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# Voriconazole dosing and therapeutic drug monitoring in children: experience from a paediatric tertiary care centre

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**Objectives:** Therapeutic drug monitoring (TDM) of voriconazole is recommended to achieve trough concentrations of 1–5 mg/L. In children, this is challenging due to age-related variability in voriconazole pharmacokinetics. This study describes our experience with voriconazole, focusing on dosing regimens, dose adjustment and TDM.

**Methods:** We reviewed the medical records of immunocompromised children who received voriconazole from July 2009 to January 2015 and had TDM. Demographic, clinical and voriconazole dosing and monitoring data were collected.

**Results:** Fifty-five children received 62 courses of voriconazole and had TDM, with a total of 256 samples taken. Only 71.0% of courses (44/62) had TDM at the correct time, and at least one therapeutic level was achieved in only 52.3% (23/44) of these. Twenty-six courses had at least one sub-therapeutic level and in only 61.5% was the dose adjusted. Patients aged <6, 6–12 and >12 years required median intravenous doses of 8.8, 7.5 and 4.0 mg/kg twice daily, respectively ($P<0.001$). With oral administration, patients aged 6–12 and >12 years required median doses of 4.7 and 4.3 mg/kg twice daily, respectively ($P=0.307$). Levels within the target range were observed to fall below 1 mg/L in 36.4% of unchanged dosing regimens. Photosensitive skin reactions (20.0%) and hepatotoxicity (12.7%) were the most frequent adverse events and occurred in children with voriconazole levels <5 mg/L.

**Conclusions:** There is significant intra- and inter-individual variability in voriconazole concentrations in children, particularly in children <6 years of age. This warrants repeated TDM throughout treatment. Standardized guidelines for TDM and dose adjustment are required in children.

## Introduction

Immunocompromised children are at significant risk of invasive fungal infections (IFIs). Voriconazole is a triazole antifungal with broad-spectrum activity against yeasts and moulds.[1] The dose approved by the EMA for children recently increased based on several pharmacokinetic studies showing inadequate drug exposure in children.[2–4] The current paediatric dosing regimen has been clinically validated in only one study.[5] European Conference on Infections in Leukaemia (ECIL) guidelines recommend therapeutic drug monitoring (TDM) with trough samples (10–12 h after the preceding dose) taken at steady-state for all children receiving voriconazole.[6] The target trough concentration of 1–5 mg/L is largely based on adult data, although there is evidence in children that trough concentrations <1 mg/L are associated with an increased likelihood of death or treatment failure.[7–9]

In children, achieving and maintaining therapeutic concentrations for the duration of therapy is difficult due to the non-linearity and age-related variability in voriconazole pharmacokinetics. Factors such as concomitant medications and polymorphisms in the cytochrome P450 (CYP450) genotype also affect voriconazole concentrations.[1,10] Ideally, TDM-guided individualized dosing should be used routinely. In addition, oral bioavailability of voriconazole is lower in children than adults, and is reduced further by coadministration with food.[11,12] Therefore, repeat TDM to ensure stable trough concentrations, particularly following dose adjustment or change in route of administration or clinical condition, is recommended.[13] There are no current guidelines for dose adjustment of voriconazole in paediatric patients.

We describe our experience with voriconazole dosing and attainment of target concentrations at a tertiary paediatric centre, with particular attention to dosing regimens, dose adjustment and TDM.

## Patients and methods

### *Study design*

We retrospectively reviewed the records of a cohort of immunocompromised children <18 years of age who were treated with voriconazole as an inpatient at The Royal Children's Hospital Melbourne (RCH) over a 5 year 7 month period (July 2009 to January 2015). RCH is a paediatric tertiary referral centre with a 34 bed oncology unit that does ~25 allogeneic stem-cell transplants each year. Patients who received voriconazole were identified using the pharmacy dispensing database. Medical records of those children who had TDM were reviewed and demographic, clinical and voriconazole dosing, monitoring and adverse effect data were collected. The study was approved by the RCH Human Research Ethics Committee (34165 A). As this was a retrospective audit ethics approval was obtained for data collection. Consent from parents or guardians was not required.

