Voriconazole Therapeutic Drug Monitoring and Empiric Dosing in Children with Cancer

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Background

- Invasive fungal infections are a serious and common comorbidity in children with cancer
- Most common pathogens are *Candida spp. and Aspergillus spp.*
- Voriconazole has a broad spectrum of activity and because of its safety and efficacy profile, it has become the first-line agent for suspected fungal infection
- The BC Children's Hospital (BCCH) empiric dose is 6 mg/kg IV q12h x 2 doses followed by 4 mg/kg IV q12h. The oral dosing recommendations vary based on age and/or weight
- Studies have shown that serum concentrations < 1 mg/L are associated with increased mortality and concentrations > 5.5 mg/L are associated with neurotoxicity
- It is unclear if current empiric dosage routinely achieves this target
- There is a lack of consensus as to need for therapeutic drug monitoring and ideal timing of sampling

Outcomes

- **Primary:**
  - Describe voriconazole serum trough concentrations achieved with empiric dosing
- **Secondary:**
  - Describe adverse events and determine if there is a correlation between dose, serum concentration, and adverse events
  - Describe which patients may require higher or lower dosages to achieve target serum conentrations

Methods

- Institutional ethics board approval received
- **Design:** Retrospective review
- **Population:** Pediatric oncology patients who received voriconazole at BCCH between Jan 2008 and Sept 2013
- **Inclusion:** Age 1 month to 19 years, cancer diagnosis, received voriconazole, and had at least one voriconazole serum concentration drawn at steady state
- **Adverse Events** defined as Naranjo score ≥ 5
- **Statistics:** Descriptive statistics; χ^2; Fisher's Exact; $p < 0.05$ statistically significant
- **Sample size:** N = 15 for 50% of patients to have serum concentration > 1 mg/L, with 25% absolute precision, and 95% confidence interval

Results

Table 1: Patient Characteristics	N = 17
Mean Age [y, (+/- SD)]	10.7 (5.5)
Male sex [N, (%)]	10 (59)
Mean weight [kg, (+/- SD)]	40.3 (21.6)
Type of infection [N, (%)]	
Proven	3 (17)
Probable	2 (12)
Possible	7 (42)
Suspected	5 (29)
Pathogens identified [N, (%)]	
None	12 (71)
Aspergillus	4 (23)
Candida	1 (6)
Outcome [N, (%)]	
Cured	10 (59)
Persistent	1 (6)
Ruled out fungal infection	2 (12)
Died (all cause)	4 (23)
Died (2^o to infection)	0 (0)
Concomitant medications that affect voriconazole serum concentration	0

Table 2: Proportion of Patients Who Achieved Target Trough Concentration With Empiric Dosage

Group	Overall (N = 15)	< 12 y or < 40 kg (N = 7)	≥ 12 y or ≥ 40 kg (N = 8)
Target Trough [N (%)]	5 (33)	1 (14)	4 (50)
Not at Target Trough [N (%)]	6 (40)	4 (57)	2 (25)

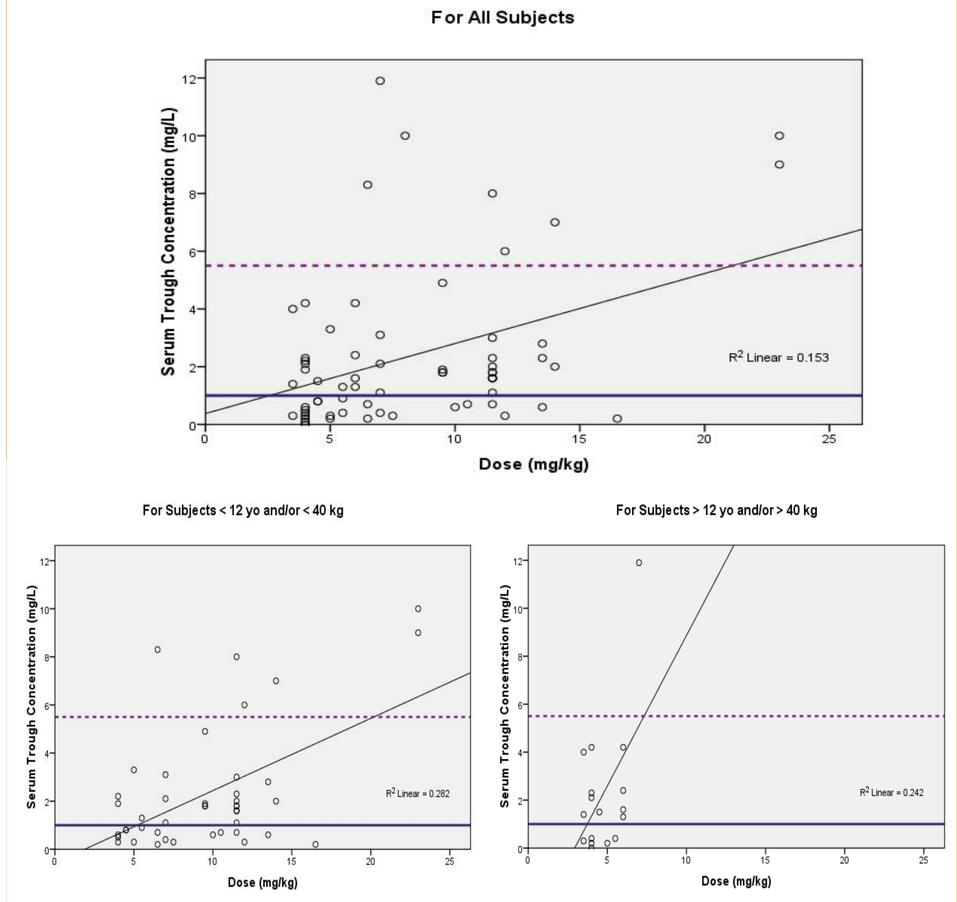
2 patients excluded: not started on standard empiric dose
4 patients: no serum concentrations measured after empiric dosage
p > 0.05 for all

Table 3: Adverse Events (N = 3)

Adverse Event	Duration of Therapy (d)	Dose (mg/kg/d)	Serum Concentration (mg/L)
Cholestasis	34	7	11.9
Hepatitis	6	4	4.2
Visual disturbance + hepatotoxicity	152	28	7

All events reversed upon dose decrease or d/c of voriconazole

Figure 1: Dose of voriconazole (mg/kg) vs Serum Concentration (mg/L)



Conclusions

- Using our current empiric dosage, 1/3 of patients achieved target serum trough concentrations
- There was no correlation between dose and concentration
- There were insufficient data to recommend a change in empiric dosage
- There was a signal for serious adverse events, even at serum concentrations below the current specified upper limit
- Recommend more standardized monitoring of serum concentrations (weekly until target achieved, and then monthly thereafter)

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