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Original Study

Pharmacokinetics of a Single Oral Dose of Robenacoxib in Hispaniolan Parrots (*Amazona ventralis*)

Hailey B. Penticoff, Thomas N. Tully, Dharmikkumar Vora, and Levent Dirikolu

Abstract: Robenacoxib is a coxib class nonsteroidal anti-inflammatory drug, and its mechanism of action involves selectively inhibiting cyclooxygenase (COX)-2 to reduce inflammation via the reduction of prostaglandin synthesis in dogs, cats, and rats. It is currently labeled for use in dogs and cats to control postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy, and castration for a maximum of 3 days. Robenacoxib has been used anecdotally in avian species at doses ranging from 2–10 mg/kg every 3–7 days to manage pain associated with inflammation in various scenarios, including treatment of proventricular dilatation disease, orthopedic pain, such as arthritis and pododermatitis, and post nail and beak trims. Robenacoxib concentrates in inflamed tissues, and its clinical effects persist longer than its short terminal half-life in blood. In this study, the pharmacokinetic parameters of a single oral dose of robenacoxib were evaluated in a group of 7 healthy, adult Hispaniolan Amazon parrots (*Amazona ventralis*). The results indicated that a single 4-mg/kg oral dose of robenacoxib was well tolerated without any adverse clinical effects. The mean peak plasma concentration was reached at 0.45 hours, with a peak concentration of 88.75 ng/mL. The $t_{1/2}$ was 1.3 ± 0.37 hours. The mean total body clearance per fraction of dose absorbed was 24.9 L/kg/hr. Robenacoxib was not detected in any bird 6 hours postadministration. Further pharmacodynamic studies of this drug, including defining the potency of robenacoxib against avian COX-1 and COX-2 enzymes, would provide stronger support for dose determination and the effectiveness of robenacoxib in psittacine birds.

Key words: Hispaniolan parrots, *Amazona ventralis*, robenacoxib, avian, pharmacokinetics, NSAID

INTRODUCTION

Avian patients, especially psittacine birds, are prone to stress both in and outside of the clinical setting. Stressors from their environment, illness, or other parameters are important factors to consider when managing these species to ensure patient comfort and accuracy in complete blood counts and chemistry panels.[1,2] Therefore, reducing stress is vital to treating the avian patient. Stress reduction is addressed in many ways, including reducing pain, minimizing handling, and providing an appropriate environment for the patient.[2] Selecting an analgesic plan that is appropriate for the planned procedure is 1 part of reducing pain. Many drugs used in veterinary medicine are available to use in birds, including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and local anesthetics, among others. Careful consideration should be made when selecting drug dosages for avian patients. Failure to determine a safe and effective dosage regimen for use in clinical trials is a frequent flaw encountered in human drug development. In veterinary medicine, this is further complicated by interspecies differences in pharmacokinetics and pharmacodynamics.[3] In exotic animal medicine, there are limited studies for any given taxa that support the efficacy of the drugs we use, and existing doses listed in formularies[4] and community forums[5] are often extrapolated from studies performed on other species that may or may not be from the same taxa or are anecdotal. Allometric scaling is a concept derived from human medicine to extrapolate doses for pediatric patients from those used in adults. It is based on the patient's weight and the expected metabolic clearance by the kidneys and liver. Although this concept could be used to choose a dose for a drug in a new animal species, it has been shown to be unreliable in avian patients when comparing different taxa.[6] For this reason, pharmacokinetic and pharmacodynamic studies are important for selecting drug doses in different species.

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In psittacine birds, NSAIDs are used to treat various inflammatory conditions. Nonsteroidal anti-inflammatory drugs inhibit cyclooxygenase (COX)-1 and COX-2 enzymes. These enzymes are involved in the production of prostaglandins, which contribute to inflammation.[7] The suppression of COX-1 is linked to the most deleterious adverse effects of NSAIDs, including the disruption of mucosa protection, platelet aggregation, and renal blood flow. These adverse effects correspond with the common disease conditions associated with chronic NSAID use, including renal injury, coagulopathies, and gastrointestinal ulcers. Typically, chronic or large doses of NSAIDs may lead to suppression of COX-1. Common NSAIDs used in avian patients include meloxicam, carprofen, diclofenac, and, anecdotally, robenacoxib.