### *Indication and outcome*

Treatment of IFI was classified using definitions of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG).[14] Outcome for proven and probable IFI was classified as a 'success' if there was a complete or partial response at the end of the treatment course and 'failure' if there was no response or death due to IFI. Empirical therapy was defined as the use of voriconazole in patients with febrile neutropenia without a focus of infection. Prophylaxis was defined as the use of voriconazole in immunocompromised children at risk of IFI. Empirical treatment and prophylaxis were classified as a 'success' if the course was completed without breakthrough fungal infection.[15]

### *Voriconazole administration and TDM*

In the absence of local guidelines for voriconazole dosing or TDM, dosing and monitoring regimens were determined by the treating clinician. A course was defined as voriconazole use lasting at least 1 day. The TDM results were included in analysis only if the child was an inpatient to ensure accurate timing of trough samples. Voriconazole concentrations were determined using a previously described HPLC method.[16] The assay was done once weekly with results available the same afternoon, resulting in a turnaround time of up to 7 days. A trough concentration taken on or after day 3 (with loading dose) or day 5 (without loading dose) of therapy was defined as steady-state. Trough concentrations of 1.0–5.0 mg/L were considered therapeutic.[6]

### *Safety*

A voriconazole-attributable clinical adverse effect was defined as an event that developed during treatment with voriconazole and was considered the most likely cause by the treating clinician or by two investigators (A. B., A. G.). Baseline (BL) and end-of-treatment liver function tests were recorded and classified based on the Common Terminology Criteria of Adverse Events (CTCAE) defined by the National Cancer Institute, USA.[17]

### *Statistics*

The non-parametric Mann–Whitney *U*-test or Kruskal–Wallis test was used to compare continuous variables. Categorical variables were compared using the $\chi^2$ test. Statistical analysis was performed using SPSS v 20.0 (IBM Corp., Armonk, NY, USA).

## Results

### *Baseline demographics and clinical details*

Over the study period, 88 patients received 102 courses of voriconazole. Of the 84 patients with available medical records, 81 received courses lasting at least 3 days, warranting TDM. Of these 81 children, only 55 had TDM performed and were therefore eligible for inclusion in the study. The median age of included patients was 10.5 (range 0.4–17.8) years. Haematological malignancy was the most common underlying diagnosis (44/55; 80.0%) and 21/55 (38.2%) were recipients of allogeneic stem-cell transplantation. Other underlying diagnoses included primary immunodeficiency (5/55; 9.1%), haemophagocytic lymphohistiocytosis (3/55; 5.5%), aplastic anaemia (1/55; 1.8%), adrenoleucodystrophy (1/55; 1.8%), post-heart transplant (1/55; 1.8%) and posterior fossa ganglioma (1/55; 1.8%).

These 55 children received 62 courses of voriconazole with a median duration of 72.5 (range 4–567) days. Two patients received four prolonged courses (>300 days) due to chronic respiratory aspergillosis in the setting of hyper-IgE syndrome. The indication for the majority of courses of voriconazole therapy was for treatment of IFI (48/62; 77.4%) (Table 1). *Aspergillus fumigatus* (two), *Candida krusei* (one), *Candida albicans* (one) and *Fusarium solani* (one) were cultured from a sterile site in five children. Concomitant antifungal therapy was prescribed in 11/62 courses (17.7%).

### *Voriconazole administration and TDM*

Voriconazole was started intravenously in 42/62 courses (67.7%), with a loading dose in 19/42 (45.2%). During the study period, the median starting intravenous and oral dose in children ≤12 years of age increased from 7.1 to 8.0 mg/kg twice daily and 5.9 to 6.9 mg/kg twice daily, respectively (2009–12 versus 2013–15). The proportion of courses with TDM also increased during the study period from 2/10 (20.0%) in 2009 to 19/23 (82.6%) in 2014.

