Pediatric Voriconazole Therapeutic Drug Monitoring:
Little People, Big Controversy

Tasha Ramsey BSc (Pharm), ACPR
PharmD Student
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Pediatric Fungal Infections

- An increasingly recognized complication of:
  - Organ transplantation
  - Childhood malignancies
  - Neonatal medicine
  - Pediatric surgery
- In-hospital mortality of immunocompromised children with invasive aspergillosis ~ 18%

Steinbach WJ, Walsh TJ. Mycoses in Pediatric Patients. Infect Dis Clin North Am. 2006 Sep;20(3):663-78.

Voriconazole

- Use is increasing because:
  - Effective against Candida and Aspergillus species
  - Favorable side effect profile and cost

Voriconazole TDM

- Pediatric patients respond differently to voriconcazole than adults
- Non-linear kinetics at doses above 7 mg/kg
- 2–11 years of age have a higher capacity for elimination per kg of body weight

Walsh et al. Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. Antimicrob Agents Chemother 2004; 48: 2166–72.

Voriconazole TDM

- Generally accepted trough range: 1-6 mg/L
  - Studies have shown failure under 2 mg/L
  - Studies have associated toxicity with troughs >5.5 mg/L
- Trough should be drawn 30 minutes prior to dosing at steady state (5-7 days after initiation of therapy)

Variables Influencing Concentrations

- Food interactions
- Drug interactions
  - Substrate and inhibitor of CYP 2C9, 2C19, and 3A4
- Genetic cytochrome P450 polymorphisms
- Self-induced metabolism
- Hepatic insufficiency
- Critical illness

Voriconazole TDM

- High inter- and intra-individual variability
  - May be associated with decreased efficacy or increased toxicity, indicating a **possible** need for therapeutic drug monitoring

Chen et al. 2012

- "Compelling evidence exists to support TDM of voriconazole in children because it can be readily measured in the desired biological matrix, its pharmacologic response is not always readily assessable**, a clear relationship exists between drug concentration and drug response**, its pharmacokinetic parameters can be unpredictable due to the presence of confounding factors, the duration of drug therapy is of a sufficient length for children to benefit from TDM, and in certain situations, the results of a voriconazole assay may provide more information than sound clinical judgment alone"
- "Thus, at this time, the routine use of TDM is recommended as a tool to individualize voriconazole doses in children"

Chen J, Chan C, Colantonio D, and Seto W. Therapeutic Drug Monitoring of Voriconazole in Children. Ther Drug Monit 2012;34:77–84

Clinical Question

P	Pediatric patients receiving voriconazole	
I	Therapeutic drug monitoring (trough 1-6 mg/L)	
C	No therapeutic drug monitoring or an alternate therapeutic range	

O	Efficacy:
	• Infection prevention
	• Infection resolution
	• Mortality reduction
		Safety:
		• Dermatological
		  • Photosensitivity/rash
		• Gastrointestinal
		  • Hepatic impairment/nausea/vomiting
		• Neurologic
		  • Irritability/dizziness
		• Renal impairment
		• Visual
		  • Hallucinations
		• Discontinuation due to AE

Search Strategy

Databases	Cochrane, Google, Google Scholar, Embase, Medline, PubMed, IPA
Search Strategy	Voriconazole, pediatrics OR children, therapeutic drug monitoring OR pharmacokinetics
Limits	English, humans, clinical trials
Results	1 Prospective 7 Retrospective 1 prospective and 2 largest retrospective included

Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: a prospective study

Pere Soler-Palacín[1]*, Marie Antoinette Frick[1], Andrea Martín-Nalda[1], Miguel Lanaspa[1], Leonor Pou[2], Eva Rosellló[3], Cristina Diaz de Heredia[4] and Concepció Figueras[1]

