

BRIEF REPORT

Differences in Voriconazole Trough Plasma Concentrations per Oral Dosages Between Children Younger and Older Than 3 Years of Age

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The relationship between trough plasma concentrations and daily doses of voriconazole was retrospectively analyzed in ≤ 18 -year-old children because optimal oral voriconazole dosages for children, especially < 2 years of age, is unknown. We demonstrated that the relationship changed around the age of 3 years, and that children < 3 years of age required higher optimal daily doses with greater variations compared with those for older children, resulting

in complicated optimal dose adjustments. Therefore, plasma concentration monitoring and individual dose adjustments are recommended for optimal and less toxic voriconazole treatments, especially for < 3 -year-old children, although additional studies are needed to validate this approach. *Pediatr Blood Cancer* 2010;54:1050–1052. © 2010 Wiley-Liss, Inc.

Key words: fungal infection; plasma monitoring; voriconazole

INTRODUCTION

Voriconazole is a third-generation, triazole broad-spectrum antifungal agent, with low toxicity and excellent bioavailability. After oral administration, it achieves plasma concentrations well above the minimal inhibitory concentrations for major pathogens [1,2]. Although intravenous or oral voriconazole is recommended for the primary treatment of invasive aspergillosis in both adults and children [1,3–5], an optimal dose of voriconazole for children, especially < 2 years of age, remains unclear. In this study, we performed trough plasma concentration monitoring of voriconazole for children 0–18 years of age who received oral voriconazole during treatments for pediatric malignancies.

METHODS

Patients and Study Design

We retrospectively examined children ≤ 18 years of age with malignancies who received voriconazole as primary antifungal prophylaxis at our hospital between November 2006 and May 2009. Clinical records of voriconazole were reviewed. Voriconazole was administered orally every 12 hr. Young children who failed to swallow tablets received crushed tablets, because an oral suspension formulation was not available in Japan. Blood samples were obtained prior to the next dosing of voriconazole, and these trough plasma concentrations were determined by high-performance liquid chromatography [6]. The initial daily dose and the adjustment of maintenance dose according to the previously monitored level were determined at the discretion of the attending physician. The target range for trough plasma concentration was determined as 1–5 $\mu\text{g/ml}$, which complied with previous reports [7–9]. This study was approved by the ethics committee, and informed consent was obtained from the parents of all the subjects.

Statistical Analysis

Linear regression lines of trough plasma concentration on dose in two age groups (< 3 and ≥ 3 years) were estimated with a mixed effects model, which contains age group, dose (degree of freedom = 1) as factors, dose-by-age group interaction, and intercept

within patient as random effects. The ratios of trough plasma concentration to daily doses were compared between the two age groups using a mixed effect model, which contains age group as a factor and intercept within patient as a random effect. Degrees of freedom were adjusted with the Satterthwaite's approximation. Significance level was two-sided 5%.

RESULTS

Patients and Voriconazole Administration

A total of 33 blood samples from 16 children (9 males and 7 females) were analyzed for trough plasma concentrations of voriconazole. Patient characteristics at the initiation of voriconazole are shown in Table I. Among 16 children, 7 were < 5 years of age and given crushed tablets. In four children, voriconazole was started with a loading dose 1.5–2 times higher than the maintenance dose for the first day; from the second day it was reduced to the maintenance dose. For these children, maintenance doses were used for analysis.

The median daily dose was 11.6 mg/kg (range, 5.7–22.7 mg/kg). The total duration of voriconazole administration was 376 days for those after chemotherapy and 126 days for those with HSCT. Concomitant drugs reported to have drug interactions with voriconazole were FK506 (one patient), cyclosporin A (one patient), vincristine (five patients), and phentanyl (two patients).

Measurements of Trough Voriconazole Concentrations

Trough plasma concentrations were monitored at a median of 5 days (range, 3–11 days) after the initiation or dose adjustment of voriconazole. The median trough plasma concentration was

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Conflict of interest: Nothing to declare.