In total, 256 samples for TDM were taken from 62 courses (median 3 per course, range 1–18), of which 176 were inpatient samples. Timing of the first TDM sample varied widely, with a median of 6 (range 2–211) days after starting therapy. Of the 176 inpatient samples, 159 (90.3%) were at steady-state and 120 (68.2%) were trough samples. These 120 inpatient trough samples taken at steady-state were included in the analysis. Overall, only 44 of 62 courses (71.0%) had inpatient TDM performed at the correct time.

Of the 44 inpatient courses that had TDM performed at the correct time, 23 (52.3%) achieved at least one therapeutic concentration, 25 (56.8%) had at least one sub-therapeutic concentration and 12 (27.3%) had at least one supra-therapeutic concentration (12 courses had concentrations both within and out of range). The dose required to achieve therapeutic concentrations was inversely related to age. Patients <6, 6–12 and >12 years required median intravenous doses of 8.8, 7.5 and 4.0 mg/kg twice daily, respectively ($P<0.001$). With oral administration, the median dose required by patients 6–12 and >12 years did not differ (4.7 versus 4.3 mg/kg twice daily, $P=0.307$) (Figure 1). However, there were only three patients in the 6–12 year cohort who achieved therapeutic concentrations with oral voriconazole. The median oral dose was not calculated for patients aged <6 years as there was only one patient who achieved a therapeutic trough concentration with a dose of 7.3 mg/kg twice daily. In children 6–12 and >12 years, there was no difference in the oral and intravenous dose required to achieve therapeutic concentrations (6–12 years, 7.5 mg/kg intravenously versus 4.7 mg/kg orally,

**Table 1.** Demographic and clinical details

| | Total | Age | | |
|---|---|---|---|---|
| | | <6 years | 6–12 years | >12 years |
| Number of courses | 62 | 13 | 23 | 26 |
| Indication | | | | |
| treatment | 48 (77.4%) | 7 | 20 | 21 |
| proven IFI | 6 (9.7%) | 0 | 5 | 1 |
| probable IFI | 19 (30.6%) | 3 | 5 | 11 |
| possible IFI | 23 (37.1%) | 4 | 10 | 9 |
| empirical | 6 (9.7%) | 2 | 2 | 2 |
| prophylaxis | 8 (12.9%) | 4 | 1 | 3 |
| Duration (days), median (range) | 72.5 (4–567) | 55 (4–318) | 77 (6–474) | 68.5 (5–567) |
| Route of administration | | | | |
| intravenous | 17 (27.4%) | 4 | 8 | 5 |
| oral | 17 (27.4%) | 5 | 5 | 7 |
| both | 28 (45.2%) | 4 | 10 | 14 |
| Loading dose (mg/kg twice daily), *n* (%) or median (range) | | | | |
| intravenous | 19 (30.6) | 7.3 (6.0–9.0) | 8.6 (6.8–12.0) | 6.0 (5.7–11.5) |
| oral | 8 (12.9) | 7.6[a] | 9.2 (6.3–11.4) | 6.0 (3.9–11.8) |
| Starting maintenance dose (mg/kg twice daily), *n* (%) or median (range) | | | | |
| intravenous | 42 (67.7) | 8.0 (4.0–8.7) | 7.1 (3.1–9.0) | 4.4 (2.9–8.8) |
| oral | 20 (32.3) | 7.3 (5.9–11.0) | 4.6 (3.7–7.1) | 4.2 (1.9–9.1) |

[a]Median not calculated if $n=1$ (i.e. value is an individual value).

