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Evidence of voriconazole pharmacokinetic variability in children and adolescents with haematological disease: proposal for therapeutic drug monitoring optimisation

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Author contributions

Pauline Lancia and Tiphaine Adam de Beaumais designed the study; Yves Medard, a technician in the laboratory, performed the monitoring dosages; Pauline Lancia collected the clinical data, performed the statistical analyses and wrote the article; Tiphaine Adam de Beaumais and Evelyne Jacqz-Aigrain reviewed the methodology and the article.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

$C_{trough,ss}$, concentration at steady-state; CYP, cytochrome P450; EMA, European Medicines Agency; HPLC-UV, high-performance liquid chromatography with ultraviolet detection; PBK, physiologically based kinetic; TDM, therapeutic drug monitoring; VCZ, voriconazole; IFI, invasive fungal infections; PO, per os; IV, intravenously; US FDA, the United States Food and Drug Administration; UV, ultraviolet.

Citation

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Abstract

Objective: Voriconazole (VCZ) is a triazole antifungal agent widely used in immunocompromised patients with suspected or proven invasive fungal infections. The achievement of therapeutic range (1-5 mg/L) is essential to maximize VCZ efficacy, as its pharmacokinetics is characterized by a wide inter- and intra-individual variability. This study aims to quantify the variability of VCZ trough concentrations in children and adolescents with haematological diseases and optimize therapeutic drug monitoring in clinical practice. **Methods:** We analysed the monitoring concentrations of all children (< 18 years old) treated with VCZ in the Haematology Department of Robert Debré Hospital between January 2014 and December 2016. Demographic, clinical data, and VCZ dosing and monitoring concentrations measured by high-performance liquid chromatography with ultraviolet detection (HPLC-UV) were analysed. Non-parametric tests were performed using SPSS IBM 24.0. **Results:** 380 trough VCZ concentrations at steady-state ($C_{trough,ss}$) were available in 79 children: 45.6% had first $C_{trough,ss}$ in the therapeutic range at first monitoring, 46.8% had $C_{trough,ss}$ below 1 mg/L and 7.6% had $C_{trough,ss}$ over 5 mg/L. Forty-one patients were treated with recommended doses but only 53% of them reached the therapeutic range. There was no impact of age, sex, biological parameters, or indication of VCZ on $C_{trough,ss}$ values. The number of $C_{trough,ss}$ in the therapeutic range increases with the number of monitoring per patient following dosage adaptations. **Conclusion:** The wide inter- and intra-individual variability of VCZ trough concentrations at recommended doses confirm the need to standardize VCZ monitoring and identify factors to be considered to prospectively adapt treatment for each patient.

Keywords: voriconazole; pharmacokinetics; variability; therapeutic drug monitoring; paediatric; haematology

Introduction

Immunocompromised children with haematological disease are at high risk of invasive fungal infections (IFI). Voriconazole (VCZ) is a second-generation antifungal triazole. It is currently used as first-line treatment for suspected or proven IFI due to its broad spectrum of antifungal activity against yeasts and moulds, including *Aspergillus* spp., *Candida* spp., *Cryptococcus Neoformans* [1–4].

Its pharmacokinetics is highly variable both within and between individuals and related to developmental, environmental and genetic factors. Voriconazole may cause hepatotoxicity, neurotoxicity visual disturbances, skin reactions, cardiac arrhythmias, and gastro-intestinal disorders [5, 6]. Many studies have demonstrated a significant relation between VCZ plasma levels and clinical efficacy and safety [6–8]. Based on adult data, the recommended therapeutic range of VCZ is between 1-5 mg/L [7, 9–12].

Voriconazole is approved for adults and children (> 2 years) by the United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA). In younger children, dosages higher than in adults and adolescents are required to achieve comparable VCZ exposure [13–18]. Monitoring of plasma concentrations is recommended to adapt dosage for increasing favourable IFI outcomes and reducing adverse effects.

