Impact of Dose Adaptations Following Voriconazole Therapeutic Drug Monitoring in Pediatric Patients

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Keyword:	voriconazole, therapeutic drug monitoring, pediatrics, azoles, pharmacokinetics
Abstract:	Voriconazole is a broad-spectrum triazole antifungal agent which has emerged as the preferred treatment of invasive aspergillosis in both children (≥ 2 years of age) and adults (1, 2). Increased voriconazole exposure has been associated with improved treatment outcome in adults, with suggested provisional cut-off points for voriconazole trough plasma concentrations (Cmin) of 1-6 mg/L (3-6). An exposure-response relationship was also established for pediatric patients, in which a voriconazole Cmin > 1 mg/L was associated with improved outcomes (7-11). Based on the relationship between voriconazole exposure and efficacy and the high inter- and intra-patient variability in pediatric patients (12-15), the importance of voriconazole therapeutic drug monitoring (TDM) in pediatric patients has been acknowledged (1, 2, 16, 17). Although TDM-based dose adjustments are performed to optimize plasma concentrations, it remains unclear if these dose adaptations in pediatric patients correspond with target attainment. We conducted a retrospective analysis in a cohort of pediatric oncology patients (both leukemia as well as lymphoma) with difficult to manage

	voriconazole concentrations and assessed the result of TDM-based dose adaptations on target attainment.

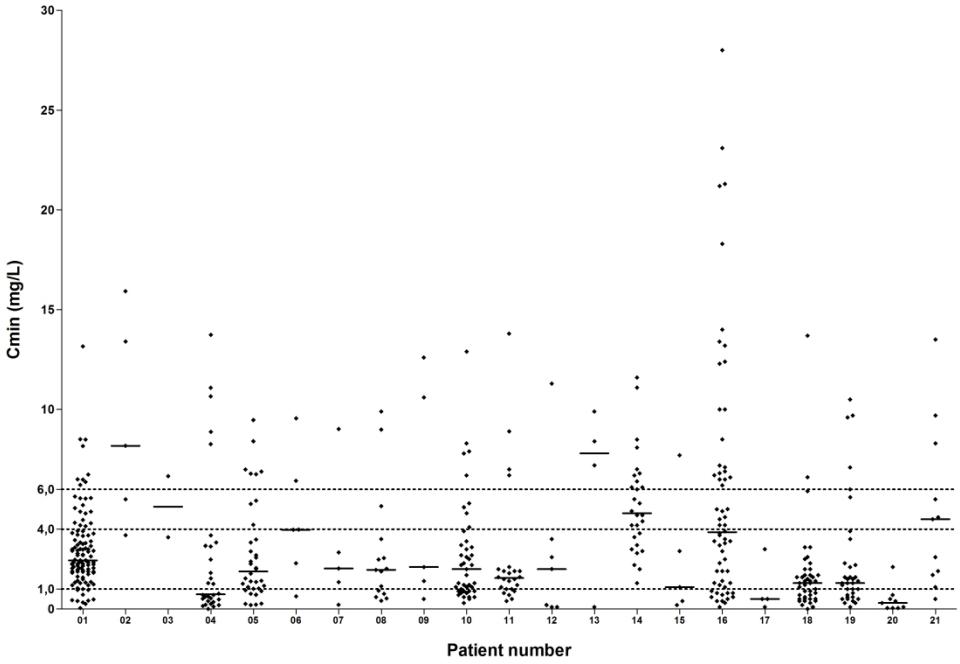

Figure 1

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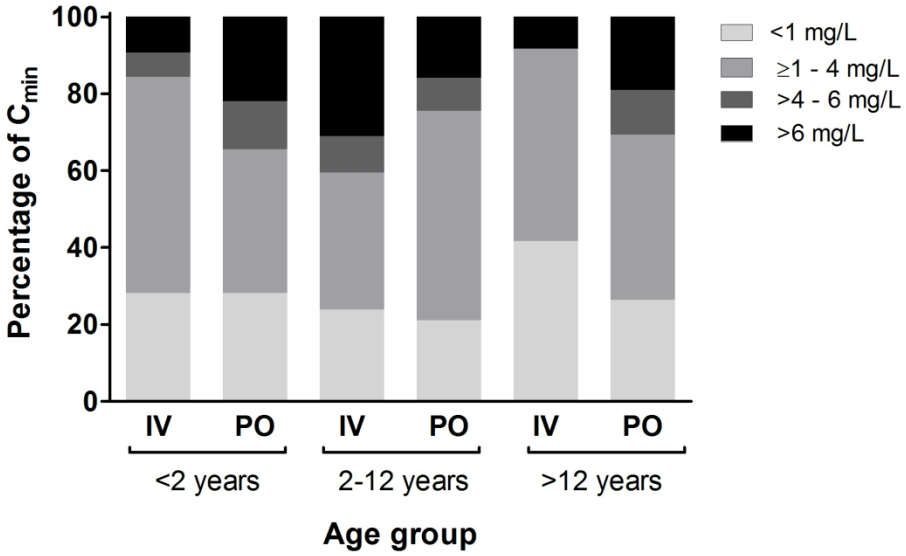

		C_{min} (% of total)			
Age group	Formulation	< 1 mg/L (n)	1 - 4 mg/L (n)	>4 - 6 mg/L (n)	> 6 mg/L (n)
< 2 years	IV	28.1 (9)	56.3 (18)	6.3 (2)	9.4 (3)
	PO	28.1 (9)	37.5 (12)	12.5 (4)	21.9 (7)
2-12 years	IV	23.8 (10)	35.7 (15)	9.5 (4)	31.0 (13)
	PO	21.1 (52)	54.5 (134)	8.5 (21)	15.9 (39)
>12 years	IV	41.7 (5)	50.0 (6)	0.0 (0)	8.3 (1)
	PO	26.3 (32)	43.0 (52)	11.6 (14)	19.0 (23)

		Median dose administered (mg/kg/day)			
Age group	Formulation	< 1 mg/L	1 -4 mg/L	>4 - 6 mg/L	> 6 mg/L
< 2 years	IV	12.2	11.9	N/A	12.9
	PO	12.2	12.3	22.0	12.6
2-12 years	IV	17.1	24.5	15.7	57.9
	PO	24.0	25.9	22.9	28.2
>12 years	IV	10.0	11.1	N/A	N/A
	PO	18.4	15.7	11.0	10.4

Figure 2

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Impact of Dose Adaptations Following Voriconazole Therapeutic Drug Monitoring in Pediatric Patients

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Abstract (243/250 words)

Voriconazole is the mainstay of treatment for invasive aspergillosis in immunocompromised pediatric patients. Although Therapeutic Drug Monitoring (TDM) of voriconazole is recommended, it remains unknown if TDM-based dose adaptations result in target attainment.

Patients < 19 years from two pediatric hematologic-oncology wards were retrospectively identified based on unexplained high voriconazole trough concentrations (C_{min} >6mg/L). Patient demographics, clinical characteristics, treatment, voriconazole dosing information, voriconazole C_{min} before and after adjustment based on TDM were obtained.