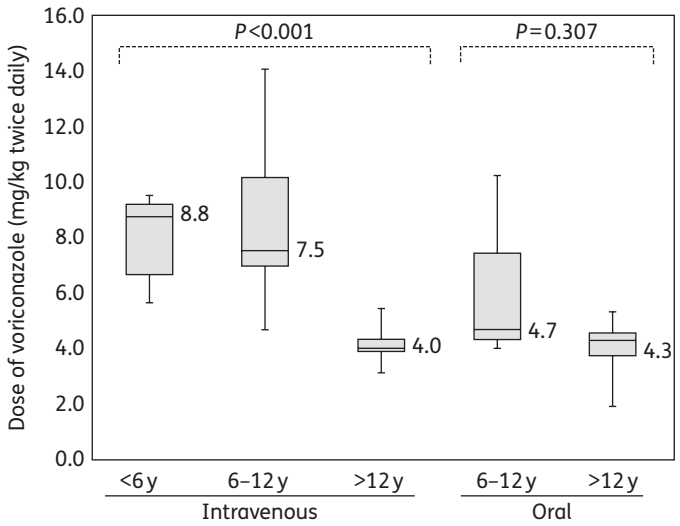


**Figure 1.** Dose required to achieve target voriconazole trough concentrations (1–5 mg/L) categorized by route of administration and age. Box plot denotes median (with value), maximum, minimum, 25th percentile and 75th percentile. y, years.

$P=0.225$; >12 years, 4.0 mg/kg intravenously versus 4.3 mg/kg orally, $P=0.815$) (Table 2).

In only 16 of the 26 courses (61.5%) with concentrations <1 mg/L was the dose adjusted. Dose adjustments varied with increments ranging from 8% to 100% of the original dose. Follow-up trough steady-state concentrations were taken after a median of 4 (range 2–59) days in only 11/16 (68.8%) courses. Of these, only three achieved therapeutic concentrations.

To determine the stability of trough concentrations with a particular dosing regimen, the subset of patients who had at least two trough samples taken at the same dose were further analysed. This subset included 16 patients who received 22 dosing regimens. There was significant intra-individual variability in trough concentrations. Of the 22 dosing regimens, 7 (31.8%) and 4 (18.2%) maintained therapeutic and sub-therapeutic concentrations, respectively; 8/22 (36.4%) had an initial therapeutic concentration followed by at least one sub-therapeutic measurement. The subsequent trough concentrations varied between 4.2% and 213% of the initial concentration.

### *Outcome*

Outcome data were analysed in patients with proven or probable IFI. Data were available for 21/25 (84.0%) courses (1 course ongoing at the end of the study period, 3 without follow-up imaging excluded). Thirteen had a successful outcome (13/21; 61.9%), while eight were classified as failure (8/21; 38.1%). One of these patients received four courses for treatment of chronic respiratory aspergillosis in the setting of hyper-IgE syndrome, which were all classified as failure. Voriconazole trough concentrations of >1 mg/L were not associated with successful outcome [success 12/28 (42.9%) versus failure 21/32 (65.6%), $P=0.077$]. There were no treatment failures with empirical therapy or prophylaxis.

**Table 2.** Voriconazole dosage, route of administration and trough concentrations

| | Voriconazole trough concentration (mg/L) | | |
|---|---|---|---|
| | <1 | 1–5 | >5 |
| Samples, *n* (%); *n*=120 | 53 (44.2) | 53 (44.2) | 14 (11.7) |
| Route of administration | | | |
| intravenous, *n* (%); *n*=78 | 34 (43.6) | 34 (43.6) | 10 (12.8) |
| oral, *n* (%); *n*=42 | 19 (45.2) | 19 (45.2) | 4 (9.5) |
| Dose (mg/kg twice daily), median (range)[a] | | | |
| <6 years | | | |
| intravenous; *n*=15 | 8.6 (4.0–11.4) | 8.8 (5.7–9.5) | 8.2[b] |
| oral; *n*=3 | 8.5 (8.5–8.6) | 7.3[b] | — |
| 6–12 years | | | |
| intravenous; *n*=28 | 8.0 (3.7–12.5) | 7.5 (4.7–14.1) | 7.8 (5.9–12.5) |
| oral; *n*=9 | 5.2 (4.0–7.1) | 4.7 (4.0–10.2) | — |
| >12 years | | | |
| intravenous; *n*=21 | 4.1 (3.1–5.0) | 4.0 (3.1–5.5) | 6.1 (4.0–8.8) |
| oral; *n*=20 | 4.1 (1.9–9.1) | 4.3 (1.9–5.3) | 5.6 (4.2–9.1) |

[a]For children receiving a specific dosing regimen who had more than one TDM sample, only one sample was included for analysis.
[b]Median not calculated if *n*=1 (i.e. values are individual values).

