Original Article

Evaluation of the Interaction of Intravenous and Oral Voriconazole with Oral Cyclosporine in Iranian HSCT Patients

Hamidreza Taghvaye Masoumi[1], Molouk Hadjibabaie[1], Mohammad Vaezi[2], Ardeshir Ghavamzadeh[2]

[1]Department of Clinical Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

[2]Hematology-Oncology and Stem Cell Transplantation Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Objective: Voriconazole as a triazole antifungal agent is widely used for prophylaxis or treatment of fungal infections in allogeneic hematopoietic stem cell transplantation (HSCT). It can increase blood concentrations of other medications including cyclosporine A (CsA) which are substrates for cytochrome P450 3A4. The aim of this study was to evaluate comparatively the interaction between oral/intravenous (IV) voriconazole and oral CsA. **Methods:** Twenty-nine recipients of allogeneic HSCT who had been already on a steady dose of CsA and were started on oral or IV voriconazole were evaluated in a prospective cohort study. Blood concentration of CsA was determined before and 5–8 days after voriconazole initiation. Plasma concentration of voriconazole was measured in steady state. The changes in blood concentration of CsA after administration of voriconazole were evaluated. **Findings:** The concentration/dose (C/D) ratio of CsA increased significantly ($P < 0.001$) after voriconazole initiation in both routes of administration (8.40%–174.10% increase in C/D ratio). The C/D ratio alteration of CsA did not differ significantly between oral and IV voriconazole group ($P = 0.405$). There was a significant correlation in all patients between plasma concentration of voriconazole and percentage of CsA C/D ratio increment ($P = 0.046$). **Conclusion:** There was a significant intrapatient variability in the magnitude of CsA blood concentration increment after voriconazole initiation. We also demonstrated that magnitude of drug interaction did not differ in IV and oral voriconazole administration. Furthermore, we found that the magnitude of drug interaction was correlated with plasma concentration of voriconazole.

Keywords: *Cyclosporine A, hematopoietic stem cell transplantation, interaction, Voriconazole*

Received: December 2016.
Accepted: February 2017.

Introduction

Invasive fungal infection is one of the most important complications in patients receiving allogeneic hematopoietic stem cell transplantation (HSCT).[1] Antifungal agents such as voriconazole are widely used for prophylaxis or treatment of fungal infections in this population.[2] Immunosuppressant agents such as cyclosporine A (CsA) are frequently administered in patients undergoing HSCT to prevent graft versus host disease and graft rejection.[3] It is well known that there is a significant drug–drug interaction between voriconazole and CsA.[4] Voriconazole is a triazole antifungal agent with appropriate activity against both *Candida* and *Aspergillus* species. It is metabolized mainly through cytochrome P450 2C19 (CYP2C19) and to a lesser extent by CYP2C9 and CYP3A4. In addition, it is known as a potent inhibitor of CYP3A4; therefore, it can increase blood concentrations of other medications which are substrates for this eliminating pathway including CsA.[5] Because of

Access this article online

Quick Response Code:

Website: www.jrpp.net

DOI: 10.4103/jrpp.JRPP_16_163

Address for correspondence:
Dr. Molouk Hadjibabaie, E-mail: hajibaba@tums.ac.ir

How to cite this article: Masoumi HT, Hadjibabaie M, Vaezi M, Ghavamzadeh A. Evaluation of the interaction of intravenous and oral voriconazole with oral cyclosporine in iranian HSCT patients. J Res Pharm Pract 2017;6:77-82.

the narrow therapeutic index of CsA, small changes in its blood concentration may lead to considerable adverse effects that will limit its use. Therefore, therapeutic drug monitoring (TDM) of CsA is important in patients receiving voriconazole concomitantly.[6]

Data about the effect of voriconazole administration on CsA blood levels in patients following HSCT are limited to a few small studies and case reports. It has been shown that blood concentration of CsA increases significantly with extensive interpatient variability when given concomitantly with voriconazole.[4,7] This high interindividual variability may be due to heterogeneity in the activity of the metabolizing enzymes CYP3A4 and CYP2C19. Therefore, the evaluation of this expected interaction seems reasonable on ethnicity-based fashion.[8] In addition, there are limited data regarding the correlation between voriconazole plasma concentration and the magnitude of interaction with CsA. It was demonstrated in one study that the plasma level of voriconazole does not play an essential role in the extent of interaction with CsA.[7] Furthermore, there is not any direct comparison between the effect of oral and intravenous (IV) voriconazole on blood level of oral CsA. To our knowledge, voriconazole plasma concentration measurement has not been done previously in Iranian adult patients receiving voriconazole.

