

Pharmacokinetics of single-dose oral atorvastatin and its metabolites support therapeutic use in orange-winged Amazon parrots (*Amazona amazonica*)

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OBJECTIVE

To evaluate the plasma concentrations and determine pharmacokinetic parameters of atorvastatin and its primary active metabolites (para- and ortho-hydroxyatorvastatin) after administration of a single oral dose in orange-winged Amazon parrots (*Amazona amazonica*).

ANIMALS

8 adult orange-winged Amazon parrots (4 male, 4 female) of varying ages.

METHODS

A compounded oral suspension of atorvastatin 10 mg/mL was administered via oral gavage at 20 mg/kg to each bird. Blood samples were collected at 10 different time points from 0 to 30 hours postadministration to evaluate plasma levels of atorvastatin, para-hydroxyatorvastatin, and ortho-hydroxyatorvastatin. Pharmacokinetic analysis was performed using noncompartmental analysis and commercially available software.

RESULTS

Mean \pm SD atorvastatin half-life, t_{\max} , and C_{\max} were 5.96 ± 11.50 hours, 1.60 ± 0.80 hours, and 82.60 ± 58.30 ng/mL, respectively. For para-hydroxyatorvastatin, the half-life, t_{\max} , and C_{\max} were 6.46 ± 54.20 hours, 5.00 ± 2.51 hours, and 34.10 ± 16.00 ng/mL, respectively, and 5.58 ± 9.92 hours, 3.38 ± 2.10 hours, and 7.35 ± 3.96 ng/mL for ortho-hydroxyatorvastatin.

CLINICAL RELEVANCE

The plasma concentrations and pharmacokinetic profile shown support the therapeutic use of atorvastatin at the dose evaluated in this species based on human pharmacokinetic data. While 20 mg/kg PO q24 hours could be used as a starting dosage until further studies evaluating multiple dose administration and efficacy in this species become available, the high interindividual variability results warrant monitoring of the treatment response to make dosing adjustments if needed.

Keywords: statin, atorvastatin, dyslipidemia, psittacine, cholesterol

Psittacine birds are long-lived species that suffer from a range of common lipid-accumulation disorders when kept in captivity. Health disorders involving hyperlipidemia and its sequelae are commonly encountered in a clinical setting, often due to inappropriate diets fed throughout life and other risk factors. As captive lifestyles associated with pet ownership are likely associated with many of these

diseases, effective treatment methods are crucial to help manage these common geriatric conditions that significantly reduce the life expectancy of psittacine birds. There is a strong species predisposition to atherosclerosis and other lipid disorders, especially within Amazon parrots (*Amazona* spp.), grey parrots (*Psittacus erithacus*), cockatiels (*Nymphicus hollandicus*), and quaker parrots (*Myiopsitta monachus*).¹⁻⁴ Female birds are also more prone to atherosclerosis in most psittacine species and also suffer from a high rate of reproductive-associated chronic dyslipidemia.

Hypercholesterolemia and some lipoprotein abnormalities have been found to be associated with

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atherosclerosis in epidemiological studies in various species of parrots.^{2,5} In addition, plasma cholesterol concentration is also strongly associated with cholesterol feeding and atherosclerosis in experimental induction of the lesions in Quaker parrots.^{6,7}

The use of statin drugs is considered a mainstay of treatment for human hyperlipidemia and atherosclerosis. Atorvastatin administration in humans (maximum recommended dose 80 mg/day) results in rapid absorption after oral administration, with maximum plasma concentrations being reached within 1 to 2 hours and elimination half-life being approximately 14 hours. Atorvastatin decreases blood cholesterol and low-density lipoprotein-cholesterol (LDL-C) by as much as 50% at higher doses and is considered one of the most potent hypolipidemic and antiatherosclerotic drugs on the market. Statins prompt this due to their function as hepatic 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, which reduce the amount of cholesterol produced by blocking primary enzymes of the mevalonate pathway needed for hepatic cholesterol synthesis.⁸ At a median dose of 40 mg/day, maximum plasma concentrations of atorvastatin in humans range from 27 to 66 ng/mL, with oral bioavailability being between 12% to 14%.⁹ However, as at least 70% of the total HMG-CoA reductase inhibitory effects of atorvastatin are attributable to its active metabolites, it is imperative that these primary metabolites be evaluated alongside the parent drug.^{9,10} In vitro, the active metabolites of atorvastatin have likewise been found to be equipotent to the parent drug.¹⁰