Since the change of dose recommendations in 2012, only a few data on therapeutic drug monitoring (TDM) was reported. The present study aimed to evaluate the variability of VCZ plasma levels in children and to identify practical issues to optimize and interpret such monitoring data in children and adolescents with haematological diseases.

Methods

VCZ dose recommendations: According to the marketing authorization (EMA and Pfizer recommendations), the following dosage schedules are recommended: 8 mg/kg/12h intravenously and 9 mg/kg/12h orally for children until 12 years or from 12 to 14 years weighing less than 50 kg, whereas it is recommended to administer 4 mg/kg/12h intravenously and 200 mg/12h orally for adolescents > 12 years and weighting > 50 kg.

Study population

The study included all paediatric patients (boys and girls under the age of 18) with haematological disease treated at Robert Debré hospital. They received VCZ (V-fend®) intravenous or orally for documented or suspected IFI who had samples drawn for VCZ monitoring between January 2014 and December 2016. The research was conducted in accordance with recommendations of the French Good Clinical Practice Guidelines (CNIL number: FkY1982439v; CEERB-RD 2017/333). Parents were informed about this study.

Study design

Demographic data were collected from medical prescriptions or informatics extraction. Voriconazole indication (primary or secondary prophylaxis, curative treatment), treatment (starting day, way of administration and dosage) and monitoring (time of sampling, dose and frequency of administration) were also reported. Monitoring was performed throughout treatment and dosage timing depended on patients' follow-up frequency at Robert Debré Hospital.

Measurements of plasma levels

Samples were collected in sodium heparin tubes. The VCZ plasma concentrations were determined using a validated high-performance liquid chromatography with ultraviolet detection (HPLC-UV) method using UHPLC Dlonex Ultimate 3000 (column Waters Acquity; BEH-phenyl 2.1*100 column, particle 1.7 µm; mobile phase: Phosphate 10 mM pH 2.5 and Phosphate 10 mM pH 2.5/Acetonitrile (30/70 proportion)) after liquid-liquid extraction to eliminate interferences. The internal standard was ketoconazole and ultraviolet (UV) detection was set at 260 nm. The standard curve ranged from 0.2 to 10 mg/L. Quality controls, QC1, QC2, QC3 were 0.4, 4, and 8 mg/L respectively. The lower limit of quantification was 0.2 mg/L.

Data analysis

Monitoring data were analysed using the therapeutic range for VCZ trough concentrations at steady-state ($C_{trough,ss}$) between 1 to 5 mg/L. According to available pharmacokinetic data, the steady state was considered after 5 days since VCZ introduction, whatever patients' age. Samples drawn with incomplete information regarding patients' characteristics or dosing information were excluded from analysis.

Two age groups were defined based on dosage recommendations (Pfizer Limited. 2012. Vfend summary of product information). The first group (G1) included children until 12 years or until 14 years if they weighed less than 50 kg. The second group (G2) included children aged 12–14 years with a weight superior to 50 kg and adolescents older than 14 years. As there is an overlap in recommendations, patients aged from 12 to 14 years weighing less than 50 kg were included in G1. Voriconazole doses were considered « recommended » if they differed by less than 10% from recommended doses.

Statistical analyses were performed by SPSS v.24.0 (IBM). Due to the significant Kolmogorov-Smirnov test applied to concentrations and dosages, non-parametric tests were performed for statistical analysis. Mann Whitney U-test or Kruskal-Wallis test was used to compare different quantitative variables between groups. Categorical variables were compared using Chi^2 test or Fisher's exact test. Spearman correlation was performed to evaluate the correlation between two quantitative variables. Tests were 2-tailed and a *P*-value inferior to 0.05 was considered statistically significant.

Results

Patients' characteristics and VCZ treatment

From January 2014 to December 2016, 506 concentrations of VCZ were measured in 98 children or adolescents with haematological diseases. A total of 126 concentrations were excluded: 66 were not at steady state, 22 were not trough levels and 38 had incomplete medical or biological information.

