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How to use PK/PD of antifungal drugs in clinical practice?

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ASIA FUNGAL WORKING GROUP
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How To Use PK/PD Of Antifungal Drugs In Clinical Practice?

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Disclosures

- None

Learning Objectives

- Overview of PK/PD parameters of an antimicrobial agents
- Clinical application, optimization of dose and frequency of administration according to PK/PD of Antifungal agents
- Voriconazole dosing in various patient population
- Need for antifungal TDM in view of variable PK

Background

- Antifungal drug resistance is a big challenge
  - Prior antifungal therapy use, suboptimal drug exposure
  - Agriculture use of antifungals has resulted in environmental reservoirs for some drug-resistant pathogens
  - Global threat of *C. auris* & azole resistant to *A. fumigatus*
- Antifungal PK is challenging due to erratic absorption (ITR, Posa suspension), drug metabolism & drug interaction, efficacy & toxicity

Cowen LE et al .Nat Rev Microbiol 2008; 6: 187–198
Verweij PE, Lancet Infect Dis 2009; 9: 789–95.

PK/PD

- Pharmacokinetics describes, how human body handles antifungal drug
  - Absorption (Bioavailability)
  - Distribution (Protein bound, penetrations to various body compartments),
  - Metabolism (Cytochrome enzymes, drug-drug interactions)
  - Elimination (Renal, GI)
- Pharmacodynamic is a link between PK, in vitro susceptibility and treatment efficacy

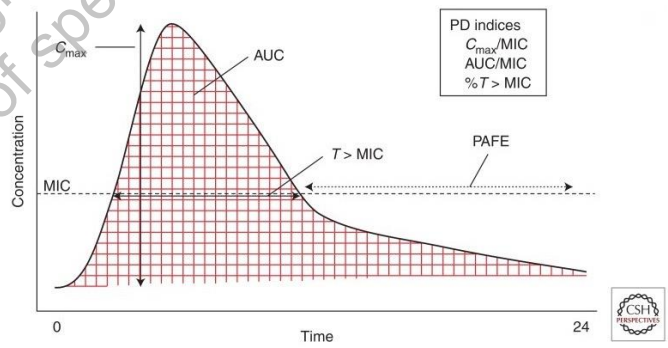
PK/PD: Clinical practice

- PK of antifungal is assessed by estimation of drug levels
- PD is examined by peak concentration in relation to MIC, AUC in relation to MIC, time above MIC, expressed as percentage of the dosing interval (%T>MIC)
- Clinical application
  - Determining dosage and frequency of administration
  - In-vitro drug susceptibility break points
  - Selection of appropriate antifungals according to site (Eye, urinary, CNS)
  - Improve clinical outcome and reduces the risk of emerging resistance

Drug Properties

- Concentration dependent killing (C_{max}/MIC)

Single dose or infrequent dosage



Pharmacokinetic/pharmacodynamic relationship of antimicrobial dosing over time relative to organism MIC. The three PD indices are also listed, including C_{max}/MIC, AUC/MIC, and %T > MIC.

- Time dependent killing property (AUC/MIC)
  - Frequent administration to keep drug level above MIC for longer duration of time (%T/MIC)
- Many drugs also have a prolonged period of fungal growth inhibition after discontinuation/decreased drug level (PAFE)