The aim of this study was to evaluate the extent of interaction between oral versus IV voriconazole with oral CsA.

Methods

This prospective cohort study was conducted from February 2015 to July 2016 at Hematology-Oncology and Stem Cell Research Center of Shariati Hospital affiliated to Tehran University of Medical Sciences. The study protocol was approved by the Ethics Committee for Human Research at Tehran University of Medical Sciences (Ethics code: IR.TUMS.REC.1394.1100).

Recipients of allogeneic HSCT 16 years of age or older who were receiving oral CsA and had been started on oral or IV voriconazole for prophylaxis or treatment of fungal infection were included in this study. Patients with baseline kidney or liver dysfunction or who were receiving other medications causing moderate-to-severe drug interaction with CsA or voriconazole were excluded from the study. In oral treatment group, patients initially received IV voriconazole 6 mg/kg as the loading dose for 2 doses followed by oral voriconazole 200 mg twice daily 1 h before or 1 h after a meal. Of patients who received voriconazole oral tablet, none had gastrointestinal (GI) disease or unstable hemodynamic condition. IV voriconazole was administered as a 6 mg/kg loading dose for two doses followed by 4 mg/kg twice daily which was infused over 1 h.

Blood laboratory parameters including serum creatinine, direct and total bilirubin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase were also monitored daily in all patients.

CsA blood concentrations were measured 1 day before and then 5–8 days after voriconazole initiation. The measurements of the CsA trough levels were performed by the standard fluorescence polarization immunoassay. To investigate the alteration of CsA blood concentration, we calculated the concentration/dose (C/D); (ng/ml)/(mg/kg) ratio of CsA before and after voriconazole initiation. Evaluation of voriconazole effect on CsA blood concentration was done by comparing the C/D ratio of CsA 5–8 days after voriconazole initiation with its C/D ratio before voriconazole administration.

Trough blood samples for voriconazole measurement were collected in heparinized tubes 5–8 days after initiation (on the same day of CsA measurement) immediately before the next dose. Samples were centrifuged (3000 rpm, 4°C, 10 min) immediately after collection. The plasma was transferred to 2 ml polypropylene tubes and stored at −70°C until assay. Voriconazole plasma concentrations were measured by high-performance liquid chromatography technique using the method described by Khoschsorur *et al*.[9] Ketoconazole was used as the internal standard. Voriconazole was supplied by Pfizer (USA), and ketoconazole was supplied by Merck (Germany).

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) software version 22 for windows (SPSS Inc., IBM Co., Chicago, IL, USA). Descriptive statistics were reported for patients using mean (median) for quantitative variables and frequency (percent) for qualitative ones. The Wilcoxon signed-rank was used for comparison of differences in the C/D ratio before and after voriconazole administration. The nonparametric Mann–Whitney U-test was used for comparison of differences in percentage of C/D ratio change between oral and IV groups. The Mann–Whitney U-test was also used to compare trough plasma concentration of voriconazole between oral and IV groups. The Spearman's rank test was used for the evaluation of correlation between trough plasma concentration of voriconazole and CsA C/D ratio. $P < 0.05$ was considered statistically significant.

Results

The interaction between voriconazole and CsA was evaluated in 29 adult patients following allogeneic HSCT.

Patients received voriconazole IV in 16 cases (55.17%) and orally in 13 cases (44.83%) on steady dose of oral CsA. Demographic and clinical characteristics of 29 patients are presented in Table 1.

The blood concentration of CsA increased in all patients after initiation of voriconazole. The median C/D ratio of CsA were 65.95 ([ng/ml]/[mg/kg]) (range: 41.80–71.57) and 91.27 ([ng/ml]/[mg/kg]) (range: 61.43–158.50) 1 day before and 5–8 days after initiation of oral voriconazole, respectively. The median C/D ratio of CsA was 49.58 ([ng/ml]/[mg/kg]) (range: 41.20–86.75) and 89.86 ([ng/ml]/[mg/kg]) (range: 57.05–169.50) 1 day before and 5–8 days after initiation of IV voriconazole, respectively.

