Bioencapsulation is a feasible method of terbinafine administration in *Emydomyces testavorans*-infected western pond turtles (*Actinemys marmorata*).

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**OBJECTIVE**
To evaluate the pharmacokinetics of terbinafine administered to western pond turtles (*Actinemys marmorata*) via oral gavage and bioencapsulated in earthworms.

**ANIMALS**
7 western pond turtles.

**PROCEDURES**
A randomized complete crossover single-dose pharmacokinetic study was performed. Compounded terbinafine (25 mg/mL; 30 mg/kg) was administered through oral gavage (OG) directly into the stomach or bioencapsulated (BEC) into an earthworm vehicle. Blood (0.2 mL) was drawn from the jugular vein at 0, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, and 120 hours after administration. Plasma terbinafine levels were measured using high-performance liquid chromatography.

**RESULTS**
Peak plasma terbinafine concentrations of 786.9 ± 911 ng/mL and 1,022.2 ± 911 were measured at 1.8 ± 2.8 and 14.1 ± 12.3 hours after OG and BEC administration, respectively. There was a significant (*P* = .031) increase in area under the curve with BEC compared to OG. Using steady-state predictions, with once-daily terbinafine administration, 3/7 and 7/7 turtles had plasma concentrations persistently greater than the minimum inhibitory concentration (MIC) for *Emydomyces testavorans* for the OG and BEC administration routes of administration, respectively. With administration every 48 hours, 3/7 turtles for the OG phase and 6/7 turtles for the BEC phase had concentrations greater than the *E. testavorans* MIC throughout the entire dosing interval.

**CLINICAL RELEVANCE**
Administration of terbinafine (30 mg/kg) every 24 or 48 hours via earthworm bioencapsulation in western pond turtles may be appropriate for the treatment of shell lesions caused by *E. testavorans*. Clinical studies are needed to assess the efficacy of treatment.

*Emydomyces testavorans* (ET) is an emerging onygenalean fungus associated with chronic shell lesions in freshwater chelonians.¹² There is currently a strong association between ET and ulcerative shell disease, resulting in morbidity and mortality.²–⁵ To date, infection has been confirmed in a wide variety of chelonians under human care, including the western pond turtle (*Actinemys marmorata*).²⁴–⁷ Western pond turtles are classified as vulnerable or endangered across their home range and are designated as a priority species for conservation under the Association of Zoos and Aquariums (AZA) Saving Animals From Extinction (SAFE) program.⁸–¹⁰ While the overall prevalence of ET in wild populations is unknown, its prevalence may be as high as 84% in head-start facilities, significantly impacting conservation efforts for this species.⁴ Effective treatment of mycoses in reptiles often requires a prolonged treatment course spanning months of orally administered antifungal medications.¹¹,¹² Terbinafine is an attractive option for antifungal therapy for the treatment of ET for several reasons; high margin of safety and rare reports of toxicity across multiple species, drug accumulation occurs within keratinized shell tissues, and the presence of in vitro published minimum inhibitory
concentration (MIC) data for ET. Broth dilution terbinafine susceptibility testing from 3 clinical ET isolates has demonstrated MICs between 15 and 60 ng/mL. However, oral medication administration in chelonians can be challenging due to the ability of individuals to pull their heads into their shells and the challenges associated with manually opening their beaks. Bioencapsulation is a method of drug administration whereby a drug is accumulated into a biological substrate. This technique has been used in human medicine to enhance solubility and control the release of antimicrobials at specific locations. Recent bioencapsulation studies have shown promise for the treatment of Alzheimer’s disease, diabetes mellitus, Gaucher’s disease, and hypertension and in the development of vaccine and allergy therapies. Bioencapsulation has been used in aquatic animal medicine to improve compliance with medical treatments by using highly palatable live food organisms, such as brine shrimp (Artemia spp.), to deliver antibiotics, antifungals, and antiparasitics. In the case of carnivorous and/or insectivorous species, bioencapsulation into a prey item for consumption by the target species presents a novel strategy for pharmacotherapeutic delivery.

The objectives of this study were to determine and compare the pharmacokinetics of single-dose terbinafine administered by oral gavage and bioencapsulation within an invertebrate vector to western pond turtles clinically affected with ET. We hypothesized that oral and bioencapsulated terbinafine would provide plasma concentrations that exceed the plasma MIC against ET (15 to 60 ng/mL) and that there would be minimal differences in plasma concentrations between the 2 delivery methods.

