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MEDICAL MYCOLOGY TRAINING NETWORK

Updates and practical guide on antifungal agents

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Updates and Practical Guide on Antifungal Agents

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Disclosures

- No Conflict of interest

Systemic Antifungals

- Ampho B deoxycholate

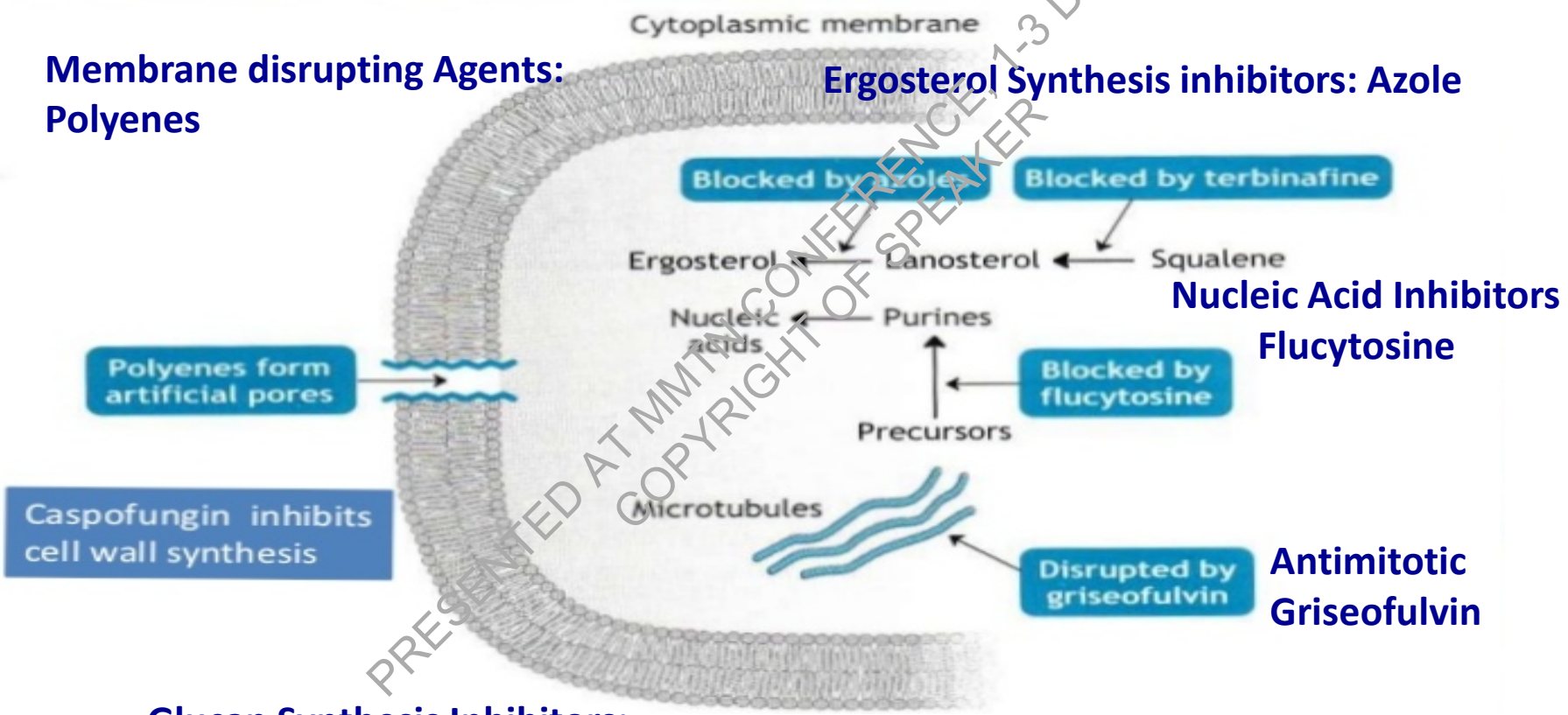
- 5Flucytosine

- First generation Azole: Itraconazole, Fluconazole
- Lipid formulations of Amphotericin B

- Second generation Azole: Voriconazole, Posaconazole
- Echinocandins

- Tab/Inj Posaconazole
- Isavuconazole

Mechanism of Action of Antifungals



Polyene: Amphotericin B/Nystatin

- Deoxycholate & Lipid formulations
- Spectrum & Resistance: Broad spectrum: Yeast, filamentous and dimorphic fungi
- Widely distributed in body
- CSF levels are undetectable
- Long elimination half-life (>15 days)
- Accumulates in the liver and spleen and to a lesser extent in the kidney, lung, myocardium, and brain
- Not metabolized
- Amphotericin B deoxycholate is excreted as unchanged drug into the feces (43%) and urine (21%)

