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Voriconazole plasma levels in children are highly variable

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Abstract

Background

The pharmacodynamic relationship between voriconazole plasma concentrations and clinical outcome has been established in several studies; however, all these studies were performed in adult patients. Until recently, only 2 studies were available on voriconazole pharmacokinetics in children under 12 years of age. Some recent data suggest that the recommended dosages for pediatric patients are insufficient to achieve adequate exposure. We measured voriconazole trough levels in our tertiary care children's hospital and critically discuss them in the light of recent literature.

Methods

All patients admitted to our children's hospital with at least one measured plasma trough level of voriconazole were included. Voriconazole plasma levels were determined by a validated method. Trough levels are analyzed in relation to patient characteristics such as underlying disease, fungal infection, treatment regimen and clinical outcome. The impact of patient- and treatment-related factors and biochemical parameters on the trough levels was statistically evaluated. Pharmacokinetic parameters were calculated in 4 patients.

Results

A total of 14 trough levels are discussed. Only 5 levels were within the therapeutic range (1-6 mg/L). Voriconazole trough levels did not correlate with the weight-based daily dose. Plasma levels of voriconazole in our dataset are highly variable and cannot be predicted, as none of the patients' characteristics, treatment-related factors or biochemical parameters were statistically significant associated with voriconazole trough levels.

Conclusion

Our study confirms that plasma levels of voriconazole in children are highly variable. Ideally, this should be prospectively confirmed in a larger pediatric population. Regular monitoring of voriconazole trough levels in all pediatric patients is recommended.

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Introduction

Voriconazole is widely used as first-line agent to treat invasive aspergillosis in immunocompromised adults. Also in children, its use is increasing [1]. During the last decade, several studies in adults demonstrated a pharmacodynamic relationship between low voriconazole levels and lack of response, and high voriconazole levels and toxicity [2,3]. However, voriconazole has very complex pharmacokinetics resulting in highly variable plasma levels. As a result, it is recommended to monitor voriconazole plasma levels in adult patients with uncontrolled infection, gastro-intestinal dysfunction, severe hepatic dysfunction, and unexplained neurological symptoms. Target trough levels should be higher than 1 or 2 mg/L to guarantee efficacy and lower than 6 mg/L to avoid toxicity [2,3].

The relationship between voriconazole plasma concentrations and outcome has only been studied in adult patients [3]. To our knowledge, until recently, only 2 studies were available on voriconazole pharmacokinetics in children under 12 years of age [4,5]. Some recent data suggest that the recommended dosages for pediatric patients are insufficient to achieve adequate exposure [6,7]. We therefore measured voriconazole trough levels measured in our tertiary care children's hospital and discuss them in the light of recent literature.

Materials and Methods

All patients (age 0-18 yrs) admitted to the pediatric ward in a 2000-bed tertiary care hospital between January, 2008 and December, 2009 with at least one measured plasma trough level of voriconazole were included in this retrospective observational study. Patients were scheduled for voriconazole plasma concentration monitoring if they were already treated for a long period, or if long-term treatment was expected. The study was approved by the institutional Ethics Committee.

Data were collected from the medical, laboratory and pharmacy records; age, sex and weight, underlying disease and infectious diagnosis, voriconazole treatment regimen (dose, route of administration, formulation), voriconazole plasma levels and sampling time, C-reactive protein levels (CRP), liver function tests, renal function tests, serum galactomannan (GM) values (determined one day before or after, or at the same day of the sampling day) and outcome (response and survival) were registered. Voriconazole plasma levels were quantified in plasma by HPLC followed by UV detection, as previously published [8]. The lower limit of quantification for voriconazole was 0.05 mcg/ml.

Correlation (r^2) between trough levels and weight-base dose, albumin levels, CRP, renal function and liver function tests was examined. The impact of age, sex, weight, survival, route of administration, co-treatment (omeprazole, phenytoin and ciclosporine), registered biochemical parameters and the total daily dose on the voriconazole trough levels (subtherapeutic (< 1 mg/L) vs. therapeutic levels (> 1 mg/L)) was examined by univariate analysis (using the unpaired t-test, Chi-square test or Mann-Whitney U test depending on the tested variable), and finally by multivariate logistic regression.

