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# Isavuconazole plasma concentrations in critically ill patients during extracorporeal membrane oxygenation

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**Background:** Isavuconazole is an antifungal drug used for treatment of invasive fungal infections. Critically ill COVID-19 and influenza patients require extracorporeal membrane oxygenation (ECMO) in cases with severe acute respiratory distress syndrome and have risk factors for invasive pulmonary aspergillosis. Little is known about isavuconazole plasma concentrations during ECMO.

**Objectives:** To determine isavuconazole plasma concentrations in seven patients treated with intravenous isavuconazole under ECMO and the influence of the ECMO circuit immediately after the first isavuconazole dose.

**Methods:** Critically ill patients treated with isavuconazole (standard doses) and ECMO were included in this study. Sixty-four blood samples used for measurement of isavuconazole concentrations were collected at several timepoints starting 2 h after the first isavuconazole dose up to 168 h. An additional 27 blood samples were drawn from the inflow and outflow line of the membrane oxygenator to assess any potential isavuconazole clearance effect of the ECMO oxygenation device and the lines.

**Results:** Median isavuconazole trough levels above 1 μg/mL (min. 0.83, max. 1.73) or 2 μg/mL (min. 0.84, max. 2.97) were achieved 24 h or 96 h after the first dose of isavuconazole. The isavuconazole plasma concentrations pre (inflow line) and post (outflow line) the membrane oxygenator were directly correlated ($\rho = 0.987$, $R^2 = 0.994$, $P < 0.001$). Post membrane oxygenator isavuconazole concentrations were directly correlated to contemporaneous samples obtained from the arterial lines of patients ($\rho = 0.942$, $R^2 = 0.945$, $P < 0.001$).

**Conclusions:** Isavuconazole concentrations might be influenced by the higher volume of distribution due to ECMO therapy, but were not altered by the ECMO oxygenator and achieved median plasma concentrations >1 μg/mL 24 h after the first loading dose.

## Introduction

Isavuconazole is a triazole antifungal agent recommended for treatment of invasive aspergillosis or mucormycosis.[1–4] Invasive pulmonary aspergillosis (IPA) has been described in patients treated for influenza-associated respiratory failure in European ICUs at rates ranging from 14% in patients without immunosuppression to 32% in immunocompromised patients.[5] Invasive mould infections are also described in COVID-19 patients and include mainly COVID-19-associated pulmonary aspergillosis (CAPA) and COVID-19-associated mucormycosis (CAM). In COVID-19 ICU patients, CAPA was found in up to 10%–17% in France, the Netherlands, Belgium and Austria.[6–9] Importantly, treatment of acute respiratory failure in the ICU can require extracorporeal membrane oxygenation (ECMO) (reported in 8% of ICU COVID-19 patients).[8] Therefore, the appropriate selection and dosage of antifungal drugs for treatment of invasive fungal infection in ECMO patients is of utmost importance.

Difficulties of voriconazole dosing in patients receiving veno-venous ECMO due to drug sequestration by the ECMO circuit have been described previously.[10] Reports of low isavuconazole levels in isolated cases receiving isavuconazole while on ECMO

and renal replacement therapy indicate that isavuconazole may be sequestrated/adsorbed within the ECMO circuit during the first days of treatment leading to low plasma concentrations.[10,11] Another reason might be the increased volume of distribution in ECMO patients.[12] Although isavuconazole is recommended as alternative (IDSA) or first-line treatment for invasive aspergillosis and mucormycosis,[2,3,13] these recommendations seem inapplicable in ECMO patients due to significantly decreased plasma concentrations of voriconazole and uncertainties regarding isavuconazole plasma concentrations.[14] Given the differences in pharmacokinetic properties between voriconazole and isavuconazole, a class recommendation against the use of azoles in ECMO patients may not be reasonable and more detailed studies evaluating the pharmacokinetics and efficacy of isavuconazole during ECMO therapy are warranted.[15]

The objective of this study was to evaluate isavuconazole plasma concentration in critically ill patients requiring veno-venous or veno-arterial ECMO.

