



Voriconazole (VCZ) dosing in pediatric patients



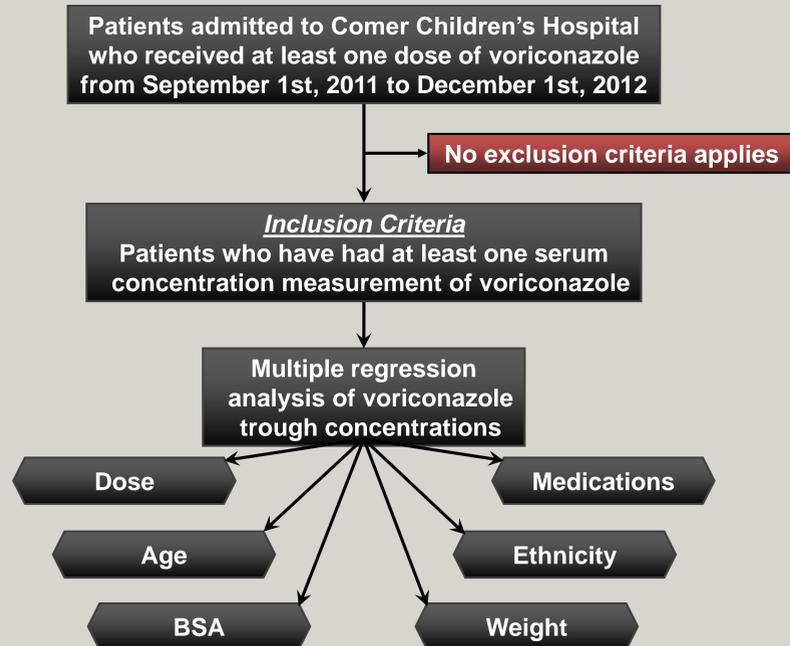
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Background

- Voriconazole is considered first line therapy for invasive *Aspergillus* in adults and is frequently used for prophylaxis in immunocompromised pediatric patients
- Single trough concentrations above 1 mg/L have been associated with survival benefit in pediatric patients.
- Trough serum concentrations above 5.5 mg/L have been associated with an increased incidence of adverse events
- Every 1 mg/L increase in trough concentration above 6 mg/L, elevates risk of hepatotoxicity by 7 – 17%
- Lower doses of 3 to 4 mg/kg every 12 hours follow linear kinetics while increased doses of 8 mg/kg every 12 hours follow nonlinear kinetics in pediatric patients.
- Saturable kinetics and self-induction of the metabolism should be considered in establishing a dosing algorithm

Methods

- Primary endpoint: evaluate patients achieving therapeutic VCZ trough levels with the initial dose over a 15 month period
- Secondary endpoints: proportion of patients requiring IV to PO dose adjustments, incidence of hepatotoxicity, and percentage of patients with clinical failure of VCZ



Results

- 24 patients received voriconazole and had at least one level drawn resulting in a total of 80 voriconazole levels
- All patients had their first voriconazole level obtained after at least 5 days of therapy

Demographics			
	Group A (< 1 yo)	Group B (1-12 yo)	Group C (> 12 yo)
# of patients	3	10	11
# of troughs	9	34	37
Age (years)	0.16 (0.15-0.26)*	8.7 (4.5-9.5)*	16.3 (15.1-17.1)*
% male	33	60	64
Weight (kg)	5.1 (4.4-5.1)*	23.1 (16-31.3)*	68.7 (54.4-86.9)*
Dose (mg/kg)	6.1 (3.7-6.6)*	7.4 (6.5-9.4)*	4 (3.1-5.5)*

* Median (range)

Troughs with the Initial Dose		
Group	Median Dose	p - value
Therapeutic (2-5.5 mg/L) n=15	5.4 mg/kg	p = 0.1984
Nontherapeutic (supratherapeutic n=3; subtherapeutic n=6)	5.9 mg/kg	

Clinical Failure				
Age (yrs)	Dose (mg/kg)	Trough (mg/L)	Route	Culture
2.4	7 (100 mg)	2.1	PO	Fusarium spp.
14.4	2.9 (200 mg)	0.8	PO	Aspergillus spp.

Incidence of Hepatotoxicity		
Group	Median Dose	Median Trough
Transient LFT elevation (n=10)	7.1 mg/kg	2.9 mg/L
No toxicity (n=14)	6.4 mg/kg	2.7 mg/L
Significance	Prob > z = 0.1431	Prob > z = 0.3053

Multiple Regression Analysis			
	Coef.	Std. Err.	Significance
Ethnicity	0.179603	0.293409	0.543
Age	0.390848	0.204848	0.062
Dose	0.006331	0.003469	0.073
PPI	-0.57946	0.724445	0.427
Weight	0.19063	0.07367	0.012
BSA	-12.4251	4.542873	0.008

•Ethnicity, age, dose, co-administration of a proton-pump inhibitor, weight, and body surface area were analyzed using multiple regression analysis

•Weight and body surface area were significant (p=0.012 and p=0.008, respectively)

•Age and dose approached significance (p=0.062 and p=0.073, respectively)

Limitations

- Potential difficulties extrapolating data from the medical record
- Sampling error resulting in a level that cannot be interpreted may occur
- Differences in dosing and actual weight as well as their documentation may confound results
- Dosing, monitoring variability, and availability of levels over the study period may reduce the power of the study
- Potential drug interactions may confound the correlation between voriconazole dose and trough concentrations

Conclusions

- Patients' age has a high impact on levels
- Patients greater than 1 year and less than 12 years of age required higher weight based doses
- Weight-based dosing among all groups did not correlate significantly with increased levels
- Weight significantly influenced troughs despite using weight-based dosing
- Three patients had a supratherapeutic trough and 6 patients had a subtherapeutic trough
- Forty-two percent of patients experienced transient elevations in liver functions tests while on voriconazole therapy

References

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Disclosure

The authors of this presentation have no financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation