Anidulafungin dosing in critically ill patients with continuous venovenous haemodiafiltration

Gerardo Aguilar1*, José Ramón Azanza2, José A. Carbonell1, Carlos Ferrando1, Rafael Badenes1, María Asunción Parra2, Belén Sadaba2, David Navarro3,4, Jaume Puig1, Amanda Miñana1, Carlos García-Marquez1, Gergana Gencheva1, Andrea Gutierrez1, Francisco J. Martí1 and F. Javier Belda1,4

1Surgical Intensive Care Unit, Department of Anesthesiology and Intensive Care, Hospital Clínic Universitario de Valencia, Valencia, Spain; 2Department of Clinical Pharmacology, University of Navarra Clinic, Pamplona, Spain; 3Department of Microbiology, Hospital Clínic Universitario de Valencia, Valencia, Spain; 4School of Medicine, University of Valencia, Valencia, Spain

*Corresponding author. Tel: +34-963-86-26-53; Fax: +34-963-86-26-44; E-mail: gerardo.aguilar@uv.es

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Background: Anidulafungin is indicated as a first-line treatment for invasive candidiasis in critically ill patients. In the intensive care unit, sepsis is the main cause of acute renal failure, and treatment with continuous renal replacement therapy (CRRT) has increased in recent years. Antimicrobial pharmacokinetics is affected by CRRT, but few studies have addressed the optimal dosage for anidulafungin during CRRT.

Patients and methods: We included 12 critically ill patients who received continuous venovenous haemodiafiltration to treat acute renal failure. Anidulafungin was infused on 3 consecutive days, starting with a loading dose (200 mg) on Day 1, and doses of 100 mg on Days 2 and 3. Blood and ultradiafiltrate samples were collected on Day 3 (during steady-state) before, and at regular intervals after, the infusion had started. Anidulafungin concentrations were determined with HPLC.

Results: On Day 3, peak plasma concentrations with the 100 mg dose were 6.2 ± 1.7 mg/L and 7.1 ± 1.9 mg/L in the arterial and venous samples, respectively. The mean, pre-filter trough concentration was 3.0 ± 0.6 mg/L. The mean AUC0–24 values for plasma anidulafungin were 93.9 ± 19.4 and 104.1 ± 20.3 mg.h/L in the arterial and venous samples, respectively. There was no adsorption to synthetic surfaces, and the anidulafungin concentration in the ultradiafiltrate was below the limit of detection.

Conclusion: The influence of CRRT on anidulafungin elimination appeared to be negligible. Therefore, we recommend no adjustments to the anidulafungin dose for patients receiving CRRT.

Keywords: echinocandins, renal replacement therapy, acute renal failure

Introduction

Invasive candidiasis is an important cause of sepsis in the intensive care unit (ICU). Its incidence is growing, and the crude mortality exceeds 50%.1 Additionally, there has been a worldwide shift in the species of Candida; thus, bloodstream infections have been caused by species different from Candida albicans.2,3 This has implications for therapy, because some non-albicans Candida species are resistant or less susceptible toazole antifungal agents. Echinocandins inhibit the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall; these drugs exhibit potent in vitro and in vivo fungicidal activity against Candida species, including azole-resistant pathogens.4 Therefore, in the ICU setting, current guidelines recommend echinocandins as the first-line treatment for invasive candidiasis.5

In the ICU, sepsis is the main cause of acute renal failure. Treatment with continuous renal replacement therapy (CRRT) has increased over recent years.6 The pharmacokinetics of antimicrobials are typically affected by CRRT, but no studies have determined the optimal dosage for echinocandin treatments during CRRT.7–10 All three echinocandins (anidulafungin, caspofungin and micafungin) are approved for the treatment of candidaemia and other select forms of invasive candidiasis. Anidulafungin is the only echinocandin that is eliminated through extrahepatic metabolism;6 this feature makes it an attractive option for patients in the ICU, where hepatic dysfunction is a common occurrence.11 We investigated the pharmacokinetics of anidulafungin in critically ill patients who were not neutropenic during CRRT. The hypothesis of our study was that, given its chemical characteristics, anidulafungin would not be removed during CRRT.
Anidulafungin dosing during CRRT

Methods

Patients

We included 12 non-neutropenic, critically ill patients with suspected or proven invasive candidiasis and anuric renal failure who were receiving CRRT. The study protocol was approved by the local ethics committee (GEF-ANI-2010-01) and the Spanish Medicines Agency (AEMPSP; Eudra-CT number: 2010-024457-36). Written informed consent was obtained from all of the patients prior to their inclusion in the study.

