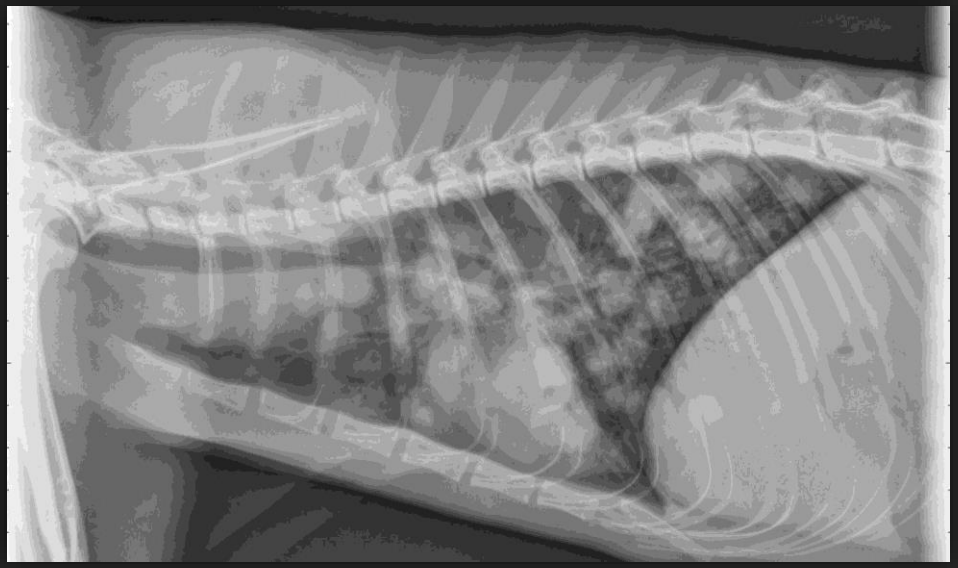
Antifungal Therapy for Small Animals



MiraVista
VETERINARY DIAGNOSTICS

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Disclosure:
Conflict of Interest

Employed by MiraVista Diagnostics

Discussion

1. History of Antifungals

2. Drug specifics
   - Azoles
   - Terbinafine
   - Amphotericin-B
   - Echinocandins

3. The Future

Antifungal targets[3]

Cell membrane

Azoles	Inhibition of lanosterol 14α demethylase
Polyenes	Punctures the ergosterol containing fungal membrane
Aureobasidin A	Glycolipid inhibitor
Terbinafine	Inhibition of squalene epoxidase

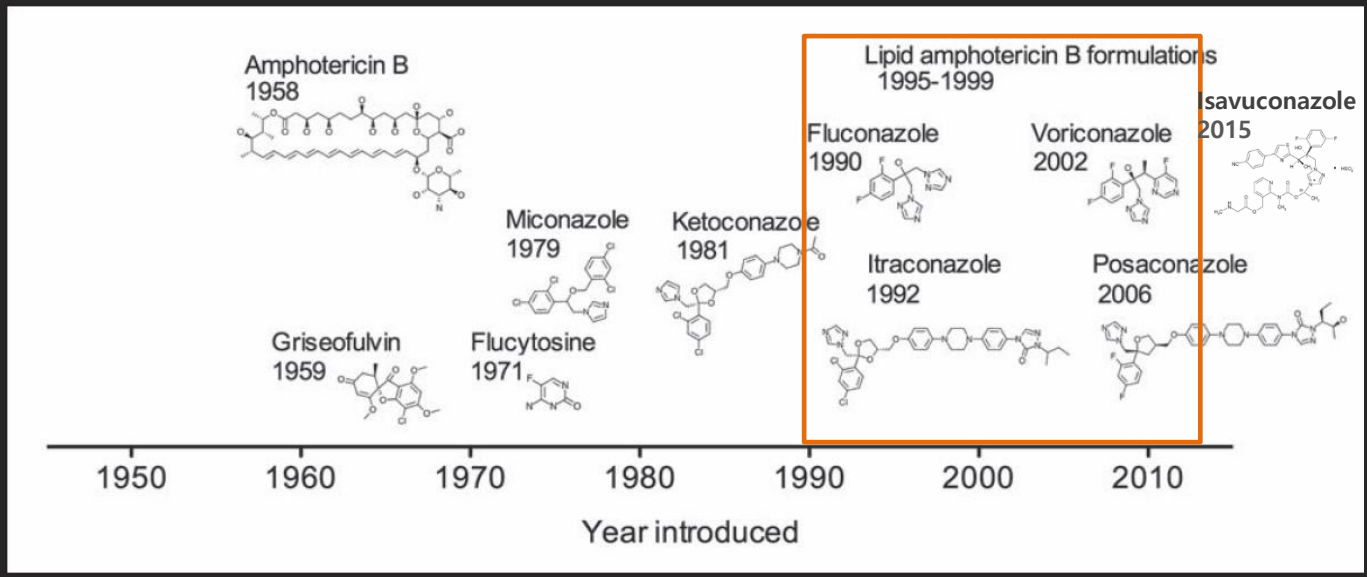
Cell wall

Echinocandins	Inhibition of β 1,3 glucan synthase
SCY 078	Inhibition of β 1,3 glucan synthase
APX001	GPI inhibitor
Nikkomycin Z	Chitin synthase inhibitor

Intracellular targets

Metabolism	
Olorofim	Inhibition dihydroorotate dehydrogenase
AR 12	Inhibition of fungal acetyl CoA synthetase 1
Nucleus	
MGCD290	Histone deacetylase (Hos2) inhibitor
Mitochondria	
T 2307	Mitochondrial membrane potential
Unknown	
VL 2397	Siderophore

Flucytosine & Griseofulvin



Van Daele R, et al. Antifungal drugs: What brings the future? MED MYC 2019;57:S328-S343.

Lewis RE, et al. Current concepts in antifungal pharmacology. MAYO CLIN PROC. 2011.

Considerations

1. Organism sensitivity
2. Tissue permeation
3. Adverse-effects
4. Formulation
5. Cost

https://healthypets.mercola.com/sites/healthypets/archive/2015/08/31/cat-pill-medication.aspx

Treatment Guidelines

Disease	Out-patient	Life-threatening	Salvage
Histoplasmosis			
Blastomycosis			
Coccidioidomycosis (Valley fever)			
Cryptococcosis* Candidiasis*			
Aspergillosis* (other molds)			

Dimorphs | Yeasts | Molds

* Sensitivity varies and some molds and yeasts are resistant. Base treatment on culture and sensitivity.

Triazoles

- First generation
  - Itraconazole (Sporanox®, Itrafungol®)
  - Fluconazole (Diflucan®)
- Second generation
  - Posaconazole (Noxafil®)
  - Voriconazole (Vfend®)

Mechanism of Action

- Inhibit fungal ergosterol synthesis
  - Lanosterol 14α-demethylase = CYP450
  - Fungal p450 > human p450
- Drug-to-Drug interactions
  - ↓ Drug Metabolism = ↑ Drug Concentrations
  - Keto > Flu > Itra
  - ❖ Ivermectin, benzodiazepines, cyclosporine, macrolide antibiotics, corticosteroids, amitriptyline, digoxin
- Inhibit adrenal cortical function
  - Cholesterol → Cortisol (p450 enzymes)
  - Keto > Flu > Itra

Question #1

Which is the first-choice treatment for mild/mod blastomycosis?