## Patients and methods

### *Study population and design*

All adult patients admitted to the ICU at Medical University of Graz and LKH Graz 2, Austria, treated simultaneously with intravenous isavuconazole and ECMO between January and December 2021 were included. Since this was an explorative study, no formal sample size calculation was performed. In brief, seven patients were included in this prospective observational study and received isavuconazole either for prophylaxis or for treatment of invasive fungal infection. In all patients, isavuconazole was given intravenously as a loading dose of 200 mg q8h for six doses, followed by a maintenance dose of 200 mg q24h, with an infusion duration of 60 min as recommended by the manufacturer. This study was conducted in accordance with the Declaration of Helsinki as well as good clinical practice regulations and was approved by the local review board of the Medical University Graz, Austria (protocol number 33-062 ex 20/21).

### *Diagnosis of fungal infection and antifungal target concentration attainment*

Fungal infections were categorized according to previously published definitions[16,17] and breakthrough infections according to ECMM/MSG criteria.[18] Antifungal treatment success, failure and death are classified according to EORTC/MSG criteria.[19] Trough concentrations of $\geq$1.0 mg/L were chosen to determine the target concentration of isavuconazole in our patient cohort.

### *Extracorporeal circuits*

The ECMO circuits consisted of a DP3 pump generating the flow rate (Medos Deltastream®, Heilbronn, Germany), a Novalung XLUNG Kit 230® membrane oxygenator with inflow and outflow lines (Xenios AG, Heilbronn, Germany) and a heat exchanger. All ECMO circuits were primed with 670 mL ($\pm$10%) of heparinized isotonic fluid. No patient received renal replacement therapy or other extracorporeal blood purification techniques during the study.

### *Sample collection*

Blood samples were obtained at following timepoints after administration of the first isavuconazole dose: 2 h, 4 h, 8 h, 12 h, 18 h, 24 h, 48 h, 72 h, 96 h, 120 h, 144 h and 168 h. For determination of isavuconazole plasma concentrations, samples were obtained from an arterial line just before scheduled isavuconazole infusions. Additionally, plasma samples from three patients were drawn from the inflow and the outflow line of the membrane oxygenator to assess any potential isavuconazole clearance effect of the oxygenation device and the lines. Blood samples were collected in tubes (Vacuette® Greiner bio-one®), immediately sent to the in-house laboratory and immediately processed as described previously.[11,20] Briefly, isavuconazole plasma concentrations were determined by using electrospray ionization tandem mass spectrometry on a Voyager TSQ Quantum triple quadrupole instrument equipped with an Ultimate 3000 chromatography system (Thermo Instruments, San Jose, California, USA).[11,20] Internal quality controls were routinely included in each test run and international robin round tests are performed in the laboratory.[21]

### *Statistical analysis*

All statistical analyses were performed using the Statistical Package for Social Sciences version 23 (SPSS Inc., Chicago, IL, USA) and/or R version 4.0.5 (www.r-project.org) using R-Studio version 1.2.1335 as programming interface. Continuous data were reported as median (IQR) and categorical data as absolute frequencies (%). Median survival was estimated with the reverse Kaplan–Meier method as reported by Schemper and Smith.[22] The Kaplan–Meier product-limit estimator was used to calculate survivor functions. $R^2$-statistics were obtained from multiple linear regression models with isavuconazole concentration after the oxygenator as the dependent variable. The Kruskal–Wallis test was used for continuous variables when comparing three or more parameters. The Kruskal–Wallis H test was used as a *post hoc* test to determine between-group differences. To identify differences between isavuconazole plasma concentration (25 variables) that were collected in the presence of multiple testing, we pre-specified a Sidák corrected $\alpha$ of association, resulting in $P$ values $\leq$0.002 to indicate statistical significance.

