Possibly Appropriate Maintenance dose of Voriconazole in pediatric patients: a single center observational study

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Research Article

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Abstract

Background: Voriconazole is a triazole antifungal agent and a commonly used first-line treatment for invasive aspergillosis (IA). The study was performed to explore the factors affecting voriconazole trough concentration and maintenance dose to optimize voriconazole dosage in pediatric patients.

Method: The demographic information, concentration data, *CYP2C19* genotypes, and clinical outcomes of eligible pediatric patients from January 1th, 2016 to December 31th, 2018 were collected retrospective .

Result: The study finally included 145 voriconazole trough concentrations from 94 pediatric patients. Steady trough concentration ranged from 0.04 to 16.11 μg/mL. Morerover, the distinction between the maximum and the minimum corrected concentration of per kilogram maintenance dosage is as high as 907 folds and children ≤2 years old showed the minimum variation compared to other individuals (P<0.001). A high inter- and intra-individual variability of voriconazole in pediatric patients were observed. Only 54.5% of the pediatric patients achieved the target range (1.0 to 5.5 μg/mL) at unadjusted initial dosage, while 35.9% of children were subtherapeutic, only 9.6% of children were supratherapeutic at unadjusted initial dosing. The younger children (≤12 years) seem to have a lower trough concentration (P=0.0096) and lower percentage of target achievements (P=0.004). And 98.97% of the maintenance dosage was below 9.0 mg/kg. For pediatric patients of different ages, it was found that most of them was underdosed. While, to achieve targeted therapeutic level for different age groups of ≤2, 2-6, 6-12, and 12-18 years, the median voriconazole maintenance doses were 5.7, 6.7, 5.0, and 3.3 mg^{-1}kg/12h, respectively had been required in order to achieve therapeutic level (P<0.001).

Conclusion: Pediatric patients especially those ≤12 years old might need a higher dosage regime to achieve therapeutic trough concentration. Importantly, early and repeat monitoring of voriconazole is essential to ensure the effectiveness and safety of voriconazole in children.

Introduction

An updated guideline in 2017 demonstrated that children undergoing allogeneic hematopoietic stem cell transplants, leukemia, prolonged neutropenia, and receiving high-dose corticosteroids were at a high risk of invasive fungal diseases with a high morbidity and mortality[1, 2]. Voriconazole, frequently used for the prophylaxis and treatment of invasive fungal infections, is a second-generation triazole antifungal agent with a broad-spectrum [3, 4]. It is also recommended as the first-line treatment of invasive aspergillosis[5]. However, the pharmacokinetic character of voriconazole is nonlinear and demonstrates obvious inter-individual and intra-individual variation. Additionally, its therapeutic index is narrow. Numerous studies also showed high steady-state plasma concentration was associated with clinical adverse events, while inadequate concentration was more likely to result to treatment failure[3, 6, 7].

Simultaneously, steady-state voriconazole trough concentration was affected by various factors, such as age, ethnicity, dosage, drug combination, genetic polymorphism of *CYP2C19* enzyme, and enzyme

activity[8-11]. Hence, in order to ensure the efficacy of antifungal and reduce adverse reactions of voriconazole, routine and repeat therapeutic drug monitoring (TDM) of the steady-state voriconazole trough concentration was strongly recommended by the European Conference on Infections in Leukemia (ECIL) guidelines[12]. However, most of the studies were about adult patients. Few studies have considered the difference of pediatric patients.

In addition, to achieve targeted voriconazole concentration (1.0–5.5 mg/L), 7 to 8 mg/kg intravenous twice daily of dose ranges were recommended in Caucasian children[13, 14]. However, there is no recommended dose for Asian children. According to the American 2021 revised " VFEND" drug label, pediatric patients 2 to less than 12 years of age and 12 to 14 years of age weighing less than 50 kg was recommended with a loading dose of 9mg/kg and a maintenance dose of 8mg/kg for intravenous use, while for oral use, the maintenance dose is also 9mg/kg (maximum dose of 350 mg every 12 hours)[15]. For pediatric patients aged 12 to 14 years weighing greater than or equal to 50 kg and those aged 15 years and older regardless of body weight use adult dosage. The adult loading dose and maintenance dose for intravenous use is only 6 mg/kg and 4 mg/kg, respectively[15]. It means that the pediatric patients should use a higher dose per body weight.

On the other hand, TDM of voriconazole in Asian children are not always available for clinician. No definite guidelines are available for voriconazole dose adjustment in pediatric patients. Not so optimistic is that, we observed that most clinicians tend to give an inadequate dose to the children. In this research, we retrospectively collected clinical outcomes of pediatric patients included through the electronic medical system in our hospital. The aim of this research was to study the appropriate dosage, the individual variation in pediatric patients of different age groups. Finally we are trying to optimize the daily administration dosage of voriconazole in this cohort.

Materials And Methods

Study design.

Children aged 1 to ≤18 who accepted voriconazole trough concentration monitoring from 1st January 2016 to 31st December 2020 were eligible for the study. The study was approved by the ethics committee of the Second Xiangya Hospital of Central South University. In addition, it was registered on ChiCTR.org with the registration number of ChiCTR1900025821(09/09/2019) and conducted according to the Declaration of Helsinki. All patients or their legal guardian provided informed consent for the usage of their clinical data and/or samples. The entire trial protocol can be accessed on the website of http://www.chictr.org.cn/index.aspx if available.

The inclusion criteria were: age of 2 to 18 years with detailed medical records. While exclusion criteria were: bodyweight of ≥50 kg when patients aged 12 to 14 years.

From the electronic medical record information system, patient's demographic and clinical data were collected, including ethnicity, age, sex, body weight (BW), *CYP2C19* genotype, underlying disease, treatment indication, site of infection, voriconazole dosing, route of administration, voriconazole trough concentrations, treatment duration, concomitant medications, adverse drug reactions, efficacy, liver function, and kidney function. The concomitant use of medications that were likely to influence voriconazole trough concentrations such as proton pump inhibitors (PPIs), glucocorticoids and immunosuppressors were also recorded.

Voriconazole administration and plasma trough concentrations.

There is no uniform dosage for the pediatric patients. Voriconazole was administrated without intervention by clinicians according to their experience or the drug package insert. The blood sample was collected three day later if the loading dose was used on the first day. Nurses collected the blood sample at least three days later within half an hour before the next dose under steady-state conditions. The remaining blood samples were saved to analyze the genotype of CYP2C19

The ideal target trough concentration of voriconazole was set as a range of 1.0 to 5.5 μg/ mL[13].

Analysis of voriconazole trough concentration

Voriconazole plasma concentration was measured by an automatic two-dimensional liquid chromatography method reported in our previous paper[16]. The linearity range was 0.35 to 11.26 μg/mL. The intra-day and inter-day precisions were 1.94% to 2.22% and 2.15% to 6.78%.

