

Case study : Invasive Mucormycosis

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Mucormycosis: Antifungal Treatment



Azoles - Posaconazole/ Isavuconazole are effective



Use is limited as stepdown therapy, intolerant to amphotericin B

Posaconazole: a broad spectrum triazole

- Spectrum:
 - Yeasts: *Candida*, *Cryptococcus*, *Trichosporon*
 - Mycelia: *Aspergillus*, *Mucorales*,
 - Dimorphic: *Histoplasmosis*, *Coccidioides*, *Blastomyces dermatitidis*
 - Difficult to treat: *Fusarium* species, *Scedosporium*
- **Fungicidal** activities: *Aspergillus fumigatus*, *Blastomyces dermatitidis*, selected *Candida* species, *Cryptococcus neoformans*, and *Trichosporon*
- **Fungistatic** activities: *Candida*, *Coccidioides*, selected *Fusarium* spp., *Histoplasma*, *Scedosporium* and *Mucorales*

Three formulations



SUSPENSION



DELAYED RELEASE
TABLETS



INTRAVENOUS
FORMULATIONS

Posaconazole:

Suspension

- Posaconazole absorbed in duodenum and jejunum
- Dissolution of drug into stomach is required for suspension
- Small and frequent dosage with fatty meals improves the rate and extent of posaconazole dissolution

