Is there a need for drug monitoring of antifungals?

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What is Therapeutic Drug Monitoring (TDM) ?

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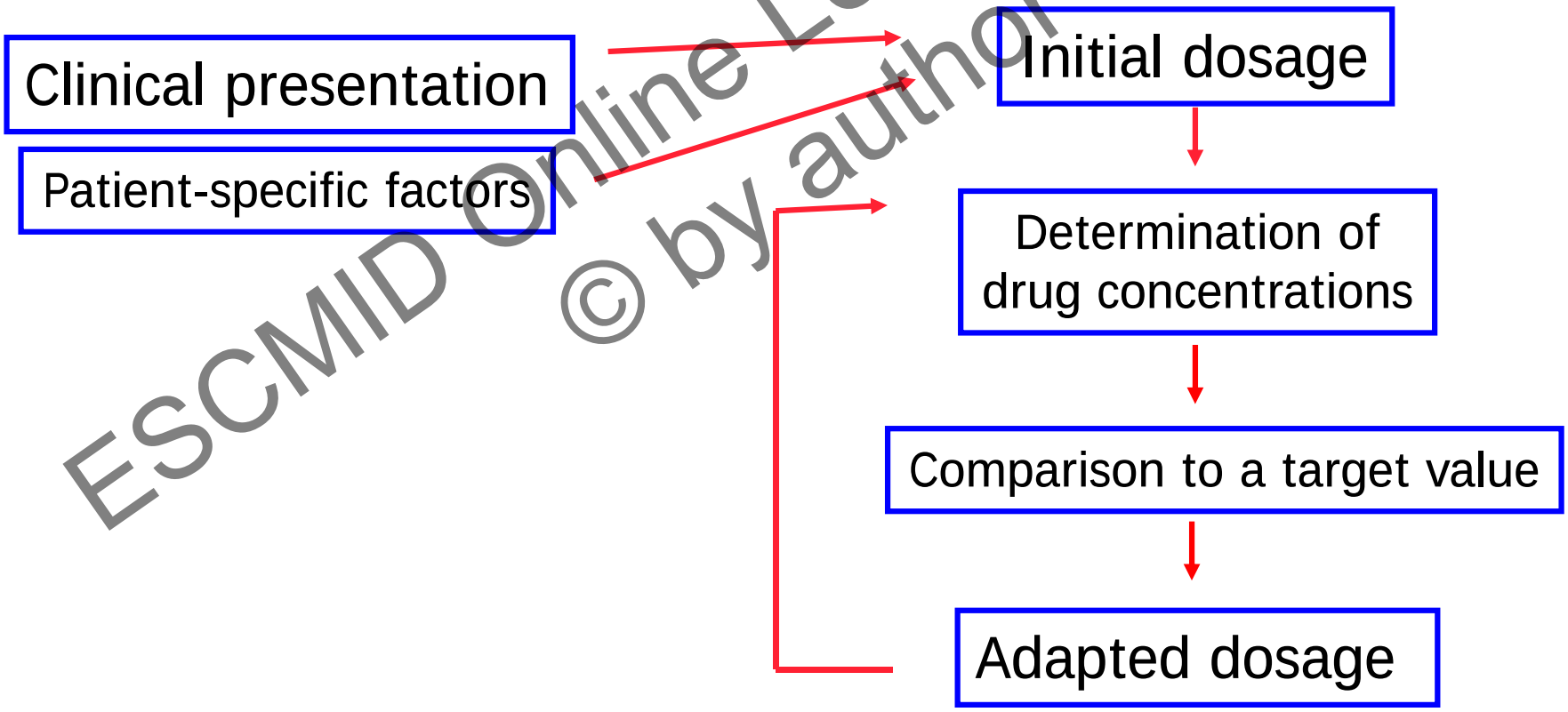
Computation **of individual dosing recomme**
based on drug concentrations in body fluids



When makes TDM sense ?

- if there is no readily available parameter of efficacy
- in drugs with high pharmacokinetic variability
- in drugs with small therapeutic window
- in populations at risk for increased toxicity

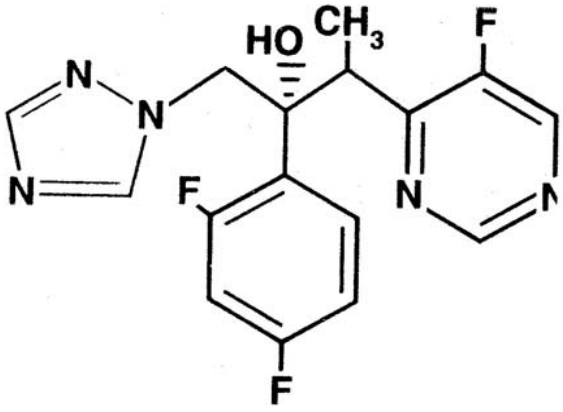
- *established concentration/effect relationships*
- *established PK/PD target parameter / surrogate*

- validated, robust and rapid analytical method

Antifungal Triazoles:

Voriconazole

Voriconazole



- ***Non-linear pharmacokinetics***
- ***Complex hepatic metabolization***
  - **Substrate/inhibitor of CYP2C9, 3A4, 2C19**
  - ***Genetic polymorphisms of CYP2C19***
- ***Number of relevant pharmacokinetic interactions***
- ***Toxicity issues***

Voriconazole: Variant CYP2C19 Alleles

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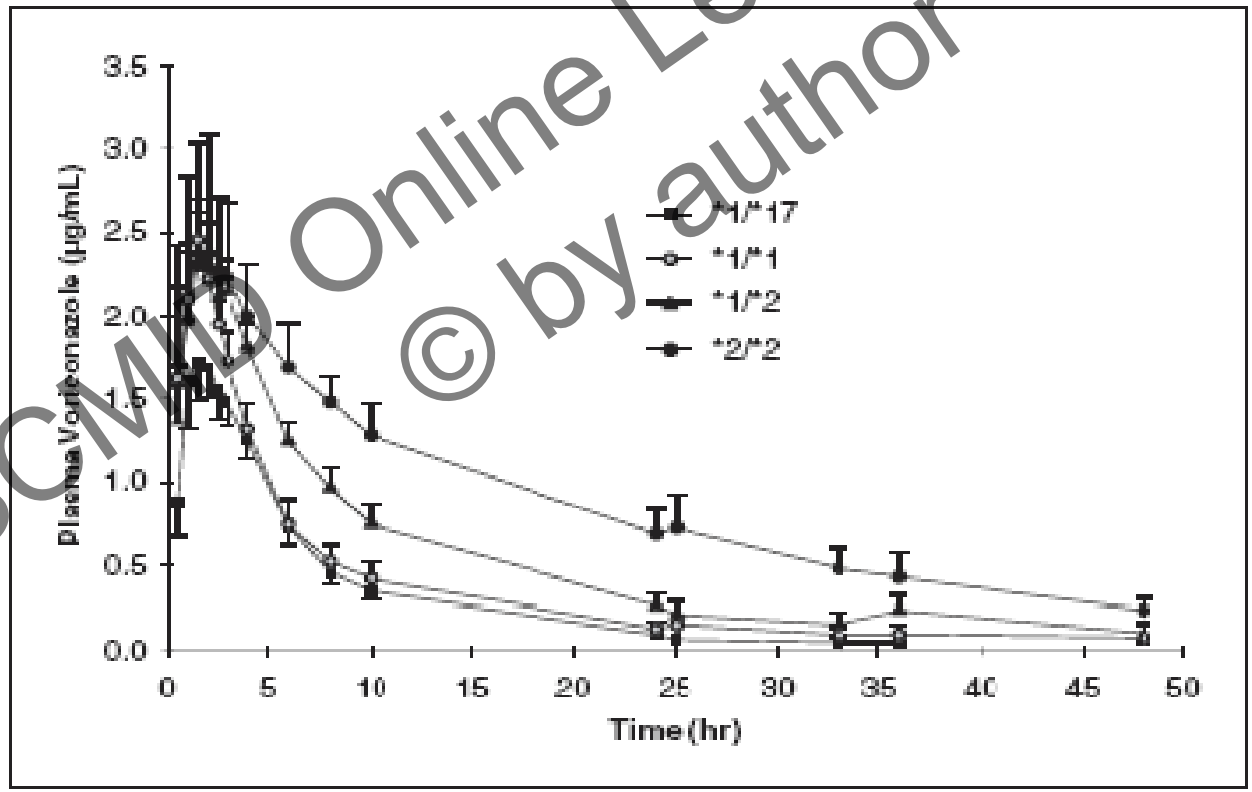
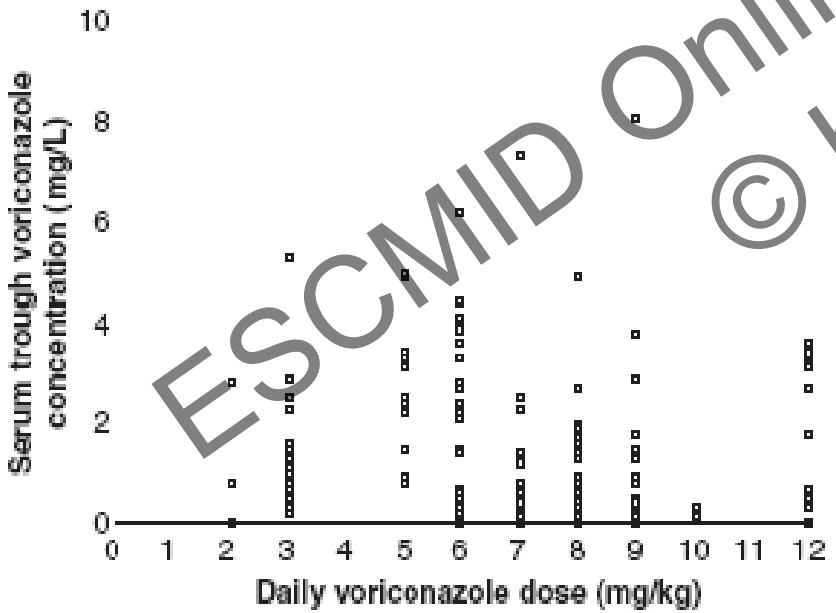
Number of variant CYP2C19 alleles explains substantial part of the wide variability voriconazole pharmacokinetics