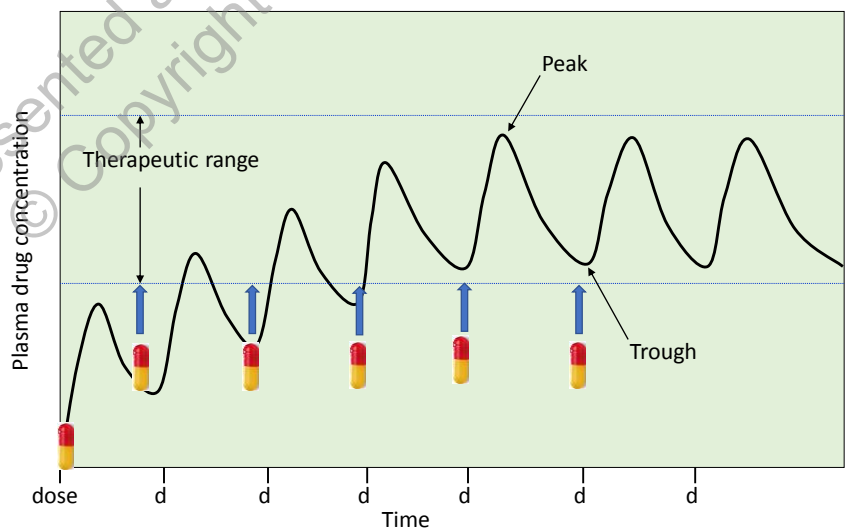
PD Properties of Antifungal Agents

Drug Class	Activity	PAFE***	PD index predictive of efficacy
Polyenes	CD*	Yes	C_{max}/MIC
Triazoles	TD**	Yes	AUC/MIC
Flucytosine	TD	No	T>MIC
Echinocandins	CD	Yes	C_{max}/MIC, AUC/MIC

*CD: concentration dependent, **TD: Time dependent, *** PAFE: Post antifungal effect

The Steady State

Shin-Woo Kim. Infect Chemother. 2008 May-Jun;40(3):133-139



Fluconazole

Grant SM, Drugs. 1990 Jun;39(6):877-916. Silling G. Mycoses. 2002.45:S39-41.
Louie A., et al. Antimicrob Ag and Chemother. 1998.42(5):1105-1109.
Andes D. et al. Antimicrob Ag and Chemother. 1999.43(9):2116-2120
Clancy CJ, Antimicrob Agents Chemother. 2005 Aug;49(8):3171-7

Linear & predictable PK over dose range 50 -800 mg/day with normal renal function

Wide tissue distribution

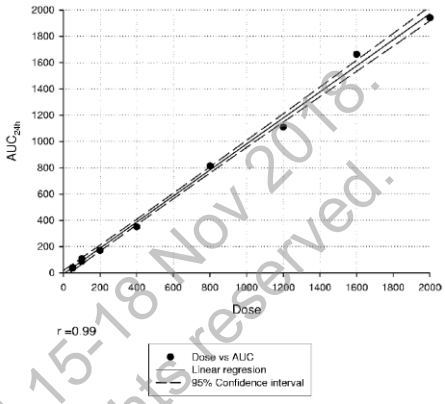
Loading dose required to reach steady state level within 24h

$t_{½}$ = 25 -40 hours

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

Patient receiving CVVH (25ml/min), CVVHD (38ml/min) has higher fluconazole clearance (normal renal function 20ml/min) and requires higher dosage



Juan L. Rodrı´guez-Tudela et al. AAC : 2007; p. 3599–3604

- A dose/MIC of 50 achieved a response rate above 90% (145 of 159)
- 5 of the 10 cases for which the dose/MIC was exactly 50 failed treatment

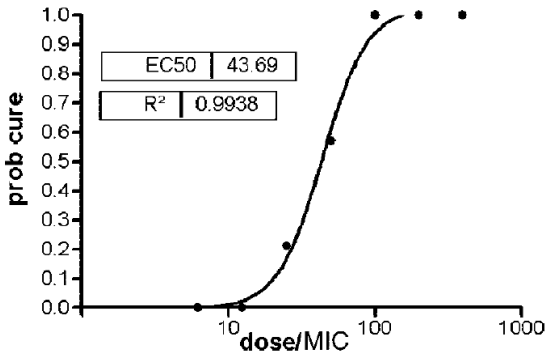


FIG. 2. Probability (prob) of cure after treatment of 132 episodes of oropharyngeal candidiasis with fluconazole.