Materials and Methods

Animals

Seven, 6-year-old, male western pond turtles (600 to 668 g) housed at the John G. Shedd Aquarium were enrolled in this study. This project was approved by the research oversight and approval committee at the John G. Shedd Aquarium. These turtles are on loan from the Washington State Department of Fish and Wildlife and were approved for participation in this study. Turtles were housed together in an acrylic 180 X 73 X 70-cm enclosure located within a temperature-controlled room (24 to 25.5 °C). Turtles had access to freshwater for swimming at all times with 2 haul-out areas for basking. The diet was varied daily between pellets (Aquatic turtle diet 5MB7, Mazuri), earthworms (Lumbricus terrestris), crickets (Gryllodes sigillatus), and capelin (Mallotus villosus). Water temperature ranged between 24.5 °C and 25 °C, and basking area temperature ranged between 36.6 °C to 37.7 °C. Full-spectrum UV light (ZooMed Laboratories, Inc) was provided on a 12-hour cycle.

The turtles were received by the John G. Shedd Aquarium in October 2017. Two turtles had a confirmed infection with ET based on shell biopsies, clinical signs, and positive cutaneous keratin ET qPCR (Wildlife Epidemiology Laboratory, University of Illinois College of Veterinary Medicine). Two turtles were strongly suspected of having ET based on clinical signs of mild irregular defects on the carapace and plastron, with bone lesions confirmed on computed tomography (CT) scans and positive cutaneous keratin ET qPCR. The remaining 3 turtles tested positive for ET via cutaneous keratin qPCR and had mild defects on the carapace and plastron confirmed on CT scans.

These animals had received multiple treatments for this infection over the past 2 years, resulting in quiescence of lesions but not a resolution of infection based on serial cutaneous keratin qPCR evaluation. No antifungal medication had been administered for 6 months prior to this study. CT scans and cutaneous keratin qPCR performed 1 month prior to the start of this study confirmed the presence of shell lesions associated with keratin inclusion cysts with confirmed ET DNA in all 7 individuals. Although infected with ET, all animals were otherwise healthy based on clinical observations (stable weight, activity, appetite, and eliminations) and unremarkable results of complete blood count, serum biochemistry, and protein electrophoresis performed 2 weeks prior to the start of this study.

Pilot studies

Oral terbinafine pharmacokinetics

To determine an appropriate dose and sampling protocol, a pilot study was performed. Three randomly assigned turtles received 30 mg/kg terbinafine by oral gavage and then were immediately fed a single earthworm each. Blood (0.2 mL) was sampled at 0, 0.5, 1, 2, 4, 8, 12, 24, 48, and 72 hours postadministration. The total amount of blood drawn was < 0.4% body weight of each individual animal. Blood was collected into lithium heparin microtainers, kept on ice, and centrifuged within 1 hour of collection. Plasma was stored at −80 °C until analysis.

Bioencapsulation

To assess the feasibility of terbinafine bioencapsulation, injection trials were performed in 10 earthworms. Earthworms were first anesthetized with isoflurane until the cessation of response to stimuli was achieved. They were then injected with sterile saline with food-coloring dye to assess for potential leakage. Each earthworm was injected with 0.8 mL of saline-dye intracelomically and then assessed for 1 hour for signs of overt leakage of dye. Earthworms were then euthanized via exposure to isoflurane for 1 hour and then transected at the level of the injection site for examination.

Single-dose pharmacokinetics of terbinafine by oral gavage and bioencapsulation

Study design

Each of the 7 turtles was randomly assigned by random number generator (RStudio, version 1.3.1073) to have terbinafine (30 mg/kg) administered via oral gavage (OG) or bioencapsulation (BEC) at time zero after a 24-hour fast. Blood (0.2 mL) was
drawn from the jugular vein at times 0, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, and 120 hours after drug administration, based on the concentration-time curves obtained during the pilot study. The total amount of blood drawn from each turtle was < 0.4% of body weight (~2.2 mL). After a 3-week washout period, based on a minimum of 10 half-lives established in the pilot data and accounting for staff availability, turtles received the alternative administration route (OG or BEC). All samples were collected in lithium heparin microtainer tubes without a gel separator and kept on ice until centrifuged within 1 hour of collection. Plasma was stored at −80°C until shipped on dry ice for sample analysis.

