

## ADVANCES IN REPTILE CLINICAL THERAPEUTICS

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**Abstract**

The standard of today's reptile practice calls on clinicians to use an ever-increasing array of diagnostic tools to gather information and obtain a definitive diagnosis. Few, if any, pathognomonic signs exist for reptile diseases, and for most clinical syndromes there is a lack of information regarding pathophysiology for one to define standard therapeutic protocols based solely on clinical signs without objective diagnostic information. For example, in the relatively distant past, clinicians treating reptile patients would routinely administer parenteral calcium to green iguanas (*Iguana iguana*) with the primary presenting clinical sign of muscle tremors. Today, veterinarians who treat reptiles recognize that the risk of soft tissue mineralization and permanent damage to arteries, renal tubules, and other tissues usually outweighs the potential short-term benefit of calcium therapy. Before calcium therapy is initiated, it is best to know the patient's ionized calcium concentration to reduce the risk of potential adverse therapeutic side effects. A problem-oriented diagnostic approach directed toward minimizing risk and maximizing therapeutic benefit is now the standard of reptile practice. Copyright 2014 Elsevier Inc. All rights reserved.

**Key words:** antibiotic; antifungal; antiparasitic; antiviral; reptiles; therapy; treatment

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**S**imilar to the class Mammalia, the class Reptilia includes a diverse group of species, each with a unique pharmacologic response to every chemotherapeutic agent. As a result, therapeutic safety and efficacy differ among species. Unlike mammals, conscious reptiles are ectothermic, so physiologic and biochemical processes are strongly influenced by body temperature.<sup>1</sup> Reasonable assumptions about each individual reptile species' metabolism and immune response can be determined only under certain conditions. In most cases, before therapeutic agents are administered, the body temperature of a reptile patient must match that of the subjects in a given pharmacokinetic study, if available. The proper body temperature helps increase the chance of duplicating the findings of the study, although pharmacokinetics and pharmacodynamics do not necessarily vary at different patient body temperatures.<sup>2-5</sup> The veterinarian should be knowledgeable of species-specific pharmacokinetics, pharmacodynamics, therapeutic efficacy, and environmental requirements before treating the animal. This is not only to predict absorption, distribution, metabolism, excretion, and the therapeutic window of the drug(s) but also to meet the environmental needs of a reptile to maximize healing and the animal's immune response.<sup>4,6,7</sup> Published doses are available for many drugs, and these may have been selected empirically, calculated with the use of allometric or other scaling technique, or obtained from published pharmacokinetic research data. It is incumbent on the clinician to evaluate whether a published dose would be safe and effective in a particular clinical case. Dosage, dosing interval, and route of administration must be evaluated on a case-by-case basis. Consult up-to-date, peer-reviewed literature to identify the species of reptile being treated and their environmental needs, optimal body temperature, and the pharmacokinetics and pharmacodynamics of the drug(s) to be used.<sup>8</sup>

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Managed thermoregulation, hydration, and nutrition are paramount for safe, effective drug therapy. Thermal options and gradients must be provided for conscious, active reptiles to thermoregulate with body temperature being monitored during the treatment period. In cases of weakness and decreased activity, thermoregulation of the patient should be actively managed as part of the therapeutic plan. Dehydrated, anorexic reptiles may not absorb, distribute, metabolize, or eliminate chemotherapeutic agents in the same manner as the healthy animals tested under controlled conditions in pharmacologic research. Thus, nursing care of dehydrated reptile patients also includes management of body fluids, electrolytes, and nutrition.

Most of the drugs used to treat reptiles are considered "extralabel" as relatively few therapeutic agents are approved for use in these species. In the United States, the Animal Medicinal Drug Use Clarification Act of 1994 and the Minor Use and Minor Species Animal Health Act of 2004 serve as guides for extralabel drug use. Prescription drugs may be used to treat disease in reptiles under the supervision of a veterinarian if (1) they are approved by the US Food and Drug Administration (FDA) for any purpose in any species, (2) a valid veterinarian-client-patient relationship exists, and (3) the FDA has not specifically prohibited extralabel use of the drug. Certain medical record and prescription label requirements must be followed to meet the regulatory obligations of veterinary licensure.<sup>9</sup>

## ADMINISTRATION AND DOSING

Dosage and route of administration are determined by the chemical, pharmacokinetic, and pharmacodynamic properties of every drug for each species. Numerous studies have been performed to understand the mechanism of action, therapeutic window, absorption, distribution, metabolism, and excretion variables of some drugs in some reptile species. However, many questions remain unanswered about the scientific basis for drug use in reptile species commonly maintained in captivity, so informed, empirical dosing is still necessary in many cases.<sup>8</sup> Veterinarians administer therapeutic agents to reptiles via oral (PO), enteral, subcutaneous (SC), intramuscular (IM), intravenous (IV), intracoelomic, intratracheal, intrapulmonary, intraosseous, intraperitoneal, intrathecal, and intracardiac routes, as well as via nebulization. Parenteral administration is

considered more reliable than the enteral route for therapeutic efficacy in reptile patients.<sup>4</sup> Sufficient evidence exists to support administration of most parenteral drugs in the cranial half of the body, when possible, to avoid the first-pass effect of drugs that are eliminated via renal tubular excretion or hepatic metabolism. Venous blood from the caudal half of the body enters the caudal vena cava through either the renal portal system and peritubular capillaries or the hepatic portal system from the abdominal or mesenteric veins and hepatocellular parenchyma.<sup>10,11</sup> Giving therapeutic agents in the caudal half of the body is acceptable for a few specific products and may be considered for other drugs when the cranial half is not available.<sup>5,12,13</sup> When giving drugs in the caudal half of a reptile patient's body, dosage is adjusted to account for the renal or hepatic first-pass effect. Intracoelomic administration of fluids or systemic drugs is not recommended. Absorption across coelomic membranes is difficult to assess in clinical patients and is not guaranteed, particularly in cases of abnormal blood proteins, coelomitis, or ascites. Intracoelomic administration of therapeutic agents has resulted in accidental needle puncture or laceration of an internal organ and accidental deposition of the agent into the intestines, reproductive tract, or urinary bladder.<sup>14</sup> Some therapeutic challenges in reptiles can be overcome by novel approaches to drug administration, including osmotic pump, dermal patch, depot formulation, vascular access port, and topical administration.

## Osmotic Pump

Alzet osmotic pumps (DURECT Corp, Cupertino, CA USA) are implanted, miniature infusion pumps designed for continuous infusion of therapeutic agents to unrestrained animals. They are available with fixed delivery rates between 0.11 and 10  $\mu\text{L}/\text{h}$ , with delivery durations between 1 day and 6 weeks. Marketed for laboratory animals, osmotic pumps range in size from 15 to 51 mm in length and 6 to 14 mm in diameter and have been used to deliver dozens of different therapeutic agents.<sup>15</sup> The "pumps" operate via an osmotic pressure difference between the tissue environment and a salt-containing osmotic sleeve. The high osmolality of the salt sleeve causes water to diffuse into the pump, across the outer semipermeable membrane and into the salt sleeve, which applies pressure on a flexible (impermeable) internal reservoir that contains the therapeutic agent. This pressure causes

the agent to be expelled via a flow moderator at a controlled, predetermined, continuous rate that is independent of the chemical properties of the agent being dispensed. Different dosing rates can be achieved by varying the concentration of the agent used to fill the pump reservoir. Virtually any commonly used parenteral drug can be delivered by osmotic pumps as the device is loaded by the user just before implantation.