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TABLE I. Patient Characteristics

Age	
Median (year)	9
Range (year)	0–18
<3 years, n (%)	6 (37.5)
≥3 years, n (%)	10 (62.5)
Sex, n (%)	
Male	9 (60.0)
Female	7 (40.0)
Weight (kg)	
<3 years, median (range)	8.6 (5.3–12.5)
≥3 years, median (range)	39.5 (16.5–49.8)
Underlying diseases, n (%)	
ALL	7 (43.8)
AML	3 (18.8)
JMML	1 (6.2)
Ewing sarcoma	2 (12.5)
Rhabdomyosarcoma	2 (12.5)
Lymphoma	1 (6.2)
State at voriconazole administration	
After hematopoietic stem cell transplantation (n)	
Patient	5
Immunosuppressive agents for cGVHD	4
Neutropenic phase after chemotherapy	
Patient (n)	12 ^a
Absolute neutrophil count at onset (/ μ l)	
Median	19
Range	0–923
Neutropenic fever (n)	6

^aIncluding one overlapping patient with monitoring also after hematopoietic stem cell transplantation.

1.6 μ g/ml (range, <0.05–6.2 μ g/ml). Seven of 10 children ≥ 3 years of age achieved the target range at first monitoring with a median initial daily dose of 8 mg/kg; these children underwent monitoring only once. In contrast, in children <3 years of age, although the median initial daily dose was higher (11 mg/kg) than that for older children, only one patient had achieved the target range at first monitoring; others required dose increases according to their previously monitored levels.

Relationship Between Plasma Concentrations and Daily Doses of Voriconazole

A scatter plot indicated that the relationship between trough plasma concentrations and daily doses of voriconazole showed an apparent change in distribution according to the patient's age: <3 and ≥ 3 years of age (Fig. 1). Thus, for further assessments, the study cohort was divided into two groups: children <3 and ≥ 3 years of age.

Estimated linear regression lines for children <3 years and ≥ 3 years of age were trough concentration = $1.93 + 0.30$ (dose–15.19) and trough concentration = $1.77 + 0.76$ (dose–7.97), respectively. Slopes for dose were significant in both age groups ($P < 0.001$), indicating the significant correlations between trough plasma concentrations and daily doses per body weight in each group. However, variations were more remarkable for children <3 years of age (Fig. 1), which made dose adjustment more complicated in these children compared with that in the older group. In addition, the ratio of trough plasma concentration to daily doses was significantly lower in children <3 years of age (median, 0.105; range, 0.004–0.274) compared with that in children ≥ 3 years of age

(median, 0.236; range, 0.035–0.434; $P = 0.015$). Overall, the median daily doses required to attain trough plasma concentrations within the target range were 17 mg/kg (range, 12–23 mg/kg; total daily dose, 100–220 mg/day) for those <3 years of age and 8 mg/kg

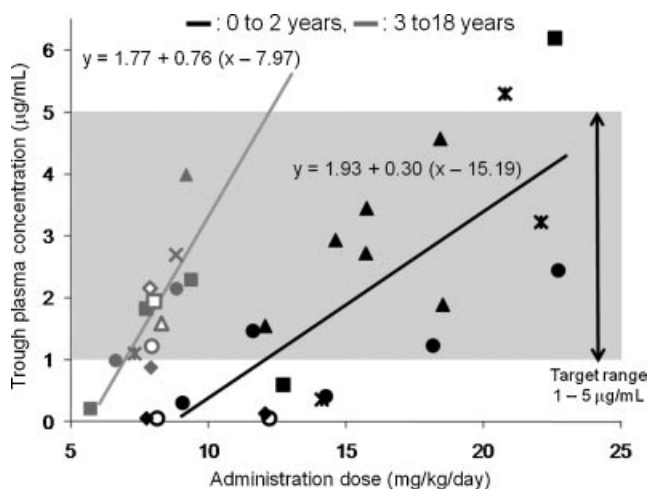


Fig. 1. Relationships between voriconazole trough plasma concentrations and daily doses per body weight. Black markers are monitored results for children 0–2 years of age; gray markers are results for children 3–18 years of age. The type of marker varies with each individual. Differences in distributions are observed according to age: <3 or ≥ 3 years. Estimated regression formula is given with each linear regression line. Target plasma concentration range is also shown in the chart.

