Pharmacokinetics after intravenous administration of flunixin meglumine in budgerigars (*Melopsittacus undulatus*) and Patagonian conures (*Cyanoliseus patagonus*)

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Objective—To investigate the disposition kinetics of flunixin meglumine when administered IV to budgerigars (*Melopsittacus undulatus*) and Patagonian conures (*Cyanoliseus patagonus*).

Design—Prospective cohort study.

Animals—8 adult Patagonian conures and 24 adult budgerigars.

Procedures—Injectable flunixin meglumine (50 mg/mL) was diluted to 10 and 1.0 mg/mL and administered IV at a dose of 5.0 mg/kg (2.3 mg/lb) to Patagonian conures and budgerigars, respectively.

Results—In budgerigars, the elimination half-life was 0.72 hours and the mean residence time was 0.73 hours. In Patagonian conures, the elimination half-life was 0.91 hours and the mean residence time was 1.20 hours. The concentration of flunixin was below the assay's limit of quantification (0.5 μg/mL) at 3 and 6 hours in budgerigars and Patagonian conures, respectively. A single budgerigar developed adverse effects (lethargy and signs of depression) for approximately 15 minutes following drug administration.

Conclusions and Clinical Relevance—The half-life of flunixin in Patagonian conures and budgerigars was short following IV administration; however, results of this study suggested that IV administration of injectable flunixin meglumine at 5.0 mg/kg resulted in plasma concentrations that could potentially be anti-inflammatory and analgesic in budgerigars and Patagonian conures. (*J Am Vet Med Assoc* 2013;242:205–208)

Analgesic drugs, along with proper care and management, can be used to alleviate signs of pain in birds, just like in mammals.[1] Few drugs are approved for use in birds in the United States, but under AMDUCA, veterinarians can administer NSAIDs in pet birds for pain alleviation and to decrease inflammation.[2] However, choosing an appropriate NSAID and dose is problematic because there is limited research into the pharmacokinetics and pharmacodynamics in birds other than chickens. Meloxicam and carprofen effectively relieve induced arthritic pain in Hispaniolan parrots (*Amazona ventralis*),[3,4] but only the pharmacokinetics of meloxicam have been reported in pigeons, ducks, turkeys, ostriches, and chickens.[5] In mallard ducks, ketoprofen suppresses thromboxane B_2 concentrations and reduces heart and respiratory rate increases due to noxious stimulus,[6,7] but data on pharmacokinetics of ketoprofen could only be found in Japanese quail (*Coturnix japonica*).[8]

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Abbreviation

HPLC	High-performance liquid chromatography

Flunixin meglumine is effective in reducing a model of arthritic pain in chickens when administered IM at doses between 3.0 and 12.0 mg/kg (1.4 and 5.5 mg/lb),[9] and a dose of 5 mg/kg (2.3 mg/lb) suppresses plasma thromboxane B_2 activity, a surrogate indicator of pain, in mallard ducks.[6] This suggests that flunixin meglumine may be an effective therapeutic agent for the treatment of signs of pain in pet birds. Pharmacokinetic studies of flunixin have been done in ducks, turkeys, pigeons, ostriches, and chickens[5,10–13]; however, to our knowledge, there are no pharmacokinetic and pharmacodynamic studies in pet birds. The scarcity of NSAID pharmacokinetic and pharmacodynamic data compels practitioners to extrapolate doses from poultry and mammal data and to rely on previous clinical experience. Extrapolation of doses for use in birds from pharmacokinetic data in mammals can be problematic.[14,15] Furthermore, extrapolation from different bird species can be fraught with problems because of the large variability in NSAID pharmacokinetic data for different avian species[5] and the dissimilarity in effectiveness and comparative toxicity of NSAIDs among avian species, possibly influenced by sex and seasonal physiology.[16,17] Additionally, some birds have been shown to be exquisitely sensitive to even low concentrations of NSAIDs, resulting in renal failure and death.[18]

Thus, more pharmacokinetic studies are needed in pet birds. The purpose of the study reported here was to determine the disposition kinetics of flunixin following IV administration of flunixin meglumine to budgerigars and Patagonian conures.