*[1]Paediatric Infectious Diseases and Immunodeficiencies Unit, Vall d'Hebron University Hospital, Barcelona, Spain; [2]Biochemistry Department, Vall d'Hebron University Hospital, Barcelona, Spain; [3]Microbiology Department, Vall d'Hebron University Hospital, Barcelona, Spain; *[4]Paediatric Oncology and Haematology Department, Vall d'Hebron University Hospital, Barcelona, Spain*

J Antimicrob Chemother 2012; **67**: 700–706

Soler-Palacin et al. 2012

Design	Prospective, SC, observational
P	Immunocompromised, age: 1m- 17y, **53% PO, 63% proven/probable** and 37% had possible invasive fungal infection (IFI) (n=**30**)
I	Therapeutic trough= 1 – 5.5 mg/L 30 min prior to the next dose on the fifth day of therapy and q weekly Efficacy: trough >1 mg/L Safety: trough <5.5 mg/L
C	Efficacy: trough <1 mg/L Safety: trough >5.5 mg/L
O	Efficacy: • Early and late response • Mortality Safety: • Photosensitivity and skin reaction, >10-fold GGT increase, GI intolerance, irritability/dizziness, visual hallucinations

Soler-Palacın et al. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: a prospective study. J Antimicrob Chemother 2012; 67: 700–706

Total
n= 30

Proven/Probable IFI
n=19 (63%)

↓

Efficacy analysis

Early response (4-6 weeks)
n=15

↓

Late response (12 weeks)
n=13

Proven/Probable/Possible IFI
n=30 (100%)

↓

Safety analysis

Proven= sterile site culture + histology

Probable= host factor, clinical features, and mycological evidence

Possible= clinical evidence

Soler-Palacın et al. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: a prospective study. J Antimicrob Chemother 2012; 67: 700–706

Assay Characteristics

- HPLC
- Specificity: ✖
- Sensitivity: ✔
  - Limit of quantification: 0.2 mg/L
- Linearity: ✖
- Precision: ✔
  - 20%
- Accuracy: ✔
  - 20%

✖= not described
✔= described

Soler-Palacın et al. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: a prospective study. J Antimicrob Chemother 2012; 67: 700–706

Results

- **196** voriconazole plasma trough measurements from **30** patients
- Dose: Median **20mg/kg/day** (range 3.5- 52)
- Duration: Median **6 weeks** (range 1–84)
- 50% of the troughs obtained were (<1 mg/L) and 7% were (> 5.5 mg/L)
- 78% of proven/probable IFI patients were on combination antifungal therapy
- DI: 90% of patients on omeprazole, and one patient on carbamazepine

Soler-Palacın et al. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: a prospective study. J Antimicrob Chemother 2012; 67: 700–706

Response

			Trough plasma levels		
Proven/Probable IFI Response	Cases n (%)	Samples n	<1 (mg/L), n (%)	≥ 1(mg/L), n (%)	P
Early (4-6 w)					
Favorable	9/15 (60)	42	16/42 (38)	26/42 (62)	**0.0268**
Unfavorable	6/15 (40)	26	17/26 (65)	9/26 (35)	
Late (12 w)					
Favorable	7/13 (54)	51	24/51 (47)	27/51 (53)	0.2015
Unfavorable	6/13 (46)	52	31/52 (60)	21/52 (40)	
Survival					
Survived	11/19 (58)	120	55/120 (46)	65/120 (54)	0.3258
Died	8/19 (42)	46	25/46 (54)	21/46 (46)	

Soler-Palacın et al. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: a prospective study. J Antimicrob Chemother 2012; 67: 700–706

Adverse Effects

		Trough plasma levels mg/L			P value
	Total	< 1	1–5.5	> 5.5	<5.5 vs > 5.5
Dermatological					
Photosensitivity and skin reaction	2			2	**0.0001**
Rash	-	-	-	-	
Gastrointestinal					
Hepatic impairment (>10-fold GGT increase)	6	2	2	2	NSS
Nausea/vomiting (GI intolerance)	1			1	NSS
Neurologic					
Irritability/dizziness	1			1	**0.0001**
Renal impairment	-	-	-	-	
Visual					
Hallucinations	2			2	NSS
Discontinuation due to AE	-	-	-	-	

