Pharmacokinetics of caspofungin and voriconazole in critically ill patients during extracorporeal membrane oxygenation

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Objectives: During extracorporeal membrane oxygenation (ECMO), drug disposition changes significantly. Plasma concentrations are altered due to an expanded circulating volume leading to a decreased elimination. In addition, adsorption and sequestration of drugs by the ECMO circuit components may further alter pharmacokinetics. Treating patients during the ECMO period with antifungals is difficult. Loss in the ECMO circuit can potentially result in sub-therapeutic levels.

Methods: Two cases are presented in which caspofungin and voriconazole levels and pharmacokinetic parameters were determined during the ECMO period.

Results: Mean caspofungin trough and peak levels were 3.73 and 11.95 µg/mL. These are comparable to previously reported ones. Also pharmacokinetic parameters were identical to those reported in the literature. It seems that caspofungin is not sequestrated by the ECMO circuit, which is expected based on its low log P value. During the first days of ECMO therapy, voriconazole trough and peak levels did not differ much from those determined prior to ECMO therapy. However, at the start of ECMO therapy, the voriconazole dose was increased from 280 to 400 mg twice daily as loss due to binding to the circuit was expected. This increase was not immediately reflected in higher voriconazole levels, which may be due to drug sequestration by the circuit. However, the voriconazole half-life was extended up to 20 h in our patient. Two days after the dose increase, levels reached troughs >10 µg/mL and peaks of around 15 µg/mL, exceeding the therapeutic interval for voriconazole. This can possibly be explained by the saturation of binding sites on the ECMO circuit.

Conclusions: Our results suggest that adequate caspofungin plasma levels are maintained during ECMO. In the case of voriconazole, it is recommended to monitor plasma levels to ensure efficacy and avoid toxicity.

Keywords: plasma levels, therapeutic drug monitoring, antifungals

Introduction

Extracorporeal membrane oxygenation (ECMO) allows prolonged cardiopulmonary support in patients with life-threatening respiratory or cardiac failure.¹

Drugs administered during ECMO exhibit complicated pharmacokinetics due to a larger volume of distribution. ECMO requires the addition of ~500 mL of exogenous blood products to prime the circuit, which increases the volume of distribution for water-soluble molecules and thus decreases their elimination.²

Moreover, it is well known that drugs such as diazepam, insulin and cyclosporine bind to polyvinylchloride bags. Similarly, drugs potentially bind to the artificial surface of the ECMO circuit.³ The physicochemical characteristics of a drug dictate the degree of uptake by the circuit. The octanol/water partition coefficient (log P) is a measure of a compound’s affinity for the organic or aqueous phase or the distribution between the two. Compounds with a high ratio will be very soluble in organic materials and can be expected to exhibit considerable loss in the ECMO circuit.³ Binding sites within the circuit seem to be saturable, leading to

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significant drug loss during the first days of treatment in a new circuit and reduced drug loss in an older circuit.³

Evaluating the efficacy of antifungals during ECMO is very difficult. Routine plasma level monitoring for these drugs is not readily available and the clinical effects cannot be easily assessed. Loss of these drugs in the ECMO circuit potentially results in sub-therapeutic plasma concentrations. In this report, two cases are presented in which caspofungin and voriconazole levels were measured during ECMO. Written informed consent was obtained for both patients.

**Patients and methods**

A 41-year-old man (80 kg) with pancreatitis was admitted with a relapse of his condition, for which he received piperacillin/tazobactam. On day 27, he suffered from septic shock. He was transferred to the ICU, antibiotics were switched to meropenem, amikacin and fluconazole, and mechanical ventilation was started. Despite maximal ventilatory settings, the optimal respiratory function could not be obtained and venovenous ECMO was started on day 29. Haemocultures revealed *Candida albicans*, but as the patient did not improve, fluconazole was switched to caspofungin (loading dose, 70 mg; maintenance dose, 70 mg once daily). On day 32, caspofungin was withdrawn as *C. albicans* was susceptible to fluconazole. The patient improved and ECMO was stopped on day 33. During caspofungin therapy, laboratory values remained stable, with a slightly decreased creatinine clearance (CLCR) (mean, 66 mL/min), elevated liver function tests (mean bilirubin, 2.32 mg/dL; mean alanine aminotransferase, 40.5 U/L) and a moderately decreased albumin level (mean 27 g/L).

