J Infect Chemother 22 (2016) 27–31

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original article

Oral administration and younger age decrease plasma concentrations of voriconazole in pediatric patients

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ARTICLE INFO

Article history:
Received 3 August 2015
Received in revised form
8 September 2015
Accepted 20 September 2015
Available online 1 November 2015

Keywords:
Voriconazole
Pediatric patients
Invasive aspergillosis

ABSTRACT

Voriconazole is used for treating or preventing invasive aspergillosis and other invasive fungal infections. To minimize adverse reactions and to maximize treatment effects, therapeutic drug monitoring should be performed. However, it is challenging to optimize daily voriconazole dosing because limited data have been published so far on pediatric patients.

We retrospectively analyzed voriconazole concentrations in patients aged 0–18 years. In addition, a literature review was conducted. In our study cohort, younger age and oral administration were significantly associated with lower plasma voriconazole concentrations ($P < 0.01$). An unfavorable outcome was associated with low concentrations of voriconazole ($P = 0.01$). Reports of voriconazole administration in pediatric patients show that higher doses are required in younger children and in patients receiving oral administration. Hence, the current data suggest that we should escalate both initial and maintenance doses of voriconazole in pediatric patients, particularly in patients of younger age receiving an oral administration of voriconazole.

1. Introduction

Voriconazole is used for the treatment and prevention of invasive aspergillosis (IA) as well as other invasive fungal infections. The morbidity and mortality of IA are still high and the adequate and appropriate use of voriconazole is essential. Drug concentrations exhibit large inter-personal variability and pharmacokinetics are complex [1]; they are influenced by the concomitant use of other drugs, genetic polymorphisms, and oral bioavailability, resulting in unpredictable dose–response relationships [2]. Therapeutic drug monitoring (TDM) is recommended for minimizing adverse reactions and for maximizing treatment effects. Because of little experience and limited data [3–5], it is particularly difficult to optimize daily dosing in pediatric patients.

Here, we retrospectively analyzed voriconazole concentrations in pediatric patients. The primary objective of our analysis was to identify the daily dose of voriconazole required to achieve therapeutic trough concentrations in pediatric patients. A secondary objective was to analyze associations between voriconazole concentrations and clinical outcomes. Further, to evaluate the optimal dose of voriconazole in pediatric patients, we compared the daily doses of voriconazole administered in this study with those administered in previous studies.

2. Patients and methods

2.1. Patients

From January 2007 to July 2014, all pediatric patients (aged <19 years) whose serum concentrations of voriconazole were measured were identified from the records of the clinical microbiological laboratory at the Kyoto University Hospital, which is a tertiary care, 1182-bed university hospital in Japan. Patients were divided into the following three groups according to their age: ≤5 years, between 6 and 12 years, and ≥13 years.

The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards.

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http://dx.doi.org/10.1016/j.jiac.2015.09.008
1341-321X/

2.2. Patient characteristics

The following medical data of patients treated with voriconazole were reviewed: age, gender, weight, underlying disease, fungal infection, route of administration (oral or intravenous), clinical outcome, number of samples taken, concomitant medications, and dose adjustments.

2.3. Definition of invasive fungal infection

Fungal infections and response to antifungal therapy were retrospectively classified according to the definitions of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC-MSG).

2.4. Safety assessment

Adverse events such as visual disturbance, encephalopathy, rash, and hepatic enzyme elevation were defined according to the criteria of the National Cancer Institute (National Cancer Institute. Common terminology criteria for adverse events: National Cancer Institute online guidelines 2006. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

2.5. Voriconazole regimen and monitoring

Infectious disease specialists prospectively advised to increase or decrease the doses in patients with trough plasma concentrations of ≤1.0 and ≥5.0 mg/L [3], respectively, with all patients undergoing voriconazole TDM.

The proposed voriconazole treatment regimen was administered at a loading dose of 6 or 8 mg/kg/dose twice on the first day, followed by a dose of 4 or 6 mg/kg/dose twice daily according to the pharmaceutical instructions.

Voriconazole trough concentration values were measured at 3–5 days after therapy initiation and once a week until therapeutic concentrations (trough concentration of <1.0 mg/L or >5.0 mg/L) were reached. Patients receiving high doses or changing doses were monitored once a week.

We considered voriconazole doses were adequate when the plasma concentrations were within 1.0≤ and <5.0 mg/L [3].