Soler-Palacın et al. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: a prospective study. J Antimicrob Chemother 2012; 67: 700–706

Conclusions

- "Although no clear relationship has been demonstrated between plasma trough levels and efficacy, our study allowed us to recommend the routine use of plasma voriconazole monitoring in pediatrics in its therapeutic indication since weekly TDM may prevent toxic plasma levels"

Soler-Palacın et al. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: a prospective study. J Antimicrob Chemother 2012; 67: 700–706

Limitations

- Observational study
- Not R, DB
- Assay: accuracy: 20%, specificity and linearity not described
- CYP2C19 polymorphism not assessed
- Combination antifungal therapy used in majority of patients
- Excluded death in efficacy analysis
- DI: 90% of patients on omeprazole, and one patient on carbamazepine
- Food interactions not described
- Do not specify number of children by age

Voriconazole Pharmacokinetics and Pharmacodynamics in Children

Michael Neely,[1,2,3] Teresa Rushing,[2] Andrea Kovacs,[1] Roger Jelliffe,[2] and Jill Hoffman[1,3]

[1]Division of Pediatric Infectious Diseases and [2]Laboratory of Applied Pharmacokinetics, Keck School of Medicine, University of Southern California, and [3]Childrens Hospital Los Angeles, Los Angeles, California

Pediatric Voriconazole PK/PD • **CID 2010:50 (1 January)** • 27

Neely et al. 2010

Design	Retrospective, SC, observational
Patients	Age: 0.8–20.5 y, **90% PO**, 26% proven, 15% probable, and **59% possible** IFI (n=46)
Objective	Analyze the association between voriconazole trough concentrations and • Efficacy: Mortality • Safety: Hepatic impairment • 1.5-5 fold increase in ALT and/or ALP

Neely et al. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin. Infect. Dis. 2010; 50:27–36

Assay Characteristics

- HPLC
- Specificity: ✔
  - No cross reactivity with 14 antimicrobial agents
- Sensitivity: ✔
  - Limit of quantification: 0.2 mg/L
- Linearity: ✔
  - Linear through ~0.2–30 mg/L
- Precision: ✔
  - <5%
- Accuracy: ✖

✖= not described
✔= described

Neely et al. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin. Infect. Dis. 2010; 50:27–36

Results

- **207 concentrations** measured from **46 patients**
- Dose:
  - PO: 2.0 to 12.9 mg/kg
  - IV: 3.4 to 10.5 mg/kg
- Troughs:
  - 99 obtained without a verified preceding dose time
  - 108 had a median sampling time of 9.0 h (range: 1.3–36.0 h) after the preceding dose

Response

Response	Number of cases (n=46)
Survival	
Died	13 (28)
Survived	33 (72)

Mortality:
Each trough <1 mg/L was associated with:
A 2.6-fold increased odds of death (95% CI: 1.6–4.8; p=0 .002)

Neely et al. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin. Infect. Dis. 2010; 50:27–36

Adverse Effects

	Total n=28, n(%)
Gastrointestinal	
Hepatic impairment	16 (57)
ALT	10 (36)
ALP	2 (7)
ALT and ALP	4 (14)

By Cox proportional hazards analysis, the risk of hepatotoxicity was not significantly associated with concentration

Neely et al. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin. Infect. Dis. 2010; 50:27–36

Conclusions

- "We found a pharmacodynamic association between a voriconazole trough <1 mg/L and survival and marked pharmacokinetic variability, particularly after enteral dosing, justifying the measurement of serum concentrations"

Neely et al. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin. Infect. Dis. 2010; 50:27–36