A 17-year-old man (65 kg) with leukaemia was admitted because of toxic megacolon complicated with shock. Upon admission, he was intubated and antibiotics were started. On day 7, invasive pulmonary and cerebral aspergillosis was suspected based on clinical grounds, cultures and antigen titres. Voriconazole (loading dose, 400 mg twice daily; maintenance dose, 280 mg twice daily; both given intravenously) was started on day 8. During the following days, respiratory function deteriorated despite maximal ventilatory settings and venovenous ECMO was started on day 14. On the same day, it was decided to increase the voriconazole dose up to 400 mg to compensate for the expected loss in the ECMO circuit. In that way, we hoped to reach adequate voriconazole levels in plasma and CSF. The patient’s renal function remained stable (mean CLCR, 92 mL/min). His bilirubin level increased with a mean of 3.36 mg/dL before ECMO, evolving to 6.94 mg/dL during ECMO.

In the venovenous ECMO circuit, as used in both patients, venous blood was removed from the vena cava inferior, and passed through a circuit consisting of PVC tubing (Medtronic Biomedicus Cannulae, Minneapolis, MN, USA), a centrifugal pump generating the flow rate (Medtronic Biomedicus, Minneapolis, MN, USA), a 1.9 m² polymethylpentene membrane oxygenator (Medos Hilit® 7000LT) and a heat exchanger, prior to being returned to the body through a cannula to the right atrium.

In both patients, trough and peak plasma levels were determined during ECMO by collecting arterial blood samples before and 1 h after each dose. Samples were immediately centrifuged (10 min at 3000 rpm) and frozen in polypropylene tubes at −20 °C (for voriconazole) or −80 °C (for caspofungin) until analysis.

Caspofungin levels were determined in plasma by HPLC [Zorbax 300SB 5 μm column; mobile phase, acetonitrile/0.1% trifluoroacetic acid (34/66) adjusted to pH 3.0; column temperature, 35 °C; flow rate, 1.5 mL/min] after a solid-phase column extraction (Vac Elut SPS 24 vacuum extraction system, elution with methanol containing 0.5 M ammonium hydroxide and 0.05% trifluoroacetic acid), as described by Schwartz et al.⁴ Roxithromycin was used as internal standard. UV detection (at 215 nm) was used instead of fluorescence detection.

Voriconazole was determined in plasma by HPLC [Spherisorb ODS-2 5 μm column; mobile phase, acetonitrile, methanol and 0.01 M TEMED pH 7.4 (30/40/30); flow rate, 1 mL/min] after liquid–liquid extraction.² Ketoconazole was used as internal standard. UV detection was set at 255 nm.

For both, linearity of the calibration curve was found in the range of 0.05–10 μg/mL. The lower limit of quantification was 0.05 μg/mL, being the lowest concentration of the standard curve with a coefficient of variation <20%. Analytical recovery (%) of caspofungin and internal standard was 58.06 ± 7.84 and 58.80 ± 9.62 (mean ± SD), respectively. Analytical recovery (%) of voriconazole and internal standard was 104.4 ± 14.1 and 86.6 ± 10.2 (mean ± SD), respectively. Coefficients of variation for intra- and inter-day precision and accuracy were all <15%, for both. Both methods were validated according to ICH guidelines.

Pharmacokinetic parameters were determined by non-compartmental analysis using WinNonlin Version 5.2.1 (Pharsight, Mountain View, CA, USA). The terminal elimination rate constant (λz) was estimated by linear regression of the natural logarithms of mean plasma concentrations versus time. The area under the plasma concentration–time curve (AUC₀–₂₄) was calculated by the linear up/down log method. The half-life (t₁/₂) was calculated as ln 2/λz. Plasma clearance was calculated as dose/AUC₀–₂₄. Volume of distribution (V) was calculated as dose/λz·AUC₀–₂₄.

