

TRIAZOLE
THERAPEUTIC DRUG MONITORING:
TO MEASURE OR NOT TO MEASURE

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Speaker Disclosure

I HAVE NO CONFLICT RELATIONSHIPS
TO DISCLOSE

Session Objectives:

- Understand the pharmacokinetic and pharmacodynamic (PK/PD) properties of voriconazole and posaconazole as they relate to Therapeutic Drug Monitoring (TDM)
- Review the current evidence on potential role of TDM for both agents with respect to efficacy and toxicity
- Final recommendation for routine TDM in clinical settings

Clinical Case

MA 43 yo male (TBW = 104 kg)
– Day +14 post 2nd alloHCT for AML
– Day +5 Voriconazole 400mg po BID
– c/o of auditory and visual hallucinations

What would you do?

- a. Do nothing . . . this is a self limiting adverse reaction that will resolve
- b. Measure serum trough voriconazole level
- c. Reduce the dose empirically to 300mg po BID

Therapeutic Drug Monitoring: Clinical Relevance

- Pharmacokinetic consideration
 - Unpredictable drug dose-exposure relationship
- Pharmacodynamic consideration
 - Established relationship between drug concentration and either efficacy or toxicity

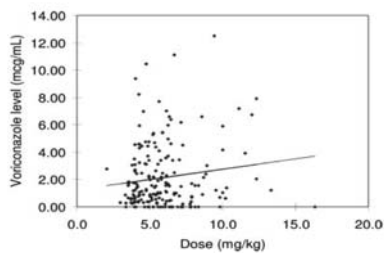
TDM clinical relevance: Voriconazole

- Pharmacokinetic consideration
 - Unpredictable drug dose-exposure relationship
 - Large pharmacokinetic variability
- Pharmacodynamic consideration

Unpredictable drug dose-exposure:

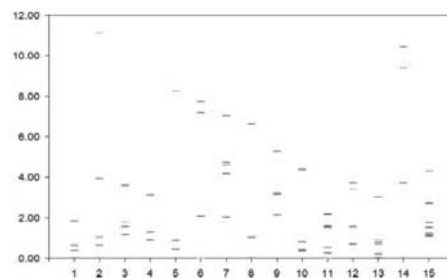
- Healthy individuals
 - Perkins et al. Antimicrob Agents Chemother 2002
- Pts with invasive fungal infections
 - Denning DW et al. CID 2002
 - Pascual A et al. CID 2008
 - Miyakis S et al. Clin Microbiol Infect 2009
- alloHSCt
 - Trifilio S et al. BMT 2005
 - Trifilio S et al. Cancer 2007
 - Bruggmann R et al. J Antimicrob Chemother 2010

Correlation between voriconazole dose and drug level ($r = 0.14$; $P = .051$)



Trifilio S, et al. Cancer 2007

Intra & Interpatient variability

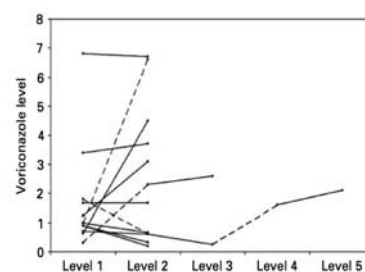


Trifilio S, et al. Cancer 2007

Why so much variability . . .

“Messy” kinetic profile!

Saturable metabolism & nonlinear kinetics



50% dosage increase can increase the level several folds.

Trifilio S, et al. BMT 2005

Genotypic Variation

- CYP 2C19 polymorphism
 - Homozygous extensive metabolizers
 - Heterozygous extensive metabolizers
 - Poor metabolizers (PM)
- Poor Metabolizers can have up to X4 Voriconazole exposure

Drug-Drug Interactions

- Both a substrate and an inhibitor of CYP 450 enzymes
- +++ drug interactions in LBMT patients
 - Cyclosporine/Tacrolimus
 - Chemotherapy agents
 - Omeprazole

TDM clinical relevance: Voriconazole

- Pharmacokinetic consideration
 - Unpredictable drug dose-exposure relationship
 - Saturable absorption
 - CYP2C19 polymorphism
 - Drug-drug interaction
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TDM clinical relevance: Voriconazole