**Terbinafine formulation**

An oral suspension (25 mg/mL) of terbinafine was compounded from commercially available tablets (NorthStar Rx; 250 mg of terbinafine/tablet) based on a published formulation shown to be stable in solution for 42 days at 25°C and 4°C. Briefly, 20 tablets were crushed into a fine powder in a mortar, then passed through a sieve and diluted to a concentration of 25 mg/mL with a 1:1 mixture of Ora-Sweet and Ora-Plus (Perrigo Company). The suspensions were made fresh for each group on the day prior to administration and stored in 2-ounce amber polyethylene prescription bottles at 4°C until administration. The suspensions were mixed prior to administration.

**Oral gavage administration**

Under manual restraint, each turtle received a single oral dose of terbinafine (30 mg/kg), administered through a curved, 18-gauge X 4-inch stainless-steel feeding tube directly into the stomach (0.72 to 0.80 mL). The gavage tube was then flushed with 2 mL of water. After being observed for signs of regurgitation, turtles were then offered a commercially sourced earthworm (*Lumbricus terrestris*) and observed for ingestion.

**Bioencapsulated administration**

Earthworms were injected with terbinafine oral suspension intracoelomically using a 27-gauge needle on a 1-mL syringe at a dose of 30 mg/kg body weight of the receiving turtle (0.72 to 0.80 mL). Injections were performed in the proximal peristomium with the needle inserted superficially at a 45° angle. Each bioencapsulated earthworm was then immediately offered to the respective turtle and then observed for obvious leakage of the terbinafine during mastication and ingestion.

**Plasma terbinafine quantification**

Standard curves for plasma analysis were prepared by fortifying untreated, pooled western pond turtle plasma with terbinafine to produce a linear concentration range of 5 to 1,500 ng/mL. The plasma quality control (QC) samples used for validation were 15, 350, and 1,200 ng/mL. The recoveries were 98% ± 13, 91% ± 3, and 95% ± 3 for 15, 350, and 1,200 ng/mL, respectively. The mean measured concentration and standard deviation for the intra-assay QC numbers were 14 ± 1, 349 ± 8, and 1226 ± 83 while the interassay numbers were 15 ± 1, 357 ± 14, and 1243 ± 12 for 15, 350, and 1,200 ng/mL, respectively. All of the relative standard deviations were < 10%. The lower limit of quantification was 5 ng/mL.

Plasma samples were analyzed using a reverse-phase high-performance liquid chromatography method. The system consisted of a 2,695 separations module, a 2,487 absorbance detector, and a computer equipped with Empower software (Empower 3 Chromatography Software; Waters Corp). Terbinafine was extracted from plasma samples using liquid extraction. Briefly, previously frozen plasma samples were thawed and vortexed, and 100 µL was transferred to a clean screw-top test tube followed by 75 µL internal standard (1.0 µg/mL butenafine). Hexane (3 mL) was added, and the tubes were rocked for 20 minutes and then centrifuged for 20 mins at 1,000 X g. The organic layer was transferred to a clean tube and evaporated to dryness with nitrogen gas. Samples were reconstituted in 250 µL of mobile phase, and 100 µL was analyzed.

The compounds were separated on a Symmetry Shield C18 (4.6 X 100 mm, 5 µm) column with a Symmetry Shield C18 guard column (Waters Corp). The mobile phase was a mixture of (A) 20 mM phosphoric acid with 0.1% triethylamine adjusted to pH 3.0 and (B) acetonitrile (65:35). The flow rate was 1.1 mL/min, and the column temperature was ambient. Absorbance was measured at 224 nm.

**Statistical analysis**

Continuous data are presented as mean ± standard deviation. Non-compartmental pharmacokinetic analysis was performed using Phoenix WinNonlin (Certara L.P.) for both OG and BEC phases. To evaluate differences in terbinafine pharmacokinetics between formulations, comparisons were made using commercial software (Prism 9; GraphPad Software Inc) between the following parameters: half-life (t1/2), maximum concentration (Cmax), time to Cmax (Tmax), area under the curve extrapolated to infinity (AUC0-∞), and mean residence time (MRT). First, data were tested for normality using the Komogorov-Smirnov test and then compared between formulations using either a paired t test or Wilcoxon signed rank test. Significance was set at P < 0.05.

