Pharmacokinetic interaction between voriconazole and ciclosporin A following allogeneic bone marrow transplantation

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Voriconazole is a novel antifungal triazole that undergoes extensive oxidative metabolization involving several CYP450 isoenzymes. We report the case of a 14-year-old patient who received voriconazole concomitant with ciclosporin A as secondary antifungal prophylaxis after bone marrow transplantation. Temporary discontinuation of voriconazole due to worsening liver function tests (LFTs) resulted in a sudden drop of ciclosporin A trough levels in blood. Ciclosporin A trough levels returned to baseline following normalization of LFTs and re-institution of voriconazole. This report emphasizes the need for careful monitoring and dose adjustments of ciclosporin A in patients receiving concomitant voriconazole, and in whom voriconazole is discontinued in order to prevent subtherapeutic ciclosporin A levels with the potential consequence of graft-versus-host disease.

Keywords: antifungals, CYP450 isoenzymes, graft-versus-host disease

Introduction

Voriconazole is a novel antifungal triazole with broad-spectrum antifungal activity and potential for widespread use in immunocompromised patients.1,2 Similar to other members of its class, voriconazole undergoes extensive oxidative metabolization involving predominantly CYP2C19, but also CYP2C9 and CYP3A4.3 Voriconazole also acts as inhibitor of CYP3A4,4 rendering it susceptible to interference with ciclosporin A, a standard agent for immunosuppression following haematopoietic stem cell transplantation.

Case report

The patient was a 14-year-old, female adolescent with acute myeloblastic leukaemia in first complete remission. Induction chemotherapy had been complicated by proven invasive pulmonary aspergillosis, which had responded to amphotericin B and for which she was placed on voriconazole as maintenance antifungal therapy. Matched unrelated bone marrow transplantation was performed after conditioning with busulphan, cyclophosphamide, melphalan plus anti-thymocyte globulin. Immunosuppression consisted of four doses of methotrexate and ciclosporin A for a scheduled duration of ~6 months post-transplantation. The starting dose of ciclosporin A per protocol was 3 mg/kg body weight/day, in two divided doses to be adjusted to trough concentrations in blood of 150–200 ng/mL.

The patient’s course during the conditioning regimen and following marrow transplantation was essentially uncomplicated. She was discharged to the outpatient clinic on day +30 with regenerating haematopoiesis, complete donor chimerism and a stable dose of 2.8 mg/kg ciclosporin A given in two equally divided daily doses. Concomitant medication included voriconazole 200 mg twice a day, valaciclovir 500 mg twice a day and trimethoprim–sulfamethoxazole 160 mg twice a day, twice weekly, for a body weight of 48 kg.

Because of steadily rising γ-glutamyltransferase and, ultimately, alkaline phosphatase (AP) values, but only mild increases in hepatic transaminases (serum glutamic pyruvic transaminase and serum glutamic-oxalic transaminase less than twice the upper limit of normal) and normal serum bilirubin and stable serum creatinine (0.8–1.1 mg/dL), voriconazole was stopped on day +56 due to presumed hepatotoxicity (Figure 1). Immediately after the discontinuation of voriconazole, there was a significant drop in ciclosporin A trough levels from stable concentrations in the range of 150–184 ng/mL (mean 171.2) to 56–111 ng/mL (mean 83.6; P = 0.01 by Mann–Whitney U-test). Since ciclosporin A trough concentrations may vary from day to day and the patient continued to do well, without any evidence of graft-versus-host disease (GvHD), no drug–drug interaction was considered and no dosage adjustment was initiated. Following improvement of liver function tests (LFTs), voriconazole was reinstituted on day +74. Ciclosporin A trough levels returned to their prior concentration range (126–144 ng/mL, mean 134.5; P = 0.01 in comparison
to ciclosporin A levels during discontinuation of voriconazole by Mann–Whitney U-test) and LFTs remained stable. Ciclosporin A was tapered starting on day +88 and discontinued at around day +130. The patient is now on day 160 post-transplantation in continued haematological remission, is doing well and continues to receive voriconazole owing to residual abnormalities on thoracic computed tomography scan.

Discussion

This report demonstrates the potential of drug–drug interactions of voriconazole and ciclosporin A in patients following haematopoietic stem cell transplantation. Discontinuation of voriconazole with continued, unchanged ciclosporin A dosing resulted in a decrease of ciclosporin A trough levels, rendering the patient at increased risk for acute GvHD.

The effects of voriconazole on the pharmacokinetics of ciclosporin A have been investigated in kidney transplant patients in a randomized, double-blind crossover study. Concomitant administration of voriconazole resulted in a 1.7-fold increase in the mean AUC of ciclosporin A along with similar increases in ciclosporin A trough concentrations. Moreover, a considerable number of patients experienced adverse events attributable to ciclosporin A toxicity during voriconazole treatment and prematurely discontinued it. In patients following allogeneic haematopoietic stem cell transplantation, the interaction between voriconazole and ciclosporin A has not been systematically studied to this date. However, it is highly relevant for clinical practice, since voriconazole is increasingly used as antifungal treatment in this complex setting. Voriconazole may be added to ciclosporin A, leading to potentially toxic ciclosporin A concentrations in blood and enhanced toxicity. *Vice versa*, as in the presented case, voriconazole may be withdrawn for various reasons, resulting in inadequate exposure of the post-transplant patient to ciclosporin A and increased risk for the onset of potentially life-threatening GvHD.

Thus, similar to itraconazole and fluconazole, clinically relevant pharmacokinetic interactions can occur with the concomitant use of voriconazole and ciclosporin A in haematopoietic stem cell transplant recipients. Close monitoring of ciclosporin A blood levels and appropriate dosage adjustments are mandatory when voriconazole is added to ciclosporin A or when voriconazole is discontinued following concomitant treatment with both drugs.

References