Combined Use of Sirolimus and Voriconazole in Renal Transplantation: A Report of Two Cases

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ABSTRACT
Voriconazole is currently contraindicated for use with sirolimus. We report our experience with voriconazole/sirolimus in two renal transplant recipients. To our knowledge, this is the first experience with voriconazole/sirolimus. An interaction requiring a 75% to 87.5% sirolimus dose reduction was noted, but goal trough levels and clinical tolerability were achieved.

VORICONAZOLE may be used first line for the treatment of fungal infection, or because an oral dosage form is available, as maintenance therapy after induction with other agents. In transplant recipients, concern surrounds successful voriconazole administration, owing to a potential interaction with the calcineurin inhibitors, and a labeled contraindication with sirolimus. The contraindication is based on a mean 7-fold increase in maximum sirolimus concentration (Cmax), and 11-fold increase in area-under-the-curve (AUC) observed in an unpublished single-dose pharmacokinetic study performed in healthy volunteers. Herein we report our experience with two renal transplant patients in whom voriconazole was administered with sirolimus.

MATERIALS AND METHODS
Patients in whom it was deemed that the best treatment included voriconazole/sirolimus combination therapy were identified during usual care. Appropriately drawn trough levels and dosages were tracked. To characterize the interaction, we calculated dose ratio (DR) as the trough level (ng/mL) divided by the dose (mg/kg). Statistical analysis was performed on a Statistical Package for the Social Sciences (SPSS, Chicago, Illinois) program, version 8. The Mann-Whitney U test was used to compare DR and levels, on and off voriconazole. A P value < .05 was considered significant.

Case 1
A 56-year-old female had Candida parapsilosis in the blood and received caspofungin and fluconazole 200 to 400 mg daily (4 days), followed by oral voriconazole 250 mg q12 hours on day 1 then 125 mg q12 hours for 3 days. No calcineurin inhibitor was used in this patient as she had short bowel syndrome, was dependent on parenteral nutrition, and frequently developed dehydration. She was maintained on sirolimus 2 to 4 mg daily and prednisone 10 mg daily.

During azole antifungal therapy (Fig 1), the sirolimus DR was 844 ± 297.5 (range: 548–1108), which was greater than the DR off the azoles, 88.7 ± 31 (range: 42–160; P < .001). Sirolimus levels (ng/mL) ranged from 13.7 to 27.7 during azole therapy, and 2.1 to 12 off azoles (P < .001). Sirolimus dose reduction of 75% was required during therapy. Pre-voriconazole QT/QTc ranged from 290 to 382/396 to 401 ms; one rhythm strip during fluconazole demonstrated QT/QTc of 440/490 ms, and no ECG was available during voriconazole. There was no evidence of liver function abnormalities or visual changes. Serum creatinine ranged from 2.2 to 5.8 mg/dL in the month preceding voriconazole, 2.8 to 3.8 mg/dL during coadministration, and 2.4 to 3.2 mg/dL during the month after coadministration. After discontinuation of voriconazole, the dose of sirolimus had to be increased to 3 mg daily to achieve target levels above 5 ng/mL.

Case 2
The second patient was a 29-year-old male with pulmonary Aspergillus fumigatus, who received 19 days of caspofungin with 15 days of amphotericin B lipid complex (ABLC). The serum creatinine increased from 0.8 to 2 mg/dL during ABLC, and therapy was then switched to voriconazole 200 mg daily. After the switch, the serum creatinine decreased from 2 mg/dL to 1.2 mg/dL over 5 days. During that time, sirolimus was added to the regimen of tacrolimus and prednisone, because it was believed that mycophenolate mofetil could not be reintroduced owing to leukopenia. Sirolimus was initiated at 6 mg load followed by 2 mg daily. During combination voriconazole/sirolimus therapy, the sirolimus DR was 856.4 ± 493.6 (range: 219.8–2101.1). Over time, an 87.5% reduction in sirolimus dose and a 75% reduction in tacrolimus dose were required.

The patient has been on voriconazole/sirolimus combination therapy for more than a year, with sirolimus trough levels (ng/mL)
ranging from 4.1 to 18.7. The combination appeared to be well tolerated, and pre-voriconazole QT/QTc intervals ranged from 294 to 342/397 to 422 ms, and on-voriconazole QT/QTc intervals ranged from 326 to 330/397 to 418 ms. No visual changes or liver function abnormalities were reported, and the serum creatinine has ranged from 1.1 to 1.5 mg/dL.

**DISCUSSION**

The voriconazole package labeling indicates the need for caution when voriconazole is administered with cyclosporine or tacrolimus, citing a study where voriconazole increased cyclosporine Cmax and AUC by 1.1-fold and 1.7 fold, respectively, with up to a 3-fold increase in trough concentration in stable renal transplant recipients.²,³ Voriconazole also increased tacrolimus Cmax and AUC by 2-fold and 3-fold, respectively, in healthy individuals,² but increased the tacrolimus trough concentration by 10-fold in one liver transplant patient.⁴ Another case documented the need for a 90% tacrolimus dose reduction when voriconazole was added,⁵ similar to the 75% reduction required in the current case. These studies and other data demonstrate a variable response to combination therapy, but also that voriconazole can be administered with the calcineurin inhibitors when careful therapeutic drug monitoring is employed.⁴–⁶ In support of this finding, the calcineurin inhibitors and sirolimus have been safely utilized with other azole antifungals.⁷–⁹

The reported 10-fold increase in sirolimus bioavailability when given with ketoconazole did not result in a labeled contraindication,¹⁰ and coadministration was found to be clinically feasible in practice.¹¹ We also report a similar finding when voriconazole and sirolimus were administered together, with an approximate 10-fold increase in DR (a surrogate for bioavailability because sirolimus troughs correlate with AUC),¹² and the need for reduction in sirolimus dose of 75% to 87.5%, but good tolerability despite considerable trough-level variability. If the sirolimus–voriconazole combination is planned, we recommend frequent and careful monitoring. Further study on the use and appropriateness of sirolimus–voriconazole is required.

**REFERENCES**