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Voriconazole drug monitoring in the management of invasive fungal infection in immunocompromised children: a prospective study

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Objectives: To evaluate voriconazole plasma level monitoring in immunocompromised children and determine the relationship of plasma levels with dose, safety and efficacy.

Methods: We used a prospective study including all consecutive children with invasive fungal infection (IFI) treated with voriconazole between August 2008 and May 2010. IFI diagnosis and clinical outcome evaluation were based on 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') definitions.

Results: A total of 196 voriconazole plasma trough measurements from 30 patients (median age 10 years) obtained during 2135 days of voriconazole therapy were analysed. Nineteen patients (63%) presented with proven or probable IFI. Voriconazole plasma levels varied widely and 73% of patients required dose adjustment. The median voriconazole dose was 20 mg/kg/day and the median duration of therapy was 6 weeks. Age 5 was the smallest value defining two groups on which the correlation between dose and plasma levels had a different behaviour, and this relationship was especially significant for patients <5 years old (Spearman's rank correlation coefficient=0.38213, $P=0.008$). For patients <5 years old the median dose to achieve therapeutic levels was 38.0 mg/kg/day (12–40.0) and for those ≥5 years old it was 15 mg/kg (4–52). Voriconazole plasma levels showed a significant relationship with early outcome ($P=0.0268$), but not late outcome ($P=0.2015$). Overall mortality was 42% and a significant relationship with voriconazole therapeutic plasma levels was not demonstrated. A significant relationship was established between plasma levels above normal range and skin and neurological toxicity ($P=0.0001$), but this could not be demonstrated for liver toxicity.

Conclusions: Our study confirms the large variability in voriconazole trough plasma levels in children and a trend to non-linear pharmacokinetics in older patients. In addition, doses significantly higher than those recommended in younger children seem warranted and a significant relationship between plasma voriconazole above the normal range and some adverse events is confirmed.

Keywords: antifungal therapy, therapeutic drug monitoring, adverse drug events, aspergillosis, candidiasis

Introduction

Invasive fungal infection (IFI) is a life-threatening disease in immunocompromised patients. IFI has high morbidity and mortality rates and its management continues to challenge clinicians. Understanding the pharmacokinetics/pharmacodynamics of antifungal drugs is extremely important for optimal drug choice and dosing regimen design. In addition, it is known that variability in plasma levels of most drugs is greater in the paediatric population.[1]

Voriconazole is a triazole with broad-spectrum antifungal activity. It is considered to be a first-line agent against invasive aspergillosis and is currently a treatment option for other IFI, such as fusariosis, scedosporidiasis and candidiasis.[2–4]

Voriconazole plasma levels are quite unpredictable because several pharmacokinetic variables influence its steady-state plasma concentration. Age, decreased absorption of oral voriconazole formulations with meals (although less significant), interactions with co-medications, self-induced metabolism, genetic cytochrome P450 polymorphisms (mainly CYP2C19)

and liver disease have been shown to impact voriconazole pharmacokinetics, leading to high inter-individual and intra-individual variability in plasma concentrations in clinical practice.[5–7] This variability may be associated with decreased efficacy or toxicity, indicating a possible need for therapeutic drug monitoring (TDM). In addition, there have been reports in both adult and paediatric patients of a significant relationship between voriconazole plasma levels and clinical efficacy and/or safety.[8–17] Therefore, it has been suggested that TDM of voriconazole concentrations should be performed to maximize efficacy and minimize adverse events.[8,9]

Given the paucity of information on voriconazole pharmacokinetics in paediatrics,[18–21] we conducted a prospective study of all paediatric patients who underwent voriconazole TDM in our centre.

The objectives of our observational study were: (i) to assess pharmacokinetic and pharmacodynamic variability of voriconazole in the treatment of children with IFI according to patients' age and route of administration; and (ii) to establish a potential relationship between voriconazole trough plasma levels and its efficacy and safety in children with proven or probable IFI.

Patients and methods

This prospective, non-interventional study was conducted at the Vall d'Hebron University Hospital, a tertiary-care centre that serves a paediatric reference population of 55131 people in the city of Barcelona, Spain.

Informed consent was obtained from all legal guardians and the study was approved by the Institutional Review Board of our hospital.