A. Fluconazole
B. Itraconazole
C. Voriconazole
D. Posaconazole

Itra v Flu

Itraconazole

- Absorption ↓ w antacid
- Capsule w food
- Blasto, Histo, Cocci = more sensitive
- No acquired resistance
- 1 capsule size
- Cost =

Fluconazole

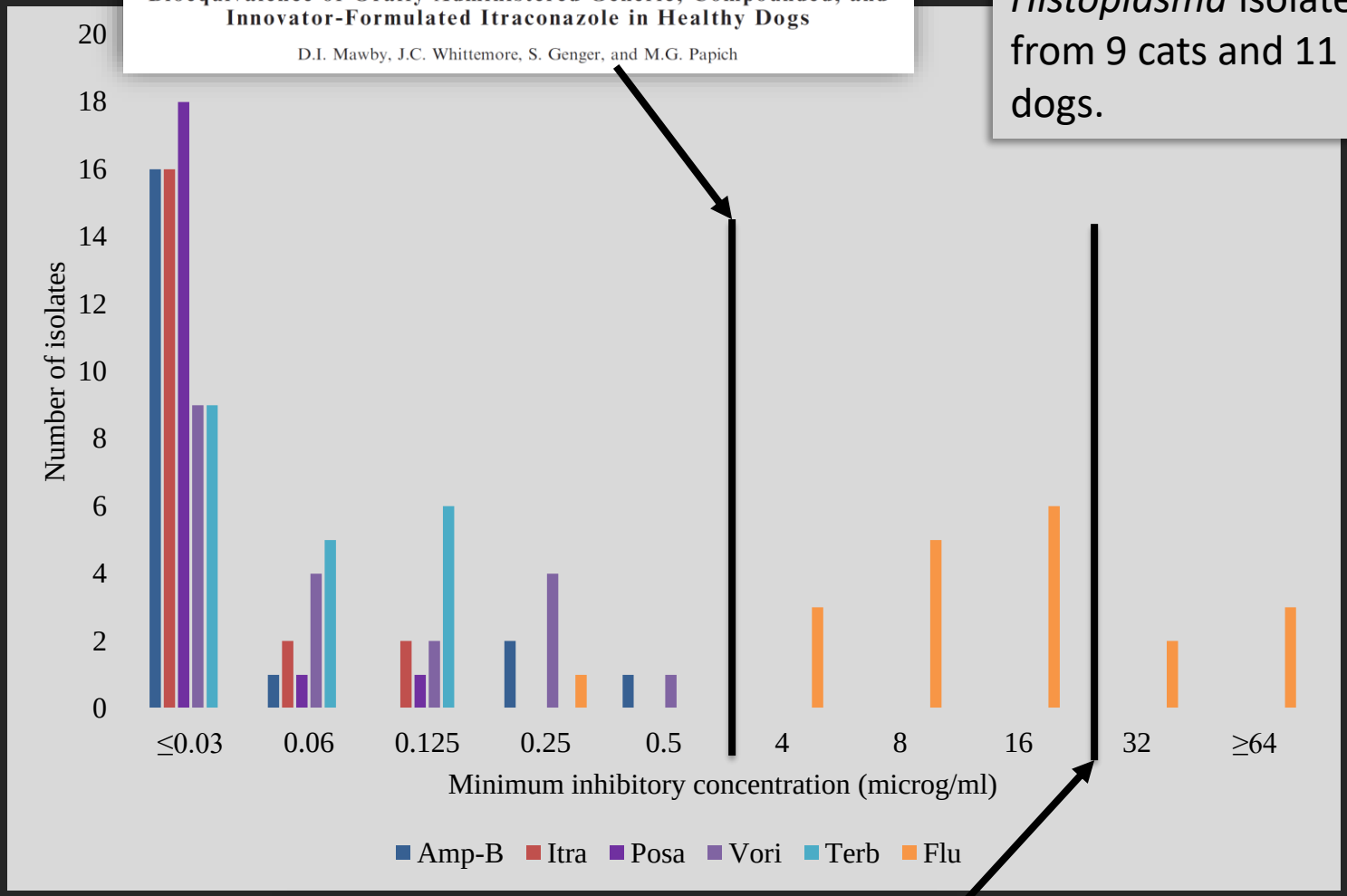
- Absorption not affected by antacid or food
- Blasto, Histo, Cocci = less sensitive
- Acquired resistance
- 4 tablet sizes
- Cost =

J Vet Intern Med 2014;28:72–77

Bioequivalence of Orally Administered Generic, Compounded, and Innovator-Formulated Itraconazole in Healthy Dogs

D.I. Mawby, J.C. Whittemore, S. Genger, and M.G. Papich

Histoplasma isolates from 9 cats and 11 dogs.



Clinical pharmacokinetics and outcomes of oral fluconazole therapy in dogs and cats with naturally occurring fungal disease

Kate KuKanich[1] | Butch KuKanich[2] | Zhoumeng Lin[2] | Amy J. Rankin[1] | Andrew S. Hanzlicek[3] | Jean-Sebastien Palerme[4] | Jonathan Bach[5] | Audrey K. Cook[6] | Amy Juracek[1] | Hyun Joo[2]

Fungus	No. Isolates	Antifungal Agent	MIC range (µg/ml)	MEC range (µg/ml)	MIC_{90}/ MEC_{90} (µg/ml) (MIC_{50}/ MEC_{50})	References
Dimorphic fungi						
Blastomyces dermatitidis	34	Anidulafungin	2-8>8	NR	(4)/NR	71,77
	5	Caspofungin	0.5-8	NR	(2)/NR	77
	6	Micafungin	>8/<0.01-0.03*	NR	NR	63
	35	Amphotericin B	≤0.03-0.25*	NR	0.25/NR	63,71
	35	Fluconazole	1.0-32*	NR	16/NR	63,71
	6	Itraconazole	≤0.01-0.03*	NR	NR	63
	5	Posaconazole	<0.03-0.06	NR	(0.05)/NR	77
Coccidioides immitis	4	Micafungin	0.01	NR	NR	63
	25	Caspofungin	≥8	NR	>8/NR	74
	29	Amphotericin B	0.06-0.5	NR	0.5/NR	63,74
	29	Fluconazole	4-64	NR	64/NR	63,74
	4	Itraconazole	0.06-0.12	NR	NR	63
Histoplasma capsulatum	5	Anidulafungin	2-4	NR	(3.6)/NR	77
	5	Caspofungin	0.5-4	NR	(1.3)/NR	77
	4	Micafungin	>8/0.03-0.06*	NR	NR	63
	4	Amphotericin B	0.06-0.5*	NR	NR	63
	4	Fluconazole	1.0-16*	NR	NR	63
	4	Itraconazole	≤0.01-0.03*	NR	NR	63
	5	Posaconazole	<0.03-0.06	NR	(0.04)/NR	77

Espinell-Ingroff A. Rev Iberoam Micol 2003; 20: 121-136

Flu- Guidelines

- Diflucan® or FDA Generic
  - 50, 100, 150, 200 mg tablets
  - 10, 40 mg/ml solution

- Dose
  - Cat = 20 mg/kg/day
  - Dog = 20 mg/kg/day

- First-choice
  - cryptococcosis, coccidioidomycosis
  - lower urinary tract infections