Robenacoxib is a coxib-class NSAID that selectively inhibits COX-2 enzymes to reduce inflammation via the reduction of prostaglandin synthesis in dogs, cats, and rats.[8–10] By selecting for COX-2, robenacoxib spares COX-1, which should reduce the likelihood of adverse reactions in the patient. Robenacoxib is not currently labeled for use in birds and is only commercially labeled for dogs and cats. It is currently available in injectable and tablet formulations. In dogs, robenacoxib has been shown to have fewer adverse effects compared with other NSAIDs, such as meloxicam and carprofen, even at doses up to 10 mg/kg.[11] In dogs and cats, robenacoxib has a relatively short half-life (0.69 hours in dogs and 1.49 hours in cats), though its analgesic effects last about 24 hours, allowing for once daily dosing.[8,9] The mechanism behind the daily dosing regimen was based on a study in cats that showed no differences in efficacy between once versus twice daily robenacoxib administered orally.[12] Results from the cat investigation demonstrated that despite its rapid clearance from the bloodstream, robenacoxib concentrations were maintained at therapeutic concentrations for 24 hours at the sites of inflammation using tissue cage models after intravenous, intramuscular, or subcutaneous routes of administration.[8] However, the level of expression and activity of COX is species specific; therefore, the level of COX-2 inhibition that robenacoxib provides must be studied in target species.[13] At the time this study in Hispaniolan Amazon parrots (HAP; *Amazona ventralis*), there had been only 1 published pharmacokinetic study of robenacoxib in an avian species, the domestic goose (*Anser anser domesticus*).[14] Peak plasma concentrations of robenacoxib in geese were obtained at 0.5 hours, with a half-life of 0.99 hours after oral administration.[14] Robenacoxib has been used to treat parrots with proventricular dilatation disease at doses ranging from 2–10 mg/kg administered intramuscularly or by mouth every 3–7 days, to varying degrees of effect.[15]

This study aimed to establish the pharmacokinetics of a single oral dose of robenacoxib in HAP. This species was selected as a representative species for common companion psittacine species; thus, the data obtained from this study will serve as a basis for future studies to establish the anti-inflammatory and analgesic effects of robenacoxib. We hypothesized that there would be rapid clearance of robenacoxib from the blood of the HAP.

MATERIALS AND METHODS

Animals

All study procedures were reviewed and approved by the Louisiana State University Institutional Animal Care and Use Committee (protocol#: 23-119). A total of 7 HAP ranging in age from 10-15 years old and weighing 263.2g-336.0g (mean: 301.6g $\pm$ 23.5) were recruited for this study. Four birds were male, and 3 were female. The birds were part of a research flock housed at Louisiana State University (Baton Rouge, LA, USA). The parrots are housed in 61 $\times$ 74 $\times$ 46-cm stainless steel cages in a temperature-controlled room and maintained on a 12-hour photoperiod. The parrots were not removed from their normal environment for the entirety of this study. The parrots are fed a commercial pelleted diet (Kaytee Exact Maintenance; Kaytee Products, Chilton, WI, USA) and provided ad libitum tap water. Blood was collected from each bird for a maximum of 4 blood samples. No more than 0.5 mL of blood was collected at each time point, with a 2-mL total volume of blood collected from each bird. The mean proportion of circulating blood volume collected at each sampling point was 0.2%, for a mean total of 0.8% total blood volume.

Experimental design

A baseline blood sample was collected from all 7 parrots (time = 0) 1 month before their initial dose of medication. Blood samples were also collected from 4 other parrots not included in the study to serve as a control group. The birds were randomly assigned time points for sample collection following time 0 (1, 2, 4, 6, 10, 14, and 24 hours), and each bird had blood collected 4 times. A 4-mg/kg dose of robenacoxib was selected based on information obtained from the published domestic goose study with consideration for overall suspected safety and efficacy, along with the likelihood of obtaining a therapeutic plasma drug concentration.[12]

Table 1. List of chemicals and reagents used for mass spectrometry following a single oral administration of robenacoxib at 4 mg/kg in Hispaniolan parrots (*Amazona ventralis*).