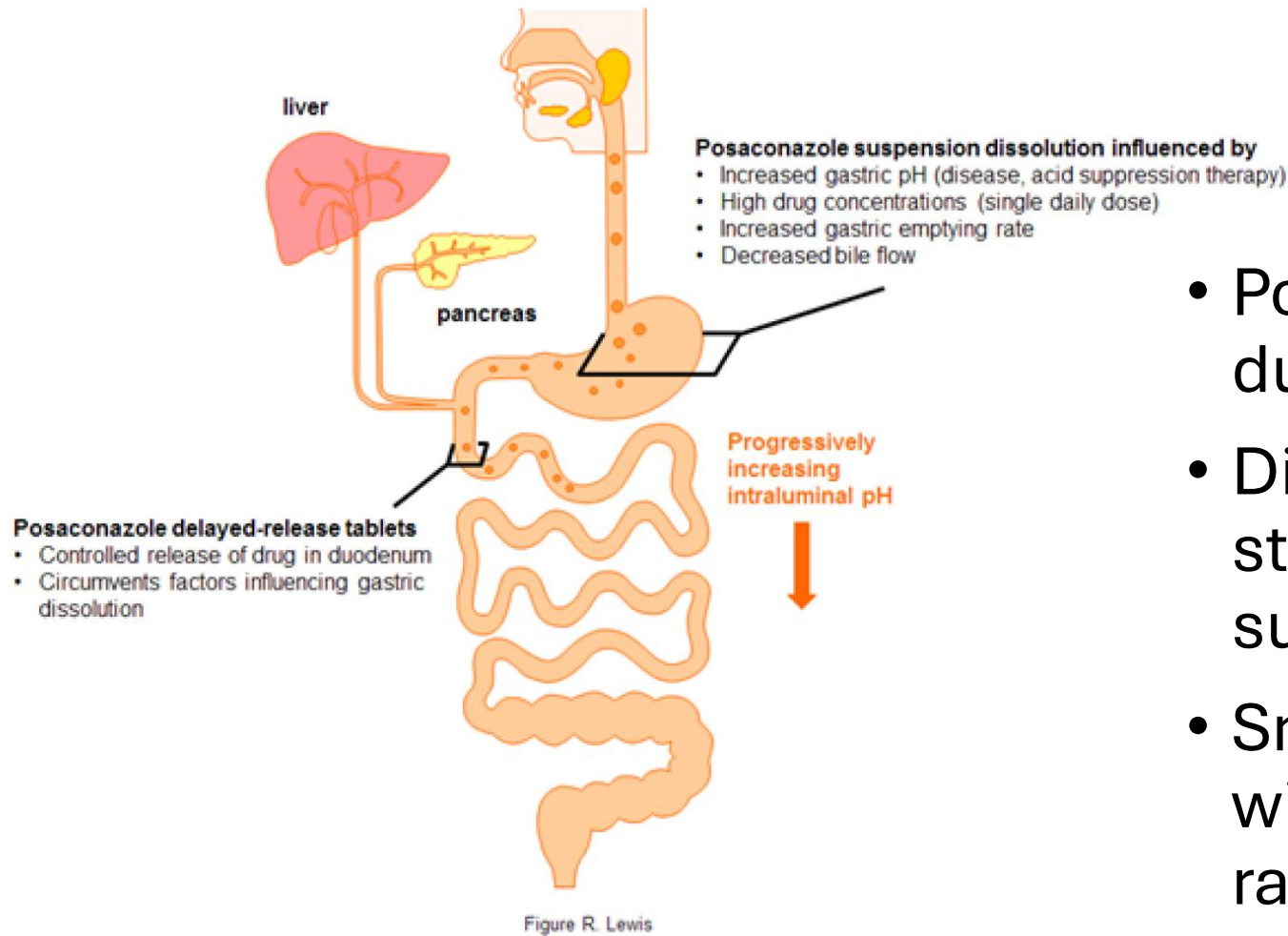


Figure 1. How a delayed-release tablet overcomes absorption barriers associated with posaconazole suspension. Image courtesy of Russell E. Lewis, PharmD.

Posaconazole: Suspension

- Displays linear PK with dosages of 50-800mg
- Saturation of absorption above 800mg/day (Suspension)
- ~7-10 days to achieve steady state concentrations (Suspension)
- Minimal differences between peak and trough levels
- Similar blood concentrations found in juveniles with comparable efficacy and safety

Posaconazole: Tablet and IV

- Both formulations circumvent the absorption problems of the oral suspension
- Convenient dosing: Once daily after a loading dose on the first day

Posaconazole Tablet

- Tablet formulation uses pH-sensitive polymers
 - Release posaconazole at a controlled rate in the duodenum
- Important benefits with tablet
 - Once daily
 - Achieves higher trough level 1400 ng/ml compared to 517 ng/ml with the oral suspension
 - Less interpatient PK variability than suspension
 - Early steady state level (24 to 48 hours with tablet compared to 7 to 10 days with suspension) (Merck 2014)
 - Acid suppressing agents does not significantly decrease the bioavailability while 20% to 40% decrease in mean AUC oral suspension
 - Can be consume regardless of food, food increases absorption of tablet

Posaconazole IV

- Achieves early steady state level
- Must be administered through Central Line, using 0.22 micron filter
- Slow IV infusion over 90 min
- IV preparation is solubilized in sulfobutylether β -cyclodextrin
- Hepatic impairment (Child-Pugh Class A, B, and C): No dose adjustment needed
 - Consider discontinue Posaconazole if patient develops Acute hepatitis during treatment

Posaconazole: Metabolism

- Substrate for the P-glycoprotein and an inhibitor of the CYP3A4
- Metabolised in the liver; 17% is glucuronidated by UGT1A4 and the remainder is eliminated unchanged
- POSA and its metabolites are eliminated by fecal (~77%) and only small fractions are detected in the urine (~14%)
- Prolong half life (>24 h) which allows this drug to be administered once daily
- Dose adjustments are not needed in patients with renal failure and patients who are on haemodialysis (except for IV preparation)

Posaconazole PK

- Posaconazole accumulates in lung, kidney, heart, and liver tissue, but not in the brain
- Brain and plasma concentrations were approximately equal
- Higher plasma concentrations may be required for brain infections
- No concentration-dependent toxicity is described
 - European Medicines Agency suggested 3.75 mg/l