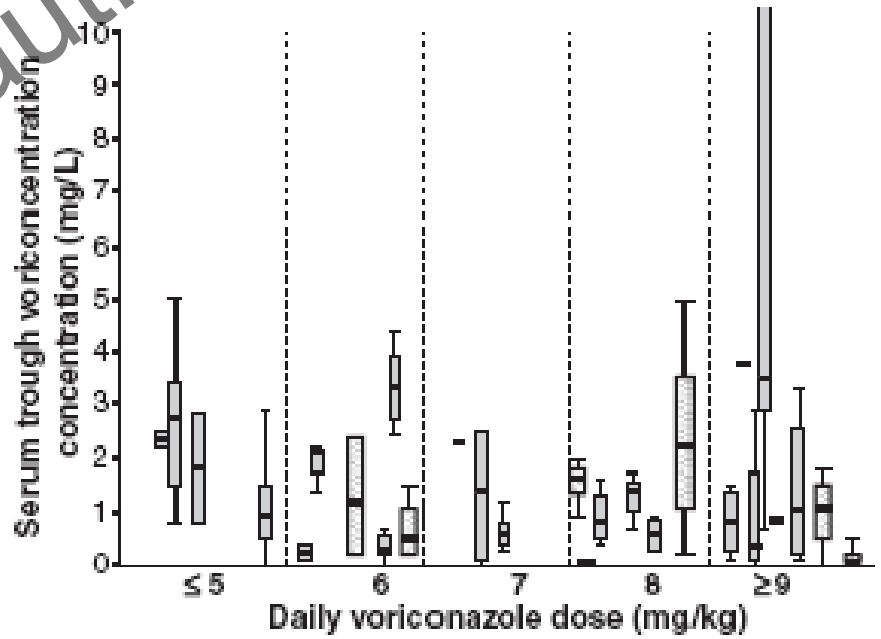


Weiss et al. JCP 2009

VCZ – Relationship of Dose and Exposure

- ***Lack of correlation between dose and trough level***
- ***Large interpatient and intrapatient variability***





Miyakis et al. CMI 2009

VCZ – Relationship of Route and Exposure

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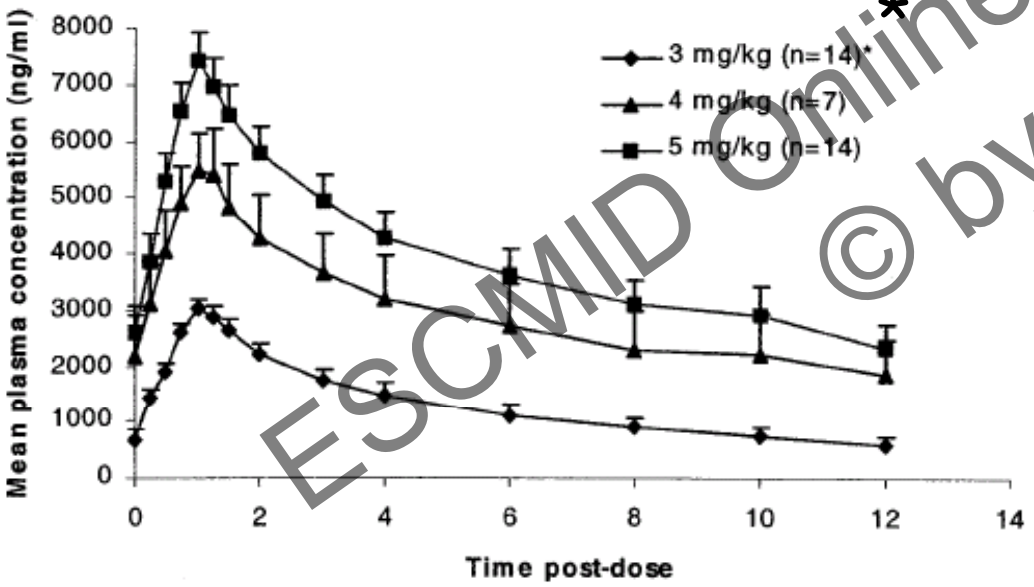
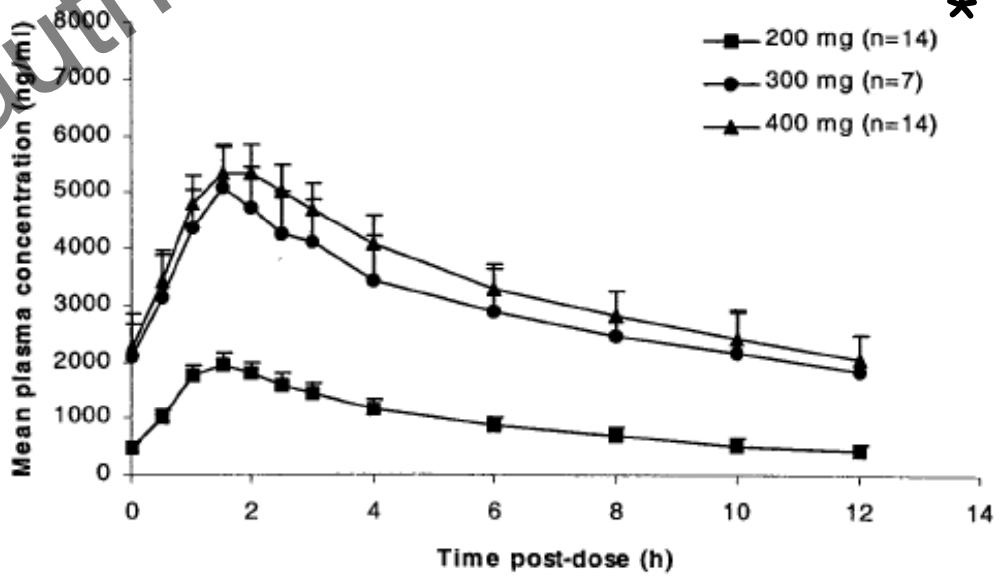
IV administration:



PO administration:



*following BID dosing; d 7 and 14, resp.

Purkins et al. 02

VCZ - Relationship of Dose and Exposure

- ***Considerable % of subjects with undetectable levels***

Voriconazole Levels by Absolute Daily Voriconazole Dose

Daily Total Dose, mg	No.	Voriconazole level, median (range)	Undetectable	<0.5 µg/mL	<2.0 µg/mL
200	4	2.16 (0–3.07)	1 (25%)	1 (25%)	2 (50%)
400	151	1.09 (0–11.11)*	22 (15%)	43 (28%)	97 (64%)
500	20	1.67 (0–5.99)	2 (10%)	4 (20%)	11 (55%)
600	18	1.57 (0–6.75)	3 (17%)	4 (22%)	11 (61%)
800	8	1.65 (0–12.50)*	2 (25%)	3 (38%)	4 (50%)
Overall	201	1.22 (0–12.50)	30 (15%)	55 (27%)	125 (62%)
P			.84	.86	.83

s/s trough levels (201 samples in 87 pts receiving mostly PO VCZ)

Trifilio et al. Cancer 07

TDM for Voriconazole: Early Clinical Descriptions

- **While the SPC states the absence of a concentration-effect relationship, one prospective and several retrospective studies with small sample sizes suggest a relationship between VCZ measurements and outcomes:**
- ***Mean random plasma concentrations of <250 ng/mL appeared to correlate with treatment failure in phase II trial of invasive aspergillosis (IA)*** [1]
- ***Random plasma concentrations >2000 ng/mL were associated with favorable responses, and concentrations <2000 ng/mL with progression in 28 pts who underwent monitoring for disease progression or drug toxicity*** [2]

[1] Denning et al. 02; [2] Smith et al.06

VCZ TDM – Correlation with Outcome in Patients with IFIs

- **Prospective analaysis of utility of measuring VCZ trough blood levels with individualized dose adjustments in a total of 181 measurements during 2388 tx days in 52 pts**
- **Dose adjustments:**
  - **50% increase in daily dose in patients with trough levels <1 mg/L and lack of response to therapy**
  - **discontinuation of therapy in patients with trough levels > 5.5 mg/L plus/minus adverse events probably related to overdosing**
- **Mixed bag of indications**
  - ***50% IA, 15% IC, 4% rare moulds; remainder: possible IFI / ET***
- **Various routes / sequences of administration**

Pascual et al. CID 2008

VCZ TDM – Correlation with Outcome in Patients with IFIs

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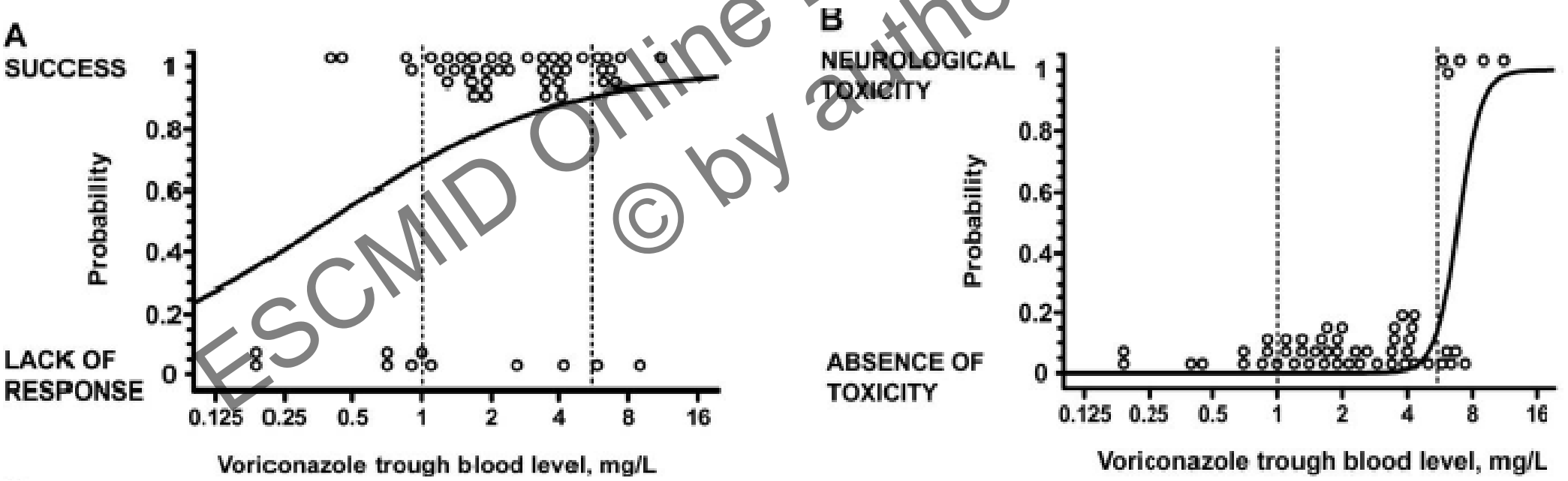
- *trough levels ≤1mg/L associated with treatment failure*
- *trough levels ≥5.5 mg/L assoc. with neurological toxicity*