(range, 7–9 mg/kg; total daily dose, 130–400 mg/day) for those ≥ 3 years of age.

Efficacy and Side Effects

Among 26 monitored voriconazole therapies during 326 days of neutropenia after chemotherapy and 126 days after HSCT, there was no evidence of fungal infection and neither elevation of galactomannan antigen nor $\beta(1,3)$ -D-glucan levels. Transient visual disturbances in two children aged 9 and 12, and mild elevation of hepatic enzyme levels in two children aged 11 and 16 after HSCT were the only side effects possibly attributed to voriconazole. No significant side effects were observed in two children whose plasma concentrations were above the target range ($>5 \mu\text{g/ml}$) during a certain period of voriconazole administration. However, the incidence of visual disturbances in these children could not be completely assessed because both children were <2 years of age. Regarding concomitant drugs, dose adjustments for FK506 and cyclosporin A were required when voriconazole was given contemporarily, while no dose-limiting side effects of vincristine and phentanyl, especially, no increased risks of vincristine neurotoxicity were observed. Thus, voriconazole was well tolerated in this study.

DISCUSSION

Recent studies on the pharmacokinetics and safety of voriconazole in children demonstrated that, unlike in adults, the elimination of voriconazole was linear in children, and the capacity for elimination was higher compared with that in adults; this was possibly due to the greater systemic metabolism and greater first-pass metabolism with higher hepatic blood flow in children compared to adults [10,11]. In these studies, however, neither the pharmacokinetics nor the optimal doses for children <2 years of age were described.

In our study, children <3 years of age, including four <2 years of age, required a significantly higher dosage compared with children ≥ 3 years of age to obtain a plasma concentration within the target range. In contrast, both children showing a plasma concentration above the target range were <2 years of age, which resulted from dose increases according to their previously monitored low plasma concentrations. Considerable variations in the plasma concentration per daily dose among children <3 years of age made dose adjustments relatively complicated compared with those for older children. Thus, plasma concentration monitoring of voriconazole is important for optimal dosing with less toxicity, especially in children <3 years of age, and careful individual dosage adjustments may be required.

In Europe, the recommended daily dosage of oral voriconazole for treating children 2–11 years of age is 200 mg b.i.d. of an oral suspension formulation or oral tablets, irrespective of body weight [3,11]. In our study, four of five children 2–11 years of age demonstrated that <400 mg per day was sufficient to maintain the trough plasma voriconazole concentration within the target range. One remaining patient had discontinued voriconazole before achieving a plasma concentration of $>1 \mu\text{g/ml}$.

Voriconazole is both a substrate for and an inhibitor of CYP2C19, CYP2C9, and CYP3A4, and allelic polymorphisms in CYP2C19 are known to result in significant variations in its plasma concentrations [3]. Because all but one Indian patient were

Japanese, high frequencies of single-nucleotide polymorphisms in Asian populations [3,12] may have contributed to slow voriconazole metabolism, and there may be racial variations for the optimal dosages of voriconazole. This suggests that an optimal daily dose of 400 mg in children 2–11 years of age may be excessive in Asian populations with a risk of trough plasma concentrations reaching toxic ranges.

From our results, we conclude the following: (1) the optimal dosage of voriconazole for children <3 years of age may be higher than that for older children and (2) trough plasma concentration monitoring of voriconazole is recommended, especially for children <3 years of age. In our study, the optimal oral dosages for children <3 and ≥ 3 years of age were 17 and 8 mg/kg, respectively. However, additional study is required in order to determine the definitive optimal dosages for infants, as well as for older Asian children, as interracial differences in metabolism should be taken into consideration.

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