Steady-state predictions of terbinafine concentrations following once daily (q 24 h) or every other day (q 48 h) 30 mg/kg OG or BEC administration were made using the NonParametric Superposition function in WinNonlin, which assumes linear pharmacokinetics are present for the investigated drug. Predicted plasma concentrations were compared to the MIC for ET, 60 ng/mL. Accumulation ratios (AR) for both formulations at both dosing intervals were also calculated:

$$AR = \frac{1}{1-e^{-\lambda_2 \tau}}$$

where $\lambda_2$ is the terminal rate constant and $\tau$ is the dosing interval.
Results

Pilot studies
In the initial pilot study (30 mg/kg), all 3 western pond turtles achieved plasma concentrations greater than the MIC for ET (60 ng/mL) by 0.5 hours and terbinafine had an average terminal phase half-life of 22.2 hours. Plasma concentrations were maintained above 60 ng/mL for at least 48 hours.

Bioencapsulation was performed with a saline/food coloring mixture (0.8 mL) in 8 earthworms with no overt evidence of leakage from the injection site. In 2 earthworms, inadvertent gastrointestinal injection occurred resulting in immediate expulsion of digesta/feces from the mouth and anus. Following humane euthanasia and transection of the remaining 8 earthworms, minimal leakage (1 to 2 drops) was noted from the site of transection.

Single dose pharmacokinetics of terbinafine
Turtles were observed to readily consume bioencapsulated earthworms with no overt evidence of terbinafine leakage or regurgitation noted. Similarly, there was no overt evidence of leakage or regurgitation when terbinafine was administered via oral gavage. Plasma terbinafine concentration-time curves are presented in Figure 1, and pharmacokinetic parameters are presented in Table 1 for both OG and BEC phases. Plasma concentrations for all western pond turtles administered terbinafine in the OG phase and 5/7 turtles in the BEC phase exceeded the target MIC concentration of 60 ng/mL by 0.5 hours after administration. The remaining 2 turtles from the BEC phase exceeded the MIC by 2 and 8 hours after administration. Three of the 7 turtles from the OG phase and 4/7 from the BEC phase remained above the MIC for ET for > 48 h. Throughout the duration of this study, all animals tolerated terbinafine well with no overt clinical signs suggestive of toxicosis or adverse reaction.

Table 1 demonstrates the major pharmacokinetic parameters compared between the 2 routes of administration (OG and BEC). AUC$_{0-\infty}$ was significantly greater (P = .031) with BEC administration compared to OG administration with 6/7 turtles displaying a higher AUC$_{0-\infty}$ in the BEC versus OG phase. While not statistically significant, 4/7 turtles had greater t$_{1/2}$ (P = .0687) and 5/7 had greater MRT (P = .723) with BEC compared to OG administration.

Steady-state predictions
Steady-state prediction parameters and accumulation ratios are presented in Table 2. With once-daily administration of terbinafine, plasma concentrations were predicted to be greater than the MIC for ET for 100% of the dosing interval in 3/7 turtles administered terbinafine by OG and in 7/7 turtles administered terbinafine via BEC. With administration every 48 hours, 3/7 turtles from the OG phase and 6/7 turtles from the BEC phase were predicted to have terbinafine concentrations higher than the MIC for ET throughout the entire dosing interval.

