

Letter to the Editor

Management of Drug-Drug Interaction between Everolimus and Azole Antifungals in a Cardiac Transplant Patient

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LETTER TO THE EDITOR

We present a case of detailed interaction between Everolimus and azole antifungals managed by therapeutic drug monitoring (TDM), illustrating influence of Voriconazole and Posaconazole on blood concentrations of Everolimus and how this interaction could be managed using a pharmacokinetic model with Bayesian dosing adaptation.

A 64-year-old Caucasian male was admitted to the infectious disease department in May 2016 for exploration of a febrile syndrome lasting for two months associated with chronic cough for 1 year. He was treated by Everolimus (Certican®) 1 mg bid since 2011 as anti-rejection drug after cardiac transplantation in 1990. His treatment also included Atorvastatin 10mg/d, Ezetimibe 10mg/d, Prasugrel 10mg/d, Aspirin 75mg/d, Pantoprazole 20mg/d, and Valsartan 80mg/d. Initial physical and morphologic assessment disclosed an upper maxillary dental abscess associated with a contiguous sinusitis and basal lung nodular infiltrates. Aspergillus serology was positive using an ELISA, but not confirmed by Western blot. Plasmatic galactomannan testing was negative. Bronchoalveolar lavage fluid analysis was negative, including bacteriological and mycological analysis, and galactomannan testing. An antimicrobial therapy with amoxicillin/clavulanic acid and appropriate dental cares allowed improvement of local abnormalities, but fever and lung nodular infiltrates persisted.

Despite discordant serological tests, Voriconazole was started on May 25th with a loading dose followed by a maintenance dose of 200mg bid, allowing a dramatic improvement of his clinical condition in three weeks, with rapid defervescence, complete cough disappearance and normalization of biological inflammatory markers (CRP level, 6.1 mg/L). First empirically, doses of Everolimus were reduced to 0.5 mg bid to manage the expected interaction. Trough blood levels of Everolimus were measured every 3 days. The target concentration was 5 to 10 ng/mL. After 15 days of empirically and complex adaptation of Everolimus doses, it was decided to adjust the dose using a

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Bayesian approach based on a one-compartment model [1], coupled with a drug-drug interaction (DDI) model implemented in NONMEM 7.2 [2]. From June 10th, we have been able to predict more precisely the next two concentrations of Everolimus after a change in regimen. For day 24 and 27, predicted and observed trough blood concentrations of Everolimus were 10.5 and 9.5 ng/mL vs 8.9 and 9.8 ng/mL respectively (yellow points on Figure 1). As the patient developed Voriconazole-induced photosensitivity during summer, antifungal therapy was switched by Posaconazole 300 mg/d on August 22th and the dose of Everolimus was increased because of a lower expected inhibition potency of Posaconazole compared to Voriconazole. First controls showed a slight overexposure (14 and 19 ng/mL). Photosensitivity almost disappeared.

Everolimus, an mTOR inhibitor, is currently used as an immunosuppressant to prevent rejection of organ transplants. The limits of the recommended therapeutic range are 3 and 8 ng/mL when combined with ciclosporin [3-5] and 5-10 ng/mL in monotherapy [6]. Bioavailability is around 16%. Terminal half-life is around of 18-35 h [7]. Coefficients of inter-individual variability for C_{min}, C_{max} and AUC are 40%, 33%, and 37%, respectively [8]. Everolimus is cleared mainly by CYP3A4 so that strong interactions are awaited with azole antifungals.

In our case, C₀/D ratio of Everolimus was higher for Voriconazole than for Posaconazole (22 and 18 respectively at day 89 and 117). These results are consistent with those of Outeda Macias et al., showing C₀/D ratio ranging from 13.9 to 20.5 for Voriconazole [9]. Billaud et al., showed Everolimus trough concentrations were 7.5-fold and 3.8-fold higher during Voriconazole and Posaconazole coprescription, respectively [10].

Everolimus AUC is increased 15.0-fold by the CYP3A4 inhibitor ketoconazole [11]. As a result, the contribution ratio of CYP3A4 (CR_{CYP3A4}) to Everolimus total clearance is about 0.95 (<https://www.ddi-predictor.org/>). According to this website tool for DDI prediction, the typical inhibition potency of Voriconazole and Posaconazole toward CYP3A4 (IR_{CYP3A4}) is 0.98 and 0.80

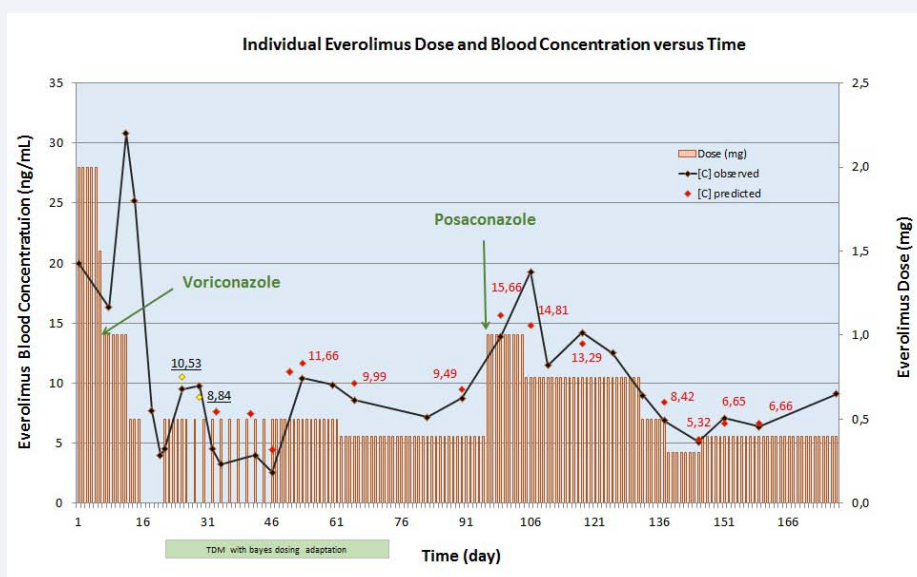


Figure 1 Individual Everolimus Dose and Blood concentration Vs Time in cardiac transplant patient.

respectively. Retrospectively, the pharmacokinetic model was fitted to the entire patient data (Figure 1), yielding a CR_{CYP3A4} of 0.62, and an IR_{CYP3A4} of 0.90 for Voriconazole and 0.53 for Posaconazole. These values are much lower than the typical values.

In our observation, it was difficult to adjust the dose without pharmacokinetic modeling assistance. Retrospective modeling of the kinetics of Everolimus and its interaction with antifungals made possible a more accurate evaluation of the interaction parameters in our patient.

Lecefel et al. concluded that an 80% decrease in Everolimus dose is needed, or even its discontinuation, on the day of the introduction of oral Voriconazole [12]. Recently, Outeda et al., for a safe co-administration, recommended a preemptive decrease to 75% of Everolimus dose with the first azole prescription [9]. In our case, a reduction by 75% of Everolimus dose was appropriate for both azoles. This case highlights the importance of TDM of Everolimus when introducing a potent inhibitor of CYP3A4, because these interactions are prone to interindividual variability.

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