Navigating Therapeutic drug monitoring of Isavuconazole in Invasive Mold Infection on Extracorporeal membrane oxygenation - A Case Report

Blain Thayer, PharmD, AAHIVP[1]; Taylor Steuber, PharmD, FCCP, BCPS[2]; Alexandria Rydz, PharmD, BCCCP[1]; Jenna Fleming, PharmD, BCCCP[1]; Justin Sorenson, PharmD[1]; Michael Arnold, PharmD[1]; Taylor Nelson, DO[3]
[1]University Hospital, Department of Pharmacy; 1 Hospital Drive, Columbia, MO 65211
[2]University of Missouri-Kansas City School of Pharmacy at MU; 809 Lewis Hall, Columbia, MO 65211
[3]University of Missouri School of Medicine-Department of Infectious Disease; 1 Hospital Drive, Columbia, MO 65211

Abstract
Background: Isavuconazole is an azole antifungal with extended activity against yeast and molds. It is highly lipophilic, largely protein bound, and has a large volume of distribution. Critically ill patients exhibit altered pharmacokinetics (PK) of antimicrobials due to physiologic changes and other organ support modalities, including extracorporeal membrane oxygenation (ECMO). Azole antifungals, including isavuconazole, are prone to significant reduction in serum concentrations during ECMO support as a result of sequestration in the circuit and mechanical destruction of the drug via centrifugal pump, often necessitating therapeutic drug monitoring (TDM). Herein, we report a case of a young male treated for suspected invasive pulmonary aspergillosis who was placed on ECMO and treated with isavuconazole. Despite escalating doses and intense TDM, therapeutic concentrations were unable to be achieved. The patient was switched to voriconazole and liposomal amphotericin B. The patient achieved clinical improvement and switched back to isavuconazole to complete a 12-week course after ECMO decannulation occurred. This case highlights the importance of isavuconazole TDM, especially during ECMO, and consideration of alternative agents if necessary.

Keywords: isavuconazole, isavuconazonium sulfate, therapeutic drug monitoring, extracorporeal membrane oxygenation

Clinical Course

A 35-year-old male with uncontrolled type one diabetes mellitus (DM) had developed a cough and was initially treated for community-acquired pneumonia with doxycycline and amoxicillin/clavulanic acid. Due to progressively worsening respiratory distress and hypoxia, he was admitted for multifocal pneumonia. Despite intravenous (IV) vancomycin and cefepime, he decompensated and transferred to our academic medical center for management of refractory hypoxia requiring mechanical ventilation, septic shock, and diabetic ketoacidosis (DKA).

Computed tomography (CT) of the chest revealed dense consolidations throughout both lungs with cystic parenchymal lesions within the right lower lobe representative of evolving necrotizing pneumonia (Figure 1). Bronchoscopy was performed, with bronchoalveolar lavage (BAL) cultures growing methicillin-susceptible *Staphylococcus aureus* (MSSA) (Figure 1). BAL Aspergillus antigen was elevated at 0.93 (normal: < 0.50), while serum Aspergillus antigen was elevated at 0.757 (normal: < 0.50).

Corresponding Author:
Taylor Steuber, PharmD, BCPS
steubertd@umkc.edu
Office: 573-884-9679
Fax: 573-884-2166
ORCID ID: 0000-0002-7656-1504

MSSA was treated with cefazolin, and isavuconazole (372 mg IV every eight hours for six doses, then 372 mg IV daily) was started for invasive pulmonary aspergillosis versus mucormycosis. BAL fungal culture was negative.

The patient continued to decline and required veno-venous (VV) extracorporeal membrane oxygenation (ECMO). The ECMO circuit used in this patient case included a Centrimag™ blood pump, Quadrox® membrane oxygenator, and 3/8th heparin coated PVC tubing. Isavuconazole was increased to 372 mg IV twice daily, and liposomal amphotericin was also initiated. Four days after ECMO cannulation, the isavuconazole level was 0.8 mcg/mL (goal: > 1 mcg/mL). After one week on ECMO and two weeks of anti-mold therapy, BAL Aspergillus antigen had risen significantly, to 3.23, and isavuconazole levels remained subtherapeutic with twice daily dosing (0.6 mcg/mL). At this point, the patient was increased to thrice daily isavuconazole, yet levels remained subtherapeutic (0.7 mcg/mL). Isavuconazole doses and concentrations by day of therapy on ECMO are displayed in Figure 2.