### *Non-compartmental pharmacokinetic analysis*

Pharmacokinetic (PK) parameters were determined by non-compartmental analysis (NCA) using the R-package 'PK'. For estimation of early pharmacokinetics during loading $AUC_{0-24}$ was determined using the log-linear trapezoidal rule. The elimination rate constant (k) was determined as the slope of the terminal part of the ln(concentration)–time curve. Half-life was determined as $ln_2/k$. CL was calculated as dose/$AUC_{0-24}$ and volume of distribution ($V_d$) as dose/k·$AUC_{0-24}$. Average concentrations ($C_{avg}$) were determined as $AUC_{0-24}$/24 h. In the case of the last trough level of a 24 h collection being missing, this level was estimated by linear regression and extrapolation on the terminal part of the natural logarithm of concentration–time curve.

## Results

### *Cohort description*

During a 12 month study period, seven patients were included in the analysis (Table 1). The median age at ECMO therapy was 58 years (IQR 50–62), and 3 (43%) were female. The patients had a median BMI of 29.8 (IQR 26.9–35.2) and 3 (43%) patients did not have any co-morbidities. No patients exhibited chronic renal impairment or hepatic failure at initiation of ECMO therapy that might have influenced isavuconazole pharmacokinetics. Most patients (86%) received veno-venous ECMO therapy due to severe acute respiratory distress syndrome (ARDS) in COVID-19. All COVID-19 patients received isavuconazole as antifungal prophylaxis in the absence of any signs of invasive mycosis at first isavuconazole administration. One patient (14%) received veno-arterial ECMO therapy following cardiac arrest during

**Table 1.** Clinical and laboratory characteristics of the study population of seven patients receiving isavuconazole and ECMO

| Variable | Patients ($n=7$) |
|---|---|
| Demographic variables | |
| Age (years) [IQR] | 58 [50–62] |
| Female gender, *n* (%) | 3 (43%) |
| BMI (kg/m$^2$) [IQR] | 29.8 [26.9–35.2] |
| Comorbidities, *n* (%) | |
| No co-existing conditions | 3 (43%) |
| Thromboembolic disease | 1 (14%) |
| Collagenosis | 1 (14%) |
| Asthma | 1 (14%) |
| Aortic valve stenosis | 1 (14%) |
| Laboratory parameters | |
| Creatinine (mg/dL) [IQR] | 0.84 [0.72–1.02] |
| Bilirubin (mg/dL) [IQR] | 0.53 [0.42–0.66] |
| AST (U/L) [IQR] | 43 [27–81] |
| ALT (U/L) [IQR] | 49 [24–84] |
| Reason for ECMO, *n* (%) | |
| ARDS (COVID-19) | 6 (86%) |
| Cardiac arrest | 1 (14%) |
| Extracorporeal circuits, *n* (%) | |
| Veno-venous ECMO | 6 (86%) |
| Veno-arterial ECMO | 1 (14%) |
| Outcomes | |
| Deceased at data cut off | 4 |
| ECMO duration (days) [IQR] | 15 [5–21] |

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019.

cardiac surgery (Table 1). In that patient, isavuconazole was initiated for treatment of putative invasive aspergillosis [positive galactomannan of 4.7 from bronchoalveolar lavage (BAL), positive BAL culture with growth of *Aspergillus fumigatus*]. During a median follow-up of 21 days (IQR 5–61), we observed four deaths with a median length of ECMO therapy of 15 days (IQR 5–21). The estimated 30, 60 and 90 day survival after initiation of ECMO therapy of the whole cohort were 51% (95% CI 12%–81%), 34% (95% CI 5%–68%) and 34% (95% CI 5%–68%), respectively (Figure S1, available as Supplementary data at *JAC* Online).

In the six COVID-19 patients receiving ECMO and isavuconazole prophylaxis, no fungal infection was observed in the observation period. The antifungal treatment outcome in the remaining patient with putative IPA could not be assessed due to intractable and consequently lethal cardiogenic shock. In total, 3/7 (43%) patients survived, and 4 had a fatal outcome.

The median duration of isavuconazole administration was 11 days (range 2–22 days, IQR 5–18 days) and was 6, 16, and 18 days in the three patients who survived. A total of 64 isavuconazole plasma concentrations were measured with a median of 10 measurements per patient (range 4–12). In three patients, 27 additional pre- and post-membrane oxygenator samples (inflow and outflow) from the extracorporeal circuit were investigated, leading to a total of 91 isavuconazole plasma concentrations.