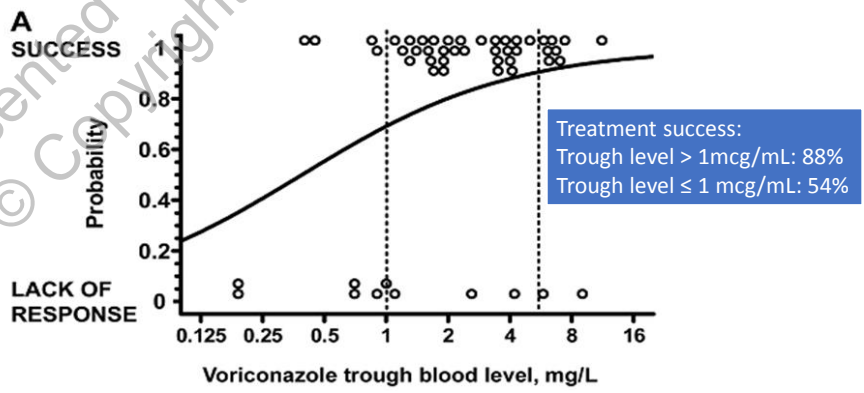
The probability of cure was shown to be a function of the dose/MIC and the EC50 was 43.7, but nonetheless, a dose/MIC just short of 100 was required to achieve a probability of cure of 90%

Voriconazole PK

- Adults
  - VCZ has high (96%) oral bioavailability
  - Displays nonlinear PK, with saturable clearance
  - Disproportionate changes when dose altered
  - **~5 days to achieve steady state concentrations**
- Children
  - VCZ oral bioavailability is 44.6 – 66%
  - Exhibits linear PK in children
  - Children may metabolise more quickly
  - Higher Dose required

Trifilio SM et al. Antimicrob Agents Chemother 2009; 53: 1793
Walsh TJ et al. Antimicrob Agents Chemother 2004; 48: 2166

