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Research Article

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Effect of Co-administration of Ketoconazole on Attainment of Desired Blood Concentration of Tacrolimus in Renal Transplant Recipients

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Abstract

Achieving and maintaining optimal tacrolimus trough levels for immunosuppression is challenging in kidney transplant patients due to its narrow therapeutic index. Ketoconazole is known for inhibiting the drug efflux activity of P-glycoprotein and CYP3A enzymes, which are involved in tacrolimus pharmacokinetics. Therefore, there is a need to investigate tacrolimus–ketoconazole coadministration. The study aims to assess the effect and safety of tacrolimus-ketoconazole coadministration in renal transplant recipients. Ethical approval was obtained from the Institutional Human Ethics Committee (IHEC/2023/038) to conduct an ambispective observational study on 14 renal transplant recipients. Tacrolimus total daily dose (TDD) and trough levels were measured before and after initiating oral ketoconazole. The concentration/dose (C_0/D) ratio was calculated, followed by safety assessments, including blood counts and renal function tests. Statistical analyses employed paired t-tests, and the significance level was <0.05. Coadministration resulted in a significant 102.45% increase in tacrolimus trough levels ($p<0.001$) and a 2.19% reduction ($p=0.33$) in TDD. The C_0/D ratio showed a mean increase of 127.74%. Blood counts remained within normal ranges, but a significant decrease in sodium ($p=0.01$) and an increase in potassium ($p=0.03$) were observed within the normal range. Tacrolimus-ketoconazole co-administration in renal transplant recipients demonstrated a substantial elevation in tacrolimus trough levels, suggesting a potential strategy for achieving therapeutic concentrations without escalating tacrolimus doses. Despite significant changes in sodium and potassium, they remained within acceptable ranges, supporting the safety of this coadministration strategy.

Keywords: Tacrolimus; Ketoconazole; Kidney transplant; Immunosuppressant; Pharmacokinetics.

1. Introduction

Kidney transplantation is the preferred treatment for End Stage Renal Disease (ESRD), offering improved quality of life and survival rates compared to long-term dialysis [1]. In order to prevent organ rejection in post-kidney transplant, patients conventionally receive a

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triple combination immunosuppression regimen involving a calcineurin inhibitor (CNI), Mycophenolate mofetil, and corticosteroids [2]. Among CNI, tacrolimus has shown improved tolerance, fewer side effects, enhanced graft survival, and lower rejection rates than other immunosuppressants [3].

Tacrolimus is a narrow therapeutic index drug extensively metabolized in the liver and small intestine by CYP3A isoenzymes. The oral bioavailability of tacrolimus is generally poor (10-20%). However, it can vary considerably among patients, ranging from 5 to 90 percent, due to the variations in expression of intestinal and hepatic CYP3A enzyme systems involved in metabolism. Additionally, an active energy-dependent transport mechanism involving a transmembrane protein called P-glycoprotein causes efflux, altering the drug absorption and further contributing to bioavailability variation [4, 5]. Due to this interpatient pharmacokinetic variability, achieving and maintaining desired drug concentration poses challenges, and adjustments are made to the dosage regimen based on whole blood levels to ensure maintenance within the therapeutic window [6].

Ketoconazole, an azole antifungal, is crucial in modulating tacrolimus pharmacokinetics. It is an inhibitor of the drug efflux activity of ABCB1 and is also a potent, selective inhibitor of CYP3A4 enzymes. Through this local inhibition, ketoconazole can alter the hepatic extraction ratio of tacrolimus and elevate the blood concentration and bioavailability [7, 8]. This pharmacokinetic drug interaction between tacrolimus and ketoconazole can eliminate the need to increase tacrolimus dose beyond the safe level. It can benefit the patient even though oral ketoconazole is associated with a mild increase in serum creatinine and decreased white blood cells [9, 10].

The target whole blood trough level suggested for maintenance of immunosuppression within the first three months post-kidney transplant is around 10-15 ng/ml [11]. The initial tacrolimus dose is calculated based on body weight, and the starting dose is 0.1mg/Kg twice a day. The subsequent dosage adjustment is done based on its highly variable bioavailability from patient to patient. The whole blood trough concentration (C_0) is the preferred marker of bioavailability even though the area under the concentration-time curve (AUC) is much more accurate as AUC requires 8-12 blood specimens, which is not financially and practically feasible [6, 12]. However, there are not enough studies assessing the impact of ketoconazole-tacrolimus coadministration. In the present study, ketoconazole's augmentation of tacrolimus trough levels was assessed in renal transplant patients, and its safety was assessed.