We also investigated whether voriconazole trough levels statistically correlate with serum GM levels (Mann-Whitney U test). Finally, weight-based doses were structured according to a weight-based dose around 4 and 7 mg/kg. We tested if these dose regimens resulted in statistically significant different trough levels (Mann-Whitney U test). All statistical analyses were performed using Stat View for Windows version 5.0.1 (SAS Institute Inc, Copyright 1992-1998).

If voriconazole peak levels (determined after the end of the infusion) were available, pharmacokinetic parameters were calculated by non-compartmental analysis using WinNonlin Version 5.2.1 (Pharsight, Mountain View, CA, USA). The terminal elimination rate constant (λ_z) was estimated by linear regression of the natural logarithms of the plasma concentrations versus time. The area under the plasma concentration-time curve (AUC_{0-12}) was calculated by the linear up/log down method.

The half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda_z$. Plasma clearance was calculated as dose/AUC . Volume of distribution (V_d) was calculated as $\text{dose}/\lambda_z \cdot \text{AUC}_{0-12}$.

Results

During the 2-year study period, a total of 16 children were treated with voriconazole in the pediatric ward. Ten of these patients (age 9 months – 18 years) were included. In some patients, more than one voriconazole plasma level was determined, totaling up to 14 samples. The majority of patients (8) suffered from hematologic malignancies and 2 patients had cystic fibrosis as underlying disease. Voriconazole was started for invasive aspergillosis in 7 patients and for allergic bronchopulmonary aspergillosis (ABPA) in the 2 patients with cystic fibrosis. It was started empirically for presumed histoplasmosis in one patient. Pulmonary involvement was the unique localization of the infection in the patients with invasive aspergillosis, no involvement of the brain or disseminated aspergillosis was diagnosed. Voriconazole dosages ranged from 3.75 up to 8.88 mg/kg bid (median: 6.95 mg/kg bid). Patients' demographics, clinical characteristics and individual trough levels are shown in Table I.

Only 5 trough levels in 5 patients were > 1 mg/L, and no levels were higher than 6 mg/L, which is considered as the breakpoint for efficacy and toxicity, respectively [3]. Trough concentrations in children younger than 12 yrs ranged from 0.09 to 4.90 mg/L (median: 0.53 mg/L), and from 0.11 to 1.71 mg/L (mean: 0.79 mg/L) in children > 12 yrs. Correlation between voriconazole trough levels and the dose is very low ($r^2 = 6.8\%$). The correlation between trough levels and all individual collected biochemical parameters was below 5%.

None of the patient-related characteristics (age, sex, weight), biochemical parameters (CRP, liver function, renal function, albumin) or therapy-related factors (total daily dose, weight-based dose, route of administration and co-treatment) had a statistically significant impact on the trough levels (all

p-values > 0.05). As expected, also in the logistic multivariate analysis, no statistically significant result was seen.

Individual doses were structured according to a dose around 4 vs. 7 mg/kg. There was no statistically significant difference in trough levels in patients with a dosing regimen of 4 mg/kg vs. 7 mg/kg (p= 0.64).

Four patients with IA showed a complete response and the CF patients suffering from ABPA had stable disease. Four patients died. Voriconazole trough levels were not statistically significant associated with serum galactomannan values (p= 0.42) nor with survival (p= 0.16).

Pharmacokinetic parameters were calculated in 4 patients as in these patients also voriconazole peak levels were available. The results are shown in Table II.

Discussion

Monitoring voriconazole plasma concentrations in children is of great clinical importance, as illustrated in this report. As shown in Table I, voriconazole levels varied widely, and no correlation between trough levels and administered dosage was observed ($r^2= 6.8\%$). Moreover, levels were therapeutic in only one third of cases. Any of the patient-related characteristics, biochemical parameters or treatment-related factors had a statistically significant impact on voriconazole trough level, confirming that voriconazole trough levels can hardly be predicted in the pediatric population.