CPY2C19 genotypes and phenotype assignment

DNA was separated from the suspending white cells and was purified with the E.Z.N.A® SQ Blood DNA Kit II method. *CYP2C19* genotypes were implemented by Sanger dideoxy DNA sequencing method with ABI3730xl-full automatic sequencing instrument (ABI Co., Carlsbad, California) Boshang Biotechnology Co. Ltd. in Shanghai, China. According to the definition of the Clinical Pharmacogenetics Implementation Consortium (CPIC)[17], *CYP2C19* phenotypes were categorized as several types based on *CYP2C19 *1, *2, *3, or *17* allele nomenclature, including ultra-rapid metabolizer (UM) , rapid metabolizer (RM), extensive metabolizer (EM), intermediate metabolizer (IM) and poor metabolizer (PM). Extensive metabolizers were considered normal or wild-type metabolizers of *CYP2C19*.

Outcome and safety assessment

The definition of IFI treatment was in accordance with 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)[18]. Meanwhile, during the whole research, voriconazole-attributable adverse reaction was recorded based on the Common Terminology Criteria for Adverse Events (CTCAE) [19] .

Statistical analysis

Data were analyzed by SPSS (version 22.0; IBM Corp, Armonk, NY, USA). Continuous variables were expressed as median (range: quartiles). Categorical data were reported as frequencies and percentages. For quantitative data, the normality was tested using Shapiro-Wilk test. Student's t-test or Mann-Whitney test was selected according to the result of normality. Chi-square test or Fisher exact test were selected to test the enumeration data. A two-tailed test with a p-value <0.05 was considered statistically significant. Results were given as point estimates or 95% confidence intervals.

Results

Demographics and clinical characteristics

Ninety-four pediatric patients were enrolled in this retrospective observational study. A total of 145 voriconazole trough concentrations were recorded. Demographics and clinical characteristics are presented in Table 1. The primary diagnosis was hematological malignancy, accounting for 76.6%, followed by respiratory infection (69.1%) and bloodstream infection (38.3%). The major infection sites were lung (66.0%) and blood (25.5%). Among the enrolled patients, only 15 (19%) patients were diagnosed with confirmed IFI. Most of the patients (n=48) were administrated prophylactically, together with therapeutically (20.2%) and empirically (28.7%), respectively. Patients' demographic data, clinical characteristics, CYP2C19 genotypes and drug combinations of the age groups of ≤2, 2-6, 6-12 and 12-18 years old are summarized in Table 1. The percentage of the age groups of ≤2, 2-6, 6-12 and 12-18 years old were 15.96%, 29.79%, 22.34% and 31.91% respectively. The sex distribution is equal in the four age groups above(P=0.6160). The median body weight and inter-quartile range (IQR) of the four age groups were 11.5(IQR: 9.2-14.0), 16.0(IQR:14.5-18.0), 30(IQR:23.5-35.8) and 54.7(IQR:43.6-61.8), respectively. Logically, it was obvious that the body weight increase as the pediatric patients get older (P<0.0001).

Table 1
Patients' demographic data and clinical characteristics.

Characteristics	Median (quartile range or percentage)	Age groups			
		≤ 2y	2y-6y	6y-12y	12y-18y
Age(y)	7.5(4.0-14.2)				
Sex(male/female)	49/45	8/7	12/16	13/8	16/14
BW(kg)	24.2(14.5–44.1)	11.5(9.2–14.0)	16.0(14.5–18.0)	30(23.5–35.8)	54.7(43.6–61.8)
Duration hospitalization(d)	31(23–46)	30(18–43)	35(27–57)	34(24–43)	25(20–42)
Underlying conditions					
Hematological malignancies	72(76.6%)	12	26	15	19
Non-hematological malignancies	8(8.5%)	2	2	3	1
Respiratory infections	65(69.1%)	8	23	15	19
Bloodstream infections	36(38.3%)	5	14	12	5
Fungal infection	18(19.1%)	3	5	8	2
Allograft renal transplantation	9(9.6%)	0	0	2	7
Infective sites					
Lung	62(66.0%)	14	14	12	22
Blood	24(25.5%)	1	11	7	5
Oral mucosa	1(1.0%)	0	1	0	0
Perineum	1(1.0%)	0	1	0	0
Undefined	6(6.4%)	0	1	2	3
IFI diagnosis					
Proven	15(16.0%)	2	5	2	6
Probable	31(33.0%)	8	8	9	6
Possible	48(51.1%)	5	15	10	18

PPIs: proton pump inhibitors

Characteristics	Median (quartile range or percentage)	Age groups			
		≤ 2y	2y-6y	6y-12y	12y-18y
Treatment indication					
Therapeutic	19(20.2%)	3	6	2	8
Empirical	27(28.7%)	6	8	7	6
Prophylactic	48(51.1%)	6	14	12	16
Clinical outcome					
Success	76(80.8%)	12	23	17	24
Failure	18(19.2%)	3	5	4	6
Concomitant therapy					
PPIs	41(43.6%)	3	12	8	18
Glucocorticoids	27(28.7%)	5	5	6	11
Antifungal drugs	14(14.9%)	4	2	2	6
Immunosuppressive agents	9(9.6%)	0	3	0	6
PPIs: proton pump inhibitors					

Drug Safety

3(3.18%) patients occurred voriconazole-related adverse reactions, 2 of them with persistent elevation of alanine aminotransferase and/or aspartate aminotransferase and vomiting just in one. One patient with a trough concentration of 5.32 μg/mL gradually recovered to normal liver function after drug withdrawal, and the other one also showed normal liver function by reducing voriconazole dosage. For one patient-administered voriconazole tablets, the symptoms of vomiting disappeared after intravenous administration. For all the three patients and the symptoms of adverse drug effects finally disappeared without stopping voriconazole.

Initial and overall concentration

Statistical analysis was performed among the 94 initial voriconazole trough concentrations and 145 overall trough concentrations between the four age groups of less than 2, 2-6, 6-12, and 12-18 years old. The result is shown in Table 2. The media initial sampling time and IQR of the four groups were 7(IQR:3-10), 8(IQR:5-13), 8(IQR:5-19) and 4.5(IQR:3-6.2) days (P=0.0235). The median initial trough concentration

of the four groups were 0.17, 0.87, 2.45 and 2.15 μg/mL (P=0.0014; Fig.1a), while the media overall concentration were 0.18, 1.19, 2.02 and 2.02 μg/mL, respectively (P=0.0096; Fig.1b). Additionally, there were significant differences in trough concentrations between the four groups.

Table 2
Patients' voriconazole administration and TDM data.