Osmotic pumps have been used in corn snakes (*Elaphe guttata*), Mojave rattlesnakes (*Crotalus scutulatus*), and green iguanas with amikacin, florfenicol, and gonadotropin-releasing hormone.<sup>16-18</sup> It is important to consider the tissue environment of the implant (availability of free water) and the pharmacokinetic and pharmacodynamic properties of the drug to be administered. This information is important when using the osmotic pump because some drugs, including amikacin, may be safer and more effective when administered in pulses.<sup>19</sup> In addition, substantial local necrosis and death occurred in 5 of 6 Mojave rattlesnakes that were given florfenicol via subcutaneously implanted osmotic pumps.<sup>17</sup> In spite of disappointing results in recently published studies, further research studies to investigate different implantation sites, other drugs, and other reptile species should be considered. Implantable, bioresorbable devices also deserve consideration, particularly for use in the treatment of dangerous and venomous animals.<sup>20</sup>

### Transdermal Patch

Fentanyl, scopolamine, nicotine, buprenorphine, naloxone, nitroglycerin, ketoprofen, and many other drugs can be delivered by transdermal patch to humans and domestic mammals. Recently, 1 study tested fentanyl that was suspended in an ethanol and cellulose gel and enclosed by a plastic barrier with a permeable adhesive membrane impregnated with a loading dose of fentanyl on prehensile-tailed skinks (*Corucia zebrata*).<sup>21</sup> The study showed that all of the skinks in the study obtained measurable plasma concentrations of fentanyl within 24 hours of patch application, and fentanyl concentrations reached the human analgesic range by 36 hours. A study using fentanyl transdermal therapeutic system (12 µg/h) applied to the cranial one-third dorsum of ball pythons (*Python regius*) with adhesive and staples showed measurable concentrations in blood after 4 hours and human analgesic concentrations (1 ng/mL)

starting at 8 hours and continuing for the remainder of the study (216 hours).<sup>22</sup> The most important finding of the transdermal drug studies is that the scaled skin of the 2 species investigated does not present an insurmountable barrier to systemic absorption of fentanyl delivered via transdermal patch. It is possible that other drugs can be delivered via transdermal patch in other reptile species; consequently, further investigations are warranted.

### Depot Formulations

Numerous chemotherapeutic agents are available in long-acting formulations. Examples of long-acting formulations that have been used in reptiles include oxytetracycline, cefovecin, ceftiofur crystalline free acid, doxycycline, tulathromycin, ivermectin, and leuprolide acetate.<sup>23-29</sup> To date, the only 1 of these therapeutic agents that proved useful was long-acting oxytetracycline for treatment of mycoplasmosis in American alligators (*Alligator mississippiensis*).<sup>26</sup>

### Vascular Access Ports

Vascular access ports are used to repeatedly collect blood samples or administer IV medications over time in humans and animals. The vascular access ports are particularly useful in pharmacokinetic studies and for cancer chemotherapy. Several authors have implanted the rubber stopper from an evacuated blood collection vial into a round plastostomy drilled ventral to the cardiac ventricle in tortoises. The port was then used to collect multiple blood samples over time, but myocardial fibrosis occurred in some of the subjects.<sup>30,31</sup>

Vascular access ports were placed into the common carotid artery to study blood gasses in 7 green iguanas and remained functional in most subjects for several weeks.<sup>32</sup> A vascular access port (CompanionPort, Norfolk Medical Products Inc, Skokie, IL USA) was placed into the ventral abdominal vein of a green iguana for lymphoma chemotherapy.<sup>33</sup> This port was replaced after 28 days because of dermal necrosis over the port, after which a second port was implanted and used for 6 months without complication.

### Topical Administration

Numerous topical medications are used in reptiles, primarily to treat wounds or skin disease. Ivermectin, ophthalmic drugs, disinfectants, creams, ointments, and lavage solutions are all

applied via the topical route to reptile patients. These applications are generally intended to deliver local therapy, and systemic uptake is usually an undesired side effect. Recently, several topical preparations for systemic therapy have been evaluated. Topical administration is ideal for antiparasitic agents because most traditional antiparasitic drugs are delivered via orogastric intubation, which can be difficult in some lizards and many chelonians. A commercially available topical treatment for intestinal parasites containing imidacloprid and moxidectin (Advantage Multi/Advocate, Bayer, Shawnee Mission, KS USA) is available for domestic companion animals (e.g., dogs and cats). The product was applied to the skin of frilled dragons (*Chlamydosaurus kingii*) and bearded dragons (*Pogona vitticeps*). After treatment, the feces no longer contained *Kalicephalus* spp. or oxyurid ova.<sup>34</sup> The safety of this imidacloprid/moxidectin topical formulation was not evaluated, therefore pharmacokinetic research is required in reptile species to determine plasma levels of this product. A commercially available topical preparation containing emodepside and praziquantel (Profender, Bayer HealthCare, Shawnee Mission, KS USA) was tested for absorption, elimination time, and efficacy in several lizards, snakes, and chelonians.<sup>35,36</sup> Both drugs were absorbed via the skin, except emodepside in a red-eared slider (*Trachemys scripta elegans*) that was placed in water approximately 1 hour after application. Treatment with emodepside/praziquantel at doses much greater than those used in mammals was followed by a marked decrease in the number of nematode ova in feces within 48 hours. Similarly, no adverse effects were observed, and fecal nematode egg counts decreased after treatment in a relatively large ( $n = 417$ ), uncontrolled clinical trial in which emodepside/praziquantel was applied to species from 4 different reptilian families.<sup>37</sup> The safety of this topical combination should be studied in reptiles as it holds great clinical promise for veterinarians who treat reptile species.

## ANTIBACTERIAL AGENTS

A variety of antibiotic drugs are currently used in reptiles. Many pharmacokinetic studies have been published regarding antibiotic plasma levels in multiple reptile species, thus background information is available to assist in selection of

dose and dosing interval. A number of individual circumstances guide antibiotic selection for each case these drugs are prescribed. Empirical antibiotic selection may be necessary in critical cases and should be based on the prevalence of specific disease pathogens, antimicrobial spectrum of activity, distribution of the drug to the affected tissues, potential side effects, metabolic and excretory pathways, volume of the formulation required, dosing interval, and ease of administration. In many cases, antibiotic agents can be withheld until culture and sensitivity results are available. Selection of antibiotic agents with a narrow spectrum of activity may help reduce the risk of iatrogenic shifting of the enteropathic and commensal bacteria in the favor of pathogenic organisms. Multiple antimicrobials may be used to combat resistant strains of bacteria through a synergistic effect.<sup>38</sup> Antibiotic drugs often used in reptile medicine include amikacin, azithromycin, ceftazidime, ciprofloxacin, clarithromycin, danofloxacin, enrofloxacin, marbofloxacin, metronidazole, oxytetracycline, piperacillin, ticarcillin, trimethoprim/sulfamethoxazole, and tylosin. Most of the drugs listed above have been in use for decades in reptile species and have been previously described.<sup>4</sup> Information presented here is limited to agents in which relatively new scientific data have recently been published (Table 1).

### Azithromycin

Azithromycin is an azalide, a subclass of macrolide antibiotics that apply their bacteriostatic effect by inhibiting protein synthesis by binding to the 50s ribosome.<sup>39,40</sup> The antimicrobial spectrum of this drug includes many Gram-positive and Gram-negative aerobic and anaerobic bacteria, including *Legionella pneumophila*, *Chlamydia* spp., and *Mycoplasma* spp. Oral preparations should not be given concurrently with aluminum- or magnesium-containing antacids or phosphate binders.<sup>39</sup> In a single-dose pharmacokinetic study in ball pythons (*P. regius*), the authors found that the drug is distributed and excreted similar to humans, and the dose, 10 mg/kg orally, is given at different frequencies based on the location of the infection: skin, every 3 days; respiratory tract, every 5 days; and liver/kidneys, every 7 days.<sup>41</sup>

### Ceftazidime

Ceftazidime is a semisynthetic, broad-spectrum, bactericidal, beta-lactam antibiotic for parenteral

