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PHARMACOLOGY

Pharmacokinetics of Anidulafungin in Critically Ill Intensive Care Unit Patients with Suspected or Proven Invasive Fungal Infections

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ABSTRACT Echinocandins, such as anidulafungin, are the first-line treatment for candidemia or invasive candidiasis in critically ill patients. There are conflicting data on the pharmacokinetic properties of anidulafungin in intensive care unit (ICU) patients. Adult ICU patients (from 3 hospitals) receiving anidulafungin for suspected or proven fungal infections were included in the present study. Patients were considered evaluable if a pharmacokinetic curve for day 3 could be completed. Twenty-three of 36 patients (7 female and 16 male) were evaluable. The median (range) age and body weight were 66 (28 to 88) years and 76 (50 to 115) kg, respectively. Pharmacokinetic sampling on day 3 ($n = 23$) resulted in a median anidulafungin area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) of 72.1 (interquartile range [IQR], 61.3 to 94.0) mg · h · liter^{-1}, a median daily trough concentration (C_{24}) of 2.2 (IQR, 1.9 to 2.9) mg/liter, a median maximum concentration of drug in serum (C_{max}) of 5.3 (IQR, 4.1 to 6.0) mg/liter, a median volume of distribution (V) of 46.0 (IQR, 32.2 to 60.2) liters, and a median clearance (CL) of 1.4 (IQR, 1.1 to 1.6) liters · h^{-1}. Pharmacokinetic sampling on day 7 ($n = 13$) resulted in a median AUC_{0-24} of 82.7 (IQR, 73.0 to 129.5) mg · h · liter^{-1}, a median minimum concentration of drug in serum (C_{min}) of 2.8 (IQR, 2.2 to 4.2) mg/liter, a median C_{max} of 5.9 (IQR, 4.6 to 8.0) mg/liter, a median V of 39.7 (IQR, 32.2 to 54.4) liters, and a median CL of 1.2 (IQR, 0.8 to 1.4) liters · h^{-1}. The geometric mean ratio for the AUC_{day7}/AUC_{day3} term was 1.13 (90% confidence interval [CI], 1.03 to 1.25). The exposure in the ICU patient population was in accordance with previous reports on anidulafungin pharmacokinetics in ICU patients but was lower than that for healthy volunteers or other patient populations. Larger cohorts of patients or pooled data analyses are necessary to retrieve relevant covariates. (This study has been registered at ClinicalTrials.gov under identifier NCT01438216.)

KEYWORDS antifungal drugs, echinocandins, pharmacokinetics, intensive care unit, invasive fungal infections

Echinocandins are deployed as primary treatment for patients with invasive candidiasis or candidemia. Anidulafungin is one of three available echinocandins currently on the market. Both the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) and Infectious Diseases Society of America (IDSA) guidelines have argued that with respect to therapeutic efficacy, all echinocandins are equally effective when it comes to treatment of invasive candidiasis or candidemia (1–3). Nevertheless, there are subtle differences in regard to pharmacokinetics (PK).

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Intensive care unit (ICU) patients may be subject to severely altered PK characteristics compared to non-critically ill patients. In this population, physiological changes, such as organ failure (hepatic and/or renal dysfunction), alterations in protein binding, capillary leakage with the consequence of an altered drug volume of distribution (*V*) and/or clearance (CL), the use of organ support (i.e., renal replacement therapy and/or extracorporeal membrane oxygenation [ECMO]), and interacting comedication, may result in highly variable PK of drugs, including antimicrobial agents (4). In addition, *V* and CL may be subject to increased inter- and intrasubject variabilities due to altered plasma protein binding (5). Also, it has been hypothesized that disease severity may result in altered drug PK behavior (6).

It has been suggested that the pharmacokinetic profile of anidulafungin in critically ill patients might be different from that in healthy volunteers, although dose adaptations are not required for patients in various clinical situations, such as renal or hepatic impairment and renal replacement therapy (6–8). However, for certain patient populations (i.e., hematology patients), body weight (and derived parameters) was shown to influence *V*, while a cyclosporine drug interaction was identified as a relevant covariant on CL (9, 10).