The C/D ratio of CsA increased significantly ($P = 0.0001$) after voriconazole initiation in both routes of administration [Figures 1-3]. The C/D ratio alteration of CsA did not differ significantly between oral and IV voriconazole group ($P = 0.405$). The median increases in C/D ratio were 54.06% (range: 20.80%–140.30%) and 55.47% (range: 8.40%–174.10%) in oral and IV voriconazole group, respectively.

The median trough plasma concentrations of IV voriconazole and oral voriconazole were 2.58 mcg/ml (range: 0.64–6.55 mcg/ml) and 2.15 mcg/ml (range: 0.5–5.78 mcg/ml), respectively. Voriconazole levels in four patients (13.79%) were <1 mcg/ml (subtherapeutic) and in four patients (13.79%) were >5 mcg/ml (supratherapeutic). Voriconazole plasma concentration did not differ significantly between oral and IV voriconazole groups ($P = 0.511$).

There was a significant correlation in all patients between plasma concentration of voriconazole and percentage of CsA C/D ratio increment ($P = 0.046$, $R = 0.373$) [Figure 4]; however, this correlation was not statistically significant when it was assessed separately in patients who received voriconazole orally ($P = 0.59$, $R = 0.165$) and IV ($P = 0.058$, $R = 0.482$).

Discussion

In the present study, we found that both IV and oral formulations of voriconazole significantly increase blood concentrations of CsA in Iranian patients receiving allogeneic HSCT. No dose-limiting or serious adverse effects associated with increased concentration of CsA were observed.

CsA is a substrate for CYP3A4 and voriconazole is a strong CYP3A4 inhibitor; therefore, drug interaction with CsA is one of the most significant common drug interactions of voriconazole. The impact of voriconazole on blood concentration of CsA has been assessed in a few previous studies.[4,7,10] Mori *et al*. demonstrated that administration of voriconazole significantly increased the blood concentration of calcineurin inhibitors (CsA and tacrolimus) after allogeneic HSCT. They concluded that uniform decrease in the dosage of calcineurin inhibitors

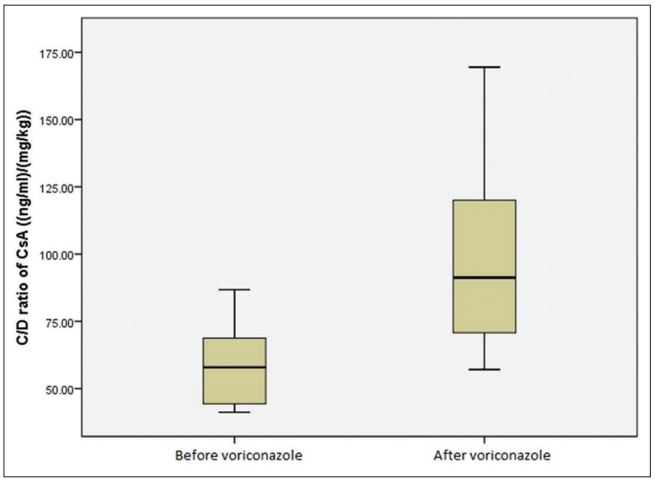

Figure 1: The concentration/dose ratio of cyclosporine A before and after initiation of voriconazole. The concentration/dose ratio increased significantly ($P = 0.0001$)

Table 1: Demographic and clinical characteristics of patients

Variables	Total (n=29)	Patients received oral voriconazole (n=13)	Patients received IV voriconazole (n=16)
Age (year)	32 (16-62)	32 (18-54)	33 (16-62)
Sex (male)	17	7	10
Body weight (kg)	58 (45-77)	55 (48-70)	59 (45-77)
Underlying disease			
AML	17	9	10
ALL	7	3	3
Lymphoma	1	0	1
Aplastic anemia	1	0	1
MDS	3	1	1

Data presented as median (range), or number of patients. ALL=Acute lymphoblastic leukemia, AML=Acute myeloid leukemia, IV=Intravenous, MDS=Myelodysplastic syndrome