**Table 3.** Liver function test abnormalities in 42 courses of voriconazole with baseline and end-of-treatment data available

| | Grade[a] (total *N*=42) | | | | |
|---|---|---|---|---|---|
| | I–IV, *n* (%) | I, *n* | II, *n* | III, *n* | IV, *n* |
| ALT | 26 (61.9) | 18 | 4 | 4 | 0 |
| Alkaline phosphatase | 9 (21.4) | 6 | 3 | 0 | 0 |
| GGT | 36 (85.7) | 7 | 14 | 9 | 6 |

[a]Graded using CTCAE definitions.

### *Safety*

Of the 55 children, 14 (25.5%) had clinical adverse effects. Photosensitive skin reactions were the most frequent, occurring in 11/55 children (20.0%) after a median of 66.5 days of therapy (range 16–474). Of these 11 patients, 5 (45.5%) discontinued therapy, of which 4 had documented resolution. The median concentration of voriconazole in the three patients who had trough samples taken within 1 month of the adverse effect was 0.4 (range 0.2–3.6) mg/L. Outcomes of those who continued therapy were not documented. Other cutaneous adverse events included rash (4/55; 7.3%) and itch (2/55; 3.6%). Two patients (2/55; 3.6%) experienced transient blurred vision. One had a voriconazole trough concentration of 12.2 mg/L. The other had subtherapeutic levels at the time of the adverse event. In both children, symptoms resolved without intervention.

Voriconazole-attributable hepatotoxicity occurred in seven patients (7/55; 12.7%) and in all cases therapy was ceased. Enzyme abnormalities were predominantly GGT, with grade III or IV hepatotoxicity in all patients (Table 3). The median trough concentration in these patients was 1.6 mg/L (range <0.1–4.8 mg/L). Repeat liver enzymes following cessation of voriconazole showed a decrease in GGT. In addition to the above seven patients, there were six children with suspected voriconazole-attributable hepatotoxicity where dose adjustment or withholding led to a reduction in GGT.

## Discussion

Our study highlights the difficulties in attaining target concentrations of voriconazole in children and the need for guidelines for voriconazole TDM. Specifically, recommendations are needed for when and how often to perform TDM and how to dose adjust voriconazole in children.

Increased doses of voriconazole have been recommended in recent years based on pharmacokinetic studies reporting inadequate drug exposure in children.[2–4] These changes are reflected in our study by an increase in median voriconazole dose during the study period. The EMA approved higher doses in younger children (2 to <12 years)—8 mg/kg intravenously twice daily (9 mg/kg day 1) and 9 mg/kg orally twice daily. Our data suggest that in children <6 years of age intravenous doses exceeding 8 mg/kg are required. This is consistent with previous retrospective studies[9,18,19] and emphasizes the importance of TDM and further clinical validation of current recommendations, particularly for children <6 years of age. Voriconazole is not recommended for use in children <2 years of age due to the lack of systematic data in this age group. If there is no alternative antifungal agent, median daily doses up to 31.5 mg/kg may be required to achieve trough concentrations >1 mg/L.[19]

A standardized approach is needed for TDM in paediatric patients. Similar to other retrospective studies,[20] our study highlights the need for improved timing of TDM samples. As initial

trough concentrations of ≤0.35 mg/L have been associated with increased mortality in adults with invasive candidiasis,[21] the first steady-state TDM should be done ideally as early as possible (day 3 of therapy) to allow prompt dose adjustment. However, this is limited by the turnaround time for voriconazole assays, which was 7 days in our hospital, similar to that reported (7–10 days) in other centres.[7] Given the complex pharmacokinetics of voriconazole, dosing and TDM should ideally be guided by population-based pharmacokinetic data and computer-based dosing algorithms. For example, a recently developed multiple-model Bayesian adaptive control algorithm may allow for dose adjustments based on voriconazole concentrations taken at any time following the preceding dose and also prior to steady-state.[22]