Characteristics	Mean (quartile range or percentage)	Age groups			
		≤ 2y	2y-6y	6y-12y	12y-18y
Duration VRC using(d)	17.5(11-26.2)	16(11–29)	22(12.2–33.7)	21(15.5–24)	13(8–24)
Administration route					
Oral	83(88.3%)	12	27	20	24
Intravenous	11(11.7%)	3	1	1	6
Initial sampling time(d)	7(3.8–11)	7(3–10)	8(5–13)	8(5–19)	4.5(3-6.2)
VRC initial C_{trough}(μg/mL)	1.56(0.30–3.38)	0.17(0.11–2.1)	0.87(0.11–2.86)	2.45(0.69–7.30)	2.14(1.05–3.19)
< 1.0	38(40.5%)	9	16	7	6
1.0-5.5	43(45.7%)	6	10	6	21
> 5.5	13(13.8%)	0	2	8	3
VRC C_{trough}(μg/mL)	1.58(0.54–3.12)	0.18(0.11–2.21)	1.19(0.22–3.27)	2.02(0.86–5.78)	2.02.(1.02–3.12)
C_{trough}: the voriconazole trough concentration					

Probability of achieving target concentration was analyzed among the four age groups. The initial probability of achieving targeted concentration was 43(45.26%), while after the dosage was adjusted, the overall probability of achieving targeted concentration increased to 78(53.79%). The distribution of the four age groups is shown in Fig.2. For the age group of less than 2 years old, 60% of the children were subtherapeutic at the initial dosing, only 40% of children achieved the target concentration of 1.0-5.5 μg/mL. The proportion of the children who failed to meet the standards decreases as the age increases. Only 20% of the children were subtherapeutic at the group of 12-18 years old (P=0.004; Fig.2a). Meanwhile, the overall subtherapeutic percentage of the four groups were 61.11%, 45.51%, 28.13% and 22.92% (P<0.001; Fig.2b).

Dosing adjustment based on TDM

According to the results of TDM, a total of 23 patients (27 samples) in 94 patients had dose regimen adjustments, among which 19 patients were adjusted once and four patients adjusted twice. Ten samples significantly increased the dose of 3.2mg/kg/d based on the lower voriconazole trough concentration (below 1.0 μg/mL). Five patients with mean trough concentration of 4.77 μg/mL (4.15-5.32μg/mL) also adjusted dose regimen, decreasing dose by 3.4mg /kg/d (2.0-4.2mg /kg/d) in four but increasing dose in one. A large proportion of Patients with high trough concentration adjusted their medication, among which voriconazole was discontinued in 3 samples, and voriconazole dose was reduced by 4.2 mg/kg/d (3.0-8.6 mg/kg/d) in 8 samples.

Initial and overall maintenance dose

The maintenance dosage for different age groups and routes of administration are shown in Fig. 3 and Fig. 4. The initial mean maintenance dosage for the four age groups were 7.10, 6.30, 5.20, and 3.35 mg/kg twice daily, respectively (P=0.0014; Fig.3a), while the overall median maintenance dosage were 7.14, 6.67, 5.10 and 3.60 mg/kg twice daily (P<0.001; Fig.3b). Under the target concentration of 1.0-5.5 μg/mL, the initial target maintenance dose of the four age groups were 5.75, 6.90, 5.10 and 3.30 mg/kg twice daily (P<0.001; Fig.4a), while the overall target maintenance dose were 5.71, 6.67, 5.09 and 3.31 mg/kg twice daily (P<0.001; Fig.4b), respectively.

According to the American " VFEND" drug label[15], there was no recommendation for pediatric patients less than 2 years old in using voriconazole. But for pediatric patients 2 to less than 12 years of age and 12 to 14 years of age weighing less than 50 kg, the maintenance dose of voriconazole was at least 8mg/kg. The media maintenance dose we obtained above ranged from 5.09 to 6.90 mg/kg twice daily. It demonstrated that the children may be underdosed when using voriconazole.

Intra-individual and inter-individual variation of voriconazole

The medication duration time of initial voriconazole TDM varied widely, with the median of 17.5 days (11-26.2 days) and seven days (3.8-11 days), respectively. Voriconazole concentration monitoring was performed only once in 59(62.77%) children. 28(29.79%) children received two measurements. Only 7(7.45%) of them received three or more TDM measurements. The variation of voriconazole were analyzed among 35(37.23%) children who received two or more TDM measurements. The intra-individual variation of voriconazole in the study cohort was relatively high. The mean intra-individual variation was 72.87%. The variable coefficient ranged from 17.4% to 142.96%. The mean inter-individual variation among 145 trough voriconazole concentration was 111.2%. The inter-individual variable coefficient ranged from 1.68% to 678.52%, which indicated that the coefficient of variation of voriconazole metabolism in children varies greatly. Scatter diagram and interpatient variability of initial and overall voriconazole trough concentration at different weight-adjusted doses in different age groups were shown in Fig.5. All these results demonstrated a large variation between the individuals.

Scatter diagram of the initial and overall maintenance dose and trough concentration are presented in Fig.6 and Fig.7 respectively. Meanwhile, the distribution of initial and overall maintenance dose within the

target concentration range is shown in Fig.7. All these figures showed a high inter- and intra-individual variability. And the oldest age groups seemed to have the lower variability, while the younger age groups less than 12 years older seemed to have a higher variability.

Discussion

The safety and using data of voriconazole in children was sorely lacking, especially in pediatric patients under 2 years old. This retrospective study highlights the distinction of using voriconazole in pediatric patients of different age groups and provides some reference for adjusting dosage in Chinese pediatric patients. Currently, for children younger than 12 years, voriconazole showed nonlinear pharmacokinetics[20, 21], warranting that more cautious dose adjustment was necessary for this group.

Our study showed large variability in voriconazole trough levels, the mean intra and inter individual variation were 72.87% and 111.2%, the result is similar to the study published before[22, 23]. Furthermore, more than 50% of children could not reach the target range of 1.0-5.5μg/mL at the initial trough concentration, it was also consistent with previous studies[24]. The initial trough concentration in children aged 2-12 was significantly higher than that in children aged under 2 years, suggested a faster metabolism for infants. In addition, the EMA approved higher doses in 2 to 12 years old children, an 8 mg/kg intravenously twice daily (9 mg/kg day 1) or a 9 mg/kg orally twice daily. Our data suggested that underdose was so prevalent that 40.5% of children failed to reach the target concentration range and voriconazole dose was inadequate in this population. Lacking guidelines for dose recommendation of voriconazole in children, voriconazole maintenance doses varied widely in the study. The group of less than 2 years old tended to have the highest subtherapeutic possibility. Moreover, overall standard probability of the age group of less than 2 years old was not improved but decreased compared to the initial concentration, from 40% to 33.33% ($P<0.001$; Fig.2B), foreboding the meaningless dose adjustment and lack of unified guidance.

Karlsson MO et al.[14] and Neely M et al.[25] illustrated the optimal dose of voriconazole was 7 mg/kg twice daily in children 2 to 12 years old. While, Shima H et al.[20] recommended that for patients younger than 2 years at least 8.5 mg/kg twice daily of voriconazole dose was needed. Therefore, further study is needed in the future to evaluate the optimal dosage in pediatric patients. In the present study, the primary administration route of voriconazole was oral administration (88.3%) rather than the intravenous route recommended by the package insert for voriconazole. However, variability in oral bioavailability caused by meals and hepatic first-pass effect might associate with lower drug exposure[26, 27], which could be the reason for sub-therapeutic trough concentration.