Patients

All consecutive paediatric patients (<18 years old) with IFI who were treated with voriconazole, alone or together with other antifungal drugs, between August 2008 and May 2010 were studied prospectively. Demographic data, underlying conditions, clinical characteristics, diagnosis of IFI, response to voriconazole therapy, concomitant medication known to modify voriconazole pharmacokinetics and voriconazole-related adverse events were recorded.

IFI definition

IFIs were classified as either proven, probable or possible according to the 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).[22] Data from patients included who did not fulfil EORTC/MSG criteria of either proven or probable IFI were included in the pharmacokinetics and safety analysis, but not in the efficacy analysis.

Voriconazole monitoring

Initial voriconazole dosing and administration route were based on current guidelines and the manufacturer's recommendations. Plasma levels were measured 30 min prior to the next dose on the fifth day of therapy, and weekly thereafter, as per clinical daily practice in our centre. The trough plasma levels were determined by a modification of a previously reported HPLC method.[8] The limit of quantification, defined as the lowest voriconazole amount that could be quantified in a plasma sample with ±20% accuracy and precision, was 0.2 mg/L. Samples below this threshold were entered as 0 mg/L. The therapeutic interval for voriconazole troughs was 1–5.5 mg/L regardless of the localization of infection, in the light of previous studies assessing the relationship between plasma concentration and outcome or toxicity.[8] If required, individualized dose adjustments were made following daily clinical practice as follows: (i) a 50% increase in daily dose in patients with pre-dose plasma concentrations <1 mg/L; (ii) an interval of administration adjustment from twice to three times a day in patients who undergo repeated 50% increases without reaching the therapeutic range; and (iii) discontinuation of voriconazole administration for 1 day in patients with pre-dose plasma concentrations >5.5 mg/L or adverse events related to voriconazole, followed by a 50% decrease in daily dose once the plasma concentration was found to be in the therapeutic range.[8] CYP2C19 polymorphism was not assessed in this study.

Clinical outcome assessment

EORTC/MSG definitions were used.[23] As noted above, only patients with proven or probable IFI were included in the efficacy analysis. Response to voriconazole was categorized into complete response (CR), partial response (PR) or stable disease (SD), progression of disease (PD) and death. Outcomes were analysed at two moments: (i) early outcome (Outcome 1), at 6 weeks of antifungal therapy in invasive filamentous fungal infection and at 4 weeks in invasive candidiasis; and (ii) late outcome (Outcome 2), at 12 weeks of antifungal therapy in all types of IFI.

Safety assessment

The type and severity of the adverse events related to voriconazole were recorded and were evaluated with the Division of AIDS (DAIDS) Adverse Events Grading Table (http://rsc.tech-res.com/safetyandpharmacovigilance) over the treatment period.

Drug–drug interactions

All co-medications that could potentially alter voriconazole levels were recorded. Doses and plasma levels in patients receiving these co-medications were not included in the statistical analysis when evaluating the relationship between voriconazole daily dose and trough plasma concentrations.

Statistical analysis

Proportions were compared with the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared with the non-parametric Wilcoxon Mann–Whitney test or the Kruskal–Wallis test, as appropriate. Statistical significance was defined by a two-sided P value of <0.05. The Spearman method was used to study the correlation of two variables. A logistic regression analysis was performed to assess whether the log-transformed voriconazole trough concentration is a significant predictor of response to therapy (coded as success, CR/PR or lack of response, SD, PD or death), safety (coded as the absence or presence of toxicity) and survival. Exploratory data analysis, obtaining the Spearman correlation coefficient between the dose and plasma levels, for different age grouping criteria, have been applied.

Results

Study population

Thirty patients (median age 10 years, range 1 month–17 years) were included during the study period; 53% were males and 70% were Caucasians. Sixty-four measurements were made in 10 patients <5 years of age. The most frequent underlying