Name	Grade	Purity (%)	Manufacturer
Methanol	LCMS	99.9	Fisher
Water	LCMS	N/A	Fisher
Acetonitrile	LCMS	99.9	Fisher
Ethyl acetate	LCMS	99.9	Fisher
Hexanes	LCMS	99.9	Fisher
0.1% formic acid in water	LCMS	99.9	Fisher
0.1% formic acid in acetonitrile	LCMS	99.9	Fisher

Abbreviation: LCMS, liquid chromatography-mass spectrometry.

All 7 parrots were manually restrained for administration of robenacoxib (4 mg/kg by mouth once; Onsior, Elanco Animal Health, Greenfield, IN, USA). The dose for each bird was calculated based on their weight, with the appropriate amount of pulverized robenacoxib tablet being weighed on an analytical scale (XP205; Mettler Toledo, Columbus, OH, USA).

For administration, the drug was suspended in 4 mL of tap water and then injected into the crop via a gavage needle. This was followed by 2 mL of tap water and 2 mL of air to verify that the entire dose was given. Each bird was monitored for regurgitation following crop placement of robenacoxib. There was no evidence of regurgitation from any of the birds during the study.

Blood collection was performed via venipuncture of the right or left jugular vein using a 3-mL syringe and a 26-G needle. At the following 8 time points, 0.5 mL was collected per sample: 0, 1, 2, 4, 6, 10, 14, and 24 hours. At time 0 hours, samples were collected 1 month before the collection of the other time points. A balanced incomplete block design was chosen for this study to limit stress associated with restraint and venipuncture. The birds were individually weighed to prevent exceeding 1% total blood volume loss over the course of 24 hours. Randomization of time points and birds was performed by computer software with a design efficiency of 0.875 (R version 3.4.3; R Foundation for Statistical Consulting, Vienna, Austria). The sample size of 7 birds was chosen based on a previous study with a similar design and significance.[16]

Following collection, the blood samples were immediately placed in lithium heparin tubes without separator gel (blood collection microtubes; Strategic Applications Inc, Lake Villa, IL, USA) and placed in a cooler of wet ice for transportation. The samples were centrifuged at 6000 *g* for 5 minutes within 1 hour of collection. The plasma was collected using individual plastic pipette tips and placed in individually labeled cryovials. The plasma samples were labeled and stored at −80°C (−112°F) until they were ready for pharmacokinetic analysis.

Chemicals, reagents, and preparation of stock solution

All drug standards and chemicals used were of analytical quality. The list of chemicals and reagents used is summarized in Table 1. Reference standards (robenacoxib and flunixin [internal standard]) were purchased from Sigma-Aldrich (St. Louis, MO, USA). The stock solutions were prepared at 1 mg/mL in methanol and diluted in methanol as a calibration standard for liquid chromatography-tandem mass spectrometry. The robenacoxib was purchased from the Louisiana State University Veterinary Teaching Hospital Pharmacy.

Extraction procedure

All samples were analyzed within 24 hours of sample submission. The extraction procedure consisted of a 2-step liquid-liquid extraction. A minimum of 100 μL of plasma was used from each sample for the detection and quantification of robenacoxib. The standard curve was generated using plasma samples collected from birds before the oral administration of robenacoxib. Flunixin at 10 ng/μL was used as an internal standard, and a 25-μL internal standard was added to each sample. Acetonitrile (500 μL) was added to each sample in a 10-mL culture tube, and samples were then vortexed for 1 minute and centrifuged at 3000 rpm for 20 minutes. The solvent was then transferred into 10-mL culture tubes, and 1-mL ethyl acetate:hexane (50:50) was added to each sample. Samples were vortexed for 1 minute, centrifuged at 3000 rpm for 20 minutes (Beckman Coulter Allegra X-14, S/N ALF18E24, Brea, CA, USA), and then 1.2 mL of solvent was transferred into clean culture tubes. To concentrate the samples, the eluents in tubes were evaporated on the Cerex 48 sample concentrator (Cerex Concentrator, S/N C481425A, Apple Valley, MN, USA) at 40°C (104°F) under a stream of nitrogen. Following evaporation, 125 μL of injection solvent (90:10; 0.1% formic acid in water: 0.1% formic

Table 2. Liquid chromatography-mass spectrometry parameters used to analyze samples from Hispaniolan parrots (*Amazona ventralis*) following a single oral administration of robenacoxib.