VCZ Trough level and outcome

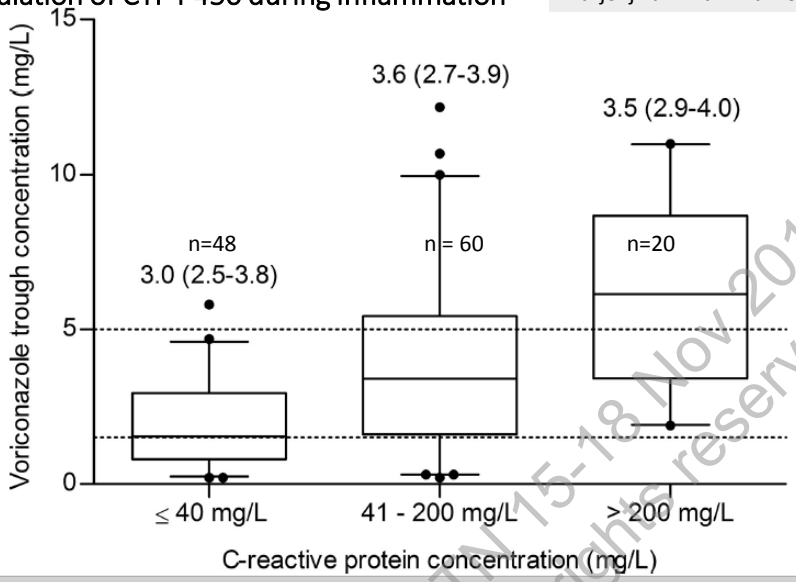


Pascual A el al. CID. 2008; 46:201-11

Inflammation & VCZ trough level

Down-regulation of CYP P450 during inflammation

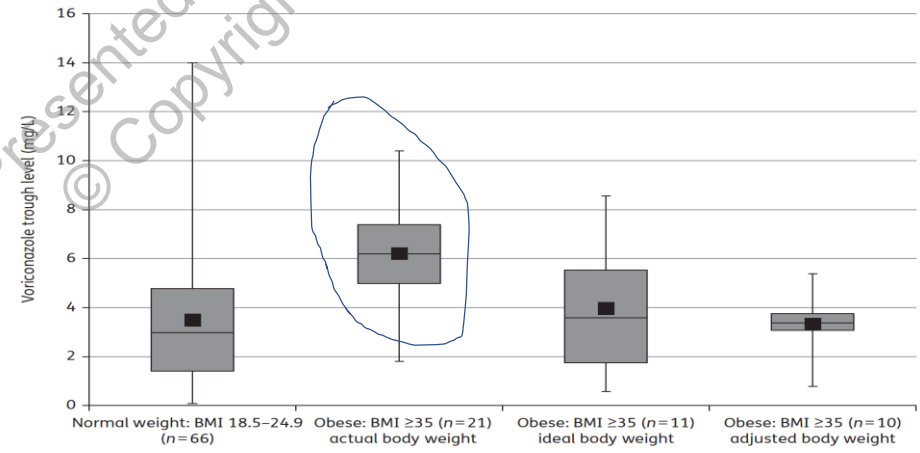
Marjolijn J. P. van Wanrooy et al AAC 2014



For every 1-mg/liter increase in the CRP concentration, 0.015 mg/liter increase VCZ trough

VCZ dosage in Obese

Higher chances of supratherapeutic VCZ levels on obese patients when dose at actual body weight



Elizabeth Koselke et al. JAC 2012

Posaconazole: Oral solution

- Displays linear PK with dosages of 50-800mg
- Saturation of absorption above 800mg/day
- ~7-10 days to achieve steady state concentrations
- Minimal differences between peak and trough levels
- Similar blood concentrations found in juveniles with comparable efficacy and safety
- Posaconazole has prolong half life (35 hours)

Courtney R et al. Antimicrob Agents Chemother 2003; 47: 2788
Krishna G et al. Antimicrob Agents Chemother 2007; 51: 812

Posaconazole: Absorption

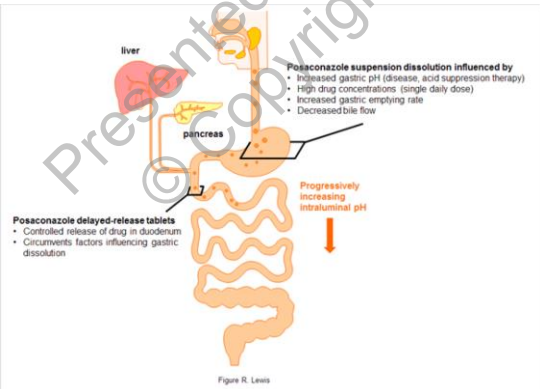


Figure 1. How a delayed-release tablet overcomes absorption barriers associated with posaconazole suspension. Image courtesy of Russell E. Lewis, PharmD.

Suspension

- Absorbed in duodenum/jejunum
- 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

Posaconazole Tablet

- Tablet formulation uses pH-sensitive polymers to release Posaconazole at a controlled rate in the duodenum
- Overcomes 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)
  - Co-administration 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
- Co-administration of the tablet with the pro-kinetic agent metoclopramide resulted in modest decreases in the C_{max} (14%) and AUC (7%) of the delayed-release tablet (Kraft 2014)

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

Posaconazole TDM & outcome

Two clinical trials evaluating Pos for prophylaxis against IFI
Study 1: pts with GVHD after hematopoietic SCT
Study 2: pts with neutropenia after chemotherapy for AML/MDS
Results: **Probability of breakthrough infection higher when Posaconazole trough splasma concentrations < 700 ng/mL**

Table 1 Posaconazole steady-state average plasma concentrations (C_{avg}) vs. clinical failure rate following administration of POS 200 mg t.i.d. in hematopoietic stem cell transplant recipients also receiving immunosuppressive therapy for graft-vs.-host disease (study 1) and in patients undergoing chemotherapy for acute leukemia or myelodysplastic syndromes (study 2)