Table 1. Patients' demographic and clinical characteristics

	Global population	Proven and probable IFI
Number of patients	30	19
Age, median (minimum–maximum)	10 years (1 month–17 years)	10 years (1 month–16 years)
Gender, male/female, *n* (%)	16 (53.3)/14 (46.7)	8 (42.1)/11 (57.9)
Ethnicity, *n* (%)		
Caucasian	21 (70)	13 (68.4)
Asian	1 (3.3)	0
Maghreb	4 (13.3)	2 (10.5)
African Black	1 (3.3)	1 (5.3)
South American	3 (10)	3 (15.8)
Underlying disease, *n* (%)		
oncohaematological malignancy	6 (20)	5 (26.3)
stem cell transplantation	10 (33.3)	6 (31.6)
solid organ transplantation	9 (30)	5 (26.3)
primary immunodeficiency	3 (10)	3 (15.8)
other	2 (6.7)	0
Isolated microorganism, *n* (%)		
A. flavus		2 (10.5)
A. fumigatus		9 (47.4)
A. fumigatus/A. terreus		1 (5.3)
Aspergillus spp.		2 (10.5)
S. prolificans		1 (5.3)
C. albicans		1 (5.3)
C. krusei		1 (5.3)
C. tropicalis		1 (5.3)
Site of infection, *n* (%)		
disseminated candidiasis[a]		3 (16)
candidaemia		0
pulmonary aspergillosis (and other moulds)		12 (63)
disseminated aspergillosis (and other moulds)[b]		4 (21)

[a]CNS (1), liver and spleen (1), multiple organ involvement (1).
[b]Lung, CNS and eyes (2), lung and liver (1), endocarditis and multiple organ involvement (1).

conditions were stem cell transplantation and oncohaematological malignancies (53.3%). Among the 30 patients treated with voriconazole, 19 (63%) had proven or probable IFI; 5 of them were neutropenic (26%) at the time of diagnosis. Patients' demographic data and clinical characteristics are summarized in Table 1.

Fifteen of 19 patients with proven or probable IFI were treated using combined antifungal therapy: echinocandins in combination with voriconazole in 8 patients and liposomal amphotericin B in 11 (some patients were treated using more than one combination at different moments).

IFIs and mycological data in the group of proven/probable IFIs

The most common infection site was the lung (37%), and IFI was disseminated in 17%. Moulds accounted for 83% of all isolates (9 *Aspergillus fumigatus*, 2 *Aspergillus flavus*, 1 *A. fumigatus/A. terreus*, 2 *Aspergillus* spp. and 1 *Scedosporium prolificans*) and yeasts for 17% (1 *Candida albicans*, 1 *Candida krusei* and 1 *Candida tropicalis*) (Table 1).

Voriconazole therapy and measurements of trough plasma levels

A total of 2135 days of voriconazole therapy, alone or as a part of a combination regimen, in 30 patients with TDM were studied. The median dose of voriconazole was 20 mg/kg/day (range 3.5–52 mg/kg/day) and the median duration of therapy was 6 weeks (range 1–84 weeks) per patient. There were no significant differences between oral and intravenous administration in the necessary dose to achieve therapeutic levels (Table 2). Patient 10 (autosomal dominant hyperIgE syndrome and *A. fumigatus* pulmonary infection with unfavourable Outcome 1 and Outcome 2,

who survived and is still on therapy) received a dose of 3.5 mg/kg/day because voriconazole levels exceeded normal (8.7 mg/L) and the patient showed related toxicity (hallucinations and dizziness) with the recommended dose. Patient 5 (heart transplantation and *A. fumigatus* pulmonary infection with favourable Outcome 1 and Outcome 2, who survived) was scaled up to 52 mg/kg/day because therapeutic levels could not be reached with lower doses and voriconazole-related toxicity was absent.

A total of 196 voriconazole trough plasma concentrations were obtained (mean number per patient 6.5, range 1–35). Among these concentrations, 46% were obtained in patients receiving intravenous voriconazole. Ninety-eight (50%) of the 196 samples were reported as <1 mg/L and 14 (7%) were >5.5 mg/L. A total of 73% of patients required a dose adjustment after voriconazole plasma levels were measured. Voriconazole plasma levels correlated significantly with the daily dose (Spearman's rank correlation coefficient=0.24044, $P=0.0009$). Age 5 was the smallest value defining two groups (<5 years and ≥5 years) on which the correlation between dose and plasma levels had a different behaviour, and this relationship was especially significant for patients <5 years old (Spearman's rank correlation coefficient=0.38213, $P=0.008$). For patients <5 years old, the median dose to achieve therapeutic levels was 38.0 mg/kg/day (range 12–40 mg/kg/day) and for those ≥5 years old it was 15 mg/kg (range 4–52 mg/kg/day) (Figure 1). In the global population the median dose to achieve therapeutic levels was 21.5 mg/kg/day (range 4–52 mg/kg/day), the median dose for suboptimal plasma levels was 20 mg/kg/day (range 3.5–52 mg/kg/day) and the median dose for supra-therapeutic plasma levels was 24.0 mg/kg/day (range 8–52 mg/kg/day).

