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Increased plasma tacrolimus concentration after single intravenous administration of voriconazole: a case of drug–drug interaction

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ABSTRACT

Tacrolimus, as one of cytochrome P450 (CYP) 4/5 substrates is known to have many drug–drug interactions. Metabolism of tacrolimus is inhibited by many drugs, such as the azole antifungal agents due to their effects on CYP 3A4/5. Implementation of therapeutic drug monitoring is recommended during tacrolimus treatment for maintaining optimal plasma concentration levels, and to avoid its toxicity. We herein report a case of a 58-year-old female patient with lupus nephritis whose plasma concentration of orally administered tacrolimus increased after a single administration of 300 mg voriconazole for suspected *Aspergillus* infection. Our observations were the result of therapeutic drug monitoring before the second administration of voriconazole. Although tacrolimus dose did not vary, the plasma tacrolimus concentration was markedly increased and concentration dose ratio was 2.1 fold more than prior to voriconazole treatment. This case suggests that even after a single intravenous administration of voriconazole, the plasma concentration of tacrolimus may increase. Dose optimization of tacrolimus by therapeutic drug monitoring soon after the first dose of voriconazole is therefore warranted to minimize the risk of tacrolimus toxicity. *Ryukyu Med. J., 33 (1~3) 41~44, 2014*

Key words: tacrolimus, voriconazole, CYP3A4/5, drug–drug interaction, therapeutic drug monitoring

INTRODUCTION

Tacrolimus, a calcineurin inhibitor, is widely used as an immunosuppressive agent after organ transplantation and in patients with immune disorders such as collagen disease. However, there are wide variations in the dosages used and it is also known that plasma concentrations of tacrolimus among individuals¹). This is partly because of drug–drug interactions due to the effect of cytochrome P450 3A4/5 (CYP3A4/5) metabolism in the liver and intestine¹⁻³). Therefore, therapeutic drug monitoring (TDM) is warranted to ensure the maintenance of optimal drug plasma concentrations and minimize the risk of drug toxic effects such as renal dysfunction^{1, 2}).

Azole antifungal agents, including itraconazole,

fluconazole, and voriconazole, are frequently used in immunosuppressed patients to prevent or treat invasive fungal infections. These azole antifungal agents are also potent inhibitors of CYP3A4, CYP3A5, CYP2C9, and CYP2C19³⁻⁵). Because the major metabolic pathway of tacrolimus involves CYP3A4/5, drug–drug interactions resulting from inhibition of CYP3A4/5 by azole antifungal agents lead to altered pharmacokinetics of tacrolimus. These interactions may be clinically relevant in terms to patient outcome.

Tacrolimus and voriconazole can be administered either orally or intravenously. A number of reports have described drug–drug interactions between orally administered tacrolimus and voriconazole or between intravenously administered tacrolimus and voriconazole⁴⁻⁸). However, to the best of our knowledge, there have

not been any reported cases after a single administration of intravenous voriconazole with orally administered tacrolimus⁵⁻⁹. The present case report describes a significantly increase in the plasma concentration of tacrolimus after a single dose of intravenous voriconazole.

CASE

A 58-year-old female patient with lupus nephritis (weight, 44 kg) was receiving prednisolone (35 mg/day) and tacrolimus (2 mg/day, once daily after breakfast). Clinical examination findings had suggested that lupus nephritis had been well controlled for 2 weeks; therefore the dose of tacrolimus was slowly tapered. On day 31 after starting tacrolimus, which had been tapered from 3 to 2 mg/day, ceftazidime (1 g/day) was administered because of a high fever (38.9°C). Defervescence occurred the next day. Fever returned (39.6°C) on day 35 with concurrent shivering. *Aspergillus* antigen was detected with β -D-glucan positivity, and chest computed tomography and X-ray showed multiple nodules in the lung caused by septic emboli of *Aspergillus*. Treatment with intravenous administration of voriconazole was therefore started. Before starting the voriconazole, a single oral dose of fluconazole (100 mg) was given to the patient on day 36. Treatment with voriconazole was started with an intravenous loading dose at 600 mg/day on days 37 (300 mg; single dose at evening) and 38 (300 mg; single dose at morning) followed by oral dosing at 400 mg/day. Renal function during the observational period was consistently reduced; i.e., the estimated glomerular filtration rate on days 31, 35, 37 and 39 were 34.3, 32.1, 22.0 and 17.1 ml/min, respectively. C-reactive protein (CRP) on days 31, 37, 38 and 39 were 1.3, 5.1, 14.5 and 13.5 mg/dl, respectively.

Before voriconazole treatment, the trough plasma concentration and concentration/dose ratio (C/D ratio) of tacrolimus on days 20 and 30 were determined to be 12.6 and 9.6 ng/ml and 220 and 210 ng/ml per mg/kg (2.5 and 2.0 mg/day, once daily after breakfast), respectively. They were markedly increased to 20.5 ng/ml and 447 ng/ml per mg/kg on day 38 before second administration of voriconazole (Fig. 1). The C/D ratio on day 38 was 2.0- and 2.1-fold higher than that of days 20

and 30, respectively. After day 38, the tacrolimus was discontinued because of a high trough level. The elimination half-life of tacrolimus, which was calculated by linear regression analysis using the log-linear decline phase, was 55.3 hours.

