Antifungal Therapy in Small Animal Medicine

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Introduction

Invasive fungal infections (IFIs) are growing in importance in veterinary and human medicine. This is due to expanding endemic geographic ranges, emerging antifungal resistance, and increasing immunosuppressed populations. Invasive fungal infections are caused by endemic dimorphic fungi (*Blastomyces*, *Histoplasma*, *Coccidioides*), yeast (*Cryptococcus and Candida*) or molds. *Aspergillus* is the most common invasive mold infection, and many others fall into one of a few broad categories – hyalohyphomycosis (non-pigmented mold), phaeohyphomycosis (pigmented mold), order Mucorales (formerly zygomycosis), and eumycotic mycetoma.

Amphotericin-b is used for life-threatening IFIs and azoles are used for mild-to-moderate disease or following (step-down) amphotericin-b therapy. These include first-generation drugs – itraconazole and fluconazole and second-generation drugs – posaconazole, voriconazole, and isavuconazole. Fluconazole and itraconazole are used most often in veterinary medicine and voriconazole and posaconazole are reserved for invasive molds or as salvage therapy when itraconazole or fluconazole treatment has failed. Limited data are available for isavuconazole in many veterinary species including cats and dogs. It is a pro-drug and there are likely important pharmacokinetic differences between species.

When choosing an antifungal drug there are at least 5 important considerations:

1. Antifungal spectrum – fungal sensitivity to drug
2. Tissue permeation – location of infection
3. Safety profile – adverse-effects; drug-to-drug interactions
4. Formulation – route of administration; solution or capsule
5. Cost – affordability

Azole Pharmacokinetics and Adverse-Effects

Azoles work by inhibiting a fungal CYP-450 enzyme (14alpha-demethylase) and decreasing the production of ergosterol, which damages the fungal cell membrane. Azoles cause lesser inhibition of mammalian metabolic CYP-450 enzymes, but enough still to cause many potential

drug-to-drug interactions (DDIs). Concurrent administration of an azole can significantly decrease metabolism, and thus increase concentrations of amitriptyline, amlodipine, benzodiazepines, cisapride, corticosteroids, cyclosporine, ivermectin, digoxin, and macrolide antibiotics. Most azoles are extensively metabolized by the liver and toxicity is more likely with decreased hepatic function. Fluconazole is the exception being mostly excreted unchanged in the urine. The most common adverse effect is gastrointestinal upset (anorexia, diarrhea, vomiting) which can be due to toxicity or adverse reaction to an excipient. The target organ of toxicity is primarily the liver and enzymes should be monitored during treatment. Toxicity can also cause ulcerative skin lesions, due to vasculitis, most commonly seen with itraconazole.[1] Voriconazole can cause neurotoxicity, especially in cats.[2] Adverse effects of itraconazole, and potentially other azoles, can be mostly avoided with therapeutic drug monitoring (see below).

The antifungal activity of azoles is determined by the area-under-the-curve when blood concentrations are plotted against minimum inhibitory concentrations (AUC/MIC). Clinically this means that the daily dose (mg/kg/day), not the frequency, is most important. As such, fluconazole and itraconazole can be administered once or twice (or four times) daily to cats and dogs.

Fluconazole

Fluconazole is a relatively small molecule with low protein binding, which leads to better permeation of immunoprotected sites such as the CNS and eyes (Table 2). It can be given with food or on an empty stomach and can be given concurrently with antacids. FDA generic tablets of several sizes (50, 100, 200 mg) and solution make is simple to dose. Fluconazole is highly bioavailable, although a recent population based pharmacokinetic study found high variability in blood concentrations in cats and dogs.[3] This suggests that therapeutic drug monitoring might be useful clinically. Dimorphic fungi such as *Histoplasma*, *Blastomyces*, and *Coccidioides* are significantly more sensitive to itraconazole as compared with fluconazole. In addition, acquired resistance to fluconazole has been reported in humans.[4] It is excreted mostly unchanged (>90%) in the urine making it ideal for fungal cystitis. Dosages might need to be decreased with kidney disease. Halving the dose when the serum creatinine is >3.0 mg/dL, is one simple guideline. Fluconazole is the drug of choice for cryptococcosis and is the most commonly used drug for coccidioidomycosis (valley fever). It can also be used to treat histoplasmosis and blastomycosis when itraconazole is not tolerated. Fluconazole is not effective against molds such as *Aspergillus*.