There is a considerable gap of knowledge on statin treatment and pharmacology in birds with few scientific publications. Atorvastatin administration at a dose of 3 mg/kg/day was associated with a reduction in hepatocellular damage and steatosis when combined with a standard diet and regression of hyperlipidemia-associated renal disease in chickens.^{11,12} Preliminary data obtained by the investigators from controlled experiments on compounded atorvastatin in Amazon parrots (10 mg/kg PO q24h for 30 days)¹³ and atorvastatin (10 mg/kg PO q12h and 24h and 20 mg/kg PO q12h, each for 14 days) and rosuvastatin (10 mg/kg PO q12-24h for 14 days) in Quaker parrots,¹⁴ which are equivalent to 10 to 20 times the human dose, failed to show statistically significant hypolipidemic effect on plasma cholesterol, triglycerides, lipoproteins, and other lipids.

Pharmacokinetic information on other statins is also limited in avian species. Plasma concentrations of compounded rosuvastatin administered orally have been evaluated in Hispaniolan Amazon parrots,¹⁵ but doses of both 10 mg/kg and 25 mg/kg largely resulted in concentrations below the limits of quantitation set at 0.025 µg/mL. Oral administration of compounded atorvastatin in hypercholesterolemic Hispaniolan Amazon parrots at a dose of 10 mg/kg every 24 hours resulted in plasma concentrations not exceeding 6.74 ng/mL during sparse sampling.¹³ In rats, which have a metabolic rate comparable to medium-sized birds, doses as high as 80 mg/kg

have been administered orally, with C_{max} (mean \pm SD of 23.44 \pm 0.53 µg/mL) being achieved at approximately 2 hours postadministration and the half-life is approximately 10 hours.¹⁶ Given these findings and initial oral statin studies performed in psittacine species, it is very likely that higher oral doses are needed to improve bioavailability and maximum plasma concentration levels. In humans, a dose of up to 80 mg/day for 14 days was well-tolerated and had significant cholesterol-lowering effects,¹⁷ and Quaker parrots were shown to tolerate atorvastatin doses of up to 20 mg/kg by mouth every 12 hours similarly well over a period of 14 days.¹⁴

The objective of this study was to determine the plasma concentrations and pharmacokinetic profile of an oral suspension of atorvastatin administered at a dose of 20 mg/kg to orange-winged Amazon parrots. It was hypothesized that plasma concentrations of atorvastatin found to have lipid-lowering effects in studied mammalian species (humans) would similarly be reached after oral administration in orange-winged Amazon parrots, and would exhibit a favorable pharmacokinetic profile supportive of use in this companion psittacine species.

Methods

Animals

Eight (4 male, 4 female) adult orange-winged Amazon parrots of varying ages (from 8 years at the youngest to 32+ years at the oldest) were used in this study. An intake physical examination, packed cell volume and total solids, and manual complete blood count were performed on each Amazon parrot to ensure appropriate health before the study. The mean \pm SD body weight was 425.9 \pm 46.7 g. For the purpose of the study, birds were housed individually in wheeled wire cages (36 [length] X 23.5 [width] X 36 [height] inches) with ad libitum access to a pelleted diet (Maintenance diet, Roudybush Inc) and water. Each cage contained at least 2 perches, a hanging toy, and a food bowl. All birds were exposed to a photoperiod of 12 hours of light and 12 hours of darkness and the temperature of the room was maintained at approximately 24°C. The study was approved by the Institutional Animal Care and Use Committee at the University of California, Davis.