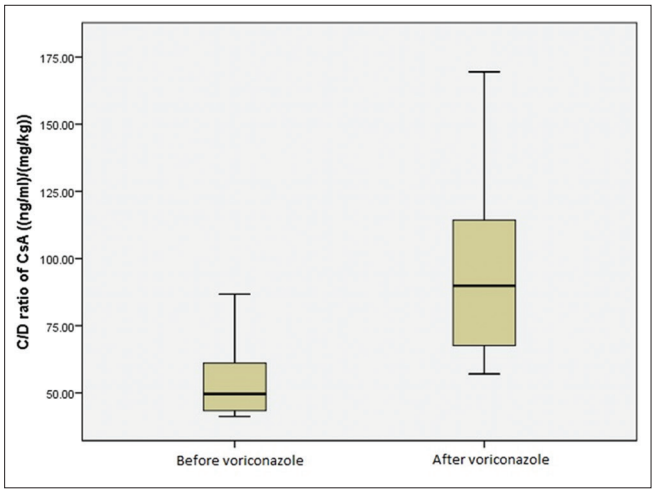

Figure 2: The concentration/dose ratio of cyclosporine A before and after initiation of intravenous voriconazole. The concentration/dose ratio increased significantly ($P = 0.0002$)

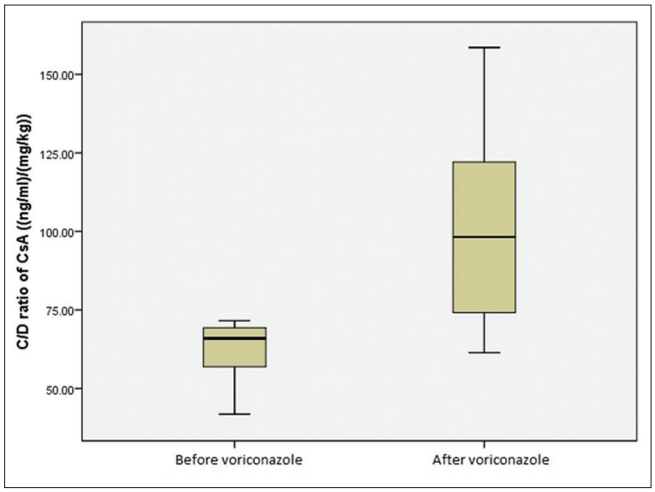

Figure 3: The concentration/dose ratio of cyclosporine A before and after initiation of oral voriconazole. The concentration/dose ratio increased significantly ($P = 0.0001$)

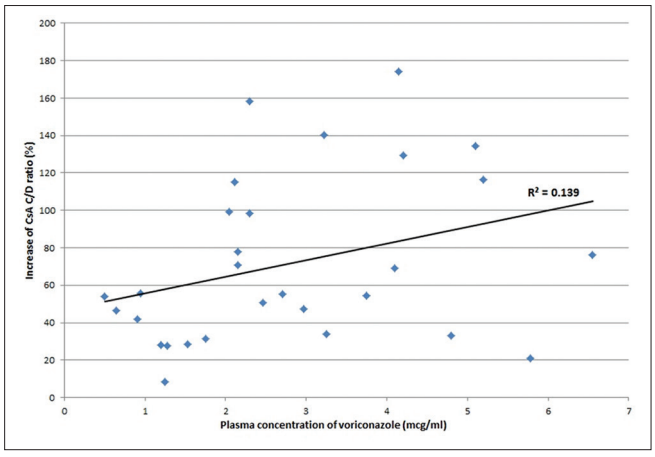

Figure 4: Correlation between plasma concentration of voriconazole and cyclosporine A concentration/dose ratio increment after voriconazole initiation. There was a significant correlation ($P = 0.046$, $R = 0.373$)

for all patients should be avoided before voriconazole administration due to the wide interindividual variability of interaction.[4]

Kikuchi *et al*. carried out a retrospective study on twenty patients who had received oral doses of CsA after allogeneic HSCT and reported the results that are consistent with those of Mori *et al.* study. They demonstrated that oral voriconazole increased the blood levels of CsA significantly. Similar to Kikuchi *et al*. study, there was a markedly wide interpatient variability of blood CsA levels after voriconazole initiation.[7]

In a randomized, double-blind, placebo-controlled, crossover study on 14 patients after renal transplantation who received CsA concomitant with oral voriconazole or placebo, Romero *et al*. found that voriconazole increased exposure to CsA 1.7-fold. They recommended that a dose reduction of 50% is indicated in all patients on initiation of voriconazole therapy. Interpatient variability of drug interaction was not evaluated in this study.[10]

In this study, we observed a wide interindividual variability in the extent of drug interaction between voriconazole and CsA (8.40%–174.10% increase in C/D ratio). Although the manufacturer recommends a preemptive decrease in the dosage of CsA immediately before voriconazole administration, it is reasonable to suggest avoiding uniform reduction in all patients according to the current and previous studies results.[4,7] We recommend frequent CsA blood concentration monitoring, once voriconazole antifungal therapy is initiated.