Current British Society for Medical Mycology guidelines recommend regular TDM until voriconazole concentrations are stable. TDM should then be repeated when there is: (i) a potential drug interaction; (ii) a change in dose; (iii) a change in route of administration; (iv) an adverse effect; or (v) an alteration in clinical condition.[13] The phenomenon of autoinduction, whereby voriconazole-induced enhanced metabolism results in declining voriconazole concentrations, has been reported in both adults[23,24] and children.[25] This may explain the sub-therapeutic levels observed after initial therapeutic concentrations in 36% of unchanged dosing regimens in our study. Protocols for TDM used in other studies include weekly monitoring for the duration of therapy[26] and twice monthly monitoring following attainment of target concentrations.[19] In the latter study, intra-patient variability observed in recipients of stem-cell transplantation led to the recommendation that monitoring at least once weekly is most appropriate.[19]

There are no guidelines for dose adjustment of voriconazole in children. Few studies describe the method of dose adjustment and it is frequently at the discretion of the treating clinician. We have shown that this results in variable dose adjustment, with doses altered by 8%–100% of the original dose. Voriconazole displays linear kinetics at sub-therapeutic dosages of 3–4 mg/kg twice daily[27] due to enhanced clearance. As a result, linear dose adjustment has been shown to improve attainment of target concentrations from 34% to 80% in children.[19] However, at the current recommended dose for children 2 to <12 years of age, voriconazole shows non-linear pharmacokinetics,[2,28] warranting more cautious dose adjustment. Adjustments by 1 mg/kg steps have been suggested[4] and pharmacokinetic modelling predicted an increase in trough concentration by 0.5 mg/L for each step.[7] However, this strategy has not been clinically validated. A protocol whereby adjustments of 50% of the original dose are made has also been used in children, although the effectiveness of this strategy was not evaluated.[26] The high proportion of unsuccessful dose adjustments in our study emphasizes the need for close monitoring.

Both adult[29–31] and paediatric[7–9] studies have demonstrated an association between trough concentrations <1–2 mg/L and poor outcome. In a retrospective paediatric study, a 2.6-fold increased odds of mortality was associated with each sub-therapeutic trough level (<1 mg/L).[7] Similarly, a correlation between treatment failure and sub-therapeutic trough concentrations at 6 weeks[8] and 12 weeks[9] was reported in two retrospective studies. A relationship between outcome and trough concentrations was not observed in our study; however, this may be due to the small number of courses eligible for inclusion in outcome analysis.

Overall, voriconazole is well tolerated in children, with a rate of adverse effects of 22.5%–27.1%.[2,3,26] The rate of photosensitive skin reactions in our study (20.0%) is comparable to other paediatric studies.[32,33] However, lower rates of 0%–6.7% have also been reported.[3,26,27] The increased frequency in our study may be explained by the increased sun exposure in Australia or the large number of children remaining on voriconazole as an outpatient.[34] Due to the reported increased risk of squamous cell carcinoma in children receiving long-term voriconazole therapy, advice regarding sun protection is essential.[35] Similar to previous reports, we found no consistent correlation between voriconazole trough concentrations and photosensitive skin reactions.[34,36,37] Voriconazole-attributable hepatotoxicity occurred in 12.7% of children, comparable to previously reported rates (14.3%–17.5%[2,3,5]). None of the patients who developed voriconazole-attributable hepatotoxicity had voriconazole concentrations >5 mg/L and therefore an association could not be determined. However, other studies have reported no relationship with trough concentrations.[2,3,7] Visual side effects were infrequent in our study and limited to blurred vision (3.6%).

Our study is limited by the retrospective study design and the lack of a standardized protocol for voriconazole dosing and TDM in our hospital. CYP2C19 genotype status was not routinely tested and ethnicity was not documented, precluding evaluation of these factors.

Clinical practice guidelines are required to standardize TDM and dose adjustment of voriconazole to improve attainment of target concentrations in children. Intra- and inter-individual variability warrants regular TDM in all children receiving voriconazole for the duration of therapy. Close monitoring is particularly important in children <6 years of age.

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## Transparency declarations

None to declare.

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