Preparation of oral atorvastatin

The oral suspension of 10 mg/mL atorvastatin was compounded by the veterinary pharmacy at the University of California, Davis Veterinary Medical Teaching Hospital. The oral suspension was compounded via suspension of 80 mg atorvastatin calcium tablets (Apotex Corp) in Ora-Plus (Paddock Laboratories) using similar published methods¹⁴ and demonstration of good stability in a variety of different vehicles.¹⁸ Preparation of the oral suspension was performed via placement of an 80 mg atorvastatin calcium tablet in the bottom of a mortar and pulverizing the tablet with a pestle until a powder was formed. The powder was then added to an Ora-Plus vehicle in the desired volume needed to

achieve a 10 mg/mL oral suspension, with thorough vortexing performed to ensure a homogeneous suspension. The suspension was visually tested for overnight stability before the performance of the study and was found to maintain the desired liquid texture when evaluated. The oral suspension was prepared the night before administration, and stored at room temperature before use. Before individual administration to the orange-winged Amazon parrots, the bottle containing the oral suspension was placed on a BenchMixer (Benchmark Scientific Inc) and thoroughly vortexed for approximately 5 minutes between each bird until a homogenous suspension was obtained. The suspension was then drawn up into individual 3-mL oral syringes for administration.

Experimental design

The orange-winged Amazon parrots were each manually restrained to allow for direct administration of the oral atorvastatin into the crop via a size 10 metal gavage tube. The Amazon parrots were not fasted before administration. Each Amazon parrot was administered a single oral dose of 20 mg/kg based on their individual body weight. The dose administered was based on prior pilot study data, with 2 birds (1 male and 1 female, different from those used in the true study) being allocated to receive varying doses of oral atorvastatin at 20 mg/kg, 40 mg/kg, or 80 mg/kg. The maximum pilot study dosage of 80 mg/kg was determined based on maximum oral doses reported in rats, a similar size vertebrate, that resulted in significant reductions in plasma cholesterol, triglycerides, and LDL-C concentrations.¹⁶ Whole blood samples were collected under manual restraint from each of the 8 birds over a total of 10 time points (0, 0.5, 1, 2, 3, 4, 8, 12, 24, and 30 hours postdrug administration). For blood collection, a volume of no more than 1% of the bird's body weight was collected during each study portion. For each time point described, 0.2 to 0.3 mL of whole blood was collected using individual U-100 0.5 mL insulin syringes (28-gauge needle) and sampled from the jugular, brachial, or metatarsal veins. Blood samples collected were placed in lithium-heparin pediatric collection tubes, kept in refrigeration at 4 °C, and centrifuged for 6 minutes at 3,500 g within 4 hours of collection. Plasma was then collected into labeled 0.5 mL cryovials and stored at -80 °C until analysis.

Plasma concentration determinations of atorvastatin, para-hydroxyatorvastatin, and ortho-hydroxyatorvastatin

Plasma calibrators were prepared by dilution of the atorvastatin, ortho-hydroxyatorvastatin (2-OH atorvastatin), and para-hydroxyatorvastatin (4-OH atorvastatin) (Cayman Chemical Company) working standard solutions with drug-free parrot plasma to concentrations ranging from 0.1 to 800 ng/mL. Calibration curves and negative control samples were prepared fresh for each quantitative assay. In addition, quality control samples (parrot plasma fortified with analyte at 3 concentrations within the

standard curve) were included with each sample set as an additional check of accuracy.

Before analysis, 50 μ L of plasma was diluted with 50 μ L of methanol:water:dimethyl sulfoxide, 1:1:1, v:v:v, and 150 μ L of acetonitrile (CAN):1M acetic acid (9:1, v:v) containing 0.005 ng/ μ L of d5-atorvastatin (Cayman Chemical Company) internal standard, to precipitate proteins. The samples were vortexed for 1 minute to mix, refrigerated for 20 minutes, vortexed for an additional 1 minute, and centrifuged in a Sorvall ST 40R centrifuge (Thermo Scientific) at 4,300 rpm/3,830 g for 10 minutes at 4 °C and 30 μ L of the supernatant injected into the liquid chromatography-tandem mass spectrometry (LC-MS/MS) system.

The analyte concentrations were measured in plasma by LC-MS/MS using positive heated electrospray ionization (HESI(+)). Quantitative analysis was performed on a TSQ Altis triple quadrupole mass spectrometer coupled with a Vanquish liquid chromatography system (Thermo Scientific). Chromatography used a Kinetex 5 cm X 2 mm 2.6 μ m column (Phenomenex) and a linear gradient of ACN in water with a constant 0.2% formic acid at a flow rate of 0.35 mL/min. The initial ACN concentration was held at 1% for 0.2 minutes, ramped to 90% over 6.7 minutes, and held at that concentration for 0.1 minutes, before re-equilibrating for 3.35 minutes at initial conditions.

