Altered Pharmacokinetics of Voriconazole in a Patient with Liver Cirrhosis

Voriconazole (VRC; Vfend [Pfizer, United Kingdom]) is a broad-spectrum triazole with activity against fungi including non-albicans Candida, Aspergillus, Fusarium, and Scedosporium species. Favorable therapeutic responses in patients with plasma VRC levels above 2.05 μg/ml were found previously (9). The main adverse effects of VRC are hepatotoxicity and blurred vision (1, 2, 4, 6, 11). Prolonged exposure to high plasma VRC concentrations (trough blood VRC levels of >5.5 μg/ml for more than 7 days) was found to be associated with an enhanced risk of serious neurological adverse events (5).

A 45-year-old male (body weight, 100 kg) with fatty-liver cirrhosis (Child-Pugh class C; model of end-stage liver disease score, 20) who was listed for liver transplantation and showed signs of portal hypertension (esophageal varices and ascites) and cholestasis (plasma bilirubin level, 20.26 mg/dl, or 346 μmol/liter) received 2 mg of VRC/kg of body weight orally twice a day because of suspected pulmonary aspergillosis. At day 30 of clinical treatment with VRC, he was transferred to the intensive care unit because of unconsciousness (Glasgow Coma Scale score, 5 of 15) and hyperventilation. Plasma VRC concentrations were determined by high-performance liquid chromatography and UV detection (3). Pharmacokinetic parameters were calculated using a noncompartmental model.

Upon admission to the intensive care unit (15 h after the last intake of VRC), the plasma VRC level amounted to 13.9 μg/ml (Fig. 1). Therefore, VRC therapy was discontinued. The patient’s condition, particularly the central nervous system symptoms, gradually improved as VRC levels slowly declined, and he could be transferred to the ward after 2 days (VRC concentration, 10.0 μg/ml). A half-life of 53.1 h (half-life in healthy volunteers, 4.7 h [7]), an apparent volume of distribution at steady state of 0.13 liters/kg (volume of distribution in healthy volunteers, 2.04 liters/kg [7]), and a VRC clearance rate as low as 1.4 ml/h/kg (clearance rate in healthy volunteers, 253.9 ml/h/kg [7]) were calculated. Even after 11 days, VRC was detectable in the plasma (0.66 μg/ml). Since diagnostic reevaluation did not reveal any signs of fungal infection, there was no need to continue antifungal treatment at that time. The patient underwent a successful liver transplantation 1 month later.

The elimination of VRC appears to be markedly prolonged in patients with decompensated liver cirrhosis, and this delay leads to potentially toxic levels of VRC in the plasma. After cytochrome P450 2C9, 2C19, and 3A4-dependent hepatic metabolism, about 80% of VRC is eliminated via the kidneys. Biliary elimination accounts for 20%. VRC displays nonlinear pharmacokinetics, with a prolonged half-life at higher concentrations (8). In patients with moderate liver cirrhosis (Child-Pugh class B), the VRC clearance rate is approximately half that in patients with normal hepatic function after oral intake. A reduction of the maintenance dose by 50% is recommended for patients with mild to moderate hepatic insufficiency (10). For patients with severely impaired liver function, a dose reduction of more than 50% appears to be required, and therapeutic drug monitoring will greatly improve therapeutic safety. Pharmacokinetic studies in patients with severe hepatic impairment should be performed in order to establish reliable dose recommendations for this group of patients, who are at high risk of developing invasive fungal infections.

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REFERENCES


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