2. Materials and Methods

2.1. Study Design

An ambispective observational study was conducted in the Nephrology department of a tertiary care hospital in Coimbatore. The Institutional Human Ethics Committee granted approval (approval number –IHEC/2023/038) for the submitted study protocol. The study focused on individuals who had undergone kidney transplantation and were on a specific immunosuppressive regimen. Individuals were included based on the eligibility criteria - those who had undergone kidney transplantation within the timeframe of 5 years from 2018 to 2023, who were at least 18 years of age, whose maintenance therapy included triple combination immunosuppression regimen (tacrolimus, mycophenolate mofetil, and corticosteroids) with eventual coadministration of ketoconazole for attainment of desired tacrolimus trough levels. Individuals were excluded if they were on immunosuppressive regimens that did not include tacrolimus or were administered other azole antifungals that could interact with tacrolimus.

2.2. Sample Size

Within the stipulated timeframe (2018-2023), the population size was 52. The sample size was calculated to be 49 using an online sample size calculation tool called RaoSoft, where the confidence interval was fixed at 95%, with a response distribution of 50% and a 5% margin of error. However, during screening within the time period, 14 patients were eligible and included in the study.

2.3. Tacrolimus Total Daily Dose (TDD) and Trough Levels

Since tacrolimus is a narrow therapeutic index drug, the initial oral dose was around 1 mg, twice a day, and the whole blood tacrolimus levels were measured using

ECLIA (electrochemiluminescence immunoassay) every 1-3 days after tacrolimus initiation for further dosage adjustment. Oral ketoconazole was administered at a once-daily dose of 100mg for an average of 14 days. The TDD and trough levels were measured right before and 2-3 days after ketoconazole administration to assess the variation in tacrolimus levels.

2.4. Determination of concentration/dose ratio

The concentration/dose [C_0/D: (ng/mL)/(mg/day] ratio of tacrolimus was calculated to help standardize the comparison and help in making a more meaningful assessment than when concentration is directly compared, especially if different doses are used. This ratio is calculated by dividing the mean tacrolimus pre-dose concentration, i.e., trough levels (C_0), by the corresponding mean TDD. The increased rate of the C_0/D ratio following the commencement of ketoconazole co-administration was assessed by comparing the ratio to its value just before the initiation of ketoconazole.

2.5. Measurement of Blood Counts and Renal Function Tests

Laboratory parameters, including blood counts (RBC, WBC, Platelet, and Hemoglobin) and renal function tests (Urea, BUN, Creatinine, Sodium, Potassium, Bicarbonate, Chloride, and Ionised calcium) were measured before and after ketoconazole coadministration to assess the effects of ketoconazole on both blood counts and renal function tests.

2.6. Statistical Analysis

Statistical analysis of the collected data was done with the help of IBM SPSS Statistics Version 29.0.1.0 (171) software. The trough levels, C_0/D ratio, and laboratory parameters were expressed as Mean ± Standard deviation. Since comparison was made within the same group, paired t-test was used to compare the differences in tacrolimus trough levels, C_0/D ratio, Renal profile (Urea, BUN, Creatinine, Sodium, Potassium, Bicarbonate, Chloride, and Ionised calcium), and Blood counts (RBC, WBC, Platelet and Haemoglobin), before and after initiation with ketoconazole. The level of significance was fixed to be <0.05.

3. Results and Discussion

A total of 14 adult patients were taken into the study; 71.4% (n=10) were male and 28.6% (n=4) were female. The majority of this population was found to have Hypertension (92.8%) as the most common comorbid condition along with ESRD, followed by Type 2 Diabetes mellitus (42.8%) and Hypothyroidism (14.2%). Among this population, 78.6% (n=11) were live donor kidney transplant recipients, and 21.4% (n=3) were cadaveric-donor recipients.

