Pharmacokinetics of fluconazole after oral administration of single and multiple doses in African grey parrots

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Objective—To determine the pharmacokinetics and effects of orally administered fluconazole in African grey parrots.

Animals—40 clinically normal Timneh African grey parrots (Psittacus erithacus timneh).

Procedure—in single-dose trials, parrots were placed into groups of 4 to 5 birds each and fluconazole was administered orally at 10 and 20 mg/kg. Blood samples for determination of plasma fluconazole concentrations were collected from each group at 2 or 3 of the following time points: 1, 3, 6, 9, 12, 24, 31, 48, and 72 hours. In multiple-dose trials, fluconazole was administered orally to groups of 5 birds each at doses of 10 and 20 mg/kg every 48 hours for 12 days. Trough plasma concentrations were measured 3 times during treatment. Groups receiving 20 mg/kg were monitored for changes in plasma biochemical analytes, and blood samples were collected on days 1 and 13 of treatment to allow comparison of terminal half-life.

Results—Peak plasma concentrations of fluconazole were 7.45 and 18.59 µg/mL, and elimination half-lives were 9.22 and 10.19 hours for oral administration of 10 and 20 mg/kg, respectively. Oral administration of fluconazole for 12 days at 10 or 20 mg/kg every 48 hours did not cause identifiable adverse effects or change the disposition of fluconazole.

Conclusions and Clinical Relevance—Oral administration of fluconazole to parrots at 10 to 20 mg/kg every 24 to 48 hours maintains plasma concentrations above the minimum inhibitory concentration for several common yeast species. The prolonged dosing interval is an advantage of this treatment regimen.

Mycotic infections are common in psittacines, especially those caused by Candida albicans and Aspergillus spp. Despite frequent use of antifungal drugs in avian practice, safe and effective dosage regimens have not been established for most antifungal agents. Treatment of fungal infections in psittacines has been primarily guided by empirical information based on response to treatment with specific antifungal drugs and by information on drug administration and disposition extrapolated from mammalian and nonpsittacine avian studies; few published pharmacologic studies exist for psittacines. This information is useful, but differences in the disposition and clearance of antifungals among species may result in poor efficacy and safety. Additional pharmacokinetic information is needed to guide the treatment of fungal diseases in psittacines.

Fluconazole is a synthetic bis-triazole antifungal agent that is available in preparations for IV or oral administration. It is now available in generic formulations in the United States, which has decreased the cost and generated more interest among veterinarians. Like otherazole antifungal agents, fluconazole inhibits fungal ergosterol synthesis in cell membranes by interfering with the cytochrome P450 enzyme system. Unlike the azoles ketoconazole anditraconazole, fluconazole is water soluble and minimally protein bound in mammals (< 15%). In the mammalian species studied (mice, cats, dogs, horses, and humans), fluconazole is widely distributed throughout the body and penetrates some pharmacologically privileged spaces, including the eye and cerebrospinal fluid. Dermal concentrations may exceed plasma concentrations in humans. Fluconazole is minimally metabolized and is excreted primarily by the kidneys; in humans, approximately 80% of the dose is excreted unchanged in urine. Reported adverse effects are uncommon. Gastrointestinal upset is the most common complaint in humans, with a reported rate of 3.7%. Dose-dependent hepatitis is rare.

Fluconazole is most active against yeasts, including C albicans, Candida tropicalis, and some strains of Candida parapsilosis and Candida glabrata. A single 150-mg dose (approx 2.5 mg/kg for the typical 60-kg woman) has been used to treat vaginal C albicans infections; multiple-dose treatment is needed to treat systemic infections. Fluconazole also has activity against Cryptococcus, Blastomyces, Coccidioides, and Histoplasma spp. Fluconazole has poor in vitro activity against most filamentous fungi; however, rats and rabbits experimentally infected with an Aspergillus sp have had clinical improvement after treatment with fluconazole.
We hypothesized that fluconazole might be useful for treating yeast infections in psittacines; however, the disposition and safety of fluconazole have not been reported for any avian species. The purpose of the study reported here was to investigate the disposition and effects of orally administered fluconazole after single and multiple doses in a psittacine species, the Timneh African grey parrot (Psittacus erithacus timneh).

