AZOLE ANTIFUNGAL THERAPEUTIC DRUG MONITORING IN LUNG TRANSPLANTATION: IMPORTANT INFORMATION OR SIMPLY BLOODLETTING?

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Invasive fungal infections (IFIs) are common after lung transplantation (15-35% of all infections\textsuperscript{1}) with mortality rates up to 60\%\textsuperscript{2}. Antifungal prophylaxis is widely used as a preventive strategy\textsuperscript{3}, and has reduced the incidence and mortality of IFIs\textsuperscript{2}. Voriconazole (VOR) is the most commonly prescribed antifungal for prophylaxis worldwide\textsuperscript{3}, as well as the drug of choice for IFIs caused by Aspergillus spp\textsuperscript{4}. Patients intolerant to VOR often receive posaconazole (POS) as an alternative\textsuperscript{3}.

**Point: Plasma concentrations are important!**

An unpredictable drug dose-exposure relationship with significant inter- and intra-patient variability in plasma concentrations, makes therapeutic drug monitoring (TDM) of azole antifungals attractive\textsuperscript{5}. Drug-drug interactions (VOR & POS), saturable absorption (POS), nonlinear saturable metabolism (VOR), CYP 2C19 isoenzyme genetic polymorphisms (VOR), and physiologic conditions associated with underlying diseases (VOR & POS) further complicate use of these drugs. In addition, lung transplant recipients exhibit reduced bioavailability (24-64\%) in comparison to that observed in non-lung transplant patients (96\%)\textsuperscript{6}.

A relationship between plasma concentrations and treatment efficacy has been described; which may substantiate the need for TDM.\textsuperscript{7-16} Mitsani\textsuperscript{17} et al found lung transplant recipients more likely to be colonized or acquire an invasive fungal infection when prophylaxis with VOR resulted in serum levels ≤1.5 μg/ml (p=0.01). Median troughs at the time of positive and negative fungal cultures were 0.92 and 1.72 μg/ml (p=0.07), respectively. Shields et al\textsuperscript{18} found cardiothoracic transplant patients receiving POS for both prophylaxis and treatment of IFIs have higher median trough concentrations in those that achieved treatment success than those experiencing failure. Concentrations >0.5 μg/ml were associated with treatment success.

Certain subgroups of patients may have a predilection to both high and low trough values\textsuperscript{17}. Patients ≥ 60 years old often have VOR troughs >4 μg/ml (p=0.02), while those with cystic fibrosis are more likely to have low trough concentrations <1 μg/ml (p=0.02). Berge et al\textsuperscript{19} further characterized VOR plasma concentrations in patients with cystic fibrosis, and determined that <25\% of lung transplant recipients achieved therapeutic trough values on standard doses of VOR (200mg PO BID).

Clinical investigations in the area of toxicodynamics have also been performed, and identified associations between VOR pharmacokinetics and toxicity. Although poorly characterized in lung transplant patients, high plasma concentrations of VOR have been associated with photopsia, neurotoxicity, cardiac arrhythmias, and, in
some studies, hepatotoxicity\textsuperscript{20}.

Counterpoint: Utility of TDM remains unproven...

This seems to bring about the same questions asked when mycophenolic acid trough monitoring was in-vogue. Consider this scenario: routine cystic fibrosis patient begins VOR for fungal prophylaxis after bilateral lung transplantation and develops photosensitivity and transaminitis; yet, VOR trough is 1.2 μg/ml. One is likely to stop VOR despite so-called sub-therapeutic dosing until the symptoms of toxicity resolve. Alternatively, consider this scenario: routine lung transplant recipient begins VOR for \textit{aspergillus niger} identified on multiple fungal growth plates from a recent bronchoalveolar lavage, has nodules on CT, and a 15% decline in forced expiratory volume (FEV\textsubscript{1}) in the absence of cellular rejection. Her VOR was dosed appropriately with 4 mg/kg PO BID maintenance and her trough is 5 μg/ml. She is exhibiting no signs or symptoms of any toxicity and her tacrolimus level is at target. Would one consider dose reduction despite impeccable drug tolerance and clear evidence of an IFI?

The data to support or refute the utility of TDM for azole antifungals in lung transplant recipients is sparse and what does exist is of relatively poor quality. While the Mitsani paper describes a reasonable breakpoint for VOR ‘efficacy’, they employ univariate statistical techniques, do not evaluate for other predictors such as preoperative fungal colonization, and poorly characterize the correlation between total dose and trough concentration\textsuperscript{17}. After loading, a fixed-dose approach of VOR 200 mg PO BID was used. Though achievement of a trough >1.5 μg/ml was associated with fewer positive fungal cultures, it was not universally protective and IFIs were not stratified by trough concentration. Lastly, toxicities appeared to occur largely in the absence of high VOR trough concentrations. Finally, the definition of IFI used here and in many of these trials was never intended to be applied to, nor has ever been validated in, lung transplant recipients.\textsuperscript{21}

TDM Recommendations:

1. Early TDM (e.g., after 5 days of treatment) should be performed for patients with an IFI. The role of TDM for prophylaxis in the context of adequate dosing remains unclear.
2. Therapeutic trough concentrations should be targeted for patients with IFIs: VOR >1.5 μg/mL; POS >0.5 μg/mL.
3. Serial TDM in the presence of a previously therapeutic level and in the absence of other drug or diet changes is unwarranted.
4. If plasma concentrations remain low despite dose modification: VOR, consider discontinuing acid-suppression (H\textsubscript{2} blocker; proton pump inhibitor) and/or administer with acidic beverage (e.g., orange juice). POS, divide dose every 6 hours and/or enhance fat consumption upon administration.

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References:


