

# Drug-Drug Interaction Between Voriconazole and Tacrolimus in a Child Indicating the Necessity of Blood Drug Concentration Monitoring

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## ARTICLE INFO

**Received:**  September 24, 2019

**Published:**  October 03, 2019

**Citation:** Yun Yun Yang, Xue bin Wang, Zhengyue Liu, Zhi jun Wang, Zhuo Wang, et al. Drug-Drug Interaction Between Voriconazole and Tacrolimus in a Child Indicating the Necessity of Blood Drug Concentration Monitoring. Biomed J Sci & Tech Res 21(5)-2019. BJSTR. MS.ID.003651.

**Keywords:** Tacrolimus; Voriconazole; Blood Drug Concentration

## SUMMARY

**What is known and Objective:** After kidney transplantation (SOT recipient), patients are required to take the immunosuppressive drug tacrolimus for a long time. We report on a child in a state of low immune function and critical condition, which is followed by severe fungal infection. It is well known that drug-drug interaction between voriconazole (VOR) and tacrolimus (TAC), there is little evidence on the dose adjustment in children about VOR and TAC. This case illustrates the importance of therapeutic drug monitoring and the effects of VOR on TAC concentration in children were investigated.

**Case Description:** A child after renal transplantation received tacrolimus for a long time, and the blood concentration of tacrolimus was increased after the use of voriconazole and the concentration of voriconazole is beyond the normal range in hospital. The clinical pharmacists adjusted the blood concentration of tacrolimus and voriconazole according to their blood concentration, so that the drugs blood concentration was maintained in the effective range and the child recovered well.

**What is New and Conclusion:** When tacrolimus and voriconazole were taken simultaneously in a child, monitoring of blood drug concentrations is essential for both drugs. We would suggest an initial 50% reduction of tacrolimus, and further dose decreases of 25% may be considered. The dose of voriconazole and should also according to the blood concentration.

## What is Known and Objective

Tacrolimus (TAC) is the mainstay immunosuppressant drug used after solid organ and hematopoietic stem cell transplantation with a narrow therapeutic index and large between-patient pharmacokinetic variability [1]. Therefore, the blood drug concentration monitoring of immunosuppressive agents is carried out regularly and is very important for transplant recipients. Voriconazole (VOR) is a triazole antifungal agent that is frequently used to treat a variety of fungal infections [2]. Particularly commonly used in immunocompromised patients who develop fungal infections, there are interactions between immunosuppressive and antifungal agents. The labeling of VOR may increase the serum concentration of TAC, when starting VOR in patients already receiving TAC, reduce TAC dose of the original dose and monitor TAC

blood levels closely, but no data on how children adjust their doses. Concentration-effect and concentration-toxicity relationships are consistently reported in both experimental and clinical contexts, and, in patients, these relationships have been defined in both adults and children. Therapeutic Drug Monitoring (TDM) should be performed in the majority of patients receiving voriconazole [3]. This case report is a valuable report that according to the results of blood drug concentration monitoring, clinical pharmacists guide rational drug use in a special patient.

## Case Description

Our patient is a 10-year-old female with lymphoid tissue hyperplastic disease (PLTD) due to IgA nephropathy received renal transplant for two months and now EB virus infection. Her

weight is 23 kg. In order to control PLTD, treatment with Rituximab injection (merovar) with 300mg intravenous (IV) combined with methylprednisolone sodium succinate IV (methylprednisolone) therapy was initially commenced and tacrolimus reduced to 1mg for 24 hours continuous micro-pump. During the treatment, the gastroscopy and gastroscopy pathology revealed Non-Hodgkin Lymphoma (NHL), the CHOP regimen was administered. On day 34 of chemotherapy intermission, the level of (1,3)- $\beta$ -D-glucan was 1215.1pg/mL and fungal infection was detected in stool. For patients with SOT, antifungal therapy should be performed early in the case of highly suspected invasive aspergillosis [4]. Clinicians treated the patient with 50mg/day IV of caspofungin, 2mg twice daily po of tacrolimus during this time and the blood drug concentrations were maintained between 5.5ng/ml and 7.7ng/mL (optimal trough levels 5-10 ng/mL).

In this period, there were no obvious abnormal change in chest computed tomography and skull computed tomography in this period. Seven days after antifungal therapy, the patient suddenly had an epileptic seizure, head MR scan is shown that left parietal nodules, considering the possibility of brain abscess remain, non-infectious factors causing intracranial lesions to wait to be discharged, central nervous system (CNS) aspergillus infection cannot be ruled out, clinicians began treatment with 100 mg (5mg/kg) twice daily of intravenous VRCZ followed by a 80 mg (4mg/kg) twice daily maintenance dose, and tacrolimus was adjusted by 0.4mg micropump for 24h. Voriconazole is the drug of choice for CNS aspergillosis [5]. Blood drug concentration monitoring of both drugs are recommended by clinical pharmacist, we had performed therapeutic drug monitoring (TDM) of VOR and TAC during follow-up. VOR concentrations were determined using High performance liquid chromatography and TAC concentrations were determined using Chemiluminescence microparticle immunoassay.

