
THE TREATMENT OF MYCOSES IN REPTILES: A REVIEW OF ANTIFUNGAL DRUGS

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ABSTRACT

With the advent of increasingly sophisticated diagnostic tools, mycoses in reptiles are nowadays often diagnosed ante-mortem and the clinician needs to decide on an optimal course of treatment. The disease process might be quite advanced by the time the animal exhibits clinical signs, as is typical of many non-traditional pet species, and therefore, delaying treatment or selecting inappropriate antimicrobials may easily cost the animal's life. In most patients, stabilization by means of fluid therapy, and thermal and nutritional support is warranted prior to initiating further diagnostic procedures, or prior to instituting specific antifungal drug therapy. Radiographs, coelomic echography, MRI or other scanning device, complement a thorough physical examination and can all help to determine the extent of fungal disease by identifying visceral dissemination or the actual extent/depth of dermatomycotic lesions. A complete blood count is useful in assessing the quality of the patient's immune response, and a serum chemistry panel may support a diagnosis of organ involvement as suspected by imaging findings, and will be used to compare with sequential serum chemistries after initiation of antifungal drugs, so that hepato- or nephrotoxicity can be identified early. Follow up imaging may also be useful to monitor treatment progress, and even determine duration of antifungal therapy. A thorough review of the husbandry is always indicated to identify and correct any perceived deficiency but in some mycoses, such as in infections with the *Chrysosporium* anamorph of *Nannizziopsis vriesii* (CANV), there may be no obvious or identifiable inadequacy in the captive husbandry.^{3,4}

Mycoses in reptiles can be cutaneous (dermatomycoses) and/or systemic (pulmonary, renal, hepatic, disseminated, etc). Dermatomycoses in reptiles are practically never restricted to the epidermis. In reptile skin infections, dermal invasion is the rule. Since reptiles possess a very thin layer of connective tissue beneath the dermis (hypodermis), and the dermis often lies directly over subjacent muscles or bone, involvement of deeper tissues is very common when compared to mammals. The most common agent of dermatomycosis in reptiles, the CANV, readily invades the dermis and underlying structures.^{3,4} Therefore, the use of systemic drugs is not only practically always indicated, but is probably essential, as the use of topical antifungal compounds is unlikely to be successful, even with thorough debridement of infected skin and tissues, without the systemic use of an efficacious antifungal drug. Topical antifungal creams and ointments are an adjunct to systemically administered drugs. There exists a plethora of topical antifungal preparations, and to cover each is beyond the scope of this paper. In selecting a topical antifungal, the clinician might want to choose an antifungal that has a different mode of action as the one being administered systemically, so that

they act in a complementary fashion.

Ideally, the choice of a systemic antifungal drug would be based primarily on the sensitivity of the fungus causing the infection. In vitro susceptibility assays for yeast isolates to various antifungal compounds has been available for many years, but is underutilized by veterinarians. For example, very rarely do clinicians or even pathologists culture yeasts to support or confirm a presumptive diagnosis of candidiasis, when the culture and speciation and sensitivity determination of *Candida* organisms in human medicine is crucial in deciding on an appropriate antifungal. Moreover, there is now a method available to determine in vitro sensitivity of filamentous fungi (molds) to antifungal drugs,⁵ but again rarely is the fungus cultured from lesions. Clinicians ideally should urge the laboratory to key pathogenic yeast or mold isolates to species, then either refer to known sensitivity patterns of the organism or, if not available, try and obtain a sensitivity profile. A review of the literature as to which fungi are most often incriminated in reptile mycoses is misleading. In many if not most instances, a causal relationship between a fungal isolate and the lesions described in the reptile was not acceptably demonstrated. One fungus, the CANV, is clearly a pathogen of crocodilians and squamate reptiles, and can act as a primary, contagious pathogen.⁴ There are also well-documented accounts of what appear to be opportunistic mycoses in which *Aspergillus*, *Paecilomyces lilacinus*, *Fusarium*, *Acremonium*, *Mucor*, and *Trichosporon* species, among others, were firmly incriminated.⁴ Of these, we know from human medicine that *Fusarium*, *Paecilomyces lilacinus*, and *Mucor* (and other *Zygomycetes*) are notoriously resistant to many antifungal drugs^{1,5} and treatment with anything but amphotericin B or itraconazole would probably be futile, hence the importance of proper identification of causal fungal agents. The sensitivity pattern of CANV isolates is currently being investigated.

There are several classes of antifungal drugs. The drugs that are currently in use in the treatment of mycoses in animals are the polyenes, the azoles, the allylamines, and in the case of dermatophytes, griseofulvin.