**Results**

Caspofungin and voriconazole plasma concentrations and pharmacokinetic parameters are shown in Tables 1 and 2, respectively.

**Discussion**

To our knowledge, this is the second report regarding monitoring of antifungals during ECMO in adults.

**Table 1. Caspofungin and voriconazole plasma concentrations**

<table>
<thead>
<tr>
<th>Day</th>
<th>Daily dose (mg)</th>
<th>Trough (μg/mL)</th>
<th>Peak (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29a</td>
<td>70</td>
<td>—</td>
<td>11.11</td>
</tr>
<tr>
<td>30a</td>
<td>70</td>
<td>2.70</td>
<td>12.21</td>
</tr>
<tr>
<td>31a</td>
<td>70</td>
<td>4.18</td>
<td>9.71</td>
</tr>
<tr>
<td>32a</td>
<td>70</td>
<td>4.31</td>
<td>14.75</td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>560</td>
<td>7.07</td>
<td>10.50</td>
</tr>
<tr>
<td>13</td>
<td>560</td>
<td>7.34</td>
<td>8.99</td>
</tr>
<tr>
<td>14a</td>
<td>800</td>
<td>7.34</td>
<td>10.90</td>
</tr>
<tr>
<td>15a</td>
<td>800</td>
<td>7.45</td>
<td>13.47</td>
</tr>
<tr>
<td>16a</td>
<td>800</td>
<td>10.55</td>
<td>14.55</td>
</tr>
<tr>
<td>17a</td>
<td>800</td>
<td>13.28</td>
<td>16.71</td>
</tr>
</tbody>
</table>

²Treatment during ECMO therapy.
Trough and peak caspofungin levels measured in the first patient during ECMO were maintained within the normal range and are comparable to those described in healthy volunteers and surgical ICU patients.6,7 This is in contrast to a recent case report in which it was concluded that ECMO highly affects caspofungin levels, resulting in low to undetectable concentrations.8 Also the half-life, clearance and volume of distribution are not very different from those calculated in healthy subjects (Tables 1 and 2).

Caspofungin is freely water-soluble and has a low log $P$ value of $2.798$, therefore sequestration by the ECMO circuit is not expected.9 As normal caspofungin plasma concentrations were reached in our patient during ECMO, sequestration did not occur, which is in accordance with its low log $P$ value.

Voriconazole levels (Table 2), as measured in the second patient, were very high, even prior to ECMO, and above the therapeutic interval of 1.5–5.5 $\mu$g/mL for trough levels as proposed in the literature.10 These levels are correlated to a very low plasma clearance, which is probably related to the patient’s impaired intrinsic metabolic capacity to metabolize voriconazole. Renal function was not impaired and drug interactions were ruled out. Moreover, the patient was genotyped as CYP2C19 wild-type, so none of the mutations (CYP2C19*2 or CYP2C19*3) leading to higher plasma concentrations was detected.

Voriconazole is poorly water-soluble and has a log $P$ value of 2.561; based on its lipophilicity voriconazole can be partially lost in the circuit.9 Mehta et al.3 examined binding to the circuit in an $ex$ $vivo$ simulation model. It was shown that at the end of a 24 h period in a blood primed extracorporeal circuit, 71% of voriconazole was lost and it was concluded that therapeutic concentrations of voriconazole cannot be guaranteed during ECMO.3 Therefore, at the start of ECMO therapy, we decided to augment voriconazole dosage from 280 to 400 mg twice daily (+43% increase in dose), probably reflecting its non-linear pharmacokinetics.10 Saturation of binding sites in the circuit could explain why the accumulation of voriconazole was only observed after a number of days. Alternatively, based on a half-life of $\geq 20$ h in our patient, it is also reasonable to accept that levels were only slowly increasing to reach a new steady-state after increasing the dose.

In conclusion, the altered pharmacokinetics of drugs during ECMO and loss due to adsorption to the circuit may have important implications for patient outcomes, especially in life-threatening conditions such as invasive aspergillosis. This is especially true for voriconazole. In contrast, caspofungin levels are well maintained during ECMO.

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### Transparency declarations
None to declare.

### References