- Second-choice
  - histoplasmosis, blastomycosis

- NOT effective against molds (*Asper)*

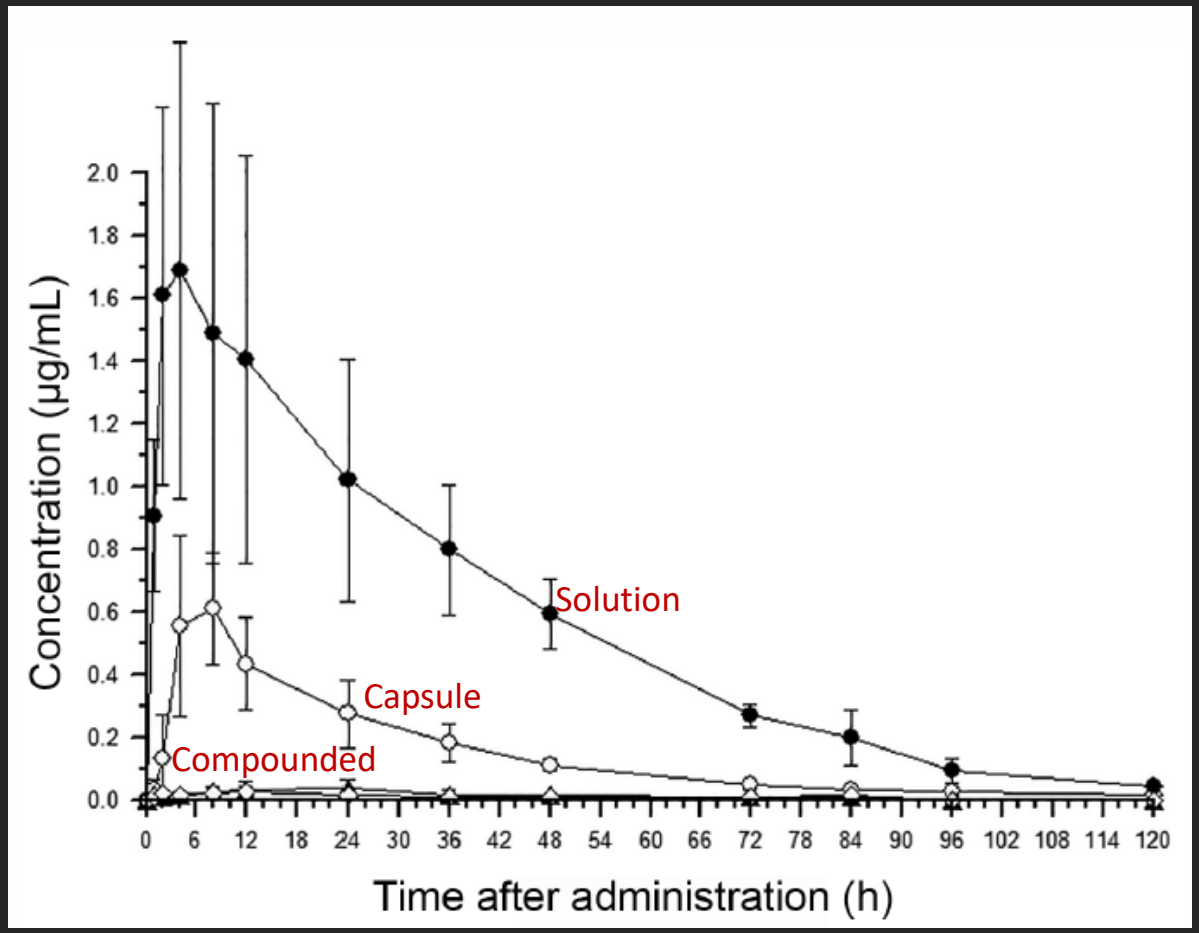
https://petvm.com/antifungal/128-fluconazole.html

Itraconazole

- Solution = ↑ bioavailable
  - Cats NOT dogs
  - Solution NOT affected by meal
- Hydroxypropyl-β-cyclodextrin (HPβCD)
  - Not in compounded solutions
- Coated beads
  - Not in compounded drugs from bulk chemical

https://www.cvs.com/drug/itraconazole

Comparison of absorption characteristics of oral reference and compounded itraconazole formulations in healthy cats



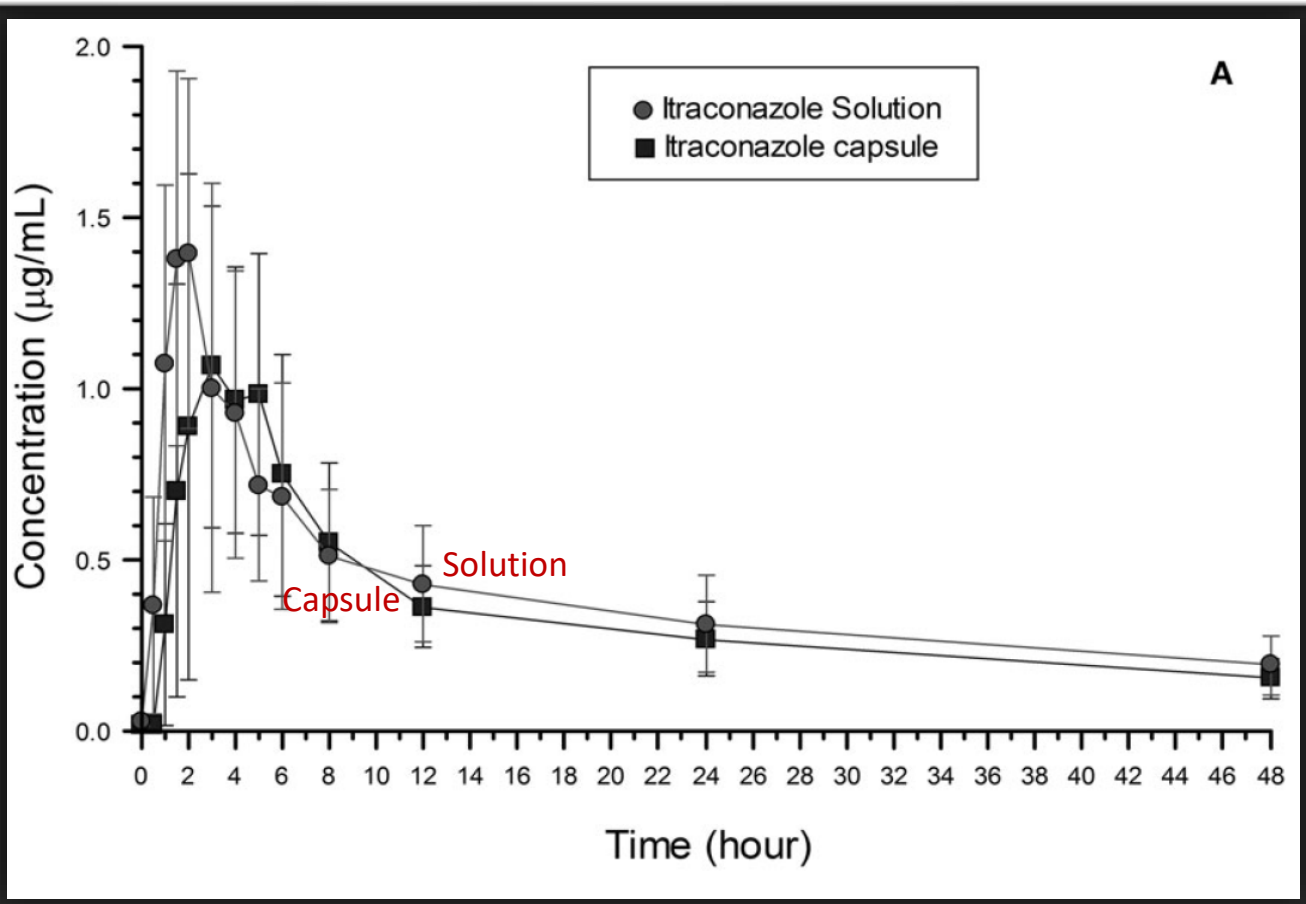
Mawby et al. Comparison characteristics of oral reference and compounded itraconazole formulations in healthy cats. JAVMA 2018;252:195-200.