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Exposure-Efficacy Evidence

	Design	Population	VORI daily dose	Exposure-Efficacy Relationship
Pascual et al. CID 2008	Prospective observational	N=52 60% heme/onc Trx of IFI	5-8mg/kg	<ul style="list-style-type: none"> • 50% trx failure when trough \leq 1 mg/L • 12% trx failure when trough $>$ 1 mg/L
Denning et al. CID 2002	Open label non-comparative	N=116 78% LBMT Trx of IFI	IV \rightarrow PO (200mg bid)	<ul style="list-style-type: none"> • 30% trx failure when random level $>$.5 mg/L • 80% trx failure when random level $<$.25 mg/L
Trifilio et al. BMT 2007	Retrospective observational	N=71 alloHSCCT Px of IFI	200mg po bid	<ul style="list-style-type: none"> • 14% break through IFI when trough $<$2mg/L • none if level $>$2mg/L
Miyakis et al. Clin Microbiol Infect 2009	Retrospective observational	N=25 SOT, BMT, HIV Trx of IFI	varied	<ul style="list-style-type: none"> • Initial SS trough [] the best predictor of survival • 100% mortality if trough \leq0.35 mg/L

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TDM clinical relevance: Voriconazole

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- Pharmacodynamic consideration
 - ☑ Exposure & efficacy
 - ☐ Exposure & toxicity

Exposure-Toxicity Relationship

- Photopsia
 - Most common
 - Concentration dependent
 - Transient; fully reversible
- Neurologic toxicity
- Hepatotoxicity

Exposure-Toxicity Evidence

Pascual	Neurotoxicity associated with level > 5.5 mg/L Hepatotoxicity associated with level > 5.5 mg/L
Trifilio	Neurotoxicity not assessed ↑AST & ALP with elevated level
Denning	Random level > 6mg/L - 27% developed abnormal LFTs
Imhof	Neurotoxicity: HR 2.27 per 0.1mg/L increase of Vori trough Hepatotoxicity: no correlation
Miyakis	Hepatotoxicity: no linear relationship
Zonios	Neurotoxicity associated with trough level > 5 mg/L

TDM clinical relevance: Voriconazole

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Voriconazole TDM Recommendation:

- Voriconazole satisfies both pharmacological preconditions for TDM
- Reasonable to target trough levels of 1-6 mg/L based on available data
- A method for dosage adjustment in response to a given concentration is not clear

Posaconazole

Much more favorable kinetic profile!

Posaconazole

- The newest extended spectrum triazole
- Structural analogue of itraconazole
- Favorable PK profile
 - Linear PK
 - Not metabolized through CYP450 enzymes
- However;
 - Saturable absorption
 - *** high fat meal ↑ absorption X4
 - Only available as oral formulation
- $T_{1/2} = 35\text{hrs}$; $V_d = 1774\text{L}$

TDM clinical relevance: Posaconazole

- Pharmacokinetic consideration
 - ☐ Unpredictable drug dose-exposure relationship
 - Exposure variability in cohorts of ill patients
 - Coefficient of variation up to 80% in BMT pts
- Pharmacodynamic consideration

TDM clinical relevance: Posaconazole

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Exposure-Efficacy/Toxicity Evidence

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Ullmann et al. NEJM 2007	RCT Phase III	IFI prophylaxis in HCT with GVHD	<ul style="list-style-type: none"> • pts with diarrhea and aGVHD had lower levels • No correlation bet level and ↑LFTs
Cornely et al. NEJM 2007	RCT Phase III	IFI prophylaxis in AML/MDS pts induction chemo	<ul style="list-style-type: none"> • pts with diarrhea and using a PPI had lower levels • No relationship bet trx failure and level; Cav = 0.32 • No correlation bet level and ↑LFTs
Walsh et al. CID 2007	Prospective open label	Salvage trx in pts with IFI refractory or intolerant	<ul style="list-style-type: none"> • Higher rate of response in pts with higher levels: • Cav = 0.13 24% response • Cav = 1.25 75% response

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Walsh et al. CID 2007	Prospective open label	Salvage trx in pts with IFI who were refractory or intolerant of conventional therapy	<ul style="list-style-type: none"> • Higher rate of response in pts with higher levels: • Cav = 0.13 mg/L → 24% response • Cav = 1.25 mg/L → 75% response

Interesting new data . . .

Conte et al. <i>Antimicrob Agents Chemother</i> 2009	<ul style="list-style-type: none"> • 25 healthy adults • Posaconazole level in <u>alveolar cells</u> were 40X higher than in plasma • levels remained above MIC 90 of <u>Aspergillus</u> (0.5 mg/L)
Farowski et al. Private files In Press 2010	<ul style="list-style-type: none"> • Pts receiving Posaconazole for IFI prophylaxis • Intracellular concentrations in <u>neutrophils</u> and <u>monocytes</u> were 22.5X & 7.7X higher than plasma

**TDM clinical relevance:
Posaconazole**

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**Posaconazole TDM
Recommendation:**

- Little evidence that posaconazole serum levels correlate with efficacy or toxicity
- Routine posaconazole TDM is Not Recommended
- Might consider TDM in cases of therapeutic failure to verify absorption or compliance