Optimized Administration of Voriconazole and Therapeutic Drug Monitoring in Children and Adolescents: A Single-Centre Retrospective Experience from China

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Introduction

Voriconazole (VRC) is a triazole anti-fungal agent and a first-line treatment for invasive fungal infection (IFI) generally. There is an obvious variation in metabolism between children and adults. The purpose of this single-center retrospective study was performed to explore the factors affecting voriconazole trough concentration(Ctrough) and to show VRC dose adjustment experience in children of several age groups in our centre.

Methods

The demographic information, concentration data, CYP2C19 genotypes and clinical outcomes of eligible children from January 1th, 2016 to December 31th, 2018 were retrospectively collected. Factors affecting the voriconazole trough concentration were statistically analyzed.

Results

A total of 145 trough concentrations in 94 patients were included in this study. 62.8.%(59 in 94) of patients achieved one or more therapeutic level. In all blood samples, 54.5% of them achieved the target concentrations; however, 35.9% were sub-therapeutic and 9.6% were super-therapeutic post multiple VRC dosing. For children ≤2, 2-6, 6-12, and 12-18 years, the median VRC maintenance doses of 5.7, 6.7, 5.0 and 3.3 mg/kg twice daily respectively had been required in order to achieve therapeutic level (P<0.001), which were lower than major recommended doses and VRC package insert doses. Co-administration of proton pump inhibitors was also an important factor that significantly affected VRC target trough concentration (P=0.001). No correlation between the maintenance dose and CYP2C19 genotypes along with the route of VRC administration was found due to small size of sampling.

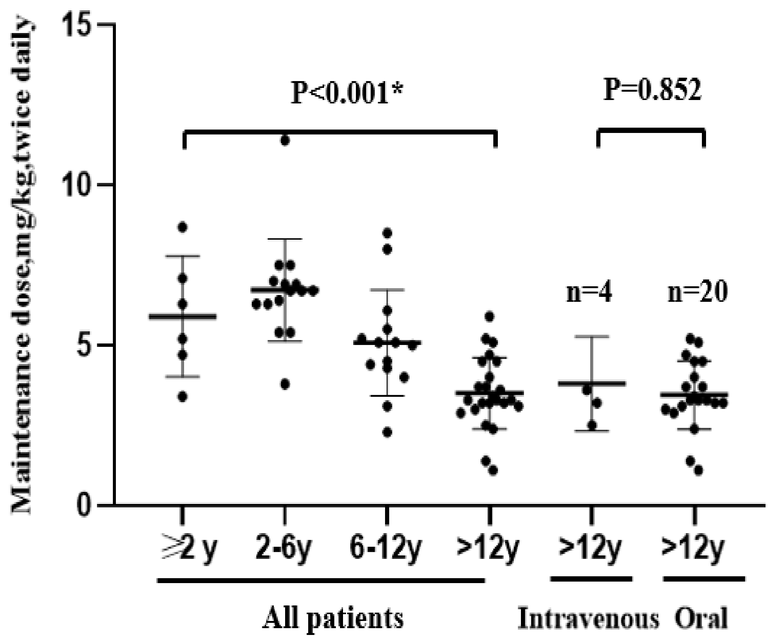

FIGURE 1. VRC maintenance doses required to achieve at least one therapeutic trough concentration (1.0-5.5μg/mL) categorized by age and route of administration (n=59).

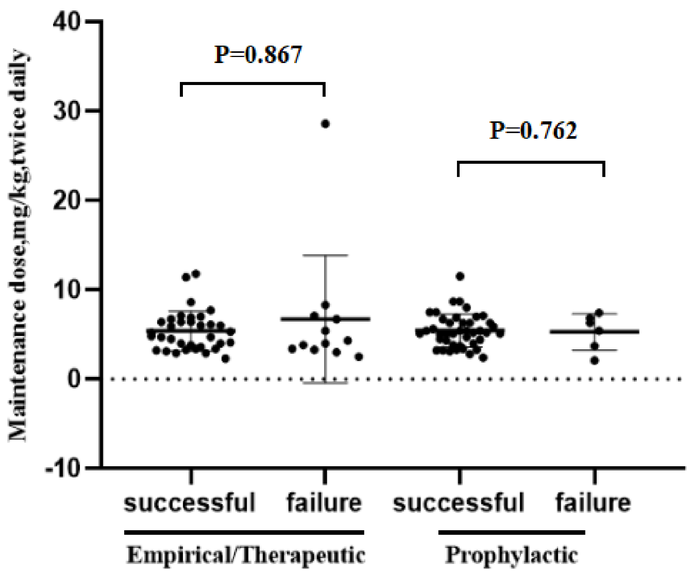

FIGURE 2. VRC maintenance doses required to achieve clinical successful and clinical failure categorized by treatment indication.