TABLE 1. Antibiotic agents with recent advances in reptile medicine									
Agent	Class	Activity	Mechanism of Action	Special Attributes	Available Routes				
Azithromycin	Azalide macrolide	Bacteriostatic	50s ribosome binding—inhibits protein synthesis	Concentrates in phagocytes and fibroblasts, reduced effectiveness at low pH	PO, IV, and water				
Ceftazidime	Semisynthetic beta-lactam	Bactericidal	Peptidoglycan disruptor	Stable against most beta-lactamases	IV and IM				
Clarithromycin	Macrolide	Bacteriostatic	50s ribosome binding—inhibits protein synthesis	Intracellular concentration > serum	PO				
Danofloxacin	Synthetic fluoroquinolone	Bactericidal	DNA gyrase inhibition	Lung concentration > plasma	IM and SC				
Marbofloxacin	Synthetic fluoroquinolone	Bactericidal	DNA gyrase inhibition	NF	PO, IM, and IV				
Metronidazole	Synthetic nitroimidazole	Bactericidal	Blocks DNA synthesis	Effective against anaerobes and protozoa	PO and IV				
Agent	Formulations Available in the USA	Synergism	Cross-Resistance	Drug-Drug Interactions	Tissue Distribution		Metabolism		
Azithromycin	Oral suspension, tablet, and injectable	NF	Erythromycin and methicillin	Phosphate binders with aluminum or phosphate	Most tissues; not CSF		None		
Ceftazidime	Injectable	Aminoglycosides and carbenicillin	Methicillin	NF	NF		Minimal		
Clarithromycin	Oral suspension and tablet	NF	Methicillin and oxacillin	Many	Most tissues; (CSF not tested)		Hepatic		
Danofloxacin	Injectable	NF	NF	Ivermectin	Most tissues		NF		
Marbofloxacin	Tablet	NF	NF	Divalent cations and sucralfate decrease absorption	Most tissues		Hepatic		
Metronidazole	Tablet and injectable	NF	NF	Potentiates coumarin anticoagulants	Most tissues		Hepatic (microsomal enzymes)		
						Antimicrobial spectrum		Notable Activity	
						Aerobes			G+ G-
Agent	Excretion	Side Effects	Overdose	Contraindications	G+	G-	G+	G-	
Azithromycin	Mostly biliary and some renal	Hepatotoxicity, nonregenerative anemia, and dysbiosis	NF	NF	Y	Y	Y	Y	<i>Mycoplasma</i> and <i>Chlamydophila</i>
Ceftazidime	Primarily urine	Decreased prothrombin and dysbiosis	Neurologic signs; reduce dose with renal insufficiency	NF	Y	Y	Y	Y	<i>Pseudomonas aeruginosa</i>
Clarithromycin	Primarily urine	Hepatotoxicity and dysbiosis	NF	Pregnancy	Y	Y	Y	Y	<i>Mycoplasma</i> , <i>Chlamydophila</i> , and mycobacteria
Danofloxacin	NF	Tissue reaction at injection site	Articular chondropathy	Pregnancy and growing juveniles	Y	Y	N	N	<i>Pasteurella</i>
Marbofloxacin	Primarily urine and some biliary	NF	Articular chondropathy	Pregnancy, growing juveniles, and CNS disorders	Y	Y	N	N	NF
Metronidazole	Primarily urine	Gastrointestinal, neurologic, hepatic, and hematopoietic	Reduce dose with decreased liver function	Blood dyscrasia, leukopenia, and pregnancy	N	N	Y	Y	NF
Agent	Notable Resistance		Dose		Dosing Interval		References		
Azithromycin	<i>E. faecalis</i>		10 mg/kg PO		See text		39-41		
Ceftazidime	<i>Bacteroides fragilis</i> and <i>Clostridium difficile</i>		20 to 22 mg/kg IM/IV		48 to 72 hours		42, 44-46		
Clarithromycin	<i>C. difficile</i>		15 mg/kg PO		3.5 days		47-50		
Danofloxacin	NF		6 mg/kg IM/SC		48 hours		8, 51, 53		
Marbofloxacin	NF		2 to 10 mg/kg PO, IM, and IV		24 to 48 hours		54-59		
Metronidazole	NF		20 mg/kg PO		24 to 48 hours		14, 60, 61, 63-65		

NF, not found; PO, per os; SC, subcutaneously; IM, intramuscular; IV, intravenous.

administration.<sup>42</sup> Ceftazidime is highly stable to most clinically important beta-lactamases (e.g., plasmid or chromosomal), therefore it is active against many organisms that are resistant to penicillins and other cephalosporins. Some clinicians prefer to reserve it for refractory infections to decrease the risk of extended-spectrum beta-lactamase development.<sup>43</sup> Ceftazidime is active against numerous Gram-negative and Gram-positive aerobes and anaerobes, particularly many antibiotic-resistant strains of *Pseudomonas aeruginosa*. The only published report of ceftazidime pharmacokinetics in squamates was a single-dose pharmacokinetic study in 1984 that included 5 snake species kept at 30°C (86°F).<sup>44</sup> The half-life of 20 mg/kg administered IM was 24 hours and the authors proposed a dosing interval of 72 hours.<sup>44</sup> A single-dose pharmacokinetic study in loggerhead sea turtles (*Caretta caretta*) maintained at 22°C to 26°C (72°F to 79°F) found a serum half-life of 19 to 20 hours, and the authors proposed a dose of 22 mg/kg every 72 hours based on their results.<sup>45</sup> In a single-dose pharmacokinetic study of ceftazidime 22 mg/kg IM with concurrent administration of fluconazole 21 mg/kg SC in cold-stunned Kemp's Ridley sea turtles (*Lepidochelys kempii*) maintained at 21°C to 24°C (70°F to 75°F),<sup>46</sup> 2 of the turtles died during the study, and *Enterococcus faecalis* was cultured from the blood and lung of 1 of the test subjects. The maximum concentration ( $C_{max}$ ) in Kemp's Ridley sea turtles was similar to that in loggerhead sea turtles (61.3 vs 69.9 µg/mL, respectively), but the half-life in Kemp's Ridley sea turtles was more than double that of loggerheads (43.9 vs 19.1 hours, respectively).<sup>45,46</sup> Ceftazidime is widely prescribed to numerous reptile species because of its broad-spectrum, low administration volume (when diluted to 100 mg/mL) and prolonged dosing interval of 48 to 72 hours. Further research with boids, lizards, tortoises, and freshwater turtles is needed to determine appropriate dosing of ceftazidime in these species.

### Clarithromycin

Clarithromycin is a semisynthetic, bacteriostatic, macrolide antibiotic that inhibits protein synthesis by binding to the 50s ribosome.<sup>47</sup> Clarithromycin is rapidly absorbed from the gastrointestinal tract in humans, with approximately 50% bioavailability, and it is metabolized by the liver into 14-hydroxy clarithromycin, which is also microbiologically active. Clarithromycin should

not be administered concomitantly with several drugs including colchicine, anticoagulants, statins (HMG-CoA reductase inhibitors), cisapride, terfenadine, pimozone, or astemizole. Clarithromycin may affect metabolism or serum concentrations of midazolam, alprazolam, digoxin, theophylline, itraconazole, carbamazepine, omeprazole, and ranitidine. Clarithromycin may be used to treat severe cases of mycoplasmosis in tortoises.<sup>48,49</sup> A recent long-term dosing study showed that clarithromycin therapy can be safe and effective (at resolving clinical signs but not eliminating the organism) in desert tortoises (*Gopherus agassizii*) to treat mycoplasmosis when 15 mg/kg clarithromycin oral suspension (50-mg/mL Biaxin oral suspension; Abbott Labs, Abbott Park, IL USA) is administered by gavage every 3.5 days (every 84 hours).<sup>50</sup> This dose results in median clarithromycin concentrations in plasma that rose from 3.32 µg/mL at 14 days to 4.79 µg/mL at 6 months, which is above the proposed target range of 2.0 µg/mL; no 14-hydroxy clarithromycin was detected. The study also showed that per rectum administration did not achieve plasma concentrations in the target range when given every 12 hours for 48 hours followed by every 24 hours for 8 days.

