differ (Dorrestein & Van Miert, 1988), and dosages for exotic avian species cannot be directly extrapolated from those of domestics.

Compared to mammals, in order to achieve comparable peak plasma concentrations, the ceftiofur dosages for birds in our study were substantially higher. Peak plasma concentrations of CFAE were achieved at the first sampling period (30 min post intramuscular injection) in both the cockatiels and Amazon parrots. These data are similar to those for other psittacine species of equivalent sizes to the cockatiels and Amazon parrots, in which the peak serum concentrations of intramuscularly injected antibiotics were at the 0.5 or 1 h sampling time (Flammer *et al.*, 1990c, 1991; Prus *et al.*, 1992). Reported MIC_{90}'s for ceftiofur for bacterial isolates from ducks with septicaemia and airsacculitis include *Escherichia coli* (1.0 μg/mL), *Salmonella spp.* (1.0 μg/mL), *Proteus mirabilis* (0.5 μg/mL), *Staphylococcus aureus* (2.0 μg/mL), and *S. intermedius* (1.0 μg/mL). MIC's for ceftiofur against *Ornithobacterium rhinotracheale* strains which were isolated from poultry and wild bird populations ranged from $\leqslant 0.12$–4.0 μg/mL (Devriese *et al.*, 1995). In this study, intramuscular ceftiofur administration at 10 mg CFAE/kg in cockatiels and Amazon parrots exceeded 1.0 μg/mL for more than 4 h in cockatiels and 8 h in Amazon Parrots. In comparison, the 0.16 mg CFAE/chick and all of the turkey poult subcutaneously administered dosages exceeded 1.0 μg/mL for more than 4 h.

In this study, the 'naive pooled data approach' was utilized for calculating the average parameters for the psittacines. This approach is a simple and useful method for obtaining average parameter estimates when data from individuals is insufficient to calculate individual parameter estimates (sparse data). When utilizing this method of data analysis, caution must be observed, however, as the method cannot differentiate intra-individual, inter-individual or residual variances because individual parameter estimates are not calculated. In addition, the average curves calculated from the derived parameters may not always follow the typical individual model function (Martin *et al.*, 1984).

This study demonstrates a major interspecies difference in ceftiofur pharmacokinetics between avian patients, and that the effective doses for ceftiofur in avian species are higher than those for mammals. There is a paucity of MIC data for ceftiofur and bacteria isolated from parrots or domestic chicks/turkey poults, therefore obtaining cultures and sensitivities for determining the optimal antibiotic treatment regime is of utmost importance. Based on this study, for cockatiels, a ceftiofur dosage of 10 mg CFAE/kg i.m. every 4 h should provide effective plasma concentrations to inhibit bacteria with MIC_{90}'s > 1.0 μg/mL. The data also indicate that higher dosages may be necessary for cockatiels with resistant bacterial infections. In contrast, a dosage of 10 mg CFAE/kg every 8–12 h should maintain effective plasma concentrations in orange-winged Amazon parrots with bacterial infections in which MIC_{90}'s are > 1.0 μg/mL. In the case of chicks and poults, ceftiofur sodium is approved by the Federal Drug Administration for use in 1-day-old chicks and turkey poults for the treatment of early mortality associated with *E. coli* organisms susceptible to ceftiofur. The recommended label doses are 0.08–0.20 mg/chick and 0.17–0.5 mg/poult. This study indicates that similar dosing regimes (0.16 mg CFAE/chick and 0.24 mg CFAE/turkey poult administered every 24 h) would be reasonable starting doses for treatment of other bacterial infections of moderate susceptibility.

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