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Influence of Sustained Low-Efficiency Dialysis Treatment on Isavuconazole Plasma Levels in Critically Ill Patients

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ABSTRACT Isavuconazole plasma concentrations were measured before and after sustained low-efficiency dialysis (SLED) treatment in 22 critically ill adult patients with probable invasive aspergillosis and underlying hematological malignancies. Isavuconazole levels were significantly lower after SLED treatment (5.73 versus 3.36 μg/ml; $P < 0.001$). However, even after SLED treatment, isavuconazole concentrations exceeded the *in vivo* MICs for several relevant *Aspergillus* species.

KEYWORDS isavuconazole, SLED, critically ill, therapeutic drug monitoring, invasive aspergillosis

Invasive aspergillosis (IA) is a relevant cause of morbidity and mortality in patients with hematological malignancies, especially when they are critically ill (1–3).

The new triazole antifungal drug isavuconazole is approved for the treatment of IA and mucormycosis and is presented in the phase 3 SECURE study as effective and well tolerated (4–6).

Renal impairment (RI) is a disease entity with high incidence in intensive care units (ICU), with renal replacement therapy (RRT) needed in up to 8% of all patients suffering from acute kidney injury. According to previous studies, dose adjustment of isavuconazole is not required in individuals with renal impairment or RRT (7). However, data on this topic are sparse. The aim of this study was (i) to investigate the influence of sustained low-efficiency dialysis (SLED) on isavuconazole plasma levels in neutropenic critically ill patients with hematologic malignancy with probable invasive pulmonary aspergillosis and (ii) to determine whether potentially decreased isavuconazole influences the effectiveness of the antifungal drug.

The study was conducted at the medical ICU of the University Hospital Technische Universität, Munich, Germany. Patients (aged ≥18 years) who received isavuconazole were eligible for study inclusion. This observational study was approved by the institutional review board of the Technical University of Munich, Munich, Germany. Written informed consent was obtained by the patients or their legal representatives.

The indication for isavuconazole treatment was made independently from the study by the ICU physician in charge in patients with proven/probable IA (based on clinical, radiological sign [computed tomography scan], and mycological criteria) and underlying hematological malignancies. Isavuconazole was administered through central venous catheters for 1 h at 200 mg three times a day (loading dose) for the first 2 days, followed by a maintenance dose of 200 mg/day.

When RRT was needed with isavuconazole medication, blood samples were not taken before the loading-dose administration was finished to reach stable baseline isavuconazole levels. After administration of the loading dose, blood samples were taken from all patients on day 3 after start of isavuconazole treatment.

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We used the commercially available Genius single-pass batch dialysis system (Fresenius Medical Care, Bad Homburg, Germany) for SLED treatment. High-flux FX60 dialyzers (Fresenius Medical Care) were used in all sessions. For all SLED treatments, a blood flow of 150 ml/min, which is equal to dialysate flow, was used. Treatment duration was 10 h.

Plasma levels of isavuconazole were obtained, as mentioned above, at the earliest on day 3 within 30 min after isavuconazole administration (end of intravenous application) and immediately after RRT, which was started after the predialysis isavuconazole level was determined. Additionally, isavuconazole levels were obtained from removed ultrafiltrate. Blood samples were taken from an arterial line using EDTA vials and centrifuged, and the plasma and the ultrafiltrate were stored at –70°C.

Isavuconazole concentrations were quantified in human plasma and ultrafiltrate by a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method using an API 5000 triple quadrupole mass spectrometer (SCIEX, Concord, ON). A total of 50 μl of each sample was deproteinized with 300 μl acetonitrile (containing the internal standard isavuconazole-D_4), subsequently vortex-shaken, and centrifuged. The supernatant was further diluted with Milli-Q water, and 10 μl of each sample was injected into the LC-MS/MS system. The lower limit of quantification was 0.107 μg/ml in plasma and 0.201 μg/ml in ultrafiltrate. The intra- and interday variability was $<$10% for plasma and ultrafiltrate.

We used IBM SPSS Statistics 23 (SPSS, Inc., Chicago, IL) for all statistical analyses in this study. To present descriptive statistics, we calculated means $\pm$ standard deviations for normally distributed continuous data and absolute and relative frequencies for categorical data (Fisher's exact test). To compare the other variables, we performed the *t* test for paired samples and the Wilcoxon signed-rank test for paired samples for normally distributed data and not normally distributed data, respectively. A *P* value below 5% ($P < 0.05$) indicated statistical significance.

The demographic and clinical characteristics of the 22 included patients who were administered isavuconazole are presented in Table 1.

Although it has been reported that RI and RRT do not influence isavuconazole levels, we found significantly lower plasma levels (maximum concentration [C_{max}]) of isavuconazole after SLED treatment (3.36 $\pm$ 1.74 [range, 1.4–9.3] versus 5.73 $\pm$ 2.98 [range, 1.9–12.2] μg/ml; $P < 0.001$), with an absolute reduction rate of 42% after dialysis. This means a relevant reduction occurred within 10 h, whereas the normal half-life of isavuconazole is 115 h (5). Isavuconazole was not detectable in ultrafiltration.