Ketoconazole was administered for an average of 14 days. The TDD and trough levels of tacrolimus were measured before and 2-3 days after ketoconazole co-administration (**Table1** and **Figure 1**). Though ketoconazole can start showing inhibitory effects on liver cytochromes within a few hours after administration, maximum inhibition is observed only after about 3 days of continuous dosing. Hence, to assess the efficacy of the coadministration, the trough levels were measured within 2-3 days post-co-administration. The mean TDD was decreased by 2.19% after initiation with ketoconazole from 6.82 ± 1.28 [mg/day] to 6.67 ± 1.24 [mg/day], which is not significant (p=0.33). In contrast, the trough levels showed a significant increase (p<0.001) of 102.45% from 3.67 ± 1.21 [ng/ml] to 7.43 ± 2.64 [ng/ml].

Table 1. Tacrolimus TDD, trough levels, and C_0/D ratio before and after ketoconazole coadministration.

Before ketoconazole[a]			After ketoconazole[a]			Decrease % of TDD	Increase %	
TDD (mg/day) [D]	Trough levels (ng/ml) [C_0]	C_0/D ratio	TDD (mg/day) [D]	Trough levels (ng/ml) [C_0]	C_0/D ratio		Trough levels (ng/ml)	C_0/D ratio
6.82 ± 1.28	3.67 ± 1.21	0.55 ± 0.21	6.67 ± 1.24	7.43 ± 2.64	1.16 ± 0.49	2.19%[b]	102.45%[c]	127.74%[c]

[a] Data presented as Mean ± Standard deviation, [b] Not Significant, [c] Significant, TDD = Total Daily Dose

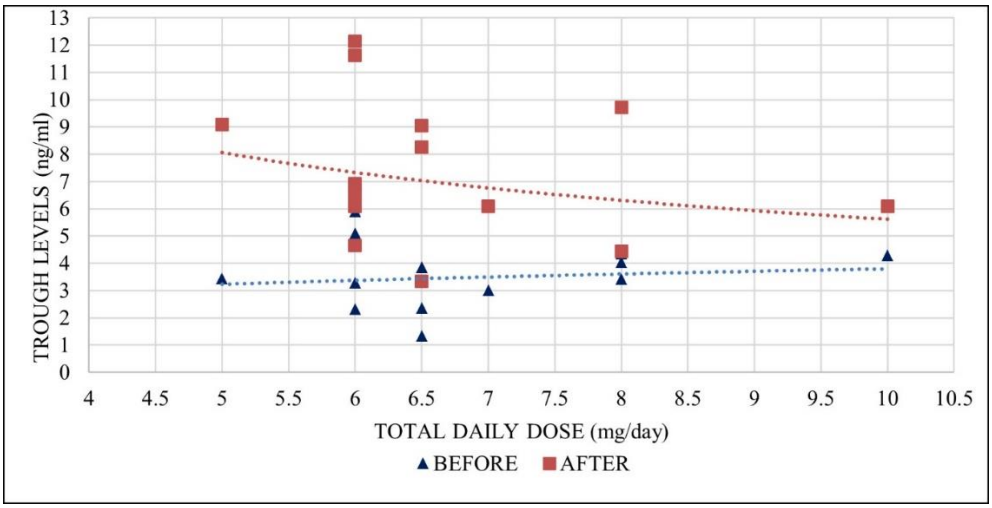

Figure 1. Tacrolimus TDD and trough levels before and after ketoconazole coadministration

The trough levels are expected to remain elevated even after a week due to the continued use of ketoconazole for 14 days. However, the concentration will stabilize at this higher level, with no further increases, unless there is a change in either tacrolimus or ketoconazole dosing. Without dose adjustments, the drug's levels will plateau because ketoconazole's effect on tacrolimus metabolism remains constant, and the body has reached a new steady state. Further monitoring is essential to ensure safety and adjust doses if necessary.

C_0/D ratio was calculated before and after ketoconazole co-administration, and a significant increase ($p<0.001$) from 0.55 ± 0.21 to 1.16 ± 0.49 was observed (**Table 1** and **Figure 2**). The mean increase in the C_0/D ratio of tacrolimus was 127.74%, with a range of 7.84 - 351.16%.

No significant change was seen with blood counts and most renal profile tests when the influence of ketoconazole coadministration on safety was assessed (**Table 2**). A significant increase in potassium (p=0.03) and a decrease in sodium (p= 0.01) was observed. Though these changes were significant, values were within the normal range.

Table 2. Effect of ketoconazole on blood counts and renal profile.