2.6. Literature review

To optimize daily voriconazole doses in pediatric patients, a literature review was conducted using PubMed databases. The adopted key words included “voriconazole” and “pediatrics.” Articles in English published from 2005 to 2015 were included. We excluded case reports. Studies reporting on voriconazole doses and concentrations in pediatric population were analyzed, and we compared our data with those of the previously published pediatric studies.

2.7. Statistical analysis

Categorical variables were compared using the Fisher's exact test. Continuous variables were compared using the Mann–Whitney U-test. A P value of <0.05 was considered to be statistically significant. The software JMP (Ver.11.0.0.0 SAS Institute Inc.) was used for analysis.

3. Results

A total of 111 plasma voriconazole trough concentration measurements in 20 patients were obtained over 992 days of voriconazole therapy. The median number of times the TDM was performed per patient was 5 (range, 2–24).

The characteristics of the 20 patients are summarized in Table 1. Patients included 6 females and 14 males, with a median age of 9.5 (range, 0–17) years. The most frequent underlying condition was hematological malignancy and all patients received stem cell transplantation. Five patients underwent solid organ transplantation. Nineteen of the 20 patients had IA. Nine of the 20 patients (particularly young children) received concomitant medication. Voriconazole was orally administered to 55% of the patients (11/20); 15% (3/20) of the patients received both intravenous and oral voriconazole, and 30% (6/20) of the patients received intravenous voriconazole. The median maintenance dose of voriconazole was 10.5 (range, 3.6–24) mg/kg/day, and the median duration of therapy was 64 (range, 9–244) days.

During the course of therapy, 18/20 patients required increased dosage based on TDM data. Eleven of the 20 [75% (6/8) of the children ≤5 years, 43% (3/7) of those aged 6–12 years, and 40% (2/5) of the children ≥13 years] patients did not achieve adequate concentrations upon initial dosing (Fig. 1).

Despite adjusted second doses, the achievement of therapeutic concentration targets remained suboptimal at second monitoring; eleven out of the 20 (55%) patients did not achieve concentrations up to ≥1 mg/L (Fig. 1).

Fig. 2 shows the distribution of the median concentrations of voriconazole. The median concentrations of intravenously and orally administered voriconazole were 1.7 and 0.4 mg/L ($P < 0.001$), respectively, in the group of patients aged ≤5 years. In the group of patients aged 6–12 years, these values were 2.6 and 0.6 mg/mL ($P < 0.001$), respectively. In contrast, the values of 1.4 mg/mL were identified both intravenously and orally in the group of patients aged ≥13 years.

Moreover, by intravenous or oral administration of voriconazole, patients aged ≤5 years had significantly lower concentrations than those aged 6–12 years ($P < 0.001$ and $P = 0.032$, respectively).

Fig. 3 shows doses at adequate concentrations *vs.* age group and route of administration. To reach an adequate concentration, the median oral dose was 30.1, 9.5, and 8.7 mg/kg/day, and the median intravenous dose was 13.1, 9.5, and 5.5 mg/kg/day in the three age groups of patients aged ≤5, 6–12, and ≥13 years, respectively. A significantly higher dose was required for oral administration in children aged ≤5 and ≥13 years ($P < 0.01$). In addition, patients aged ≤5 years required a significantly higher dose to achieve adequate treatment concentrations than those aged 6–12 years ($P < 0.01$) and ≥13 years ($P < 0.01$).

The median voriconazole concentration of 1.8 mg/L in 15/20 patients (75%) with a positive clinical response was significantly higher than the median concentration of 0.6 mg/L in the remaining five patients (25%) with disease progression ($P = 0.005$). Moreover, voriconazole concentrations at first monitoring were significantly lower in patients with unfavorable responses than in patients with favorable responses (0.2 and 1.7 mg/L, respectively; $P = 0.01$; Table 2).

Asymptomatic liver enzyme elevation (NCI grade 1) was observed in only one patient treated with a voriconazole concentration of 1.3 mg/L. This adverse event resolved after the discontinuation of voriconazole. Other adverse effects, such as neurological symptoms, were not observed.

Table 3 shows the recommended dose of voriconazole in previous studies and in the present study. A total of 155 eligible studies were identified. Case reports and studies not specifically mentioning optimal dosing were excluded; eventually, five studies were included. These reports showed that pediatric patient doses are subject to extensive variation. Doses ranging from 5.5 to 32.6 mg/kg/day were necessary to achieve adequate drug