Materials and Methods
Animals—Forty adult Timneh African grey parrots weighing 295 to 375 g were used. All birds were judged healthy on the basis of physical examination and daily observation for at least 1 year prior to the study. These birds had not received any drugs within the previous 12 months. Birds were housed as surgically sexed pairs in suspended wire cages in rooms maintained at 18° to 22°C with a 12-hour photoperiod. They were fed water and a commercial pelleted parrot diet ad libitum. The North Carolina State University Institutional Animal Care and Use Committee approved the experimental protocol.

Experimental design for single-dose trials—Parrots were weighed and assigned to experimental groups that received one of the following doses of fluconazole orally: injectable fluconazole formulation at 10 mg/kg,9 fluconazole suspension (made from compounded tablets) at 10 mg/kg, or fluconazole suspension at 20 mg/kg. The injectable fluconazole formulation was reconstituted as directed by the manufacturer with saline (0.9% NaCl) solution to create a solution of 2 mg/mL. This solution was then diluted to 1 mg/mL with distilled water. A fluconazole suspension of 2 mg/mL for oral administration was made from 200-mg compounded fluconazole tablets9 by grinding the tablets with a mortar and pestle and mixing the powder with distilled water containing 30% methylcellulose. Methylcellulose was added as a suspending agent. The injectable solution and suspension were thoroughly mixed in separate containers by use of a magnetic stirrer for 4 minutes and then swirled in an Erlenmeyer flask just prior to delivery. Drug was delivered into the crop with a 12-F rubber feeding tube attached to a 6-mL syringe.

To avoid collecting excessive blood from individuals, birds in each study were placed into groups and each group was bled at 2 or 3 different time points. Naïve pooling of data points was used to generate a mean plasma fluconazole concentration at each time point, and these data were used for pharmacokinetic analysis. For study of the fluconazole suspension at 10 mg/kg, 20 birds were placed into 4 groups of 5 birds each and plasma samples for fluconazole assay were collected from each group at 2 or 3 of the following times: 1, 3, 6, 9, 12, 24, 31, 48, 60, and 72 hours after fluconazole administration. Birds in groups A through D were bled at the following times after fluconazole administration: group A birds at 3, 9, and 60 hours; group B birds at 6, 24, and 48 hours; group C birds at 12 and 31 hours; and group D birds at 1 and 72 hours. To study the injectable fluconazole formula and fluconazole suspension at 10 and 20 mg/kg, respectively, 12 birds were placed into 3 groups of 4 birds each and blood samples for analysis of plasma fluconazole concentrations were collected from each group at 3 of the following times: 1, 3, 6, 9, 12, 24, 31, 48, and 72 hours after fluconazole administration. Birds in groups A through C were bled at the following times after fluconazole administration: group A birds at 1, 9, and 48 hours; group B birds at 12, 24, and 31 hours; and group C birds at 3, 6, and 72 hours. Use of the fluconazole suspension resulted in exclusion of data from 1 bird in each experiment (ie, fluconazole at 10 and 20 mg/kg) because the birds regurgitated after fluconazole administration.

Blood samples (0.7 to 1 mL) were collected by venipuncture of the basilic or right jugular veins with heparinized syringes. Samples were centrifuged (6,600 × g) and plasma was decanted within 1 hour of collection. Plasma samples for determination of fluconazole concentrations were stored at −70°C until analyzed.

Experimental design for multiple-dose trial—Parrots used in the single-dose trials were rested for a minimum of 2 months prior to use in the multiple-dose trial. Twenty birds were allocated to 4 groups of 5 birds each. Birds in groups 1 and 2 received fluconazole at 20 mg/kg, PO; birds in group 3 received fluconazole at 10 mg/kg, PO; and birds in group 4 (ie, control group birds) received saline solution at 10 mL/kg, PO. All birds were dosed every 48 hours for 12 days. Suspensions of the crushed compounded fluconazole tablets were used for all fluconazole treatment groups.