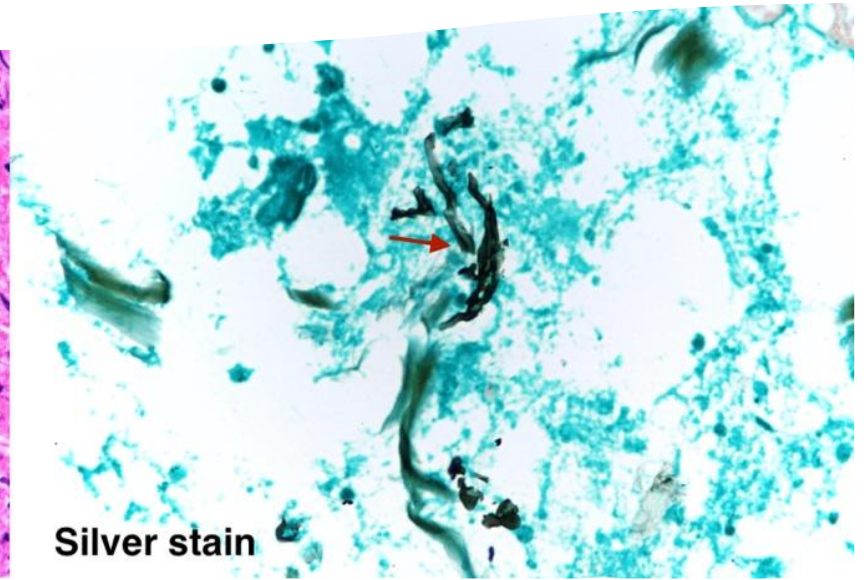
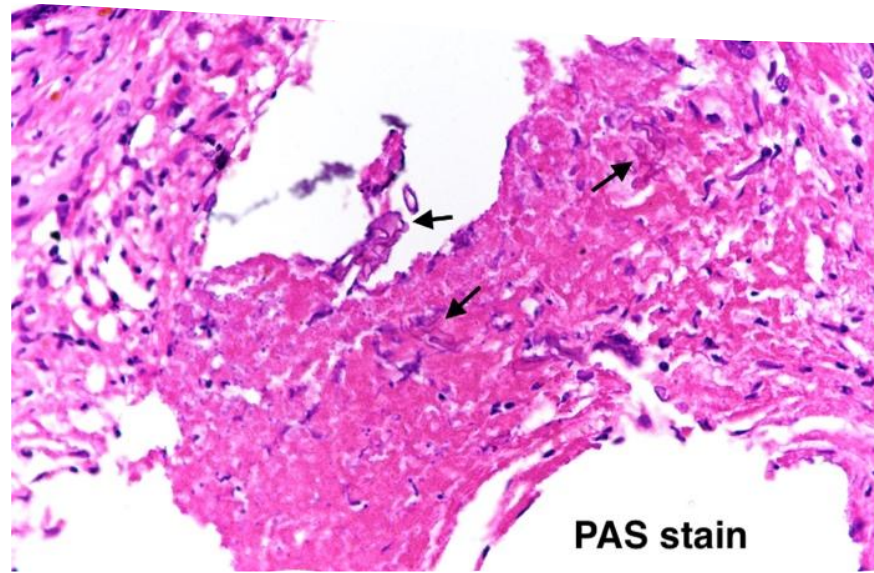
Case 1

- 71/male. without comorbidities had a covid-19 illness in the mid-September 2020
 - He received ICU care with BiPAP support
 - Remdesivir, steroids, tocilizumab, and convalescent plasma along with heparin and supportive care
- He had an episode of candidemia (*candida hemulonii*) during covid-19 pneumonia,
 - Two-week of Caspofungin
- He complained of back pain while on treatment for candidemia
 - MRI showed psoas, paravertebral, and epidural collection with L4-5 vertebral discitis
 - Psoas abscess aspiration pus grew mucormycosis and no other bacterial or fungal pathogens

ID assessment: Summary of presentation

- No prior co-morbidities
- Received immunosuppressant (Steroids, Tocilizumab)
- Episode of candidemia
- Clinical Impression
 1. *C. hemulonii* is likely to be *C. auris*
 2. Candida vertebral discitis with paravertebral and psoas collection
 3. Mucormycosis is a possibility in view of COVID-19, & Steroids usage
 4. Isolation of mucorales from aspirated pus can't be contaminant

Further assessment



- Diagnostic Intervention:
 - Biopsy taken from infected disc/ vertebra,
 - Epidural, paravertebral collection aspirated
- Microbiological study:
 - Direct microscopy showed aseptate mycelia, the culture grew *Rhizopus* species
 - MALDI-TOF and gene sequencing: *R. microsporus*
 - Drug Susceptibility: amphotericin MIC: 4 µg/ml, Posaconazole: 4 µg/ml, and itraconazole: 4 µg/ml.
- Histopathology from vertebral body/ disc showed aseptate mycelia

Treatment

- L-AmB dosage increased from 5mg/kg/day to 7.5mg/kg/day
- The patient underwent second surgical debridement with vertebral fixation after 3 weeks of l-AmB
 - Repeat fungal workup was negative
- He completed 6 weeks of liposomal amphotericin B.
- Tablet Isavuconazole was overlapped with liposomal amphotericin B last week and continued with Isavuconazole and supportive care

Treatment- follow up

- After completion of 8 weeks of antifungal treatment
- Patient required third surgery (Vertebral fixation)
 - Tissue grew Mucorales,
 - Isavuconazole changed to Posaconazole
 - L-AmB added for 2 more weeks
 - *R. microsporus*: Posaconazole/ Amphotericin MIC 4.0 µg/ml