- *Blood levels >1 mg/L reached after increasing the dosage with complete resolution of infection in all 6 cases*

Pascual et al. CID 2008

VCZ TDM – Correlation with Outcome in Patients with IFIs

- Retrospective analysis of 147 voriconazole TDM in 25 patients with proven/probable IFIs and ≥2 VCZ drug concentrations

- Mostly (48%) SOT-patients, mostly (60%) mould infection
- Various reasons for TDM, efficacy > toxicity > interactions

- Methods: Classification and Regression Tree (CART-) analysis
  - Initial VCZ trough at steady state
  - Median VCZ trough for each pt

- Endpoints: Association to IFI-related mortality, microbiological and/or clinical success

Miyakis et al. CMI 2009

VCZ TDM – Correlation with Outcome in Patients with IFIs

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- ***Initial trough level at s/s of < 0.35 ug/mL predictive of mortality***
- ***Median trough level at s/s of >2.2 ug/mL predictive of treatment success***

Voriconazole concentration	Mortality due to or with invasive fungal infection: Death	Survival	Microbiological and/or clinical success: Failure	Success
Initial trough concentration[a]				
<0.35 mg/L	3	0	3	0
>0.35 mg/L	2	20	7	15
OR and 95% CI	11 (2.9–41.2)[b]		3.1 (1.7–5.8)[b]	
Median trough concentration[a]				
<2.2 mg/L	5	11	10	6
>2.2 mg/L	0	9	0	9
OR and 95% CI	1.5 (1.1–2.0)[c]		2.7 (1.4–5.0)[c]	

[a]Initial and median concentration cut-offs were determined by classification and regression tree analysis.

Miyakis et al. CMI 2009

VCZ PK and PD in Pediatric Patients

- **Pharmacokinetics and pharmacodynamics based on 108 VCZ measurements in 40 pts with ≥1 sample and variable indications for VCZ**
- **2-compartment Michaelis-Menton PK model fit the data best but explained only 80% of the observed variability**
- *Crude mortality rate was 28% and* ***each trough serum level of VCZ <1000 ng/mL was associated with a 2.6 fold increased odds of death*** *(95% CI, 1.6-4.8, p=0.002) in Cx proportional hazards model*
- **Simulations predicted an IV dose of 7mg/kg or an oral dose of 200 mg BID to achieve a trough >1000 ng/mL in most pts**

Neely et al. CID 2010

TDM for Voriconazole: Correlation with Toxicity

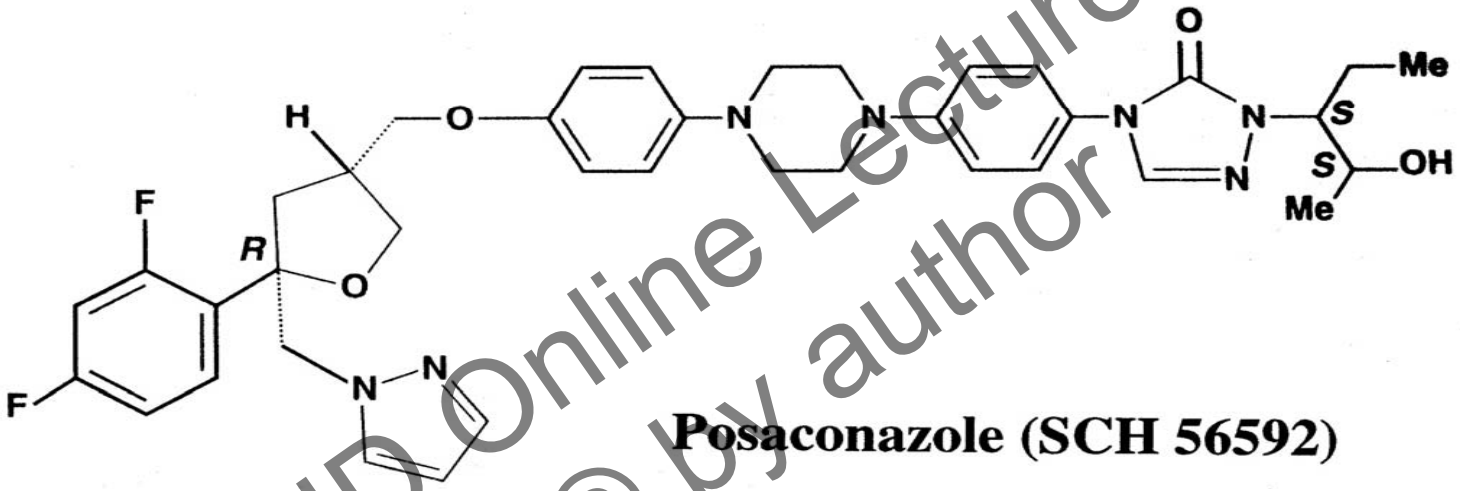
- Analysis of ~3000 samples of ~1000 pts. enrolled on clinical trials of the manufacturer revealed relationship between random VCZ concentrations and visual disturbances and AST, AlkPhos, and bilirubin abnormalities [1]
- Random concentrations >6000 ng/mL appeared to be associated with AEs in phase II trial of IA [2]
- Correlation of high trough concentrations >5500 ng/mL also made with neurological AEs [3]
- Patients with neurological (including visual disturbances) [4] or severe AEs [5] had higher trough concentrations than patients without these AEs