### Danofloxacin

Danofloxacin mesylate is a synthetic fluoroquinolone for subcutaneous injection in cattle.<sup>51</sup> The FDA-approved label dose is 8 mg/kg once or 6 mg/kg repeated in 48 hours for bovine respiratory disease associated with *Mannheimia (Pasteurella) haemolytica* and *Pasteurella multocida*. Danofloxacin has a half-life in cattle of 3 to 6 hours and has negligible accumulation. Danofloxacin can cause a transient local tissue reaction at the injection site. A study assessing the effects of concomitant treatment with ivermectin and danofloxacin in sheep showed that the danofloxacin elimination half-life and systemic exposure (area under the curve) increased.<sup>52</sup> A single-dose pharmacokinetic study was performed in loggerhead sea turtles after IV, IM, and SC administration of 6 mg/kg.<sup>53</sup> Elimination half-life was 18.7 hours after SC administration and 14.7 hours after IM administration. Maximum plasma concentration and time to maximum concentration after SC and IM administration were similar for both routes (approximately 10 µg/mL and 1.5 hours, respectively). The authors speculate

that danofloxacin 6 mg/kg IM or SC every 48 hours could be safe and effective against bacteria with a minimum inhibitory concentration (MIC)  $\leq 0.5$   $\mu\text{g}/\text{mL}$  in loggerhead sea turtles and called for a multidose pharmacokinetic study to test the hypothesis. Danofloxacin has been administered at 6 mg/kg SC every 48 hours for 30 days to treat chronic mycoplasmosis in *Gopherus* sp. tortoises.<sup>8</sup>

### Marbofloxacin

Marbofloxacin is a synthetic, broad-spectrum, bactericidal fluoroquinolone antibiotic approved by the FDA for skin and soft tissue infections in dogs and cats and for urinary tract infections in dogs.<sup>54</sup> Marbofloxacin is soluble in water but solubility decreases in alkaline conditions. Pharmacokinetic studies have been performed in ball pythons, loggerhead sea turtles, and red-eared sliders, and its metabolites have been studied in ball pythons.<sup>55-59</sup> In the ball python, 10 mg/kg of marbofloxacin was administered IV or PO to animals maintained at 30°C, (86°F), and testing continued for only 24 hours, thus the half-life could not be calculated; however, the authors proposed a dosage of 10 mg/kg every 48 hours.<sup>57</sup> The pharmacokinetic studies in loggerhead sea turtles maintained at 26°C (78.8°F) to 28°C (82.4°F) included dosing of marbofloxacin at 2 mg/kg IM, IV, and PO.<sup>55,59</sup> Although maximum concentrations and half-life differed somewhat among administration routes, the authors proposed that administration of marbofloxacin at 2 mg/kg every 24 hours is sufficient for all 3 administration routes. In another study, marbofloxacin was administered at a dose of 2 mg/kg IV and IM to red-eared sliders in the forelimbs and hindlimbs.<sup>56</sup> Bioavailability was 77% for IM forelimb and 63% for IM hindlimb administration, but no significant difference was found for AUC, clearance, or half-life between locations. The authors determined that IV administration of marbofloxacin at a dose of 2 mg/kg every 24 hours is appropriate for organisms with an MIC  $\leq 1$   $\mu\text{g}/\text{mL}$ , and IM administration at a dose of 2 mg/kg every 24 hours is appropriate for organisms with an MIC  $\leq 0.25$   $\mu\text{g}/\text{mL}$ . The authors recommend that higher doses of marbofloxacin should be investigated in reptile species.

### Metronidazole

Metronidazole is an oral, synthetic, nitroimidazole antiprotozoal and antibacterial agent. Metronidazole is bactericidal against obligate

anaerobes (MIC ranging from 0.25 to 8  $\mu\text{g}/\text{mL}$ ) and is protozoacidal against numerous protozoa with an in vitro MIC of  $\leq 1$   $\mu\text{g}/\text{mL}$ .<sup>60</sup> The antimicrobial action of metronidazole targets DNA synthesis, in that metronidazole acts as an electron acceptor in the phosphoroclastic reaction and causes breaks in the adenine-thymine base pairing. Although antimicrobial resistance is uncommon with metronidazole, it is possible. Metronidazole is a basic compound with a pKa value of 2.62 and is moderately soluble in water (approximately 10 mg/mL at 25°C) at pH 2.5 to 8.0; the pH of the IV infusion is 5.8.<sup>60,61</sup> Oral suspensions of metronidazole using pH-appropriate suspending agents can be procured from licensed compounding pharmacies and are generally the most appropriate formulation for accurate dosing in reptile patients. Metabolism of metronidazole to the 2-hydroxymethyl metabolite occurs in the liver, and decreased plasma clearance occurs in patients with decreased liver function but not in patients with renal insufficiency. Side effects of metronidazole administration include nausea, vomiting, ataxia, reversible neutropenia, dysuria, yeast overgrowth, encephalopathy, seizures, and peripheral neuropathy. Elevated liver enzyme activities in plasma have been reported in reptiles.<sup>4</sup> Serious toxic side effects in reptiles can occur at doses between 40 and 100 mg/kg.<sup>4,62</sup> Metronidazole potentiates the effect of coumarin anticoagulants, and concomitant administration with drugs that induce microsomal liver enzymes (e.g., phenytoin and phenobarbital) may accelerate the elimination of metronidazole. Drugs that decrease microsomal liver enzymes (e.g., cimetidine) may prolong the half-life of this drug and decrease its plasma clearance.<sup>60</sup> Metronidazole is trichomonocidal and amebicidal for protozoa with in vitro MIC  $\leq 1$   $\mu\text{g}/\text{mL}$ .<sup>60</sup> Pharmacokinetic studies of metronidazole administered to red-eared sliders, colubrid snakes (*E. guttata* [*Pantherophis guttatus*] and *Elaphe obsoleta* [*Pantherophis obsoletus*]), and green iguanas have been published.<sup>14,63-65</sup> In red-eared sliders, a single intracoelomic dose of metronidazole, 20 mg/kg, was administered with the maximum plasma concentration being 25  $\mu\text{g}/\text{mL}$  at 5 hours after injection, and the elimination half-life being 27 hours.<sup>14</sup> The authors suggest an intracoelomic metronidazole dose of 20 mg/kg every 48 to 72 hours, depending on the MIC of the organism it is directed against, but caution that adverse effects do occur; thus, the intracoelomic route may not be safe. In colubrid snakes, single doses of

metronidazole at 20, 50, 100, and 150 mg/kg PO have been studied, and multiple 20-mg/kg doses have also been studied.<sup>63,65</sup> The maximum plasma concentration varies from 12.8 µg/mL, after 20 mg/kg PO of metronidazole was administered every 48 hours for 6 days, to 2039 µg/mL, after a single dose of 150 mg/kg PO. The half-life was 15 hours after the first 20-mg/kg dose, 23 hours after the sixth dose, and 26 hours after the 150-mg/kg dose. No clinically significant adverse behavioral, hematologic, or biochemical effects were observed other than mildly elevated plasma lactate dehydrogenase activity after the last 20-mg/kg dose and mildly decreased glucose after the 50- and 150-mg/kg single doses in subjects of the multiple drug dose study. Taken together, the results support a metronidazole dose of 20 mg/kg every 48 hours in *Elaphe (Pantherophis)* spp. snakes. Higher doses should be reserved for resistant infections so that the risk of adverse effects is avoided. A pharmacokinetic study of a single 20-mg/kg dose followed by 20 mg/kg every 24 hours for 10 days in green iguanas found a C<sub>max</sub> of 7.6 µg/mL after the single dose with a half-life of 12.7 hours and a C<sub>max</sub> of 22.8 µg/mL after 10 days.<sup>64</sup> No adverse hematologic, biochemical, or behavioral effects were observed after the 10-day treatment trial. The authors concluded that metronidazole administered at 20 mg/kg every 48 hours would be sufficient for “most” infections and that the dosing frequency could be increased to every 24 hours for resistant strains with MICs ≥ 8 µg/mL.