Itraconazole

As compared with fluconazole, it is a larger molecule with higher protein binding, and is a more potent p-glycoprotein substrate- leading to relatively lower concentrations in immunoprotected sites. Due to very high lipid solubility, absorption of the capsule is increased with a meal. In contrast, the solution can be given with food or on an empty stomach. Absorption is dependent on the acidic gastric environment and is decreased by concurrent administration of antacids. To facilitate oral bioavailability, FDA-approved itraconazole solution contains a solubilizing excipient (beta-cyclodextrin). Likewise, FDA-approved capsules contain drug coated spheres which increase solubility. Compounded itraconazole made from bulk chemical lacks these important excipients, resulting in very low GI absorption. As such, compounded drug consistently provides sub-therapeutic blood concentrations.[5-7]

Even with FDA-approved drug, there is considerable animal-to-animal variability in GI absorption.[5] This, along with dose-dependent adverse effects and known therapeutic blood concentrations, support the use of therapeutic drug monitoring. Itraconazole blood levels can be measured by chromatography-mass spectrometry or bioassay. The bioassay, a pharmacodynamic test, measures the antifungal activity of sera by quantifying inhibition of fungal growth in the lab. It has the advantages of measuring itraconazole and active metabolites (OH-itraconazole) and is significantly less expensive. OH-itraconazole has similar antifungal potency as the parent drug.[8] In dogs, on average, OH-itraconazole reaches blood concentrations similar to parent drug, but like humans, there is likely wide animal-to-animal variation in metabolite: parent drug concentrations.[9,10] In one study OH-itraconazole concentrations were negligible (5% parent drug) in cats for which active metabolites remain unknown.[11] Chromatography-spectrometry has the advantage of not being affected by concurrent administration of other antifungal drugs but is considerably more expensive and does not measure all active metabolites.

If itraconazole solution is not feasible for smaller animals, FDA-approved capsules can be opened and put over soft food or placed into smaller capsules. Moreover, every other day administration of a 100 mg capsule has been shown to achieve therapeutic blood concentrations in healthy cats.[12] FDA-approved generic itraconazole capsules are essentially equivalent to Sporanox® capsules and provides significant cost-savings.[7] Itrafungol® (Elanco, 10 mg/ml) is FDA approved for the treatment of dermatophytosis in cats. It is essentially equivalent to Sporanox® and can be used off-label for the treatment of IFIs in cats or dogs. FDA-approved generic itraconazole

solution has an identical ingredient list to Sporanox® solution, but published pharmacokinetic data are not currently available for cats or dogs.

Posaconazole and Voriconazole

Posaconazole and voriconazole are next generation itraconazole and fluconazole, respectfully. They were developed to provide an expanded activity against invasive molds and are FDA-approved for the prevention or treatment of invasive molds (*Aspergillus*) or candidiasis in humans. With FDA-approved generic formulations now available, these drugs are more affordable for pet-owners. In cats and dogs, posaconazole and voriconazole have been used to treat invasive mold infections, including aspergillosis, with mixed results.[13-17] Both are effective against *Histoplasma*, *Blastomyces*, *Coccidioides,* and *Cryptococcus,* and can be used as salvage therapy, if treatment with itraconazole or fluconazole fails. Cross-resistance between fluconazole and voriconazole has been demonstrated, which should be considered when choosing a drug to follow fluconazole treatment failure.[4]

Posaconazole is available as a solution (40 mg/ml), which works best for cats and small dogs, and as an extended-release tablet (100 mg) which can be dosed every other day in dogs (15 kg and larger). For cats and smaller dogs in which the solution is not feasible, splitting the extended-release tablet might be an option. This is supported by reasonable bioavailability in humans with feeding tubes were the tablet is crushed before administration.[18] Therapeutic drug monitoring is recommended in this case. Like itraconazole, posaconazole is highly lipophilic and is better absorbed with a meal. Concurrent antacid administration can lead to decreased absorption.

