MiraVista
VETERINARY DIAGNOSTICS

FEATURED ARTICLE

THERAPEUTIC DRUG MONITORING (TDM) FOR DOGS AND CATS TREATED WITH ITRACONAZOLE FOR WITH SYSTEMIC MYCOSES

By Drs. Janelle Renschler and Joseph Wheat

Itraconazole absorption is highly variable and treatment outcome and toxicity correlate with blood levels [1]. For this review, we focus on itraconazole monitoring for systemic mycoses including histoplasmosis, blastomycosis, coccidioidomycosis and cryptococcosis.

Therapeutic drug level monitoring (TDM) is recommended when using itraconazole for treatment of systemic mycoses in humans [2], but studies are lacking to evaluate the relationship of blood levels with outcome (specifically establishing the therapeutic concentration). Clinical recommendations are largely based on differences in blood levels between responders and nonresponders. The mean itraconazole concentration was 6.5 µg/mL in humans treated successfully for coccidioidomycosis and 4.0 µg/mL in non-responders [3]. In cryptococcal meningitis, all patients with itraconazole levels above 1.0 µg/mL responded compared with 66% of those with levels below 1.0 µg/mL [4]. The mean itraconazole concentration in patients with invasive aspergillosis was 6.5 µg/mL in responders and 4.2 µg/mL in non-responders [4]. Andes recommended a trough level of >1 µg/mL to 2 µg/mL for treatment of systemic mycoses [2].

TDM is also recommended in veterinary patients [1, 5]. A 1996 study by Legendre, et al. in dogs with blastomycosis found no association of blood concentrations with successful outcome [1]. Concentrations were > 5 µg/mL in 70% of dogs that responded to treatment and 64% of those that failed treatment or relapse. 25% of dogs died, mostly during the first 2 weeks caused by respiratory failure. 28% of survivors relapsed, probably because itraconazole was administered for only 2 months, rather than inadequate blood level. Mean blood concentrations were higher in dogs receiving 10 mg/kg/d (13.5 µg/mL) than 5 mg/kg/d (3.6 µg/mL). Serum alkaline phosphatase (ALP) and alanine aminotransferase levels (ALT) correlated with itraconazole levels. Toxicity occurred in 30% of dogs receiving 10 mg/kg/d and 8% receiving 5 mg/kg/d.

FDA approved itraconazole capsules must be administered with food to achieve maximum absorption and blood levels. However, blood levels are variable in patients receiving the recommended dosage, ranging from subtherapeutic to potentially toxic. Itraconazole blood levels performed at MiraVista Diagnostics are presented in Table 1. The therapeutic range in Table 1 differs from what we reported previously (3.0 µg/mL to 9.9 µg/mL) [5].

Levels should be measured at steady state after initiating therapy or changing the dose, at 14 days in dogs and 21 days in cats. Loading doses of 10 mg/kg/d for 3 days provides therapeutic levels more rapidly and are recommended. As itraconazole half-life is long, the timing of the specimen after dosing is not critical but trough levels (lowest level of the dosing interval, just before the next dose) are recommended.

Table 1

Concentration category	Concentration	Compounded, powder (n=43)	Generic, pelletized (n=40)	Sporanox (n=33)
Subtherapeutic	< 2.0 µg/mL	43 (100%)	9 (22%)	7 (21%)
Therapeutic	2.0 - 5 µg/mL	0 (0%)	4 (10%)	10 (30%))
Potentially toxic[6]	> 5.0 µg/mL	0 (0%)	27 (68%)	16 (49%)

HEADQUARTERS
4705 Decatur Blvd. | Indianapolis, Indiana 46241, USA

888.841.8387
miravistavets.com

MiraVista
VETERINARY DIAGNOSTICS

FEATURED ARTICLE

Itraconazole formulations. Generic FDA approved itraconazole is preferred. Generic itraconazole, compounded pelletized itraconazole capsules, and brand name Sporanox capsules contain “pelletized” drug coated onto spheres and polyethylene glycol, which improves absorption. Itraconazole capsules should be administered with food for better absorption. Blood levels and bioavailability were three times higher taken with food [see Sporanox capsule package insert].

Sporanox oral solution contains cyclodextrin which improves bioavailability as compared with capsules but blood levels in dogs are comparable using the oral solution or capsules [7].

Compounded non-FDA approved itraconazole powder is not pelletized and does not contain cyclodextrin. It is poorly absorbed and does not achieve therapeutic concentrations [5, 8].

Blood Level Determination Methods. Itraconazole levels may be quantified by a biological assay (bioassay) which measures inhibition of growth of a Candida strain in agar plates. The bioassay determines the combined effect of parent itraconazole and its hydroxy metabolite, both which have antifungal activity. The disadvantage of the bioassay is that levels may be falsely elevated in patients who are receiving or have recently received other antifungal agents (e.g., amphotericin B, fluconazole, or terbinafine).