Blood samples for plasma fluconazole analysis were collected from birds in groups 1, 3, and 4 at 48 hours after drug or saline solution administration on days 3, 7, and 9 and at 24 hours after drug or saline solution administration on day 14. Plasma samples for fluconazole analysis were collected from group 2 birds at 24, 32, and 48 hours following the first drug dose administered on day 1 and following the last drug dose administered on day 12. Group 2 birds were included to enable measurement of terminal half-life at the start and end of the experiment. Birds in all groups were monitored for signs of fluconazole toxicity. Birds were observed daily between 8:00 AM and 9:00 AM. Their activity level and condition of their droppings were scored by means of 4-point scales. Activity levels of birds were rated as follows: 1 = minimal, 2 = reduced, 3 = normal, and 4 = excessive. Characteristics of the droppings were rated as follows: 1 = scant quantity, 2 = diarrhea, 3 = normal quantity and quality, and 4 = polyuria. Parrots in groups 1, 3, and 4 were examined and weighed after each blood sample collection. The PCV, plasma total solids, and a panel of plasma biochemical tests (aspartate aminotransferase, alanine aminotransferase, albumin, total bile acids, calcium, creatine kinase, cholesterol, glucose, lactate dehydrogenase, phosphorus, total protein, and uric acid) were measured during the week before treatment and on days 7 and 14 in group 1, 2, and 4 birds. Biochemical analyses were performed on plasma samples by use of an automated analyser9 with the wet chemistry method. Water consumption was monitored by adding 150 mL of tap water to bowls in the morning and then measuring the amount remaining 24 hours later. An identical bowl was placed inside the room but outside of the cages to correct for evaporation.

Determination of fluconazole concentration—Fluconazole concentrations in plasma were determined by use of high-performance liquid chromatography with UV detection. The high-performance liquid chromatography system consisted of a pump, an automatic injector, and a variable-wavelength UV detector set at 210 nm. Computer software9 was used to record data from the system.

For high-performance liquid chromatography, fluconazole was eluted on a C-8 reverse-phase column with an isocratic mobile phase of 70% 0.01M potassium phosphate monobasic buffer (pH 3) and 30% acetonitrile at a flow rate of 1 mL/min and a constant column temperature of 40°C. Mobile-phase components were filtered and degassed before use. The mobile phase was sparged with helium throughout the analysis.

Stock solutions of fluconazole were prepared at concentrations of 1 mg/mL dissolved in acetonitrile. These solutions were further diluted with the mobile phase to obtain spiking solutions ranging in concentrations from 10 to 600 µg/mL. These solutions were used to spike blank
plasma from an African grey parrot for quality control and calibration standards. Concentrations of the calibration standards ranged from 0.50 to 30 μg/mL. Calibration curves were plotted on a linear graph of concentration versus response (absorbance units) by use of weighted least-squares regression. By use of plasma from an African grey parrot, new calibration standards were prepared on each day of analysis. All calibration curves were linear with an Rs value > 0.99. The within-day precision was within 15% of the mean value, and the accuracy was within 15% of true concentrations for all fortified concentrations. Analysis of a blank plasma sample pooled from 14 birds was performed to verify that no interfering peaks were found in the chromatogram. The limit of quantification for this assay (based on a signal-to-noise ratio of 10) was 0.10 μg/mL.

Samples (fortified samples and incurred samples) were prepared by first adding 100 μL of a 1:4 mixture of acetoniitrile-methanol to a microcentrifuge tube, followed by a 200-μL aliquot of each plasma sample. Tubes were vortexed to precipitate protein from the sample. After the addition of 1 mL of double-distilled water, tubes were vortexed again and then centrifuged at 7,200 g for 4 minutes. C-18 cartridges were inserted into a solid-phase extraction manifold and conditioned with 2 mL of 100% methanol followed by 2 mL of distilled water. Solid-phase extraction was used to further clean the samples by vacuuming (12.7 cm Hg) 500 μL of the sample (or fortified standard) through a C18 dual-zone cartridge. Cartridges were washed with 2 mL of double-distilled water and dried by applying the vacuum for 1 minute. Fluconazole was eluted with 1 mL of a 1:4 mixture of acetoniitrile-methanol. The eluate was evaporated under a flow of nitrogen in a heated water bath (45°C) for 20 to 25 minutes. Each sample was then reconstituted with 200 μL of mobile phase, vortexed, and transferred to a high-performance liquid chromatography injection vial. The injection volume was 40 μL. The retention times for fluconazole ranged from 3.2 to 3.4 minutes. The concentration of fluconazole in each sample was estimated from the response and linear regression analysis by use of the calibration curve generated from the run for the day.