Voriconazole is available as a solution (40 mg/ml) that works best for cats and small dogs and tablets (50 mg and 200 mg) for medium-large breed dogs. Voriconazole can cause neurotoxicity, especially at higher doses in cats. A more recent PK study showed that dosages used in previous reports of neurotoxicity were likely much too high.[2,19] Findings from that study supported a dose of 12.5 mg (total dose) every 3 days in cats. The use of voriconazole is cats needs further research.

Amphotericin B

Nephrotoxicity is the dose-limiting property of amphotericin B. Lipid or liposomal formulations (Abelcet® or AmBisome®) are less nephrotoxic and thus provide higher tolerable doses. Currently, AmBisome® is more commonly used in veterinary medicine. It is a small (<100 nm) sphere with an inner aqueous core. As compared with Abelcet® and amphotericin deoxycholate

it has a much higher Cmax and AUC due to lower clearance by the mononuclear phagocytic system.[20,21] Highest concentrations are found in the liver and spleen. Relatively lower concentrations reaching the renal tubule are responsible for less nephrotoxicity. It is estimated that AmBisome® is 8-10 times less nephrotoxic as compared with amphotericin deoxycholate.
Amphotericin binds ergosterol and damages the fungal cell membrane. It binds to intracellular and extracellular fungal organisms.[20] It is fungicidal and reaches therapeutic drug concentrations quickly. Maximum blood concentration (Cmax) determines the antifungal activity. As such, it is given IV every other day or 3 days / week (M, W, F). The animal should be well hydrated before administration. Kidney values and blood electrolytes (Na, K, Cl) should be checked before each dose. Cumulative doses of up to 12 mg/kg in cats and 24 mg/kg in dogs are recommended, but lower doses can be beneficial. Once reconstituted, AmBisome® is good for at least 1 week if refrigerated.

There is contradictory data regarding the antagonism of amphotericin-b by concurrent administration of an azole.[22-25] Due to this, and lack of evidence that concurrent administration is beneficial, it is recommended to follow amphotericin with azole (step-down) treatment when treating dimorphic (*Blasto, Cocci, Histo*) fungal infections. In contrast, there is evidence of synergism with itraconazole or fluconazole for yeasts (*Crypto*) and voriconazole or posaconazole for certain molds (*Asper*).[25,26]

Terbinafine

Terbinafine mechanism of action is inhibition of squalene epoxide reductase damaging the fungal cell membrane. In healthy dogs, with a single oral dose of 30-35 mg/kg, blood concentrations exceeded the MIC for *Blastomyces* and *Histoplasma* for ≥18 hours.[27,28] Terbinafine acts synergistically with azoles and amphotericin-b against many species of molds and yeasts.[29,30] In the published veterinary literature it has been used most often in combination with an azole to treat invasive mold infections. It reaches high concentrations in the skin and has been used as sole agent to treat sporotrichosis in dogs.[31] In addition, terbinafine is used as part of combination therapy to treat gastrointestinal pythiosis – a fungal-like organism (oomycete).[32,33] Adding terbinafine to azole therapy could be considered for salvage therapy for dimorphic fungal infections or invasive yeast infections, when transition to voriconazole or posaconazole is not feasible. This treatment combination needs further investigation in veterinary species.