Therefore, 380 serum concentrations in 79 patients were obtained under steady-state conditions ($C_{trough,ss}$). Patients and treatment characteristics at the first monitoring at steady-state are summarized in Table 1. Most of the patients were treated for acute leukaemia and initiated VCZ at 9.4 (0.9-16.5) years old for suspected or proven infection after allogenic hematopoietic stem cell transplantation.

Voriconazole concentrations at the first measurement were evaluated according to the therapeutic range and corresponding doses

Table 2 describes the distribution of $C_{trough,ss}$. Forty-five percent of patients had $C_{trough,ss}$ in the therapeutic range and 53% of them had received the recommended dosage, however, 47% of patients had $C_{trough,ss}$ inferior to 1 mg/L and 49% of them were treated with the recommended dose whereas 8% with a higher dose recommended. In addition, 8% of patients had $C_{trough,ss}$ superior to 5 mg/L and all had received either the recommended or a higher than recommended dose. When recommended doses are considered, 44% of patients had $C_{trough,ss}$ below the efficiency threshold and 10% above.

Table 3 reports the different $C_{trough,ss}$ (below, within and over the therapeutic range) according to dose and route of administration showing no difference between $C_{trough,ss}$ groups ($P > 0.05$). There was no impact of age, sex, biological parameters (creatinemia, urea), initial disease, the indication of VCZ on $C_{trough,ss}$ values ($P > 0.05$, consequently data not shown).

Table 1 Patients and voriconazole treatment at the first monitoring at steady-state characteristics

		Total	Age group 1	Age group 2
Total number of patients		79 (100.0%)	60 (75.9%)	19 (24.1%)
Demographic data				
Age (years)		9.4 (0.9–16.5)	8.1 (0.9–14.4)	15.5 (12.4–16.5)
Sex (girls/ boys)		46 (58.2%)/ 33 (41.8%)	36 (60.0%)/ 24 (40.0%)	10 (52.6%)/ 9 (47.4%)
Weight (kg)		34.0 (9.6–74.0)	25.2 (9.6–54.8)	55.2 (42.0–74.0)
Underlying haematologic disease				
ALL		39 (49.4%)	28 (46.7%)	11 (57.9%)
AML		19 (24.1%)	14 (23.3%)	5 (26.3%)
Medullary aplasia		12 (15.2%)	11 (18.3%)	1 (5.3%)
JMLL		3 (3.8%)	3 (5.0%)	0 (0.0%)
Others		6 (7.6%)	4 (6.7%)	2 (10.5%)
VCZ treatment at first $C_{trough,ss}$				
Indication	Prophylaxis	34 (43.0%)	27 (45.0%)	7 (36.8%)
	Suspected or proven IFI	45 (57.0%)	33 (55.0%)	12 (63.2%)
Transplantation status	Pre-transplant	31 (39.2%)	25 (41.7%)	6 (31.6%)
	Post-transplant	48 (60.8%)	35 (58.3%)	13 (68.4%)
Route of administration	Orally	51 (64.6%)	38 (63.3%)	13 (68.4%)
	Intravenously	28 (35.4%)	22 (36.7%)	6 (31.6%)
Doses administered (mg/kg/12h)	Orally	5.9 (2.4–13.8)	8.1 (2.5–13.8)	3.9 (2.4–6.0)
	Intravenously	7.5 (2.8–13.3)	7.8 (4.2–13.3)	3.7 (2.8–4.6)
Biological parameters	Creatininemia (mmol/L)	40.0 (14.0–89.0)	31.0 (14.0–62.0)	58.0 (38.0–89.0)
	Urea (mmol/L)	4.4 (0.8–12.6)	4.3 (0.8–12.6)	5.0 (1.5–11.7)

Values are presented as percentages or medians (range). (G1) included children until 12 years or until 14 years if they weighed less than 50 kg. The second group (G2) included children aged 12-14 years with a weight superior to 50 kg and adolescents older than 14 years. Percentages were calculated for each item per age group. ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia; JMML, juvenile chronic myelomonocytic leukemia; IFI, invasive fungal infection.