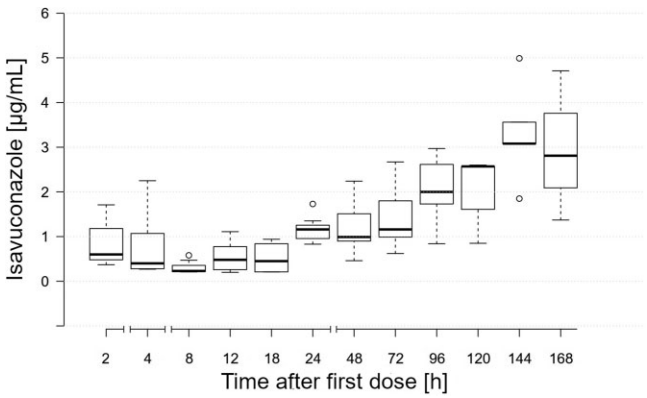


**Figure 1.** Isavuconazole plasma concentrations in ECMO patients at given timepoints after first isavuconazole dose. At dedicated isavuconazole administration timepoints, samples were obtained just before the next scheduled isavuconazole infusions.

Due to clinical reasons (e.g. medical interventions/treatments, changes in critical care treatment goals, death prior to scheduled samples) some samples were missing at certain scheduled timepoints. Plasma concentrations at given timepoints are shown in Figure 1, Table 2 and Figure S2.

### *ECMO circuit effect on isavuconazole concentration*

To clarify whether the extracorporeal circuit (membrane oxygenator and lines/cannulas) might affect isavuconazole pharmacokinetics by sequestration or adsorption, we measured isavuconazole plasma levels in samples drawn from the inflow and the outflow lines of the membrane oxygenator and from the patient by arterial blood sampling. The isavuconazole plasma concentrations pre (inflow line) and post (outflow line) the membrane oxygenator were strictly and directly correlated in our ECMO cohort ($\rho=0.987$, $R^2=0.994$, $P<0.001$) (Figure 2a). To exclude sequestration or adsorption within the ECMO inflow and outflow lines/cannulas, we additionally compared the post membrane oxygenator isavuconazole plasma levels with contemporaneous samples obtained from the arterial line of the patient and again found a highly significant and robust correlation of both isavuconazole concentrations ($\rho=0.942$, $R^2=0.945$, $P<0.001$) (Figure 2b). To support these results, we compared all measurements as outlined above and found no significant difference between the sampling sites at each timepoint.

### *Non-compartmental PK analysis*

PK parameters were calculated for the first 24 h after isavuconazole administration. The median (IQR) $AUC_{0-24}$, CL and $V_d$ were 15.60 (12.21–18.93) mg·h/L, 26.9 (18.4–35.3) L/h and 6.11 (3.88–8.33) L, respectively. The median $C_{min}$ was 0.24 (0.22–0.50) mg/L, median $C_{max}$ was 1.3 (1.10–1.72) mg/L and the median $C_{avg}$ was 0.67 (0.60–0.75) mg/L.

## Discussion

ECMO is increasingly required in ICU patients at risk for invasive fungal diseases, including those with COVID-19-associated acute

**Table 2.** Isavuconazole plasma concentrations (μg/mL) in samples drawn at given timepoints after first isavuconazole dose

| Variable | Timepoint after isavuconazole first dose | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 h | 4 h | 8 h | 12 h | 18 h | 24 h | 48 h | 72 h | 96 h | 120 h | 144 h | 168 h |
| No. of samples taken[a] | 6 | 6 | 6 | 6 | 4 | 6 | 7 | 6 | 6 | 4 | 4 | 3 |
| Plasma concentration (μg/mL) | | | | | | | | | | | | |
| Median | 0.85 | 0.65 | 0.24 | 0.52 | 0.65 | 1.09 | 0.99 | 1.21 | 2.31 | 2.09 | 3.32 | 2.81 |
| Minimum | 0.37 | 0.27 | 0.21 | 0.20 | 0.21 | 0.83 | 0.46 | 0.62 | 0.84 | 0.85 | 1.85 | 1.37 |
| Maximum | 1.71 | 2.25 | 0.58 | 1.11 | 0.94 | 1.73 | 2.24 | 2.67 | 2.97 | 2.60 | 4.99 | 4.71 |
| IQR | 0.51–1.22 | 0.31–1.16 | 0.22–0.41 | 0.36–0.88 | 0.39–0.65 | 0.92–1.30 | 0.94–1.51 | 1.03–2.07 | 1.59–2.61 | 1.42–2.57 | 2.77–3.91 | 2.09–3.76 |