Detection and quantification were conducted using selective reaction monitoring (SRM) of initial precursor ion for atorvastatin (mass to charge ratio (m/z) 559), 2-OH atorvastatin and 4-OH atorvastatin ((m/z) 575), and d5-atorvastatin ((m/z) 564). The response for the product ions for atorvastatin (m/z 250, 276, 440), 2-OH atorvastatin and 4-OH atorvastatin (m/z 250, 292, 440, and 466), and d5-atorvastatin (m/z 255, 445) were plotted, and peaks at the proper retention time-integrated, using Quanbrowser software (Thermo Scientific). Quanbrowser software was used to generate calibration curves and quantitate analytes in all samples by linear regression analysis. A weighting factor of 1/X was used for all calibration curves.

The responses for all analytes were linear and gave correlation coefficients of 0.99 or better. Accuracy was reported as percent nominal concentration and precision as percent relative standard deviation (**Table 1**). The technique was optimized to provide a limit of quantitation of 0.1 ng/mL and a limit of detection of approximately 0.05 ng/mL for all analytes.

Pharmacokinetic analysis

A noncompartmental analysis was performed on the plasma atorvastatin and metabolite concentrations using a commercially available computer software program (Phoenix WinNonlin version 8.3; Certara Inc). The maximum plasma concentration (C_{max}) and time to maximal plasma concentration (t_{max}) were obtained directly from the plasma concentration data. The area under the concentration-versus-time curve from time 0 to the last measured concentration at 30 hours (AUC 0-last), the terminal rate constant (λ_{2}), terminal half-life ($t_{1/2}$), and the coefficient

Table 1—Accuracy and precision values for LC-MS/MS analysis of atorvastatin, 2-OH atorvastatin, and 4-OH atorvastatin in parrot plasma.

Analyte	Concentration (ng/mL)	Accuracy (% nominal concentration)	Precision (% relative SD)
Atorvastatin	0.3	101	7.0
	2.0	107	4.0
	20.0	99.0	3.0
2-OH atorvastatin	0.3	99.0	7.0
	2.0	104	5.0
	20.0	101	5.0
4-OH atorvastatin	0.3	100	5.0
	2.0	104	3.0
	20.0	103	5.0

of variation for these parameters were determined. Pharmacokinetic parameters for atorvastatin, para-hydroxyatorvastatin, and ortho-hydroxyatorvastatin are reported as harmonic mean (\pm SD) values.

Results

Plasma concentrations of atorvastatin, para-hydroxyatorvastatin, and ortho-hydroxyatorvastatin after a single oral administration of 20 mg/kg atorvastatin to the 8 orange-winged Amazon parrots are depicted (**Figure 1**), with select pharmacokinetic parameters being described (**Tables 2-4**). Mean atorvastatin half-life, t_{max} , and C_{max} were 5.96 ± 11.50 hours, 1.60 ± 0.80 hours, and 82.60 ± 58.30 ng/mL, respectively. For para-hydroxyatorvastatin, the half-life, t_{max} , and C_{max} were 6.46 ± 54.20 hours, 5.00 ± 2.51 hours, and 34.10 ± 16.00 ng/mL, respectively, and 5.58 ± 9.92 hours, 3.38 ± 2.10 hours, and 7.35 ± 3.96 ng/mL for ortho-hydroxyatorvastatin.