Twenty-one patients, median (range) age 7.0 (1.2-18.5) years, were identified in two centres. First C_{min} (3.1mg/L [0.1-13.5]) was obtained after 3 days (1-27) of treatment. The median of all C_{min} (n=485, median 11 per patient) was 2.16mg/L (0.0 (undetectable)–28.0), with 24.1% of C_{min} <1mg/L, 48.9% 1-4mg/L, 9.3% 4-6mg/L and 17.7% >6mg/L. Intrapatient variability was large (94.1% for IV, 88.5% for PO). Dose increases at C_{min} <1 mg/L resulted in an increased C_{min} in 76.4%, with 60% between 1-4 mg/L. Dose decreases at C_{min} >6 mg/L resulted in a decreased C_{min} in 80%, with 51% between 1-4 mg/L. Overall in 45% of the cases (33 out of 55 and 12 out of 45) therapeutic targets were attained after dose adjustment.

Fifty-five percent of initial C_{min} was outside the therapeutic target of 1-4mg/L, with multiple dose adaptations required to achieve therapeutic concentrations. Only 60% and 51% of dose adaptations following sub- and supra-therapeutic C_{min}, respectively, did result in target attainment. Intensive and continuous TDM of voriconazole is a prerequisite for ensuring adequate exposure in pediatric patients.

Introduction

Voriconazole is a broad-spectrum triazole antifungal agent which has emerged as the preferred treatment of invasive aspergillosis in both children (≥ 2 years of age) and adults [1, 2].

Increased voriconazole exposure has been associated with improved treatment outcome in adults, with suggested provisional cut-off points for voriconazole trough plasma concentrations (C_{min}) of 1-6 mg/L (3-6). An exposure-response relationship was also established for pediatric patients, in which a voriconazole C_{min} > 1 mg/L was associated with improved outcomes [7-11]. Based on the relationship between voriconazole exposure and efficacy and the high inter- and intra-patient variability in pediatric patients [12-15], the importance of voriconazole therapeutic drug monitoring (TDM) in pediatric patients has been acknowledged [1, 2, 16, 17]. Although TDM-based dose adjustments are performed to optimize plasma concentrations, it remains unclear if these dose adaptations in pediatric patients correspond with target attainment.

We conducted a retrospective analysis in a cohort of pediatric oncology patients (both leukemia as well as lymphoma) with difficult to manage voriconazole concentrations and assessed the result of TDM-based dose adaptations on target attainment.

Materials and Methods

Study design and patients

This retrospective analysis was carried out in the pediatric hematology-oncology wards of two university hospitals in the Netherlands (Radboud university medical centre, Nijmegen and Sophia Children's Hospital, Erasmus Medical Center, Rotterdam). From August 2007–May 2014, the results from routinely performed TDM of voriconazole in both hospitalized and ambulant pediatric patients were evaluated. Patients < 19 years who received voriconazole orally (PO) or intravenously (IV) were included if more than one voriconazole C_{min} was determined, of which at least one concentration was >6 mg/L during treatment. Due to the retrospective nature of the study, written informed consent was deemed not necessary.

Data collection

Data was collected from the patients' medical records and included patient demographics (e.g. age, gender, body weight), voriconazole treatment data (e.g. route of administration, treatment duration, total daily dose, dose adjustments) and TDM data (e.g. plasma trough concentrations [C_{min}], number of samples per patient, number of sub- and supra-therapeutic C_{min}). Concomitant medications with or without a known or suspected interaction with voriconazole exposure were reported.

Voriconazole dosing and dose adjustments

Initial dosing and administration of voriconazole was according to the Summary of Product Characteristics (SmPC) of voriconazole, but could be increased or decreased based on clinical indications and TDM results. End of treatment was defined by successful clinical response, or by discontinuation due to a lack of clinical response, or adverse events. Consistent with institution guidelines during the study period, adequate voriconazole exposure was defined as C_{min} between 1-4 mg/L. If the patient showed no signs of hepatotoxicity (*i.e.* liver function tests no more than three

times the upper limit of normal), C_{min} up to 6 mg/L were accepted. The 4 mg/L target concentration to prevent hepatotoxicity has been established in Asian patients particularly(18, 19). In Caucasion people this relation has not been established with a clear cut-off value. Rather an increase in drugs concentration, results in an increased chance of encountering hepatotoxicity(20). In case of sanctuary infection sites or disseminated disease, the lower threshold was set to 2 mg/L (*i.e.* 2-4 mg/L or 2-6 mg/L). Target concentrations remain subject to debate but our target concentrations are in line with the recently published ESCMID guideline(2) and the ECIL guideline [available online via www.ecil-leukaemia.com]

In case of a sub- or supra-therapeutic voriconazole C_{min} (< 1 or > 6 mg/L), dose adjustments, assuming near-linear pharmacokinetics in children [14], to reach adequate C_{min} were subsequently made. A follow-up sample within 1 week was recommended. Dosing frequency was initially two times daily, but could be increased to three times daily in an attempt to reach adequate voriconazole exposure.

Therapeutic Drug Monitoring

TDM was performed as standard of care, but frequency of sampling was dependent on individual decisions made for each patient. First TDM sample was recommended at steady state concentrations of the drug, which is at least two days after initiation of voriconazole therapy or following dose adaptations. Only blood samples withdrawn within a 1 hour period prior to the next dose were included in the analysis to ascertain a trough concentration. Decisions on dose adaptations were made by experts in the field with knowledge on PK of voriconazole taking in mind the clinical condition of the patient.

Analytical assay

Voriconazole plasma concentrations were measured twice weekly using an in-house, validated ultra-performance liquid chromatography (HPLC) method with either a fluorescence or MSMS detection method (Waters).

Data analysis

A Spearman rank-order correlation was run to determine the relationship between voriconazole dose and C_{min} using SPSS 20.0 (SPSS inc., IL, USA). A p-value of <0.05 was considered statistically significant. Intra-patient variability of voriconazole C_{min} was analyzed in patients who had at least three voriconazole C_{min} at similar doses and formulations.

RESULTS

Patients

Twenty-one patients (8 male, 13 female) were eligible for analysis. Median (range) age at first dose was 7.0 years (1.2–18.5 years), of which 3 patients (14.3%) were <2 years, 11 (52.4%) between 2 and 12 years, and 7 (33.3%) between 12 and 19 years. Median (range) weight and BMI were 21.9 kg (9.5–65) and 17.7 kg/m^2 (14–25.4), respectively (Table 1).

Voriconazole therapy

Patients received voriconazole therapy for a median (range) of 118 days (17–866; Table 1). The median total daily dose per kg (range) was 23.1 mg/kg (6.1–109.6). Initial voriconazole administration was IV in 15 (71.4%) and PO in 6 (28.6%) of patients. Five patients received voriconazole orally only, 2 only IV, and 14 received a combination of both. In four patients voriconazole was given TID at some time as part of their management strategy for a median (range) of 60 days (6–397) with a median total daily dose of 34.4 mg/kg (13.6–109.6). Median intra-individual variability of voriconazole dose was 94.1% during IV therapy (dose range: 12.2–16.0 mg/kg/day) and 88.5% during PO therapy (dose range: 10.5–44.1 mg/kg/day).

Therapeutic drug monitoring – initial C_{min}

The first measurement of voriconazole C_{min} was performed at a median (range) of 3 days (1–27) after start of treatment, with a median (IQR) C_{min} of 3.1 mg/L (1.34-7.0; Table 1). Upon first measurement, 11 out of 21 (52.4%) patients reached a C_{min} between 1-6 mg/L (7 of these patients received voriconazole IV, 4 PO). Of the remaining 10 patients who had a voriconazole concentration <1 mg/L or >6 mg/L at first measurement, 5 out of 9 patients (55.5%) required only 1 dose adaptation to achieve a C_{min} between 1-6 mg/L. Target concentrations in these 9 patients were attained after a median (range) of 15 days (8-123). One patient was unable to achieve target values during the entire

length of voriconazole therapy despite TDM-based dose adaptations. After the first suboptimal C_{min}, TDM-based dose adaptations were performed within a median of 2 days. A very weak positive correlation between voriconazole dose and initial C_{min} was calculated, which was not statistically significant (r^2=0.05, p=0.82).

