MiraVista
VETERINARY DIAGNOSTICS

CLINICAL TREATMENT & MONITORING

Antifungal Therapy – Past, Present, and Future

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 enzootic dimorphic fungi (*Blastomyces*, *Histoplasma*, *Coccidioides*), yeast (*Cryptococcus* and *Candida*) or molds. *Aspergillus* is a common pathogenic mold and opportunistic molds commonly fall into one of a few categories – hyalohyphomycosis, phaeohyphomycosis, 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. No data is available for isavuconazole in veterinary species.

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

1. **Antifungal spectrum** – organism sensitivity to drug
2. **Tissue penetration** – location of infection
3. **Safety profile** – drug adverse-effects
4. **Formulation** – route of administration
5. **Cost of drug** – affordability

Azole Pharmacokinetics and Adverse-effects

Azoles work by inhibiting a fungal CYP-450 enzyme, inhibiting the production of ergosterol, which is vital for fungal cell membrane integrity. Azoles cause lesser inhibition of mammalian metabolic CYP-450 enzymes, but enough to cause many potential drug-drug interactions (DDIs). Concurrent administration of an azole can significantly decrease metabolism, and thus increase blood concentrations of amitriptyline, amlodipine, benzodiazepines, cisapride, corticosteroids, cyclosporine, ivermectin, and macrolide antibiotics. Most azoles are metabolized by the liver and toxicity is more likely with decreased hepatic function. The primary adverse-effect of azoles is hepatoxicity and liver enzymes should be monitored during treatment. Skin lesions, due to vasculitis, have also been reported which are most common with itraconazole [1]. Adverse effects of itraconazole can be mostly avoided with therapeutic drug monitoring of itraconazole blood levels (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). 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 daily to dogs and cats.

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Fluconazole

Fluconazole is a relatively small molecule with low protein binding, which leads to better penetration of immunoprotected sites such as the CNS and eye. 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 fluconazole an affordable option. Fluconazole is highly bioavailable, although a recent population based pharmacokinetic study found high variability in blood concentrations [2]. 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 to inherent resistance, acquired resistance to fluconazole has been reported. Fluconazole is excreted mostly unchanged in the urine making it ideal for fungal infections of the urinary tract. Doses might need to be decreased with kidney disease. 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

Itraconazole, as compared with fluconazole, is a larger molecule with higher protein binding leading to relatively lower concentrations in immunoprotected sites. Due to high lipid solubility, absorption of the capsule is increased with a fatty 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 the concurrent administration of antacids. To facilitate oral bioavailability, itraconazole solution contains a solubilizing agent (cyclodextrin) and capsules contain drug coated spheres. Compounded itraconazole lacks these important inactive ingredients, and due to very low GI absorption, compounded drug consistently provides sub-therapeutic blood concentrations. Even when FDA approved drug is used, there is considerable variability in the GI absorption between animals [3]. This, along with dose-dependent adverse effects and known therapeutic blood concentrations, supports the use of itraconazole therapeutic drug monitoring. Itraconazole blood levels can be measured by chromatography-mass spectrometry or by bioassay. The bioassay measures the antifungal activity of the blood by measuring the inhibition of the growth of a fungus in the lab. It has the advantages of measuring itraconazole and active metabolites (hydroxy-itraconazole) and is significantly less expensive.

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.

For smaller animals, if the itraconazole solution is undesirable, FDA approved capsules can be opened and put over soft food or placed into smaller capsules. Moreover, every other day administration of 100 mg capsules has been shown to achieve therapeutic blood concentrations in cats [4]. FDA approved generic itraconazole capsules are essentially equivalent to Sporanox® capsules and provide significant cost-savings [5,6]. When administration of solution is feasible, Itrafungol® (Elanco, 10 mg/ml) is approved for the treatment of dermatophytosis in cats. It is equivalent to the innovator product (Sporanox®) and can be used off-label for the treatment of IFIs in dogs and cats. FDA approved generic itraconazole solution has an identical ingredient list to Sporanox® solution, but published pharmacokinetic data are not available for dogs or cats.

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Posaconazole and Voriconazole

Posaconazole and voriconazole are next generation itraconazole and fluconazole, respectfully. They have an expanded spectrum of activity against molds and are FDA approved for the prevention or treatment of invasive mold or candidiasis in humans. In dogs and cats, posaconazole and voriconazole have been used to treat invasive mold infections including aspergillosis with mixed results. Posaconazole and voriconazole are both effective against *Histoplasma, Blastomyces, Coccidioides*, and *Cryptococcus* and can be used as salvage therapy if treatment with itraconazole or fluconazole fails. With FDA approved generic formulations now available, these drugs are now more affordable. Posaconazole is available as a solution (40 mg/ml), which works best for small dogs and cats and as an extended release tablet (100 mg) which can be dosed every other day in dogs (15 kg and larger). Voriconazole is available as a solution (40 mg/ml) that works best for cats and small dogs and tablets (50 mg and 200 mg) that work well for medium-large breed dogs.

Amphotericin B

Nephrotoxicity is the dose-limiting property of amphotericin B. Newer lipid or liposomal encapsulated formulations (Abelcet® or Ambisome®) are less nephrotoxic and thus provide higher tolerable doses. Amphotericin 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 amphotericin B 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, liposomal formulations are good for at least 1 week if refrigerated and drug is removed from the vial aseptically. There is contradictory data regarding the antagonism of amphotericin-b by concurrent administration of an azole. Due to this, and lack of evidence that concurrent administration is beneficial, it is recommended to follow amphotericin with azole (step-down) treatment but not administer the two drugs concurrently.

Table 1. Recommended antifungal treatment for select invasive fungal infections in dogs and cats.

Disease	Mild-Moderate	Life-threatening	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 (molds)	Posa +/- Terb	Amp-b	

Itra, itraconazole; Flu, fluconazole; Posa, posaconazole; Vori, voriconazole; Amp-b, lipid or liposomal encapsulated amphotericin b; Terb, terbinafine.

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Table 2. Recommended dosage of select antifungal drugs in dogs and cats.

Drug	Species	Formulation	Dose	Route
Itraconazole*	Dog	Capsule or Solution	10 mg/kg/day for 3 days then 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	
Amphotericin B (lipid or liposomal)	Dog	Solution	1-2 mg/kg EOD Cumulative dose 24 mg/kg	IV
	Cat	Solution	0.5-1 mg/kg EOD Cumulative dose 12 mg/kg	

*Starting dose only. Individualized dose should be determined based on itraconazole blood levels.

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