Moreover, analysis about initial and overall maintenance dosage under target voriconazole concentration in our center found that the media maintenance doses required to achieve the target concentration for children less than 2 years old was is roughly around 5.70 mg^{-1}kg/12h, while the media dose for the children between 2 to 6, 6 to 12, and 12 to 18 years old were approximately 6.80, 5.09 and 3.30 mg^{-}

[1]kg/12h, which were all lower than the recommended dosage of drug instruction. Additionally, it is obvious that children aged 12-18 had the lowest maintenance dose (P<0.001) (Fig.1). Above all, except for children less than 2 years old, children had lower maintenance dose than the recommended dose levels. And the initial dose of the age group less than 2 years old is obviously higher than the initial target dose of other groups.

Similar to that reported (7–10 days) in other centers[25], the average time of the first TDM blood sampling in our hospital was 7 days (3.8-11days). In a randomized controlled trial[28], the first TDM blood sampling was done on the fourth day after the initiation of voriconazole, which was calculated based on data from the literature so that it coincided with the target trough concentration range (1.0–5.5 mg/L). However, Miyakis S et.al[29] showed that the initial trough concentrations of ≤ 0.35 μg/mL were significantly associated with increased mortality in pediatric with invasive candidiasis, so it was advised that the first steady-state TDM should be done ideally as early as possible (day 3 of therapy) to allow prompt dose adjustment. Our findings are consistent with the previous study[30]. Further exploration of the clinical implication of this drug interaction is imperative.

Another critical factor affecting voriconazole therapeutic trough concentrations was the polymorphism of *CYP2C19*. The *CYP2C19* genotypic and phenotypic variability were extensive among different ethnic groups but was controversial concerning voriconazole treatment. Generally, Caucasians or Africans have a lower proportion of PM metabolizers than Asians (2% to 5%, 6%, and 13% to 23%, respectively). Furthermore, for Caucasians and Africans, it is about 4 times more proportion in the Asian than them among the *CYP2C19∗17* allele[30-34]. No *CYP2C19*17* allele was found in our study. Normally, individuals who are CYP2C19 ultrarapid metabolizers have decreased trough voriconazole concentrations, delaying achievement of target blood concentrations; whereas poor metabolizers have increased trough concentrations and are at increased risk of adverse drug events[17]. However, this was not found in our study. It was probably that the sample was too small and too many confounding factors existed. Hicks JK et al.[35] emphasized that a starting dose above 14 mg/kg/day could be recommended for all pediatric patients except for *CYP2C19* extensive metabolizers. Based on the age and *CYP2C19* genotypes, the voriconazole dose regime could be better determined, and variation of drug trough concentrations could dramatically decrease. Therefore, available *CYP2C19* genotype before the initial administration of voriconazole could improve the accuracy and safety of initial dosing[36].

A guideline for voriconazole dose optimization is imperative in pediatric patients. A randomized controlled trial implemented by Park WB et al.[28] developed a dose adjustment strategy as following: increasing another 100% doses when the trough level was <1.0 mg/L, on the contrary, reducing doses by 50% when the trough level was >5.5 mg/L, but if there were adverse events, withholding voriconazole and reduce subsequent doses. However, only 45.1% of patients in 51 patients whose concentrations did not reach the target had the dose adjustment. Moreover, almost all the children younger than 2 failed to reach the target concentration in the first TDM. Whether this optimized dosage strategy applicable to children ≤2 years old was unclear. Zembles TN et al.[37] had described their voriconazole optimized dosing

strategy in three patients younger than 2 years and emphasized that a higher initial dose and perhaps 8 hours interval dosing schedule should be given to achieve voriconazole target therapeutic concentrations. Besides, Kendre'a M et al.[38] showed a regimen of 6 mg/kg, 3 times per day for intravenous, and proved its safety in a preterm infant younger than 3 months. Because voriconazole is not routinely monitored in children in our hospital, voriconazole trough concentration was seldom monitored again after adjusting the dose. Finally, the dose-adjusted treatment response was significantly improved compared with the initial response. A pediatrician should recognize the importance of therapeutic drug monitoring of voriconazole and refer to the interpretation results of TDM conducted by clinical pharmacists in dosage adjustment.

Given orally or intravenously, Voriconazole is well tolerated in most patients, with a rate of adverse reactions of 3.2%, which is much lower than previously reported (20.0%)[24]. Visual disturbances and photosensitive skin reactions were difficult to be detected and explained in pediatric may be one reason for that lower rate of adverse reactions.

Finally, our study is a single-center retrospective study. So, there are a few limitations in study design and analysis. Firstly, too small sample size restricts the difference significance analysis. Secondly, no uniform guidelines and standardized protocol for voriconazole dose adjustment based on TDM data, resulting in a few confusions in doctors when adjusting doses. Thirdly, the number of *CYP2C19* genotypic and phenotypic is too tiny to detect the difference between trough concentration and genotypes. In addition, obesity, alkaline phosphatase, co-administered drugs and other single nucleotide polymorphisms such as the SLCO1B3, SLCO1B1, SLC22A6, ABCB1, ABCG2, SLCO3A1, ABCC2, SLC22A1, ABCB11 and NR1I2 genes, were reported to be associated with decreased metabolism of voriconazole to its inactive N-oxide 56 metabolite [33, 34, 39, 40]. However, this was not assessed in our study.

Conclusion

In conclusion, there is considerable inter-individual and intra-individual variability with voriconazole trough concentration in children. Younger pediatric patients less than 12 years old tend to have a higher inter and intra-individual variability than the children over 12 years old. Thus, they should be given more attention when using voriconazole. Meanwhile, the age group of less than 2 years old might need to have a higher dosage regime. The early, routine, and repeat TDM of trough concentration is extremely necessary in order to ensure safety and effective treatment. Therefore, a large, multi-center prospective study is imperative to identify and validate dose-optimization strategies for pediatric patients in the future. The maintenance doses required to achieve the target concentration for children less than 2, 2 to 6, 6 to 12, and 12 to 18 years old years old were approximately about 5.70, 6.80, 5.09 and 3.30 $mg^{-1}kg/12h$ respectively. Children aged 12-18 had the lowest maintenance dose ($P<0.001$). Although the initial dose of the age group less than 2 years old is obviously higher than the initial target dose of other groups, children less than 2 years old still administrate lower maintenance dose than recommended dose levels and are in the risk of insufficient dose.

Declarations

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Author Contributions

Yi-chang Zhao and Yang Zou wrote the main manuscript.

Bi-kui Zhang, Miao Yan, and Yi-chang Zhao designed research

Dan Tang, Yi-wen Xiao, Feng Wang, Da-xiong Xiang performed the statistic analysis.

Feng Yu and Chen-lin Xiao reviewed the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available by request.