[1] Lutsar et al. 03, Tan et al. 06; [2] Denning et al. 02; [3] Pascual et al. 09 [4] Imhof et al. 06 [5] Miyakis et al. 09

Antifungal Triazoles:

Posaconazole

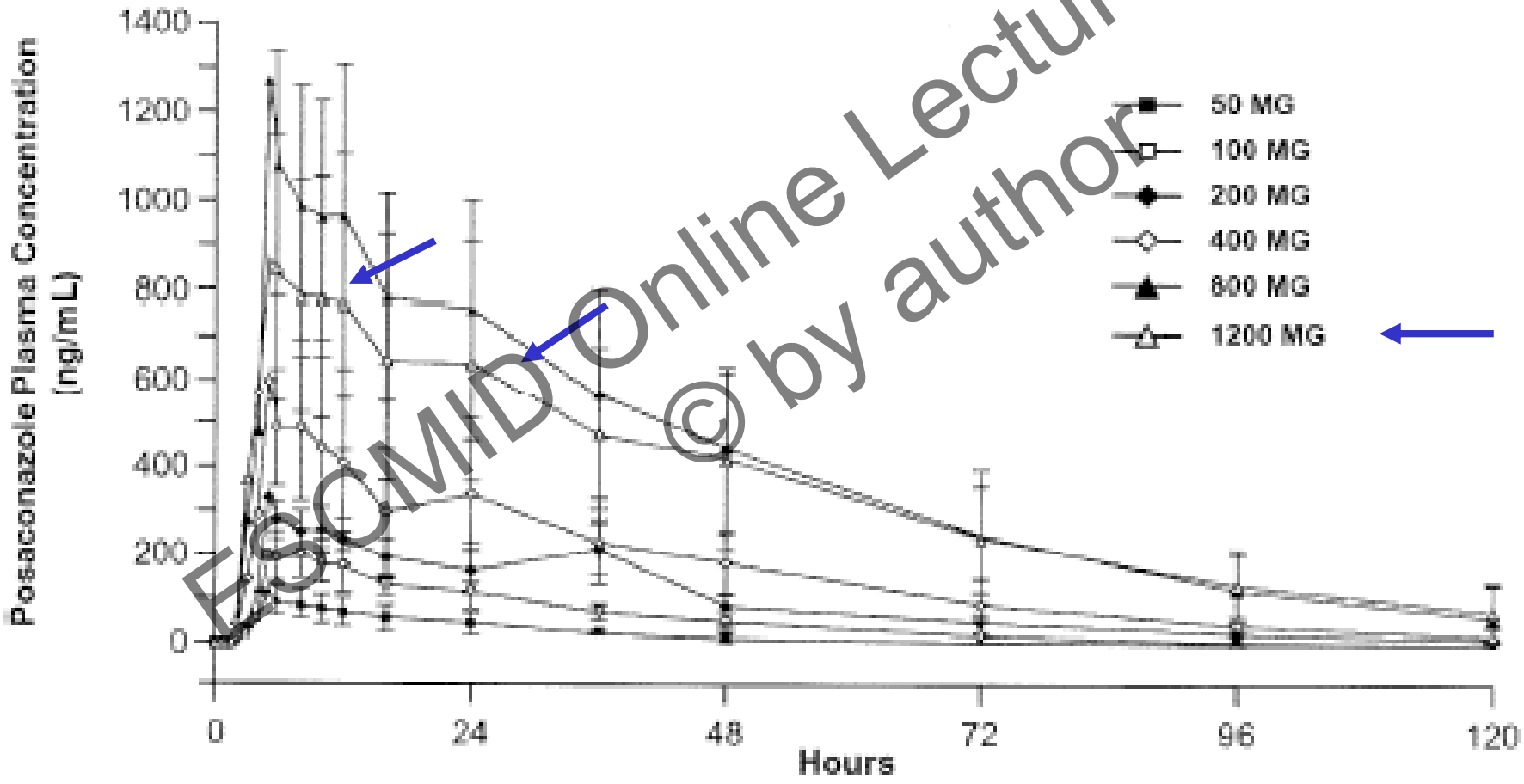
Posaconazole



Posaconazole (SCH 56592)