Therapeutic drug monitoring – all C_{min}

In total, 485 samples were obtained with a median (range) concentration of 2.16 mg/L (undetectable -28; Table 1). Four concentrations (0.8%) were reported as below the lower limit of quantification. A median (range) of 11 samples (2-109) were drawn per patient, of which 117 (24.1%) were <1 mg/L, 237 (48.9%) between 1-4 mg/L, 45 (9.3%) between 4-6 mg/L and 86 (17.7%) >6 mg/L. An overview of all C_{min} per patient is shown in Figure 1. There was no significant correlation between voriconazole dose and all $C_{min,}$ (r_s (485)=0.02, p=0.59). A C_{min} <1 mg/L was most frequently encountered in patients >12 years receiving voriconazole IV, whereas patients 2-12 years suffered most frequently from C_{min} >6 mg/L (Figure 2).

Voriconazole dose adaptations

A total of 108 dose increases and 135 dose decreases were made, of which 50.9% when Cmin < 1, and 33.3% Cmin > 6 (see table 1). Out of a 117 cases with a C_{min} <1mg/L prompted a dose increase in 47.0% (n=55) of occurrences, which resulted in an increased C_{min} at follow-up sampling in 76.4% (n=42) of cases. In 60% (n=33) of dose increases following a concentration of <1 mg/L, this led to a therapeutic C_{min} between 1–4 mg/L (median 1.7 mg/L). In these 33 cases, the total daily dose was increased from a median of 18.3 mg/kg/day to 22.7 mg/kg/day (24.0%).

Out of 86 cases with a C_{min} of >6 mg/L (median 8.29 mg/L) this prompted a dose decrease in 52.3% (n=45) of cases, of which 80.0% (n=36) resulted in a subsequent lower C_{min} at follow-up sampling. These dose decreases resulted in a C_{min} of <6mg/L in 51.1% (n=23) of cases and even led to

concentrations between 1-4 mg/L (median 2.3 mg/L) in 26.7% (n=12). In these 12 cases, the total daily dose was decreased from a median of 23.5 mg/kg/day to 16.8 mg/kg/day (39.9%).

Discussion

Here, we present our experience with voriconazole TDM in a cohort of 21 pediatric patients with difficult to control voriconazole C_{min}, characterized by at least one C_{min} >6 mg/L, enabling us to assess the result of TDM-based dose adaptations on voriconazole target attainment.

Overall, 18.5 % of all doses adjustments made, based on TDM, resulted in target concentrations (1-4 mg/L). The vast majority (95.2%) of the patients in our study were able to achieve at least one therapeutic concentration (1-4 mg/L) after TDM-based dose adjustments. This is in a similar range of the reported value of 80% in a study from Bartelink *et al.*, although voriconazole target values of 1-5 mg/L were used in this study [21].

Of the total number of 485 voriconazole C_{min}, 24.1% was <1 mg/L, which is correlated with increased likelihood of treatment failure in children [7-9]. In case of such a subtherapeutic C_{min}, voriconazole dose was increased in 47.0% of cases. Accordingly, 60% of dose increases resulted in the desired therapeutic C_{min} of 1-4 mg/L, with a median dose increase from 18.3 mg/kg/day to 22.7 mg/kg/day. Previous studies have reported that dose adjustments to median doses of 20–40 mg/kg/day were required to obtain therapeutic plasma concentrations of >1 mg/L [9, 10, 22]. In addition, 17.7% of the total number of voriconazole C_{min}were >6 mg/L, which is regarded as a cut-off concentration for hepatotoxicity in adults (23), although no clear correlation is seen in pediatric patients [7, 24, 25] . At these supratherapeutic concentrations, voriconazole dose was lowered in 52.3% of cases, resulting in a C_{min} between the target range of 1-4 mg/L in 26.7% of cases (decreasing the median dose from 23.5 mg/kg/day to 16.8 mg/kg/day).

Age is one of the most important factors influencing voriconazole plasma exposure, as voriconazole clearance has been shown to be much higher in children under the age of 12, and oral bioavailability of voriconazole is lower in children (65%), compared to adults (96%) [14, 26]. As a result, several studies reported similar voriconazole exposure in children (<12 years) compared to adults with IV doses of 7-9 mg/kg BID [13, 14, 26]. This prompted higher dosing regimens in children compared to adults. Although

voriconazole has been reported to display near-linear pharmacokinetics in children receiving multiple doses of 3 mg/kg and 4 mg/kg BID IV[15] (i.e. doses that have been found effective in clinical trials with adults), increasing evidence suggests saturated (non-linear) pharmacokinetic behavior is observed in children receiving doses higher than 7 mg/kg BID. We found no predictable relationship between dose and C_{min} (Figure 1,2) and it remains unclear from current literature if such a relationship exists. Given the high maintenance doses in our study (median 23.1 mg/kg/day), this could explain the absence of a dose/concentration relationship. Another explanation could be found in the high intra-subject variability in voriconazole C_{min} both after IV and PO dosing (figure 1), which is consistent with other pediatric studies [12-14, 26].

Due to the retrospective nature of this study, laboratory data on the majority of our patients was limited and often obtained only on the day of voriconazole TDM. In addition, markers for hepatic function were not always investigated in parallel. It was therefore not possible to draw any conclusions on the yet unclear relationship between voriconazole C_{min} and hepatotoxicity in pediatric patients. Because the focus of our study on the relationship between dose adjustments and target attainment, we did not monitor for voriconazole-related adverse events (e.g. neurological adverse events, phototoxic skin reactions and potentially proarrhythmic conditions) in relation to dose or exposure.

Despite rapid dose adaptations after the first subtherapeutic C_{min} in our study (median of 2 days), a median of 15 days were required to obtain an adequate C_{min}, increasing the risk of inadequately treated fungal infections and unfavourable outcome. Of all dose adaptations following both sub –and supratherapeutic C_{min}, only 45% resulted in a therapeutic C_{min} between 1-4 mg/L at the following concentration measurement. If we would stretch the therapeutic targets to 1-6 mg/L (assuming all C_{min} between 4-6 mg/L were acceptable based on adequate liver function tests), 56% of dose adaptations would result in target attainment.

Dose adaptations were done by experts with expertise in the field of antifungal pharmacology but without a nomogram. For purposes of personalized dosing, there is an urgent need to implement advanced pharmacometric models with "clinician-proof" software, that can take into account all important determinants for treatment response. Nowadays model-informed precision dosing (MIPD) can be deployed as a technique to forecast dosing in the individual. Programs such as InsightRx, DoseMe and Best Dose fulfil this need and are being tested in the clinic. To take advantage of this approach, solid pharmacokinetic models must be available to be used in MIPD. Here we can still gain knowledge for this specific drug and the current population as the unexplained inter-individual variability in published models remains very large. Before implementation in routine patient management these models must be prospectively validated to demonstrate its value. In addition the software must comply to relevant legislation (for instance CE label in Europe) when deployed outside of a research scope. Nevertheless this is the way forward taking advantage of a platform for individualized treatment with visual feedback.