Funder

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Statement

The research was approved by the Ethics committee of the Second Xiangya Hospital of Central South University and was registered on the website of http://www.chictr.org.cn/index.aspx with ChiCTR.org Registration number of ChiCTR1900025821 (09/09/2019). I declare that all methods were carried out in accordance with relevant guidelines and regulations in the manuscript on behalf of all the other authors.

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Figures

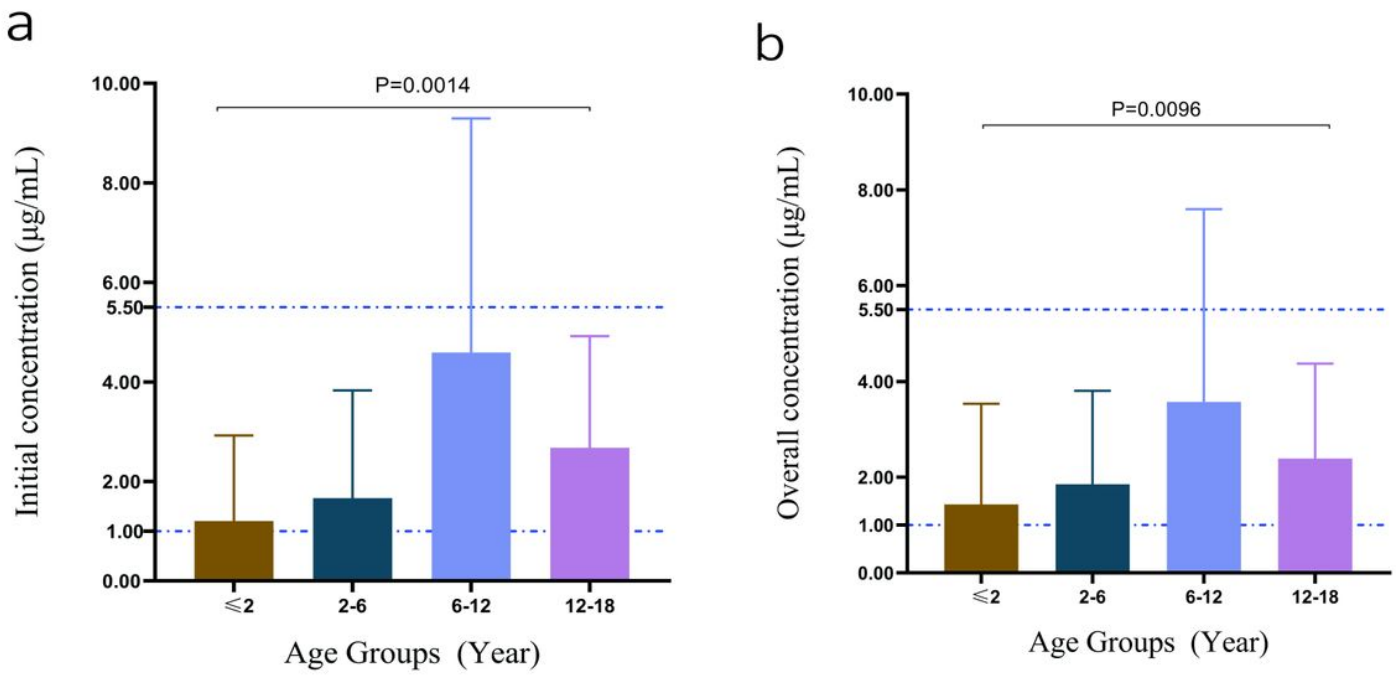

Figure 1

Initial and overall trough concentration of different age groups. The initial(a) and overall(b) trough concentration of the following age groups: 0 to 2 years old, 2 to 6 years old; 6 to 12 years old; over 12

years old. The P value for each group is indicated above the figure.

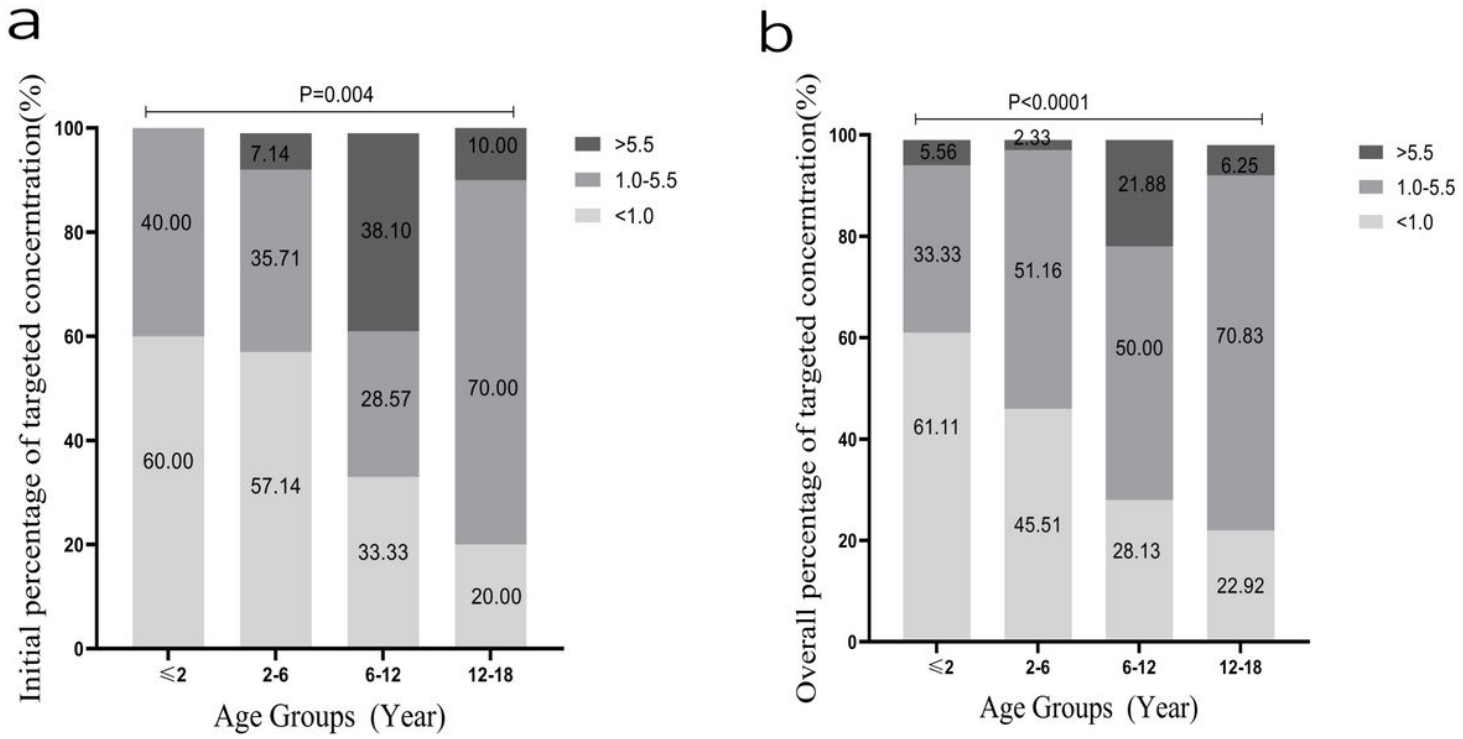

Figure 2

Probability of achieving targeted concentration in different age groups. The initial(a) and overall(b) distribution of different concentration grades of the following age groups: 0 to 2 years old, 2 to 6 years old; 6 to 12 years old; over 12 years old. The P value for each group is indicated above the figure.