Physical & PK of Lipid formulations lipid composition contributes to PK parameters

Property	Ampho B deoxycholate	L-AmB	ABLC	ABCD
Composition		HSPC:Chol: DSPG: 10:5:4	DMPC:DMPG: 7:3	Cholesteryl Sulphate
Structure	Miscelles	Unilamellar spherical liposomes	Ribbons	Discs
Ampho B: Lipid ratio	NA	1:9	1:3	1:1
Size (nm)	0.035	80	1600-11000	122 X 4
Dose (mg/kg)	1.0	5	5	5
Cmax (µg/ml)	1.5 -2.9	83 ± 35.2	1.7	2.9
AUC (µg-/hml)	17.1 -36	555 ± 311	14 ± 7	36
Half life (h)	24	8.6 ± 3.1	173.4	28.2
Vd (L/kg)	5.0 ± 2.8	0.16	131 ± 57.7	4.1
Cl (ml/h/kg)	38 ± 15	11 ± 6	436 ± 188	112

ABDC: Toxicities & Drug interactions

- Infusion related: Induced by toll-like receptor (TLR)-2 activation, resulting in a pro-inflammatory cytokine response
- Nephrotoxicity: Dose dependent
- Hepatotoxicity: generally rare and mild
- Drug Interactions:
  - Not metabolized by CYP 450
  - Renal toxicity augmented by co-administration of other nephrotoxic drugs

5 Flucytosine

(100mg/kg/day)

- Activity is limited to yeasts (Candida & Cryptococcus)
- Rapid emergence of resistance with monotherapy
- High bioavailability
- Penetrates all body cavities and organs including CSF, vitreous fluid and urine
- Toxicity: Bone marrow & Hepatic
- Not metabolized by CYP 450

Triazole: Spectrum

- Fluconazole:
  - Candida species except Krusei, higher MIC for Glabrata, gullermondei, rugosa
  - Cryptococcus species
  - Dimorphic fungi: Histoplasma, coccidiodomycosis & Blastomycosis
- Itraconazole:
  - Same as Fluconazole
  - Aspergillus species including fumigatus, nidulans, terreus
  - Paracoccidiodomycosis, Basidiobolomycosis, sporothrix
  - minimum activity against fusarium
- Voriconazole:
  - Aspergillus species, Candida Species including Krusei, Dimorphic fungi
  - Fusarium, Scedosporium
  - No activity against Mucor
- Posaconazole:
  - Voriconazole plus Mucormycosis
- Isavuconazole:
  - Similar to posaconazole

Fluconazole: Ideal PK parameters

12mg/kg loading, 6mg/kg qd

- Excellent safety profile
- Oral bioavailability > 90%
- Loading dose required to reach steady state level within 24h
- $t_{½}$ = 25 -40 hours
- Widely distributed: CSF & Aqueous/vitreous concentrations exceeding 60 & 70 % of serum concentration
- Renally excreted as unchanged with very high urinary concentration

- TDM is not required
- Several ideal pharmacokinetic parameters
  - Linear & predictable PK over dose range 50 -800 mg/day with normal renal function
    - **AUC** = administered dose, i.e. 800mg produce AUC of 800ml/L
- **Predictable blood levels:** every 100 mg results in level of 5µg/ml, 800mg = 40µg/ml in healthy volunteers
- Dose/MIC ratio of 50 was associated with increased likelihood of fluconazole failure*

*Cornelius J C . AAC 2005

Voriconazole:

6mg/kg loading, 4mg/kg q12h

- VCZ has high (96%) oral bioavailability
- Food reduces absorption by 22%
- Demonstrates nonlinear kinetics in adults, irrespective of the route of administration
- VCZ is extensively metabolized by CYP2C19
- VCZ pharmacokinetics has high interpatient variability due to CYP2C19 genetic polymorphism and drug –drug interactions

- Transient visual disturbances, typically start within 30 minutes after dosing
- Increase transaminases, rash, photosensitivity, hallucinations, jaundice and encephalopathy
- Higher VCZ level is associated with higher incidence of toxicity
- Long term therapy: painful periostitis and exostoses

- VCZ TDM is required

Posaconazole

Suspension: 200mg q6hX1 week, 400mg q12h
IV & Delayed release tab: 300mg q12 X1 day followed by qd