## ANTIFUNGAL AGENTS

Fungal infections occur with enough frequency in reptile species that antifungal therapy has become a routine part of clinical practice. Similar to antibiotics, antifungal agents are best selected in response to a specific etiologic diagnosis. Fungal culture should precede therapy, but antifungal sensitivity testing is not practical in most cases. Empiric selection of antifungal drugs may be necessary while awaiting culture results, which can take weeks. Drug selection should be based on the prevalence of a specific fungal organism, antifungal spectrum of activity, distribution of the antifungal drug to the diseased tissues, potential side effects, metabolic and excretory pathways, volume of the formulation required to deliver the necessary dose, dosing interval, and ease of administration. Multiple antifungal drugs may be used concomitantly to overcome the limitations of 1

drug alone or to expand the treatment spectrum of activity. Topical agents are frequently combined with systemic agents to effectively treat severe fungal dermatitis (e.g., *Chrysosporium* anamorph of *Nannizziopsis vriesii* [CANV]). A vaccine trial showed no difference between dermatologic lesions or septicemia between vaccinated and control bearded dragons experimentally infected with CANV.<sup>66</sup> This review is limited to those agents in which new information is available.

## Amphotericin B

Amphotericin B is a polyene antifungal produced from a strain of *Streptomyces nodosus*. Amphotericin B acts to increase membrane permeability by binding to sterols in cell membranes of sensitive fungi. Amphotericin B also binds to the sterols in vertebrate cell membranes, which is believed to account for its toxicity in animals and humans. Amphotericin B is available as an injectable product and in lipid complex.<sup>67</sup> The lipid complex formulation has increased peak concentration, clearance time, volume of distribution, and terminal elimination half-life when compared with amphotericin B desoxycholate. Amphotericin B may cause a severe reaction when used concurrently with other drugs. Drugs with which amphotericin B should not be used include antineoplastic chemotherapeutics, corticosteroids, cyclosporin A, digitalis glycosides, flucytosine, imidazole antifungal agents (e.g., ketoconazole, clotrimazole, and fluconazole), other nephrotoxic agents, tubocurarine, and zidovudine. Treatment of a reptile patient with amphotericin B can cause increases in levels of blood urea nitrogen, uric acid, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, and amylase. Amphotericin B can cause decreased blood phosphorus and increases or decreases in blood glucose levels. Amphotericin B is likely to cause nephrotoxicosis in reptiles and is contraindicated in reptiles with renal insufficiency.<sup>68</sup> Amphotericin B is active against *Aspergillus* spp., *Blastomyces* spp., *Candida* spp., *Coccidioides* spp., *Cryptococcus* spp., and *Histoplasma* spp. in mammals. Resistance can occur, particularly with prolonged therapy. The in vitro MIC against CANV cultured from captive lizards was 2 µg/mL for amphotericin B.<sup>69</sup> There are clinical reports of its use in nebulization, intratracheal, and intrapulmonary therapy in reptile patients.<sup>62,70,71</sup>

## Itraconazole

Itraconazole is a synthetic triazole antifungal agent. It exerts its antifungal action by inhibiting <sup>14</sup>C-demethylation of ergosterol, a cell wall component of fungi.<sup>72</sup> Itraconazole is available in capsules and oral solution. Itraconazole is insoluble in water, slightly soluble in alcohols, freely soluble in dichloromethane, has a pKa of 3.70, and a log-log (n-octanol/water) partition coefficient of 5.66 at pH 8.1. The oral solution is best absorbed in fasting humans, as opposed to the capsules, which should be taken with food because low pH is required for absorption. Itraconazole is metabolized by the cytochrome P450 isoenzyme system (CYP3A4), which results in several metabolites, primarily hydroxyitraconazole. Itraconazole may undergo saturable metabolism with multiple doses, and the dosing interval may be longer than predicted by single-dose pharmacokinetic studies.<sup>69,72</sup> Approximately 40% of the itraconazole dose is excreted as inactive metabolites in urine, up to 18% is excreted unchanged in feces, and less than 0.03% is excreted unchanged in human urine. Itraconazole is widely distributed to tissues, especially lipophilic organs such as skin. Itraconazole is minimally distributed to aqueous humor of the eye, cerebrospinal fluid, urine, and saliva when inflammation is not present.<sup>73</sup> As itraconazole is primarily metabolized by the liver, blood levels should be monitored in patients with hepatic insufficiency, and dosing intervals should be adjusted to maintain blood levels above the MIC of the target fungus. Itraconazole is active against *Blastomyces* spp., *Aspergillus* spp., *Histoplasma* spp., *Coccidioides* spp., *Cryptococcus* spp., *Paracoccidioides* spp., *Sporothrix* spp., and *Trichophyton* spp. Itraconazole can be active against some isolates of *Candida*, but many are resistant. It is not active against *Zygomycetes* spp., *Fusarium* spp., *Scedosporium* spp., or *Scopulariopsis* spp.

Itraconazole has been used to effectively treat CANV infections in reptiles. Itraconazole can cause rapid hepatotoxic effects including liver failure and death in humans, and its use is contraindicated in patients with hepatic insufficiency.<sup>72</sup> Itraconazole can cause anorexia and weight loss in bearded dragons. In 1 treatment trial, 5 of 7 bearded dragons died on days 5, 20, 22, 36, and 54 of treatment with itraconazole oral solution (Sporanox, Janssen-Cilag, Berchem, Belgium) administered at 5 mg/kg every 24 hours PO, although histopathologic evidence of hepatotoxicity was absent.<sup>69,74</sup> Itraconazole

accumulates over time in CANV-infected bearded dragons, reaching a steady-state plasma concentration of 4 to 8 µg/mL after approximately 10 days.<sup>69</sup> In vitro MIC<sup>90</sup> of itraconazole for CANV cultured from infected bearded dragons was 0.25 µg/mL. The fungus could no longer be cultured from lesions after 4 weeks of treatment. In a different treatment trial, 7 bearded dragons were successfully treated for CANV with itraconazole (and clotrimazole), but 6 were euthanized.<sup>75</sup> A group of green anacondas (*Eunectes murinus murinus*) infected with CANV were treated with itraconazole (Sporanox Oral Solution, Ortho Biotech, Raritan, NJ USA) at 1 of 2 dosages of itraconazole, either 10 mg/kg every 48 hours for 14 days or 10 mg/kg every 24 hours for 7 days then every 48 hours for 7 days; plasma levels of the drug reached 4.3 to 9.0 µg/mL and persisted for at least 14 days after treatment.<sup>76</sup> A series of cases showed that itraconazole was effective without adverse side effects at metabolically scaled doses (0.5 to 1.7 mg/kg PO every 53 to 75 hours for 148 to 184 days) in the treatment of *Aspergillus* spp. infection in 2 lizard species and 2 snake species (total of 7 cases).<sup>77</sup> Therefore, because itraconazole appears to be well absorbed after oral administration, has efficacy against fungal infections, and is of questionable safety, further pharmacokinetic studies, preferably in fungus-infected patients, are warranted.