Pharmacokinetic analysis—Pharmacokinetic analyses were performed by use of standard methods and equations and computer software for kinetic modeling with the least-squares method. The Akaike information criterion, residual sum of squares, and analysis of the residual plots were used to discriminate between models. A weighting factor of W = 1/Y2 was used for the curve analysis, where Y is the plasma concentration of fluconazole. Data obtained after oral administration of single doses of fluconazole were best described by use of a 1-compartment open model with first-order inputs, characterized by the following equation:

\[ C_t = \frac{Dose \times K_{01}}{V_d \times (K_{01} - K_{10})} \times (e^{-K_{10}t} - e^{-K_{01}t}) \]

where \( C_t \) is the plasma concentration at time t, \( V_d \) is the volume of distribution, \( K_{01} \) is the rate of absorption, and \( K_{10} \) is the rate of elimination and \( F \) is the fraction of drug absorbed.

The \( K_{01} \), \( K_{10} \), half-lives corresponding to \( K_{01} \) and \( K_{10} \), VDF, CL/F, \( C_{max} \), and time to \( C_{max} \) were calculated from compartmental analysis by use of standard pharmacokinetic methods. Values for volume of distribution and clearance are listed as needing correction for systemic absorption. True values are not known because IV administration of fluconazole was not performed. In the multiple-dose trial, the terminal half-life was equal to 0.693/terminal rate constant as derived from the terminal slope of the concentration-time profile plotted on a semilogarithmic graph.

Statistical analysis—Values are expressed as mean ± SEM. The SEM was used as a result of the small sample sizes. Differences in body weight and the fluconazole plasma concentrations in group 2 birds at the start and end of the multiple-dose trial were analyzed by use of the Wilcoxon rank sum test; a 1-way ANOVA on ranks was used to compare differences in fluconazole concentrations on days 3, 7, and 9 of the multiple-dose trial. Commercial software was used to perform calculations. Values of \( P < 0.05 \) were considered significant.

Results

Single-dose trials—Plasma concentrations versus time curves and pharmacokinetic parameters were derived from the single-dose trials (Figures 1–3; Table 1). Doubling the dose of fluconazole (ie, the suspension) from 10 to 20 mg/kg resulted in an approximate 3.4- and 2.5-fold increase in mean area under the curve and \( C_{max} \), respectively. We could not calculate the true oral absorption of fluconazole in this study because IV administration of fluconazole was not performed. Therefore, results for volume of distribution and clearance are reported as VD/F and CL/F.

Multiple-dose trials—Mean trough plasma fluconazole concentrations at 48 hours after administration were < 1.5 μg/mL for the dose of 10 mg/kg (overall median, 0.90 μg/mL; range, 0 to 2.49 μg/mL) and ranged from 2.3 to 4.3 μg/mL for the dose of 20 mg/kg (overall median, 3.77 μg/mL; range, 1.91 to 6.78 μg/mL; Figure 4). At 48 hours after fluconazole administration, no fluconazole was detected in plasma samples of 1 bird treated with a dose of 10 mg/kg. On day 14, mean plasma concentrations at 24 hours after fluconazole administration were 4.7 (median, 3.4 μg/mL; range, 1.93 to 5.19 μg/mL) and 6.8 μg/mL (median, 7.2 μg/mL; range, 1.45 to 9.25 μg/mL) in birds given fluconazole at 10 and 20 mg/kg, respectively. When plasma fluconazole concentrations on days 3, 7, and 9 were compared, a significant difference was found only between days 7 and 9 in birds given fluconazole at 10 mg/kg. Plasma concentrations were used to calculate elimination half-lives (Figure 3). The mean elimination half-life was 11.4 and 16.3 hours on days 1 and 13, respectively. No significant differences were found in mean plasma concentrations when mea-
surements obtained at the same time points on days 1 and 13 of treatment were compared. No adverse effects of treatment were observed and no abnormalities were observed in the parameters measured during the daily behavioral observations. Water consumption was measured daily but was judged to be inaccurate because birds bathed and placed food in their water bowls. Mean percent body weight loss between days 1 and 13 of the multiple-dose trial was 1.1 ± 0.1%, 1.9 ± 0.1%, and 2.6 ± 0.1% in the birds receiving fluconazole at 20 mg/kg, fluconazole at 10 mg/kg, and saline solution at 10 mL/kg, respectively. No significant difference in the body weight loss was found between treatment group birds and control group birds. Most hematologic and plasma biochemical parameters were within reference ranges at the start and end of the 14-day treatment period. Exceptions include a mild transient increase in plasma creatine kinase activity (range, 447 to 968 U/L; reference range, 135 to 410 U/L) in 2 birds before treatment, 2 birds on day 7, and 3 birds on day 14. A mild-to-moderate increase in plasma bile acid concentrations (range, 108 to 162 µmol/L; reference range, 12 to 96 µmol/L) was seen in 1 bird before treatment, a different bird on day 7 (group 1 bird), and another bird on day 14 (control group bird). One bird (group 3 bird) had a transient mild increase in plasma lactate.