Suggested PK parameters with successful outcome

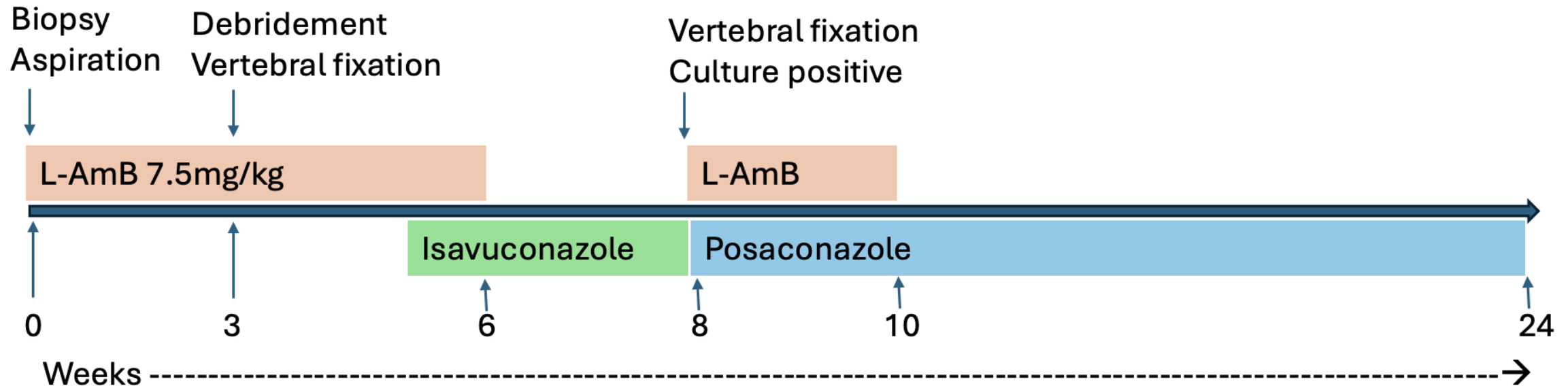
- AUC/MIC ratios of 167 to 187 were found to be predictive of successful treatment of *Aspergillus* species
- *Rhizopus oryzae* an AUC/MIC of >100 has been shown to be sufficient
- In practice, an AUC/MIC ratio of 200 is advised for infections with *Aspergillus* spp.
- C_{\min} /MIC ratio of 5–8 corresponds to an AUC/MIC ratio of 200
- Our patient:
 - *Rhizopus microsporus*: MIC 4.0
 - Posa: Level 3.2mg/L
 - $AUC/MIC = 3.2/4 = 0.8$ – unfavorable for the successful outcome

Treating fungal pathogen with higher MIC

- Retrospectively study from 2 Dutch academic medical centres
- Posaconazole high dose, high trough of > 3 mcg/ml reported safe and effective in the treatment
- Azole resistant aspergillus, mucormycosis, sanctuary site infection and salvage therapy

Antifungal Treatment:

- We have no further treatment options
- Patient was clinically stable/ improving
- Recovered completely, Rx stopped at 6 months



Why did patient respond ?



Intracellular Concentrations of Posaconazole in Different
Compartments of Peripheral Blood[∇]

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Angela Steinbach,¹ Maria J. G. T. Rüping,¹ and Carsten Müller⁵

TABLE 1. Mean posaconazole concentrations and ratios between
the intracellular and extracellular concentrations^a

Blood compartment	Mean PSC concn ± SD (ng/ml)	C/E ratio ± SD
PBMCs	12,764 ± 14,057 ^b	22.5 ± 21.2
PMNs	4,031 ± 3,692 ^b	7.66 ± 6.50
RBCs	50.8 ± 46.18 ^b	0.09 ± 0.05
Plasma	603.2 ± 475.9	