The only polyenes currently available are nystatin and amphotericin B. Polyenes act very rapidly by binding to ergosterol in the fungal cell membrane, causing alterations in the membrane integrity and leading to leakage of metabolites and electrolytes with ensuing cellular death.^{1,5} Polyenes are active against a wide spectrum of fungi, but their toxicity is a major downfall. Nystatin (e.g., Mycostatin™ Bristol Myers-Squibb, Nilstat™ Wyeth-Ayerst) is used topically to treat mucosal and cutaneous mycoses, usually yeast infections. It is not absorbed across the gastrointestinal mucosa or skin and therefore toxicity is only a minor issue. A liposomal formulation of nystatin (Nyotran™ Aronex Pharmaceuticals) is being tested for intravenous use and may become available for treatment of systemic mycoses in the future.⁵ Amphotericin B deoxycholate (Fungizone™ Bristol Myers-Squibb) has long been available. It is given intravenously and is efficacious against most mycotic agents, but it is highly nephrotoxic, even after decades of trying to find a less toxic mode of delivery.^{1,5} Newer formulations, such as the amphotericin B colloidal dispersion (Amphocil™ and Amphotec™ Sequus Pharmaceutica), amphotericin B lipid complex (Abelcet™ Enzon Pharmaceuticals) and liposomal amphotericin B (Ambisome™ Nexstar Pharmaceuticals) appear to

be significantly less nephrotoxic while maintaining the same wide antifungal spectrum.^{1,5} These are all administered intravenously as infusions. In humans, fever, chills, myalgia, hypoxemia, respiratory difficulties and anaphylaxis are all potential side effects of these amphotericin B infusions. While there appear to be less side effects with the liposomal amphotericin B formulation,⁵ the systemic use of any of the amphotericin B formulations requires repeated venous access and close monitoring for any side effect or toxicities. Since it does not cross epithelial barriers, amphotericin B may be nebulized as an adjunct to treatment of pulmonary mycoses. The newer amphotericin B formulations have not been investigated in reptiles.

The azoles that are readily available are ketoconazole, fluconazole, and itraconazole but voriconazole has just recently been marketed, and posaconazole and ravuconazole are in the later phases of testing. Like all azoles, ketoconazole (Nizoral™ Janssen Pharmaceutica) targets the cytochrome P₄₅₀ 14 α -demethylase enzyme, a crucial step in the elaboration of ergosterol from lanosterol.^{1,5} Ketoconazole has less affinity to the fungal cell membrane than fluconazole or itraconazole, and is more toxic.^{1,5} Its spectrum is also not as wide as itraconazole. Its use has largely been replaced by the newer azoles. Fluconazole (Diflucan™ Pfizer Pharmaceuticals) is a widely used triazole in the treatment of candidiasis and cryptococcosis. It can be administered orally or intravenously, penetrates the blood-brain barrier, and is eliminated in the urine, making it useful in the treatment of funguria and renal yeast infections. However, it has a limited spectrum when compared to itraconazole and the newer azoles, and has no activity against *Aspergillus* nor other filamentous fungi (molds), a major disadvantage.^{1,5} *Candida krusei*, increasingly involved in human yeast infections, and documented as a pathogen of birds,² is inherently resistant to fluconazole. Itraconazole (Sporanox™ Janssen Pharmaceutica) comes in oral and intravenous formulations. The liquid suspension is much more readily absorbed from the gut than the capsule formulation, and should always be used.⁵ Itraconazole has a wide spectrum that approximates that of the polyenes. It is active against yeasts, including many fluconazole-resistant *C. krusei* and *C. glabrata* isolates, against most dimorphic fungi, against aspergilla and other moulds, and against dermatophytes.⁵ It concentrates in the corneum of the skin in the same way griseofulvin does,⁵ and can therefore be very useful in limiting the progression of dermatomycosis in reptile patients. While it has been thought that it does not penetrate the blood-brain barrier, recent studies suggest that higher doses of itraconazole may be efficacious in the treatment of brain abscesses caused by *Aspergillus* or other molds.⁵ In humans, side effects to itraconazole treatment are mild and non-specific, similarly to fluconazole, and hepatotoxicity is rare. Limited experience with itraconazole in bearded dragons suggests that anorexia and hepatotoxicity may be more common than in humans, but ideal an dosage in reptiles is not known. Voriconazole (VFend™ Pfizer Pharmaceuticals) is new on the market and comes in an oral and an intravenous formulation. It seems to have a greater inhibiting power on the cytochrome P₄₅₀ 14 α -demethylase than itraconazole and has a slightly wider spectrum that includes *Fusarium* species and possibly some *Zygomycetes* at higher doses.⁵ Side effects in humans are dose related and include elevations in hepatic enzymes. About 30% of humans given voriconazole experience transient visual disturbances, a peculiar side-effect not seen with other azoles. Posaconazole is another new triazole being developed by Schering-Plough Pharmaceuticals with properties similar to voriconazole.⁵ Its activity against *Zygomycetes* is particularly appealing. It

comes in a tablet and an oral suspension form but is not yet available. There is little data on ravuconazole (Bristol Myers Squibb), and no data that would make it sound superior to itraconazole, voriconazole or posaconazole.