Table 1—Mean pharmacokinetic parameters of fluconazole after oral administration in Timneh African grey parrots (Psittacus erithacus timneh).

<table>
<thead>
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<th>Variables</th>
<th>Injectable formulation (10 mg/kg)</th>
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<th>Suspension of tablets (20 mg/kg)</th>
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<td>10.19</td>
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<tr>
<td>CL/F (mL/h/kg)*</td>
<td>53.39</td>
<td>64.71</td>
<td>38.25</td>
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</table>

*Ture values for systemic absorption (F) are not known because IV administration of fluconazole was not performed.

Figure 2—Plasma concentrations of fluconazole in Timneh African grey parrots (fitted curve [solid line]; open circles [individual samples]) after oral administration of a fluconazole suspension at a single dose of 10 mg/kg.

Figure 3—Plasma concentrations of fluconazole in Timneh African grey parrots (fitted curve [solid line]; closed diamonds [individual samples]) after oral administration of a fluconazole suspension at a single dose of 20 mg/kg.

Figure 4—Mean ± SEM plasma concentrations of fluconazole in Timneh African grey parrots after oral administration at 10 or 20 mg/kg, every 48 hours for 12 days. Samples on days 3, 7 and 9 were collected 48 hours after fluconazole administration. Samples on day 13 were collected 24 hours after fluconazole administration.

Figure 5—Mean ± SEM plasma concentrations of fluconazole in Timneh African grey parrots at the start (day 1) and end (day 13) of a 12-day multiple-dose treatment regimen (20 mg/kg, PO, q 48 h).
Discussion

To our knowledge, results of our study represent the first data to describe the disposition of fluconazole in any avian species. The terminal half-life of fluconazole in Timneh African grey parrots (9 to 16 hours) is similar to that of cats (12 to 25 hours) and dogs (15 hours); shorter than that of humans (22 to 44 hours), horses (38 to 42 hours), and sea turtles (132 to 139 hours); and longer than that of rats (4 hours). In the multiple-dose trial, the terminal half-life increased 1.4-fold when values on day 1 and 13 were compared; however, plasma concentrations did not differ significantly, so it is likely that the half-life difference is the result of random variability. Plasma concentrations at 24 and 48 hours after fluconazole administration on days 1 and 13 were similar to each other and to those observed in the single-dose trial. Fluconazole does not accumulate nor appear to alter its own metabolism at the doses and treatment period of our study.

Adverse effects of fluconazole are uncommon in humans but can include headache, rash, vomiting, abdominal pain, diarrhea, and dose-dependent hepatic toxicity. Two birds regurgitated during fluconazole administration in the single-dose trials. This may have been caused by adverse effects of fluconazole but was most likely a consequence of gavage administration and handling. We did not see regurgitation nor detect adverse effects of treatment in the multiple-dose trial with fluconazole administration at either 10 or 20 mg/kg, every 48 hours. Birds maintained body weight and had normal droppings and behavior. The transient, mild increases in plasma creatine kinase activity seen in a few birds were likely the result of muscle damage caused by handling and were not considered clinically important. The clinical importance of single occurrences of an increase in plasma bile acid concentrations seen on 3 days in 3 birds (including 1 control group bird) is unknown. High plasma bile acid concentrations can indicate hepatic dysfunction; however, we have observed transient, apparently benign increases in plasma bile acid concentrations in African grey parrots previously. Anemia was found in 2 birds (1 control group bird and 1 bird treated with fluconazole at 20 mg/kg) at the end of treatment. The cause is unknown but may be the result of repeated blood sample collection. Although adverse effects were not found during our study with healthy birds, they might occur when fluconazole is used in ill birds.

