Correlation between voriconazole dosage regimen at steady state and CYP3A4 rs4646437 polymorphism

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Background: Voriconazole (VCZ) is prescribed worldwide for invasive fungal infection. VCZ is predominantly metabolized by CYP2C19 and CYP3A4 enzymes. Recent reports revealed CYP3A4 has become an important enzyme for the VCZ metabolism in patients with poor activity of CYP2C19. CYP3A4 mutant alleles such as rs4646437 and CYP3A4*22 influence VCZ concentration. CYP3A4*22 was found in Caucasians but null in East Asian population. CYP3A4 rs4646437 was found in Asian and Caucasian populations. The prevalence of CYP3A4*22 and CYP3A4 rs4646437 were not investigated in Thais. The correlation between CYP3A4 rs4646437 polymorphisms and VCZ dosage regimen was limited. Therefore, the aim of this study was to determine the correlation between CYP3A4 rs4646437 polymorphisms and VCZ dosage regimen in Thai patients with invasive fungal infection. Moreover, we investigated prevalence of CYP3A4 rs4646437 and CYP3A4*22 in Thai healthy volunteers.

Material and Method: One hundred healthy volunteers were enrolled from blood donors at blood blank of Srinagarind Hospital. Forty five invasive fungal infected patients treated with VCZ at Srinagarind and Ramathibodi hospital were enrolled. VCZ blood concentrations were determined at steady state (≥5th day after treatment) and all of the blood levels were in therapeutic range. Clinical data of the patients were reviewed. CYP3A4 polymorphisms was determined by real-time PCR technique with specific TaqMan® probe and primer. VCZ blood concentration was determined by HPLC method.

Result: Genotype frequencies for CYP3A4 rs4646437 GG, GA and AA in 100 Thai healthy volunteers were 65%, 28%, and 7%, respectively. CYP3A4*22 mutant allele was not found in Thais. The genotype frequencies of CYP3A4 rs4646437 showed a statistically significant difference from Chinese and Caucasian populations (P<0.005). The frequencies of CYP3A4 rs4646437 GG, GA, and AA in 47 patients were 68.9%, 26.7%, and 4.4%, respectively. VCZ dosages at steady state for the patients carrying CYP3A4 rs4646437 GG, GA and AA did not show a statistically significant difference (7.79 ±1.93 VS 6.97±1.58 VS 9.80±1.92 mg/kg/day, respectively) (P= 0.118).

Conclusion: Homozygous mutant of CYP3A4 rs4646437 in healthy Thai volunteers was higher than other populations. Correlation between CYP3A4 rs4646437 mutant alleles and VCZ doses was not found in this study.