The allylamines also inhibit ergosterol biosynthesis but target a different enzyme, the squalene epoxidase.^{1,5} Terbinafine (Lamisil™ Novartis Pharmaceuticals) comes in a topical cream formulation and an oral formulation. In humans, it is used mainly against dermatophytes and in cases of onychomycoses but is active in vitro against a variety of fungi, including many molds. It is well tolerated by humans and side effects, when present, are usually gastrointestinal although reversible agranulocytosis has been reported. Amorolfine (Loceryl™ Roche Laboratories) and butenafine (Mentax™ Penederm Inc.) are topical allylamines that appear to be fungicidal and active against a wide spectrum of dermatophytes, yeasts, as well as filamentous and dematiaceous fungi. They penetrate nails (keratin) and achieve good local MICs. Loceryl™ is marketed as a nail lacquer that creates a non-water soluble film that persists for 1 wk, while Mentax™ is a topical cream. Allylamines have not been explored much in veterinary medicine, and even less so in reptiles. Their safety and wide spectrum would seem to warrant further investigation of their use in reptiles, if only as an alternative to azoles, and the fact that these drugs target a different step in the ergosterol biosynthesis suggest they also could be useful as a topical adjunct to systemic azole therapy.

The cells of vertebrates do not have a cell wall as fungal cells do. Therefore antifungal drug that target the cell walls are keenly sought. Echinocandins are such a group of drugs. They are inhibitors of the biosynthesis of glucan, a major and crucial fungal cell wall component.^{1,5} Caspofungin (Cancidas™ Merck Research Laboratories) is the only currently available echinocandin and has only been marketed very recently. It is only available as an intravenous formulation, administered as a slow infusion that appears much to be much better tolerated than amphotericin B. Caspofungin is active against aspergilla and yeasts. Micafungin (Fujisawa Healthcare Inc.) should also be available soon and is very similar in its spectrum to caspofungin. Anidulafungin (Eli Lilly Pharmaceuticals) is being investigated as an oral formulation, in contrast to the traditional intravenous route of administration for echinocandins.

Dermatophyte (*Microsporum*, *Trichophyton*, *Epidermophyton*) infections are restricted to the corneum and superficial strata of the epidermis, but to date there is no clear evidence to support the notion that reptiles are susceptible to dermatophytosis, and there are no convincing accounts of reptile dermatophytosis in the literature. Griseofulvin has long been the drug of choice in the treatment of dermatophytosis but has now been supplanted in human medicine by terbinafine and itraconazole, both of which are less toxic and do not require as long a course of treatment. Griseofulvin inhibits mitosis by interfering with microtubules. The spectrum of activity of griseofulvin, other than dermatophytes, is unclear. Griseofulvin (Fulvicin U/F™ Schering Plough and Gris-PEG™ Pedinol) is still currently available.

Other drugs are also under investigation. Among those, drugs that target chitin synthesis (nikkomycin, lufenuron) have yielded conflicting results, or have had very restricted spectrum of

activity.^{1,5} However, these chitin synthase inhibitors are typically very safe, and their potential use could warrant some investigation should they have any demonstrable activity against the CANV.

Duration of treatment should be based on the resolution of lesions, as demonstrated by follow up imaging or biopsies. Dosages and modes of administration (e.g., slow vs fast rate infusions) of antifungal drugs are still very much being debated in human medicine, even for drugs that have been around for decades.⁵ We know little of the kinetics and safety of antifungal drugs in reptiles, a very heterogeneous class of animals, and research in this area is sorely needed. In human medicine, some drugs (e.g., itraconazole) are now being given as pulse therapy (e.g., 1 wk on, 1 wk off, etc.) on the basis that they persist in the body for some time. Now that in vitro sensitivity for filamentous fungi has become available, we may be able to determine MICs of seemingly efficacious drugs and use those as target tissue concentrations to be maintained when considering pulse therapy. Investigation in the efficacy and safety of terbinafine and voriconazole would also be helpful as their use would provide reasonable alternatives to itraconazole when treating reptile mycoses.

Information was gathered from the references below, as well as the very useful web site <http://www.doctorfungus.org/index.htm>, which readers are encouraged to visit.

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