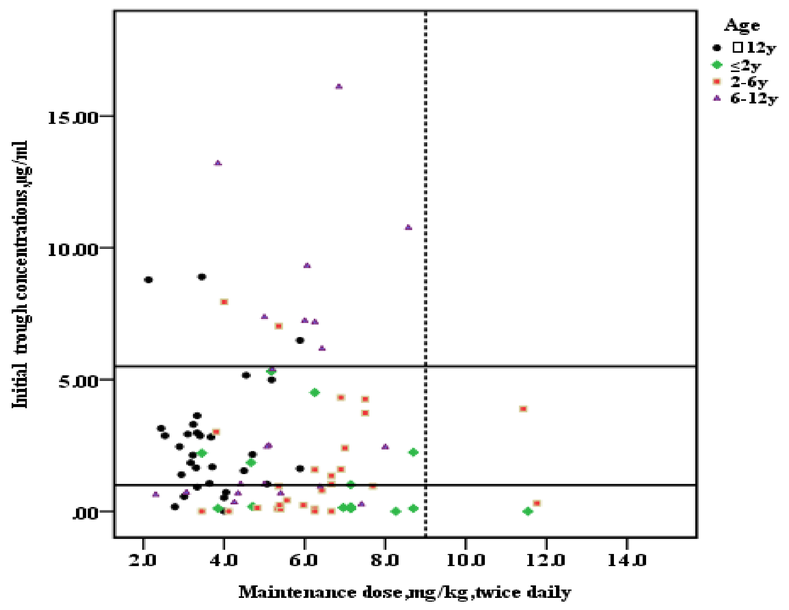

FIGURE 3. Distribution and interpatient variability of initial voriconazole trough concentrations at different weight-adjusted maintenance doses (n=94).

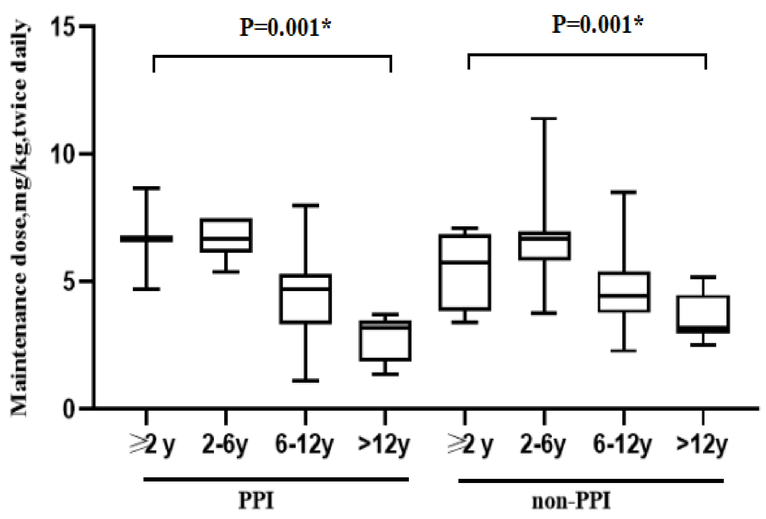

FIGURE 4. Box plot of VRC maintenance dose requiring to achieve at least one therapeutic trough concentration (1.0-5.5μg/mL) categorized by age and PPI coadministration, which was represented by median, minimum, maximum, and interquartile range .

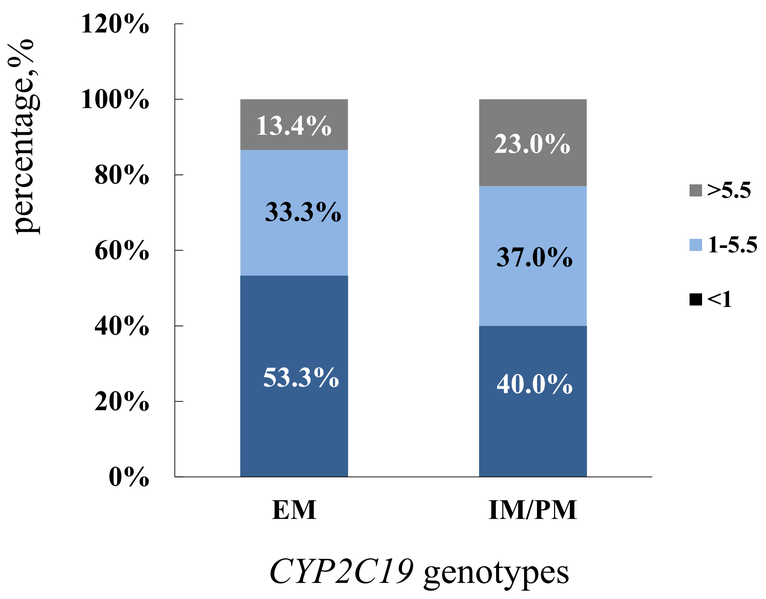

FIGURE 5. Proportion of three CYP2C19 genotypes with sub-therapeutic, therapeutic, and super-therapeutic voriconazole initial Ctrough (n=45).

Conclusions

In order to ensure the effectiveness and safety of voriconazole in children, early and repeat monitoring of voriconazole serum concentration is a powerful tool. Younger pediatric patients might need a higher dosage regime to achieve therapeutic trough concentration. The determination of voriconazole initial dose based on CYP2C19 genotypes may also be a clinical decision-making method, which needs to be confirmed by further studies.

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