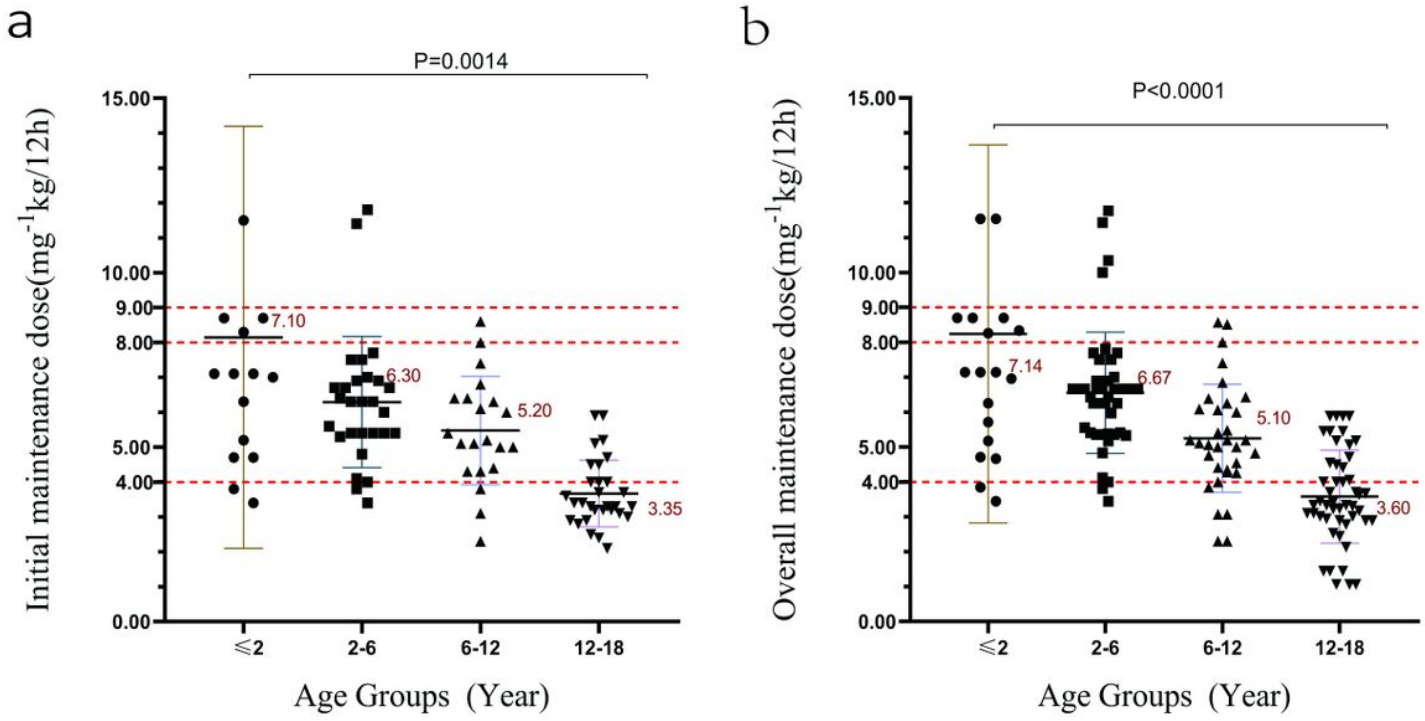

Figure 3

The initial(a) and overall(b) maintenance dosage for different age groups. The initial(a) and overall(b) maintenance dosage of the following age groups: 0 to 2 years old, 2 to 6 years old; 6 to 12 years old; over 12 years old. The maintenance dosage is weight-adjusted. The P value for each group is indicated above the figure.