Given the difficulty of target attainment despite dose adaptations, together with the prior observed relationship between voriconazole exposure and efficacy and adverse events and the large inter -and intrapatient variability in children, this study underscores the indispensable need for voriconazole TDM in severely immunocompromised pediatric patients early in the course of treatment with multiple follow-up samples during therapy when aiming to optimize treatment outcomes.

263 Table 1. Baseline characteristics (n=21).

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Demographics	
Gender	
Male (n [%])	8 (38.1)
Female (n [%])	13 (61.9)
Median age at first VCZ[a] dose (yrs [range])	7.0 (1.2 – 18.5)
Age class (yrs)	
0 – <2 (n [%])	3 (14.3)
2 – <12 (n [%])	11 (52.4)
12 – 18 (n [%])	7 (33.3)
Race	
Caucasian (n [%])	18 (85.7)
Negroid (n [%])	2 (9.5)
Asian (n [%])	1 (4.8)
Median weight (kg [range])	21.9 (9.5 – 65)
Median BMI (kg/m^2 [range])	17.7 (14 – 25.4)
Voriconazole therapy	
Median days of VCZ[a] therapy (n [range])	118 (17-866)
Intravenous administrations (%)	12.5
Oral administrations (%)	87.5
Median total daily dose (mg [range])	400 (120-2400)
Median total daily dose per kg (mg/kg [range])	23.1 (6.1 – 109.6)
Patients on temporarily TID[b] dosing (n [%])	4 (19)
Median days of TID[b] dosing (n range)	60 (6 – 397)
Median total daily dose during TID dosing (mg/kg [range])	34.4 (13.6 – 109.6)
TID dosing administrations (% of total)	11.1
Therapeutic drug monitoring	
Median days until first measurement of VCZ[a] C_{min}[c] (n [range])	3 (0 – 27)
Median plasma concentration of first C_{min}[c] (mg/L [IQR[d]])	3.1 (1.34 – 7.0)
Initial C_{min} adequate (% of all patients)[e]	11 (52.4)
Intravenous administration (%)	7 (63.6)
Oral administration (%)	4 (36.4)
Initial C_{min} below therapeutic range (% of all patients)	4 (19)
Intravenous administration (%)	3 (75)
Oral administration (%)	1 (25)
Initial C_{min} above therapeutic range (% of all patients)	6 (28.6)
Intravenous administration (%)	4 (66.7)
Oral administration (%)	2 (33.3)
Total C_{min}	485
<1 mg/L (n [%])	117 (24.1)
1 – 4 mg/L (n [%])	237 (48.9)
4 – 6 mg/L (n [%])	45 (9.3)
>6 mg/L (n [%])	86 (17.7)

Median concentration of all C_{min} (mg/L; range)	2.16 (0 – 28.0)
Dose adaptations	
Dose adaptations (n [%])	243 (50.1)
Dose increases (total)	108
Dose increase at C_{min} <1 mg/L (n [%])	55 (47)
Resulted in increase in Cmin	42 (76.4)
Resulted in C_{min} 1 – 4 mg/L	33 (60)
Dose decrease (total)	135
Dose decrease at C_{min} >6 mg/L	45 (33.3)
Resulted in decrease in C_{min}	36 (80.0)
Resulted in C_{min} <6 mg/L	23 (51.1)
Resulted in C_{min} 1 – 4 mg/L	12 (26.7)

[a]VCZ = voriconazole, [b]TID = three times per day, [c] C_{min} = trough concentration, [d]IQR = Interquartile range, [e]Adequate therapeutic range of voriconazole C_{min} is considered to be between 1 and 4 mg/L (1-6 if adequate liver function tests). Subtherapeutic C_{min} at <1 mg/L, supratherapeutic C_{min} at >6 mg/L.

Figure 1. Overview of all voriconazole trough concentrations at varying doses (n=485) in 21 patients

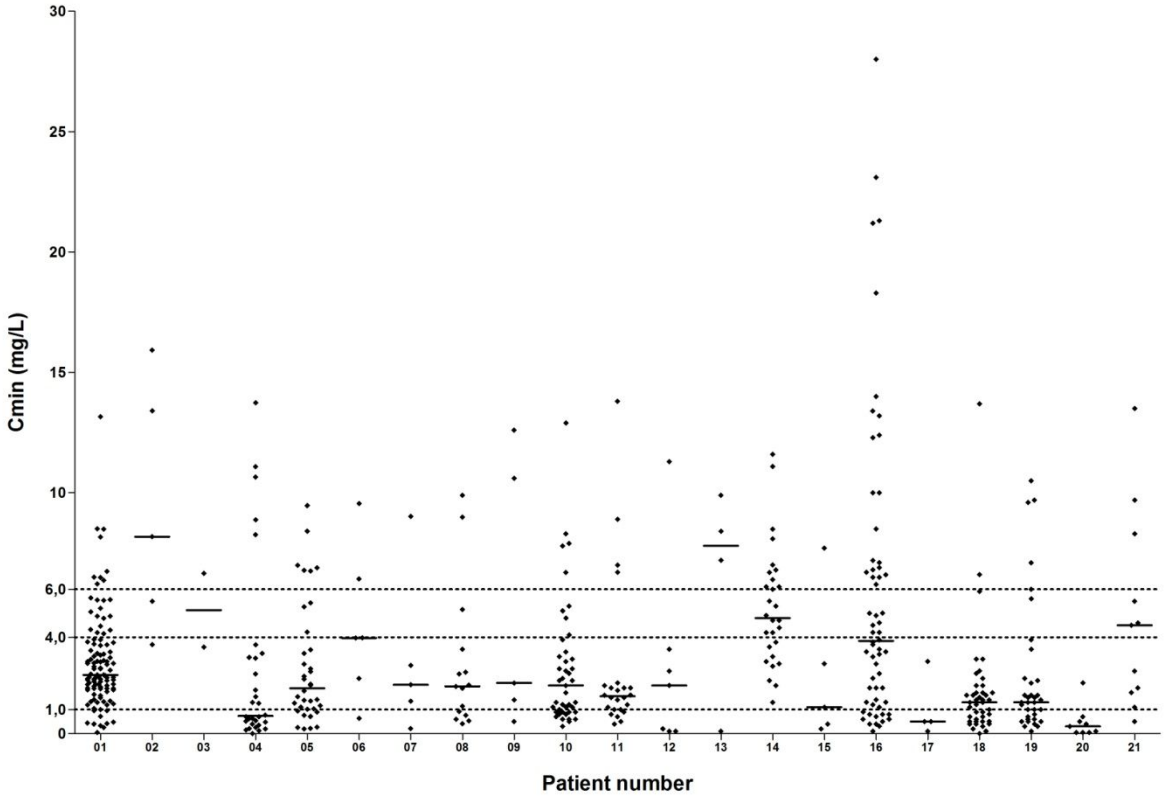
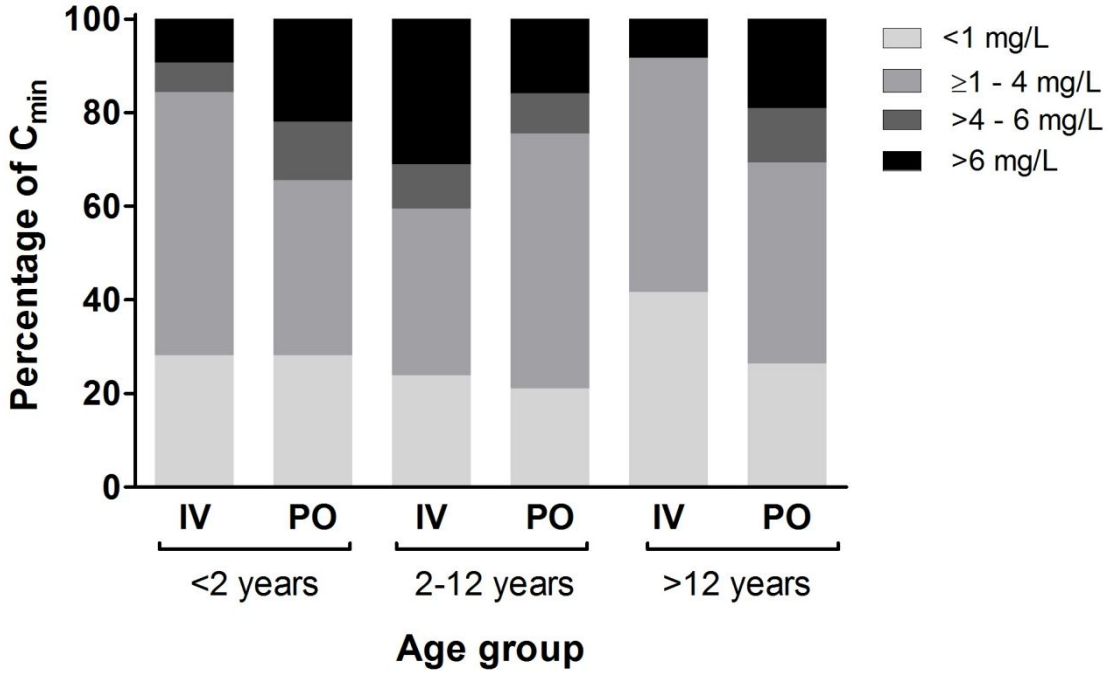