DISCUSSION

We have herein reported a substantially increased plasma trough concentration, high C/D ratios, and a prolonged half-life of orally administered tacrolimus after a single 300 mg intravenous dose of voriconazole. We assume that even a single intravenous dose of voriconazole may seriously affect the metabolism of tacrolimus via the drug-drug interaction involving CYP3A4/5. Although this case patient received a single 100 mg oral dose of fluconazole, which is another azole antifungal agent that inhibits CYP3A4, the influence of fluconazole on tacrolimus metabolism in our case was assumed to be limited because Mañez et al.¹⁰ reported that in patients under tacrolimus immunosuppression, after one day co-administered with 100 mg of fluconazole, tacrolimus median plasma concentration increases 1.4 fold, but it had decreased to before co-administration level in next day. Hence, our report is consistent with other reports of drug-drug interactions between tacrolimus and azole antifungal agents.

Because CYP3A4/5 is distributed in the liver and intestine, additional inhibition of the small intestine metabolism of tacrolimus is expected to be more profound after oral rather than intravenous administration of voriconazole. In fact, Sprit et al.⁶ reported that tacrolimus trough levels, which had been approximately 6 to 7 ng/ml with intravenous voriconazole, immediately increased to 10 to 11 ng/ml after switching to oral voriconazole in a patient after liver transplantation. However, our case warns that even a single dose of intravenous voriconazole may inhibit tacrolimus metabolism, particularly when orally administered, and may subsequently increase the plasma concentration of tacrolimus. It is well known that most of the adverse effects occurred at a blood concentration higher than 20 ng/ml¹¹. In this present case, there were reduced renal functions in days 38 and 39. The declining renal function combined with increased CRP and their resulting inverse relationship

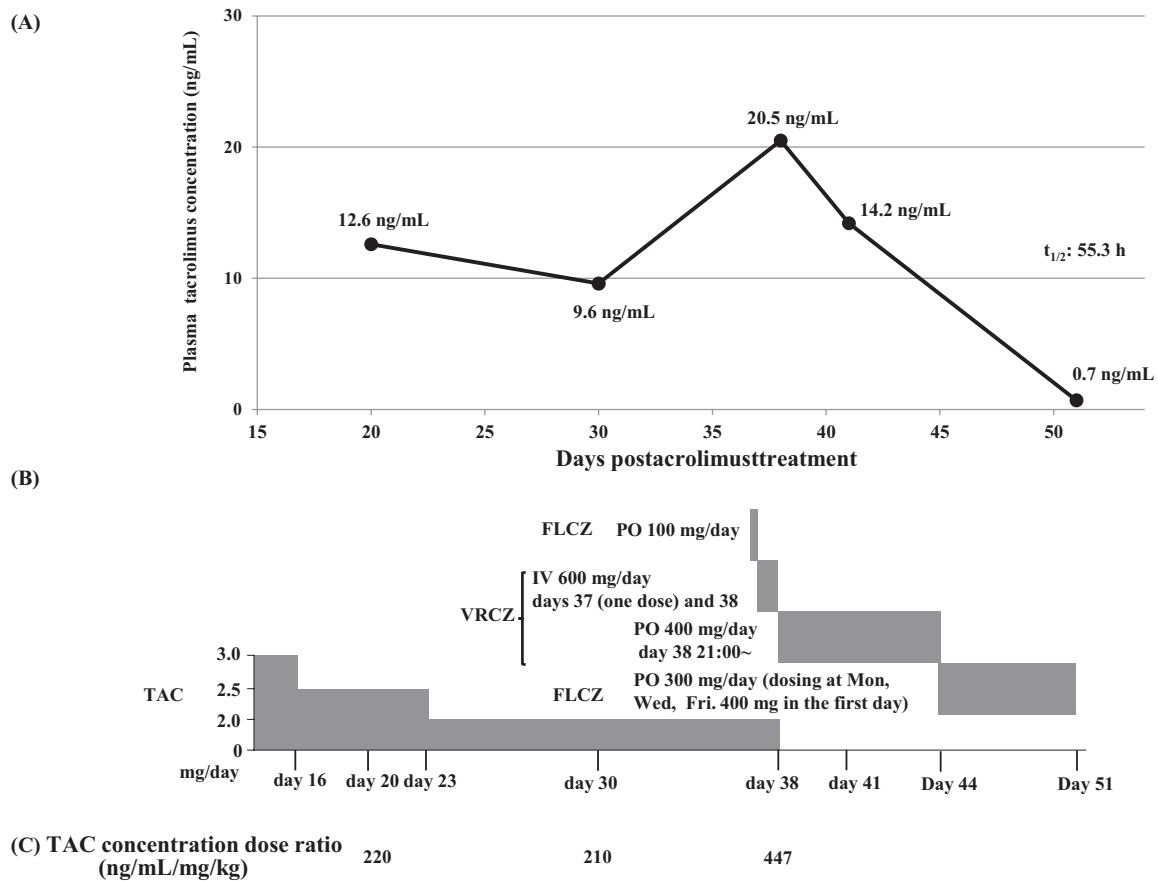


Fig. 1 (A) Plasma concentrations of tacrolimus (closed circles), and calculated half-life from elimination phase. $t_{1/2}$, half-life. (B) Course of treatment with tacrolimus and azole agents. TAC, tacrolimus; FLCZ, fluconazole; VRCZ, voriconazole; PO, per os; IV, intravenous. (C) Concentration dose ratio of tacrolimus.

indicates a possible inflammatory response. Although tacrolimus trough level was slightly above the 20 ng/ml, it is unlikely that high tacrolimus plasma concentration directly induced renal dysfunction. Therefore, implementation of TDM following intravenous administration of voriconazole is contribute to avoid increase plasma tacrolimus concentration, and reduced the risk of tacrolimus toxic effects.

In conclusion, even after a single intravenous dose of voriconazole, which is assumed to have a minimal effect on the gut metabolism of tacrolimus, the plasma concentration of tacrolimus may increase. Optimization of the tacrolimus dose or performance of TDM soon after the first dose of voriconazole is warranted to minimize the risk of tacrolimus toxicity.

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