Table 2 Number of patients with voriconazole concentrations at steady state at the first evaluation within or out therapeutic range and corresponding doses

		VCZ trough concentrations					
		below		within		above	
Number of patients receiving VCZ dosages (n)	79	37	47%	36	45%	6	8%
Inferior to recommended doses	26	16	62%	10	38%	0	0%
	33%	43%		28%		0%	
At recommended doses	41	18	44%	19	46%	4	10%
	52%	49%		53%		67%	
Superior than recommended doses	12	3	25%	7	58%	2	17%
	15%	8%		19%		33%	

Values are presented in effective (n) and percentages (%).

Table 3 Concentrations at the first evaluation at steady-state within or out of therapeutic target and corresponding voriconazole doses

	VCZ trough concentrations			
VCZ administered doses (mg/kg/12h)	<1 mg/L	1–5 mg/L	> 5mg/L	*P*-value
Orally	6.5 (2.4–9.4)	4.6 (2.5–13.3)	9.1 (3.9–13.8)	0.1
Intravenously	5.9 (2.8–13.3)	7.9 (3.6–11.5)	7.3 (7.3–7.3)	0.4
Lower than recommended doses				
Orally	5.5 (2.4–7.5)	4.3 (2.5–5.7)	/	0.2
Intravenously	4.2 (2.8–5.9)	6.0 (5.7–6.2)	/	0.1
At recommended doses				
Orally	8.5 (2.7–9.4)	8.1 (3.0–9.8)	8.8 (3.9–9.1)	0.6
Intravenously	7.7 (3.7–8.2)	7.9 (3.6–8.4)	7.3 (7.3–7.3)	0.5
Higher than recommended doses				
Orally	6.0 (6.0–6.0)	10.8 (4.3–13.3)	12.2 (10.6–13.8)	0.5
Intravenously	11.7 (10.1–13.3)	10.6 (4.6–11.5)	/	0.5

Values are presented in median and range.

Evaluation of VCZ dosage according to therapeutic range throughout treatment

Including following monitoring at steady-state per patient, a total of 380 $C_{trough,ss}$, i.e., 3 (1–25) per patient, were measured at steady state in 79 patients. Their number differs between patients, depending on clinical presentation, initial $C_{trough,ss}$ value, modification of dosage or route of administration, duration of treatment. As a result of repeated measures, the number of $C_{trough,ss}$ in the therapeutic range increased with the monitoring (Figure 1A, based on data from 79 patients with a number of $C_{trough,ss}$ per patient ranging from 1 to a maximum of 10). This VCZ monitoring throughout treatment revealed: a) 36 patients (45.6%) reached an adequate $C_{trough,ss}$ at the first measurement at steady-state obtained after a median delay of 14.0 (5.0–120.0) days since the introduction of voriconazole; b) 21 patients (26.6%) never reached the therapeutic range (but 8 patients had only one $C_{trough,ss}$ available); c) 22 children (27.8%) who were not in the therapeutic range at the first measurement, had adequate $C_{trough,ss}$ after a median delay of 30.0 (13.0–188.0) days since the introduction of voriconazole. This corresponds to 1 (0–4) dose modifications since the analysis of the first monitoring at steady state.

The median oral dose at adequate first $C_{trough,ss}$ was higher in children with first $C_{trough,ss}$ initially out of therapeutic range compared to children with initial $C_{trough,ss}$ in therapeutic range (7.8 (1.9–12.5) mg/kg/12h versus 4.6 (2.5–13.3) mg/kg/12h). Regarding intravenous administration, the median intravenous dose was 7.2 (3.2–17.3) mg/kg/12h and 7.9 (3.6–11.5) mg/kg/12h, in patients with initial $C_{trough,ss}$ out and those with initial $C_{trough,ss}$ in target range, respectively.