Figure 2. Voriconazole C_{min} distribution (%) per formulation per age group



		C_{min} (% of total)			
Age group	Formulation	< 1 mg/L (n)	1 - 4 mg/L (n)	>4 - 6 mg/L (n)	> 6 mg/L (n)
< 2 years	IV	28.1 (9)	56.3 (18)	6.3 (2)	9.4 (3)
	PO	28.1 (9)	37.5 (12)	12.5 (4)	21.9 (7)
2-12 years	IV	23.8 (10)	35.7 (15)	9.5 (4)	31.0 (13)
	PO	21.1 (52)	54.5 (134)	8.5 (21)	15.9 (39)
>12 years	IV	41.7 (5)	50.0 (6)	0.0 (0)	8.3 (1)
	PO	26.3 (32)	43.0 (52)	11.6 (14)	19.0 (23)

		Median dose administered (mg/kg/day)			
Age group	Formulation	< 1 mg/L	1 - 4 mg/L	>4 - 6 mg/L	> 6 mg/L
< 2 years	IV	12.2	11.9	N/A	12.9
	PO	12.2	12.3	22.0	12.6
2-12 years	IV	17.1	24.5	15.7	57.9
	PO	24.0	25.9	22.9	28.2
>12 years	IV	10.0	11.1	N/A	N/A
	PO	18.4	15.7	11.0	10.4

C_{min}: trough concentration. IV: intravenous. PO: Oral.

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Impact of Dose Adaptations Following Voriconazole Therapeutic Drug Monitoring in Pediatric Patients

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Abstract (243/250 words)

Voriconazole is the mainstay of treatment for invasive aspergillosis in immunocompromised pediatric patients. Although Therapeutic Drug Monitoring (TDM) of voriconazole is recommended, it remains unknown if TDM-based dose adaptations result in target attainment.

Patients < 19 years from two pediatric hematologic-oncology wards were retrospectively identified based on unexplained high voriconazole trough concentrations (C_{min} >6mg/L). Patient demographics, clinical characteristics, treatment, voriconazole dosing information, voriconazole C_{min} before and after adjustment based on TDM were obtained.

Twenty-one patients, median (range) age 7.0 (1.2-18.5) years, were identified in two centres. First C_{min} (3.1mg/L [0.1-13.5]) was obtained after 3 days (1-27) of treatment. The median of all C_{min} (n=485, median 11 per patient) was 2.16mg/L (0.0 (undetectable)–28.0), with 24.1% of C_{min} <1mg/L, 48.9% 1-4mg/L, 9.3% 4-6mg/L and 17.7% >6mg/L. Intrapatient variability was large (94.1% for IV, 88.5% for PO). Dose increases at C_{min} <1 mg/L resulted in an increased C_{min} in 76.4%, with 60% between 1-4 mg/L. Dose decreases at C_{min} >6 mg/L resulted in a decreased C_{min} in 80%, with 51% between 1-4 mg/L. Overall in 45% of the cases (33 out of 55 and 12 out of 45) therapeutic targets were attained after dose adjustment.

Fifty-five percent of initial C_{min} was outside the therapeutic target of 1-4mg/L, with multiple dose adaptations required to achieve therapeutic concentrations. Only 60% and 51% of dose adaptations following sub- and supra-therapeutic C_{min}, respectively, did result in target attainment. Intensive and continuous TDM of voriconazole is a prerequisite for ensuring adequate exposure in pediatric patients.

Introduction

Voriconazole is a broad-spectrum triazole antifungal agent which has emerged as the preferred treatment of invasive aspergillosis in both children (≥ 2 years of age) and adults [1, 2].

Increased voriconazole exposure has been associated with improved treatment outcome in adults, with suggested provisional cut-off points for voriconazole trough plasma concentrations (C_{min}) of 1-6 mg/L (3-6). An exposure-response relationship was also established for pediatric patients, in which a voriconazole C_{min} > 1 mg/L was associated with improved outcomes [7-11]. Based on the relationship between voriconazole exposure and efficacy and the high inter- and intra-patient variability in pediatric patients [12-15], the importance of voriconazole therapeutic drug monitoring (TDM) in pediatric patients has been acknowledged [1, 2, 16, 17]. Although TDM-based dose adjustments are performed to optimize plasma concentrations, it remains unclear if these dose adaptations in pediatric patients correspond with target attainment.

We conducted a retrospective analysis in a cohort of pediatric oncology patients (both leukemia as well as lymphoma) with difficult to manage voriconazole concentrations and assessed the result of TDM-based dose adaptations on target attainment.

Materials and Methods

Study design and patients

This retrospective analysis was carried out in the pediatric hematology-oncology wards of two university hospitals in the Netherlands (Radboud university medical centre, Nijmegen and Sophia Children's Hospital, Erasmus Medical Center, Rotterdam). From August 2007–May 2014, the results from routinely performed TDM of voriconazole in both hospitalized and ambulant pediatric patients were evaluated. Patients < 19 years who received voriconazole orally (PO) or intravenously (IV) were included if more than one voriconazole C_{min} was determined, of which at least one concentration was >6 mg/L during treatment. Due to the retrospective nature of the study, written informed consent was deemed not necessary.

Data collection

Data was collected from the patients' medical records and included patient demographics (e.g. age, gender, body weight), voriconazole treatment data (e.g. route of administration, treatment duration, total daily dose, dose adjustments) and TDM data (e.g. plasma trough concentrations [C_{min}], number of samples per patient, number of sub- and supra-therapeutic C_{min}). Concomitant medications with or without a known or suspected interaction with voriconazole exposure were reported.