Standard Article

J Vet Intern Med 2017;31:1163–1169

Pharmacokinetics and Relative Bioavailability of Orally Administered Innovator-Formulated Itraconazole Capsules and Solution in Healthy Dogs

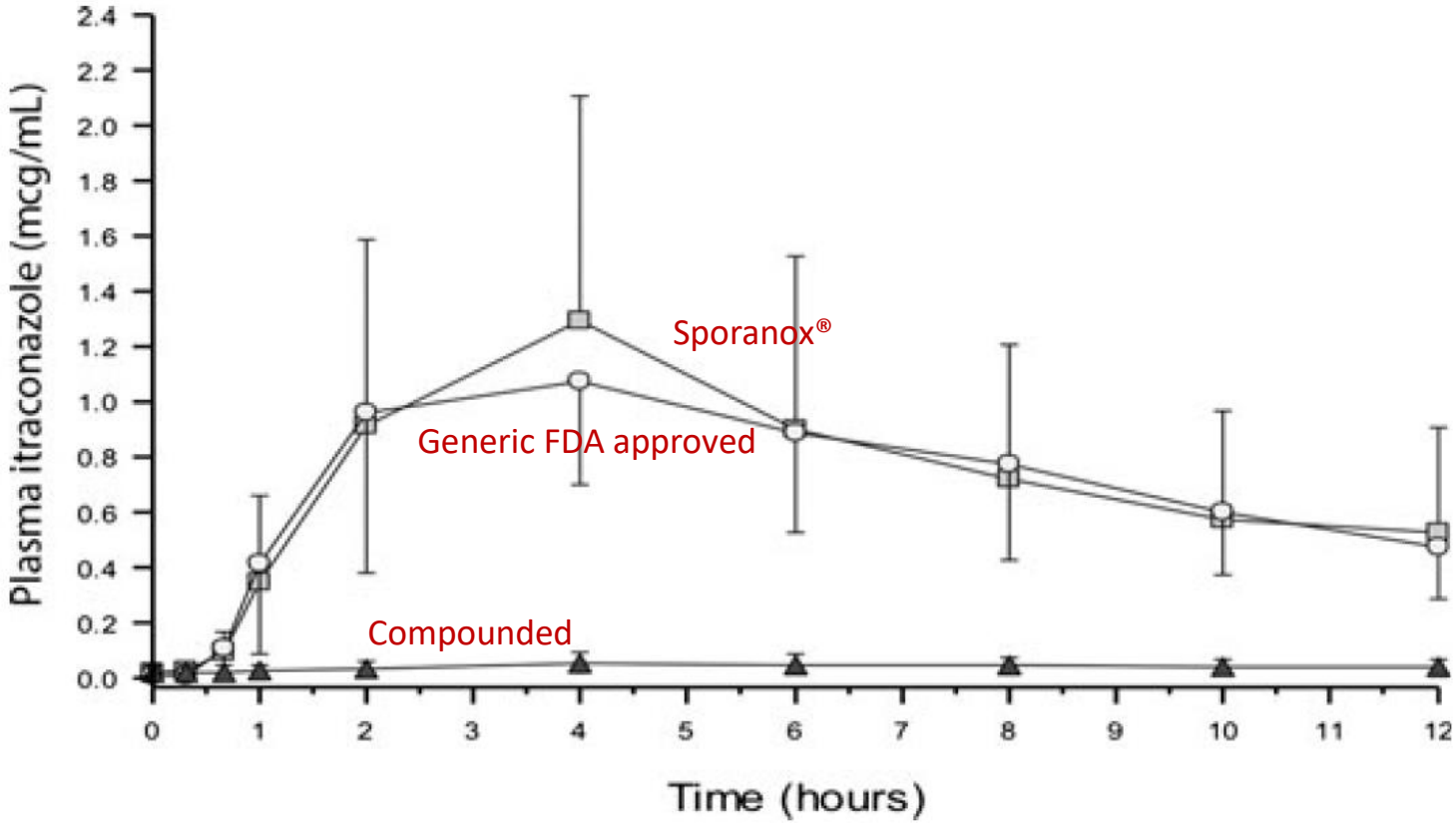
A.E. Hasbach, D.K. Langlois, E.J. Rosser Jr, and M.G. Papich



J Vet Intern Med 2014;28:72–77

Bioequivalence of Orally Administered Generic, Compounded, and Innovator-Formulated Itraconazole in Healthy Dogs

D.I. Mawby, J.C. Whittemore, S. Genger, and M.G. Papich

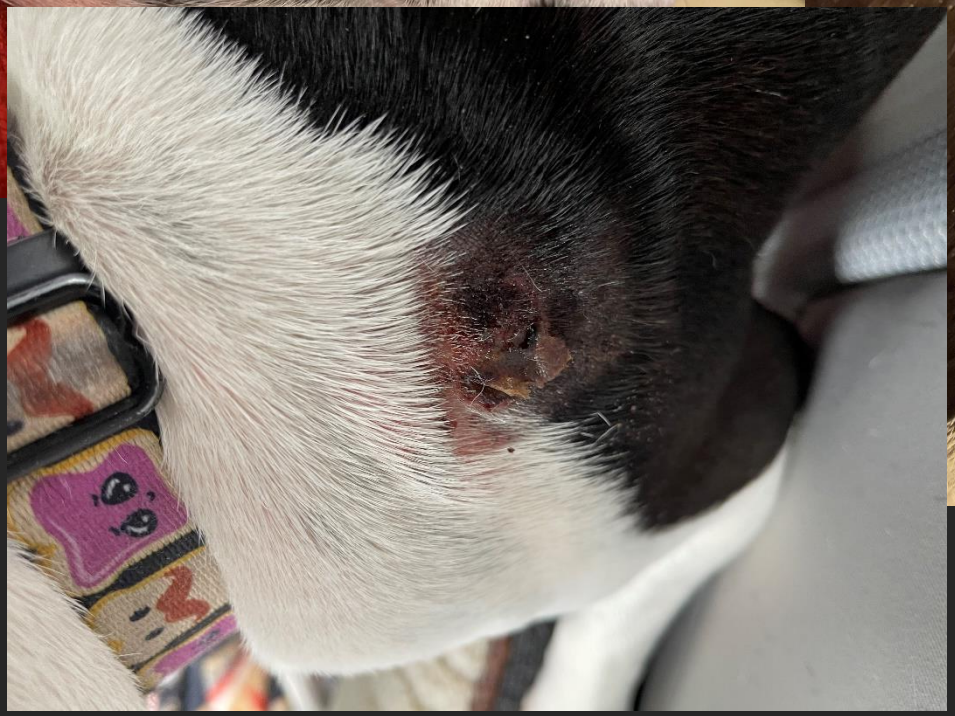


Mawby et al. Bioequivalence of orally administered generic, compounded, and innovator-formulation itraconazole in healthy dogs. JAVMA 2018;252:195-200.

Question #2

This Golden receiving 10 mg/kg/day of itra for blasto has improved clinically but after 2 mos. of treatment developed skin lesions. What's the most likely underlying cause?

