Poster

# [P27-2] P27-2: Anti-infective drugs (7): Antifungals

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## [P27-2-5] Voriconazole TDM based on both unchanged drug and metabolite concentrations in Japanese patients

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### Background

Voriconazole (VRCZ), an azole antifungal, exhibits nonlinear pharmacokinetics. VRCZ is metabolized mainly by cytochrome P450 (CYP) 2C19 to inactive voriconazole N-oxide (VNO). CYP2C19 mutant type (lack of ability to metabolize) is generally found in more than 60% of Japanese population. Together with the nonlinear pharmacokinetics, this genetic mutation can thus cause a high VRCZ level to its hapatotoxicity in Japanese patients. However, CYP2C19 genotyping is difficult and uncommon in TDM practice. This study aimed to examine the relationship between VNO/VRCZ concentration ratio and CYP2C19 genotype.

### Methods

Patients were included who received intravenous or oral VRCZ at least for three days in Kagoshima University Hospital from July 2013 to December 2015. Blood samples were collected just before the next administration. Plasma concentrations of VRCZ and VNO were measured using a validated high-performance liquid chromatography. Genetic polymorphism was analyzed using Invader Plus method. CYP2C19 genotypes were classified as extensive (wild) metabolizer for *1/*1, intermediate metabolizer for *1/*2 and *1/*3, and poor metabolizer for *2/*2 and *3/*3 alleles.

### Results

The study subjects were 18 men and 12 women (10 for extensive, 8 for intermediate and 12 for poor metabolizers), with mean age of 54.0 years old (range 15-80) and weight of 52.1 kg (29.3-76.9). Obtained plasma were 103 samples. VRCZ concentrations were not different among the three metabolizer groups. However, VNO/VRCZ concentration ratios were different among 2.3 ±2.0 (mean ±standard deviation) for extensive, 1.4 ±1.0 for intermediate and 1.2 ±1.2 for poor metabolizers, respectively (statistical significance between extensive and intermediate metabolizers, and between extensive and poor metabolizers).

### Conclusions

VNO/VRCZ ratios decreased in order of extensive, intermediate and poor metabolizers. The results show that VNO/VRCZ ratio can be a good predictor for determining CYP2C19 genotype, although its cut-off values need to be further established. As an alternative method of CYP2C19 genotyping in TDM practice, CYP2C19 phenotyping by simultaneous measurement of plasma VRCZ and VNO concentrations and then calculation of VNO/VRCZ ratio is suggested to be an easy and useful method to evaluate ability to metabolize VRCZ in Japanese patients.