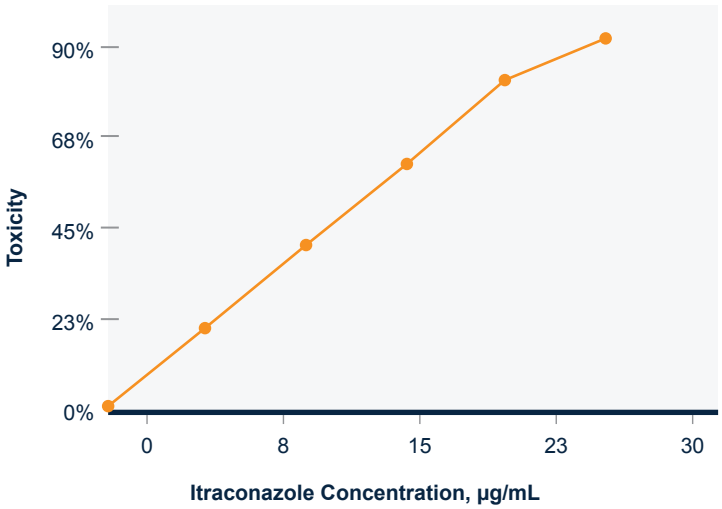
The serum specimen should be frozen and shipped with a cold pack for next day or second day delivery to prevent degradation of the drug, causing falsely-low blood levels. They may be stored refrigerated for up to 14 days before shipment. MiraVista’s Itraconazole Bioassay Test Code is 312 and 2019 pricing is $43.00 per test.

Levels of itraconazole and its hydroxy metabolite may be determined by high pressure liquid chromatography (HPLC) or mass spectroscopy (MS). The advantage of these methods is their ability to measure itraconazole and hydroxy itraconazole in the presence of other antifungal agents. These methods are much more expensive than bioassay (often cost prohibitive in veterinary medicine). The laboratory performing the test should be contacted for interpretation of levels measured by these methods as published guidelines are not available. The guidelines for the bioassay should not be used for interpretation of levels measured by HPLC or MS.

Toxicity. Toxicities are usually caused by high blood levels [6]. A human study reported 31% of patients with levels below 17 µg/mL experienced toxicity compared to 86% of those with levels above 17.1 µg/mL. Toxicity occurred in 20 to 40% of patients with levels between 5 and 10 µg/mL and may occur with levels between 2 and 5 µg/mL. Furthermore, levels above 5 µg/mL are unnecessary: dose reduction reduces toxicity and cost.

Fluid retention (21%) and gastrointestinal intolerance (21%) were the most common toxicities observed in humans [6]. Gastrointestinal toxicities included loss of appetite, abdominal pain, and diarrhea. Gastrointestinal toxicities resolved rapidly when itraconazole was stopped or the dosage was reduced. Other toxicities took longer to resolve. Central nervous system toxicity occurred in 19% and included neuropathy, tremor, sleep

Figure 1.



HEADQUARTERS
4705 Decatur Blvd. | Indianapolis, Indiana 46241, USA

888.841.8387
miravistavets.com

disturbance, and loss of interest. Diffuse nonpruritic maculopapular rash (7%) resolved after stopping treatment and may be caused by hypersensitivity rather than blood levels. Hepatic toxicity with a bilirubin > 3 times the reference limit occurred in 2% of patients. Congestive heart failure occurred in 1% of patients. Itraconazole also can cause hypertension and hypokalemia [Sporanox package insert].

Toxicities in dogs resemble those in humans. Median ALT levels were higher in dogs in the 5 mg/kg twice daily group (84 IU/L) than the once daily group (35 IU/L). ALT and ALP elevation in the absence of clinical findings of hepatitis can be managed by dose reduction or discontinuation until they have resolved, after which itraconazole could be resumed at a lower dosage [1]. Ulcerative skin lesions (a sign of cutaneous vasculitis) also occurred in dogs receiving 10mg/kg/d.

Most toxicities resolve within a week or two after discontinuing or reducing the dose of itraconazole. Drug levels should be rechecked 2 weeks later to verify the level is therapeutic but nontoxic. If necessary, in patients with clinical findings of hepatitis, itraconazole can be resumed at a lower dose once clinical findings are resolved and ALT and ALP levels declined, with careful monitoring of ALT, ALP, bilirubin, and itraconazole blood levels [1, 9].

Drug interactions. Itraconazole inhibits cytochrome P450 CYP3A4 isoenzymes and may increase levels of drugs cleared by that mechanism. Inducers of CYP3A4 accelerate metabolism of itraconazole and may cause treatment failure because of subtherapeutic blood levels. Macrolide antibiotics may increase concentrations of itraconazole (see Sporanox package insert for specific interactions). Drugs that decrease gastric acid secretion reduce itraconazole blood levels. Fatal cardiac arrhythmias have been reported in patients receiving itraconazole and terbinafine [10-12]. Review potential drug interactions in patients receiving medications that affect or are affected by hepatic metabolism.

Cost. Cost for one-month treatment in a 20 kg dog and 4 kg cat are presented in table 2 (GoodRx.com for Indianapolis, August 2019). Check for the current cost in your area. Many veterinarians choose fluconazole because of its lower cost but the cost advantage is small, and fluconazole is less effective than itraconazole for histoplasmosis, blastomycosis and for coccidioidomycosis involving bones. Additionally, overall treatment cost may be higher with fluconazole due to the longer course required for resolution of the disease, additional monitoring (antigen levels, serum chemistry profile, etc.)., and treatment of relapses.