- *linear pharmacokinetics up to 800 mg*
  no CYP-mediated hepatic metabolization
  inhibitor, but no substrate of CYP 3A4
- *No toxicity issues, but issues with absorption*

Dose-Linearity in Volunteers



Courtney et al. 03

Posaconazole: Inter-Patient Variability

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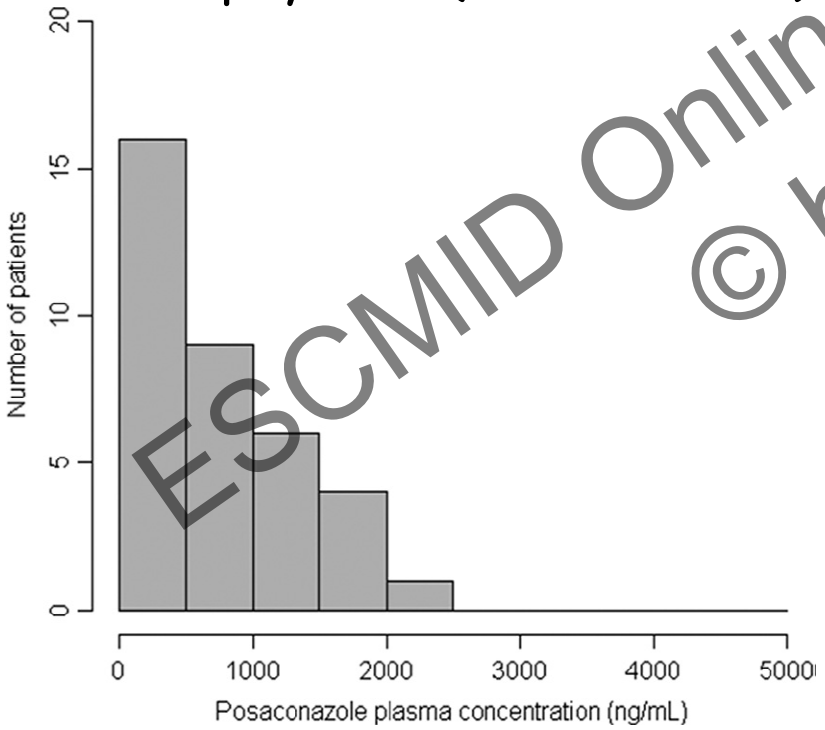
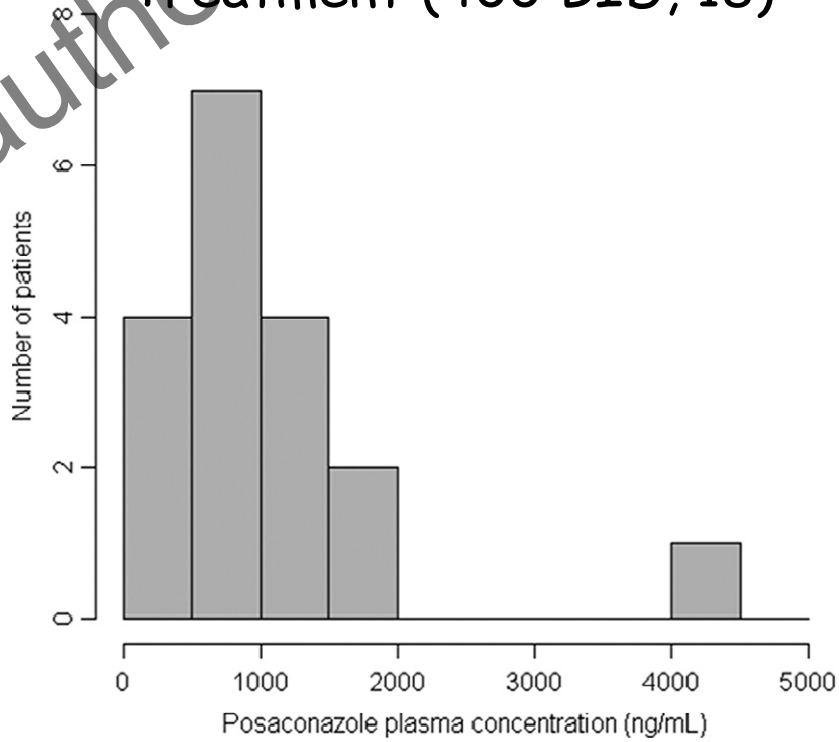
Plasma concentrations at 1st measurement:

Prophylaxis (200 TID, 36)



Treatment (400 BID, 18)



Lebeaux et al. 09

TDM for Posaconazole: Clinical Trial Data

- ***Is TDM indicated to guide PCZ prophylaxis?***
  - **Food, gastric pH, gastric motility and mucosal disease (mucositis, diarrhea) affect absorption and explain interindividual PK variability**

➡ **No significant relationship between exposure and preventative efficacy in large prophylaxis studies**