Intra-patient variability of trough concentrations at steady state

There is wide intra-individual variability in trough concentrations of VCZ: the median ratio of the highest to the lowest $C_{trough,ss}$ per patient at the same weight-adjusted dose was 2.1 (1.0–14.1). Figure 2 showed the variability of $C_{trough,ss}$ for each patient with at least 3 monitoring at the same specific weight-adjusted dose (mg/kg/12h), (i.e., 185 $C_{trough,ss}$ in 30 patients were available).

Analysis of trough concentrations at steady state in two different age groups

As defined, G1 and G2 differed by age and consequently by recommended VCZ doses. At the first measurement, the median oral dose in G1 was 8.1 (2.5–13.8) mg/kg/12h and 3.9 (2.4–6.0) mg/kg/12h in G2. The median intravenous dose was 7.8 (4.2–13.3) mg/kg/12h in G1 and 3.7 (2.8–4.6) mg/kg/12h in G2. The number of $C_{trough,ss}$ in the therapeutic range at first monitoring was not different between G1 and G2 (for 27/60 patients (45%) versus 9/19 patients (47%)).

The number of $C_{trough,ss}$ below 1 mg/L (for 47% of patients) or over 5 mg/L (< 10% of patients) were also similar. Figure 3 shows the distribution of the first $C_{trough,ss}$ measures compared to age group and route of administration of VCZ. No correlation between doses and $C_{trough,ss}$ has been found in each age group ($P > 0.05$). When the target $C_{trough,ss}$ was reached, the median VCZ oral dose was 8.1 (2.5–13.3) mg/kg/12h and 4.3 (1.9–7.1) mg/kg/12h, respectively in G1 and G2 whereas voriconazole intravenous dose was 8.3 (5.7–17.3) mg/kg/12h and 4.1 (3.2–4.6) mg/kg/12h in G1 and G2 (Figure 4). Dose distribution in the two different age groups was extended. Respectively 28/60 (46.7%) patients in G1 and 13/19 patients (68.4%) in G2 received recommended VCZ doses. In terms of target $C_{trough,ss}$, it was reached for 12/28 patients of them in G1 and 7/13 of them in G2 group.

The whole duration of treatment was monitored in 40 patients and lasted 69.0 (13.0–260.0) and 76.5 (12.0–321.0) days respectively in G1 (n = 39) and G2 (n = 10). If the last monitoring is considered, only 54.3% of patients in G1 and 81.3% of patients in G2 were in the therapeutic range (Figure 1B).