Materials and Methods

Animals—Eight adult Patagonian conures (*Cyanoliseus patagonus*), ranging in weight from 252 to 288 g (0.554 to 0.634 lb; mean, 273 g [0.601 lb]), and 24 adult budgerigars (*Melopsittacus undulatus*), ranging in weight from 32 to 54 g (0.07 to 0.12 lb; mean, 43 g [0.09 lb]), of undetermined sex were used. The birds were assessed as healthy by physical examination and medical history. The Patagonian conures were housed either individually or in pairs in flight cages at the Schubot Exotic Bird Health Center, were fed a commercial diet[a] supplemented with 1/4 cup of fresh fruits and vegetables, and had access to water ad libitum. The budgerigars were housed 8 to 12 birds/cage at the Schubot Exotic Bird Health Center, were fed a mixed-seed diet consisting predominately of millet and canary seed, and had access to a cuttlebone and water ad libitum. An animal use protocol detailing the experimental protocol was reviewed and approved by the Texas A&M University Office of Research Compliance.

Experimental protocol—Commercially available injectable flunixin meglumine[b] at an initial concentration equivalent to 50 mg of flunixin/mL was diluted to a concentration of 10 and 1.0 mg/mL with sterile saline (0.9% NaCl) solution for use in the Patagonian conures and Budgerigars, respectively, just prior to administration. The dilute flunixin meglumine was then administered at a dose of 5.0 mg/kg into the right jugular vein.

For Patagonian conures, blood samples (approx 200 µL/sample) were collected the day prior to drug administration and at 5, 10, and 20 minutes and 1, 1.5, 2, 3, 4, and 6 hours after drug administration. Patagonian conures were randomly assigned to 4 sampling times, then sampling times were manipulated so that an individual bird's collections included at least an early, mid, and later time across the study's time course. Excluding samples collected the day prior, a maximum of 4 samples/bird were taken; a minimum of 3 samples were collected at each time period. Blood samples were collected from the basilic vein with a 26-gauge 3/8-inch needle in a 1-mL tuberculin syringe preconditioned with a lithium heparin solution. After collection, samples were immediately transferred into a silicone-coated collection tube[c] containing 12.5 U of lithium heparin, placed on ice, and transported to the laboratory within 2 hours afterward for processing. The plasma samples were centrifuged (2,200 × *g*) for 10 minutes. The plasma was decanted, placed in labeled cryogenic storage vials, and stored at –80°C until assayed.

In budgerigars, blood samples (approx 200 µL/sample) were collected the day prior to drug administration and at 2, 5, 10, 30, and 45 minutes and 1, 1.5, and 3 hours after drug administration. Excluding samples collected the day prior, budgerigars were randomly assigned to 1 sampling time; 3 birds were sampled at each time period. Blood samples were collected from the right jugular vein with a 27-gauge 1/2-inch needle on a 1-mL tuberculin syringe preconditioned with a lithium heparin solution. After collection, samples were handled and processed similarly to those from the Patagonian conures.

Analytic method for flunixin—Plasma concentrations of flunixin were determined by HPLC[d] via a method described elsewhere.[13] Forty microliters of acetonitrile were added to 40 µL of plasma; 4 µL of phenylbutazone (1.11 µg/mL) were added to each sample as an internal standard. Samples were mixed vigorously for 10 seconds and then centrifuged (1,200 × *g*) for 10 minutes. After centrifugation, 40 µL of the acetonitrile phase was transferred to an autosampler vial that contained 50 µL of water. With an injection volume of 15 µL, HPLC analysis was performed at a flow rate of 1.0 mL/min on a 5-µm C_{18} column[e] with a mobile phase that consisted of 65% acetonitrile and 35% of an aqueous solution containing 0.86% (vol/vol) phosphoric acid, tetrahydrofuran, and triethylamine in HPLC-grade water. The chromatograms were acquired at 240 nm at a retention time of approximately 5.1 minutes. The limit of quantification was 0.5 µg/mL, calculated as 10 times the signal-to-noise ratio. Control samples were prepared at 3, 18, and 50 µg/mL in blank chicken plasma and used to determine mean accuracy and between- and within-day coefficient of variation estimates. Mean accuracy was 1.09%, 1.11%, and 1.08%; within-day coefficient of variation estimates were 2.5%, 2.8% and 1.5%; and between-day coefficient of variation estimates were 7.7%, 2.6%, and 1.5% for the 3, 18, and 50 µg/mL control samples, respectively. Calibration curves, consisting of 0.5, 2, 5, 10, 20, 40, 60, and 80 µg/mL in blank chicken plasma, were generated for every batch assayed and had correlation coefficients ≥ 0.998. The reported measured flunixin concentration was a mean of triplicate runs of a prepared sample.