[a]At timepoints 2 h, 4 h, 8 h, 12 h no samples were available from patient no. 3, at timepoint 18 h no samples were available from patients 3, 5 and 6; at timepoints 72 h and 96 h no samples were available from patient no. 5; at timepoint 120 h no samples were available from patients 3, 5 and 7; at timepoint 144 h no samples were available from patients 3, 5 and 6; at timepoint 168 h no samples were available from patients 3, 5, 6 and 7.

respiratory failure. While some of these patients require systemic antifungal therapy, data regarding the effect of ECMO therapy on isavuconazole plasma concentrations is rare.[11,23,24] Thus, the influence of ECMO on isavuconazole plasma concentration especially in the early phase of isavuconazole administration (loading doses) cannot not be extracted from current literature. An ECMO circuit may increase the volume of distribution through haemodilution occurring at the initiation of ECMO by administration of priming solutions (i.e. saline), which might primarily affect hydrophilic drugs. The membrane oxygenator and the tubes comprise a large surface area for potential drug sequestration, particularly for lipophilic drugs.[25]

In this study we investigated isavuconazole plasma levels in seven critically ill patients undergoing ECMO therapy including measurement of pre- and post-membrane oxygenator concentrations to assess a potential adsorption or sequestration effect on isavuconazole within the extracorporeal circuit. We found that the median isavuconazole concentration was above 1 μg/mL 24 h after the first isavuconazole dose. Additionally, extracorporeal (pre- and post-membrane oxygenator) and concentrations in samples drawn from the arterial line were nearly identical, revealing that the extracorporeal circuit *per se* during ECMO therapy does not affect plasma levels of isavuconazole. This finding is consistent with unchanged plasma concentrations of isavuconazole between the pre-dialysis and post-dialysis access lines in haemodialysis and was attributed to the very high protein binding (>99%) and thus low potential for drug removal.[26] In healthy volunteers, the median isavuconazole plasma concentration was 1.1 μg/mL 2 h after administration of the equivalent of 200 mg of BAL4815 (the active form of isavuconazole).[27] In our cohort we measured a median concentration of 0.85 μg/mL and in three patients isavuconazole concentrations of 1.1 μg/mL (BMI 40.9), 1.26 μg/mL (BMI 27.7) and 1.71 μg/mL (BMI 26) at this particular timepoint (<1 μg/mL in the others). The higher volume of distribution due to ECMO therapy and systemic inflammation in the context of critical illness as well as higher body weight of our patients (mean ± SD 94 ± 17 kg) compared with the healthy volunteers (80 ± 9 kg) might have contributed to the lower isavuconazole concentrations. Even after receiving the second dose 8 h after first loading dose, median isavuconazole plasma concentrations slowly increased from 0.24 μg/mL just prior to the second dose to 0.52 μg/mL 4 h and 0.65 μg/mL 8 h after the second dose. Twenty-four hours after the first loading dose and with the additional application of two doses q8h as recommended, the median isavuconazole plasma concentration was 1.09 μg/mL. Thus, in critically ill ECMO patients higher loading doses of isavuconazole might be necessary to reach higher levels as fast as in healthy volunteers. This finding is in line with previous findings on posaconazole plasma concentrations measured in six ECMO patients.[28] The anticipated posaconazole plasma concentration of ≥1 μg/mL was attained 48 h after the first loading dose and simulation from that data showed that the probability of target attainment (1 μg/mL) was 59% at this timepoint. These findings indicate that higher doses of posaconazole might be necessary in ECMO patients to overcome the low azole concentrations in the early phase of treatment.