LC Column	MacMod ACE Excel, 5 μm, C18, 2.1 × 75 mm
Flow	0.3 mL/min
Solvents	**A:** 0.1% Formic acid in Water, **B:** 0.1% Formic acid in Acetonitrile
Gradient	2% B at t = 0 min, then 75% B in t = 1 min, then increased to 98% B in t = 3 min, hold at 98% B for 2 min, then reduced back to 2% B in t = 7 min, and then re-equilibrate at 2% B until t = 8 min.
Injection volume	20 μL
Run time	8 min
Polarity	Positive
Ion source	Heated electro spray ionization
Spray voltage, kv	Positive: 4.00
Acquisition mode	Parallel reaction monitoring
Sheath gas	50
Aux gas	7
Sweep gas	2
Capillary temp, °C	275
Aux gas heater temp, °C	350
S-lens RF level	60
Maximum IT time, ms	100
AGC target	$3e^6$
Scan range	50–750 m/z
Resolution	70 000

Abbreviations: LC-MS, liquid chromatography-mass spectrometry; MS, mass spectrometry; LC, liquid chromatography; Aux, auxiliary; RF, radio frequency; IT, injection time; AGC, automatic gain control; t, time; m/z, mass-to-charge ratio.

acid in acetonitrile) was added to the dried residue and vortexed for 1 minute.

Instrumentation and data analyses

Liquid chromatography was performed on a Thermo Q-Exactive Mass Spectrometer coupled with a Thermo Ultra-High Performance Liquid Chromatography system equipped with Thermo Accela ALS 2.4.0 autosampler (Thermo Fisher Scientific, San Jose, CA, USA). The entire system was controlled using Windows NT Workstation and Tracefinder Software Version 3.3 (Microsoft, Redmond, WA, USA). Instrument parameters are summarized in Table 2. Quantification relied on the elaboration of standard curves based on the ratio of robenacoxib *m/z* 328.099552→ 262.08337 peak areas (robenacoxib concentrations 0.25, 0.5, 1, 5, 10, 50, and 100 ng/mL) to corresponding peaks of the internal standard flunixin *m/z* 297.08454→ 279.07349 fragmentation. The qualifier ions used for robenacoxib were *m/z* 247.05992 and 234.05212, and for flunixin were *m/z* 264.05005 and 259.06729. Respective retention times averaged 5.358 ± 0.017 minutes for robenacoxib and 5.81 ± 0.017 minutes for flunixin. Sample concentration values were interpolated from the elaborated standard curves. The limits of detection and quantitation were 0.1 and 0.25 ng/mL, respectively. Linearity was 0.995 ± 0.0034 and was assessed by averaging 3 standard curve coefficients of determination (R^2). Carryovers were 0% and 0.06% for robenacoxib and flunixin, respectively, and were determined by measuring the peak areas of robenacoxib or flunixin in blanks following the highest calibrator injection. The mean accuracy percent (±SD) and precision percent were 116 ± 15 and 13% at 1 ng/mL, 99% ±2.9 and 2.9% at 5 ng/mL, 97 ±7.5% and 7.7% at 10 ng/mL, and 99 ±2.2% and 2.2% at 50 ng/mL, respectively, from extracted samples analyzed on 4 different days.

Pharmacokinetics

Pharmacokinetic analysis was carried out with a 1-compartmental method using commercial software (Version 8.3 Certara; Phoenix Inc WinNonLin Software, Princeton, NJ, USA). Pharmacokinetic parameters calculated following subcutaneous administration of a 4-mg/kg dose of robenacoxib included first-order absorption rate constant (K01), absorption half-life ($t_{1/2K01}$), terminal elimination rate constant (K10), terminal elimination half-life ($t_{1/2}$), maximum observed plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration time curve from time 0 to infinity ($AUC_{0\text{-}inf}$), apparent total body clearance per fraction of dose absorbed (Cl/F), and apparent volume of distribution per fraction of dose absorbed (V/F).

Table 3. Pharmacokinetic parameters of robenacoxib in the 4 randomly assigned groups of Hispaniolan parrots (*Amazona ventralis*) (n = 7) following a single oral administration of 4 mg/kg robenacoxib.