## Voriconazole

Voriconazole is a triazole antifungal agent that is effective by inhibiting fungal cytochrome P450-mediated 14- $\alpha$ -lanosterol demethylation, which is essential for ergosterol inhibition. Voriconazole is more selective for fungal organisms than mammalian cytochrome P450 enzyme systems.<sup>78</sup> Voriconazole is available as a lyophilized powder for IV infusion, film-coated tablets for oral administration, and as a powder for oral suspension. Pharmacokinetic results in humans are similar after the oral and IV routes, and maximum plasma concentrations are achieved 1 to 2 hours after dosing. Voriconazole is widely distributed into tissues and is metabolized by cytochrome P450 enzymes to metabolites including N-oxide voriconazole, which has minimal antifungal activity and accounts for 72% of the circulating metabolites. Metabolism varies among species, and autoinduction of metabolism by cytochrome P450 3A11 occurs in mice but not humans.<sup>79</sup> Voriconazole is eliminated primarily

via hepatic metabolism; less than 2% of the oral dose is excreted unchanged in the urine of humans, and more than 80% of the metabolites are recovered in the urine. Doses of voriconazole should be adjusted according to plasma levels of the drug in patients with hepatic insufficiency. After oral administration, no dose adjustment is necessary in patients with renal insufficiency, but IV administration should be avoided because of accumulation of the IV vehicle (sulfobutyl ether beta-cyclodextrin sodium). The terminal elimination half-life of the drug is dose dependent because the pharmacokinetics of voriconazole is nonlinear. Serious drug interactions occur with concomitantly administered agents that are also metabolized via the cytochrome P450 enzyme system. Side effects in humans include visual disturbances, gastrointestinal disturbances, hepatic toxicity, fetal toxicity in pregnant women, and electrocardiac disturbances. Voriconazole is effective against fungi including *Aspergillus* spp., *Candida* spp., *Fusarium* spp. (except *Fusarium solani*), and *Scedosporium* spp. Drug resistance has not been studied thoroughly, but strains that are resistant to fluconazole or itraconazole may also show reduced sensitivity to voriconazole. In vitro voriconazole sensitivity (MIC<sup>90</sup>) of CANV that was isolated from captive lizards was 0.0625 µg/mL.<sup>69</sup>

When voriconazole was used to treat CANV in bearded dragons, only 1 of 7 dragons died compared with 5 of the 7 treated with itraconazole; in those that survived, the disease was cleared with the treatment of voriconazole (Vfend, Pfizer, Ixelles, Belgium) dosed at 10 mg/kg PO every 24 hours for 4 to 9 weeks.<sup>69</sup> The steady-state plasma concentration of voriconazole was 3.4 to 5.7 µg/mL in the aforementioned study, but substantial interindividual variation was observed. A giant girdled lizard (*Cordylus giganteus*) was treated for CANV with voriconazole tablets (Vfend, Pfizer, Ltd, Sandwich, England) suspended in water, 10 mg/kg PO every 24 hours for 10 weeks.<sup>80</sup> After 3 days, this treatment regimen resulted in a steady-state plasma concentration of approximately 2.0 to 3.5 µg/mL. In vitro MIC of the cultured CANV was 0.25 µg/mL for voriconazole. Weekly fungal culture of the skin wounds showed negative findings during weeks 7 to 10 of treatment and for 3 weeks after treatment. Pharmacokinetics of voriconazole was determined after a single SC injection (5 mg/kg) in red-eared sliders.<sup>81</sup> The maximum plasma concentration in the red-eared sliders was greater than 1 µg/mL at 1 hour and 2 hours after injection. This route of administration of voriconazole is likely to require a

much higher dose and short dosing interval to maintain a plasma concentration that is more than the MIC of many organisms.

### Terbinafine

Terbinafine hydrochloride is an allylamine antifungal agent and can be fungicidal in vitro depending on the concentration and the fungal species.<sup>82</sup> Terbinafine exerts its antifungal action by inhibiting biosynthesis of ergosterol via inhibition of squalene epoxidase enzyme. The effect of terbinafine causes fungal death primarily through increased membrane permeability from high concentrations of squalene, not ergosterol deficiency. Terbinafine is freely soluble in methanol and methylene, soluble in ethanol, and slightly soluble in water. Pharmacokinetics for this drug has not been determined in a reptile species. In mammals, terbinafine is well absorbed after oral administration, with peak plasma concentrations generally occurring within 2 hours after administration.<sup>83</sup> Terbinafine is lipophilic and becomes concentrated rapidly in the stratum corneum of the skin. This antifungal agent has a terminal half-life of 200 to 400 hours in tissue (e.g., adipose and skin), making it well suited for treating fungal dermatoses. Terbinafine is metabolized in the liver via several CYP isoenzymes but not cytochrome P450; the metabolites have little antifungal activity.<sup>82</sup> Terbinafine is primarily excreted in urine, and dosing should be adjusted in patients with renal insufficiency. Terbinafine is active against fungi including *Trichophyton* spp., *Candida* spp., *Epidermophyton* spp., and *Scopulariopsis* spp. In vitro sensitivity of CANV isolated from the skin of bearded dragons (MIC<sup>90</sup>) to terbinafine was 2 µg/mL.<sup>69</sup> Terbinafine has been administered to reptiles, but no pharmacokinetic data are available. Topically applied terbinafine was administered concomitantly with topical chlorhexidine and oral ketoconazole to treat CANV in a bearded dragon and 2 green iguanas.<sup>84,85</sup> The therapeutic combination brought about clinical resolution of CANV infection, but it is unclear what treatment effect could be attributed to terbinafine because of the confounding effects of the other therapeutic agents. Terbinafine was used to successfully treat *Exophiala oligosperma* phaeoerythromycosis infecting the carapace in an Aldabra giant tortoise (*Aldabrachelys* [*Geochelone*] *gigantea*). Initially, terbinafine was used topically in combination with oral itraconazole and then, because of a lack of

clinical response, the treatment regimen was switched to oral terbinafine 3.4 mg/kg PO every 24 hours for 15 months.<sup>86</sup> Plasma concentrations of terbinafine were not measured during treatment.

## ANTIPARASITIC AGENTS

A number of antiparasitic agents are currently being used to treat endoparasites and ectoparasites in reptiles. Effective treatment addresses the life cycle and ecology of the parasite. For example, it is essential to know what tissues the parasite affects, whether it is directly transmitted, has intermediate hosts, has free-living life stages, and whether it participates in the transmission of other infectious agents. Treatment may or may not include antiparasitic drug therapy. Commonly used antiparasitic drugs include albendazole, fenbendazole, fipronil, ivermectin, metronidazole, oxfendazole, paromomycin, permethrin, ponazuril, praziquantel, pyrantel pamoate, toltrazuril, and trimethoprim/sulfas. Promising newer products include combinations of imidacloprid/moxidectin and emodepside/praziquantel that are topically administered. This review is limited to a few notable agents about which there are recently published data. Topical treatment with imidacloprid/moxidectin (Advantage Multi/Advocate, Bayer, Shawnee Mission, KS USA) and emodepside/praziquantel (Profender, Bayer HealthCare, Shawnee Mission, KS USA) has shown promise for the treatment of internal parasites in reptiles and are reviewed previously.

### Benzimidazoles

Albendazole, fenbendazole, and oxfendazole are frequently used benzimidazole antiparasitic agents that exert their antiparasitic action by selectively binding and damaging tubulin, preventing tubulin polymerization, and inhibiting microtubule formation.<sup>87,88</sup> At higher concentrations, benzimidazoles disrupt metabolic pathways within helminths and inhibit enzymes such as malate dehydrogenase and fumarate reductase. Fenbendazole is insoluble in water and only marginally absorbed after oral administration; peak blood levels of 0.07 to 0.11 µg/mL have been reported in mammals, and up to 50% is excreted unchanged in the feces. The small amount of absorbed fenbendazole is metabolized by cytochrome P450 and other microsomal enzymes in the liver to metabolites including oxfendazole; some extrahepatic metabolism also occurs.<sup>89</sup> Benzimidazoles are effective against some species

of nematodes, trematodes, cestodes, and flagellated protozoans. Benzimidazole toxicity is generally rare in most species, but mortality has been reported after overdoses.<sup>89-92</sup> Relative toxicity of these anthelmintics in order of most toxic to least toxic appears to be albendazole > oxfendazole > fenbendazole.<sup>93</sup> Toxicosis leads to lesions that mimic radiation, by targeting rapidly dividing cells, including bone marrow and intestinal epithelium. These drugs also cause hepatotoxicosis, teratogenic effects, and tumor promotion.<sup>91</sup> Benzimidazoles should be used with caution in gravid and pregnant animals and should be avoided in animals diagnosed with septicemia. In a safety study without a control group, 6 quarantined Hermann's tortoises (*Testudo hermanni*) at a zoological facility were monitored for 125 days after treatment with fenbendazole (50 mg/kg PO every 24 hours for 5 days and then the same dose repeated on days 20 to 24).<sup>90</sup> No changes were observed in appetite or behavior of the treated tortoises. The total white blood cell count did not change throughout the study, though some shifts in the proportions of white blood cell types and some mild transient biochemical changes were observed at some of the sampling events. The changes were generally consistent with a response to parasite death, and the authors posited that side effects of fenbendazole may have been involved. In an efficacy study, fenbendazole and oxfendazole were compared regarding their efficacy against intestinal oxyurid nematodes in Hermann's tortoises after single oral doses of 100 mg/kg and 66 mg/kg, respectively.<sup>94</sup> Both treatments eliminated shedding of oxyurid ova in feces after 32 days; therefore, a second treatment was not necessary.