Limitations

- Not R, DB
- No comparison trough range
- Retrospective
- Observational
- Assay accuracy not described
- CYP 2C19 genotype not specified
- Food interactions not addressed
- Dose modifications for sub or supra therapeutic levels not provided
- Adherence for outpatients
- 99 (48%) were obtained after outpatient dosing with no verified preceding dose time
- Of those with a verified preceding dose time, trough was drawn at a median of 9h (range: 1.3–36.0 h) post dose

Monitoring of voriconazole plasma concentrations in immunocompromised paediatric patients

Stephanie Pieper[1], Hedwig Kolve[2], Hans G. Gumbinger[3], Grazyna Goletz[1], Gudrun Würthwein[4] and Andreas H. Groll[1]*

[1]Infectious Disease Research Program, Centre for Bone Marrow Transplantation and Department of Pediatric Hematology/Oncology, University Children's Hospital Münster, Münster, Federal Republic of Germany; [2]Central Pharmacy Department, University Hospital Münster, Münster, Federal Republic of Germany; [3]Institute for Pharmacology and Toxicology, University Hospital Münster, Münster, Federal Republic of Germany; [4]Coordinating Centre for Clinical Trials (KKS), University Hospital Münster, Münster, Federal Republic of Germany

J Antimicrob Chemother 2012; **67**: 2717–2724
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Pieper et al. 2012

Design	Retrospective, SC, cohort
Patients	Immunocompromised, age: 0.2–18 y, **81% PO**, **78%** using voriconazole for IFI **prophylaxis**, 13% for probable/proven IFI, 7% for possible IFI, and 2% for empiric therapy (**n=74**)
Objective	To explore trough concentrations and their association with : Efficacy: • Success • Failure Safety: • Laboratory and clinical AE • Discontinuation due to to AE

Pieper et al. Monitoring of voriconazole plasma concentrations in immunocompromised paediatric patients. J. Antimicrob. Chemother.2012; 67:2717– 2724.

Assay Characteristics

- HPLC
- Specificity: ✖
- Sensitivity: ✔
  - Limit of quantification: 0.2 mg/L
- Linearity: ✖
- Precision: ✔
  - Intra- and inter-day variability: 10%
- Accuracy:✔
  - 10%

✖= not described
✔= described

Pieper et al. Monitoring of voriconazole plasma concentrations in immunocompromised paediatric patients. J. Antimicrob. Chemother.2012; 67:2717– 2724.

Results

- **251 samples** were obtained from **101 treatment courses** in **74 patients**
- **Median** maintenance **dosage**: **4.8 mg/kg q 12h** (range 2.2–17.4)
- **Duration:** Median of **40 days** (range 6–1002)
- Trough: 12 hour post dose at steady state (12h post LD or day 6 of maintenance therapy)
- 58% had voriconazole concentrations ≤1.0 mg/L
- Voriconazole was combined with other systemic antifungal agents in 6 of 20 courses for therapy of fungal infections

Pieper et al. Monitoring of voriconazole plasma concentrations in immunocompromised paediatric patients. J. Antimicrob. Chemother.2012; 67:2717– 2724.

Response

Response	Prophylaxis/ Empiric (n=81) %	Probable/Proven/ Possible IFI (n=20) %	Total (n=101) %
Success	83	40	75
Failure	17	60	25
Died	0	20	3.9

Soler-Palacın et al. Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: a prospective study. J Antimicrob Chemother 2012; 67: 700–706

Adverse Effects

	% (n=101 courses)
Dermatological	
Photosensitivity	6
Rash	5
Gastrointestinal	
Hepatic impairment	
ALP	15
ALT	51
AST	45
Bili	24
Nausea/vomiting	1
Neurologic	
Insomnia	1
Lack of concentration	1
Irritability/dizziness	-
Vertigo	1
Renal impairment	19
Visual	
Hallucinations	-
Photophobia	3
Discontinuation due to AE	9.9

Pieper et al. Monitoring of voriconazole plasma concentrations in immunocompromised paediatric patients. J. Antimicrob. Chemother.2012; 67:2717– 2724.