The present research focuses on the pharmacokinetics of anidulafungin and elaborates on existing and new knowledge on the behavior of this drug.

(This work was presented as a poster at the 2016 European Congress of Clinical Microbiology and Infectious Diseases.)

RESULTS

Patients. Thirty-six patients in the ICUs of three Dutch hospitals were included in the present study. Of these patients, 23 completed the first pharmacokinetic curve (day 3) and were eligible for the analysis; their baseline demographics and clinical characteristics are shown in Table 1. The median duration of anidulafungin therapy was 5 days (range, 3 to 14 days). Patients were discontinued from this study for a wide variety of reasons, including clinical success, death, transfer to another ward, switch to another antifungal therapy, an alternative diagnosis/unproven fungal infection, and removal of an arterial catheter.

A total of 8 patients completed the second pharmacokinetic curve (day 7). A total of 321 samples were drawn. The median (interquartile range [IQR]) area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) on day 3 was 72.1 (61.3 to 94.1) mg · h/liter, and the median (IQR) AUC_{0-24} on day 7 was 82.7 (73.0 to 129.5) mg · h/liter. The median (IQR) daily trough concentration (C_{24}) on day 3 was 2.2 (1.9 to 2.9) mg/liter, and that on day 7 was 2.8 (2.2 to 4.2) mg/liter. The median (IQR) maximum concentration of drug in serum (C_{max}) on day 3 was 5.3 (4.1 to 6.0) mg/liter, and that on day 7 was 5.9 (4.6 to 8.0) mg/liter. An overview of all PK parameters on both PK days is shown in Table 2. The mean plasma concentration-time curves for day 3 and day 7 are shown in Fig. 1.

The geometric mean ration (GMR) for the AUC_{day7}/AUC_{day3} term was 1.13 (90% confidence interval [CI], 1.03 to 1.25), indicating that statistically significant differences were not reached. A paired-samples *t* test for the 8 subjects that completed both curves did demonstrate that the mean AUC_{day7} was significantly higher than the mean AUC_{day3} ($P = 0.048$).

The median interindividual coefficient of variation (CV) for anidulafungin trough concentrations (C_{24}) (from day 2 to the end of therapy) amounted to 46.7% (range, 29.4 to 63.9% [$n = 22$]), and the median intraindividual CV was 14.6% (range, 0.9 to 29.6% [$n = 22$]) over the same period. Daily trough concentrations (C_{24}) are shown in Fig. S1 in the supplemental material. The anidulafungin C_{24} correlated well with AUC on day 3 ($r^2 = 0.95$) and day 7 ($r^2 = 0.97$) (Fig. S2).

Covariates. The anidulafungin PK parameters AUC_{0-24}, clearance, and volume of distribution were not influenced by covariates (gender, body weight and the related parameters body mass index [BMI] and lean body mass [LBM], APACHE II score, SOFA

TABLE 1 Baseline demographics of the participants in this study

Parameter[a]	Value for evaluable ICU patients (n = 23)
Demographic characteristics	
Gender	
Male (n [%])	16 (70)
Female (n [%])	7 (30)
Median (range) age (yr)	66 (28–88)
Elderly (≥65 years) (n [%])	14 (61)
Race	
Caucasian (n [%])	21 (91)
African (n [%])	2 (9)
Mean (range) wt (kg)	76 (50–115)
Mean (range) BMI (kg/m^2)	25 (17–33)
Clinical characteristics	
Kidney function/renal replacement therapy (n [%])	
MDRD value of >50 ml/min/1.73 m^2	13 (57)
MDRD value of 31–50 ml/min/1.73 m^2	4 (17)
MDRD value of 10–30 ml/min/1.73 m^2	6 (26)
Any form of dialysis	11 (48)
Hypoalbuminemia (n [%])	
25–34 g/liter	2 (9)
15–24 g/liter	10 (43)
<15 g/liter	11 (48)
Disease severity scores	
Mean (range) SOFA score	
Day 3 (n = 22)	8.6 (3–19)
Day 7 (n = 8)	5.9 (3–11)
APACHE II score upon admission to ICU	
Mean (range) score	25 (16–43)
Score of ≤20 (n [%])	3 (14)
Score of >20 (n [%])	19 (86)