Thus, despite RRT, isavuconazole levels in this study were comparable with previous data that found isavuconazole levels of 2 to 3 mg/liter suggesting adequate drug exposure (8, 9). However, as demonstrated in our study, isavuconazole levels are markedly decreased after SLED treatment in critically ill patients.

Conventional hemodialysis is predominantly a passive diffusional process driven by an unbound concentration gradient between plasma water and dialysate (10). Isavuconazonium sulfate is a water-soluble prodrug that has high protein binding of isavuconazole ($>$99.9%) predominantly to albumin (4, 5).

The high protein binding of isavuconazole and adsorption to the synthetic surfaces of the SLED equipment might explain the decline in isavuconazole concentration (C_{max}) after SLED therapy (11, 12). Moreover, as reported in our study, it might be that isavuconazole is not only bound to albumin but also to other serum components or that a different binding potency of albumin in the presence of serum might be influenced by the critically ill circumstances, e.g., pH abnormalities (13).

However, because the limit of determination/quantification (lower limit of quantification) for isavuconazole is 0.201 mg/liter in the dialysate, the dialysate concentration may, theoretically, amount to 0.2 mg/liter. Because isavuconazole was not eliminated from the circulation by filtration in a greater amount, a clearance of isavuconazole by hemodialysis was not described. This means clearance by dialysis was low or negligible.

Several studies concluded that routine therapeutic drug monitoring (TDM) of isavuconazole is not necessary (5). Andes et al. (14) found that 90% of the patients in

TABLE 1 Basic parameters, risk/host factors, and renal replacement data

Characteristic[a]	Value ($n = 22$)
Age (yr)	54 ± 12
Male (*n* [%])	16 (56)
APACHE II score	25 ± 6
SOFA score	12 ± 3
Reason for ICU admission (*n* [%])[b]	
Pneumonia	20 (90)
Urosepsis	2 (10)
Underlying disease (*n* [%])	
Acute myeloid leukemia	6 (27)
Acute lymphoid leukemia	2 (9)
Non-Hodgkin lymphoma	8 (36)
Multiple myeloma	2 (9)
Myelodysplastic syndrome	4 (19)
Stem cell transplant recipients (*n*)	
Allogenic stem cell	10
Autologous stem cell	4
Neutropenia (*n* [%])	22 (100)
SLED data	
Running time (h)	10
Ultrafiltration (ml [mean ± SD])	2,130 ± 320
Kt/V (mean)	1.05
Probable invasive aspergillosis (*n*)	22
Galactomannan from BAL fluid	
Positive results (*n*)	14
Optical density index (mean ± SD)	2.7 ± 0.4
Microbiological evidence (*n*)	12
ICU stay (days [mean ± SD)	16 ± 7
Mortality rate (*n* [%])	16 (72)

[a]APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, sequential organ failure assessment score; BAL, bronchoalveolar lavage; SLED, sustained low-efficiency dialysis; *Kt/V*, urea clearance by time divided by the urea volume.
[b]All patients had septic shock.

whom concentrations of 1 μg/ml could be reached have a putative therapeutic concentration.

Typically, the area under the curve (AUC)/MIC ratio is calculated to predict outcome and exposure of isavuconazole. Based on our data with plasma levels of the antifungal before and after SLED therapy, we calculated instead that the C_{max}/MIC ratio expresses effectiveness of isavuconazole (15).

The total C_{max}/MIC ratio was 4,584 predialysis and 2,688 postdialysis for our in-house MIC of 0.00125 for *Aspergillus fumigatus*. This is in the line with guidelines (C_{max}/MIC ratio, 1,600, calculated with isavuconazole levels of previous studies) and comparable to EUCAST MICs (C_{max}/MIC ratios: *A. fumigatus* [MIC, 0.001], 2,000; *Aspergillus nidulans* [MIC, 0.025], 800; *Aspergillus terreus* [MIC, 0.001], 2,000) (16). The C_{max}/MIC ratio was above the target value for all patients in this study.

To predict the outcome for IA based on the C_{max}/MIC ratio was challenging in this study cohort. Critically ill patients with hematological malignancies combined with high APACHE II scores, sequential organ failure assessment scores, and multiorgan failure have high mortality rates even without IA. This might explain the high mortality rate in this study group even with sufficient isavuconazole plasma levels.

Although, we see the strength of our results, our study had several limitations. First, the study was conducted in a single center. Second, the study had an observational character without interventions. Third, there was no control group of critically ill patients without SLED treatment.

In conclusion, isavuconazole levels are affected by RRT. Therefore, correct drug dosing and TDM are crucial, especially in critically ill patients and patients receiving RRT or other extracorporeal techniques that may influence therapeutic drug concentrations.

Furthermore, the AUC/MIC ratio and the influence of several RRT/SLED therapies over a time period of several days have to be evaluated in further studies.

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We have no conflicts of interest to declare.

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