CRRT

The type of CRRT provided to all patients was continuous venovenous haemodiafiltration (CVVHDF). CVVHDF was performed with a polysulphone haemofilter that had a membrane surface area of 1.4 m² (Fresenius, Germany). CVVHDF was performed with a roller pump (Brady, Vienna, Austria) connected to an automatic balancing system (Equaline; Amicon, Ireland). The blood flow rates were 160–180 mL/min; CVVHF flow rates were adjusted according to clinical demand. The dose of therapy was 25–30 mL/kg/h. Replacement fluid (multiBic; Fresenius, Germany) was administered through the membrane and into the venous limb of the circuit. The membranes were changed every 24 h. A continuous infusion of sodium heparin was used as an anticoagulant; the dose was adjusted to achieve an activated partial thromboplastin time (APTT) of between 35 and 45 s (up to 1.4 times greater than the control APTT).

Sampling and drug analysis

Anidulafungin (Ecalta 100 mg powder and solvent; Pfizer Corporation Austria GesmbH, Vienna, Austria) was diluted and administered intravenously on three consecutive days. On the first day, 200 mg of anidulafungin was diluted in 500 mL of isotonic saline solution and infused over 3 h. On the following 2 days, 100 mg of anidulafungin was diluted in 250 mL of isotonic saline solution and administered over 1.5 h.

Blood samples were collected on Day 3, at steady-state, from the arterial and venous lines of the extracorporeal circuits. Samples were collected before the third dose infusion had started and at 0.5, 1, 1.5, 2, 4, 6, 8, and 24 h after the infusion had begun. At the same times, ultrafiltration samples were collected from the outlet of the ultrafiltrate compartment of the haemofilter.

Anidulafungin concentrations in plasma and ultrafiltrate were measured with HPLC on an Agilent 1200 SL apparatus. Drug analysis is described in the Supplementary data (available at JAC Online).

Pharmacokinetic analysis

Five parameters were calculated from the plasma concentration profiles of anidulafungin: (i) the AUC₀–₂₄, based on the linear trapezoidal rule, was calculated for both arterial and venous data; (ii) the elimination t½, was calculated for arterial data with Phoenix 6.3 version software (PhoenixTM WinNonlin®, Certara L.P.), with no compartment analysis; and (iii, iv and v) the Cmax, Ctrough and Tmax were extracted from observed arterial values.

Results

The 12 patients included had suspected (n=9) or proven (n=3) invasive candidiasis. Table S1 (available as Supplementary data at JAC Online) shows the patients' characteristics. Plasma and ultrafiltrate samples were analysed. In two cases, the plasma samples collected at 24 h were drawn after the start of the next dose; therefore, those values were not included in pharmacokinetic analysis. The peak plasma anidulafungin concentrations with the 100 mg dose on Day 3 were 6.2 ± 1.7 mg/L and 7.1 ± 1.9 mg/L in the arterial and venous samples, respectively (Figure 1). The mean pre-filter trough anidulafungin concentration was 3.0 ± 0.6 mg/L.

The individual and mean AUCs of plasma anidulafungin are summarized in Table 1. Statistically significant differences were observed in the values of the arterial and venous AUCs (P=0.003). No anidulafungin was detected in the ultrafiltrate.

Discussion

Our results showed the pharmacokinetics of anidulafungin during CVVHDF, which resembled the results from previous studies that had measured pharmacokinetics in healthy adults and patients with fungal infections. The anidulafungin concentrations, measured 24 h after the third dose of the antifungal, were, in all cases, above the MIC₉₀ published for Candida and Aspergillus species, including Candida parapsilosis (2 mg/L). Although the pharmacokinetic parameter of relevance in the echinocandins is the AUC/MIC, it is noteworthy that the lowest trough concentration measured among our patients (2.16 mg/L, patient 11) was above the MIC₉₀ for C. parapsilosis.