Voriconazole dosing and dose adjustments

Initial dosing and administration of voriconazole was according to the Summary of Product Characteristics (SmPC) of voriconazole, but could be increased or decreased based on clinical indications and TDM results. End of treatment was defined by successful clinical response, or by discontinuation due to a lack of clinical response, or adverse events. Consistent with institution guidelines during the study period, adequate voriconazole exposure was defined as C_{min} between 1-4 mg/L. If the patient showed no signs of hepatotoxicity (*i.e.* liver function tests no more than three

times the upper limit of normal), C_{min} up to 6 mg/L were accepted. The 4 mg/L target concentration to prevent hepatotoxicity has been established in Asian patients particularly(18, 19). In Caucasion people this relation has not been established with a clear cut-off value. Rather an increase in drugs concentration, results in an increased chance of encountering hepatotoxicity(20). In case of sanctuary infection sites or disseminated disease, the lower threshold was set to 2 mg/L (*i.e.* 2-4 mg/L or 2-6 mg/L). Target concentrations remain subject to debate but our target concentrations are in line with the recently published ESCMID guideline(2) and the ECIL guideline [available online via www.ecil-leukaemia.com]

In case of a sub- or supra-therapeutic voriconazole C_{min} (< 1 or > 6 mg/L), dose adjustments, assuming near-linear pharmacokinetics in children [14], to reach adequate C_{min} were subsequently made. A follow-up sample within 1 week was recommended. Dosing frequency was initially two times daily, but could be increased to three times daily in an attempt to reach adequate voriconazole exposure.

Therapeutic Drug Monitoring

TDM was performed as standard of care, but frequency of sampling was dependent on individual decisions made for each patient. First TDM sample was recommended at steady state concentrations of the drug, which is at least two days after initiation of voriconazole therapy or following dose adaptations. Only blood samples withdrawn within a 1 hour period prior to the next dose were included in the analysis to ascertain a trough concentration. Decisions on dose adaptations were made by experts in the field with knowledge on PK of voriconazole taking in mind the clinical condition of the patient.

Analytical assay

Voriconazole plasma concentrations were measured twice weekly using an in-house, validated ultra-performance liquid chromatography (HPLC) method with either a fluorescence or MSMS detection method (Waters).

Data analysis

A Spearman rank-order correlation was run to determine the relationship between voriconazole dose and C_{min} using SPSS 20.0 (SPSS inc., IL, USA). A p-value of <0.05 was considered statistically significant. Intra-patient variability of voriconazole C_{min} was analyzed in patients who had at least three voriconazole C_{min} at similar doses and formulations.

RESULTS

Patients

Twenty-one patients (8 male, 13 female) were eligible for analysis. Median (range) age at first dose was 7.0 years (1.2–18.5 years), of which 3 patients (14.3%) were <2 years, 11 (52.4%) between 2 and 12 years, and 7 (33.3%) between 12 and 19 years. Median (range) weight and BMI were 21.9 kg (9.5–65) and 17.7 kg/m^2 (14–25.4), respectively (Table 1).

Voriconazole therapy

Patients received voriconazole therapy for a median (range) of 118 days (17–866; Table 1). The median total daily dose per kg (range) was 23.1 mg/kg (6.1–109.6). Initial voriconazole administration was IV in 15 (71.4%) and PO in 6 (28.6%) of patients. Five patients received voriconazole orally only, 2 only IV, and 14 received a combination of both. In four patients voriconazole was given TID at some time as part of their management strategy for a median (range) of 60 days (6–397) with a median total daily dose of 34.4 mg/kg (13.6–109.6). Median intra-individual variability of voriconazole dose was 94.1% during IV therapy (dose range: 12.2–16.0 mg/kg/day) and 88.5% during PO therapy (dose range: 10.5–44.1 mg/kg/day).

Therapeutic drug monitoring – initial C_{min}

The first measurement of voriconazole C_{min} was performed at a median (range) of 3 days (1–27) after start of treatment, with a median (IQR) C_{min} of 3.1 mg/L (1.34-7.0; Table 1). Upon first measurement, 11 out of 21 (52.4%) patients reached a C_{min} between 1-6 mg/L (7 of these patients received voriconazole IV, 4 PO). Of the remaining 10 patients who had a voriconazole concentration <1 mg/L or >6 mg/L at first measurement, 5 out of 9 patients (55.5%) required only 1 dose adaptation to achieve a C_{min} between 1-6 mg/L. Target concentrations in these 9 patients were attained after a median (range) of 15 days (8-123). One patient was unable to achieve target values during the entire

length of voriconazole therapy despite TDM-based dose adaptations. After the first suboptimal C_{min}, TDM-based dose adaptations were performed within a median of 2 days. A very weak positive correlation between voriconazole dose and initial C_{min} was calculated, which was not statistically significant (r^2=0.05, p=0.82).

Therapeutic drug monitoring – all C_{min}

In total, 485 samples were obtained with a median (range) concentration of 2.16 mg/L (undetectable -28; Table 1). Four concentrations (0.8%) were reported as below the lower limit of quantification. A median (range) of 11 samples (2-109) were drawn per patient, of which 117 (24.1%) were <1 mg/L, 237 (48.9%) between 1-4 mg/L, 45 (9.3%) between 4-6 mg/L and 86 (17.7%) >6 mg/L. An overview of all C_{min} per patient is shown in Figure 1. There was no significant correlation between voriconazole dose and all $C_{min,}$ (r_s (485)=0.02, p=0.59). A C_{min} <1 mg/L was most frequently encountered in patients >12 years receiving voriconazole IV, whereas patients 2-12 years suffered most frequently from C_{min} >6 mg/L (Figure 2).

Voriconazole dose adaptations

A total of 108 dose increases and 135 dose decreases were made, of which 50.9% when Cmin < 1, and 33.3% Cmin > 6 (see table 1). Out of a 117 cases with a C_{min} <1mg/L prompted a dose increase in 47.0% (n=55) of occurrences, which resulted in an increased C_{min} at follow-up sampling in 76.4% (n=42) of cases. In 60% (n=33) of dose increases following a concentration of <1 mg/L, this led to a therapeutic C_{min} between 1–4 mg/L (median 1.7 mg/L). In these 33 cases, the total daily dose was increased from a median of 18.3 mg/kg/day to 22.7 mg/kg/day (24.0%).

Out of 86 cases with a C_{min} of >6 mg/L (median 8.29 mg/L) this prompted a dose decrease in 52.3% (n=45) of cases, of which 80.0% (n=36) resulted in a subsequent lower C_{min} at follow-up sampling. These dose decreases resulted in a C_{min} of <6mg/L in 51.1% (n=23) of cases and even led to

concentrations between 1-4 mg/L (median 2.3 mg/L) in 26.7% (n=12). In these 12 cases, the total daily dose was decreased from a median of 23.5 mg/kg/day to 16.8 mg/kg/day (39.9%).

Discussion

Here, we present our experience with voriconazole TDM in a cohort of 21 pediatric patients with difficult to control voriconazole C_{min}, characterized by at least one C_{min} >6 mg/L, enabling us to assess the result of TDM-based dose adaptations on voriconazole target attainment.

Overall, 18.5 % of all doses adjustments made, based on TDM, resulted in target concentrations (1-4 mg/L). The vast majority (95.2%) of the patients in our study were able to achieve at least one therapeutic concentration (1-4 mg/L) after TDM-based dose adjustments. This is in a similar range of the reported value of 80% in a study from Bartelink *et al.*, although voriconazole target values of 1-5 mg/L were used in this study [21].