Pharmacokinetic analysis—Data for plasma concentrations of flunixin were analyzed via a naïve pooled data approach and a commercially available software program.[f] Exponential terms to describe the concentration-time data set were evaluated on the basis of minimizing the sum of least squares. Parameters collected directly from the software were half-life of elimination, elimination rate constant, mean residence time, area under the curve to the last measurable concentration, area under the curve extrapolated to infinity, area under the moment curve extrapolated to infinity, volume of distribution based on area under the curve, clearance, and initial plasma concentration the day prior to drug administration.

Results

Intravenous administration of flunixin meglumine was tolerated well by all Patagonian conures and all but 1 budgerigar; 1 budgerigar became lethargic, with signs of depression, and sat fluffed on the cage floor for approximately 15 minutes following drug administration. Data from this bird were not excluded from analysis. Flunixin was not detected in any sample taken prior to dosing. In Patagonian conures, the concentration of flunixin in all samples taken at 6 hours after administration was below the assay's limit

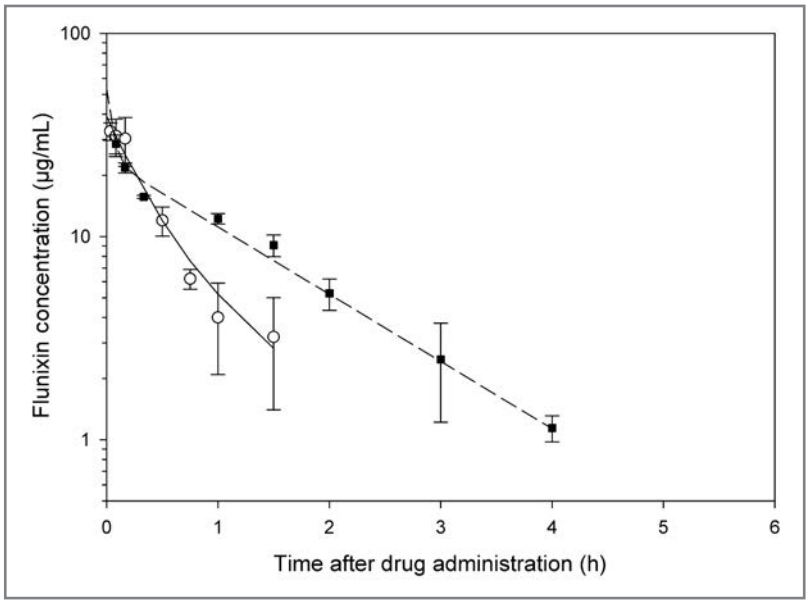

Figure 1—Predicted plasma concentration-time curve and mean ± SD plasma concentrations of flunixin following IV administration of flunixin meglumine at a dose of 5.0 mg/kg (2.3 mg/lb) to Patagonian conures (*Cyanoliseus patagonus*; closed squares with dashed line; n = 8) and budgerigars (*Melopsittacus undulatus*; open circles with solid line; 24).

Table 1—Estimation of pharmacokinetic parameters for flunixin administered IV as flunixin meglumine at 5.0 mg/kg (2.3 mg/lb) to Patagonian conures (*Cyanoliseus patagonus*) and budgerigars (*Melopsittacus undulatus*).

Parameter	Patagonian conures (n = 8)	Budgerigars (n = 24)
$t_{½}\lambda_z$ (h)	0.91	0.72
λ_z (h^{-1})	0.762	0.965
MRT (h)	1.20	0.73
AUC_{0-t} (µg•h/mL)	31.98	19.06
$AUC_{0-\infty}$ (µg•h/mL)	33.23	22.40
AUMC (µg•h•h/mL)	39.88	16.53
Vd_{area} (L/kg)	0.198	0.231
Clearance (L/h/kg)	0.150	0.223
C_0 (µg/mL)	53.2	39.0

AUC_{0-t} = Area under the curve to the last measurable concentration. $AUC_{0-\infty}$ = Area under the curve extrapolated to infinity. AUMC = Area under the moment curve extrapolated to infinity. C_0 = Initial plasma concentration at time zero. λ_z = Elimination rate constant. MRT = Mean residence time. $t_{½}\lambda_z$ = Half-life of elimination. Vd_{area} = Volume of distribution based on area under the curve.

of quantification of 0.5 µg/mL. In the budgerigars, the concentration of flunixin in all samples taken at 3 hours after administration was below the assay's limit of quantification. Plasma concentration-time curves for IV administered flunixin for each bird species were determined (**Figure 1**), as were estimated pharmacokinetic parameters (**Table 1**).