Parameter	Before[a]	After[a]	P- Value
RBC	2.94 ± 3.07	3.07 ± 0.41	0.09
WBC	9.49 ± 2.93 × 10^9/L	9.93 ± 2.91 × 10^9/L	0.58
Haemoglobin	8.58 ± 1.51 g/dL	8.98 ± 1.31g/dL	0.06
Platelet	191.14 ± 56.35 × 10^9/L	217.07 ± 50.85 × 10^9/L	0.08
Urea	57.92 ± 44.51 mmol/L	56.07 ± 38.46 mmol/L	0.51
BUN	27.01 ± 20.81 mg/dL	26.20 ± 17.98 mg/dL	0.54
Creatinine	1.24 ± 0.78 mg/dL	1.65 ± 1.67 mg/dL	0.3
Sodium	136.50 ± 2.53 mmol/L	135.00 ± 2.71 mmol/L	0.01*
Potassium	3.96 ± 0.48 mmol/L	4.31 ± 0.38 mmol/L	0.03*
Bicarbonate	22.37 ± 3.34 mmol/L	21.79 ± 2.79 mmol/L	0.32
Chloride	103.78 ± 5.84 mmol/L	104.14 ± 4.68 mmol/L	0.79
Ionized calcium	1.07 ± 0.074 mmol/L	1.08 ± 0.08 mmol/L	0.58

[a] Data presented as Mean ± Standard deviation, * Significant, RBC = Red blood cells, WBC = White blood cells, BUN = Blood urea nitrogen

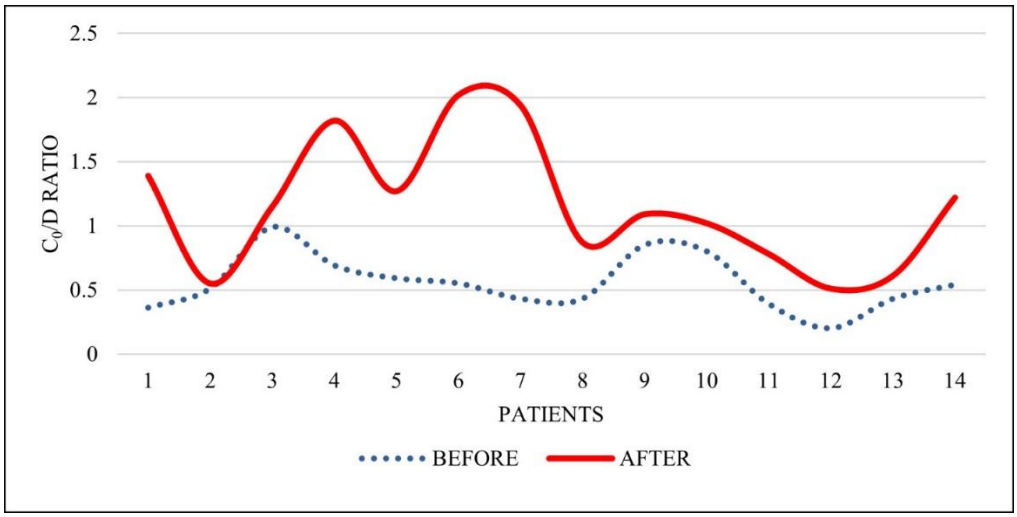

Figure 2. C_0/D Ratio before and after ketoconazole coadministration

The coadministration of ketoconazole with tacrolimus resulted in a substantial increase of 102.45% in tacrolimus trough levels in post-renal transplant patients, showing the beneficial effect of ketoconazole in attainment of desired trough levels without the need for elevating the tacrolimus dose beyond the safe level. Several studies highlight the interaction between tacrolimus and other azoles in transplant recipients. Osowski CL et al. investigated bone marrow transplant patients and found a 16% increase in tacrolimus concentration with high-dose fluconazole, though the change was not statistically significant [13]. In another study by Leather H et al., Haematopoietic stem cell transplant (HSCT) recipients saw an 83% rise in tacrolimus levels after coadministration with intravenous itraconazole [14]. The impact of ketoconazole coadministration with other CNI, such as cyclosporine, has also been extensively studied; however, very few trials and research have been reported on tacrolimus and ketoconazole, making our study a necessity.

The results published by Soltero et al. and El-Dahshen et al. [15, 16] also showed attainment and maintenance of desired tacrolimus trough levels with ketoconazole coadministration similar to our study. Notably, both their studies showed dose reduction, whereas, in our study, dose adjustment was not required after ketoconazole coadministration to maintain tacrolimus's desired range.