It has been shown in several pharmacokinetic studies that voriconazole is cleared much more rapidly in children than in adults [4,5]. Pharmacokinetic profiles are different in these two populations [4,5]. Voriconazole clearance in adults is non-linear within the therapeutic dose range (3 to 5 mg/kg), which means that plasma levels will raise disproportionately when the dose is increased [9]. In

contrast, the clearance in children remains linear over a comparable dose range [4,5]. In addition, the oral bio-availability of voriconazole is two-fold lower in children (45%) than in adults (96%) [5].

These observations suggest that hepatic metabolism in children differs from that in adults, which was recently explored and confirmed by Yanni et al [10]. In this study, the in vitro metabolism of voriconazole by liver microsomes from 6 children between 2 and 10 years of age was compared with that of adults, to explore the role of the metabolizing hepatic enzymes CYP2C19, CYP3A4 and flavin-containing monooxygenase 3 (FMO3). It was shown that voriconazole N-oxide, the major metabolite, was formed three-fold quicker in liver microsomes from children compared to that from adults. In vitro studies in which the contributing enzymes were selectively inhibited showed that the contribution of FMO3 and CYP2C19 was much larger in children than in adults, whereas CYP3A4 played a more prominent role in adults. It seems that CYP2C19 and FMO3 have a higher catalytic activity in children versus adults, as the expression of both enzymes is not significantly different in both populations. A higher dose of voriconazole (7 mg/kg instead of 4 mg/kg bid) for children has already been approved in Europe in 2005 [11]. In our study, weight-based doses ordered around 4 mg/kg vs. 7 mg/kg did not result in statistically significant different voriconazole plasma levels. Our data might even suggest that a dose of 7 mg/kg bid is not able to compensate for the enhanced clearance in all cases. These results should however be interpreted with caution, given our very small study population.

Pharmacokinetic parameters were calculated in 4 children. As shown in Table II, clearances vary greatly among the patients, and differ from those calculated in adults [9]. It is difficult to draw conclusions from these calculations, as these were only calculated in 4 patients, with varying age, characteristics and underlying disease. The marked pharmacokinetic variability, shown in Table II, however emphasizes the need for regular measurement of serum concentrations.

Very recently, the association between plasma concentration and outcome was investigated by a retrospective review of the clinical outcome of 46 children in which several voriconazole plasma

levels were measured [6]. A statistically significant association was found between crude mortality and voriconazole trough levels lower than 1 mg/L; a cut-off that is consistent with the breakpoint found in adults [6]. In our study, no statistical significant association was found between the clinical course of the infection (CRP levels, serum GM levels and survival) and plasma trough levels. Again, this should be interpreted prudently, considering the very limited patient population.

In our cases, intravenous administration did not result in the highest levels (Table I). However, in patient 5, a correlation between route of drug administration and voriconazole exposure was seen. Three consecutive plasma concentrations were quantified, the first during intravenous treatment, the latter two during oral treatment and these were much lower. In patient 4, the voriconazole plasma level was highly therapeutic (4.90 mg/L). However, hepatomegaly and hepatic tumour infiltration was shown on autopsy, which may have resulted in decreased metabolism and explain this high voriconazole level.

Toxic levels of > 6 mg/L were not measured, despite dosages up to 9 mg/kg bid in our case series. In only one patient (no. 9), an adverse event clearly linked to voriconazole treatment, i.e. phototoxicity, was observed. Recent reports indicate that photosensitivity reactions are particularly occurring after chronic administration, and are not clearly related to high or toxic plasma levels.¹² This was also the case in our patient, the patient was treated for more than 6 months with voriconazole; her plasma level was only 0.09 mg/L.

To optimize voriconazole plasma concentrations, drug-drug interactions, especially those mediated by CYP450, should be avoided [3]. Plasma levels are drastically lowered by enzyme inducers including rifampin, phenobarbital and carbamazepine. Concomitant use with these drugs is contraindicated.³ When phenytoin is associated, C_{max} and AUC of voriconazole decrease with 49 and 69% respectively, as shown in healthy adult volunteers [13]. Increasing the dose of voriconazole from 4 mg/kg to 5 mg/kg bid in case of IV administration, would compensate for this effect, as was also achieved in patient 10 [13].