### Toltrazuril and Ponazuril

Toltrazuril and its principle metabolite ponazuril are triazinetrione antiprotozoal compounds with activity against several genera of the Apicomplexa including *Eimeria*, *Isospora*, *Hepatozoon*, *Toxoplasma*, *Sarcocystis*, *Neospora*, and possibly others.<sup>95-98</sup> Ponazuril is available as an oral paste (Marquis, 15% w/w, Bayer Animal Health, Shawnee Mission, KS USA) but can be compounded into an oral suspension by a licensed pharmacist. Toltrazuril is available outside of the United States as a solution to be applied in drinking water of poultry (Baycox solution 2.5% and 10%, Bayer) and as an oral suspension (Baycox 2.5% and 5% suspension, Bayer). The pH of ponazuril oral paste is 5.7 to 6, and the pH of 2.5% toltrazuril

solution is 8 to 10. Toltrazuril is rapidly metabolized in the liver to the sulfone derivative, ponazuril.<sup>97</sup> These drugs exert a coccidiocidal effect on intracellular coccidial stages by interfering with division of the nucleus, amino acid and fatty acid metabolism, and the electron transport system of mitochondria through ballooning of the endoplasmic reticulum and, in macrogametes, by damaging the wall-forming bodies.<sup>95,96,98</sup> There is no effect on oocysts. An additive effect can be achieved by concomitant administration of toltrazuril with an ionophore in the treatment of coccidiosis in poultry.<sup>96</sup> A concentration of 0.1- to 1.0- $\mu\text{g}/\text{mL}$  ponazuril is sufficient to kill *Sarcocystis neurona*, which causes equine protozoal myeloencephalitis when horses serve as aberrant hosts for the organism. The peak serum concentration of ponazuril was 5.6  $\mu\text{g}/\text{mL}$  18 days after oral administration in horses, and the peak concentration in cerebrospinal fluid was 0.21  $\mu\text{g}/\text{mL}$  after 15 days.<sup>95</sup> The elimination half-life in horses of ponazuril is approximately 4.5 days. Acute toxicity of toltrazuril in rats, mice, and chickens required overdoses of 100 times the recommended therapeutic dose, with an LD<sub>50</sub> range of 1600 to 5000 mg/kg; no observable effect occurred in mammals after a ponazuril dose of 90 mg/kg.<sup>96,98</sup> A 2-day treatment of toltrazuril in the drinking water (7 mg/kg) is sufficient to treat intestinal coccidiosis in poultry, and daily oral administration of ponazuril (5 mg/kg) for 28 days is recommended for treatment of protozoal myeloencephalitis in horses. A clinical report in chameleons stated that toltrazuril was effective at eliminating shedding of coccidian oocysts, with no side effects being observed.<sup>99</sup> A pilot study in bearded dragons reported that coccidian oocysts were found on fecal flotation before treatment with ponazuril dosed at 30 mg/kg PO every 48 hours for 2 treatments but not after.<sup>100</sup> An incidental finding in a group of 10 bearded dragons in an experimental cryptosporidiosis/paromomycin study was that treatment of a naturally occurring coccidiosis (presumed *Isospora amphiboluri*) with ponazuril (Marquis, Bayer Inc, Montreal, Quebec, Canada) dosed at 30 mg/kg PO every 48 hours for 3 treatments and then again after 3 months, 30 mg/kg every 48 hours for 6 treatments was not effective at eliminating the infestation.<sup>101</sup> Histologic examination of the intestines immediately after the second treatment period showed mild to moderate intracellular stages of the coccidian in the enterocytes of all but 1 of the 10 dragons. Toltrazuril (Baycox 5%, oral suspension, Bayer Vital GmbH, Germany), dosed at 15 mg/kg every 48 hours for 30 days, and ponazuril (90 mg/mL compounded), dosed at 30 mg/kg PO every 24 hours for 4 days and repeated for 2 to 4 treatments at least 2

weeks apart, have been used to treat intranuclear coccidiosis of testudines in several species of tortoise, and both drugs appear to be associated with improved survival, cessation of parasite shedding (negative results on polymerase chain reaction testing after treatment), and resolution of clinical signs in cases that are treated early in the course of the disease.<sup>102</sup> Controlled clinical trials and pharmacokinetic studies are needed for the use of ponazuril and toltrazuril in reptiles.

### Paromomycin

Paromomycin is an oral aminoglycoside antiparasitic agent closely related to neomycin. Like all aminoglycosides, paromomycin exerts its cidal effect by binding to the 16s ribosomal RNA subunit inhibiting protein synthesis. Paromomycin is very soluble in water but, similar to other aminoglycosides, is poorly absorbed after oral administration, except in cases of severe intestinal ulceration. Paromomycin is eliminated almost exclusively unchanged in the feces. Paromomycin has antibacterial activity, which can be an undesirable effect when used to treat intestinal amebiasis, cutaneous leishmaniasis, or cryptosporidiosis because intestinal dysbiosis can occur when used for prolonged periods at high doses. Paromomycin has been used with limited success in reptiles to treat refractory intestinal amebiasis and cryptosporidiosis.<sup>101,103-107</sup> Treatment with paromomycin 100 mg/kg PO every 24 hours for 7 days and then every 84 hours for 90 days in a group of Hermann's tortoises diagnosed with cryptosporidiosis initially controlled clinical signs and shedding, but the disease recrudesced after 9 months.<sup>103</sup> A colony of leopard geckos (*Eublepharis macularius*) with naturally occurring cryptosporidiosis were treated with 50 to 800 mg/kg paromomycin (Humatin, Parke-Davis, Morris Plains, NJ USA) PO every 24 hours; the treatment was associated with improvement in clinical signs and reduced oocyst shedding that returned when treatment was suspended.<sup>107</sup> In a different clinical trial, treatment of 4 leopard geckos with paromomycin (100 mg/kg every 24 hours for 7 days, and then every 84 hours for 72 days) brought about improvement of clinical signs and negative fecal examination findings in 3 of the geckos but did not eliminate infection.<sup>104</sup> Two Gila monsters (*Heloderma suspectum*) with naturally occurring cryptosporidial infections were treated with paromomycin at a dosage of 300 to 360 mg/kg PO every 48 hours for 14 days, which was repeated at 6 months; fecal samples were negative for cryptosporidia after 2 weeks of treatment and

remained parasite free for at least 1 year.<sup>106</sup> A group of 10 hatchling (1 month old) bearded dragons were experimentally infected with *Cryptosporidium* from a naturally infected adult, and 5 of the lizards were treated with paromomycin (Humatin 250-mg capsules, Erfa, Montreal, Quebec, Canada) in saline (500 mg/5 mL) 100 mg/kg every 24 hours for 7 days, followed by every 84 hours for 72 days; the other 5 bearded dragons served as controls.<sup>101</sup> This treatment did not control shedding of the organism in the feces; therefore, a second round of treatment was initiated using a dose of 360 mg/kg every 48 hours for 10 days. This second treatment regimen did eliminate the cryptosporidia; infection was present in 4 of 5 control bearded dragons and in none of 5 treated bearded dragons on histologic examination of the gastrointestinal tract.