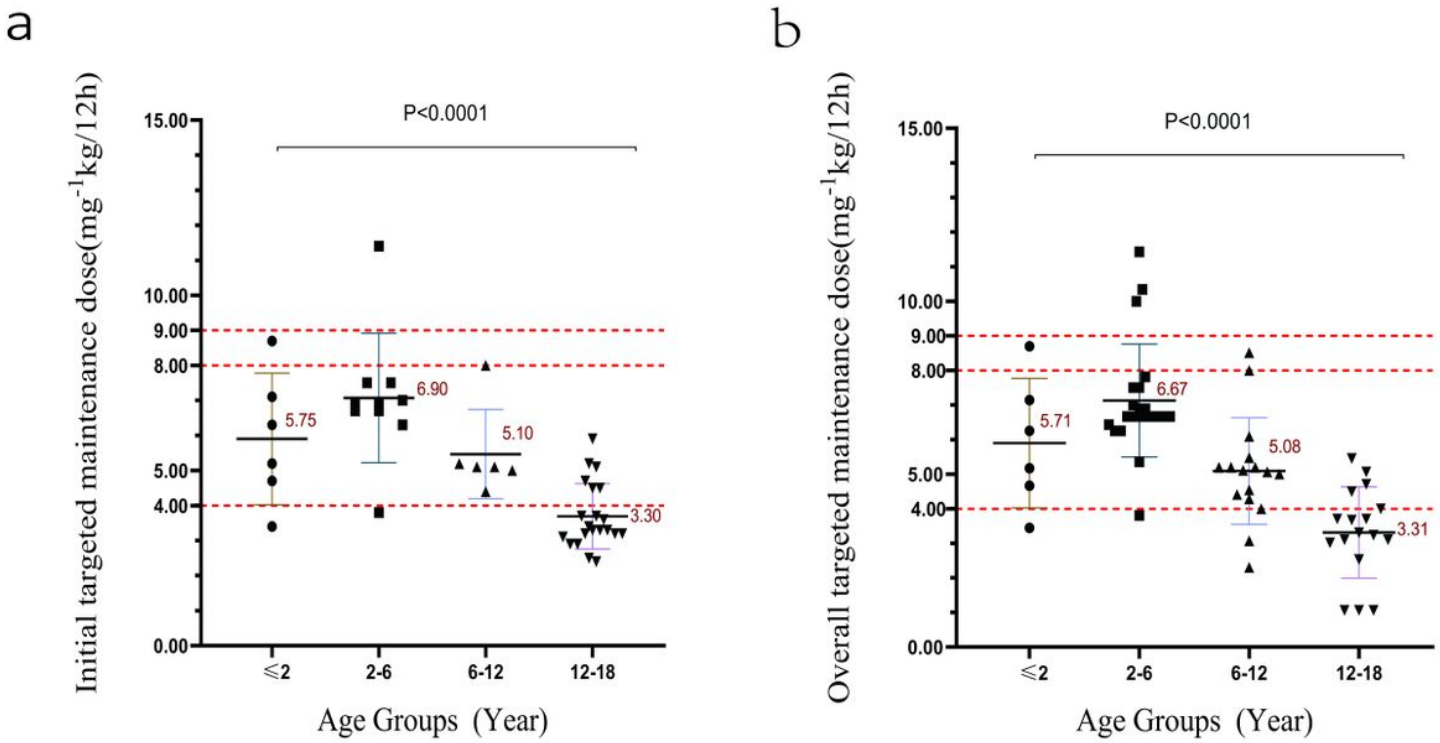

Figure 4

The initial(a) and overall(b) maintenance dosage for different age groups under targeted concentration of 1.0-5.5μg/mL. The initial(a) and overall(b) maintenance dosage of the following age groups: 0 to 2 years old, 2 to 6 years old; 6 to 12 years old; over 12 years old within the targeted concentration of 1.0-5.5μg/mL. The maintenance dosage is weight-adjusted. The P value for each group is indicated above the figure.

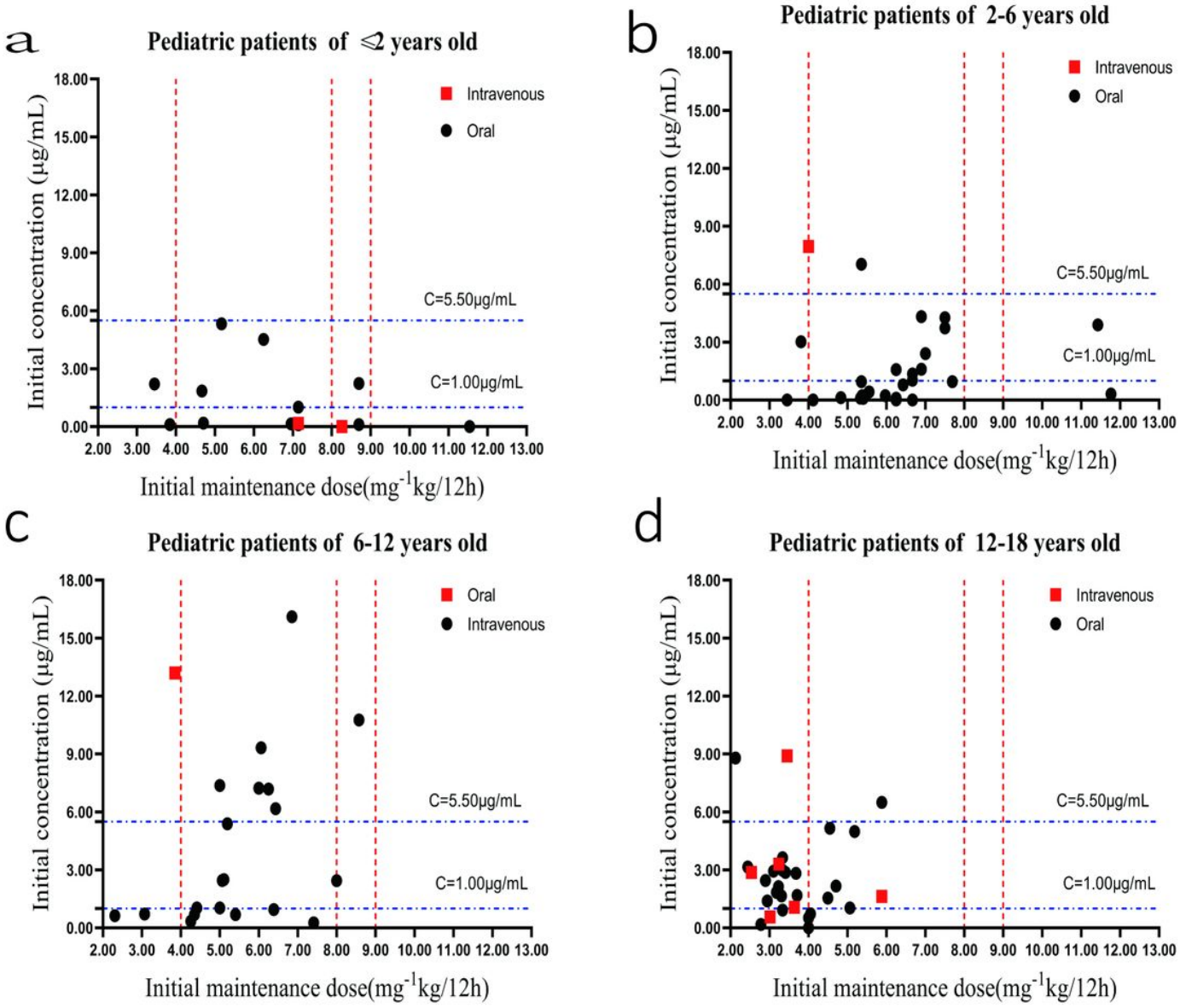

Figure 5

Scatter diagram of initial voriconazole trough concentration at different maintenance dosage. Initial voriconazole trough concentration scatter diagram and interpatient variability at different weight-adjusted doses of the following age groups: 0 to 2 years old (a), 2 to 6 years old (b) ; 6 to 12 years old (c) and over 12 years old (d). The maintenance dosage is weight-adjusted. The P value for each group is indicated above the figure.