CYP2C19 polymorphism as a major metabolizing pathway of voriconazole may influence the extent of drug interaction. Since voriconazole blood concentrations in slow metabolizers of CYP2C19 may be higher than fast metabolizers, we expect that these patients experience more significant drug interaction between voriconazole and CsA. Although Iwamoto *et al*. showed that CYP2C19 polymorphism contributes to the extent of drug interaction between tacrolimus and voriconazole, Kikuchi *et al*. found that the magnitude of CsA level increment did not correlate with plasma concentrations of oral voriconazole.[7,11] We identified a significant correlation between trough plasma concentration of voriconazole and the increase in the CsA C/D ratio in Iranian population, and our results suggest that the magnitude of drug interaction between CsA and voriconazole is affected by the plasma concentration of voriconazole. However, after subanalysis it was found that this correlation did not exist in patients who received voriconazole orally as has been demonstrated previously in Japanese population.[7,11] Genetic polymorphism

of CYP3A4, CYP3A5, and CYP3A7 seems to be a relevant reason for this absence of correlation.[12,13] In patients received voriconazole orally, both hepatic and GI CYP heterogeneity may be contributed to this wide variability.[14] It should be noted that the correlation between voriconazole plasma concentration and magnitude of interaction with CsA also was not statistically significant in patients who received voriconazole IV, but $P = 0.058$ was close to a significant difference. Considering the significant correlation in all patients (patients who received voriconazole orally and IV), the lack of such correlation in IV group was possibly attributed to small sample size. We found that although the magnitude of drug interaction between IV voriconazole and CsA was greater than oral voriconazole and CsA, the differences were not significant. Mori *et al*. also found that C/D ratio changes of calcineurin inhibitors were not significantly different between IV and oral voriconazole groups.[4] Based on the high bioavailability of oral voriconazole (over 90%) and absence of GI disorders, these results could be reasonable.[5]

The results of the current study indicate that trough concentration of CsA increases significantly within 5–8 days after voriconazole initiation. It has not been clarified in previous studies that how much time after coadministration, the interaction reaches the steady state. However, it has been demonstrated that the magnitude of interaction between CsA and ketoconazole (another azole) becomes fully apparent days to weeks after coadministration.[15] Inhibition of CYP3A4 begins immediately after voriconazole administration; therefore, it seems reasonable to suggest that TDM of CsA should be performed as soon as possible after steady state is reached (within 5 days after initiation of voriconazole). TDM of CsA should be done at least two times/week for the first 2 weeks and then every 2–3 weeks after the initiation of concomitant therapy.[15,16] Furthermore, on discontinuation of voriconazole therapy, TDM of CsA should be considered for immunosuppressant dose adjustment to maintain the concentration of calcineurin inhibitor (CNI) within therapeutic target range.[17,18]

To our knowledge, this is the first study evaluating the trough plasma concentration of voriconazole in Iranian adult patients following allogeneic HSCT. This was also the first study assessing the relationship between the routes of voriconazole administration and the magnitude of interaction with CsA.

This study has some limitations. In addition to small sample size, CYP2C19 genetic polymorphism as a major metabolizing pathway of voriconazole was not assessed. CYP2C19 genetic polymorphism may contribute to interpatient variability of voriconazole plasma concentration and magnitude of interaction with CsA.

There was a significant interpatient variability in the magnitude of CsA blood concentration increment after voriconazole initiation; therefore, we recommend CsA level monitoring as soon as possible after start of coadministration. Due to narrow therapeutic index of CsA, waiting for at least 5 days for CsA TDM before any reduction in CsA dose at the initiation of voriconazole may put patients at risk for CsA major toxicities such as nephrotoxicity.

Regarding rapid initiation of metabolism inhibition, if the facilities of rapid and consecutive measurement of CsA blood level are not provided, it is reasonable to reduce CsA dose preemptively at least based on minimum extend of interaction that has been reported in various studies. We also demonstrated that the magnitude of drug interaction did not differ in IV and oral voriconazole administration. Furthermore, we found that the magnitude of drug interaction was correlated with plasma concentration of voriconazole. This interaction should be investigated in larger sample sizes in future studies.

