Antifungal Therapy in Birds
Old Drugs in a New Jacket

Gunther Antonissen, DVM, MSc, PhD[a,b,*],
An Martel, DVM, MSc, PhD, DECZM (Wildlife Population Health)[b]

KEYWORDS

• Amphotericin B • Antifungal • Drug formulation • Itraconazole • Nanoparticles • Nebulization • Terbinafine • Voriconazole

KEY POINTS

- Large interspecies and interindividual variability can be found in the pharmacokinetics of antifungal drugs in birds, which can significantly affect drug safety and efficacy.
- The absorption of antifungals is affected by numerous factors, including drug formulation and gastrointestinal anatomy and physiology.
- New antifungal drug delivery systems enhance drug stability, reduce off-target side effects, prolong residence time in the blood, and improve drug efficacy, and should therefore be considered in the treatment of mycoses.
- Nebulization seems to be a promising method to deliver antifungals in the respiratory tract of birds; however, therapeutic output is influenced by drug formulation and nebulizer type.

INTRODUCTION

The early diagnosis of systemic fungal diseases in birds, especially aspergillosis, remains challenging because the clinical signs are usually nonspecific and there still is no single reliable noninvasive diagnostic test available in birds.[1–3] Consequently, antifungal therapy is frequently administered empirically for presumptive invasive fungal infections in these patients without a definitive diagnosis being made. However, different factors need to be considered in the rational drug selection of antifungal therapy. First, the selected antifungal drug must be able to penetrate the center of infection in a concentration to which the fungus is susceptible. However, fungi, in

Disclosure Statement: The authors have nothing to disclose.
G. Antonissen is supported by a postdoctoral fellowship from the Research Foundation, Flanders (12V6418N).
[a] Department of Pharmacology, Toxicology and Biochemistry, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium; [b] Department of Pathology, Bacteriology and Avian Diseases, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium
* Corresponding author. Department of Pharmacology, Toxicology and Biochemistry, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium.
E-mail address: Gunther.Antonissen@UGent.be

Vet Clin Exot Anim 21 (2018) 355–377
https://doi.org/10.1016/j.cvex.2018.01.009 **vetexotic.theclinics.com**

contrast with bacteria, are eukaryotes, and consequently most antifungal agents are also toxic to the eukaryotic host cells. Therefore, taking into account their (often narrow) therapeutic index, no perfect antifungal agent exists. Nevertheless, in the last decades, newer and less toxic antifungals, including the azoles and echinocandins, have been developed for use in human medicine. Aside from the chemical structure, the impact of antifungal drug formulation and route of administration on treatment safety and efficacy have been investigated as well.[4]

Because knowledge of avian antifungal treatment is limited, treatment protocols are often developed empirically, based on case reports, or extrapolated from humans or other animal species. Because of the narrow therapeutic index, the dosing of antifungal drugs should be done carefully, with dose extrapolation preferably based on more advanced allometric and physiologically based pharmacokinetic (PK) modeling.[5] In avian medicine, different antifungal agents are being used, but most of these substances have not been approved for administration in birds.[6] However, recently (2014) the first antifungal product (itraconazole 10 mg/mL oral solution; Fungitraxx, Avimedical, Hengelo, The Netherlands) was registered for ornamental birds in Europe (EMA/698698/2013). The purpose of this review is to describe the interrelation of antifungal drug formulation, administration route, therapeutic–toxic range, and treatment outcome in fungal diseases, with a particular emphasis on aspergillosis in companion birds.

MECHANISM OF ACTION

In general, the main targets for antifungal drug development are cell wall polymer (glucans, chitin, mannoproteins), cell membrane (especially ergosterol) biosynthesis, DNA and protein synthesis (topoisomerases, nucleases, elongation factors and myristoylation), and signal transduction pathways (protein kinases and protein phosphatases).[7,8] The 3 major groups of antifungal agents in clinical use, that is, polyenes, azole derivatives, and allylamines, all owe their antifungal activities to the inhibition of synthesis or direct interaction with ergosterol (the predominant component of the fungal cell membrane).[8,9]

Amphotericin B and nystatin are polyene macrolides that act by binding to ergosterol. This binding alters the membrane permeability, causing leakage of sodium, potassium, and hydrogen ions, which eventually leads to cell death. Polyenes have a broad antifungal spectrum, including a variety of yeasts (eg, *Candida* spp) and molds (eg, *Aspergillus* spp).[9]

Azoles inhibit the enzyme cytochrome P450-dependent 14-α-sterol demethylase, which is required for the conversion of lanosterol to ergosterol. Exposed fungi become depleted of ergosterol and accumulate 14-α-methylated sterols. This action causes disruption of membrane structure and function, thereby inhibiting fungal growth.[9,10] Azoles are classified as imidazoles (including clotrimazole, miconazole, enilconazole, and ketoconazole) or triazoles (including itraconazole, fluconazole, and voriconazole) based on possessing 2 or 3 nitrogen atoms in the 5-membered azole ring, respectively. Depending on the particular compound, azole antifungal agents have fungistatic and broad-spectrum activity against most yeasts and filamentous fungi.[9] With the exception of voriconazole, azoles are known to be fungistatic at the doses used in birds and need several days to reach steady-state concentrations.[11]

Finally, allylamines (eg, terbinafine) act by a reversible, noncompetitive inhibition of the squalene epoxidase, a key enzyme in the cyclization of squalene to lanosterol, resulting in an ergosterol depletion and squalene accumulation. The antifungal spectrum of terbinafine includes yeast (fungistatic) as well as dermatophytes and molds (fungicidal).[6,9,12]