When administered intravenously suboptimal plasma levels were related with a median dose of 14 mg/kg/day (range 8–38 mg/kg/day) and levels above normal were related with a median dose of 22 mg/kg/day (range 8–28 mg/kg/day), with significant differences (Kruskal–Wallis $P=0.0188$).

Table 2. Voriconazole dosage, route of administration and trough plasma levels

	Trough plasma levels (mg/L)		
	<1	1–5.5	>5.5
Samples, *n* (%); *N*=196	98 (50)	84 (43)	14 (7)
Route of administration			
oral, *n* (%); *N*=105	52 (50)	49 (46)	4 (4)
intravenous, *n* (%); *N*=91	46 (51)	35 (38)	10 (11)
Dosage (mg/kg/day), median (range)			
overall	20 (3.5–52)	20 (3.5–52)	24 (8–52)
oral	22 (3.5–52)	30.5 (3.5–52)	26 (9.5–52)
intravenous	14 (8–38)	20 (8–40)	22 (8–28)

Response to voriconazole therapy

The mortality rate in the global population was 40% (12 of 30). Of the 19 patients with proven or probable IFI, 42% died (8 of 19). Only half of these deaths (21%) were due to the IFI *per se* (all of them were related to mould infection and in three-quarters the cases included CNS involvement). Although the EORTC/MSG criteria would consider any death during the pre-specified period of evaluation, regardless of attribution when evaluating response to antifungal therapy, four patients who died from their underlying disease were excluded from the efficacy analysis in the present study since all of them died between the second and third week after voriconazole was initiated. Moreover, results remain unchanged when including these patients in the outcome analysis, both for Outcome 1 and Outcome 2 (data not shown). A greater percentage of patients who died had suboptimal voriconazole levels, although the difference was not statistically significant, probably due to the small sample

Table 3. Relationship between voriconazole plasma levels and Outcome 1, Outcome 2 and survival

			Trough plasma levels (mg/L)		
	Number of cases	Number of samples	<1, *n* (%)	≥1, *n* (%)	*P*
Outcome 1 (until week 4 or 6 for yeasts and moulds, respectively)					
all	15	68	33	35	$P=0.0268$
favourable	9	42	16 (38.1)	26 (61.9)	
unfavourable	6	26	17 (65.4)	9 (34.6)	
Outcome 2 (until week 12 for both yeasts and moulds)					
all	13	103	55	48	$P=0.2015$
favourable	7	51	24 (47.1)	27 (52.9)	
unfavourable	6	52	31 (59.6)	21 (40.4)	
Survival status					
died	8	46	25 (54.3)	21 (45.7)	$P=0.3258$
survived	11	120	55 (45.8)	65 (54.2)	

included (Table 3). Patients who survived had a similar percentage of suboptimal and therapeutic levels. It has to be considered that most patients with proven or probable IFI were receiving, at some point, combined antifungal therapy. Thus, this could interfere when evaluating voriconazole efficacy itself.

Fifteen patients were included in the evaluation of Outcome 1. Among them, nine (60%) had a favourable outcome (three complete responses and six partial responses), two remained stable, three had disease progression and one died. Voriconazole trough plasma levels ≥1 mg/L during the first 4 or 6 weeks for yeasts and moulds, respectively, were statistically associated with a favourable Outcome 1 ($P=0.0268$) (Table 3 and Figure 2). No significant relationship could be demonstrated for route of administration or median dosage.

Thirteen patients were included in the evaluation of Outcome 2, since two more patients were excluded for the efficacy analysis at 12 weeks of therapy (one premature death and one patient transferred to another hospital). Among these patients, seven (54%) had a favourable outcome (five complete responses and two partial responses), two patients remained stable, one patient's infection progressed and three patients died (Table 3). No relationship could be established between voriconazole trough plasma levels ≥1 mg/L until week 12 and Outcome 2 in either week 2 or week 12 (Table 3). Similarly, no relationship was found with route of administration and dosage to Outcome 2.