Timneh African grey parrots are difficult subjects for pharmacokinetic studies because of their expense, temperament, and small body size and the difficulty of repeated blood sample collection. These factors influenced our study design. Administering drugs to parrots is difficult for veterinarians and bird owners, so treatment regimens with a long dosing interval were selected. A study on IV administration would have allowed calculation of bioavailability and VD but was not included because of the difficulty of IV administration and the potential risk of toxic drug effects and vessel damage in these small, expensive birds. Results of oral administration of the injectable fluconazole formulation were studied to rule out differences in absorption that may be caused by compounding or dissolution of tablets. The area under the curve for the injectable fluconazole formulation was 21.12% greater than that for fluconazole suspension. This may indicate greater bioavailability of the injectable formulation; however, the difference could also be the result of random variability. A suspension of fluconazole for oral administration is commercially available but was not tested in our study.

Naive pooling of data from multiple birds was used to calculate pharmacokinetic parameters and plot the concentration versus time curves. This was necessary because the small size of the birds precluded collecting blood samples for all time points from a single bird. It is a limitation that this method does not allow measurement of variability in the calculated pharmacokinetic parameters because the pooled concentrations are analyzed as if they are derived from a single bird. In addition, blood sample collection times were clustered in group B birds in the study of oral administration of the injectable fluconazole formulation (10 mg/kg) and fluconazole suspension (20 mg/kg). It may have been more representative of the population to allocate groups to time points in an overlapping manner, rather than grouping some time points as was done in our study. These limitations could affect the precision of the pharmacokinetic values reported in our study but are unlikely to alter dosage recommendations.

The mean C_{max} of fluconazole after oral administration of the fluconazole suspension at 10 and 20 mg/kg was 7.45 and 18.59 µg/mL, respectively. These values are similar to the reported C_{max} in humans treated with fluconazole at 3.3 or 6.6 mg/kg (10.1 and 18.9 µg/mL, respectively). Authors of 1 review article suggest that for optimum treatment of candidiasis in humans, the steady-state concentrations should fluctuate between a peak of 20 µg/mL and trough of 3 µg/mL. In the multiple-dose trial, mean trough concentrations measured on days 3, 7, and 9 following fluconazole administration at 20 mg/kg every 48 hours were 4.1, 2.5, and 3.1 µg/mL, respectively, indicating that this dose maintains adequate trough concentrations.

Fluconazole has potential for treating yeast infections in psittacines. The susceptibility of Candida organisms to fluconazole varies depending on the Candida spp and strain. We were unable to find antimycotic drug susceptibility data for yeast isolated from psittacine or other birds; however, data for humans are available. In a recent survey of 728 isolates of Candida organisms isolated from humans, the 90% MIC of fluconazole for C albicans, C tropicalis, C parapsilosis, and C glabrata was 0.5, 1, 8, and 63 µg/mL, respectively. If C albicans susceptibility is similar in parrots, fluconazole administration at 10 mg/kg every 48 hours would maintain plasma concentrations above the 90% MIC for the entire dosing interval for most birds. Fluconazole administration at 10 mg/kg every 24 hours or at 20 mg/kg every 24 to 48 hours would like-
ly be effective for the treatment of a yeast with an MIC < 6 µg/mL. *Candida glabrata* and *C. parapsilosis* have greater resistance, and the MIC of the infecting agent would need to be measured before deciding to use fluconazole as a method of treatment.

Results of our study indicate that treatment with fluconazole administered orally at 10 to 20 mg/kg every 24 to 48 hours can maintain plasma concentrations in African grey parrots that exceed the MIC of many strains of *C. albicans* and *C. tropicalis*. Lower doses might be effective for highly susceptible yeast strains. The capture and restraint needed to orally administer drugs to parrots are challenging, so the prolonged dosing interval of 24 to 48 hours is a marked advantage of this treatment regimen. Although promising, additional trials and clinical observations are needed to prove that this dosage regimen is safe and effective in ill birds and other psittacine species.

### References