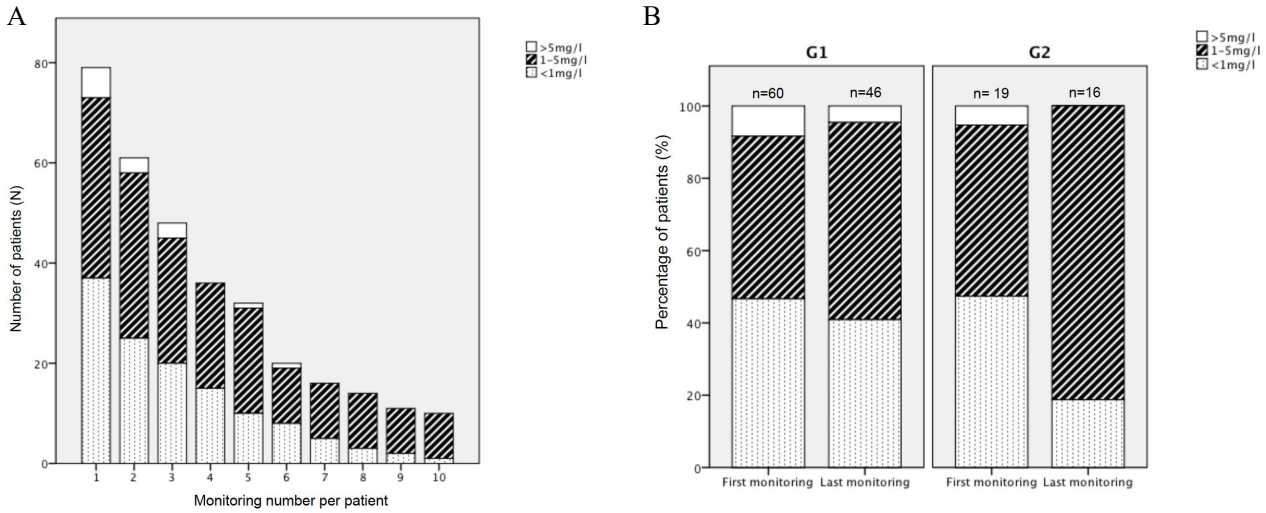

Figure 1 Distribution of children in therapeutic range. (A) Proportion of patients reaching the target voriconazole $C_{trough,ss}$ according to the number of voriconazole $C_{trough,ss}$ measurements per patient; (B) Distribution of $C_{trough,ss}$ in age groups G1 and G2 at two different periods. (first and last monitoring at steady performed in the pharmacology department at Robert Debré hospital and analysed per patient). (G1) included children until 12 years or until 14 years if they weighed less than 50 kg. The second group (G2) included children aged 12-14 years with a weight superior to 50 kg and adolescents older than 14 years.

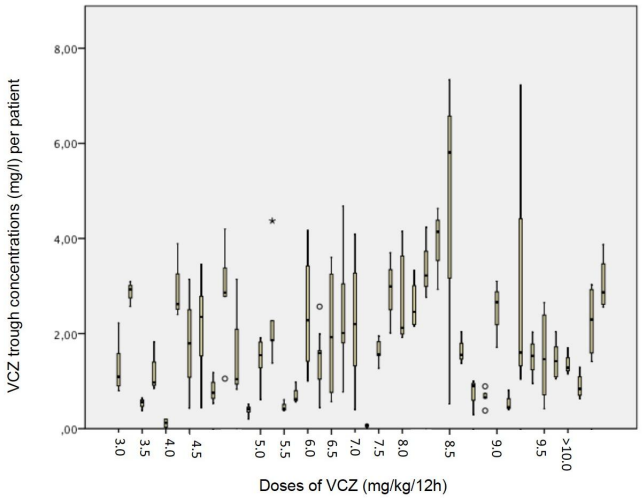

Figure 2 Intra-patient variability of voriconazole serum levels (median, minimum, maximum, Interquartile Range per patient at a specific weight-adjusted dose). Patients who had 3 or more measurements at two different doses, were included. VCZ, voriconazole.

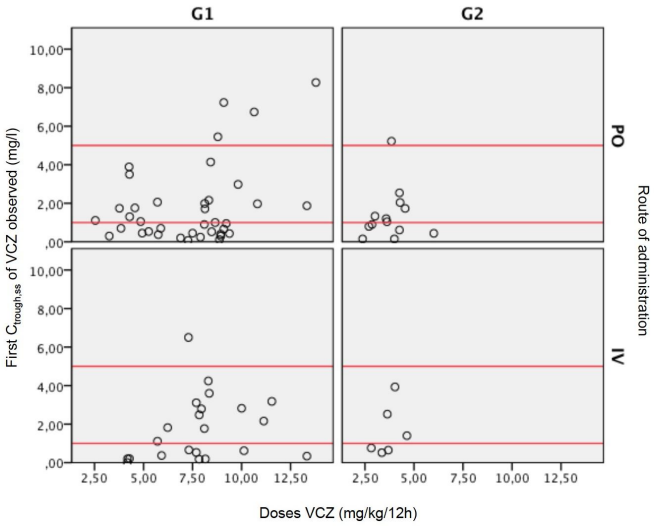

Figure 3 Distribution of $C_{trough,ss}$ at first monitoring at steady state in G1 and G2. Black lines indicate the limits of the therapeutic range (1-5 mg/L). VCZ, voriconazole; $C_{trough,ss}$, trough concentration at steady-state; PO, per os; IV, intravenously.