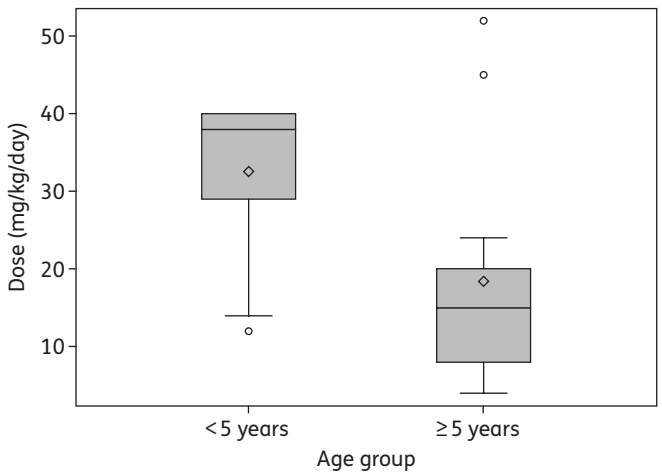

Figure 1. Voriconazole doses in patients <5 years old and ≥5 years old achieving trough therapeutic plasma levels of voriconazole (1–5.5 mg/L). Median and mean values of administered voriconazole for patients <5 years old were 38.00 mg/kg/day and 32.59 mg/kg/day, respectively. Median and mean values of administered voriconazole for patients ≥5 years old were 15.00 mg/kg/day and 18.46 mg/kg/day, respectively.

Safety of voriconazole therapy

Twelve adverse events were documented in eight patients (Table 4). Eight of them occurred when voriconazole plasma concentrations were >5.5 mg/L, leading to transient voriconazole discontinuation in all these patients. The most common adverse effects were elevated liver enzymes (>10-fold increase in γ-glutamyl transferase), neurological disturbances and phototoxicity skin reactions. Five of six patients with liver toxicity had received stem cell transplantation. A significant relationship was demonstrated between above-normal plasma voriconazole levels and neurological and skin side effects ($P=0.0001$), but this could not be demonstrated for liver toxicity. All adverse events disappeared after drug discontinuation.

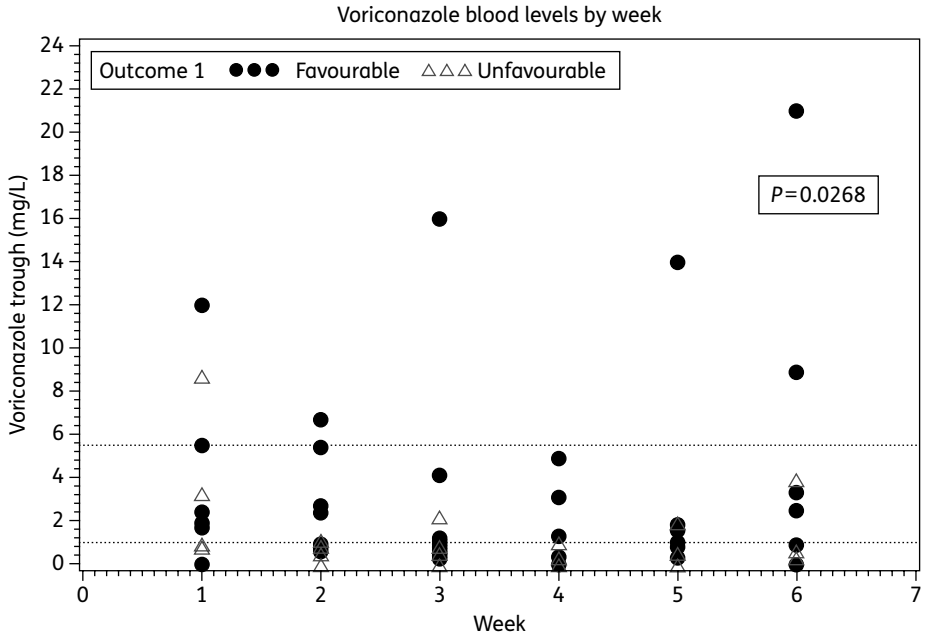

Figure 2. Relationship between voriconazole trough therapeutic plasma levels until week 4 (yeasts)/week 6 (moulds) and Outcome 1.

