Why are the Therapeutic Drug Monitoring Results of Voriconazole Inconsistent with CYP2C19 Genetic Testing?

Sir,

Voriconazole is a second-generation triazole antifungal agent, an attractive option for the treatment or prevention of aspergillosis and candidal infections. Previous studies have confirmed that the therapeutic effects and adverse reactions of voriconazole are closely related to its steady-state plasma concentration.[1,2] The latter is affected by a variety of factors, such as age, gender, weight, inflammation, cytochrome P450 genotype, and the use of concomitant medications, resulting in differences in the clinical outcomes.[3-5] An increasing number of studies have shown that therapeutic drug monitoring (TDM) and *CYP2C19* genetic polymorphisms have great guiding significance for the clinical safety and effectiveness of voriconazole.[3-5]

A 49-year woman (height 164 cm; weight 77 kg; body surface area 1.833 m^2) was admitted to the Department of Haematology following follicular lymphoma for >9 years. Many chemotherapy schemes, such as CHOP, R-FC, and R-, were used, and radiotherapy was performed due to mediastinal invasion. This admission was intended to start a new chemotherapy cycle.

On day 2, the patient had a cough with white and sticky sputum. Based on the chest computed tomography, the clinicians considered a fungal infection and empirically started voriconazole, with a dosing regimen of 200 mg, every 12 h. On day 3, urinary microscopy showed white blood cells (WBCs) (2+), with the count of WBCs in sediment being 474 /μL, indicating urinary tract infection, and levofloxacin injection of 0.4 g once daily was added.

On day 8, the patient's cough and expectoration did not improve. The TDM result of voriconazole was 0.15 μg/mL, which was lower than the concentration range recommended by the guideline.[3] The pharmacist suggested that the dose of voriconazole should be adjusted to 400 mg q12 h, but was not adopted by the clinicians.

On day 11, the patient still had severe cough. TDM result of voriconazole was 0.12 μg/mL. This time the dose of voriconazole was adjusted to 400 mg q12 h.

On day 14, the TDM result of voriconazole was 0.18 μg/mL, which was still low. In order to find out the cause, the pharmacist suggested *CYP2C19* genetic testing. On day 15, genetic test results showed *CYP2C19*2* (*AG*), *CYP2C19*3* (*GG*), and *CYP2C19*17* (*CC*). According to these results, the expression of *CYP2C19* activity in this patient was poor, and the blood concentration should have been high on the standard dose. However, the TDM result of voriconazole in this patient was very low even after the dose had been doubled.

Faced with the contradiction between TDM and genetic testing results, the clinical pharmacist had in-depth communication with the patient, in particular, about the medications. It was found that the patient had a history of epilepsy and was currently taking carbamazepine by herself, but did not inform the clinicians about this.

Carbamazepine, a powerful inducer of *CYP450*, can significantly reduce the blood concentrations of voriconazole, and now the combination of carbamazepine with voriconazole has been explicitly prohibited in the package insert of voriconazole.[5] Therefore, voriconazole was stopped and caspofungin (the first dose of 70 mg and the maintenance dose of 50 mg qd) was started. The patient's infection was quickly controlled. On day 24, the CHOP chemotherapy was given.

In this case, the clinicians first empirically started voriconazole considering invasive fungal infections, but it was ineffective. TDM and *CYP2C19* genetic testing results did not explain the therapeutic failure of the drug. After detailed communication with the patient, it was eventually found that the poor effect was caused by the drug interaction between carbamazepine and voriconazole, and the patient's condition improved after voriconazole was changed to caspofungin, indicating the important role of a thorough history taking in clinical treatment.

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