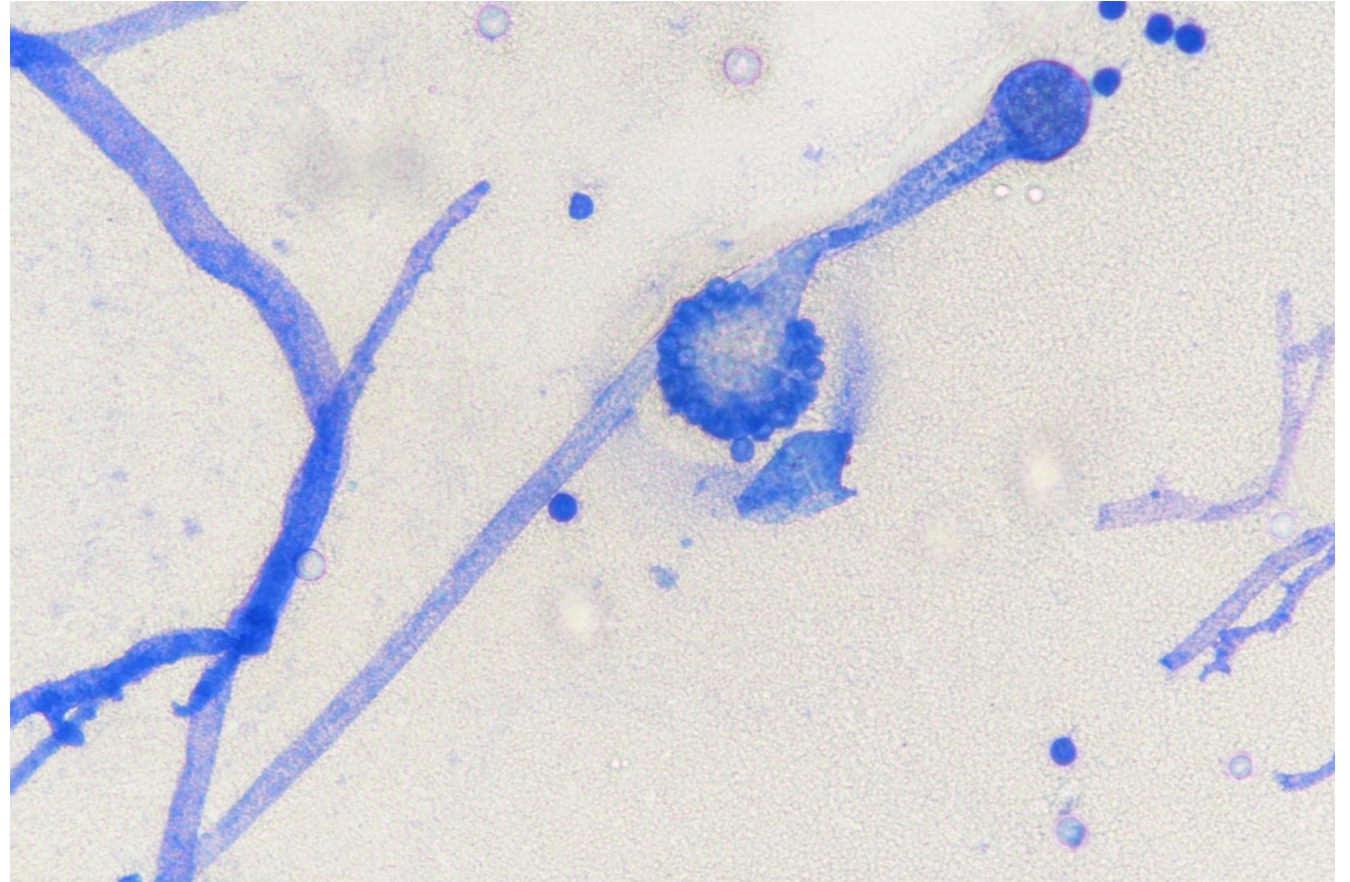
^a PBMCs, peripheral blood mononuclear cells; PMNs, polymorphonuclear leukocytes; RBCs, red blood cells; PSC, posaconazole; C/E, ratio between intra-cellular and extracellular concentrations.

^b *P* < 0.001 compared to plasma (ANOVA and Dunnett T3 test).

Improved antifungal activity was observed both in vitro and in an in vivo invasive pulmonary aspergillosis mouse model

Case 2

- MP, 53/Male, diabetics came with the diagnosis of Post Covid paranasal aspergillus sinusitis
- Tab Voriconazole started
- Subjected for voriconazole level, repeat sinoscopic examination and biopsy after 5 days
- Repeat biopsy
- Direct microscopy: broad aseptate fungi
- Culture grew *Cunninghamella*



Case Contd.

- Patient developed anaphylactoid reaction following L-AmB infusion
- Posaconazole tablet: Level 2.3 mg/L,
- Posa to Isavu as markedly prolonged QTc
- Isavuconazole 3.1 mg/L
- 3 months of Antifungals, recovered fully

Sample ID : IL-4687
Date of Report : 08-06-2021
Identification : *Cunninghamella spp.*
Method of Identification : Phenotype
Antifungal susceptibility method : CLSI- M38-A2*

S.no.	Antifungal	MIC(μ g/ml)
1.	Amphotericin B	2.0
2.	Voriconazole	4.0
3.	Itraconazole	0.25
4.	Posaconazole	0.25
5.	Caspofungin	0.03
6.	Anidulafungin	0.03
7.	Micafungin	0.03