[a]MDRD value, value obtained via the modification of diet in renal disease equation.

score, Child-Pugh score, liver function, renal function, renal replacement therapy, and serum albumin [n = 23 patients per variable]).

No drug interactions (such as with cyclosporine) were found from 7 days prior to starting anidulafungin until 3 days after stopping therapy.

DISCUSSION

We performed a study on anidulafungin in critically ill patients to define its pharmacokinetics and to investigate potential relationships with covariates. Our results confirm previous reports that exposure in ICU patients is lower than that in healthy volunteers (11, 12). Three studies, including ours, found lower exposures in ICU patients than in other reference cohorts. Our study is, to our knowledge, the largest to date. We found exposures comparable to those reported for a cohort of 20 patients receiving anidulafungin at the licensed dose of 100 mg once a day (QD) (after an appropriate loading dose; mean exposure ± standard deviation [SD] = 69.8 ± 24.1 mg · h/liter). In the latter study, the authors could not identify any relevant covariates by use of a univariate linear regression analysis (6). A study of 9 ICU patients found an even lower

TABLE 2 Anidulafungin pharmacokinetic parameters on days 3 and 7

Parameter	Median value (IQR)	
	Day 3 (n = 23)	Day 7 (n = 8)
AUC_{0-24} (mg · h/liter)	72.1 (61.3–94.0)	82.7 (73.0–129.5)
CL (liters/h)	1.39 (1.06–1.63)	1.21 (0.78–1.37)
V (liters)	46.0 (32.2–60.2)	39.7 (32.7–55.6)
C_{24} (trough concn) (mg/liter)	2.17 (1.91–2.87)	2.78 (2.23–4.23)
C_{max} (peak concn) (mg/liter)	5.27 (4.08–5.99)	5.86 (4.64–8.02)
$t_{1/2}$ (h)	23.4 (21.0–25.9)	27.2 (20.9–35.1)

