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Insufficient serum caspofungin levels in a paediatric patient on ECMO

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ABSTRACT

Caspofungin, aechinocandin, is a relatively new lipophilic antifungal drug. Little is known concerning the pharmacokinetics of caspofungin in children. Extracorporeal membrane oxygenation (ECMO) allows prolonged cardiopulmonary support in patients with life-threatening respiratory or cardiac failure. Pharmacokinetics may be altered by ECMO. We describe the case of a paediatric patient on ECMO with severe pneumonia and sepsis, who had subtherapeutic exposure of caspofungin despite normal to high dosages of caspofungin. Therapeutic drug monitoring is warranted.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) allows prolonged cardiopulmonary support in patients with life-threatening respiratory or cardiac failure. Pharmacokinetics may be severely altered by ECMO. We describe the case of a paediatric patient on ECMO with severe pneumonia and sepsis, who had subtherapeutic exposure of caspofungin despite normal to high dosages of caspofungin.

2. Case

Two weeks after admission to a general hospital an 11 months old baby girl was transferred to the paediatric intensive care of the Children's hospital, with persisting infection, neutropenia, thrombopenia and an imminent respiratory insufficiency. On admittance the patient had a respiratory rate of 32/min, mild subcostal retractions, crepitations on both sides and pleural rubbing. Her pulse was 170/min, with adequate circulation and a central refill < 2 s.The initial blood culture was positive for *Staphyloccus aureus*. Antibiotics were started. In the next couple of days, her condition worsened and she was intubated and mechanically ventilated. The infection parameters did not decrease, despite multiple regimens of antibiotics. No other pathogens were cultured. Ventilatory parameters deteriorated and trombopenia as well as neutropenia worsened. A bronchoalveolar lavage was performed that yielded both a positive galactomannan test and positive cultures for *Candida albicans* and *Candida tropicalis*. Veno-venous ECMO was started (iLA-activve® and the iLA membrane ventilator®, Novalung GmbH). Simultaneously, voriconazole (50 mg twice daily) was started with a trough level of 2.3 mg/l after 4 days of therapy (normal range 2–5 mg/l). Caspofungin was started with a loading dose of 78 mg/m^2, followed by 78 mg/m2 once daily instead of a standard dosage of 50 mg/m^2. Because of critical illness and expected different pharmacokinetics a higher dose was given [1]. Caspofungin blood concentrations were measured (by means of High Pressure Liquid Chromatography with fluorescence detection) at t=210 (7.43 mg/l), 405 (3.80 mg/l), 720 (2.62 mg/l) and 1410 min (1.02 mg/l) after the first dosage. An Area under the Curve (AUC) of caspofungin was calculated by means of WinNonLin 5.2 non-compartmental analysis using linear-log trapezoidal method. The AUC after the loading dose was considered subtherapeutic: 69 mg h/l (average AUC of caspofungin dosage 50 mg/m^2 in children associated with a favourable outcome is 140 mg h/l) [2]. Clearance (0.04 l/h/kg) was higher than described in literature [3]. Nine days after admittance to our children's hospital, the clinical situation deteriorated with severe pulmonary haemorrhage, gastrointestinal bleeding and progressive multiorgan failure. Based on severe lung damage and lack of improvement on maximal therapy of uncontrolled fungal sepsis, further treatment was deemed futile and ECMO support was terminated. The patient died before adjusting the dose of caspofungin.

3. Discussion

This patient on ECMO had subtherapeutic exposure of caspofungin despite normal to high dosages of caspofungin.

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Little is known concerning the pharmacokinetics of caspofungin in children. A caspofungin dosage of 50 mg/m^2 (70 mg/m^2 on day 1) in 10 young children 3 to 24 months of age resulted in therapeutic caspofungin concentrations [2]. In our patient the AUC was lower, 69 versus 140 mg h/l, 2 and clearance was higher than described in caspofungin population kinetics [3] Trough (1.02 mg/l) and peak concentration (7.43 mg/l) were lower compared to literature (3.73 resp. 11.95 mg/l) [4]. Although dosage was relatively high (78 mg/m^2 in comparison to 50–70 mg/m^2), levels were considered subtherapeutic, indicating that ECMO, the patient's condition or other drug therapy can affect caspofungin concentration. Furthermore, interpatient variability may play a role.

The influence of ECMO on pharmacokinetics is dependent on the characteristics of the drug and the ECMO system. Caspofungin is freely water-soluble and has a low log *P* value; therefore significant sequestration by the ECMO circuit may not be expected [5]. A possible explanation can be that ECMO may influence the metabolism of caspofungin by altering the metabolism of caspofungin. Metabolism could also have been influenced by the inflammatory response in the patient, analogous to the effect on CYP450 metabolism [6]. Furthermore, total volume of the ECMO circuit was 360 ml which is about 60% of the total circulating volume of our patient. Hemodilution may play a part in increasing volume of distribution [7]. No information is available for caspofungin concentrations in paediatric ECMO patients. In adults, trough and peak caspofungin concentrations were within the normal range and the authors concluded that caspofungin dosage adjustment is not warranted [3]. However, in another case report in an adult ECMO patient, it was concluded that ECMO highly affects caspofungin levels, resulting in low to undetectable concentrations [8].The reasons for these differences need to be explored, but may lay in differences between ECMO systems, patient's condition or interpatient variance. Moreover, the blood concentration of caspofungin might be affected by other drugs, but no known interacting drugs were identified in the patient. Therapeutic drug monitoring may be a tool to dose caspofungin in these patients.

In our patient, caspofungin was measured after the first loading dosage and had not reached steady state. The AUC can be increased at steady state. However, the clearance, which will not change at steady state, is significantly higher in our patient than reported in literature. This is contrary to most reports of altered PK in ECMO patients [5]. However we found similar increases in clearance for other drugs in ECMO patients [9,10]. In conclusion, although this is a single case report, it supports the need for therapeutic drug monitoring in (paediatric) ECMO patients to attain concentrations within population average that correspond with a favourable outcome

Conflict of interest

There are none.

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Not applicable.

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