- Available in Suspension, delayed release tablet and IV
- Drawback of suspension formulation:
  - Requires frequent dosing with food (preferably a high-fat meal) to ensure adequate oral absorption
- New delayed release tablet (100mg) and injectable formulations now approved by FDA for clinical use
- Both formulations circumvent the absorption problems of the oral suspension
- Convenient dosing of posaconazole: Once daily after a twice-daily loading dose on the first day

Dolton MJ et al. *Antimicrob Agents Chemother*. 2012;56:5503-5510

Posaconazole: Absorption

- Posaconazole absorbed in duodenum and jejunum
- Absorption of Posaconazole Suspension requires dissolution of drug in to stomach
- The rate and extent of posaconazole dissolution is maximized when the drug is taken as smaller, more frequent doses with a high-fat meal
  - Which lowers gastric pH, prolongs gastric residence time, and stimulates splanchnic blood and bile flow
  - Rapid gastric transit, elevated pH slow down the rate and extent of dissolution & less absorbable drug reaches to duodenum and jejunum

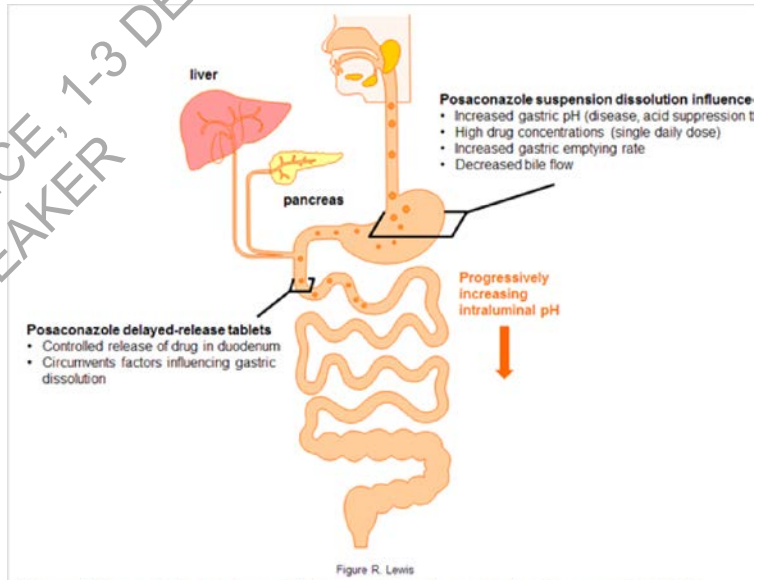


Figure 1. How a delayed-release tablet overcomes absorption barriers associated with posaconazole suspension. Image courtesy of Russell E. Lewis, PharmD.

Posaconazole Tablet

- Tablet formulation uses pH-sensitive polymers to release posaconazole at a controlled rate in the duodenum
- It overcomes many of the issues associated with poor gastric dissolution of the drug
- Important benefits with tablet
  - Patient achieves higher trough level 1400 ng/ml (loading dose of 300 mg BD on day 1 followed by 300 OD) compared to 517 ng/ml with the oral suspension(200 mg 4 times daily) (Ezzet 2005; Duarte 2012)
  - Early steady state level (24 to 48 hours with tablet compared to 7 to 10 days with suspension) (Merck 2014)
  - Coadministration of acid suppressing agents (antacids, H2-receptor antagonists, proton pump inhibitors) does not significantly decrease the bioavailability of the delayed-release tablet while 20% to 40% decrease in mean AUC oral suspension
  - Administration with food increases absorption of tablet

Percival KM et al. *Curr Fungal Infect Rep*. 2014;8:139-145
Ezzet F et al. *Clin Pharmacokinet*. 2005;44:211-220.
Merck Sharp & Dohme Corp. Noxafil Package Insert. New Jersey, 2014
Durate RF et al. Abstract A-1934. Presented at the 52nd ICAAC. San Francisco, Sept 9-12, 2012.

Posaconazole tablets: Limitations

- It can't be divided or crushed, administered through gastric feeding tubes
- Coadministration of the tablet with the prokinetic agent metoclopramide resulted in modest decreases in the Cmax (14%) and AUC (7%) of the delayed-release tablet (Kraft 2014)

Kraft WK et al. *Antimicrob Agents Chemother.* 2014;58:4020-4025

IV Posaconazole

- IV preparation is solubilized in sulfobutylether β-cyclodextrin
- Achieves early steady state level
- Must be administered through Central Line (High infusion related ADR when administered through peripheral line)
- Similar safety profile

Isavuconazole

- Available in Oral and IV: high oral bioavailability and the absorption is not significantly affected by food intake or gastric acidity
- Dose recommendation:
  - 200mg q8h (PO/IV) X 2 days followed by 200mg OD
  - Dose adjustment in patients with liver impairment, a 50% dose reduction is recommended
  - Dose reductions are not required for patients with renal insufficiency or dialysis
- Nursing mother shouldn't breast feed as in animal models showed level up to 17 times plasma level