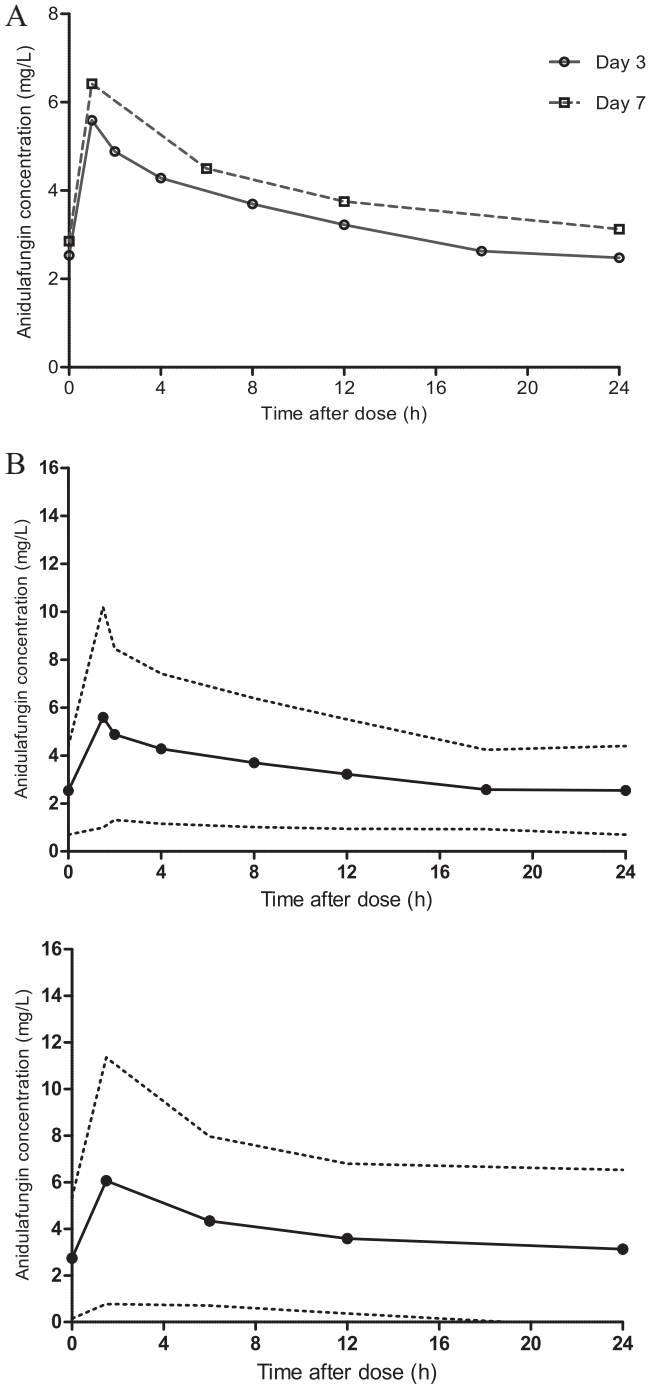

FIG 1 (A) Anidulafungin PK curves for day 3 (solid line) versus day 7 (dashed line). Data are mean concentrations per time point calculated from the individual sample results. (B) Anidulafungin concentration-time curves. Data are mean anidulafungin concentrations with 95% CI (upper and lower limits). (Top) Day 3; (bottom) day 7.

average exposure, i.e., 55 mg · h/liter, but the authors did not investigate any potential covariates (13). In contrast to these three studies, Liu et al. reported an exposure of 92.7 mg · h/liter for ICU patients (in a substudy of a prospective, multicenter, phase IIIb study of anidulafungin in ICU patients), which was nearly identical to those for healthy volunteers and a general patient population (8, 14). The cause of these differences remains to be identified. The two large independent studies were observational studies,

and there were very limited restrictions with regard to inclusion. This contrasts with the study of Liu et al., which had a more stringently selected cohort of patients.

We can hypothesize a number of reasons for the lower exposure in the cohort of ICU patients. These reasons are identical to the possible causes of lower micafungin exposure previously reported in another study from our group (15). These possible causes include (i) altered protein binding, (ii) impacts of disease severity, and (iii) a higher average body weight for this cohort than for reference populations. In the present case, both weight and disease severity did not reveal significant relationships to exposure, but the spread in weight in our cohort was likely too small for detection of a relevant difference. The degree of protein binding was not assessed (as it was technically not feasible), and therefore we cannot confirm that a larger unbound fraction is the cause of lower exposure.

The observed interpatient variability was moderate and comparable to those in previous studies (6, 8). This corroborates previous publications in which the variability in exposure was higher for ICU patients than for reference populations, such as healthy volunteers and a general patient population (as might be expected). Anidulafungin showed interpatient variability similar to those for other echinocandins (15, 16). The intrapatient variability was limited and was comparable to those for other echinocandins as well (15, 16). This limited intrapatient variability must be considered a beneficial drug property, as it confirms that the pharmacokinetic behavior is not influenced by many factors present in critically ill patients. Once treatment is adequate, it will most likely remain adequate.

From a visual inspection of the trough concentrations, it might appear that trough concentrations in the early phase of treatment are lower than those at a later stage. This was confirmed by the statistically different exposures of anidulafungin on day 3 versus day 7. This may prompt more aggressive dosing at the beginning of therapy. However, at the moment, it is unclear if this has any clinical consequences.