Isavuconazole was used prophylactically in six patients with COVID-19-associated ARDS, which was in line with our local ICU COVID-19 guideline and a result of high rates of CAPA observed

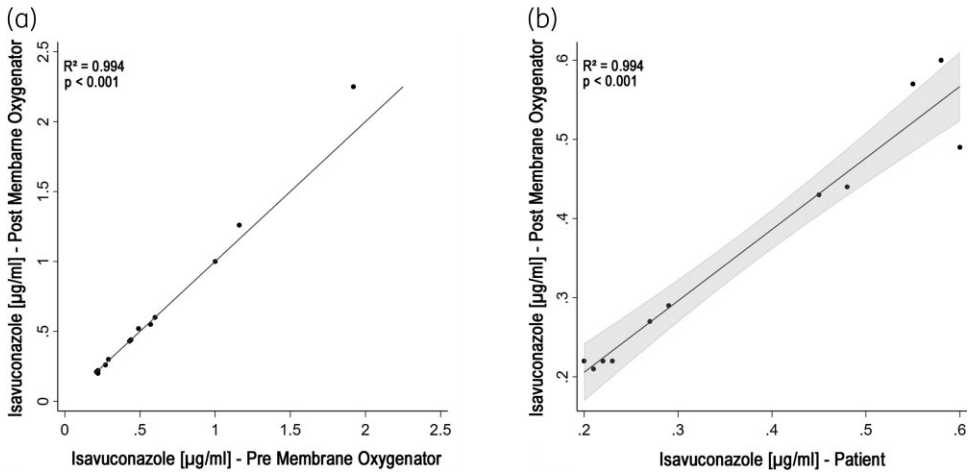


**Figure 2.** Correlation of isavuconazole concentrations (a) in samples pre (inflow line) and post (outflow line) the membrane oxygenator of the ECMO circuit and (b) in arterial blood samples from the patient and post membrane oxygenator (outflow line) of the ECMO circuit. The shaded area indicates the 95% CI.

in those without prophylaxis.[6] In our cohort, 6/7 ECMO patients had a BMI ≥26 and suffered from COVID-19-associated ARDS. Based on data from previous clinical studies, similarity in exposures between obese and non-obese patients has been found and no isavuconazole dose adjustment has been suggested for obese patients.[29] Previously, we reported isavuconazole plasma concentrations of 1 μg/mL (48 h after the first isavuconazole administration), 2.42 (14 days after first isavuconazole administration), 3.68 (33 days) and 3.42 μg/mL (41 days), respectively, in a severely obese patient (BMI 39.6).[11] In the study presented here we found isavuconazole plasma concentrations of 1.01 μg/mL (24 h after isavuconazole initiation) to 1.85 μg/mL (144 h after isavuconazole administration) and 0.9 μg/mL (24 h) to 4.99 μg/mL (144 h) in those two patients with high BMIs (39 and 40). Standard doses of isavuconazole therefore seem suitable in obese ECMO patients as sufficient levels are reached after 24 h.

In the past there were no recommendations for isavuconazole therapeutic drug monitoring except for breakthrough infection or lack of treatment success, treatment of pathogens with reduced susceptibility or potential drug–drug interaction.[30,31] Some authors have noted that determination of a single trough isavuconazole level at steady-state (≥day 3) is probably sufficient to ensure drug levels obtained in clinical isavuconazole studies and to avoid concentrations associated with toxicity.[32–34] The target for isavuconazole trough levels has been described as above 1 μg/mL[11,35] or 2 μg/mL.[26,32] These target levels were achieved 24 h or 96 h after the first dose of isavuconazole in our ECMO patient cohort.

In summary, although isavuconazole concentrations may influenced by the higher volume of distribution due to ECMO therapy, they were not altered by the ECMO oxygenator, and median plasma concentrations >1 μg/mL were achieved 24 h after the first loading dose of 200 mg.

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## Supplementary data

Figures S1 and S2 are available as Supplementary data at *JAC* Online.

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