A. Bacterial pyoderma
B. Progressive blasto
C. Food allergy
D. Itra toxicity



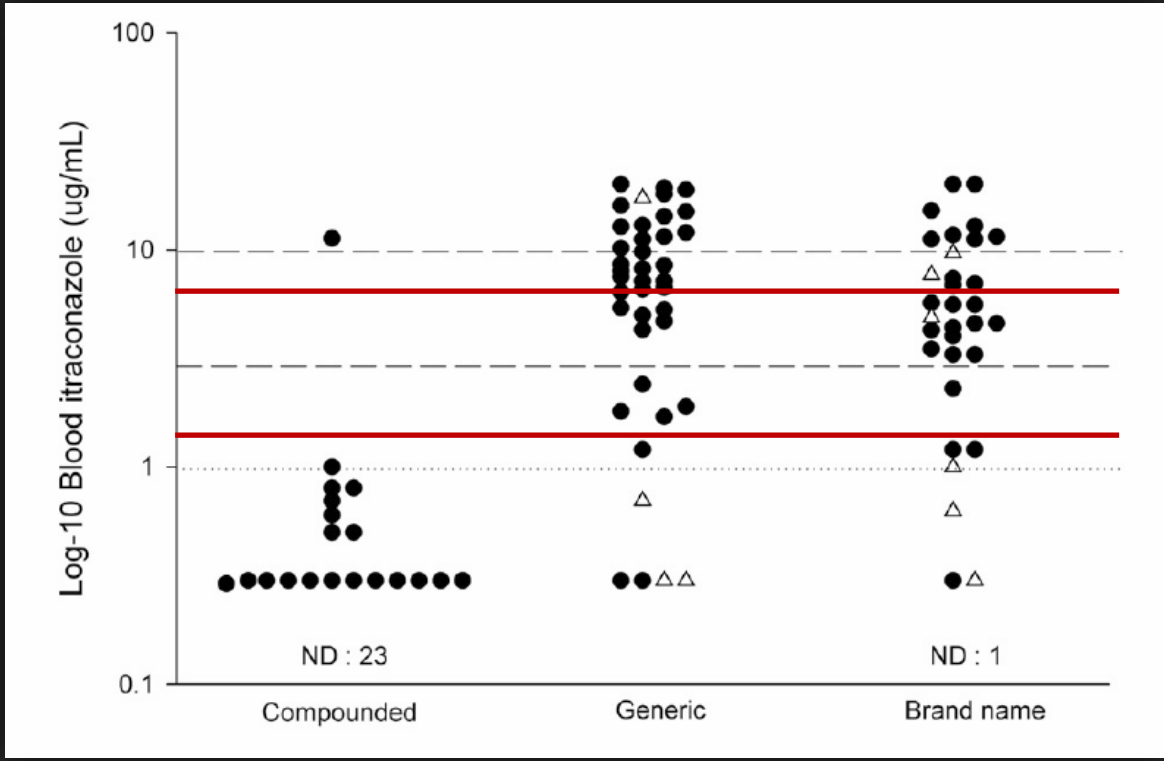
Itra- Adverse Effects

- Hepatotoxicity*
  - 60% ↑ ALT w mean itra 13 ug/ml
  - 12% ↑ ALT w mean itra 3 ug/ml
- Vasculitis - ulcerative skin lesions*
  - 7.5% of dogs w mean itra 13 ug/ml
  - 0% of dogs w mean itra 3 ug/ml
- Negative inotrope
  - Data from dogs and humans
  - Use caution w severe heart disease

*Legendre AM, et al. Treatment of blastomycosis with itraconazole in 112 dogs. J Vet Int Med. 1996;10:365-371.

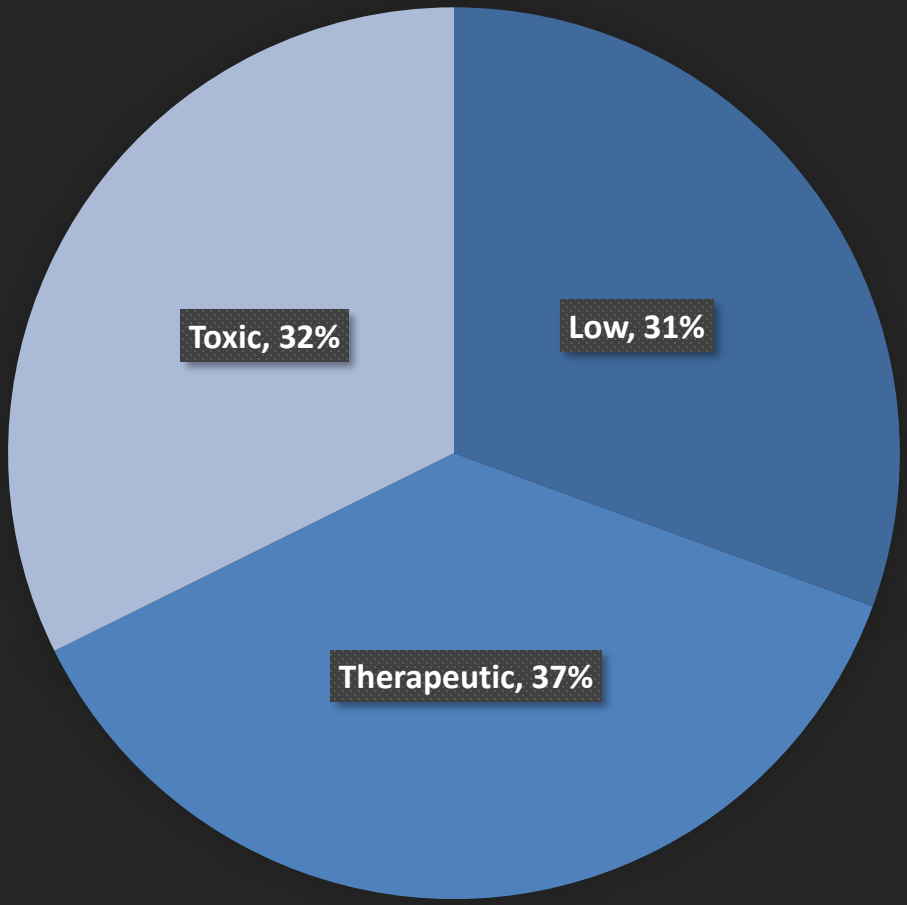
Comparison of Compounded, Generic, and Innovator-Formulated Itraconazole in Dogs and Cats

Janelle Renschler, DVM, PhD, DACVP, Amanda Albers, BS, Hanna Sinclair-Mackling, BS, Lawrence Joseph Wheat, MD



Renschler J. et al. Comparison of compounded, generic, and innovator-formulated itraconazole in dogs and cats. JAHAA 2018;54:195-200.

Itraconazole blood levels (n=2000)



Itraconazole
Therapeutic Drug Monitoring

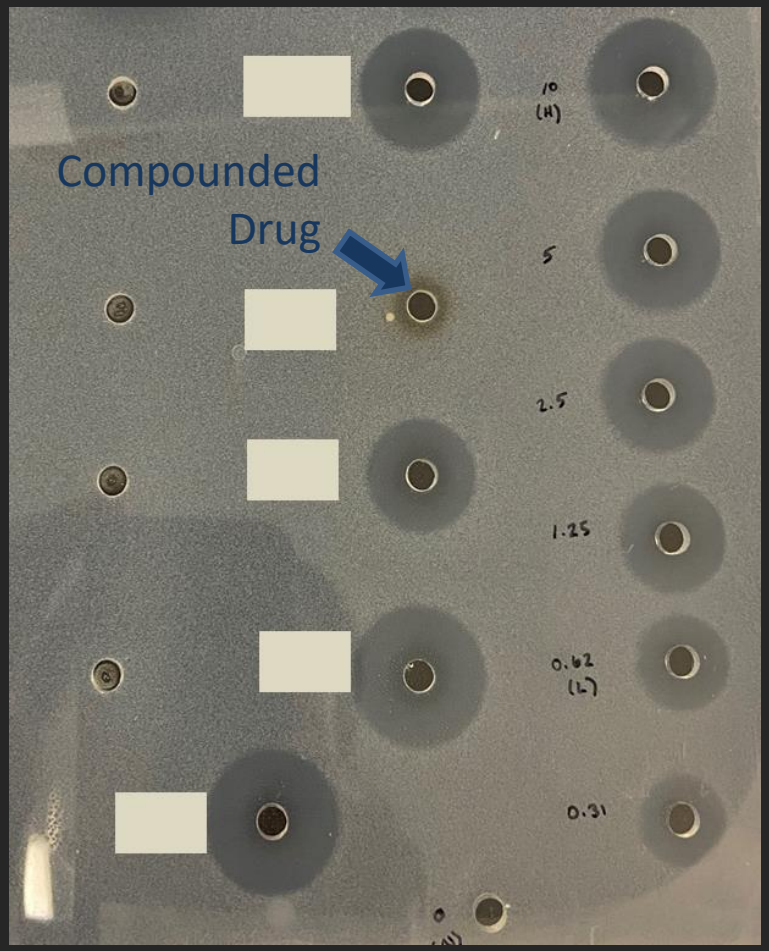
Bioassay

- Pharmacodynamic
  - Inhibition of fungal growth
- Itra + metabolites
- Lower cost ($40)
- Affected by other antifungal drugs
- Target trough:
  - 2-7 mcg/ml

LC-MS

- Pharmacokinetic
  - Direct measurement
- Parent drug only
- Higher cost ($120-500)
- Not affected by other antifungal drugs
- Target trough:
  - 0.5 – 1 mcg/ml itra
  - 0.5 – 1 mcg/ml OH-itra

Itraconazole Bioassay



Itrafungol® for IFI?

