

Successful Management of Voriconazole-Associated Hyponatremia with Therapeutic Drug Monitoring

Ren-ai Xu, Guan-yang Lin, Lu-feng Hu, Da-wei Shi, Xiao-lan Ye, Yun-jie Liu, Xiao-feng Pan, Chun-hong Zhang, Xiu-hua Zhang

Department of Pharmacy, The First Affiliated Hospital of Wenzhou Medical College, Wenzhou, China

Voriconazole is a broad-spectrum triazole antifungal agent and the first-choice therapy for invasive aspergillosis (IA) (1). Although voriconazole is generally well tolerated, anecdotal case reports have described unexpected severe adverse events related to voriconazole, such as hyponatremia, which potentially could result in death (2–4). We report a case of successful voriconazole treatment of invasive pulmonary aspergillosis (IPA) in a hyponatremia patient.

A 72-year-old man with a 10-year history of chronic obstructive pulmonary disease (COPD) was admitted to our respiratory department because of acute exacerbation. Because of his positive aspergillus sputum cultures before admission, he had a higher risk of developing IPA. The patient was treated with intravenous voriconazole (two loading doses of 6 mg/kg of body weight and then 4 mg/kg every 12 h) for 2 weeks and then changed to oral voriconazole tablets at a dose of 200 mg every 12 h. A definite diagnosis of IPA was soon obtained from a computed tomography (CT)-guided percutaneous lung biopsy specimen evidencing *Aspergillus fumigatus* in culture (5). Twenty-six days after commencing voriconazole therapy, the patient showed somnolence and malaise symptoms. Electrolyte levels showed that his sodium level was 104 mmol/liter but that his potassium and creatinine levels were normal. Therapeutic drug monitoring (TDM) was performed, and the voriconazole plasma trough concentration (voriconazole C_0) was high (7.10 $\mu\text{g/ml}$). Two days after the discontinuation of voriconazole and infusion of 3% saline, the patient's mental status and hyponatremia recovered. Our goal voriconazole C_0 range was 1.0 to 5.5 $\mu\text{g/ml}$. The voriconazole C_0 (0.68 $\mu\text{g/ml}$), obtained 11 days after a half-dose reduction of voriconazole (200 mg/day), was not within the therapeutic range. Since his voriconazole C_0 remained subtherapeutic (0.68 $\mu\text{g/ml}$), we increased the dose to 300 mg/day after he was discharged from the hospital. Thirteen days after the treatment, the voriconazole C_0 increased to 1.38 $\mu\text{g/ml}$, which mostly achieved the target concentration of ≥ 1.0 $\mu\text{g/ml}$. The patient remained asymptomatic, and repeat CT findings showed near resolution of lung lesions upon follow-up in our outpatient department. The *CYP2C19* genotype was classified as heterozygous extensive metabolizer (*CYP2C19*1/CYP2C19*2*).

It is well known that *CYP2C19* genetic polymorphisms make it particularly difficult to predict exposure to voriconazole and its potential dose-dependent toxicity (6). Indeed, voriconazole C_0 s of ≥ 1.0 $\mu\text{g/ml}$ have been associated with improved responses to therapy and survival (7, 8). Increased adverse events have been associated with voriconazole C_0 s of >5.0 to 6.0 $\mu\text{g/ml}$ (9, 10). As a consequence, TDM may be a useful tool to optimize voriconazole therapy. In our case, the voriconazole C_0 was 7.10 $\mu\text{g/ml}$, which is considered in the toxic range. Therefore, voriconazole-associated hyponatremia may be concentration dependent. Instead of discontinuing antifungal therapy, it was decided to reduce the voriconazole dose to 200 mg/day, and the voriconazole C_0 was sub-

therapeutic (0.68 $\mu\text{g/ml}$). Finally, TDM revealed an adequate voriconazole C_0 (1.38 $\mu\text{g/ml}$) 13 days after dose adjustment to 300 mg/day, suggesting that the dose regimen for this patient was appropriate. So, voriconazole-related hyponatremia suggests that the clinical utility of routine TDM of voriconazole reduces drug-related adverse events and improves treatment outcome in invasive fungal infections.

In conclusion, this case suggests that fatally severe hyponatremia can develop after initiation of voriconazole antifungal therapy. Furthermore, this experience confirms that the appropriateness of voriconazole dose adjustment instead of therapy interruption should be considered according to the voriconazole C_0 . We believe that TDM is useful to determine the voriconazole dosage in a voriconazole-related hyponatremia patient.

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Address correspondence to Xiu-hua Zhang, wzhangxiuhua@yahoo.cn, or Chun-hong Zhang, zch760217@163.com.

X.-H.Z. and C.-H.Z. contributed equally to this work.

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