We found that the anidulafungin concentration did not fall to zero during CRRT. The two main mechanisms of drug removal during CRRT are haemofiltration and haemodialysis (explained in the Supplementary data at JAC Online). A third potential mechanism is adsorption to the surfaces of synthetic materials used during the procedure. However, the clinical importance of the adsorption of antibacterials and antifungals is currently unknown and little clinical information is available about this phenomenon. Leitner et al. found that the anidulafungin concentration during CRRT was lower at the post-filter side than the pre-filter side of the membrane in seven patients, but they found no relevant differences between pre- and post-filter anidulafungin concentrations in three patients. Maximal differences in anidulafungin concentrations between the venous and arterial samples (AV differences) were measured at 2 h after beginning the loading dose (19% ± 6%). This difference had steadily decreased to 9% ± 2% at 72 h. Those authors concluded that the adsorption to the membrane might explain the AV difference, and the time-dependent decline in this difference might be due to saturation of the synthetic surfaces.
In the present study, in contrast to the Leitner et al.9 study, the mean concentration of anidulafungin was slightly higher in the post-filter line than in the pre-filter line. This finding allowed us to rule out an adsorption phenomenon. Furthermore, although the blood samples were taken only on Day 3 (steady-state) in our patients, the synthetic surfaces (including the membrane) were changed every 24 h. Therefore, the saturation phenomenon in our study should be independent of the day of blood sample extraction.

We hypothesized that the differences between the Leitner et al.9 study and our study might be explained by different plasma collection methods. In our study, the blood samples were drawn through ports positioned immediately before and after the filter. Thus, the slightly higher anidulafungin concentration in the blood samples obtained immediately after the filter was most likely to be a concentration effect of ultrafiltration that occurred due to the reduced plasma volume that passed through the filter. However, in the study by Leitner et al.,9 the positions of blood sampling in the extracorporeal circuit were not described. Therefore, we reasoned that, if they had sampled the venous blood at a distance from the filter, for example, in a port placed after the inlet of the replacement fluid, some dilution might have occurred. Thus, the lower venous concentrations compared with the arterial concentrations observed by the authors could be due to a dilutional effect of the replacement fluid; this could explain the fall in the drug concentration in the venous sample.19 When we contacted the authors about this point, they could not rule out the possibility that the lower post-filter concentrations might be due to a dilutional effect rather than the adsorption of anidulafungin to the filter. Nonetheless, in both studies, therapeutic anidulafungin levels were achieved at all sampling times.

The primary limitation of this study was the small sample size; however, this is typical in pharmacokinetic studies of antimicrobial agents during CRRT.9 Additionally, we collected blood and ultrafiltration samples only on Day 3. However, we decided to take the samples at that time because we estimated that it would take 3 days to achieve steady-state. Finally, as in the study by Leitner et al.,9 we cannot exclude the possibility that a change in extracorporeal anidulafungin removal may occur with different filtration rates. Nevertheless, recent guidelines do not recommend higher doses of therapy than those used in our study for patients with severe sepsis or septic shock.20

In conclusion, CRRT appeared to have a negligible effect on anidulafungin elimination. Therefore, we recommend no adjustments to the anidulafungin dose for patients that receive CRRT.

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Transparency declarations
G. A. received funds for speaking at meetings organized on behalf of Astellas, Gilead, Merck Sharp and Dohme (MSD) and Pfizer. G. A. also received unrestricted research grants from Astellas, MSD and Pfizer. J. R. A. received unrestricted research grants from Astellas, MSD and Pfizer. J. R. A. also received unrestricted research grants from Gilead and Pfizer. D. N. received funds for speaking at meetings organized on behalf of Astellas, MSD and Pfizer. D. N. also received unrestricted research grants from Astellas and Pfizer. All other authors: none to declare.

Supplementary data
Additional information on HPLC and mechanisms of drug removal during CRRT, as well as Table S1, are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References

Table 1. Pharmacokinetics of anidulafungin in 10 patients during CVVHDF on the third day of treatment; the dose (100 mg) was given at time = 0

<table>
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<th>Patient</th>
<th>AUC_{0–24} (mg·h/L) arterial</th>
<th>venous</th>
<th>difference venous to arterial (%)</th>
<th>C_{max} (mg/L) arterial</th>
<th>C_{trough} (mg/L) venous</th>
<th>t_{1/2} (h) arterial</th>
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<td>11±9</td>
<td>6.2±1.7</td>
<td>3.0±0.6</td>
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