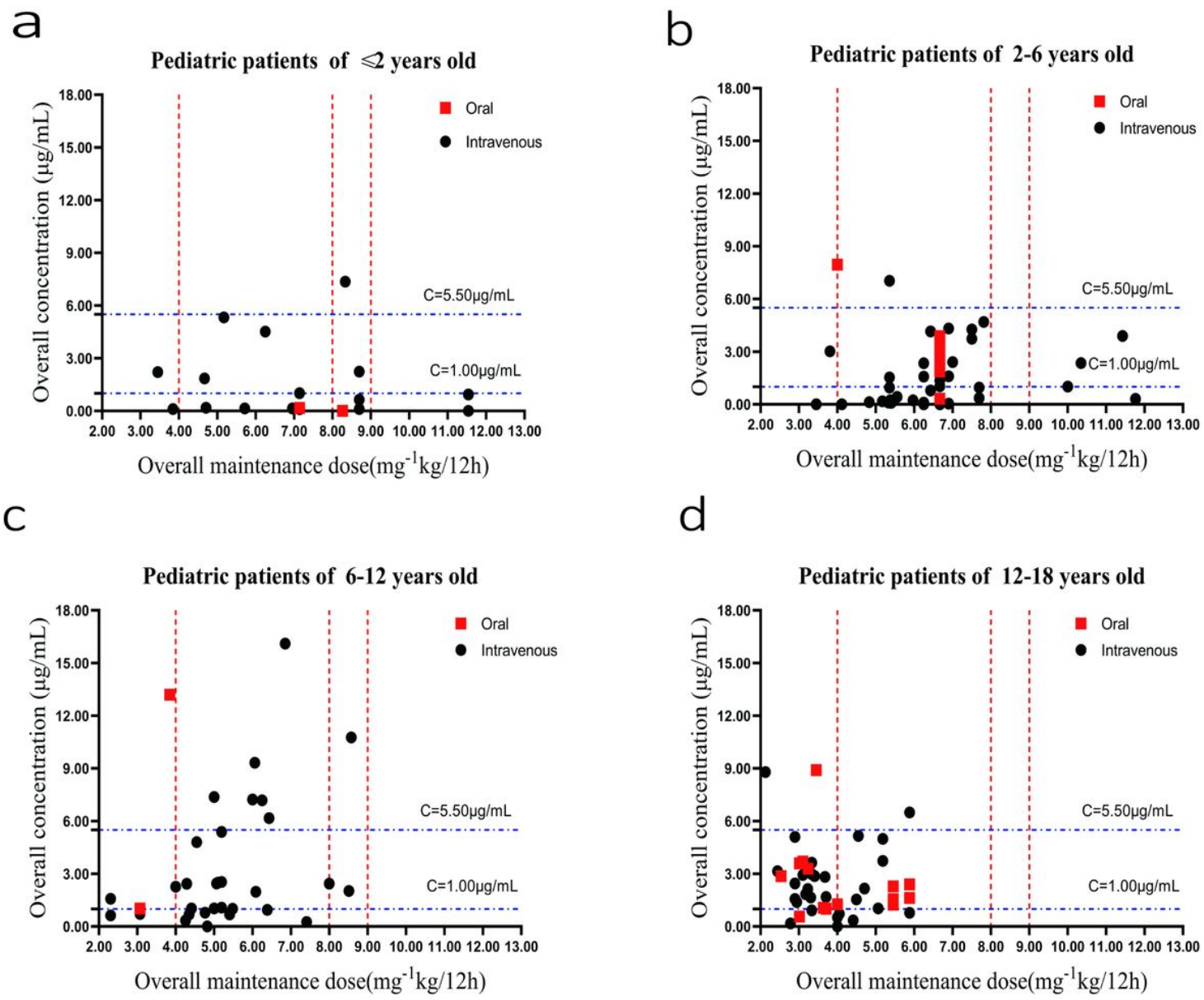

Figure 6

Scatter diagram of overall voriconazole trough concentration at different maintenance dosage. Overall voriconazole trough concentration scatter diagram and interpatient variability at different weight-adjusted doses of the following age groups: 0 to 2 years old (a), 2 to 6 years old (b) ; 6 to 12 years old (c) and over 12 years old (d). The maintenance dosage is weight-adjusted. The P value for each group is indicated above the figure.

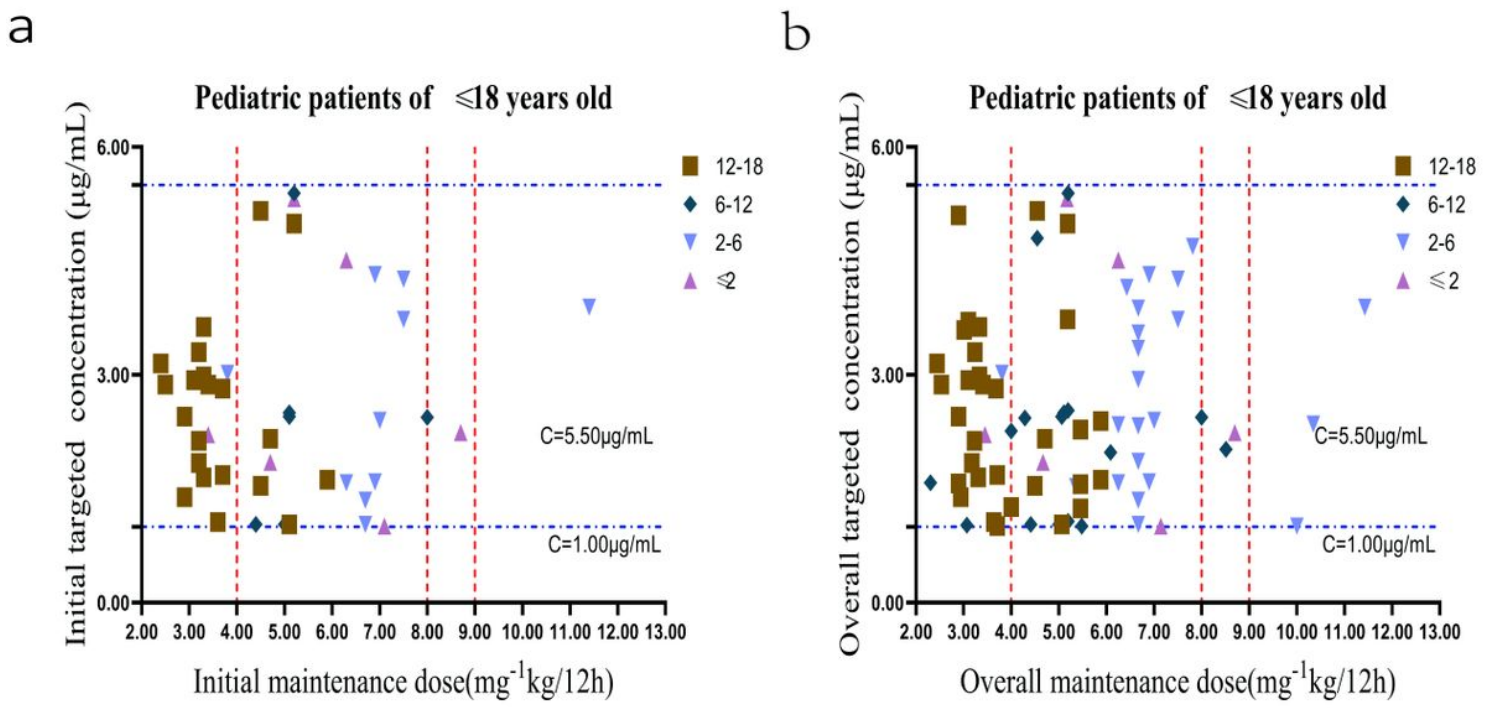

Figure 7

Scatter diagram of the initial(a) and overall(b) voriconazole trough concentration at different maintenance dosage under targeted concentration of 1.0-5.5μg/mL. The initial(a) and overall(b) voriconazole trough concentration scatter diagram and interpatient variability at different weight-adjusted doses of the following age groups: 0 to 2 years old , 2 to 6 years old ; 6 to 12 years old and over 12 years old. The maintenance dosage is weight-adjusted. The P value for each group is indicated above the figure.