Echinocandins

The mechanism of action is inhibition of β-glucan synthase and the lack of β-glucan damages the fungal cell wall. Echinocandins have a low oral bioavailability, and all are administered via IV injection. There are 3 FDA approved echinocandins – Caspofungin (Cancidas®), micafungin (Mycamine®), and anidulafungin (Eraxis®). Caspofungin and micafungin are available as FDA-approved generics. Caspofungin is labelled for invasive aspergillus and candidiasis while micafungin and anidulafungin are labelled for invasive candidiasis. The efficacy of an echinocandin can be in part determined by how much β-glucan is found in the fungal cell wall. *Cryptococcus* contains essentially no β-glucan and the dimorphic fungi (*Blasto, Cocci, Histo*) contain less than *Candida*, *Pneumocystis*, and many molds (*Asper*).

Overall echinocandins are well-tolerated with very few drug-to-drug interactions. They are not extensively hepatically metabolized and the dose does not need to be adjusted with kidney disease. In the published literature they have been used for the treatment of invasive molds in veterinary species.[34,35] They could also be considered for invasive candidiasis or pneumocystis.

CNS and Eyes

Treatment of CNS and ocular fungal disease is of particular interest due to the blood-brain and blood-aqueous barriers. In general, the following drug characteristics lead to increased entry:

1. Smaller molecular weight
2. Lower protein binding
3. Higher lipophilicity
4. Less potent p-glycoprotein substrate

Molecular weight and protein binding are the most important factors for permeation into immunoprotected sites. For example, doubling the molecular weight from 300 to 600 Da decreases the drug permeation by 100-fold. While lipophilicity increases drug entry, it also causes higher protein binding and lipophilic drugs are often more potent substrates for p-glycoprotein. For those reasons, the most lipophilic drugs do not necessarily enter immunoprotected sites at highest concentrations.

Fluconazole vs. Itraconazole- It remains unclear which is preferred for CNS or ocular disease in veterinary species. Based on physiochemical properties, fluconazole is the ideal azole for entering immunoprotected sites. CSF concentrations of fluconazole are generally high (CSF >80% of plasma), while concentrations of itraconazole are negligible. CSF concentrations often underestimate brain or meningeal concentrations, though.[36] For example, in one study of healthy dogs receiving chronic itraconazole therapy, brain tissue concentrations were similar to plasma.[37] In addition, with inflammation, blood brain and aqueous barriers are disrupted leading to higher drug concentrations. Once in the CNS or eye, itraconazole accumulates in tissues. As described above, dimorphic fungal pathogens are inherently more sensitive to itraconazole. Collectively this explains why in animal models of fungal meningitis, the effectiveness of itraconazole is either superior or not significantly different from fluconazole.[23,38]

Voriconazole is an intriguing option for CNS and ocular disease. In healthy dogs, CSF concentrations reach 20% of that found in plasma.[39] This is due to relatively small molecular size and moderate protein binding (Table 2). Like itraconazole, amphotericin-b and echinocandin concentrations are negligible in CSF which also underestimate brain/meningeal concentrations.[36] All of the aforementioned drugs can be used effectively for the treatment of fungal meningitis. Lipid or liposomal encapsulated amphotericin-b should be considered for any life-threatening CNS fungal infection in cats or dogs. For many animals with CNS or ocular involvement, no antifungal drug works quick enough alone, and anti-inflammatory corticosteroids are also indicated.[40]

Table 1. Mechanism of action, adverse effects, and recommended treatment monitoring of select antifungal drugs.