Authors' Contribution

Hamidreza Taghvaye Masoumi contributed in data acquisition, literature search, data analysis, and manuscript preparation. Molouk Hadjibabaie contributed in concept, manuscript editing, and study design. Mohammad Vaezi contributed in concept, and study design. Ardeshir Ghavamzadeh contributed in concept, and study design.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Girmenia C, Ferretti A, Barberi W. Epidemiology and risk factors for invasive fungal diseases in hematopoietic stem cell transplantation. Curr Opin Hematol 2014;21:459-65.
2. Karthaus M. Prophylaxis and treatment of invasive aspergillosis with voriconazole, posaconazole and caspofungin: Review of the literature. Eur J Med Res 2011;16:145-52.
3. Solomon SR, Nakamura R, Read EJ, Leitman SF, Carter C, Childs R, *et al.* Cyclosporine is required to prevent severe acute GVHD following T-cell-depleted peripheral blood stem cell transplantation. Bone Marrow Transplant 2003;31:783-8.
4. Mori T, Aisa Y, Kato J, Nakamura Y, Ikeda Y, Okamoto S. Drug interaction between voriconazole and calcineurin inhibitors in allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant 2009;44:371-4.
5. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/

pharmacodynamic profile of voriconazole. Clin Pharmacokinet 2006;45:649-63.

6. Dolton MJ, Mikus G, Weiss J, Ray JE, McLachlan AJ. Understanding variability with voriconazole using a population pharmacokinetic approach: Implications for optimal dosing. J Antimicrob Chemother 2014;69:1633-41.
7. Kikuchi T, Mori T, Yamane A, Kato J, Kohashi S, Okamoto S. Variable magnitude of drug interaction between oral voriconazole and cyclosporine A in recipients of allogeneic hematopoietic stem cell transplantation. Clin Transplant 2012;26:E544-8.
8. Wang YY, Zhang M, Lu FM, Jiao Z, Qiu XY. CYP3A4 genetic polymorphisms predict cyclosporine-related clinical events in Chinese renal transplant recipients. Chin Med J (Engl) 2012;125:4233-8.
9. Khoschsorur G, Fruehwirth F, Zelzer S. Isocratic high-performance liquid chromatographic method with ultraviolet detection for simultaneous determination of levels of voriconazole and itraconazole and its hydroxy metabolite in human serum. Antimicrob Agents Chemother 2005;49:3569-71.
10. Romero AJ, Le Pogamp P, Nilsson LG, Wood N. Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. Clin Pharmacol Ther 2002;71:226-34.
11. Iwamoto T, Monma F, Fujieda A, Nakatani K, Gayle AA, Nobori T, *et al.* Effect of genetic polymorphism of CYP3A5 and CYP2C19 and concomitant use of voriconazole on blood tacrolimus concentration in patients receiving hematopoietic stem cell transplantation. Ther Drug Monit 2015;37:581-8.
12. Crettol S, Venetz JP, Fontana M, Aubert JD, Pascual M, Eap CB. CYP3A7, CYP3A5, CYP3A4, and ABCB1 genetic polymorphisms, cyclosporine concentration, and dose requirement in transplant recipients. Ther Drug Monit 2008;30:689-99.
13. Zochowska D, Wyzgal J, Paczek L. Impact of CYP3A4*1B and CYP3A5*3 polymorphisms on the pharmacokinetics of cyclosporine and sirolimus in renal transplant recipients. Ann Transplant 2012;17:36-44.
14. Lown KS, Kolars JC, Thummel KE, Barnett JL, Kunze KL, Wrighton SA, *et al.* Interpatient heterogeneity in expression of CYP3A4 and CYP3A5 in small bowel. Lack of prediction by the erythromycin breath test. Drug Metab Dispos 1994;22:947-55.
15. Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. Pharmacotherapy 2006;26:1730-44.
16. Katzenmaier S, Markert C, Riedel KD, Burhenne J, Haefeli WE, Mikus G. Determining the time course of CYP3A inhibition by potent reversible and irreversible CYP3A inhibitors using A limited sampling strategy. Clin Pharmacol Ther 2011;90:666-73.
17. Osowski CL, Dix SP, Lin LS, Mullins RE, Geller RB, Wingard JR. Evaluation of the drug interaction between intravenous high-dose fluconazole and cyclosporine or tacrolimus in bone marrow transplant patients. Transplantation 1996;61:1268-72.
18. Trifilio SM, Scheetz MH, Pi J, Mehta J. Tacrolimus use in adult allogeneic stem cell transplant recipients receiving voriconazole: Preemptive dose modification and therapeutic drug monitoring. Bone Marrow Transplant 2010;45:1352-6.