While no major safety concerns were identified while on treatment with isavuconazole, slight elevations in some liver function tests were observed. After two weeks of treatment, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) peaked at 112 units/L (normal <41 units/L) and 47 units/L (normal 10 to 50 units/L), respectively, while on thrice daily dosing, but they returned to normal the next day while on the same dose. Alkaline phosphatase peaked at 599 units/L (normal 40 to 129 units/L) while on

DOI: https://doi.org/10.24926/iip.v16i2.6563

twice daily dosing; however, this continued to downtrend even after switching to thrice daily dosing. Total bilirubin remained normal while on treatment. Additionally, no significant changes in QTc interval were noted. The patient was then switched to voriconazole along with liposomal amphotericin.

Serum Aspergillus antigen improved to < 0.50 by day 22 of antifungal treatment. After one month of isavuconazole followed by voriconazole, the patient's family declined further treatment with triazoles, and liposomal amphotericin monotherapy was continued. The patient clinically improved and ECMO decannulation occurred after seven weeks, at which time isavuconazole was resumed with a plan to complete an additional 12 weeks.

Discussion/Conclusion

Isavuconazonium sulfate is the latest azole antifungal approved with extended spectrum of activity against yeast and molds.[1] The active moiety (isavuconazole) is highly lipophilic, largely protein bound (98%), and has a large volume of distribution (Vd = 450 L).[1] Critically ill patients often exhibit altered pharmacokinetics of antimicrobials due to pathophysiologic changes and other organ support modalities, including ECMO.[2] Due to hemodilution and drug sequestration in the ECMO circuit, and given the high lipophilicity, protein binding, and Vd, isavuconazole may be prone to significant reduction in serum concentrations with concomitant ECMO.[2] Furthermore, our case involved the Quadrox® membrane oxygenator, a lipid-based membrane used to facilitate gas exchange. Lipophilic medications are likely to be sequestered in the oxygenator membrane. Azole antifungals, including isavuconazole, are prone to significant reduction in serum concentrations during ECMO support as a result of sequestration in the circuit and of mechanical destruction of drug via centrifugal pump, as could be represented in our case with inability to reach therapeutic concentrations despite tripling the normal maintenance dose.

Other reports have investigated the potential impact of ECMO on isavuconazole serum concentrations. One study reported consistent subtherapeutic concentrations in four patients with invasive fungal or mold infections on ECMO in combination with renal replacement therapy (RRT) (0.88 [IWR 0.71-1.21]). One patient reached a level of 1.69 mcg/mL after an unspecified dose increase.[3] The ECMO configurations were not specified.[3] Another study followed seven critically ill adults receiving isavuconazole (one for invasive aspergillosis on VA ECMO and six for prophylaxis on VV ECMO).[4] The authors found that, at standard doses, isavuconazole concentrations were greater than 1 mcg/mL 24 hours after the initial dose and greater than 2 mcg/mL after 96 hours, contrasting with our observations.[4] In a series of four patients receiving standard-dose isavuconazole on VV ECMO, two patients achieved concentrations greater than 1 mcg/mL and two did not.[5] Two additional reports of concentrations of isavuconazole, in combination with amphotericin B, during VV ECMO for invasive aspergillosis and VA ECMO for blastomycosis required doubling the dose to maintain concentrations greater than 2 mcg/mL.[6,7]

Our case is the first to describe failure to achieve isavuconazole concentrations greater than 1 mcg/mL despite increasing to thrice daily dosing (600 mg/d) and not receiving RRT during therapy. These findings, along with previous reports, highlight the importance of TDM and consideration for alternative agents, if possible, as high variability in isavuconazole concentrations has been documented in critically ill patients on ECMO.[1-7]

Conflict of Interest Statement/Funding Support Statement: BT is a speaker for Abbvie, Inc. The remaining authors have no relevant financial or non-financial interests to disclose. No funding was received in support of this manuscript.

IRB Approval: University of Missouri IRB-approved (Case Report Form #405596)

References

1. Lyster H, Sheakar K, Watt K, Reed A, Roberts JA, Abdul-Aziz MH. Antifungal dosing in critically ill patients on extracorporeal membrane oxygenation. Clin Pharmacokin. 2023;62:931-942.
2. Mertens B, Wauters J, Debaveye Y, et al. The impact of extracorporeal membrane oxygenation on the exposure to isavuconazole: a plea for thorough pharmacokinetic evaluation. Crit Care. 2022;26:227.
3. Zurl C, Waller M, Schwameis F, et al. Isavuconazole treatment in a mixed patient cohort with invasive fungal infections: outcome, tolerability and clinical implications of isavuconazole plasma concentrations. J Fungi (Basel). 2020;6(2):90.
4. Kreigl L, Hatzl S, Zurl C, et al. Isavuconazole plasma concentrations in critically ill patients during extracorporeal membrane oxygenation. J Antimicrob Chemother. 2022;77(9):2500-2505.
5. Mertens B, Wauters J, Debaveye Y, et al. The impact of extracorporeal membrane oxygenation on the exposure to isavuconazole: a plea for thorough pharmacokinetic evaluation. Crit Care. 2022;26(1):227.
6. Zhao Y, Seelhammer TG, Barreto EF, Wilson JW. Altered pharmacokinetics and dosing of liposomal amphotericin B and isavuconazole during extracorporeal membrane oxygenation. Pharmacother. 2020;40(1):89-95.
7. Miller M, Kludjian G, Mohrien K, Morita K. Decreased isavuconazole trough concentrations in the treatment of invasive aspergillosis in an adult patient receiving

DOI: https://doi.org/10.24926/iip.v16i2.6563

extracorporeal membrane oxygenation support. Am J Health Syst Pharm. 2022;79(15):1245-1249.

