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Pharmacocinétique de l'amphotéricine B liposomale chez un patient sous oxygénation extracorporelle

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Introduction

Amphotericin B is a macrocyclic polyene with a broad-spectrum antifungal activity indicated in the management of invasive fungal infections and leishmaniasis. Lipid formulations were developed to improve drug tolerability. The recommended regimen for liposomal amphotericin B in invasive pulmonary aspergillosis is 3-5 mg/kg daily infused over 30-60 minutes.

Extracorporeal membrane oxygenation (ECMO) is a complex life-support technique which aims to compensate cardiac and/or respiratory function in case of organ failure. Its potential for interacting with the pharmacokinetics of several drugs used in the intensive care unit (ICU) is well documented. Drug sequestrations within ECMO components, as well as release from binding sites and increase in drug clearance or volume of distribution have been reported [1]. Liposomal amphotericin B may interact with ECMO device due to its physicochemical properties, but limited data is available on this subject.

Patient and methods

We report the case of a 33-year-old woman admitted to our ICU for acute respiratory distress syndrome in April 2017 (day 0). The patient had a history of Hodgkin lymphoma diagnosed in 2008, which required hematopoietic stem cell transplantation and intensive chemotherapy in April 2017. Two weeks before ICU admission, the patient presented with cough associated with chest pain and dyspnea initially treated with amoxicillin. Despite antibacterial treatment, her status worsened, and she was admitted to the ICU. On day 1 *Aspergillus fumigatus*, *Streptococcus pneumonia*, and *Moraxella catarrhalis* were isolated from bronchoalveolar lavage (BAL) culture. Voriconazole and piperacillin-tazobactam were initiated. Invasive pulmonary aspergillosis diagnosis was confirmed by chest imaging and elevated galactomannan antigen in BAL initially at 1.956 (threshold <0.5). Minimum inhibitory concentrations for voriconazole, micafungin, and amphotericin B were 0.19, 0.012, and 0.38 µg/mL. On day 16 hemiplegia associated with microbiological failure (galactomannan antigen >6 in BAL and positive culture) led to the addition of micafungin. Respiratory symptom worsening on day 34 led to

switching to liposomal amphotericin B (4 mg/kg/day, 6-hour infusion). Veno-venous ECMO was required while culture and antigen for *Aspergillus fumigatus* were still positive. Due to the complexity of the situation, a complete pharmacokinetic profile of amphotericin B was assessed at steady state on day 47 to guide therapy. Despite antifungal therapy, the patient's clinical condition continued to worsen until death on day 55.

Blood samples were collected before infusion and 2, 4, 6, 8, 16, and 20 hours after drug infusion. Drug levels were determined using liquid chromatography paired with a photodiode array detector. Pharmacokinetic parameters were estimated using a non-compartmental analysis with the PKSolver software [2].

Results and discussion

Despite the non-linear kinetic of liposomal amphotericin B, the pharmacokinetic parameters obtained in our case patient were similar to those reported in critically ill non-ECMO patients [3] (Table 1). As previously published, the use of ECMO may significantly alter pharmacokinetic profiles of commonly used drugs. Physiological changes such as a larger volume of distribution or a prolonged elimination have been reported [4, 5]. The increase in volume of distribution is usually related to a dilutional effect associated with a loss of drug in the membrane oxygenator or polyvinylchloride tubing. Due to its molecular size and lipophilicity, liposomal amphotericin B is expected to be absorbed or sequestrated by circuit component. However, the volume of distribution calculated for our patient was similar to values observed in critically ill patients without ECMO [3]. This result also depends on the severity of the patient's underlying illness which could explain the difference with neutropenic patients and healthy volunteers [6, 7]. The elimination of the drug can also be prolonged in case of organ failure and increase in volume of distribution. In the present case, the drug elimination was comparable to critically ill patients and longer than in the two other groups of patients (i.e., neutropenic patients and healthy volunteers) [3, 6, 7]. Hence, the ECMO device did not seem to alter the clearance of liposomal amphotericin B. Furthermore, the exposure (i.e., the area under the curve [AUC]) was, in the present

case, closer to the value reported in ICU patients and healthy volunteers than in neutropenic patients (133, 171, 171 versus 555 µg.h/mL, respectively). Moreover, the trough concentration measured 20 hours after the onset of infusion was 4.9 µg/mL, a result close to a very similar case where liposomal amphotericin B measured at H13 and H18 was respectively 5.8 and 6.2 µg/mL [8]. On the contrary, the C_{max} measured in our patient was lower than that described in critically ill non-ECMO patients (8.7 versus 14.4 µg/mL). This may result from the extended infusion duration performed in our patient. Extending infusion duration, which aimed to decrease renal toxicity, could have decreased treatment efficacy due to the concentration-dependent antifungal activity of amphotericin B. These findings might be in favor of a minor impact of ECMO on liposomal amphotericin B pharmacokinetics.

Conclusion

We presented the first case of a complete pharmacokinetic profile of amphotericin B in a patient treated with ECMO. ECMO did not seem to have modified the pharmacokinetics of amphotericin B suggesting that no dose adjustment should be necessary in similar patients. However, further studies are warranted to confirm this observation.

Declaration of interest

The authors declare no competing interest.

Contribution of authors

JBF, MCV, and CT collected the data and wrote the article.

PB and AF ensured the clinical management of the patient.

AP performed the pharmacokinetic analysis.

EB and FL supervised the work, wrote and approved the article.

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Tableau 1. Paramètres pharmacocinétiques de l'amphotéricine B liposomale chez des patients sous ECMO versus sans ECMO.

Table 1. Pharmacokinetic parameters of liposomal amphotericin B in patients with ECMO vs non-ECMO patients.

	Present case	**Heinemann *et al.* [3]**	**Coukell&Brogden [4]**	**Bekersky *et al.* [5]**
Patients	ECMO	Critically ill patients	Neutropenic patients	Healthy volunteers
Number of patients	1	16	10	5
Dose (mg/kg/day)	4	1.2 to 4.2	5	2
Infusion duration (hours)	6	1	1-2	2
C_{max} (µg/mL)	8.7	14.4	31.4	22.9
AUC_{0-24h} (µg h/mL)	133	171	555	171
V_d (L/kg)	0.40	0.42	0.10	0.77
$t_{1/2}$ (h)	18.3	13.1	6.8	6.0
CL (mL/h/kg)	16.2	22.0	11.0	9.7

AUC_{0-24} = area under the plasma concentration-time curve from 0 to 24 hours; C_{max} = peak plasma drug concentration; CL = total plasma clearance; $t_{1/2}$ = mean elimination half-life; V_d = volume of distribution.