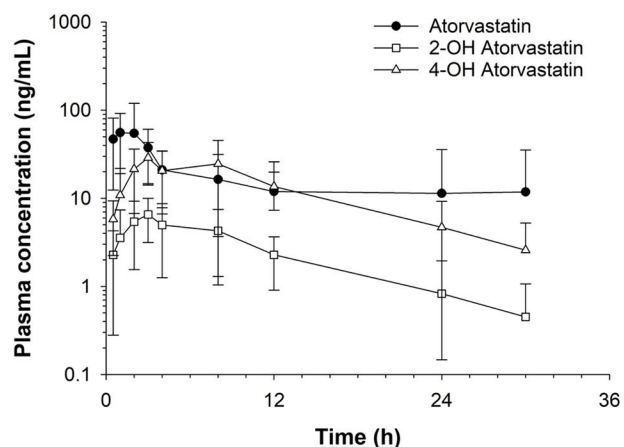


Figure 1—Plasma atorvastatin, para-hydroxyatorvastatin, and ortho-hydroxyatorvastatin concentrations (means \pm SD in ng/mL) plotted over time (hours) in 8 orange-winged Amazon parrots administered a single oral dosage of 20 mg/kg atorvastatin.

Table 2—Pharmacokinetic parameters for atorvastatin after administration of 20 mg/kg of atorvastatin as a 10 mg/mL oral suspension to orange-winged Amazon parrots (n = 8).

Pharmacokinetic parameter	Mean \pm SD	Median	Range
C_{max} (ng/mL); CV%	82.60 ± 58.30 ; 70.5%	53.70	37.10–211.60
t_{max} (h); CV%	1.60 ± 0.80 ; 52.5%	1.50	0.50–3.00
λ_{z} (1/h); CV%	0.10 ± 0.10 ; 53.4%	0.14	0.02–0.17
$t_{1/2}$ (h); CV%	5.96 ± 11.50 ; 108.6%	5.16	4.03–36.90
AUC_{last} (h X ng/mL); CV%	327.50 ± 158.30 ; 48.3%	254.70	162.90–537.90

All parameters were generated using noncompartmental analysis.

AUC_{last} = Area under the curve to the last time point collected. C_{max} = Maximum plasma concentration. CV% = Coefficient of variation. λ_{z} = Terminal rate constant. $t_{1/2}$ = Elimination half-life. t_{max} = Time of maximal plasma concentration.

Table 3—Pharmacokinetic parameters for para-hydroxyatorvastatin after administration of 20 mg/kg of atorvastatin as a 10 mg/mL oral suspension to orange-winged Amazon parrots (n = 8).

Pharmacokinetic parameter	Mean \pm SD	Median	Range
C_{max} (ng/mL); CV%	34.10 ± 16.00 ; 46.9%	33.00	16.90–68.00
t_{max} (h); CV%	5.00 ± 2.51 ; 50.1%	3.50	3.00–8.00
λ_{z} (1/h); CV%	0.11 ± 0.07 ; 53.4%	0.11	0.00–0.22
$t_{1/2}$ (h); CV%	6.46 ± 54.20 ; 185.6%	6.44	3.19–159.60
AUC_{last} (h X ng/mL); CV%	347.20 ± 151.00 ; 43.5%	354.60	168.10–664.10

See key in Table 2.

Table 4—Pharmacokinetic parameters for ortho-hydroxyatorvastatin after administration of 20 mg/kg of atorvastatin as a 10 mg/mL oral suspension to orange-winged Amazon parrots (n = 8).

Pharmacokinetic parameter	Mean ± SD	Median	Range
C _{max} (ng/mL); CV%	7.35 ± 3.96; 53.9%	7.37	2.67–12.20
t _{max} (h); CV%	3.38 ± 2.10; 61.2%	3.00	1.00–8.00
Lambda _z (1/h); CV%	0.12 ± 0.07; 59.1%	0.13	0.03–0.22
t _{1/2} (h); CV%	5.58 ± 9.92; 98.1%	5.37	3.09–27.90
AUC _{last} (h X ng/mL); CV%	68.30 ± 37.10; 54.2%	59.30	24.40–120.80

See key in Table 2.

Three of the study birds did not exhibit the anticipated gradual decline in plasma concentrations over time for the parent atorvastatin. A separate study bird was found to have a considerably higher maximum plasma atorvastatin concentration compared to the mean (211.58 ng/mL compared to a mean of 82.60 ng/mL). No adverse effects (vomiting, diarrhea, hyporexia/anorexia, or lethargy) were detected in any of the birds throughout the course of the study.