### Sulfadimethoxine

Sulfadimethoxine is a long-acting sulfonamide that exerts its antiprotozoal effect by competing with para-aminobenzoic acid in the biosynthesis of tetrahydrofolic acid in the pathway to form folic acid, thereby interfering with nucleic acid synthesis. Sulfonamides are effective only in organisms that synthesize folate, and consequently have no effect on vertebrates because they obtain their folate from their diet. Sulfadimethoxine is bacteriostatic against a number of Gram-positive and Gram-negative bacteria, and has activity against some rickettsia and protozoa including *Toxoplasma* and coccidia, although resistance can occur.<sup>108</sup> Sulfadimethoxine is active against asexual stages of coccidia and not oocysts, thus prolonged treatment is required. In a controlled treatment trial, sulfadimethoxine (Albon, Pfizer Animal Health, New York, NY USA) dosed at 50 mg/kg was administered by mouth every 24 hours for 21 days to 12 coccidia-infested bearded dragons maintained at 30°C (86°F).<sup>109</sup> Shedding of coccidian oocysts ceased in 10 of the 12 treated and none of the 12 control (saline-treated) dragons by week 4 of the study. The authors suggest that longer treatment may improve treatment effectiveness of sulfadimethoxine.

### ANTIVIRAL AGENTS

Numerous viruses infect reptiles, and a causal relationship between disease and the viral pathogen has been established in a few cases; diagnostic tests are currently available for several reptile viruses. Nursing care is the mainstay of antiviral therapy for individual patients, and immune stimulators and antiviral drugs may be

occasionally useful. Reptile patients testing positive for a virus should be isolated from uninfected cohorts to prevent further transmission. Vaccine trials have shown promise for poxvirus in crocodylians but not herpes virus in tortoises or paramyxovirus in snakes.<sup>4,110,111</sup> A few antiviral drugs have been evaluated for reptiles and may help improve an individual patient's clinical condition; however, in general, antiviral drugs are not expected to eliminate infection, and it is possible that an infected reptile would shed infective virus after treatment. Antiviral agents that have been evaluated in reptiles include acyclovir, ganciclovir, and valacyclovir.<sup>112-114</sup>

### Acyclovir

Acyclovir is a synthetic purine nucleoside analogue that interferes with nucleic acid synthesis and is active against herpes viruses.<sup>115</sup> The inhibitory activity of acyclovir is highly selective because of an affinity for thymidine kinase encoded by herpes viruses, which phosphorylates acyclovir into a nucleotide analogue that is further converted by a series of enzymes into acyclovir triphosphate. Acyclovir triphosphate stops replication of herpes virus DNA by competitive inhibition of viral DNA polymerase, incorporation into and termination of the growing DNA chain, and inactivation of viral DNA polymerase.<sup>113,115</sup> Acyclovir is available in tablets, capsules, oral suspension, and by injection. Acyclovir's average bioavailability after oral administration in humans is 10% to 20%, and food does not affect absorption of the drug. The elimination half-life and total body clearance of acyclovir are dependent on renal function in humans, thus the dose should be reduced in patients with renal insufficiency.<sup>115</sup> Coadministration of probenecid with acyclovir increases the elimination half-life of acyclovir, and adverse side effects are rare in humans. An in vitro study of acyclovir efficacy against a herpes virus isolated from a Hermann's tortoise (*T. hermanni*) indicated that a dose of 50 µg/mL reduced the virus content of cultures to below the limit of detection.<sup>112</sup> The pharmacokinetics of acyclovir in marginated tortoises (*Testudo marginata*) over a 24-hour period after being administered 80 mg/kg PO every 24 hours for 7 days has been reported.<sup>114</sup> The maximum plasma concentration of acyclovir in the tortoises occurred 6.9 ± 4.2 hours after administration and was 1.40 ± 0.45 µg/mL; the tissue concentrations were not evaluated. The elimination half-life was 8.9 ± 3.8 hours, and the

authors proposed that a higher milligram dose be administered every 12 to 24 hours. A recently published study<sup>113</sup> on the pharmacokinetics of acyclovir in North American box turtles (*Terrapene carolina*) after a single oral dose of 40 mg/kg valacyclovir (the esterified form that is rapidly converted to acyclovir after oral administration) found the elimination half-life to be 14.6 hours, and the  $C_{max}$  of 1.94  $\mu\text{g}/\text{mL}$  was reached 13.0  $\pm$  7 hours after administration. Prolonged lethargy was noted in 1 turtle after receiving the dose of valacyclovir. The authors proposed that a dosage of valacyclovir of 40 mg/kg PO every 24 hours would be sufficient to achieve a steady-state level above 0.8  $\mu\text{g}/\text{mL}$  in plasma. It is possible the proposed doses of valacyclovir in the common box turtle and acyclovir in the marginated tortoise may be sufficient to treat herpes virus in tortoises even though plasma levels are much lower than the in vitro inhibitory concentration because acyclovir concentrates in herpes virus-infected tissues. For comparison, the MIC is 0.45  $\mu\text{g}/\text{mL}$  in humans, 3  $\mu\text{g}/\text{mL}$  in horses, and 18  $\mu\text{g}/\text{mL}$  in cats. A topical preparation is also available (5% acyclovir, Zovirax, GlaxoSmithKline Inc, Research Triangle Park, NC USA). A few clinicians suggest acyclovir may be useful in treatment of herpes virus stomatitis in tortoises.<sup>116,117</sup> Further research measuring the tissue levels of acyclovir achieved in herpes virus-infected tissue after oral administration and the efficacy of treatment is necessary. Valacyclovir may also have some effect on iridoviruses, consequently further research is warranted.<sup>113</sup>

### Ganciclovir

Ganciclovir is a synthetic guanine derivative that is active against human cytomegalovirus and herpesvirus.<sup>118</sup> Ganciclovir's mechanism of action is similar to acyclovir and has a solubility of 2.6 mg/mL in water at 25°C (77°F) and pKa values of 2.2 and 9.4. As a monosodium salt, ganciclovir sodium, ganciclovir has a solubility of approximately 6 mg/mL at 37°C (98.6°F). When reconstituted with water, the pH of the IV solution is 11. The in vitro MIC for cytomegalovirus ranges from 0.02 to 3.48  $\mu\text{g}/\text{mL}$ . Ganciclovir inhibits mammalian cell proliferation at concentrations as low as 30  $\mu\text{g}/\text{mL}$  and is eliminated primarily via the kidneys; therefore, the dosage should be reduced in patients with renal insufficiency. Viral resistance to ganciclovir has been found in humans who have not been previously treated with this drug.<sup>118</sup> Pharmacokinetic values for ganciclovir

have not been determined in reptile species, but an in vitro study showed that ganciclovir was effective at a dose of 25 and 50  $\mu\text{g}/\text{mL}$  against a herpes virus cultured from a Hermann's tortoise.<sup>112</sup>

### ANALGESIC AND ANESTHETIC AGENTS

Knowledge about reptile analgesia and analgesic agents has increased substantially in recent years. Some of the most important findings describe how to measure the effect of treatment (antinociception) and what opioid receptors are most important in reptile species. Analgesics commonly used in reptile medicine include butorphanol, buprenorphine, morphine, oxymorphone, tramadol, ketoprofen, and meloxicam. An excellent review of recent advances was recently published.<sup>119</sup> A similar thorough review of reptile anesthesia is also available.<sup>12</sup> A number of reports have since been published describing the use of alfaxalone in reptiles.<sup>120-122</sup> Alfaxalone is currently a preferred induction agent, when available, and should be used together with analgesic agents and followed by endotracheal intubation, positive pressure ventilation, and gas anesthesia.

### SUMMARY

Currently, veterinarians who treat reptile species are able to make much more informed decisions about therapeutic protocols than ever before. It remains true that many of the most commonly used drugs in clinical practice have yet to be studied in the most common reptile species, but an increasing amount of new information is available to guide treatment plans. When research information is incomplete regarding the reptile species being treated, background knowledge about the basic chemistry and pharmacology data from other vertebrates is essential. This review identifies some of the most important gaps in our knowledge regarding therapeutic use in reptile patients and is intended to encourage additional research directed toward answering these critical questions to keep moving the field forward.

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