Of the total number of 485 voriconazole C_{min}, 24.1% was <1 mg/L, which is correlated with increased likelihood of treatment failure in children [7-9]. In case of such a subtherapeutic C_{min}, voriconazole dose was increased in 47.0% of cases. Accordingly, 60% of dose increases resulted in the desired therapeutic C_{min} of 1-4 mg/L, with a median dose increase from 18.3 mg/kg/day to 22.7 mg/kg/day. Previous studies have reported that dose adjustments to median doses of 20–40 mg/kg/day were required to obtain therapeutic plasma concentrations of >1 mg/L [9, 10, 22]. In addition, 17.7% of the total number of voriconazole C_{min}were >6 mg/L, which is regarded as a cut-off concentration for hepatotoxicity in adults (23), although no clear correlation is seen in pediatric patients [7, 24, 25] . At these supratherapeutic concentrations, voriconazole dose was lowered in 52.3% of cases, resulting in a C_{min} between the target range of 1-4 mg/L in 26.7% of cases (decreasing the median dose from 23.5 mg/kg/day to 16.8 mg/kg/day).

Age is one of the most important factors influencing voriconazole plasma exposure, as voriconazole clearance has been shown to be much higher in children under the age of 12, and oral bioavailability of voriconazole is lower in children (65%), compared to adults (96%) [14, 26]. As a result, several studies reported similar voriconazole exposure in children (<12 years) compared to adults with IV doses of 7-9 mg/kg BID [13, 14, 26]. This prompted higher dosing regimens in children compared to adults. Although

voriconazole has been reported to display near-linear pharmacokinetics in children receiving multiple doses of 3 mg/kg and 4 mg/kg BID IV[15] (i.e. doses that have been found effective in clinical trials with adults), increasing evidence suggests saturated (non-linear) pharmacokinetic behavior is observed in children receiving doses higher than 7 mg/kg BID. We found no predictable relationship between dose and C_{min} (Figure 1,2) and it remains unclear from current literature if such a relationship exists. Given the high maintenance doses in our study (median 23.1 mg/kg/day), this could explain the absence of a dose/concentration relationship. Another explanation could be found in the high intra-subject variability in voriconazole C_{min} both after IV and PO dosing (figure 1), which is consistent with other pediatric studies [12-14, 26].

Due to the retrospective nature of this study, laboratory data on the majority of our patients was limited and often obtained only on the day of voriconazole TDM. In addition, markers for hepatic function were not always investigated in parallel. It was therefore not possible to draw any conclusions on the yet unclear relationship between voriconazole C_{min} and hepatotoxicity in pediatric patients. Because the focus of our study on the relationship between dose adjustments and target attainment, we did not monitor for voriconazole-related adverse events (e.g. neurological adverse events, phototoxic skin reactions and potentially proarrhythmic conditions) in relation to dose or exposure.

Despite rapid dose adaptations after the first subtherapeutic C_{min} in our study (median of 2 days), a median of 15 days were required to obtain an adequate C_{min}, increasing the risk of inadequately treated fungal infections and unfavourable outcome. Of all dose adaptations following both sub –and supratherapeutic C_{min}, only 45% resulted in a therapeutic C_{min} between 1-4 mg/L at the following concentration measurement. If we would stretch the therapeutic targets to 1-6 mg/L (assuming all C_{min} between 4-6 mg/L were acceptable based on adequate liver function tests), 56% of dose adaptations would result in target attainment.

Dose adaptations were done by experts with expertise in the field of antifungal pharmacology but without a nomogram. For purposes of personalized dosing, there is an urgent need to implement advanced pharmacometric models with "clinician-proof" software, that can take into account all important determinants for treatment response. Nowadays model-informed precision dosing (MIPD) can be deployed as a technique to forecast dosing in the individual. Programs such as InsightRx, DoseMe and Best Dose fulfil this need and are being tested in the clinic. To take advantage of this approach, solid pharmacokinetic models must be available to be used in MIPD. Here we can still gain knowledge for this specific drug and the current population as the unexplained inter-individual variability in published models remains very large. Before implementation in routine patient management these models must be prospectively validated to demonstrate its value. In addition the software must comply to relevant legislation (for instance CE label in Europe) when deployed outside of a research scope. Nevertheless this is the way forward taking advantage of a platform for individualized treatment with visual feedback.

Given the difficulty of target attainment despite dose adaptations, together with the prior observed relationship between voriconazole exposure and efficacy and adverse events and the large inter -and intrapatient variability in children, this study underscores the indispensable need for voriconazole TDM in severely immunocompromised pediatric patients early in the course of treatment with multiple follow-up samples during therapy when aiming to optimize treatment outcomes.

263 Table 1. Baseline characteristics (n=21).

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Demographics	
Gender	
Male (n [%])	8 (38.1)
Female (n [%])	13 (61.9)
Median age at first VCZ[a] dose (yrs [range])	7.0 (1.2 – 18.5)
Age class (yrs)	
0 – <2 (n [%])	3 (14.3)
2 – <12 (n [%])	11 (52.4)
12 – 18 (n [%])	7 (33.3)
Race	
Caucasian (n [%])	18 (85.7)
Negroid (n [%])	2 (9.5)
Asian (n [%])	1 (4.8)
Median weight (kg [range])	21.9 (9.5 – 65)
Median BMI (kg/m^2 [range])	17.7 (14 – 25.4)
Voriconazole therapy	
Median days of VCZ[a] therapy (n [range])	118 (17-866)
Intravenous administrations (%)	12.5
Oral administrations (%)	87.5
Median total daily dose (mg [range])	400 (120-2400)
Median total daily dose per kg (mg/kg [range])	23.1 (6.1 – 109.6)
Patients on temporarily TID[b] dosing (n [%])	4 (19)
Median days of TID[b] dosing (n range)	60 (6 – 397)
Median total daily dose during TID dosing (mg/kg [range])	34.4 (13.6 – 109.6)
TID dosing administrations (% of total)	11.1
Therapeutic drug monitoring	
Median days until first measurement of VCZ[a] C_{min}[c] (n [range])	3 (0 – 27)
Median plasma concentration of first C_{min}[c] (mg/L [IQR[d]])	3.1 (1.34 – 7.0)
Initial C_{min} adequate (% of all patients)[e]	11 (52.4)
Intravenous administration (%)	7 (63.6)
Oral administration (%)	4 (36.4)
Initial C_{min} below therapeutic range (% of all patients)	4 (19)
Intravenous administration (%)	3 (75)
Oral administration (%)	1 (25)
Initial C_{min} above therapeutic range (% of all patients)	6 (28.6)
Intravenous administration (%)	4 (66.7)
Oral administration (%)	2 (33.3)
Total C_{min}	485
<1 mg/L (n [%])	117 (24.1)
1 – 4 mg/L (n [%])	237 (48.9)
4 – 6 mg/L (n [%])	45 (9.3)
>6 mg/L (n [%])	86 (17.7)

Median concentration of all C_{min} (mg/L; range)	2.16 (0 – 28.0)
Dose adaptations	
Dose adaptations (n [%])	243 (50.1)
Dose increases (total)	108
Dose increase at C_{min} <1 mg/L (n [%])	55 (47)
Resulted in increase in Cmin	42 (76.4)
Resulted in C_{min} 1 – 4 mg/L	33 (60)
Dose decrease (total)	135
Dose decrease at C_{min} >6 mg/L	45 (33.3)
Resulted in decrease in C_{min}	36 (80.0)
Resulted in C_{min} <6 mg/L	23 (51.1)
Resulted in C_{min} 1 – 4 mg/L	12 (26.7)

[a]VCZ = voriconazole, [b]TID = three times per day, [c] C_{min} = trough concentration, [d]IQR = Interquartile range, [e]Adequate therapeutic range of voriconazole C_{min} is considered to be between 1 and 4 mg/L (1-6 if adequate liver function tests). Subtherapeutic C_{min} at <1 mg/L, supratherapeutic C_{min} at >6 mg/L.