On the 4<sup>th</sup> day after treatment with VOR and TAC was adjusted for oral administration by 2mg twice, the serum concentration of VOR was 1.1 mg/L on the first measurement. Studies variously identified target concentrations of  $\geq 1$ mg/L or  $\geq 2$  mg/L as being associated with improved outcomes, whilst one large study found no relationship between exposure and clinical outcome. Both suggest that a trough concentration: MIC target of 2–5mg/L [6]. According to date of relate literature and guidelines, for the children 2 to <12 years and weight <50kg, loading dose: IV: 9 mg/kg/dose every 12 hours for 2 doses on day 1, Maintenance: IV: 8 mg/kg/dose every 12 hours; monitor serum concentrations to maintain trough >2 mcg/mL [7-9]. Depending on that, we suggest that adjust the dose of VOR to 160mg(8mg/kg) twice. On the 7<sup>th</sup> day, we recommend reduce the tacrolimus dose to 1 mg twice because of the high trough tacrolimus level (26.4 ng/mL), VOR is metabolized via oxidative mechanisms and inhibits CYP3A4 activity (as well as CYP2C19 and 2C9), which results in a number of clinically relevant drug–drug interactions that have been extensively reviewed elsewhere [10].

The drug interaction between VOR and tacrolimus has been recognized, with VRCZ increasing serum tacrolimus concentration

via competitive inhibition of CYP3A4[11], On the 10<sup>th</sup> day, the concentration of tacrolimus was 10.6ng/ml, and also halved the dose of tacrolimus and the serum concentration of VRCZ was 5.6 ng/mL, and reduced the dose of VRCZ to 140mg (7mg/kg) IV twice and monitor trough concentrations closely. In pediatric patients <50 kg, therapeutic drug monitoring is critical to ensure efficacy and minimize toxicity; may consider switching to oral therapy once patient is stable and able to tolerate. A trough concentration to minimize drug-related toxicity is <4–6 mg/L, Concentration–toxicity relationships for voriconazole have been estimated in several key studies. Trough concentrations that are associated with greater probability of toxicity vary from study to study, and include  $\geq 4$ ,  $\geq 5$  and  $\geq 6$  mg/L [6]. Active dosage adjustment to keep serum concentrations 5.5 mg/L prevents voriconazole-related toxicity [12]. on the 18<sup>th</sup> day, The serum concentration of VRCZ was 2.1 ng/mL and tacrolimus was 4.2 ng/ml. The patient generally recovered well.

### What Is New and Conclusion

This is the first report on the adjustment of voriconazole in children depend on therapeutic drug monitoring and when TAC and VOR used simultaneously, we would suggest an initial 50% reduction and recommend close monitoring of TAC. Further dose decreases of 25% may be required. In addition, monitoring voriconazole trough concentrations may be beneficial to facilitate dose adjustment in critically ill pediatric patients due to large inter-individual variability in exposure. In this case, clinical pharmacists participate in clinical work through blood drug concentration monitoring results and drug interactions.

### Acknowledgments

Special thanks to the Lihong Gao of the therapeutic drug monitoring room.

### References

1. Kelly A Birdwell, Brian Decker, Julia M Barbarino, Peterson JF, Stein CM, et al. (2015) Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. *Clin Pharmacol Ther* 98(1): 19-24.
2. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, et al. (2002) Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 347: 408-415.
3. H Ruth Ashbee, Rosemary A Barnes, Elizabeth M Johnson, Richardson MD, Gorton R, et al. (2014) Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother* 69: 1162-1176.
4. (2016) Organ transplantation branch of Chinese medical association, organ transplant doctor branch of Chinese medical association. Guidelines for the clinical diagnosis and treatment of invasive fungal disease in Chinese solid organ transplant recipients.
5. Schwartz S, Ruhnke M, Ribaud P, Corey L, Driscoll T, et al. (2005) Improved outcome in central nervous system aspergillosis, using voriconazole treatment. *Blood* 106(8): 2641-2645.
6. H Ruth Ashbee, Rosemary A Barnes, Elizabeth M Johnson, et al. (2014) Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother* 69: 1162-1176.

7. Hope WW, Castagnola E, Groll AH, Roilides E, Akova M, et al. (2012) ESCMID guideline for the diagnosis and management of Candida diseases 2012: prevention and management of invasive infections in neonates and children caused by Candida spp. Clin Microbiol Infect 18(7): 38-52.
8. Friberg LE, Ravva P, Karlsson MO, Liu P (2012) Integrated population pharmacokinetic analysis of voriconazole in children, adolescents, and adults. Antimicrob Agents Chemother 56(6): 3032-3042.
9. Peter G Pappas, Carol A Kauffman, David R Andes, Clancy CJ, Marr KA, et al. (2016) Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clinical Practice Guideline for the Management of Candidiasis-CID-162(4): 1-50.
10. Bruggemann R JM, Alffenaar J WC, Blijlevens N MA, et al. (2009) Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis 48: 1441-1458.
11. Eisuke Mochizuki, Kazuki Furuhashi, Tomoyuki Fujisawa, et al. (2015) A case of treatment with voriconazole for chronic progressive pulmonary aspergillosis in a patient receiving tacrolimus for dermatomyositis-associated interstitial lung disease. Respiratory Medicine Case Reports 16: 163-165.
12. Park WB, Kim NH, Kim KH, Lee SH, Nam WS, et al. (2012) The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. Clin Infect Dis 55: 1080-1087.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2019.21.003651

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