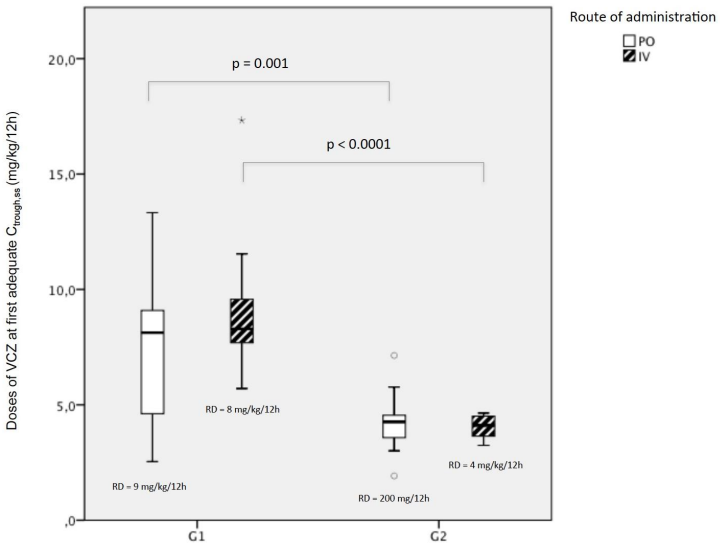

Figure 4 Doses required to achieve therapeutic range by route of administration in G1 and G2 group. RD, Recommended doses; VCZ, Voriconazole; $C_{trough,ss}$, trough concentration at steady-state; PO, per os; IV, intravenously.

Discussion

This study confirmed the wide inter- and intra-individual variability of VCZ monitoring concentrations measured in paediatric patients with haematological disease treated for suspected or proven IFI. We demonstrated that standardized conditions and quality of monitoring could improve results interpretation, treatment modifications and treatment outcomes.

Voriconazole is rapidly absorbed in adults and its hepatic metabolism depends on different cytochrome P450 (CYP) isoenzymes (CYP2C19, CYP2C9 and CYP3A4). Steady-state plasma concentrations are reached in approximately 5 days [19]. At recommended doses, the pharmacokinetics is non-linear, highly variable both in adults and children [20] and the relation between VCZ dose and pharmacokinetic parameters or trough concentrations at steady-state remains a matter of debate. A significant correlation between doses and trough concentrations in patients of different age groups, from infants to adolescents has been proved in some studies [21–23]. Conversely, others have confirmed this correlation but only in younger children or adolescents [24, 25], while no correlation have been found in others studies [8, 26, 27].

The therapeutic range of VCZ concentrations was validated in adults and values between 1 and 5 mg/L were demonstrated to be effective, associated with improved response increasing survival and reducing side effects [7, 9–12]. In the same way, trough concentrations below 1 mg/L in children were associated with risk of failure therapy [25, 28, 29] while adverse events occurred with concentrations at a steady state over 5 mg/L [5, 21, 23, 30].

According to pharmacokinetic variability and narrow therapeutic range, monitoring of VCZ concentrations is recommended to adapt treatment to individual patients but is not mandatory [31]. It was performed on paediatric patients treated in the haematology department. We first included all samples received from clinicians and analysed the information on patients' characteristics and dosage regimens. In the first step, we had to exclude 25% of the samples because of missing or misleading information related to doses, sampling time or covariates required to interpret the data. This first selection of samples illustrated that the conditions required to allow the interpretation of drug monitoring are not always fulfilled. In particular, at least five days after VCZ initiation are required to reach steady-state concentrations and interpret monitoring concentrations resulting in treatment changes if out of the therapeutic range.

Our data showed that only approximately 50% of the patients treated with doses recommended in the marketing authorisation had trough concentrations in the therapeutic range at first monitoring at steady state. In addition, first $C_{trough,ss}$ below the therapeutic range were associated with more than 50% of patients receiving lower than recommended doses. This suggests that, in the first step, administration of recommended doses will increase the number of patients with trough concentrations in the target, however, in agreement with previous reports, recommended paediatric doses did not always allow to reach the therapeutic target in children [29, 32–34].

