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Potential voriconazole and caspofungin sequestration during extracorporeal membrane oxygenation

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Sir: A 31-year-old woman (weighing 50 kg) was admitted to our ICU for cardiogenic shock caused by fulminant myocarditis. Twelve hours later, extracorporeal oxygenation membrane (ECMO) support via percutaneous arterial and venous femoral cannulae was initiated; the system comprised a membrane oxygenator (Quadrox Bioline, Jostra-Maquet, Orléans, France) and a centrifugal pump (Rotaflow, Jostra-Maquet). Continuous venovenous hemodialfiltration (PRISMA machine; respective blood, dialysate and ultrafiltration flows: 120 ml/min, 500 ml/h and 1,000 ml/h) was started because of acute renal failure.

Six days later, *Aspergillus fumigatus* was isolated from pulmonary secretions, obtained via bronchoalveolar lavage (BAL), and extensive tracheal pseudomembranous lesions. Although her serum was galactomannan-antigen-negative (enzyme immunoassay, Bio-Rad), the BAL galactomannan index was 4.8 (threshold, 0.5). Combined intravenous (IV) antifungal therapy was initiated with voriconazole [6 mg/kg bid day 1, then 4 mg/kg bid] and caspofungin (70 mg day 1, then 50 mg/day). Because of persistent *A. fumigatus*-positive tracheal lesion cultures on D11, respective antifungal doses were increased to 8 mg/kg bid and 70 mg/day. On D14, persistent extensive tracheal pseudomembranous lesions, positive BAL and tracheal aspirate cultures and a BAL galactomannan index of 8 indicated treatment failure. On D15, voriconazole was stopped, and based on in vitro results [1], caspofungin was combined with IV liposomal amphotericin B (3 mg/kg/day) and flucytosine (1.5 g/day); nebulized liposomal amphotericin B (25 mg bid) was also administered.

Table 1 Blood levels of antifungals during ECMO

Molecule ICU (antifungal treatment) day	Time since last dose (h)	Dose (mg)	Blood concentration (mg/l)
Voriconazole (IV)			
13 (7)	24	400 × 2	0.5
14 (8)	24	400 × 2	Undetectable
Caspofungin			
14 (8)	24	70	Undetectable
15 (9)	22	70	Undetectable
16 (10)	22	70	3.4
17 (11)	13	70	Undetectable
18 (12)	14	70	1.8
Liposomal amphotericin B			
16 (10)	13	150	5.8
17 (11)	18	150	6.2

The patient was weaned from ECMO 21 days after ICU admission. BAL cultures became negative 16 days after starting the three-drug regimen, followed shortly thereafter by an undetectable galactomannan index. The patient was discharged from the ICU on D53. During ECMO, voriconazole, caspofungin and amphotericin B levels in blood collected from the indwelling arterial line were determined by high-performance liquid chromatography (respective quantification limits: 0.2, 0.5 and 0.1 mg/l; see Table 1).

ECMO improves outcomes of patients with fulminant myocarditis [2]. During ECMO, drugs exhibit complex pharmacokinetics due to the larger volume of distribution, and their binding to various extracorporeal circuit components may markedly alter the pharmacokinetics of commonly used agents [3]. Molecular size, degree of ionization and physicochemical drug properties, e.g., the octanol–water partition coefficient, which is associated with a drug's lipophilicity, may influence the degree of binding to plastics [3]. A recent ex vivo study [4] demonstrated a 71% 'loss' of voriconazole, a finding consistent with our very low or undetectable circulating levels, despite high doses, that is clinically relevant because of the significant association between trough blood voriconazole levels and outcome [5]. A renal replacement role was unlikely because nonhigh-volume hemodialfiltration contributes minimally to voriconazole elimination. ECMO also affected caspofungin pharmacokinetics, while blood amphotericin B levels remained within the therapeutic range. To the best of our knowledge, no data are available concerning blood caspofungin concentrations in patients on ECMO.

In such patients, because adequate blood voriconazole and caspofungin concentrations may not be

guaranteed, they should be monitored and liposomal amphotericin B could be preferred for invasive fungal infections. Further studies examining the effect of newer ECMO circuits on circulating antifungal levels are warranted.

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