Parameters	Units	Group 1	Group 2	Group 3	Group 4	Mean ± SD
K01	1/hr	0.76	10	11	4.8	6.64 ± 4.8
K10	1/hr	0.78	0.6	0.52	0.39	0.573 ± 0.16
$t_{1/2\ K01}$	hr	0.9	0.07	0.06	0.14	0.293 ± 0.41
$t_{1/2}$	hr	0.9	1.2	1.3	1.8	1.3 ± 0.37
Tmax (median)	hr	1.3	0.3	0.3	0.6	0.45 ± 0.47
Cmax	ng/mL	133	121	77	24	88.75 ± 49
$AUC_{0\text{-inf}}$	hr*ng/mL	467	250	171	77	241.3 ± 166
V/F	mL/kg	10 913	27 648	44 848	133 818	54307 ± 54788
Cl/F	mL/hr/kg	8566	16 027	23 358	51 911	24 966 ± 18 952

Abbreviations: K01, first order absorption rate constant; K10, terminal elimination rate constant; $t_{1/2\ K01}$, absorption half-life; $t_{1/2}$, terminal elimination half-life; T_{max}, time to maximum plasma concentration; C_{max}, maximum observed plasma concentration; $AUC_{0\text{-inf}}$, area under the plasma concentration from time 0 to infinity; V/F, apparent volume of distribution per fraction of dose absorbed; Cl/F, apparent total body clearance per fraction of dose absorbed.

RESULTS

None of the 7 parrots exhibited any clinical signs of disease for the duration of the study. Appetite, thirst, and fecal output remained consistent. The birds' activity levels were normal before, during, and after administration of robenacoxib, with no notable changes in mentation throughout the 24-hour sample collection period.

For this investigation, the pharmacokinetics of a single oral dose of robenacoxib at 4 mg/kg to HAP, using naïve, averaged data and noncompartmental analysis, are presented in Table 3 and Figures 1 and 2. Robenacoxib was detected in all plasma samples between 1 and 6 hours postdrug administration. The mean ± SD plasma elimination half-life and C_{max} were 1.3 ± 0.37 hours and 88.75 ± 49.0, respectively (Table 3). The median ± SD T_{max} was 0.45 ± 0.47.

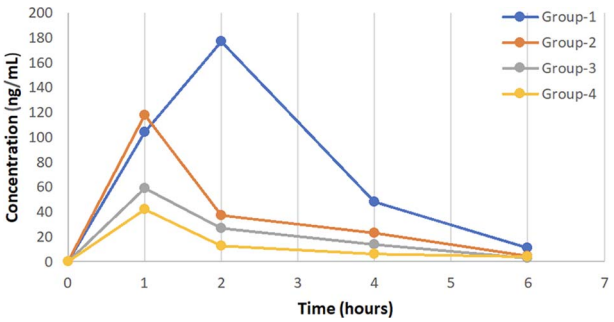

Figure 1. Plasma concentrations of robenacoxib in the 4 study pharmacokinetic groups of Hispaniolan Amazon parrots (*Amazona ventralis*) (n = 7) following a single oral administration of robenacoxib at 4 mg/kg. The drug was no longer detected 6 hours post-administration. Peak concentrations ranging from 20 to 120 ng/mL were reached at 1 hour for 3 of 4 groups.

DISCUSSION

The NSAIDs are among the most common drugs used in veterinary practice and include nonselective NSAIDs (eg, ketoprofen, flunixin, and diclofenac), selective NSAIDs (eg, carprofen, meloxicam, robenacoxib), and non–COX-inhibiting NSAIDs (eg, grapiprant). Nonselective NSAIDs inhibit both COX-1 and COX-2, while selective NSAIDs will inhibit 1 or the other (typically COX-2). The suppression of COX-1 is most associated with adverse events.[7] Toxicity associated with nonselective NSAIDs has been especially well-documented in *Gyps* vultures.[17,18] Meloxicam is a commonly used NSAID in veterinary medicine that preferentially inhibits COX-2, though this selectivity decreases as its dose increases.[19] Its use and safety have been