	Study 1 ($N = 252$)[a]		Study 2 ($N = 215$)[a]	
Quartile	Posaconazole C_{avg} (ng/ml)[b]	Clinical failure rate	Posaconazole C_{avg} (ng/ml)[b]	Clinical failure rate
1st Q	21.5–557 (289)	44% (28/63[c])	89.65–322 (206)	55% (29/53)
2nd Q	557–915 (736)	21% (13/63)	322–490 (406)	37% (20/54)
3rd Q	915–1,563 (1,239)	18% (11/63)	490–733.5 (612)	46% (25/54)
4th Q	1,563–3,650 (2,607)	18% (11/63)	733.5–2,200 (1,467)	28% (15/54)

PK, pharmacokinetic; POS, posaconazole oral suspension; t.i.d., three times daily.
[a]PK data sets. [b]Range (midpoint value). [c]Number of patients with clinical failure/number of all patients in each quartile.

Cornely OA et al. NEJM. 2007; 356:348-359, Ullman AJ et al. NEJM. 2007; 356:335-347
Jang SH et al. Clin Pharmacol Ther. 2010;88:115-119

Isavuconazole PK/PD

- Oral and IV formulations
  - Highly water soluble ⟹ no cyclodextrin vehicle for IV (vs. voriconazole + posaconazole)
- Bioavailability: 98%, IV to oral interchangeable
- Linear kinetics
- Volume of distribution: 450L, > 99% protein bound
- Half-life: 100-130 hours
- Metabolism: liver, CYP3A4 + CYP3A5

MiceliM and C Kauffman. Isavuconazole: a new broad-spectrum triazoleantifungal agent. CID. 2015. 61:1558-65.
RybakJ, Marx K, et al. Pharmacotherapy. 2015. 35(11):1037-51.

5 Flucytosine

- Absorption: rapid, 80-90%
- Penetrates in to CNS, eye, and urine
- Excretion: Kidney (90%)
  - Reduced 5-FC clearance with renal dysfunction
- Narrow Therapeutic Index (30-80 mg/L)
- Drug concentration vs. toxicity
  - Concentration dependent toxicity (Peak >100 mg/L)
  - Blood dyscrasias, hepatic injury, or GI disturbances
  - Occurs with elevated levels for prolonged period (>2 weeks)

Lynman C.A., et al. Drugs. 1992.44:9-35. Bennett J.E., et al. NEJM,1979.301:126-31
Summers K., et al. JAC. 1997. 40:753-764, Hope WW, et al. AAC. 2006; 50: 3680-3688

Echinocandins

- In vitro studies: Concentration dependent killing with prolong PAFE
- In vivo; serum kinetic studies C_{max}/MIC predictive of efficacy and tissue kinetic study favors AUC/MIC
- Caspofungin: displayed linear pharmacokinetics
- Caspofungin exposure is lower in ICU patients;
  - Suggested dose of Caspofungin of 1 mg/kg bodyweight for critically ill patients

Van der Elst KC, et al. Low caspofungin exposure in patients in intensive care units. Antimicrob Agents Chemother. 2017;61:e01582–e01616

Amphotericin B deoxycholate

- Concentration dependent killing, C_{max}/MIC correlate best with Ampho antifungal activity
- Continuous infusion is better tolerated, less toxicity and less mortality compared to short infusion
- Antifungal activity is adequate with continuous infusion remains to be clarified

Eriksson U, Seifert B, Schaffner A. Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. BMJ. 2001;322:579–82.

Lipid Formulations of Amphotericin B

- Lipid formulations are not as potent as amphotericin B deoxycholate on mg/kg basis
- 3-5mg/kg dosage is required for treatment of most of the fungal infections
- Achieve low serum levels but tissue levels in lung, kidney , liver and brain are high

Summary

- Understanding of antifungal PK/PD parameters are important for dose optimization in various patient population, frequency of administration
- TDM for selected antifungal is required to improve clinical outcome and avoid drug toxicity
- Fluconazole has ideal PK parameters while newer agent Isavuconazole & Posaconazole tablet has also favorable PK

Q&A

Please use a microphone or submit a question card

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