Omeprazole is associated with higher and sometimes toxic levels of voriconazole, due to inhibition of CYP2C19 [2]. Two of the patients discussed in our report were treated simultaneously with omeprazole (Table I), however, levels were low in these patients and no statistically significant impact of omeprazole on voriconazole trough levels were found ($p= 0.78$).

As FMO is prominently involved in the metabolism of voriconazole in children, it would be useful to further explore potential drug-drug interactions mediated by and polymorphic expression associated with these enzymes. The contribution of FMO to the variability in voriconazole exposure in children is possibly underestimated as most investigations are performed using in vitro tests optimised for CYP activity.

Conclusion

In conclusion, our study confirms that plasma levels of voriconazole in children are highly variable. Voriconazole trough levels can hardly be predicted as none of the patients' characteristics, biochemical parameters or treatment-related factors were statistically significant associated with these levels. Our results should of course be confirmed in a larger pediatric population. We suggest to start voriconazole, preferably intravenously, at least in a dose of 7 mg/kg bid in children. Besides, voriconazole levels should be monitored regularly and doses should be adjusted as necessary to guarantee long-term efficacy.

Transparency Declaration

None to declare.

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Table I Patients' demographics and clinical characteristics

Patient	Sex	Age (yrs)	Weight (kg)	Underlying disease	Infectious diagnosis (EORTC classification)	Dose (mg, bid)	Dose (mg/kg, bid)	Route	Sample on day x of voriconazole treatment	Trough level (mg/L)	Concomitant medication
1	f	18	19	cartilage hair hypoplasia, allo HSCT	IA (probable)	80	4.2	orally	16	1.72	Omeprazole, cyclosporin
2	f	15	32	CF	ABPA	120	3.75	orally	6	0.12	
3	f	2	9	AML	IA (probable)	70	7.8	orally	32	0.32	
4	f	2	9	AML	IA (probable)	70	7.8	iv	8	4.9	
5a	f	6	18	JMML	IA (probable)	120	6.7	iv	50	0.86	Omeprazole
5b	f	6	18	JMML	IA (probable)	120	6.7	orally	116	0.10	Omeprazole
5c	f	6	18	JMML, allo HSCT	IA (possible)	160	8.9	orally	134	0.52	Omeprazole, cyclosporin
6	m	11	26	AML	IA (probable)	200	7.7	orally	4	2.34	
7	f	9 m	7	SCID, allo HSCT	IA (probable)	50	7.2	orally	4	1.93	
8a	m	8	42	cutaneous T-cell non Hodgkin lymphoma	empiric	200	4.8	iv	6	0.28	
8b	m	8	42	cutaneous T-cell non Hodgkin lymphoma	empiric	300	7.1	iv	11	0.53	
9	f	11	29	CF	ABPA and chronic Scedosporium infection	200	6.9	orally	178	0.09	
10a	f	14	44	severe aplastic anemia, allo BMT	IA (probable)	180	4.1	iv		0.41	Phenytoin
10b	f	14	44	severe aplastic anemia, allo BMT	IA (probable)	220	5	iv		1.17	Phenytoin, Cyclosporine

Note: HSCT, hematopoetic stem cell transplantation; CF, cystic fibrosis; AML, acute myelogenous leukemia; JMML, juvenile myelomonocytic leukemia; SCID, severe combined immunodeficiency; BMT, bone marrow transplantation, IA; invasive aspergillosis; EORTC, European Organisation for Research and Treatment of Cancer; iv, intravenously.

Table II Pharmacokinetic parameters calculated in 4 patients

Patient number	2	3	4	10b	Reference values adults [9]
trough (mg/L)	0.12	0.32	4.9	1.17	--
peak (mg/L)	1.15	0.94	17.60	11.71	3-4.7
t_½ (h)	7.05	14.52	12.47	6.91	6
AUC₀₋₁₂ (mg.h/L)	15.24	15.11	270.0	154.64	13
Cl (ml/min.kg)	8.19	17.16	0.96	1.07	3.33-8.33
Vd (L/kg)	5.0	21.6	1.04	0.64	4.6