Drug/Class	Mechanism of Action	Adverse Effects	Tx Monitoring
Azole	Cell membrane – inhibits 14alpha-demethylase decreasing ergosterol synthesis damaging membrane.	GI – anorexia, vomiting, diarrhea Hepatoxicity Cutaneous vasculitis Neurotoxicity – Vori (cats)	Liver enzymes at 2-4 weeks then every 1-6 months during tx
Amphotericin-B	Cell membrane – binds to ergosterol and causes pores damaging membrane.	Nephrotoxicity Hypersensitivity Phlebitis	Creatinine, BUN, and electrolytes before each treatment
Terbinafine	Cell membrane – inhibits squalene epoxide reductase decreasing ergosterol synthesis damaging membrane.	GI – anorexia, vomiting, diarrhea Hepatotoxicity	Liver enzymes at 2-4 weeks then every 1-6 months during tx
Echinocandin	Cell wall – inhibits Beta-glucan synthase damaging cell wall.	GI – vomiting Hypersensitivity	

Table 2. Antifungal drug physiochemical properties.

Drug	Molecular weight (Da)	Lipophilicity (Log P)	Protein binding (%)	P-glycoprotein substrate
Fluconazole	309	2.2	10	+
Itraconazole	705	7.0	98	++
Voriconazole	349	2.6	58	+
Posaconazole	700	6.1	99	+
Ambisome	<100 nm	1.0	>95	-
Amp-B deoxycholate	924	1.0	>95	-
Caspofungin	1093	-2.8	98	-
Micafungin	1291	-3.8	98	-
Anidulafungin	1140	0.2	98	-

Adapted from. Kethireddy S, et al. CNS pharmacokinetics of antifungal agents. *Exp Opin Drug Metab Toxicol* 2007.[41]
LogP is a measure of lipophilicity – higher the number = more lipophilic.

Table 3. Recommended antifungal drug(s) for select invasive fungal infections in cats and dogs.

Disease	Mild-Moderate (outpatient)	Life-threatening (hospitalized)	Salvage
Blastomycosis	Itra > Flu	Amp-b	Posa > Vori
Histoplasmosis	Itra > Flu	Amp-b	Posa > Vori
Coccidioidomycosis	Itra = Flu	Amp-b	Posa = Vori
Cryptococcosis	Flu > Itra	Amp-b	Posa = Vori
Aspergillosis (other molds)*	Posa + Terb Vori + Terb	Amp-b + Terb	Amp-b +/- Echinocandin +/- Azole

Itra, itraconazole; Flu, fluconazole; Posa, posaconazole; Vori, voriconazole; Amp-b, lipid or liposomal encapsulated amphotericin b; Terb, terbinafine.*Antifungal sensitivity of invasive molds varies and culture and sensitivity testing is recommended.

Table 4. Recommended dosage of select antifungal drugs in cats and dogs.

Drug	Species	Formulation	Dose	Route
Itraconazole*	Dog	Capsule or Solution	5 mg/kg/day	PO
	Cat	Capsule	10 mg/kg/day	
		Solution	5 mg/kg/day	
Fluconazole	Dog	Tablet or Solution	20 mg/kg/day	PO
	Cat	Tablet or Solution	20 mg/kg/day	
Posaconazole	Dog	Tablet ER	5 mg/kg EOD	PO
		Solution	5 mg/kg BID	
	Cat	Solution	15 mg/kg once then 7.5 mg/kg/day	
Voriconazole	Dog	Tablet or Solution	5 mg/kg BID	PO
	Cat	Solution	12.5 mg (total dose) q 72 h	
Terbinafine	Dog	Tablet	30 mg/kg/day	PO
	Cat	Tablet	125 mg (total dose) / day	
Amphotericin B (lipid or liposomal)	Dog	Solution	1-2 mg/kg EOD (cumulative 24 mg/kg)	IV
	Cat	Solution	0.5-1 mg/kg EOD (cumulative 12 mg/kg)	
Caspofungin	Dog	Solution	1 mg/kg/day	IV
	Cat	Solution	1 mg/kg once then 0.75 mg/kg/day	
Micafungin	Dog	Solution	2 mg/kg/day	IV
	Cat	Solution	?	

ER, extended release. *Starting dose only. Individualized dose should be determined based on itraconazole blood levels.

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