Figure 1. Overview of all voriconazole trough concentrations at varying doses (n=485) in 21 patients

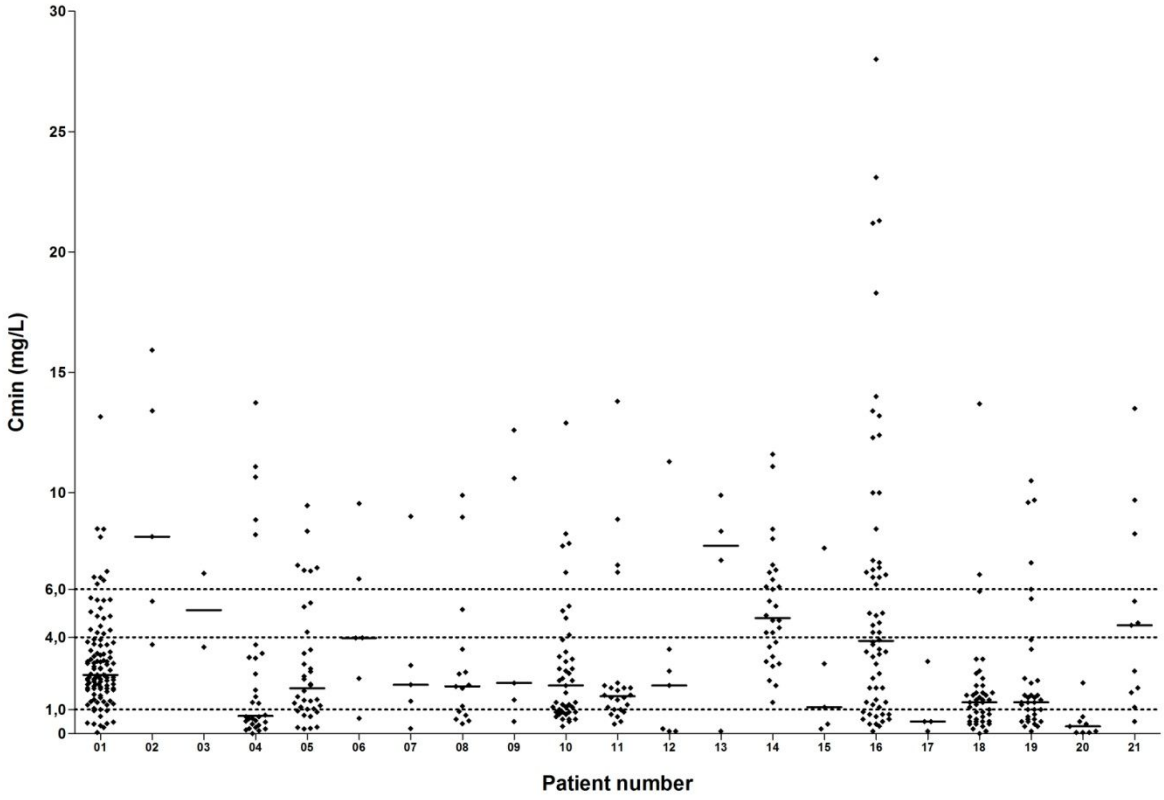
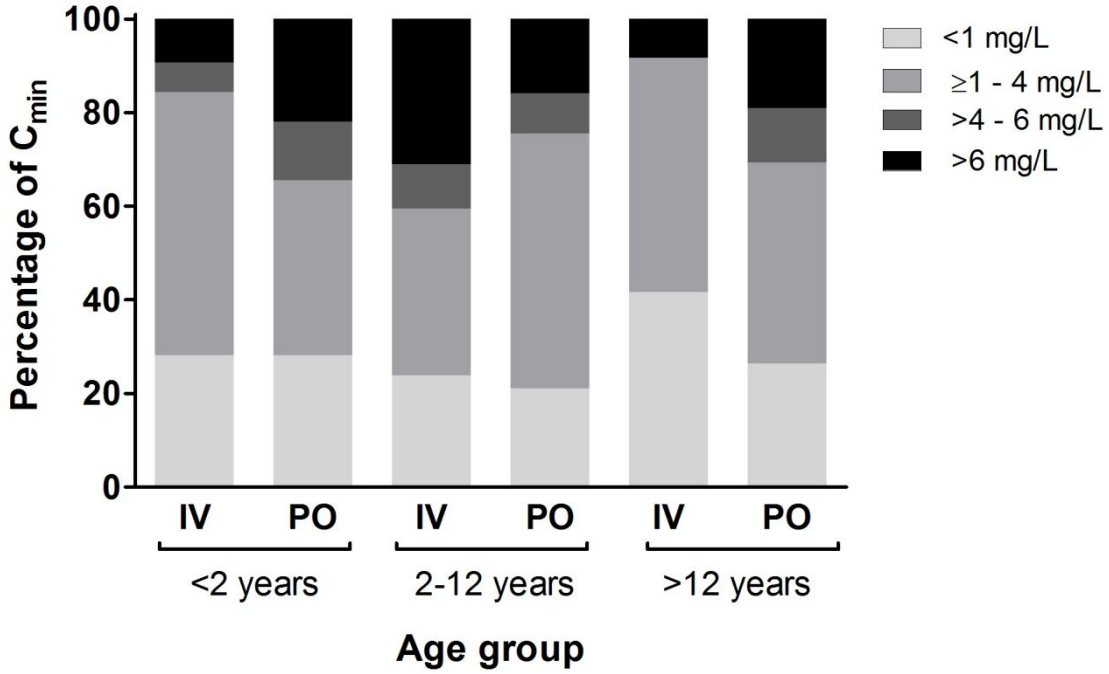


Figure 2. Voriconazole C_{min} distribution (%) per formulation per age group



		C_{min} (% of total)			
Age group	Formulation	< 1 mg/L (n)	1 - 4 mg/L (n)	>4 - 6 mg/L (n)	> 6 mg/L (n)
< 2 years	IV	28.1 (9)	56.3 (18)	6.3 (2)	9.4 (3)
	PO	28.1 (9)	37.5 (12)	12.5 (4)	21.9 (7)
2-12 years	IV	23.8 (10)	35.7 (15)	9.5 (4)	31.0 (13)
	PO	21.1 (52)	54.5 (134)	8.5 (21)	15.9 (39)
>12 years	IV	41.7 (5)	50.0 (6)	0.0 (0)	8.3 (1)
	PO	26.3 (32)	43.0 (52)	11.6 (14)	19.0 (23)

		Median dose administered (mg/kg/day)			
Age group	Formulation	< 1 mg/L	1 -4 mg/L	>4 - 6 mg/L	> 6 mg/L
< 2 years	IV	12.2	11.9	N/A	12.9
	PO	12.2	12.3	22.0	12.6
2-12 years	IV	17.1	24.5	15.7	57.9
	PO	24.0	25.9	22.9	28.2
>12 years	IV	10.0	11.1	N/A	N/A
	PO	18.4	15.7	11.0	10.4

C_{min}: trough concentration. IV: intravenous. PO: Oral.

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VJC is now an employee of Gilead. At the time of research he was employed by Radboudumc

Other have no conflicts of interest with regards to this work.

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