Figure 1—Mean ± SD plasma terbinafine concentration over time following oral gavage (OG) or bioencapsulated (BEC) administration of a single dose of terbinafine (30 mg/kg) to 7 male western pond turtles (Actinemys marmorata). Concentration versus time graphs are depicted using both a linear scale (initial curve) and semilog plot (insert).
Table 1—Values for noncompartmental pharmacokinetic parameters after administration of terbinafine (30 mg/kg) via oral gavage (OG) and bioencapsulation (BEC) to 7 male western pond turtles (Actinemys marmorata).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oral gavage (OG)</th>
<th>Bioencapsulated (BEC)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Min</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>786.9 ± 245.8</td>
<td>(50.5–1,177.2)</td>
<td>179.6</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>1.8 ± 0.7</td>
<td>(1.6–4.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>26.2 ± 12.7</td>
<td>(16.2–44.9)</td>
<td>12.7</td>
</tr>
<tr>
<td>λ&lt;sub&gt;z&lt;/sub&gt; (h&lt;sup&gt;−1&lt;/sup&gt;)</td>
<td>0.03 ± 0.01</td>
<td>(0.02–0.04)</td>
<td>0.02</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-last&lt;/sub&gt; (h·ng/mL)</td>
<td>10,574 ± 2,560</td>
<td>(138.2–2,824.3)</td>
<td>1,086</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;ss&lt;/sub&gt; (h·ng/mL)</td>
<td>10,907 ± 2,560</td>
<td>(138.2–2,824.3)</td>
<td>1,086</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;ssExtrap&lt;/sub&gt; (%)</td>
<td>8.7 ± 0.7</td>
<td>(8.0–20.4)</td>
<td>1.2</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>35.3 ± 727.1</td>
<td>(17.8–196)</td>
<td>17.8</td>
</tr>
</tbody>
</table>

AUC<sub>0-last</sub> = Observed AUC. AUC<sub>ss</sub> = The AUC from time 0 to infinity. AUC<sub>ssExtrap</sub> = % of AUC extrapolated beyond last observation. λ<sub>z</sub> = Elimination rate constant. MRT = Mean residence time.

*P < .05, statistically significant difference. P values depict the statistical difference between OG and BEC.

Table 2—Predicted average terbinafine concentrations at steady state for administration of terbinafine (30 mg/kg) administered via oral gavage (OG) and bioencapsulation (BEC) using 24- and 48-hour dosing intervals.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oral gavage (OG)</th>
<th>Bioencapsulated (BEC)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>q 24 h Administration</td>
<td>q 48 h Administration</td>
<td>q 24 h Administration</td>
</tr>
<tr>
<td>C&lt;sub&gt;ss&lt;/sub&gt; (ng/mL)</td>
<td>469.2 ± 245.8</td>
<td>(138.2–2,824.3)</td>
<td>234.4 ± 245.8</td>
</tr>
<tr>
<td>T &gt; MIC (%)</td>
<td>88 ± 30</td>
<td>(21–100)</td>
<td>56 ± 42</td>
</tr>
<tr>
<td>AR</td>
<td>2.1 ± 0.7</td>
<td>(1.6–3.2)</td>
<td>1.4 ± 0.3</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation (range).

AR = Accumulation ratio. C<sub>ss</sub> = Predicted average terbinafine concentration at steady state. T > MIC = Percentage of dosing interval during which plasma concentrations were predicted to be greater than the MIC for ET (60 ng/mL).

Discussion

The data presented in this study support that terbinafine, administered via OG and BEC at a dose of 30 mg/kg, is sufficient to reach target MICs for ET and may be a useful therapy with either route of administration in treating infections caused by ET. The results demonstrate that bioencapsulation is a feasible method for terbinafine administration in western pond turtles given that the AUC for BEC is higher than the OG, corresponding to overall greater terbinafine exposure.

Following a single dose given by oral gavage, terbinafine reached its maximal plasma concentration at 1.8 hours, on average. The T<sub>max</sub> of terbinafine given via OG was similar to that of red-eared sliders (Trachemys scripta elegans, 1.3 hours), cats (Felis catus, 1.3 hours), horses (Equus ferus caballus, 1.7 hours), and dogs (Canis lupus familiaris, 2.0 hours) but faster than that of red-tailed hawks (Buteo jamaicensis, 3.4 hours), African penguins (Spheniscus demersus, 4.0 hours), Hispaniolan amazon parrots (Amazona ventralis, 6.4 hours), and bearded dragons (Pogona vitticeps, 13.0 hours). 29–35

Given the small sample size of this study, the study was likely underpowered to detect statistical differences. The difference in T<sub>max</sub> between the administration groups (BEC and OG) was not statistically significant (P = .062), and administration of terbinafine via BEC reached maximal plasma concentration at 14.1 hours on average compared to 1.8 hours in the OG group.