Important PK parameters


- Prolonged half-life (>75 hours) with convenient OD dosing
- IV or oral formulation follows dose-dependent PK
- Less inter-patient variability in drug levels (high oral bioavailability & consistent metabolism)
- Highly protein bound (>99%),
- Distributed to Brain, lung, liver and bone
 - CSF & ocular levels expected to be low
 - Minimal active drug is excreted in the urine
- IV formulation does not contain the sulfobutylether β -cyclodextrin
- Isavuconazole is a substrate for CYP3A4, moderate inhibitor of CYP3A4 and excreted in the feces

Isavuconazole TDM

- TDM for Isavuconazole is not routinely recommended
- IDSA recommends in progressive aspergillus infection, non-compliant patients, poor absorption
- Critically ill patients exhibit significantly lower isavuconazole levels compared to non-ICU patients
- Factors such as elevated BMI, higher SOFA scores, and the presence of sepsis have been associated with lower drug levels



Isavuconazole Concentration in Real-World Practice: Consistency with Results from Clinical Trials

David Andes,^a  Laura Kovanda,^b A. Desai,^b Therese Kitt,^b M. Zhao,^a Thomas J. Walsh^c

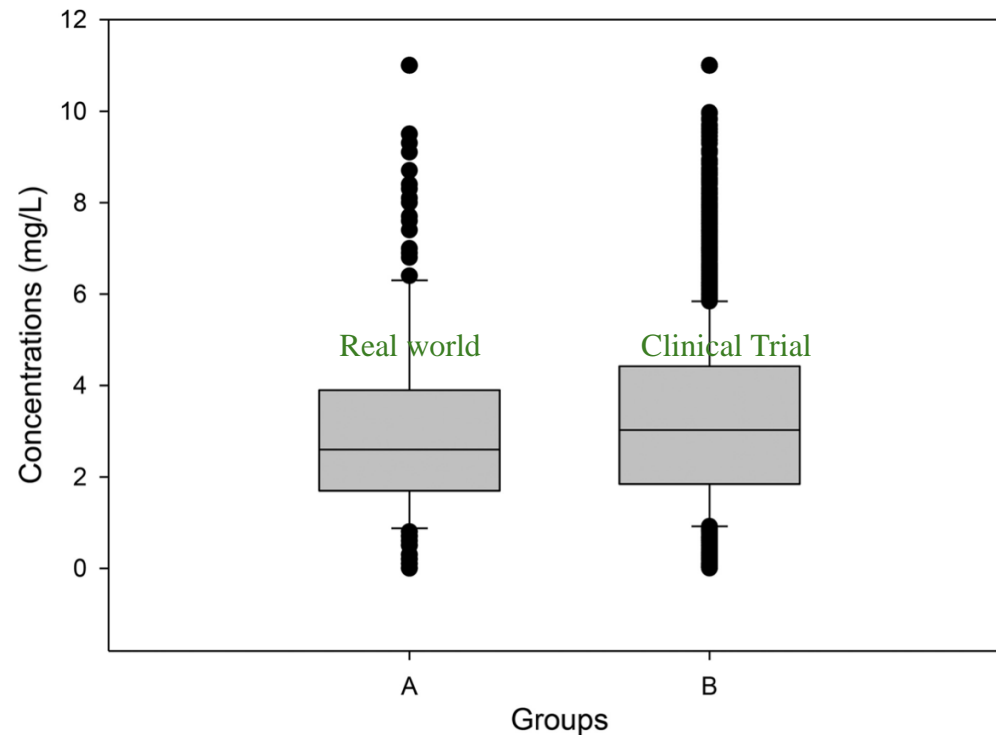
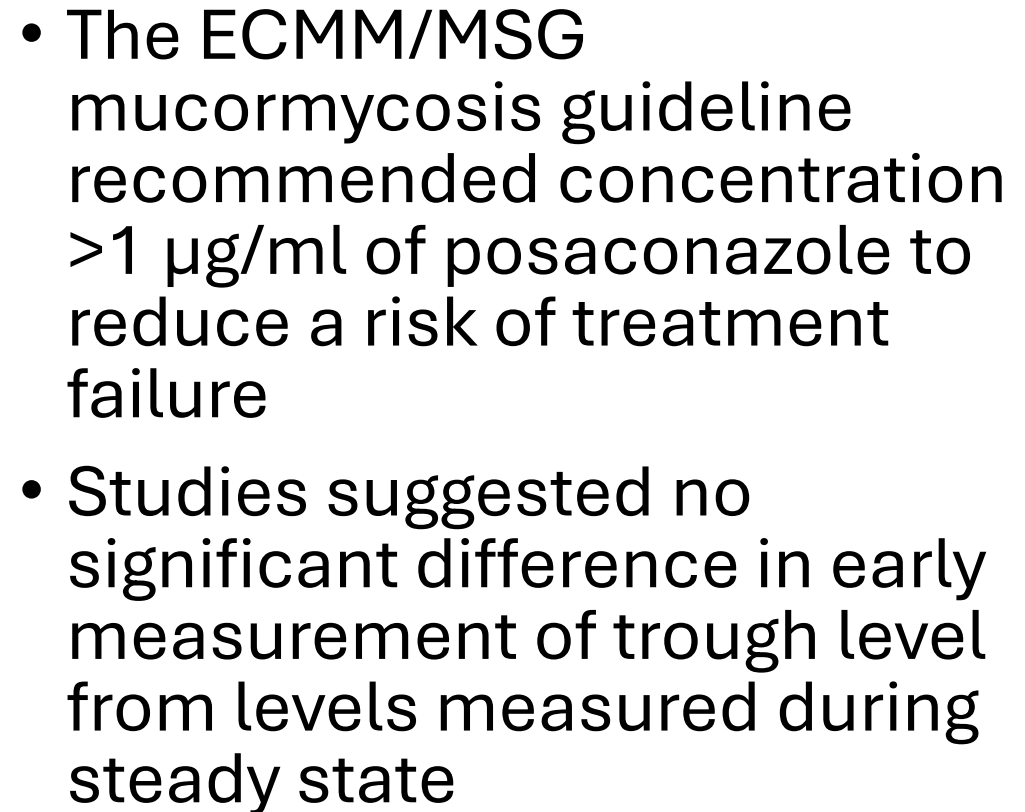


