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Pharmacokinetics of anidulafungin during venovenous extracorporeal membrane oxygenation

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Echinocandins are currently considered the first-line treatment for invasive candidiasis (IC) in the intensive care unit (ICU) [1, 2]. However, extracorporeal membrane oxygenation (ECMO), a rescue therapy used in patients with severe acute respiratory distress syndrome (ARDS) [3], could alter the pharmacokinetics of certain drugs [4]. We prescribed anidulafungin for suspected IC in a patient with severe ARDS on ECMO and measured the plasma concentrations of the drug using high-performance liquid chromatography (HPLC).

A 69-year-old male patient was admitted to the ICU with septic shock secondary to peritonitis. The anti-infective treatment was based on surgical source control and broad spectrum antimicrobial therapy, including anidulafungin at usual doses. The patient developed severe ARDS. ECMO with Novalung iLA Activve™ was initiated, maintaining ultraprotective ventilation. Femoral (23 F) and jugular (19 F) cannulas (Novalung™, Germany) were inserted with 4.5 L/min blood flow and 4 L/min gas flow. Urine samples and pre-filter and post-filter blood samples were collected before starting the eight-dose anidulafungin infusion and 0.5, 1, 1.5, 2, 4, 6, 8, and 24 h after the infusion ended. Anidulafungin was well tolerated without relevant adverse effects.

A non-compartmental pharmacokinetic analysis was performed using Abbottbase Pharmacokinetic Systems™ (Abbott Laboratories, Illinois, USA). The maximum and trough plasma concentrations (C_{max} and C_{min}, respectively) were estimated directly from concentration-time data. The area under the plasma concentration-time curve over the 24-h dosing interval (AUC_{0-24}) was estimated using the linear trapezoidal rule for both pre-filter and post-filter data. Clearance (CL) was estimated as dose/AUC_{0-24}. The apparent volume of distribution at steady state (V_{ss}) was estimated as the product of CL and mean residence time (MRT).

C_{max} and C_{min} were 13.5 and 2.19 mg/L, respectively (Fig. 1). Pre-filter and post-filter AUC_{0-24} were 107 and 111 mg/h/L, respectively; V_{ss} was 18.9 L; CL was 0.933 L/h. Urine anidulafungin concentrations were negligible. All pharmacokinetic data were comparable to published data in critically ill patients with and without other types of extracorporeal support [5].

Regarding the use of anti-infective drugs in patients on ECMO, most pharmacokinetic data on this topic are from neonatal studies of antibiotics [4]. To the best of our knowledge, this report is the first on the pharmacokinetics of anidulafungin in a critically ill patient on ECMO. In our case, the therapy had little effect on the pharmacokinetics, suggesting that the dose of anidulafungin does not need adjustment. However, future studies are needed to confirm these findings.

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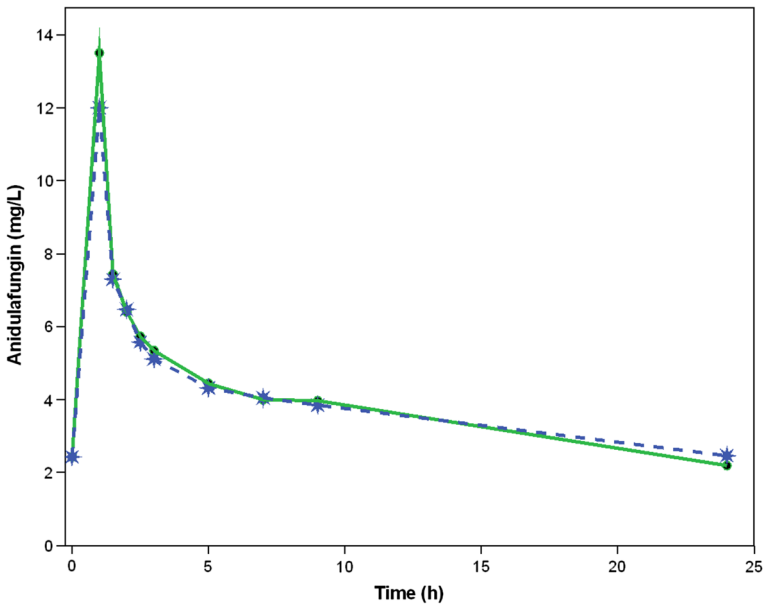

Fig. 1 Plasma anidulafungin concentrations over 24 h. Solid and dotted lines represent the concentrations in the pre-filter and post-filter sides of the membrane, respectively. Urine concentrations of anidulafungin were very low and close to the limit of detection for the analytical procedure used (0.05 mg/L)

Abbreviations

ARDS: Acute respiratory distress syndrome; AUC_{0-24}: Area under the plasma concentration-time curve over the 24-h dosing interval; CL: Clearance; C_{max}: Maximum plasma concentration; C_{min}: Trough plasma concentration; ECMO: Extracorporeal membrane oxygenation; HPLC: High-performance liquid chromatography; IC: Invasive candidiasis; ICU: Intensive care unit; MRT: Mean residence time; V_{ss}: Apparent volume of distribution at steady state

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Availability of data and materials

All relevant data are within the paper and its supporting information files. All data are fully available without restriction.

Authors' contributions

GA conceived the study, participated in its design, and helped draft the manuscript. RF, CE, and MA participated in designing the study and carried out the pharmacokinetics study. JMA, JAC, AV, and JP participated in analyzing and interpreting the data. DN and FJB participated in designing and coordinating the study and helped draft the manuscript. All authors read and approved the final manuscript.

Competing interests

GA received funds for speaking at meetings organized on behalf of Astellas, Gilead, Merck Sharp and Dohme (MSD), and Pfizer, as well as unrestricted research grants from Astellas, MSD, and Pfizer. DN received funds for speaking at meetings organized on behalf of Astellas, MSD, and Pfizer and received unrestricted research grants from Astellas and Pfizer. All other authors declare that they have no competing interests.

Ethics approval and consent to participate

The study (ANI-ECMO-2016) was approved by the local ethics committee (INCLIVA, Institute of Research, Valencia, Spain) and written informed consent obtained from the patient's next of kin.

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