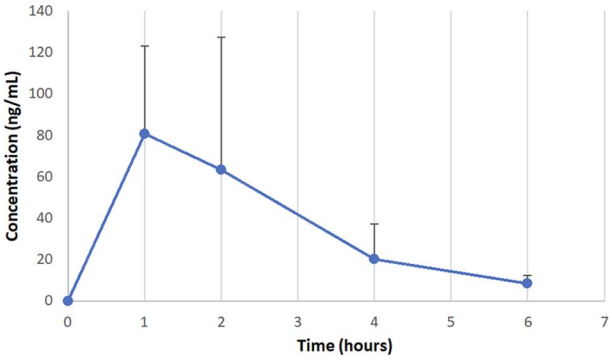

Figure 2. Mean plasma concentrations nanogram/milliliter of robenacoxib in the 4 study pharmacokinetic groups of Hispaniolan Amazon parrots (*Amazona ventralis*) (n = 7) following a single oral administration of robenacoxib at 4 mg/kg. Concentrations were no longer detected 6 hours post-drug administration. Mean peak plasma concentration (80 ng/mL) was reached after 1 hour. The drug was no longer detected 6 hours post-administration.

well-documented in several avian species, including grey parrots (*Psittacus erithacus*)[20] and HAP.[21]

Robenacoxib is an NSAID of the coxib class and is a highly selective COX-2 inhibitor. It is currently labeled for use in dogs and cats to control postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy, and castration for a maximum of 3 days.[22,23] Robenacoxib concentrates in inflamed tissues, and its clinical effects persist longer than its short terminal half-life in blood.[24] There are published studies that show that chronic administration of robenacoxib in dogs and cats for long-term management of osteoarthritis is safe.[11,24–27] In this study, the pharmacokinetic parameters of a single oral dose of robenacoxib were evaluated in a group of 7 healthy adult HAP. The results indicated that a single 4-mg/kg oral dose of robenacoxib was well tolerated without any adverse clinical effects. The mean peak plasma concentrations were reached at 0.45 hours, with a peak concentration of 88.75 ng/mL. In cats, the maximum inhibition of prostaglandin E2 was observed at a plasma concentration of robenacoxib of 35.4 ng/mL.[8] The $t_{1/2}$ was 1.3 ± 0.37, slightly longer than the half-life found in geese (0.99 hours).[14] The mean Cl/F in liters per kilogram per hour in our study was 24.9, compared with 0.14 L/h/kg in geese. The median T_{max} of 0.45 ± 0.47 was similar to that noted in geese (0.5 hours).[14] Robenacoxib was not detected in any bird 6 hours postadministration.

To the authors' knowledge, this study is the first to investigate the pharmacokinetics of robenacoxib in a psittacine species. The results of the study suggested that the robenacoxib remains in plasma for up to 6 hours postadministration of an oral dose. Further studies would be necessary to confirm these results. The dose of robenacoxib chosen for this study was based on the results published for the use of the drug in domestic geese.[14]

This study had several limitations. First, the small sample size of 7 birds increased the probability for individual differences in pharmacokinetics. Second, robenacoxib was not detected in any bird 6 hours postadministration. Another limitation of the study is that after the absorption phase, there were 3 data points for calculating pharmacokinetic parameters in all groups, except in group 1, where only 2 data points were available during the elimination phase. Third, robenacoxib was not administered intravenously; therefore, some of the pharmacokinetic parameters (Vd, Cl, bioavailability) still need to be determined in parrots. Finally, additional studies would be necessary to determine the pharmacodynamic and systemic analgesic effects of robenacoxib in psittacine birds. Future research directions may include the use of whole blood assays or tissue cage models. There is a study that used whole blood assays in emus (*Dromaius novaehollandiae*) to determine the potency of meloxicam against COX-1 and COX-2 through pharmacodynamic analysis.[28] The use of whole blood assays was successful in determining that the empirical dose selected for the study was too low for once daily dosing in emus.[28]

Although we did not observe any adverse clinical effects in our sample population, the lack of published therapeutic doses of robenacoxib in psittacines means that the lowest dose possible should be prescribed to avoid any adverse effects associated with robenacoxib in other species (eg, dogs: hyporexia, vomiting, diarrhea; cats: infections, hyporexia, vomiting, lethargy).[22,23] For veterinary staff and clients to feasibly and reliably administer robenacoxib orally to their avian patients, a compounded form of the drug in an oral suspension would likely be necessary in a practical setting.

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