- FDA approved
  - dermatophytosis
- Identical ingredient list to Sporanox®
  - 10 mg/ml
  - Cyclodextrin
  - Flavoring
- ≈1/3 cost

https://www.vetsupplysource.com/itrafungol-oral-solution-52ml.html

Cat or Small Dog Itra- Dosing Options

- Divide FDA cap
  - Smaller capsule
  - Open place over food
- EOD dosing in cats*
  - 100 mg EOD
  - Monitor blood levels

https://www.cvs.com/drug/itraconazole

JOURNAL OF
Veterinary Pharmacology and Therapeutics

J. vet. Pharmacol. Therap. **39**, 27–31. doi: 10.1111/jvp.12231.

Alternate-day dosing of itraconazole in healthy adult cats

*Middleton SM, et al. Alternate-day dosing of itraconazole in healthy adult cats. J VET PHARMACOL THERAPEUT 2015;39:27-31

Itra- Guidelines

- FDA Generic, Itrafungol®, or Sporanox®
  - **NOT COMPOUNDED!!**
- Give capsule w/ food
- Avoid concurrent antacid
- Dose:
  - D = 5 mg/kg/day
  - C = 5 mg/kg/day (solution)
  - C = 10 mg/kg/day (capsule)
- Therapeutic Drug Monitoring
  - Trough (within 4 hours of next dose)
    - D: 2 wk after staring
    - C: 3 wk after starting

https://www.vetsupplysource.com/itrafungol-oral-solution-52ml.html

Tissue Concentrations[1]

Drug	Mol Wt.	Protein Binding	Lung	Liver	Spleen	Skin	CSF	Bone	Synovium
FLU	305	12	1.1-1.6 (1.2 cat)[2]	3.4	6.1	11-40	1.0-2.3 (0.9 cat)[2]	0.3	0.88
ITRA	706	99.8	0.9-7 (5 dog)[4]	3-12 (12 dog)[4]	1.0-3.1	0.5-10 (10 dog)[4]	0-12	4.7	0.5-5
VORI	349	51	0.3-3.2	1.1-7.4	0.4-3.5	NA	0.2-1 (0.2 dog)[3]	5	0.25 (0.2 dog)[3]
POSA	700	97	>5	NA	NA	0.5-5	<0.5	NA	NA

1. Felton T, et al. Tissue penetration of antifungal agents. CLIN MICRO REVIEW 2014;27:68-88.
2. Vaden SL, et al. Fluconazole in cats: pharmacokinetics following intravenous and oral administration and penetration into cerebrospinal fluid, aqueous humour, and pulmonary epithelial lining fluid. J VET PHARMCOL THERAP 1997;20:181-186.
3. Lemetayer JD, et al. Pharmacokinetics and distribution of voriconazole in body fluids of dogs after repeated oral dosing. J VET PHARMACOL THERAP 2015;38:451-456.
4. Heykants J, et al. The pharmacokinetics of itraconazole in animals and man. REC TRENDS DISC DEV EVAL ANTIFUNGAL AGENT. 1987:32Supp:223-249.

Comparison of Oral Fluconazole and Itraconazole for Progressive, Nonmeningeal Coccidioidomycosis

A Randomized, Double-Blind Trial

John N. Galgiani, MD; Antonino Catanzaro, MD; Gretchen A. Cloud, MS; Royce H. Johnson, MD; Paul L. Williams, MD; Laurence F. Mirels, MD; Faris Nassar, MD; Jon E. Lutz, MD; David A. Stevens, MD; P. Kay Sharkey, MD; Vipul R. Singh, MD; Robert A. Larsen, MD; Kathy L. Delgado, LPN; Cynthia Flanigan, BS; and Michael G. Rinaldi, PhD, for the National Institute of Allergy and Infectious Diseases–Mycoses Study Group

Background: In previous open-label noncomparative clinical trials, both fluconazole and itraconazole were effective therapy for progressive forms of coccidioidomycosis.

Objective: To determine whether fluconazole or itraconazole is superior for treatment of nonmeningeal progressive coccidioidal infections.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: 7 treatment centers in California, Arizona, and Texas.

Patients: 198 patients with chronic pulmonary, soft tissue, or skeletal coccidioidal infections.

Intervention: Oral fluconazole, 400 mg/d, or itraconazole, 200 mg twice daily.

Measurements: After 4, 8, and 12 months, a predefined scoring system was used to assess severity of infection. Findings were compared with those at baseline.

Results: Overall, 50% of patients (47 of 94) and 63% of patients (61 of 97) responded to 8 months of treatment with fluconazole and itraconazole, respectively (difference, 13 percentage points [95% CI, −2 to 28 percentage points]; $P = 0.08$). Patients with skeletal infections responded twice as frequently to itraconazole as to fluconazole. By 12 months, 57% of patients had responded to fluconazole and 72% had responded to itraconazole (difference, 15 percentage points [CI, 0.003 to 30 percentage points]; $P = 0.05$). Soft tissue disease was associated with increased likelihood of response, as in previous studies. Azole drug was detected in serum specimens from all but 3 patients; however, drug concentrations were not helpful in predicting outcome. Relapse rates after discontinuation of therapy did not differ significantly between groups (28% after fluconazole treatment and 18% after itraconazole treatment). Both drugs were well tolerated.

Conclusions: Neither fluconazole nor itraconazole showed statistically superior efficacy in nonmeningeal coccidioidomycosis, although there is a trend toward slightly greater efficacy with itraconazole at the doses studied.

Ann Intern Med. 2000;133:676-686. www.annals.org

For author affiliations, current addresses, and contributions, see end of text.

Question #3

What to do if first-line treatment fails (salvage therapy)?

A. Check Itra- blood level
B. Switch to Posaconazole
C. Switch to Voriconazole
D. Add terbinafine
E. All the above

Posa- vs. Vori-

Posaconazole

- Next generation itra-
- Noxafil®
- FDA generic
  - Approved:
    - Prevent *Aspergillus*
- *Histo, Blasto, Cocci*
- Formulations:
  - 100 mg ER tablet
  - 40 mg/ml solution
- Higher cost

Voriconazole

- Next generation flu-
- Vfend®
- FDA generic
  - Approved:
    - Treat *Aspergillus*
- *Histo, Blasto, Cocci*
- Formulations:
  - 50 & 200 mg tablets
  - 40 mg/ml solution
- Lower cost

JOURNAL OF
Veterinary Pharmacology and Therapeutics

J. vet. Pharmacol. Therap. **38**, 451–456. doi: 10.1111/jvp.12208.

Pharmacokinetics and distribution of voriconazole in body fluids of dogs after repeated oral dosing

J. D. LEMETAYER*
P. M. DOWLING†
S. M. TAYLOR* &
M. G. PAPICH‡

- Repeated dosing dogs
- Drug concentrations:
  - CSF:Plasma = 0.20
  - Synovial:Plasma = 0.22
  - Aqueous:Plasma = 0.19
- BID dosing is required