Peak plasma concentrations in western pond turtles were similar between both routes of administration (787 ± 1,171 and 1,022 ± 785 ng/mL for OG and BEC, respectively). These concentrations were greater than that of bearded dragons and horses administered a 20-mg/kg dose (434 and 310 ng/mL, respectively), red eared sliders, and African penguins receiving a 15-mg/kg dose (201 and 300 ng/mL, respectively). Hispaniolan amazon parrots receiving a 60-mg/kg dose (353 ng/mL), and western pond turtles administered an 18-mg dose (27 to 91 mg/kg) via nebulization (no plasma levels detected). 30–33,35,36

The greater Cmax in western pond turtles may be due to species differences in absorption, potentially secondary to gastrointestinal environment, terbinafine solubility, or delayed metabolism given their slower overall metabolic rate. However, both routes of administration resulted

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enrolled in this study had no evidence of hepatic or renal compromise on diagnostic testing, species differences in hepatic and renal function including slower glomerular filtration rates (5 to 25 mL/kg/h), the impact of ambient temperature on metabolism, and potential effects of the renal and hepatic portal systems in reptiles may alter terbinafine pharmacokinetics compared to birds and mammals.

In our study, plasma concentrations at steady state were predicted based on a single OG and BEC dose of terbinafine, which is a first step in establishing a dosing interval. When administered via BEC, a 30-mg/kg terbinafine dose was predicted to result in plasma concentrations greater than the highest reported MIC of ET for the entire dosing interval in all 7 turtles when given once daily and 6/7 turtles when given every 48 hours. In contrast, a 30-mg/kg dose administered by OG either every 24 or 48 hours was predicted to achieve concentrations greater than the highest published MIC for ET in only 3/7 turtles throughout the dosing interval. Although steady-state plasma drug concentrations can be predicted from single-dose data, these predictions rely on the assumptions that there is no enzyme induction nor saturation kinetics, which is unknown in western pond turtles, although neither has been reported for terbinafine in other chelonians. These predictions were also used to determine the proposed dosing interval based on the assumption of terbinafine being time dependent in its antifungal action in cheloni- ans. It is currently not known whether terbinafine is time or concentration dependent in its antifungal action thus leading to uncertainty in the design of a dosing interval for this species. Additionally, all turtles in this study were males. In bearded dragons, females had higher plasma terbinafine concentrations than males, suspected to be due to higher volumes of distribution from seasonal plasma protein fluctuations from vitellogenesis. In the current study, all turtles had unremarkable complete blood count, serum biochemistry, and protein electrophoresis results. Further research is necessary to assess for potential differences in terbinafine pharmacokinetics between males and females. In this study, the multiple dose predictions were determined from turtles that were fasted for 24 hours, which is impractical for chelonians requiring multiple dose therapy. Future research should assess whether feeding will affect the pharmacokinetics of terbinafine administered to western pond turtles. Additional limitations of this study include a small sample size and lack of multidose data, both of which could be addressed in future larger-scale studies. Furthermore, the turtles enrolled in this study, while deemed systemically healthy based on bloodwork, were clinically affected to differing degrees with ET. Thus, disease burden could have affected absorption, distribution, metabolism, or elimination.

Turtles in this study showed intersubject variability in plasma concentrations as reflected in the wide range of C_max for both OG (179.6 to 2,757 ng/mL) and BEC (332.8 to 2,560.9 ng/mL). This interindividual variation is likely a reflection of differential
absorption, distribution, and clearance between individuals. A high degree of interindividual variability has also been reported in dogs, cats, bearded dragons, Hispaniolan Amazon parrots, red-tailed hawks, African penguins, and red-eared sliders following oral administration of terbinafine.29–35 There is also the potential for concentration variability between the batches of terbinafine solution given the randomized complete crossover design of this study. The high variation in plasma concentrations should be taken into consideration when evaluating response to treatment in clinical cases, given that some animals may not achieve effective concentrations.

In conclusion, terbinafine (30 mg/kg) administered every 24 to 48 hours via bioencapsulation within an earthworm vehicle may be useful in treating infections caused by ET in western pond turtles by producing plasma concentrations greater than the MIC (60 ng/mL) for ET. Similarly, oral gavage of 30 mg/kg terbinafine followed by a small meal may be useful in treating ET, although steady-state predictions were less favorable for this route of administration. Multiple-dose pharmacokinetic and controlled treatment trials are needed to confirm these recommendations.

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