FIG 2 Box and whisker plot of clinical-use (A) and trial (B) isavuconazole concentrations.

Sample	Mean	Median	SD	Coefficient of variation
Real world: n= 283	2.98 µg/ml	2.6 µg/ml	1.91 µg/ml	64
Clinical trial: n=	3.3 µg/ml	3.02 µg/ml	2.18 µg/ml	66

Mean concentrations in clinical use were statistically lower than those in trial patients ($P=0.014$)

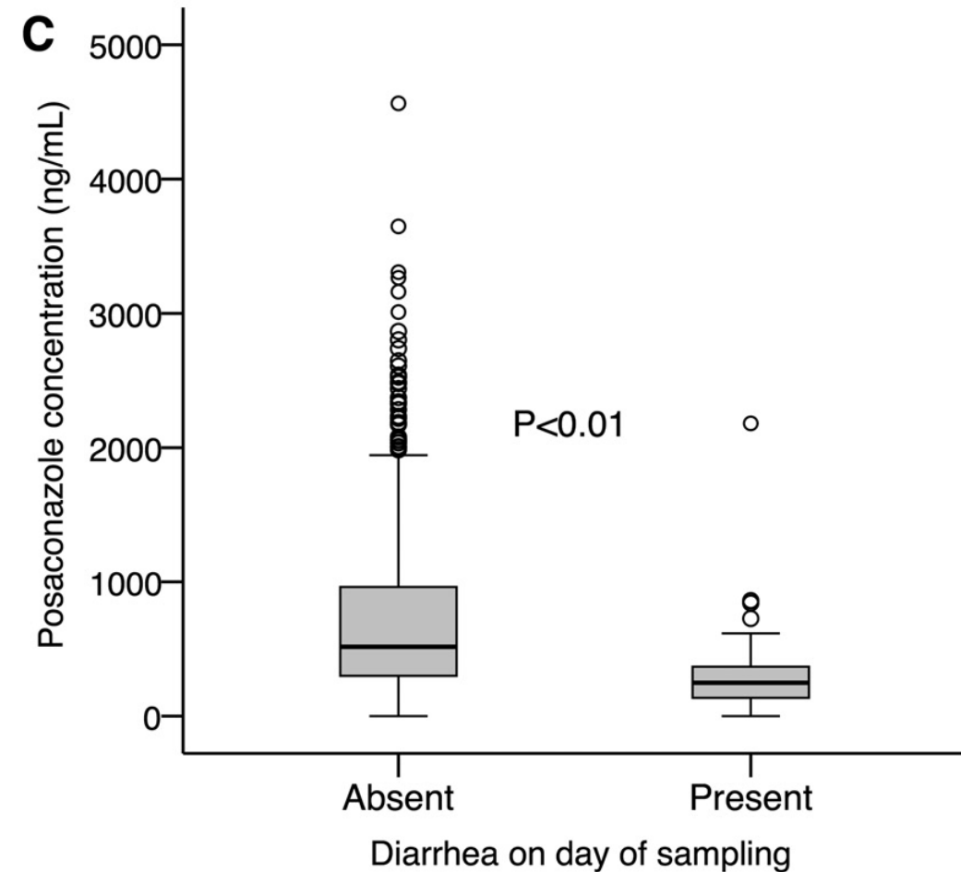
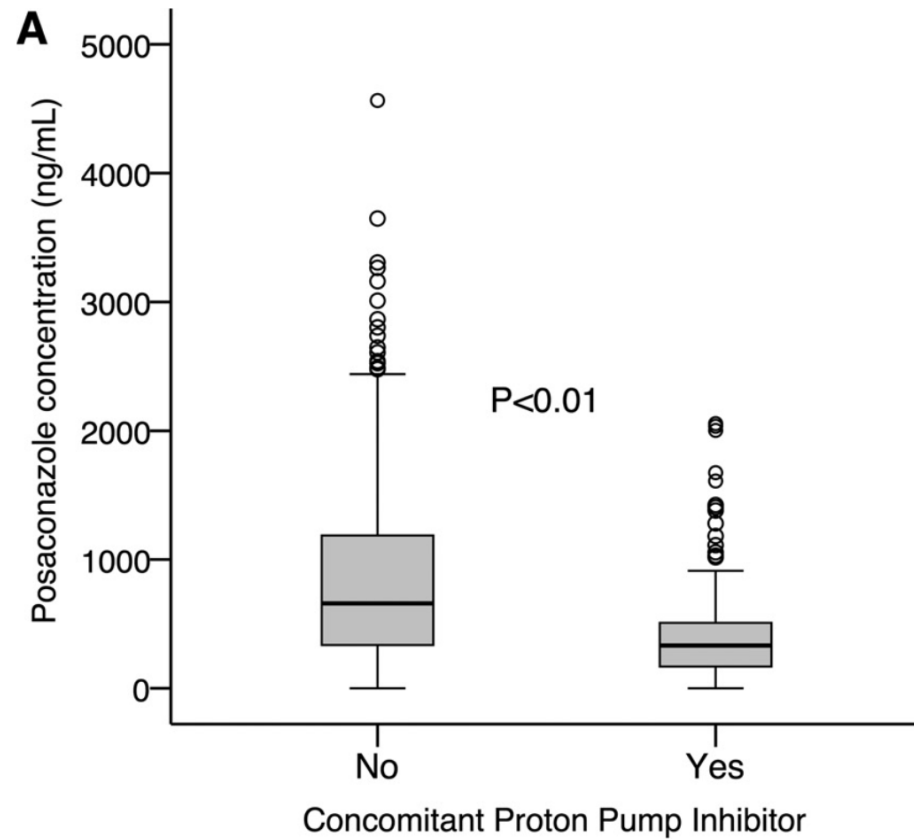
TDM performed on 4th day of treatment after loading dose on first day



Dose adjustment for subtherapeutic

- Increasing dose from 300 mg to 400 mg/d: disproportional 81.8% increase in median C_{\min} (haematological patients)
- Twice-daily dosing if 400mg is subtherapeutic (probable saturation of absorption)

Factors associated with Low Posaconazole



Posaconazole ADR

- Low occurrence of hepatotoxicity and cardiotoxicity
- No clear relationship between posaconazole exposure and treatment-related toxicity
- Pseudo-hyperaldosteronism
 - Itraconazole primarily causes AME by 11 β -HSD2 inhibition
 - Posaconazole cause CYP11B1 inhibition and accumulation of the mineralocorticoids 11-deoxycorticosterone (DOC) and 11-deoxycortisol
 - Posaconazole cause more AME than itraconazole, due to different mechanisms
 - Higher posa level found in patients with pseudohyperaldosteronism (3.0 vs 1.2 mg/ mL)

Take Home message

- Posaconazole and Isavuconazole are broad-spectrum antifungal agent
- Newer formulations of Posa has markedly improved pharmacokinetic
- Isavuconazole has linear PK
- Very convenient Once a day administration
- Routine TDM is not required for Isavuconazole

Take home message

- Posa: TDM guided therapy helps clinician to improve outcome
- TDM will be useful in certain difficult to treat situation
 - Site of fungal Infection (CNS)
 - Fungal Pathogen (Mucorales, Scedosporium, Fusarium species)
 - Antifungal susceptibility (Resistant fungi, higher MIC)
 - Other factors potentially affect PK parameters (Drug interactions, absorption, liver/kidney disease, obesity)



Thank You