Table 4. Side effects described in the global population

	Total number	Trough plasma levels <1 mg/L	Trough plasma levels 1–5.5 mg/L	Trough plasma levels >5.5 mg/L	Severity
Neurological side effects					1 severe; 1 moderate; 1 mild
visual hallucinations	2	—	—	2	
irritability/dizziness	1	—	—	1	
Gastrointestinal and hepatic side effects					6 severe; 1 mild
>10-fold increase in γ-glutamyl transferase	6	2	2	2	
gastrointestinal intolerance	1	—	—	1	
Phototoxicity and skin reactions	2	—	—	2	2 moderate
Total	12	2	2	8	7 severe; 3 moderate; 2 mild

Drug–drug interactions

Only one patient received concomitant carbamazepine; obviously, voriconazole plasma levels were extremely low until carbamazepine was discontinued. Ninety percent of patients received concomitant omeprazole that was properly dosed. No other drugs that could influence voriconazole plasma levels were recorded.

Discussion

The most extensive prospective study to date on monitoring voriconazole plasma concentrations in the paediatric population is presented, with a follow-up of 2135 days of treatment with this drug in 30 patients <18 years of age. Half of the patients enrolled had a haemato-oncological disease or had undergone haematopoietic stem cell transplantation and were treated with voriconazole for filamentous fungi, often as part of a combined antifungal regimen. These data coincide with the findings of previously published paediatric studies.[18,20]

Although determination of the area under the curve (AUC) would provide a more accurate measurement of the real exposure to voriconazole, it is difficult to obtain in daily clinical practice. Consequently, trough concentrations are used as a practical alternative in pharmacokinetic studies of voriconazole.[8,9,11,19,20,24,25] Evaluation of the trough concentrations in our study established an extensive inter-individual variability already reported in previous publications.[8,9,11–19,20,24,25] Approximately half of the determinations obtained in our patients revealed subtherapeutic levels and 7% were >5.5 mg/L. Dose modification according to levels was required in up to 73% of our patients at some time during treatment, which confirms the need for monitoring.

The present study reinforces the idea of a significant relationship between the dosage administered and the resulting plasma concentration in the paediatric population, a relationship that seems much more overt in our patients <5 years old. This is consistent with the fact that children, in contrast with adult patients,[8,9,26] show linear pharmacokinetics for voriconazole. In addition, the median dose that yields therapeutic plasma concentrations in children <5 years of age is 38 mg/kg/day, much higher than the 14 mg/kg/day currently recommended for this age group, which seems to be adequate for children ≥5 years old.

This notwithstanding, no statistically significant relationship was demonstrated between plasma voriconazole concentration and overall survival, in contrast with other studies.[20,24] However, a higher percentage of subtherapeutic plasma voriconazole concentrations was observed in the patients who died. These discrepancies in relation to previous studies may be due to the prospective design of our study, which involved immediate dose modification and possibly a better prognosis in these patients. This fact is reinforced by the low mortality of the present study (42% overall and 21% directly related). Furthermore, the small sample size may also influence these differences.

The relationship between plasma voriconazole concentration within the therapeutic range and favourable Outcome 1 was not maintained for Outcome 2. Thus, the initial trend of a sustained relationship between plasma concentration and overall efficacy could not be demonstrated in the present study. Nevertheless, data from the efficacy analysis should be interpreted with caution since most of the evaluated patients (15 of 19 patients with proven or probable IFI) were treated using combination therapy. In addition, the differences with regard to Pascual *et al.*[8] and Miyakis *et al.*[24] could be attributed to the use of EORTC/MSG response criteria to antifungal treatment in our study.[23] No correlation between the dosage administered or administration route and the clinical evolution for Outcome 1 or Outcome 2 was demonstrated. On the other hand, a relationship was demonstrated between supertherapeutic concentrations and toxicity, particularly neurological and cutaneous, unlike other studies.[8,11,14,16,24,26] A direct relationship between hepatic toxicity and supertherapeutic voriconazole levels could not be established, as in some previous publications,[10,13,15] so it could be an idiosyncratic-type adverse effect. It is important to stress that all of the adverse effects observed resolved with the discontinuation of treatment.

In conclusion, although no clear relationship has been demonstrated between plasma trough levels and efficacy, our study allowed us to recommend the routine use of plasma voriconazole monitoring in paediatrics in its therapeutic indication since weekly TDM may prevent toxic plasma levels, especially in the ≥5 years old group, where the dose/plasma level relationship is less predictable. In addition, in the <5 years old group the

optimal dose must still be determined and may be much higher than the one currently recommended for this age group.

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Transparency declarations

None to declare.

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