We did not find any statistical relationships between anidulafungin exposure and relevant covariates. In previous research from our group, we identified fat-free mass as an influence on the volume of distribution of anidulafungin in a linear fashion in hematological patients (9), in addition to body weight (10). This relationship was not confirmed in the current study of critically ill patients, nor were any other factors identified. Most likely, the sample size is too small to reveal significant relationships for a group of patients that inherently has widely varying pharmacokinetics (4).

The clinical consequences of the lower exposure in this cohort are subject to debate, as efficacy might be compromised in the setting of lower exposure (17, 18). For our population, data on susceptibility are lacking because the primary focus of this research was to investigate the pharmacokinetics of anidulafungin in a real-life cohort of patients without restrictions for entry into the study. The consequence of the focus on pharmacokinetics is that no conclusion can be drawn regarding the exposure-response relationship. Nevertheless, this finding does imply that caution against undertreatment should be taken and that attention should be given to this issue in future studies. In view of the wide variety of indications for antifungal therapy, e.g., against different pathogens and for different underlying diseases and disease severities, large groups of patients will be needed to determine whether a lower exposure is detrimental for clinical endpoints. This is relevant specifically when the offending organism is less susceptible to the drug. In the early phase of treatment, susceptibility profiles might not yet be available. A patient will be less likely to have a suboptimal clinical response if the exposure is optimized (which is obvious because we assume an exposure-response relationship). One option is for every patient to receive a higher loading dose, but this approach might be hampered by major budget impacts. Another option is to monitor exposure by means of therapeutic-drug monitoring (TDM) and to adapt the dose in individuals with lower-than-average exposures, but this is more likely to be beneficial under steady-state conditions than in the very early phase of treatment. Simultaneously, it would be worthwhile to integrate data on pathogen susceptibility once these become available to further improve therapy. The definition of solid clinical breakpoints

and the application of TDM for echinocandins must be demonstrated in a prospective clinical trial. Additional analyses such as those done by Liu et al. for anidulafungin and Martial et al. for caspofungin (7, 19, 23), with a real-life cohort of patients, should be the first step for future analyses.

MATERIALS AND METHODS

This study was a single-cohort, multiple-center, open-label, phase IV pharmacokinetic study performed over 24 months and is registered under ClinicalTrials.gov identifier NCT01438216. Three Dutch university hospital departments of intensive care medicine (Amsterdam, Utrecht, and Nijmegen) participated in this study. The study was carried out in accordance with the applicable rules of the Arnhem-Nijmegen research ethics committee and with informed consent. The study was conducted in compliance with the Declaration of Helsinki.

Study population. Patients aged 18 years and above who had a central venous catheter or arterial catheter in position, who were admitted to an intensive care unit, and who received anidulafungin for suspected or proven candidemia or invasive candidiasis were eligible for this study.

Patients were included if anidulafungin therapy was started maximally 2 days before inclusion. There were no exclusion criteria for the study. An empirical size of at least 20 evaluable patients was chosen (20).

Treatment. Anidulafungin was administered parenterally according to the specifications in the summary of product characteristics (21). All patients received a loading dose of 200 mg QD on day 1 followed by 100 mg QD maintenance therapy until the end of therapy. All infusions were given according to local protocols, at an infusion rate of 1.1 mg/min. Treatment was monitored as long as possible, with a maximum period of 14 days during which drug concentrations were measured daily and 3 days after the last dose to allow determination of terminal elimination.

Clinical parameters. Upon patient inclusion, the following parameters were registered: gender, age, weight, body mass index, lean body mass (determined according to the formula of Janmahasatian et al. [22]), ICU admission diagnosis, anidulafungin indication, and clinical characteristics. In addition, the APACHE II score (within 24 h of ICU admission), SOFA score, Child-Pugh score, and comedication were registered. During the study, weight, body mass index, lean body mass, and SOFA score were registered on days on which pharmacokinetic curves were performed.

Laboratory data. Biochemical and hematological parameters were determined on a routine basis at least three times per week and on PK days. Chemistry included the following parameters: serum electrolytes, bilirubin, alkaline phosphatase (AP), aspartate aminotransaminase (ASAT), alanine aminotransaminase (ALAT), γ-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), albumin, creatinine, uric acid, and C-reactive protein.