J Vet Intern Med 2010;24:647–649

Adverse Neurologic Events Associated with Voriconazole Use in 3 Cats

J.M. Quimby, S.B. Hoffman, J. Duke, and M.R. Lappin

- Neurotoxicity seen with higher doses[1]
  - 10 mg/kg/day

Pharmacokinetics of voriconazole after intravenous and oral administration to healthy cats

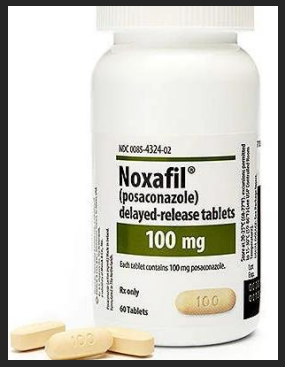
- No neurotoxicity seen w lower doses[2]
  - Suggests 12.5 mg (total dose) q 72 h

1. Quimby JM, et al. Pharmacokinetics of voriconazole after intravenous and oral administration to healthy cats. J VET INT MED 2010;24:647-649.
2. Vishkautsan P, et al. Pharmacokinetics of voriconazole after intravenous and oral administration to healthy cats. AM J VET RES 2016;77:931-939.

Vori- Guidelines

- Dog:
  - 5 mg/kg BID
- Cat:
  - 12.5 mg (total dose) q 72 hours
    - more info needed
- Consider therapeutic drug monitoring
  - Auto-induction of metabolism
- Clinical Uses
  - Invasive molds (*Aspergillus*)
  - Salvage therapy if itra- or flu- fails
    - *Blasto, Histo, Cocci, Crypto*

https://www.californiapetpharmacy.com/voriconazole-200mg-per-tablet.html



Posa- Guidelines

J Vet Intern Med 2016;30:1703–1707

Posaconazole Pharmacokinetics in Healthy Cats after Oral and Intravenous Administration

D.I. Mawby, J.C. Whittemore, L.E. Fowler, and M.G. Papich

Posaconazole pharmacokinetics after administration of an intravenous solution, oral suspension, and delayed-release tablet to dogs

Jennifer Kendall BS
Mark G. Papich DVM, MS

- Dose:
  - Dogs
    - ER tablet = 5 mg/kg EOD
    - Solution = 5 mg/kg BID
  - Cats
    - Solution = 15 mg/kg once then 7.5 mg/kg SID
- Clinical Uses
  - Invasive molds (*Aspergillus)*
  - Salvage therapy if itra- or flu- fails
    - *Blasto, Histo, Cocci, Crypto*

https://www.clinicaltrialsarena.com/projects/noxafil-posaconazole-for-treatment-of-fungal-infections/

Terbinafine

- Inhibits squalene epoxide reductase
  - ↓ production ergosterol = damage fungal cell membrane
- Well-tolerated & inexpensive
  - GI upset and hepatotoxicity are possible
- Single oral dose 30-35 mg/kg[1,2]
  - Healthy large breed dogs
  - Cmax = 3.5-4 ug/mL
  - **≥ 18h MIC for *Blastomyces* & *Histoplasma***

1. Sakai MR, et al. Terbinafine pharmacokinetics after single dose oral administration in the dog. VET DERM 2011;22:528-534.
2. Williams MM, et al. Pharmacokinetics of oral terbinafine in horses and Greyhound dogs. VET PHARM THER 2011;34:232-237.

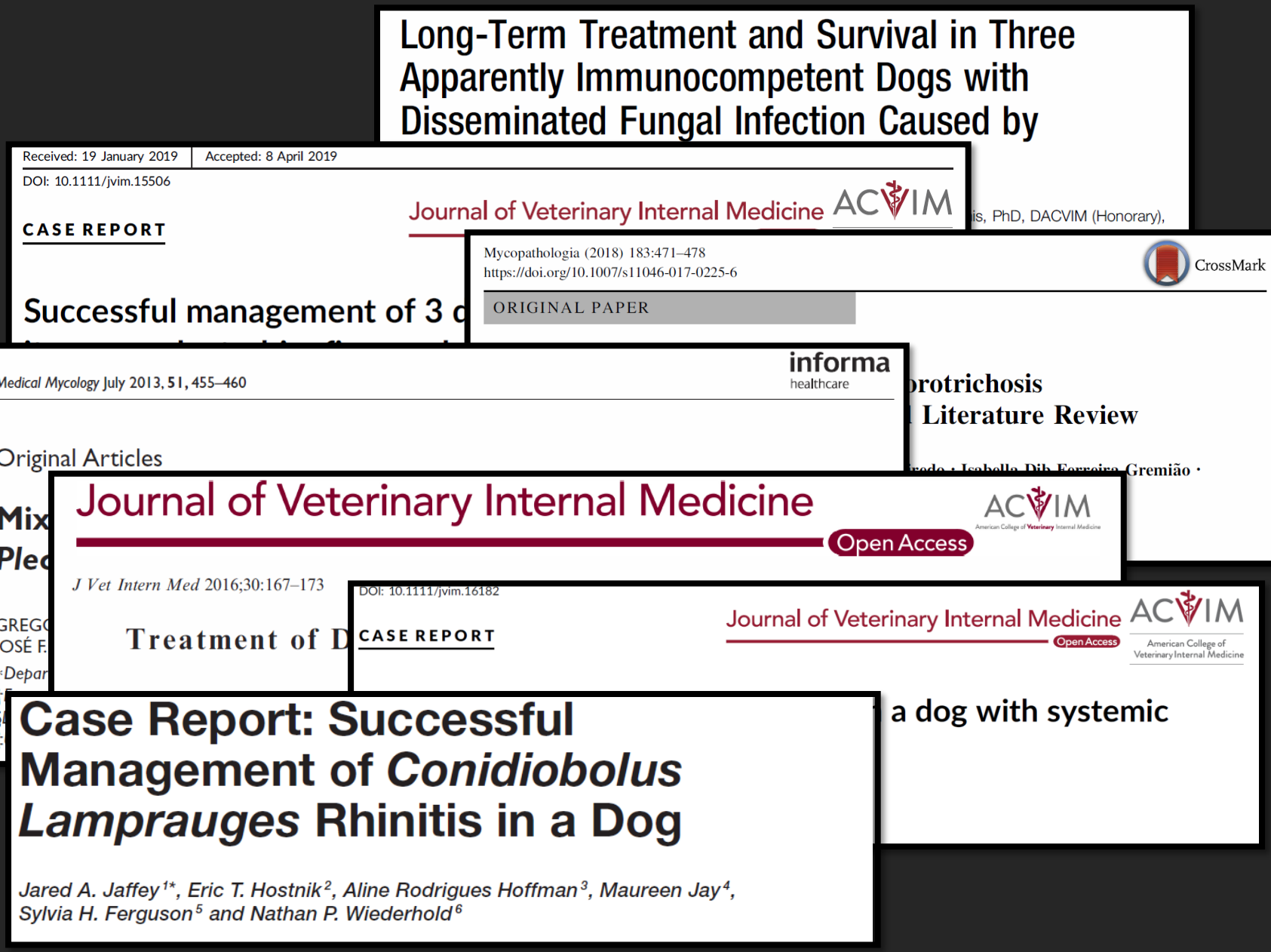
Terbinafine Synergism w Azole

Table 2 MICs* of terbinafine (Terb) alone and in combination with amphotericin B (AmB), itraconazole (Itra), voriconazole (Vori) and fluconazole (Flu)

