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

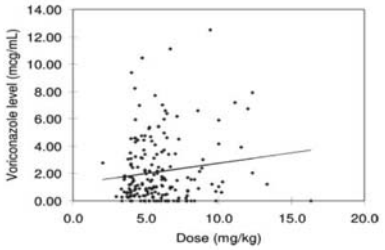
TDM clinical relevance: Voriconazole

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

Unpredictable drug dose-exposure:

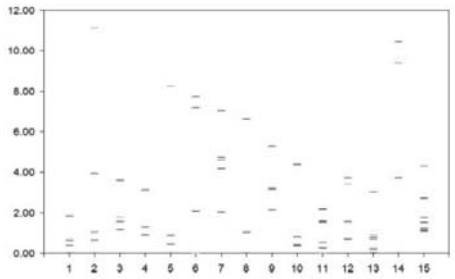
- Healthy individuals
  - Perkins et al. Antimicrob Agents Chemother 2002
- Pts with invasive fungal infections
  - Denning DW et al. CID 2002
  - Pascual A et al. CID 2008
  - Miyakis S et al. Clin Microbiol Infect 2009
- alloHSCT
  - Trifilio S et al. BMT 2005
  - Trifilio S et al. Cancer 2007
  -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

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



Trifilio S, et al. Cancer 2007

Intra & Interpatient variability

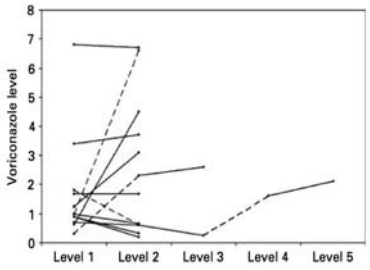


Trifilio S, et al. Cancer 2007

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
- Pharmacodynamic consideration
  - □ Established relationship between drug concentration and either efficacy or toxicity

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	• 50% trx failure when trough ≤ 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→PO (200mg bid)	• 30% trx failure when ransom level > .5 mg/L • 80% trx failure when random level < .25 mg/L
Trifilio et al. BMT 2007	Retrospective observational	N=71 alloHSCT Px of IFI	200mg po bid	• 14% break through IFI when trough <2mg/L • none if level >2mg/L
Miyakis et al. Clin Mirobiol Infect 2009	Retrospective observational	N=25 SOT, BMT, HIV Trx of IFI	varied	• Initial SS trough [ ] the best predictor of survival • 100% mortality if trough ≤0.35 mg/L

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Pascual et al. (CID 2008)
Prospective observational study
N=52 60% with hematological malignancy
Trx of IFI; Daily dose 5-8mg/kg
- 46% trx failure when trough ≤ 1 mg/L
- 12% trx failure when trough > 1 mg/L

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Miyakis et al. (Clin Mirobiol Infect 2009) Retrospective observational N=25 SOT, BMT, HIV Trx of IFI • Initial SS trough concentration was the best predictor of survival • 100% mortality if trough ≤0.35 mg/L • median [vori] >2.2 mg/L was the best predictor of response				
		Px of IFI		• none if level >2mg/L
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TDM clinical relevance: Voriconazole

- Pharmacokinetic consideration
  - ☑ Unpredictable drug dose-exposure relationship
- 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

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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
- T1/2 = 35hrs; Vd = 1774L

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

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Exposure-Efficacy/Toxicity Evidence

	Design	Population	Exposure-Efficacy/Toxicity Relationship
Ullmann et al. NEJM 2007	RCT Phase III	IFI prophylaxis in HCT with GVHD	• 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	• 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	• 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
Higher rate of response in pts with higher levels:
•Cav = 0.13 mg/L → 24% response
•Cav = 1.25mg/L → 75% response

Interesting new data . . .

Conte et al. *Antimicrob Agents Chemother* 2009	• 25 healthy adults • Posaconazole level in alveolar cells were 40X higher than in plasma • levels remained above MIC 90 of Aspergillus (0.5 mg/L)
Farowski et al. Private files In Press 2010	• Pts receiving Posaconazole for IFI prophylaxis • Intracellular concentrations in neutrophils and monocytes 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