Important PK parameters

- Prolonged half-life (>75 hours) with convenient OD dosing
- High oral bioavailability & consistent metabolism
- Predictable, linear pharmacokinetics with no relevant food effect
- Highly protein bound (>99%)
- CSF & occular levels expected to be low (achieves sufficient brain parenchymal level to inhibit fungus)
- IV formulation does not contain the sulfobutylether β-cyclodextrin
- Isavuconazole is metabolized by hepatic CYP450 enzymes and excreted in the feces
- Minimal active drug is excreted in the urine like voriconazole, posaconazole

Pettit NN, Carver PL. Ann Pharmacother. 2015 Jul;49(7):825-42

Drug Interactions

- Isavuconazole is a substrate of cytochrome 450 (CYP) 3A4/5
- Inhibitor of CYP 3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6 enzymes
- Inhibitor of P-glycoprotein (P-gp), breast cancer resistant protein (BCRP), human organic cation transporter (OCT2) transporters
- Mild inducer of CYP 2B6
- Avoid concomitant CYP3A4 inducers like rifampicin or inhibitors like lopinavir/ritonavir
- Coadministration of P-gp substrate like colchicin, digoxin, Mycophenolate requires close monitoring and TDM

Pettit NN, Carver PL. Ann Pharmacother. 2015 Jul;49(7):825-42

Echinocandins: Spectrum

- All three candins have similar spectrum
- Fungicidal activity against *Candida* species, high MIC for *C. parapsilosis*, *gulliermondeii*
- Fungistatic activity against Aspergillus species
- Does not include *Cryptococcus* spp, endemic dimorphic fungi, Mucorales, *Fusarium* spp, or *Scedosporium* spp
- Resistance to Candida spp is relatively low, less than 3%, and is primarily mediated by mutations in 2 conserved regions of the gene-encoding glucan synthase

Echinocandins: Pharmacology

	Caspofungin	Micafungin	Anidulafungin
Absorption/PK	Not orally absorbed/ Lineal Pharmacokinetics		
Distribution	Extensive into the tissues, Liver, lungs, Kidney and heart minimal CNS penetration		
Metabolism	Hepatic spontaneous degradation, hydrolysis and N-acetylation		Chemical degradated Not hepatically metabolized
Urine concentrations	Limited urinary excretion. Not dialyzable		
CSF Penetration	Brain, not CSF		
Half-life	9-23 hours	11-21 hours	26.5 hours
Dose	70 mg IV on d1, 50	100 mg IV	200 mg IV on d1, 100

Dowell JA et al. J Clin Pharmacol, 2007, Dowell JA et al. J Clin Pharmacol, 2004

Echinocandins

	Caspofungin	Micafungin	Anidulafungin
Dose Adjustment Liver disease CYP Inducers	Yes 70mg d1 then 35mg 70mg daily	None	None
CYP 3A4 Inhibition	No	Yes, Weak	No
Drug Interactions	Yes Rifampin, Efavirenz, Nevirapine, Tacrolimus, cyclosporine Phenytoin, dexamethasone Carbamezapine	Yes Sirolimus ↑ Nifedipine ↑	Some with cyclosporine

Dowell JA et al. J Clin Pharmacol, 2007, Dowell JA et al. J Clin Pharmacol, 2004
Cappelletty et al. Pharmacotherapy 2007;27:369-8

Echinocandins—Adverse Effects

- Generally well tolerated
- Phlebitis, GI side effects, Hypokalemia
- Abnormal liver function tests
- Caspofungin
  - Tends to have higher frequency of liver related laboratory abnormalities
  - Higher frequency of infusion related pain and phlebitis

Mitochondrial damage related cardiac myosite injury reported

Use of combination antifungal therapy

- Difficult scenario, more expert opinion then evidence
- Well established in treatment of Cryptococcal meninigitis
  - Rapid CSF sterilization with Ampho B + 5FC combination
- No adequate data in other fungi
- No benefit of combination antifungal therapy in Mucormycosis

Perfect JR. Clinical Infectious Diseases 2010; 50:291–322

Summary

- Three major class of antifungals (Polyene, Triazoles and ecchinocandins) available to chose for systemic fungal infections
- Clinicians should be careful for drug-drug interactions with Triazole
- Echinocandins has cidal activity against candida
- Newer formulations of Posaconazole has improved bioavailability
- Isavuconazole has a broad spectrum antifungal activity