Voriconazole Therapeutic Drug Monitoring is Necessary for Children with Invasive Fungal Infection

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Purpose: To determine the clinical significance of voriconazole therapeutic drug monitoring (TDM) in the pediatric population.
Methods: Twenty-eight patients with invasive fungal infections administered with voriconazole from July 2010 to June 2012 were investigated retrospectively. Fourteen received TDM, and 143 trough concentrations were analyzed. All 28 patients were assessed for adverse events and treatment response six weeks into treatment, and at the end.
Results: Out of 143 samples, 53.1% were within therapeutic range (1.0–5.5 mg/L). Patients administered with the same loading (6 mg/kg/dose) and maintenance (4 mg/kg/dose) dosages prior to initial TDM showed highly variable drug levels. Adverse events occurred in 9 of 14 patients (64.3%) in both the TDM and non-TDM group. In the TDM group, voriconazole-related encephalopathy (n=2, 14.3%) and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation (n=8, 57.1%) occurred with serum levels in the toxic range (>5.5 mg/L), whereas blurred-vision (n=2, 14.3%) occurred within the therapeutic range (1.18 mg/L and 3.9 mg/L). The frequency of voriconazole discontinuation due to adverse events was lower in the TDM group (0.0% vs. 18.2%, P=0.481). Overall, 57.2% of the patients in the TDM group versus 14.3% in the non-TDM group showed clinical response after 6 weeks (P=0.055), whereas 21.4% in the TDM group versus 14.3% in the non-TDM group showed response at final outcome (P=0.664). In the TDM group, 67.0% of the serum levels were within therapeutic range for the first 6 weeks; however 45.5% were within therapeutic range for the entire duration.
Conclusion: Routine TDM is recommended for optimizing the therapeutic effects of voriconazole.

Key Words: Therapeutic drug monitoring, Voriconazole, Child, Invasive aspergillosis, Invasive fungal infection

Introduction

Invasive fungal infections (IFI) are among the most important causes of morbidity and mortality
in immunocompromised patients. With advances in treatment options for hematologic malignancies, the clinical outcome of immunocompromised patients has improved, resulting in an increasing number of patients living with a profoundly compromised immune system. One of the sequelae to such phenomenon is the increase in the incidence of IFI over the past decade\(^1,2\). Because of the seriousness of the disease and its fatal outcome, IFI has become an eminent obstacle in the outcome of immunocompromised patients.

Novel agents are continually being discovered targeting fungal infections\(^3\). It has been reported that in patients with invasive aspergillosis, initial therapy with voriconazole compared to amphotericin B led to better outcome and improved survival\(^4\). Therefore, voriconazole is now being used extensively in patients with IFI\(^5\).

Voriconazole is a second generation triazole with broad spectrum of antifungal activity, indicated for use in the treatment of invasive aspergillosis, candidiasis, as well as other IFI\(^6\). It is known to reach steady-state concentrations after 5–7 days, but can be reduced to 1–2 days by starting with a loading dose\(^7\). Indicated in both adults and children, voriconazole is known to have non-linear pharmacokinetics in adults. Many studies have demonstrated that pharmacokinetics of voriconazole in children are different from that of adults: while some studies demonstrate linear plasma pharmacokinetics\(^8,9\), other studies show that children have high inter-patient variability which limits the accurate prediction of pediatric voriconazole exposure based on adult dosages\(^10\).

The high morbidity and mortality of IFI warrants aggressive yet specified treatment, and because voriconazole has a narrow therapeutic margin and unpredictable serum levels, the awareness for therapeutic drug monitoring (TDM) is increasing. This study aimed to determine the implications of voriconazole TDM on the clinical outcome and adverse events in pediatric immunocompromised patients.

**Materials and Methods**

1. **Patients**

We reviewed the medical records at Seoul National University Children’s Hospital (SNUCH), a tertiary care, 350-bed pediatric referral hospital with an electronic medical record system. This was a retrospective study on pediatric patients with hematologic disease or immunosuppression, who were administered voriconazole. Voriconazole became available at SNUCH in July of 2005, and from July 2005 to June 2012 a total of 57 pediatric patients were administered voriconazole. Voriconazole TDM became available as a clinical study in November 2008, and was performed on pediatric patients starting July 2010.

Between July 2010 and June 2012, a total of twenty-eight patients aged 18-years old or younger were included in this study. All patients who received voriconazole at least once for treatment or prophylaxis of IFI were included. Fourteen patients underwent voriconazole serum level monitoring, and a total of 143 serum trough concentrations were analyzed. All 28 patients administered with voriconazole were assessed for voriconazole-related adverse events and treatment response six weeks into treatment, and at final outcome.