Figure 1. Computed Tomography of the Chest Revealing Multifocal Necrotizing Pneumonia and Bronchoscopy Images

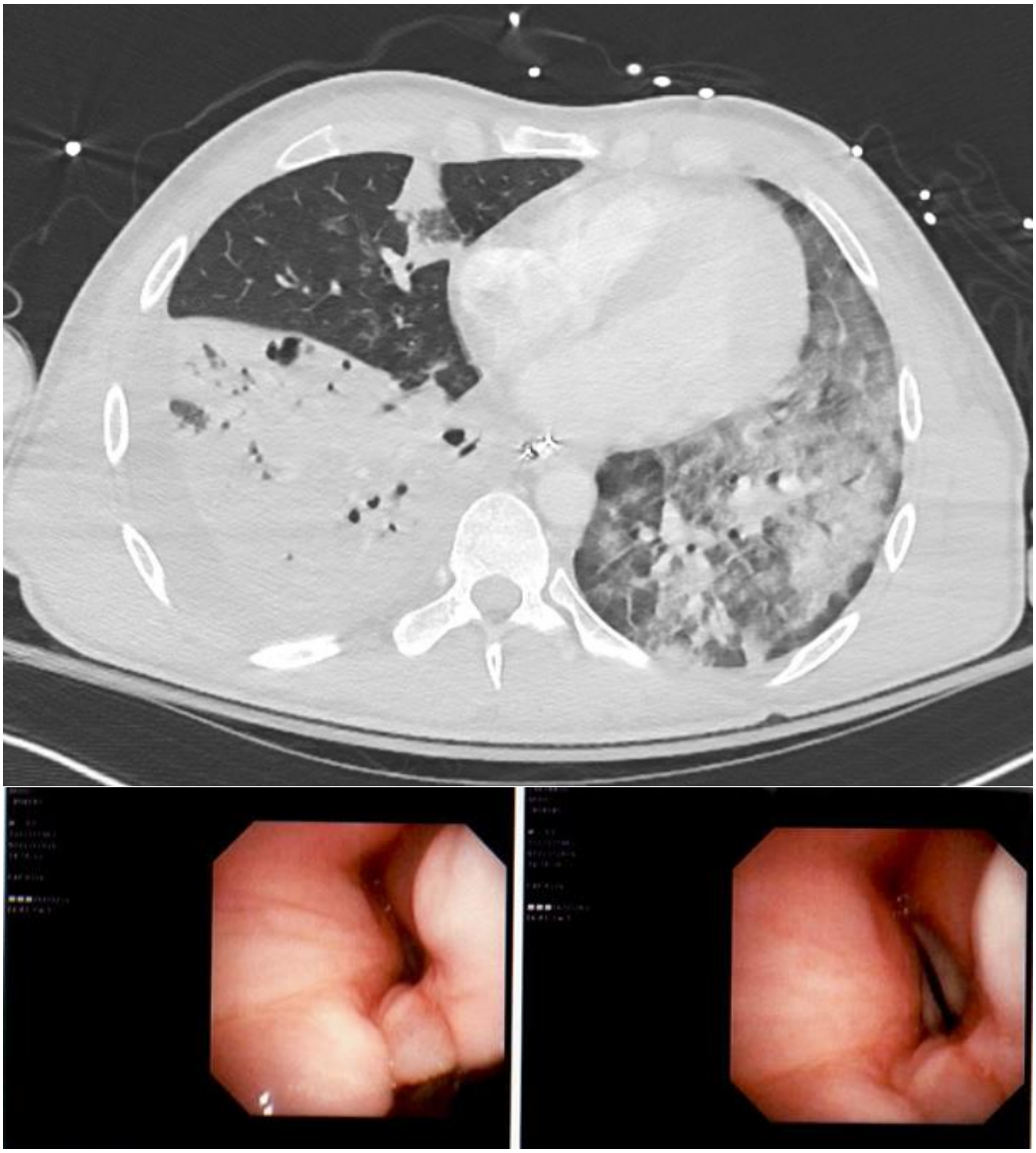

Figure 2. Isavuconazole Trough Concentrations During Treatment Course While on ECMO