Isolate	Single drugs (μg ml^{-1})		Combination (μg ml^{-1})		Interaction (FICI/type)	
Drugs	Terb	AmB	Terb	AmB		
NFI 0159	2	1	0·5	0·5	0·75	Additive
NFI 0239	2	1	0·5	0·008	0·26	Synergy
NFI 4001	2	1	0.5	0·015	0·27	Synergy
NFI 4002	2	1	0.5	0·008	0·26	Synergy
NFI 0921	0·06	1	0·016	0·002	0·25	Synergy
Drugs	Terb	Itra	Terb	Itra		
NFI 0159	2	0·25	0·004	0·016	0·06	Synergy
NFI 0239	2	0·25	0·016	0·008	0·04	Synergy
NFI 4001	2	1	0·004	0·016	0·02	Synergy
NFI 4002	2	0·5	0·004	0·016	0·03	Synergy
NFI 0921	0·06	1	0·016	0·002	0·25	Synergy
Drugs	Terb	Vori	Terb	Vori		
NFI 0159	2	0·125	0·125	0·008	0·13	Synergy
NFI 0239	2	1	0·06	0·125	0·16	Synergy
NFI 4001	2	2	0·125	0·125	0·13	Synergy
NFI 4002	2	2	0·06	0·125	0·09	Synergy
NFI 0921	0·06	1	0·016	0·002	0·25	Synergy
Drugs	Terb	Flu	Terb	Flu		
NFI 0159	2	> 128	0·5	0·008	0·25	Synergy
NFI 0239	2	> 128	1	0·001	> 0·5	Additive
NFI 4001	2	> 128	1	0·001	> 0·5	Additive
NFI 4002	2	> 128	1	0·001	> 0·5	Additive
NFI 0921	0·06	> 128	0·016	0·008	0·25	Synergy

*, MIC defined as drug concentration causing 100% growth inhibition; FICI, fractional inhibitory concentration index.

Ryder NS, et al. Synergistic interaction of terbinafine with triazoles or amphotericin B against Aspergillus species. MED MYC 2001;39:91-95.


Long-Term Treatment and Survival in Three Apparently Immunocompetent Dogs with Disseminated Fungal Infection Caused by
Received: 19 January 2019 Accepted: 8 April 2019
DOI: 10.1111/jvim.15506
Journal of Veterinary Internal Medicine ACVIM
CASE REPORT
Successful management of 3 c
Mycopathologia (2018) 183:471–478
https://doi.org/10.1007/s11046-017-0225-6
CrossMark
ORIGINAL PAPER
Medical Mycology July 2013, 51, 455–460
informa
healthcare
Original Articles
Literature Review
Journal of Veterinary Internal Medicine
ACVIM
Open Access
J Vet Intern Med 2016;30:167–173
Treatment of D
DOI: 10.1111/jvim.16182
CASE REPORT
Journal of Veterinary Internal Medicine
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ACVIM
American College of Veterinary Internal Medicine
a dog with systemic
Case Report: Successful Management of Conidiobolus Lamprauges Rhinitis in a Dog
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Terbinafine Guidelines

- Combination w/ azole
  - Progressive histo, blasto, cocci, crypto
  - Invasive molds - aspergillosis
- Monitor liver enzymes
- Dose:
  - Dog: 30 mg/kg/day
  - Cat: 125 mg/day (total dose)
  - Give w/ food

Question #4

What's the most effective antifungal for life-threatening invasive fungal infection?

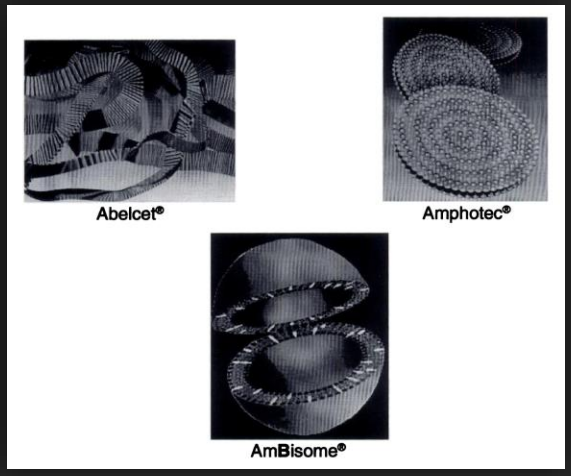
A. Amphotericin-B
B. Fluconazole
C. Terbinafine
D. Flucytosine

Amphotericin B

- Original formulation
  - Deoxycholate (Fungizone®)
- Complexed Amp-B
  - Lipid complex (Abelcet®)
  - Liposome encapsulated (AmBisome®)
  - Colloidal dispersion (Amphotec®)

https://www.mims.com/drug/info/ambisome?type=full

Abelcet® & AmBisome®



1. Less entry into renal tubule
   - 8-10 x less nephrotoxic
2. Concentrates liver, spleen, & lungs
3. Macrophage activator
   - Potentiates phagocytosis & fungicidal activity
4. Released @ sites inflammation (lipases)

Boswell GW, et al. AmBisome (liposomal amphotericin B): a comparative review. J Clin Pharmacol;38:583-592.

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AmBisome® Dosing

- D: 1–2 mg/kg EOD IV over 2-4 h
- C: 0.5–1 mg/kg EOD IV over 2-4 h

- Max cumulative dose:
  - D: up to 24 mg/kg
  - C: up to 12 mg/kg

- IV fluids = 2 x maintenance rate
  - 30 m before - 2 h after infusion

- Kidney values + electrolytes
  - Delay dose if kidney values are increasing

- Handling and Administration

https://www.mims.com/drug/info/ambisome?type=full

SQ Protocol

- Deoxycholate formulation
- 0.5-0.75 mg/kg in 350 ml 0.45% NaCl
- 2-3 times / week
- Tissue irritation possible
  - <20 mg/L concentration

O'Brien CR, et al. Long –term outcome of therapy for 59 cats and 11 dogs with cryptococcosis. AUS VET J 2006;84:384-392.

Amp-B Guidelines

- Any life-threatening IFI
- IV Ambisome or Abelcet
  - SQ Amp-B deoxycholate – less expensive option
- Monitor kidney values + electrolytes
- Step-down therapy w/ azole
  - Dimorphic
- Concurrent therapy w/ azole
  - Mold or Yeast
- Concurrent corticosteroid
  - Inflammation from drug and dying fungal organisms

Treatment Guidelines

Disease	Out-patient	Life-threatening	Salvage
Histoplasmosis	Itraconazole > Fluconazole	Amphotericin-B	Posaconazole > Voriconazole Terbinafine + azole
Blastomycosis	Itraconazole > Fluconazole	Amphotericin-B	Posaconazole > Voriconazole Terbinafine + azole
Coccidioidomycosis (Valley fever)	Fluconazole = Itraconazole	Amphotericin-B	Posaconazole > Voriconazole Terbinafine + azole
Cryptococcosis* Candidiasis*	Fluconazole > Itraconazole	Amphotericin-B	Posaconazole > Voriconazole
Aspergillosis* (other molds)*	Posaconazole + terbinafine Voriconazole + terbinafine	Amphotericin-B	Amphotericin-B + Azole +Terbinafine +/- Echinocandin

Dimorphs | Yeasts | Molds

* Sensitivity varies and some molds and yeasts are resistant. Base treatment on culture and sensitivity.

The Future

- Isavuconazole
  - Favorable safety profile in humans
  - *Aspergillus* + molds, dimorphs, yeasts
- Oteseconazole (phase 3)
  - Tetrazole
  - ↑ selectivity fungal CYP450
- VT-1598 (phase 1)
  - Tetrazole

The Future continued…

- Rezafungin
  - Long acting Echinocandin – 1x weekly humans
  - Difficult to reach locations – abscess or necrosis
  - *Candida auris, Aspergillus spp.*
- Encochleated Amphotericin B
  - Oral formulation
  - Phospholipid bilayers rolled into spirals
  - Released intracellularly = ↓ systemic side-effects
  - Highest concentrations in liver and spleen

Questions

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