Apart from directly comparing the trough levels of tacrolimus before and after initiating ketoconazole, we also used the C_0/D ratio for a quantitative evaluation, which reflects both the concentration and dose of tacrolimus. In a study by Mori T et al., comparisons using C_0/D ratios were made and reported with itraconazole and tacrolimus, showing maintenance of the desired tacrolimus range after coadministration with itraconazole. [17] In two other studies by Zhao YC et al. and Mori et al., elevation in C_0/D ratios was observed on the co-administration of tacrolimus with voriconazole [18, 19]. However, similar comparisons have not been done with ketoconazole. A significant increase in the C_0/D ratio was found, indicating that concomitant usage of ketoconazole with tacrolimus was beneficial in potentiating tacrolimus trough levels. Though the mean increase of the C_0/D ratio was found to be 127.74%, it is highly variable, ranging from 7.84% to 351.16%. Hence, dose adjustment should be done individually, and further evaluation may be required.

On assessing safety, no significant change was observed in the blood counts within the normal range. On the other hand, a significant change was observed in sodium (decrease) and potassium (increase), which can be associated with the elevated trough levels due to the inhibition of Na-K ATPase at the collecting duct by tacrolimus, resulting in the reduction of sodium uptake and impairment of potassium secretion [20]. Though both sodium and potassium levels were within the

normal range, as these changes were significant, further evaluation in a larger population for a longer duration is needed.

The key limitation of our study lies in the discrepancy between the calculated and actual sample sizes. Despite having a higher target, we obtained fewer participants due to our focus on a specific subgroup that matched our eligibility criteria and our study's objectives, which could potentially limit our findings' generalizability. However, the consistency of the observed outcomes across our limited samples suggests that our findings are still robust within this specific population. Nonetheless, future studies with larger and more diverse populations will be necessary to validate these results further.

Future research should focus on larger, multi-center studies to validate these findings and assess the long-term safety of tacrolimus-ketoconazole coadministration. Comparative studies with other azoles and calcineurin inhibitors would provide broader insights into improving immunosuppressive regimens. The degree of inhibition of liver cytochromes by azoles causing elevation in tacrolimus concentration varies, as shown by an invitro study by Zhang S et al. [21] ketoconazole was found to have the strongest inhibitory effect on tacrolimus metabolism, followed by itraconazole, voriconazole and finally fluconazole. Further studies substantiating these findings could be beneficial. Additionally, exploring alternative methods to enhance tacrolimus bioavailability could provide safer or more effective options for improving immunosuppression management in kidney transplant recipients.

Conclusion

Coadministration of ketoconazole with tacrolimus effectively increased tacrolimus trough levels without requiring a dose elevation. The study demonstrates this combination's safety and potential benefits in maintaining therapeutic concentrations. Periodical monitoring is essential for individualized dose adjustments, ensuring clinical relevance and safety in post-renal transplant patients.

Conflicts of Interest Statement

The authors declare that they have no conflicts of interest.

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There was no use of artificial intelligence in the making of this article.

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References

1. Kasiske BL et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. Kidney international. 2010;77(4):299-311. https://doi.org/10.1038/ki.2009.377
2. Neuwirt H, Rudnicki M, Schratzberger P, Pirklbauer M, Kronbichler A, Mayer G. Immunosuppression after renal transplantation. memo-Magazine of European Medical Oncology. 2019;12:216-221. https://doi.org/10.1007/s12254-019-0507-4
3. Bentata Y. Tacrolimus: 20 years of use in adult kidney transplantation. What we should know about its nephrotoxicity. Artificial organs. 2020;44(2):140-152. https://doi.org/10.1111/aor.13551
4. Christians U, Strom T, Zhang YL, Steudel W, Schmitz V, Trump S, Haschke M. Active drug transport of immunosuppressants: new insights for pharmacokinetics and pharmacodynamics. Therapeutic drug monitoring. 2006;28(1):039-044. https://doi.org/10.1097/01.ftd.0000183385.27394.e7
5. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. Clinical pharmacokinetics. 2004;43:623-653. https://doi.org/10.2165/00003088-200443100-00001
6. Andrews LM, Riva N, de Winter BC, Hesselink DA, de Wildt SN, Cransberg K, van Gelder T. Dosing algorithms for initiation of immunosuppressive drugs in solid organ transplant recipients. Expert opinion on drug metabolism & toxicology. 2015;11(6):921-936. https://doi.org/10.1517/17425255.2015.1033397
7. Tuteja S, Alloway RR, Johnson JA, Gaber AO. The effect of gut metabolism on tacrolimus bioavailability in renal transplant recipients1, 2. Transplantation. 2001;71(9):1303-1307. https://doi.org/10.1097/00007890-200105150-00021