Discussion

In the present study, pharmacokinetic analysis after IV administration of flunixin at a dose of 5.0 mg/kg indicated plasma concentrations that could potentially be anti-inflammatory and analgesic in budgerigars and Patagonian conures. A single budgerigar developed adverse effects (lethargy and signs of depression) for approximately 15 minutes following drug administration.

The half-life of elimination for flunixin in budgerigars (0.718 hours) was shorter than that in Patagonian conures (0.91 hours), and initial plasma concentrations were also less in budgerigars (Table 1). Although these values are appreciably less than the half-life for flunixin in chickens, which ranged from 5.5 to 6 hours,[5,11–13] the half-lives for flunixin in budgerigars and Patagonian conures were longer than in ostriches, ducks, turkeys, or pigeons, which were 0.17, 0.43, 0.54, and 0.62, respectively.[5,10] Area under the curve extrapolated to infinity showed the same trend; those in the budgerigars and Patagonian conures were less than in chickens but greater than in ostriches, ducks, turkeys, or pigeons.[5,10–13] There appears to be little phylogenetic relationship in some of the reported pharmacokinetic parameters, considering that the half-life and mean residence time of the Galliformes and Anseriformes (chickens, turkeys, and ducks) bracket those of the Columbiformes and Psittaciformes (budgerigars, Patagonian conures, and pigeons).

We chose to study pharmacokinetics of flunixin in small (budgerigar) and medium-sized (Patagonian conure) parrots because flunixin meglumine is recommended as an analgesic, antipyretic, and anti-inflammatory in numerous avian taxa, including Psittaciformes, raptors, Anseriformes, Gruiformes, and ratites, with doses ranging from 0.5 to 10 mg/kg (0.23 to 4.5 mg/lb) for differing species of birds.[19,20] A dose of 5 mg/kg was selected for this initial study because it is approximately halfway between the lowest and highest recommended doses and is effective in reducing arthritic pain and suppressing plasma thromboxane B_2 activity in other avian species.[6,9]

In this study, a single budgerigar became lethargic, with signs of depression, and sat fluffed on the cage floor for approximately 15 minutes following flunixin meglumine administration. Changes in the bird's normal physiologic state could have affected the drug's pharmacokinetics. Thus, the inclusion or exclusion of the sample taken from this bird could affect predicted population pharmacokinetic profile. Because the sample's measured flunixin concentration was within 3 SDs of the estimated mean concentration at the time point and thus not an apparent outlier data point, the data were included in the analysis.

Other adverse effects of NSAIDs include regurgitation and tenesmus after oral administration, frank blood in the feces after prolonged use, and most concerning, renal ischemia and tissue damage after IM administration. Muscle necrosis occurs following IM administration of flunixin.[6,21] Histopathologic changes in the kidneys vary with the dose of flunixin meglumine, duration of treatment, and hydration status.[6,21,22] Although the true incidence of NSAID adverse effects in avian species remains unknown, multiple adverse effects of these drugs in both captive and free-living avian species have been reported. Serum biochemical analysis before and after drug administration may have been useful in light of

the reported adverse effects; however, this was not done and may have been of little prognostic usefulness following a single dose of flunixin meglumine. A study[22] that monitored budgerigars for toxicity when flunixin meglumine was administered IM at 5.5 mg/kg (2.5 mg/lb) once daily for 3 or 7 days found that there were no significant changes in plasma uric acid and protein concentrations from those of control birds. Additionally, no changes were noted in the hematologic or serum chemistry parameters of northern bobwhites administered flunixin meglumine at a dosage of 0.1 to 32.0 mg/kg (0.045 to 14.5 mg/lb), IM, daily for 7 days, even though water was withheld from them 24 hours prior to the first dose.[21] These results suggest that flunixin meglumine is a safe drug in birds when used appropriately. This study provides preliminary data for the use of flunixin meglumine in future pharmacokinetic and pharmacodynamic studies and in clinical applications.

a. ZuPreem Parrot & Conure Fruitblend, Premium Nutritional Products Inc, Shawnee, Kan.
b. Banamine, Schering-Plough Animal Health Corp, Union, NJ.
c. Capiject 3T-MLH lithium heparin capillary blood collection tube (latex-free), Terumo Medical Corp, Somerset, NJ.
d. Model 1090-L-series II diode array detector, Hewlett-Packard Analytical, Wilmington, Del.
e. Econosphere, Alltech Association, Deerfield, Ill.
f. PK Solutions 2.0, Summit Research Services, Montrose, Colo.

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