In order to investigate the impact of age, we considered two groups of treated children, based on the two age groups defined in the marketing authorization. Similarly, when the two age groups are considered, only half of the patients received the recommended doses and among them, about 50% had VCZ trough concentrations in the therapeutic range. Similar results were found in two other studies [27, 35].

In our study, no significant impact on patients' characteristics, biological parameters, and VCZ dosages was found. However, various other factors have been discussed to contribute to VCZ inter-individual variability [6, 10] 1) As confirmed in our study, age is an important factor of variability. Voriconazole clearance is higher in young children than in older children and adults [20, 28, 36, 37] and oral bio-availability is reported to be lower in children compared to adults (44.6% vs. 96%) [20, 38]. According to data previously reported, EMA approved an increased dose regimens in younger based on pharmacokinetics studies in children [13, 14, 17]. 2) Pharmacogenetic as VCZ is extensively metabolized to N-oxide voriconazole through 2C19, is a relevant factor. Previous studies have shown the important impact of 2C19 genetic variants in VCZ plasma levels both in adults and children [39–41]. 3) Drug interactions, as VCZ is extensively metabolized, drug interactions with metabolism will influence elimination and steady-state concentrations [42]. In children, proton pump inhibitors, antiepileptic drugs, immunosuppressant, among others, are substrates of CYP2C19 and CYP3A4 and such associations with VCZ will result in changes in drug exposure [19, 43, 44]. 4) Food intake may also influence VCZ serum levels as the bioavailability of VCZ was reduced by 22% when administered with food compared with fasting [45]. 5) Recent studies also identified the impact of inflammation status on the VCZ plasma level [46, 47].

According to the wide variability, resulting from many factors, some of which are difficult to control, a standardized protocol to monitor trough concentrations considering doses, route of administration, age, comedications, should be followed to conduct and interpret monitoring, also considering 2C19 genotype [48]. The first monitoring should be planned early after the initiation of treatment, remembering that the therapeutic range is defined with steady-state concentrations. However, dose adjustments can also be performed before a steady state to reach therapeutic range as soon as possible [49]. In our study, the number of monitoring at steady-state was variable and some patients never reached the therapeutic target. The delay between the initiation of VCZ therapy and the time to achieve this target is sometimes too long for out-patients; consequently, recommendations on how to adapt dosage are needed.

As monitoring demonstrated a significant improvement in treatment outcomes in patients who benefited from therapeutic drug monitoring versus those who did not [29], and due to a lack of guidelines, we propose a procedure to standardize monitoring in children: 1) The first monitoring must be performed soon as possible to permit early dose adjustment and a first $C_{trough,ss}$ in therapeutic range taking into account the inflammatory status of children (albumin level and C-reactive protein level). 2) Each monitoring must be performed at least once per week due to the wide variability. 3) At changes of doses/route of administration/comedications or in case of suspected non-compliance/adverse reactions, new monitoring could be done. 3) Dosage adjustments must be based on real trough concentrations at steady-state, i.e., only just prior to the next administration of VCZ.

Recently, the PBK model was performed to determine VCZ plasma concentration including age, CYP3A4 and CYP2C19 genetics and infectious fungal genera. This model permitted to predict exposure in children after intravenous VCZ treatment [50]. Additional data is needed to improve the model. The next step could be to perform a Bayesian model to select initial doses in children starting on VCZ, taking into account all factors previously described to reduce this variability in VCZ trough concentrations.

Conclusion

Our study, in agreement with previous paediatric reports, confirms wide inter- and intra-individual variability in trough VCZ concentrations. We identified that the initial dosage does not always follow the marketing authorization and recommended doses do not always result in the achievement of the therapeutic target in children. We demonstrated that VCZ monitoring is complementary to age-adapted dosage recommendations. In order to optimize treatment, identification of all factors that impact individual data is required to allow optimal dosage adaptation, based on the disease, drug interactions and individual CYP2C19 genotype. It is crucial to achieve rapid development of guidelines to standardize protocols for TDM of VCZ.

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