Cats and small dogs pose challenges for use of 100 mg capsules. Alternatives include Sporanox solution (more expensive than generic itraconazole) and compounded pelletized itraconazole capsules. At least two veterinary pharmacies provide that service: (http://www.pethealthpharmacy.com (623-214-2791); https://petapothecary.com/ (414) 247-8633).

ItraFungol is FDA approved for treating dermatophyte infections in dogs and cats. The ItraFungol package insert indicates that the average concentration at steady state in cats receiving 5 mg/kg/d is 1 µg/mL. None of the results in Table 1 were from dogs or cats receiving ItraFungol. We have consulted on a cat that failed treatment with 10 mg/kg/d ItraFungol and the itraconazole concentration was <0.3 µg/mL.

MiraVista
VETERINARY DIAGNOSTICS

FEATURED ARTICLE

Table 2. Cost for one month of treatment for 20 kg dog or 4 kg cat (GoodRx.com)

	20kg dog	20kg dog	4 kg cat	20 kg dog	4kg cat	4 kg cat
	Generic Itraconazole, 100mg, #30 (3000mg)	Sporanox Itraconazole 100mg, #30 (3000mg)	Sporanox, solution 10mg/mL, 150ml per bottle (1600 mg) (2 bottles required)	Generic Fluconazole 200mg tablet, #30 (6000mg)	Generic Fluconazole solution, 40mg/mL, 35 ml bottle (2400mg) 2 bottles required	ItraFungol, 40mg/ml, 52ml bottle, (4800mg), 3 bottles required
Costco	$45.43	$844.34	$687.05	$33.44	$42.80	
CVS	$89.84	$891.54	$692.99	$71.01	$71.59	
Walmart	$76.82	$911.40	$692.58	$41.23	$70.44	
Chewy						$147.00
Dose	5 mg/kg/d	5 mg/kg/d	10 mg/kg/d	10 mg/kg/day	10mg/kg/ BID	10 mg/kg/d
Lowest cost*	$45.43 Costco	$844.34 Costco	$687.05 Costco	$33.44 Costco	$42.80 Costco	$147.00 Chewy

*fluconazole 10mg/kg/d in dogs and 10mg/kg/BID in cats, itraconazole 5mg/kg/d dogs, 5mg/kg/BID cats

** Pricing data provided by https://www.goodrx.com/. Input your location for accurate local pricing which may vary regionally and pricing changes frequently.

REFERENCES

1. Legendre, A.M., et al., *Treatment of blastomycosis with itraconazole in 112 dogs.* J. Vet. Intern. Med, 1996. **10**(6): p. 365-371.
2. Andes, D., A. Pascual, and O. Marchetti, *Antifungal therapeutic drug monitoring: established and emerging indications.* Antimicrob. Agents Chemother, 2009. **53**(1): p. 24-34.
3. Tucker, R.M., et al., *Itraconazole therapy for nonmeningeal coccidioidomyosis: Clinical and lablroatoy observation.* J. Am. Acad. Dermatol, 1990. **23**: p. 593-601.
4. Denning, D.W., et al., *Itraconazole therapy for cryptococcal meningitis and cryptococcosis.* Arch. Intern. Med, 1989. **149**: p. 2301-2308.
5. Renschler, J., et al., *Comparison of Compounded, Generic, and Innovator-Formulated Itraconazole in Dogs and Cats.* J Am Anim Hosp Assoc, 2018. **54**(4): p. 195-200.
6. Lestner, J.M., et al., *Toxicodynamics of itraconazole: implications for therapeutic drug monitoring.* Clin Infect. Dis, 2009. **49**(6): p. 928-930.
7. Hasbach, A.E., et al., *Pharmacokinetics and Relative Bioavailability of Orally Administered Innovator-Formulated Itraconazole Capsules and Solution in Healthy Dogs.* J Vet Intern Med, 2017. **31**(4): p. 1163-1169.
8. Mawby, D.I., et al., *Bioequivalence of orally administered generic, compounded, and innovator-formulated itraconazole in healthy dogs.* J. Vet. Intern. Med, 2014. **28**(1): p. 72-77.
9. Plumb, D.C., *Plumb's Veterinary Drug Handbook.* 9th Edition ed. 2018, Stockholm, Wisconsin: Pharma Vet Inc. 1428.
10. Lortholary, O., et al., *[Systemic diseases and infections: current questions].* Presse Med, 1996. **25**(8): p. 370-5, 377-8.
11. Crane, J.K. and H.T. Shih, *Syncope and cardiac arrhythmia due to an interaction between itraconazole and terfenadine.* Am J Med, 1993. **95**(4): p. 445-6.
12. Tran, H.T., *Torsades de pointes induced by nonantiarrhythmic drugs.* Conn Med, 1994. **58**(5): p. 291-5.

HEADQUARTERS
4705 Decatur Blvd. | Indianapolis, Indiana 46241, USA

888.841.8387
miravistavets.com