8. Floren LC et al. Tacrolimus oral bioavailability doubles with coadministration of ketoconazole. Clinical Pharmacology & Therapeutics. 1997;62(1):41-49. https://doi.org/10.1016/S0009-9236(97)90150-8
9. Fernandez PC, Wallace DW, Ryan K, Lin Q, Hollister AS. Effects of oral ketoconazole on renal function in healthy volunteers. Clinical Pharmacology & Therapeutics. 2005;77(2):81.https://doi.org/10.1016/j.clpt.2004.12.202
10. Bonhomme-Faivre L, Forestier F, Auchere D, Soursac M, Orbach-Arbouys S, Farinotti R. Chronic administration of verapamil, ketoconazole and carbamazepine: impact on immunological parameters. International journal of pharmaceutics. 2002;238(1-2):133-137. https://doi.org/10.1016/S0378-5173(02)00056-X
11. Schiff J, Cole E, Cantarovich M. Therapeutic monitoring of calcineurin inhibitors for the nephrologist. Clinical Journal of the American Society of nephrology. 2007;2(2):374-384. https://doi.org/10.2215/CJN.03791106
12. Zhang X, Lin G, Tan L, Li J. Current progress of tacrolimus dosing in solid organ transplant recipients: pharmacogenetic considerations. Biomedicine & Pharmacotherapy. 2018;102:107-114. https://doi.org/10.1016/j.biopha.2018.03.054
13. 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 27;61(8):1268 -1272. https://doi.org/10.1097/00007890-199604270-00026
14. Leather H, Boyette RM, Tian L, Wingard JR. Pharmacokinetic evaluation of the drug interaction between intravenous itraconazole and intravenous tacrolimus or intravenous cyclosporin A in allogeneic hematopoietic stem cell transplant recipients. Biol Blood Marrow Transplant. 2006;12(3):325-334. https://doi.org/10.1016/j.bbmt.2005.10.022
15. Soltero L, Carbajal H, Rodriguez-Montalvo C, Valdés A. Coadministration of tacrolimus and ketoconazole in renal transplant recipients: Cost analysis and review of metabolic effects. InTransplantation proceedings 2003;35(4): 1319-1321.https://doi.org/10.1016/S0041-1345(03)00450-0
16. El-Dahshan KF, Bakr MA, Donia AF, Badr AE, Sobh MA. Ketoconazole-tacrolimus coadministration in kidney transplant recipients: two-year results of a prospective randomized study. American journal of nephrology. 2006;26(3):293-298. https://doi.org/10.1159/000094133
17. Mori T, Aisa Y, Kato J, Nakamura Y, Ikeda Y, Okamoto S. Drug interaction between oral solution itraconazole and calcineurin inhibitors in allogeneic hematopoietic stem cell transplantation recipients: an association with bioavailability of oral solution itraconazole. International journal of hematology. 2009;90:103-107. https://doi.org/10.1007/s12185-009-0344-z
18. Zhao YC et al. The Effect of Voriconazole on Tacrolimus in Kidney Transplantation Recipients: A Real-World Study. Pharmaceutics. 2022 7;14(12):2739. https://doi.org/10.3390/pharmaceutics14122739
19. Mori T et al. Drug interaction between voriconazole and tacrolimus and its association with the bioavailability of oral voriconazole in recipients of allogeneic hematopoietic stem cell transplantation. Int J Hematol. 2012;95(5):564-569. https://doi.org/10.1007/s12185-012-1057-2
20. Lee CH, Kim GH. Electrolyte and acid-base disturbances induced by clacineurin inhibitors. Electrolytes & Blood Pressure: E & BP. 2007;5(2):126-30. https://doi.org/10.5049/EBP.2007.5.2.126
21. Zhang S, Pillai VC, Mada SR, Strom S, Venkataramanan R. Effect of voriconazole and other azole antifungal agents on CYP3A activity and metabolism of tacrolimus in human liver microsomes. Xenobiotica. 2012;42(5):409-416 https://doi.org/10.3109/00498254.2011.631224.