Discussion

After administration of a 20 mg/kg body weight dose of oral atorvastatin, plasma concentrations of the parent atorvastatin and its 2 primary active metabolites (para- and ortho-hydroxyatorvastatin) were measurable at each time point assessed and were well-tolerated by all study birds.

The pharmacokinetic parameters obtained for atorvastatin in the orange-winged Amazon parrots can be compared to those reported in human, canine, and rodent studies. In humans, atorvastatin at a dosage of 2.5 to 80 mg/day is readily absorbed, with a C_{max} of 4.34 to 187 ng/mL within 1 to 2 hours and a half-life of approximately 14 hours.^{19–21} In dogs administered both single and repeat doses of atorvastatin ranging from 5 to 10 mg/kg, a C_{max} of 2.17 to 10 ng/mL was reached within approximately 1.5 hours and exhibited a half-life of approximately 1.4 hours.²² The same study additionally looked at these parameters in mice given the same 5 to 10 mg/kg dosage, and determined a C_{max} of 19.2 to 85.8 ng/mL within 0.25 hours and a half-life of approximately 3 to 5 hours.²² In comparing these values with those obtained from the orange-winged Amazon parrots in this study, the parrots reach plasma concentrations that are considered to be therapeutic in humans, though with a shorter half-life and t_{max}, likely given their higher metabolism.

The pharmacokinetic parameters of the metabolites, para- and ortho-hydroxyatorvastatin, were of note in this study given the extended t_{max} of the metabolites compared to the parent atorvastatin. For instance, the t_{max} of the para-hydroxyatorvastatin was 5.00 ± 2.51 hours, meaning that it will still provide HMG-CoA reductase inhibition well after the parent drug is gone. In humans, at least 70% of the HMG-CoA reductase inhibitory effects are due to active metabolites, which are thought to extend the half-life to 20 to 30 hours.^{19,21} In dogs, the active metabolites of para- and ortho-hydroxyatorvastatin

similarly had a longer t_{max} of approximately 3 to 5 hours compared to the parent atorvastatin.²² This distinction between the parent drug and metabolites is an important consideration in terms of dosage and frequency of atorvastatin in a clinical setting, and recommendations on dosing should therefore take these metabolites into account. Given that both atorvastatin and its 2 active metabolites were still readily measurable at the final 30-hour timepoint, this combined with the ongoing HMG-CoA reductase activity of the metabolites supports that atorvastatin may be effective as a once-daily medication at a dose of 20 mg/kg in orange-winged Amazon parrots.

The pharmacokinetic profiles exhibited important variability between individuals, as evident by the high coefficient of variation for many of the parameters assessed. Individual factors such as possible saturation of metabolism or physiological effects such as variations in hepatic function or genetic polymorphism in the cytochrome responsible for atorvastatin metabolism, as described in humans,¹⁰ could have led to varied plasma concentration results between birds. Given that atorvastatin is primarily metabolized by the liver, aberrations in older study birds with potential for hepatic disease in aging psittacines could be considered, and the birds displaying the largest variability in plasma concentrations in this study were on the younger side, with an age range of 8 to 21 years.

The variability in plasma concentrations could have also been related to the preparation or administration of the compounded oral atorvastatin itself, though considered less likely. In creating the oral atorvastatin suspension, 80 mg atorvastatin calcium tablets were dissolved in Ora-Plus as was performed in previously published methods¹⁴ and the demonstration of good stability in a variety of different compounds that are included in Ora-Plus.¹⁸ The suspension was thoroughly vortexed each time before administration to every individual bird to ensure a grossly homogeneous suspension. However, a direct stability study could not be performed to evaluate the oral suspension created for this study and would be useful before performance of future studies to ensure adequate homogeneity of the mixture. Administering the atorvastatin without a prior fast may have also resulted in altered drug absorption, as there remains a paucity of information regarding statin metabolism in avian species. In humans, atorvastatin administration with concurrent food consumption has been shown to have some effects on

t_{\max} and C_{\max} , though the net effects on total drug reaching the plasma are negligible.²³ Current recommendations for statin use in humans allow it to be administered with or without food.²⁴ In the current study, it was elected not to fast the birds so as to mimic the ready availability of food that is present in both at-home and clinical scenarios.