Pharmacokinetic sampling. Samples for a pharmacokinetic curve were drawn on day 3 ± 1 of treatment, at time zero (predose), the end of infusion (90 min), and 2, 4, 8, 12, 18, and 24 h postinfusion. Patients were eligible for analysis if this curve could be completed (i.e., at least 7 of 8 samples were available for analysis). For quantification of intraindividual variation, samples for a second pharmacokinetic curve were drawn on day 7 ± 1, at time zero (predose), the end of infusion, and 6, 12, and 24 h postinfusion. Additional trough samples were drawn daily on all other study days for up to 14 days of therapy and until 3 days after cessation of anidulafungin therapy. Blood samples were collected in lithium-heparin-containing tubes and stored immediately at 4°C. Within 48 h, samples were centrifuged for 5 min at 1,900 × *g*. Plasma was aspirated, transferred to plastic tubes, and stored at −80°C until analysis.

Analytical method. Anidulafungin concentrations were determined by a validated ultraperformance liquid chromatography (UPLC) method. Samples were pretreated with a protein precipitation solution (using acetonitrile). The dynamic range of the assay for anidulafungin was 0.008 to 8.43 mg/liter, with an accuracy range ($n = 15$), which was concentration dependent, of 94.2% to 103.5%. Intraday precision varied between 0.87% and 1.84%, and interday precision varied between 0.53% and 1.58%. The stability of anidulafungin was not affected by three freeze-thaw cycles.

Pharmacokinetic analysis and statistical analysis. Pharmacokinetic parameters (AUC_{0-24}, C_{max}, C_{24}, half-life [$t_{1/2}$], V, CL, and terminal elimination rate constant [k_e]) were calculated using noncompartmental analysis (Phoenix, version 6.3). The AUC_{0-24} was calculated using the linear up-log down trapezoidal rule. In addition, C_{max} and C_{24} were observed directly from the data. The half-life was calculated by using the term ln $2/k_e$, with k_e determined by linear regression of the terminal points of the log-linear plasma concentration-time curve. V was calculated using the formula V = dose/AUC × k_e, and CL was calculated using the term dose/AUC_{0-24}.

A paired *t* test was performed on the log-transformed pharmacokinetic parameters for days 3 and 7 in order to detect statistically significant differences over time. Geometric mean ratios (GMRs) with 90% confidence intervals (CI) falling entirely within the range of 0.80 to 1.25 were considered to indicate no significant difference in pharmacokinetic parameters.

The associations between logarithmically transformed anidulafungin AUC_{0-24} values and patient-related factors, including age, weight (plus the related parameters BMI and LBM), APACHE II score, SOFA score, liver enzymes (ALAT, ASAT, AP, bilirubin, GGT, and LDH), and other laboratory parameters (albumin and creatinine), were analyzed by use of Pearson correlation coefficients, and independent *t* tests were used to compare the logarithmically transformed anidulafungin AUC_{0-24} values and gender.

A univariate linear regression analysis was performed for patient factors that had a relationship with the log-transformed values of AUC_{0-24} based on visual inspection of scatterplots and correlation

outcomes. Next, stepwise multiple linear regression analyses between patient factors and log-transformed AUC_{0-24} values were performed for patient factors showing a significant linear regression in the univariate regression analysis. Forward inclusion was based on P values of <0.05, and backward deletion was based on P values of >0.1.

Statistical analyses were performed using SPSS, version 20.0 (SPSS Inc., Chicago, IL). P values of <0.05 were considered to be statistically significant.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01894-16.

TEXT S1, PDF file, 0.09 MB.

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V.M.-B. and R.J.M.B. designed the study. V.M.-B. conducted the study. D.W.D.L., A.R.J.G., and P.P. recruited patients for the study. V.M.-B. was responsible for data management. R.J.M.B. analyzed the data. All authors read and approved the manuscript for publication.

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