Results

- No consistent correlations between trough concentrations and response or adverse effects
- Threshold value of 5.5 mg/L was **not** found to be discriminative for increases in hepatic function parameters

Pieper et al. Monitoring of voriconazole plasma concentrations in immunocompromised paediatric patients. J. Antimicrob. Chemother.2012; 67:2717– 2724.

Conclusions

- "Variability was high and no predictable dose-concentration – effect relationships were observed"
- "Nevertheless, based on a comprehensive pharmacokinetic and pharmacodynamic analysis that also included pediatric patients, we strongly advocate TDM of voriconazole in pediatric patients with life-threatening IFIs"

Pieper et al. Monitoring of voriconazole plasma concentrations in immunocompromised paediatric patients. J. Antimicrob. Chemother.2012; 67:2717– 2724.

Limitations

- Not R, DB
- No comparison trough range
- Retrospective
- Observational
- Assay specificity and linearity not described
- CYP 2C19 genotype not specified
- Drug and food interactions not addressed
- Dose modifications for sub or supra therapeutic levels and statistical analysis not provided
- Voriconazole was combined with other systemic antifungal agents in 6 of 20 courses for therapy of fungal infections
- Final conclusion recommending TDM based on another, primarily adult, trial
- Do not specify number of children by age

Clinical Question

P	Pediatric patients receiving voriconazole	
I	Therapeutic drug monitoring (trough 1-6 mg/L)	
C	No therapeutic drug monitoring or an alternate therapeutic range	

O	Efficacy:
	• Infection prevention
	• Infection resolution
	• Mortality reduction
		Safety:
		• Dermatological
		  • Photosensitivity/rash
		• Gastrointestinal
		  • Hepatic impairment/nausea/vomiting
		• Neurologic
		  • Irritability/dizziness
		• Renal impairment
		• Visual
		  • Hallucinations
		• Discontinuation due to AE

Overall Efficacy

- Soler-Palacin et al. 2012:
  - **Trough concentrations >1 mg/L** showed a statistically **significant relationship with early outcome at 4-6 weeks**
- Neely et al. 2010:
  - Mortality: **Each trough <1 mg/L** was **associated with**:
    - **A 2.6-fold increased odds of death (95% CI: 1.6–4.8; p . 002)**
- Pieper et al. 2012:
  - No consistent correlations between trough concentrations and response or mortality

Overall Safety

- Soler-Palacin et al. 2012:
  - **Trough concentrations >5.5 mg/L** demonstrated a statistically significant relationship with **neurological and skin side effects**
- Neely et al. 2010:
  - Risk of hepatotoxicity was **not** significantly associated with voriconazole concentrations
- Pieper et al. 2012:
  - No consistent correlations between trough concentrations and adverse effects
  - **Troughs >5.5 mg/L were not found to increase hepatic function** parameters

Summary

- There does not appear to be a clear relationship between drug concentration and drug response
- Further research is required to determine the optimal role for voriconazole TDM
- I would not routinely monitor voriconazole trough levels

References

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- Chen J, Chan C, Colantonio D, and Seto W. Therapeutic Drug Monitoring of Voriconazole in Children. Ther Drug Monit 2012;34:77–84

Voriconazole Dosing

- C and W Pediatric Drug Dosage Guidelines 6th ed:
  - IV:
    - LD: 6 mg/kg IV q12h X 2 doses
    - Maintenance: 4 mg/kg/dose IV q12h
      - Reduce to 3 mg/kg/dose if patient is unable to tolerate
  - PO: </= 12 yo
    - LD: 10 mg/kg/dose po q12h X 2 doses
    - Maintenance: 100 mg/dose po q12h
  - PO: >12 yo
    - </= 40 kg: LD: 200 mg/dose po q12h X 2 doses, Maintenance: 100 mg/dose po q12h
    - > 40kg: LD: 400 mg/dose po q12h X 2 doses, Maintenance: 200 mg/dose po q12h