The pharmacokinetic parameters were calculated via a noncompartmental analysis. This allowed for individual plotting of the concentrations obtained, though can be challenging when the data is not normally distributed. An alternative method that could be considered in pharmacokinetic studies with similar data distribution would be a nonlinear mixed effect model, which allows the modeling of data from multiple individuals together to provide a better fit and display data points as a population model.²⁶ It was elected to proceed with noncompartmental analysis in this study to highlight the individual variability that can be seen with atorvastatin in companion psittacine, as has also been appreciated in similar statin studies in companion psittacine species.¹³⁻¹⁵

This study has several limitations. One such limitation was the number of birds used in the study population. Given that only 8 orange-winged Amazon parrots were evaluated, this allows for individual variation to have a greater effect on overall group results, particularly in terms of the individuals that displayed more erratic plasma concentrations of the parent atorvastatin compared to the other birds. A variety of age groups, ranging from 8 years at the youngest to 32+ years at the oldest (the oldest bird was wild-caught), was a desired component of this study in an effort to mimic the variation in patient age that is frequently encountered in a clinical setting. However, this age variability may also make a direct comparison of pharmacokinetic data challenging should variability in drug metabolism exist between age groups. Offering the oral atorvastatin to birds that were not fasted before administration, though also a planned component of the study, could have interfered with the outcome of the plasma concentrations if, unlike humans,^{23,24} atorvastatin metabolism is more significantly affected by concurrent food administration in companion psittacine species. And lastly, in evaluating the concentration-time curve for the atorvastatin and its 2 active metabolites, all 3 compounds were still readily measured above the limit of quantitation at the final timepoint of 30 hours. Given this, future studies could extend the sampling timeline out further to better determine when these compounds become nonmeasurable in the plasma, rather than having to focus on extrapolation methods.

As this was the first study to evaluate the pharmacokinetic parameters of oral atorvastatin in orange-winged Amazon parrots, there are a plethora of future studies that can be performed to further investigate this medication in companion psittacines. A multi-dose study could allow for the evaluation of pharmacokinetic data over an extended period of time, as would be needed to treat companion

psittacines with clinical conditions such as hypercholesterolemia and other lipoprotein abnormalities. A study looking directly at oral bioavailability would also be of value, as it is generally very low for statins in humans and remains relatively unknown in avian species. Administration of this medication to other companion psittacine species that are similarly prone to lipid disorders, such as grey parrots, cockatiels, and Quaker parrots,¹⁻⁴ would allow for valuable evaluation of differences in drug metabolism that may exist between species. In comparison, there is not a single dose of atorvastatin in humans, and dose recommendations depend on what the therapeutic objectives are;^{8,9} the same may hold true for birds. Repeating pharmacodynamic studies at higher doses of atorvastatin, such as those evaluated in this study and precluding pilot study data, would also prove useful to assess whether increased doses are needed to prompt clinical decreases in lipid profile parameters.

This study allowed for the determination of the plasma concentrations and pharmacokinetic profile of an oral suspension of 10 mg/mL atorvastatin administered at a dose of 20 mg/kg in orange-winged Amazon parrots. The results obtained from the present study are supportive of this drug's potential for therapeutic use in this species, as demonstrated by its ability to reach plasma concentrations considered to be therapeutic in humans. As measurable concentrations of both the parent atorvastatin and its 2 active metabolites were each present at the final timepoint of 30 hours and readily above the limit of quantitation of 0.1 ng/mL, atorvastatin administered at 20 mg/kg PO q24 hours could be used as a starting dosage until further studies evaluating multiple dose administration and efficacy in this species become available. This dosage frequency is recommended given that the parent atorvastatin was still readily measurable above 10 ng/mL at the end of the study timeline, and at least 70% of the total HMG-CoA reductase inhibitory effects of atorvastatin are attributable to its active metabolites that also remained in active plasma circulation.^{9,10} However, the high interindividual variability results warrant monitoring of the treatment response to make dosing adjustments if needed. Additional pharmacokinetic (multi-dose) and pharmacodynamic studies in both Amazon parrots and other companion psittacines may shed additional light on the usefulness of atorvastatin in these birds as well.

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Disclosures

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