➡ **MIC90 values of Aspergillus spp and limited clinical data suggest a dosing target of ≥500 ng/mL; the FDA recommends a dosing target of ≥ 700 ng/mL**

Ullmann 06; Gubbins 06; Ullmann 07; Krishna 07; Cornely 07; Krishna 09; Lebeaux 09

TDM for Posaconazole: Clinical Trial Data

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- ***Is TDM indicated to guide PCZ treatment?***

➡ **apparent correlation of exposure and efficacy in the invasive aspergillosis salvage study**

➡ **A mean average plasma concentration of 1250 ng/mL associated with higher success**

Quartile	No. of subjects[a]	Plasma C_{max} Mean ng/mL	Plasma C_{max} CV, %	Plasma C_{avg} Mean ng/mL	Plasma C_{avg} CV, %	No. (%) of responders
1	17	142	51	134	45	4 (24)
2	17	467	27	411	21	9 (53)
3	17	852	15	719	12	9 (53)
4	16	1480	16	1250	28	12 (75)

NOTE. C_{avg}, average plasma concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation.

[a] Data were available for 67 patients with available plasma concentrations of posaconazole.

Thus far, no exposure/toxicity relationship

Walsh et al. 07

TDM for Posaconazole: Clinical data (1)

- **Retrospective single center review of all PCZ levels measured between 4/06 and 7/08 after ≥5 days of treatment**

  - **44% and 22% PCZ <500 ng/mL in prophylaxis (200 BID; n=36) and treatment (400 BID, n=18) arm**
  - **Low PCZ concentrations associated with digestive disease, diarrhea and mucositis**
  - **The only two breakthrough infections in the prophylaxis arm were associated with concentrations < 500 ng/mL**

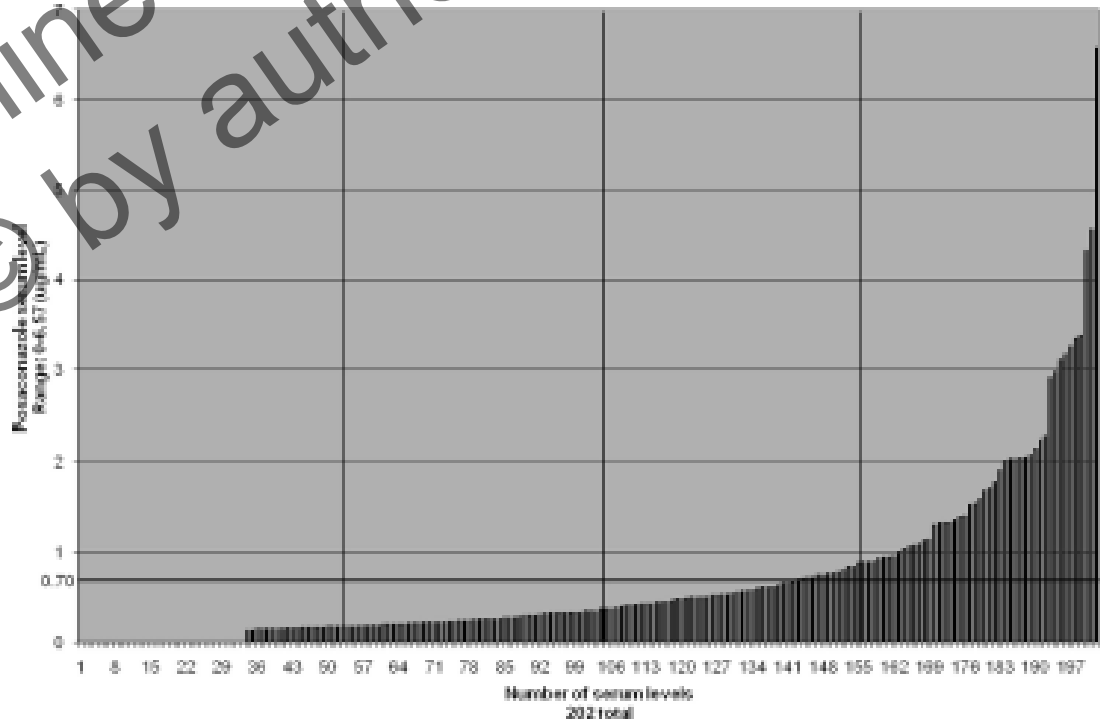
Lebeaux et al. 09

TDM for Posaconazole: Clinical data (2)

- **Retrospective review of all PCZ concentrations measured between 12/07 and 12/08 by a reference laboratory**

  - **No information on dose, timing of the sample, and indication**

    - **60% <500**
    - **70% <700**
    - **80% <1000 ng/mL**



Thompson et al. 09

Conclusions and Open Issues

Conclusions and Open Issues

- Despite considerable progress, there is ample room for improvement in management of IFIs; the pharmacology of VCZ and oral PCZ makes them candidates for TDM
- Evidence suggestive, but no proof of concept
- Issues that need to be resolved before implementation
  - therapeutic range (dosing target)
  - optimum sampling schedule
  - turnaround time of results
  - Models/ algorithms for dose modifications
  - Situations at which to consider alternative agents
- larger scale effort appears warranted to systematically investigate drug monitoring of triazoles