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## Pharmacokinetics of antifungal drugs in severely ill patients

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# CHAPTER 3

## Low but sufficient anidulafungin exposure in critically ill patients

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## ABSTRACT

The efficacy of anidulafungin is driven by the area under the concentration-time curve (AUC)/MIC ratio. Patients in intensive care may be at risk for underexposure. In critically ill patients with an invasive *Candida* infection, the anidulafungin exposure and a possible correlation with disease severity or plasma protein levels were explored. Concentration-time curves were therefore obtained at steady state. Anidulafungin concentrations were measured with a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The MIC values of *Candida* species were determined with the Etest. The target AUC/MIC ratio was based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) data. Twenty patients were included. The patients received a maintenance dose of 100 mg once daily after a loading dose of 200 mg on the first day. The mean ( $\pm$  standard deviation) AUC, maximum concentration of drug in plasma ( $C_{\max}$ ), and minimum concentration of drug in plasma ( $C_{\min}$ ) were  $69.8 \pm 24.1$  mg\*h/L,  $4.7 \pm 1.4$  mg/L, and  $2.2 \pm 0.8$  mg/L, respectively. The MIC values of all cultured *Candida* species were below the EUCAST MIC breakpoints. The exposure to anidulafungin in relation to the MIC that was determined appeared sufficient in all patients. The anidulafungin exposure was low in our critically ill patients. However, combined with the low MICs of the isolated *Candida* strains, the lower exposure observed in comparison to the exposure in the general patient population resulted in favorable AUC/MIC ratios, based on EUCAST data. No correlation was observed between anidulafungin exposure and disease severity or plasma proteins concentrations. In patients with less-susceptible *Candida albicans* or *glabrata* strains, we recommend considering determining the anidulafungin exposure to ensure adequate exposure.

## INTRODUCTION

Invasive candidiasis is a serious problem in intensive care unit (ICU) patients. From a retrospective matched case-control study in the United Kingdom between 2003 and 2007, the attributable mortality of candidiasis in ICU patients was estimated to be 28.3% (1).

One of the risk factors for mortality of patients with candidemia is inadequate antifungal therapy (2-4). For fluconazole, apart from delayed start of treatment (5), the area under the concentration-time curve (AUC) divided by the MIC has an impact on the mortality of patients with invasive *Candida* infections (6). Echinocandins are relative new antifungal agents that are valuable for the treatment of patients with invasive candidiasis (7). Anidulafungin compared favorably with fluconazole in critically ill patients, particularly if given as empirical therapy (8). In a neutropenic murine disseminated candidiasis model, the AUC/MIC ratio of anidulafungin was a good predictor of efficacy (9, 10).

Anidulafungin has predictable pharmacokinetics in healthy volunteers; exposure is dose dependent and there is a low inter-individual variability (11). In patients with fungal disease, anidulafungin clearance appeared to be approximately 30% higher in patients with invasive candidiasis than in patients with esophageal candidiasis. Patients with invasive candidiasis were more severely ill than the patients with esophageal candidiasis (12). For caspofungin, the trough concentrations were more variable and correlated with albumin concentrations in surgical intensive care patients (13). However, at this moment, there are limited data available on the pharmacokinetics of anidulafungin in critically ill patients (14).

The objective of this study was to determine the anidulafungin concentrations and exposure in critically ill patients and explore a possible correlation with disease severity or plasma protein levels.

## MATERIAL AND METHODS

**Patients and ethics.** This study was performed in the University Medical Center Groningen, the Netherlands, between June 2010 and November 2011. The trial was registered at ClinicalTrials.gov under registration no. NCT01047267. Patients were

eligible for inclusion if they were at least 18 years old, admitted to an intensive care unit, and diagnosed with invasive candidiasis. Diagnosis of invasive candidiasis was based on isolation of *Candida* species obtained from a sterile site. Patients were excluded if they were neutropenic or were allergic to echinocandins or any of the excipients of anidulafungin.

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The study protocol was approved by the local institutional ethics committee. Written informed consent was obtained from the patient or the legal representative of the patient.

**Study design and procedures.** Patients were treated with anidulafungin, starting with a loading dose of 200 mg on day one and continuing with a maintenance dose of 100 mg once daily.

On the first day of treatment, samples were drawn to measure anidulafungin plasma concentrations at 3 and 12 hours after start of the 3-h infusion of the loading dose. A concentration-time curve was obtained at day 3 ( $\pm$  1 day) after the start of anidulafungin. Blood samples were taken just before administering anidulafungin and at 1.5, 2, 3, 4, 6, 8, 12, and 24 h after the start of the infusion. In addition, every 3 days during treatment, blood samples for anidulafungin trough concentrations were collected during ICU admission.

For each patient included, data were collected from the medical chart, including demographic data, medical history, and laboratory parameters. Total body water volumes were estimated using the method of Watson (15).

Predictive scoring systems were used to assess the disease severity. Disease severity scores have been developed to measure disease severity and overall prognosis of patients, not to explain variability in pharmacokinetics, although they were successfully used earlier for this purpose (16-19). The scores that were calculated were the acute physiology and chronic health evaluation II (APACHE II) (20), logistic organ dysfunction system (LODS) (21), multiple organ dysfunction score (MODS) (22), organ dysfunctions and/or infection (ODIN) (23), simplified acute physiology score (SAPS II) (24), SAPS 3 (25), and sepsis-related organ failure assessment (SOFA) (26). All these different scores capture different aspects of disease severity; we

calculated all of these scores to search for an appropriate disease severity score to correlate with anidulafungin exposure. The disease severity was assessed on the day that the concentration-time curve was obtained. On the same day, albumin and total protein concentrations in plasma were measured. Mortality was assessed at day 28 of treatment.

**Anidulafungin pharmacokinetics.** Blood samples (4mL) were drawn into Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ) tubes. Plasma was separated and frozen at  $-80^{\circ}\text{C}$  until it was processed. All samples were determined with a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method that was validated according to the guidelines for bioanalytical method validation of the FDA(27). Sample preparation consisted of protein precipitation using aculeacin A as internal standard. The method is accurate (bias ranging from  $-3.0$  to  $1.9\%$ ) and precise (within-run and between-run coefficients of variation of  $2.2$  to  $7.7\%$  and  $1.6$  to  $9.0\%$ , respectively). All calibration curves were linear over a range of  $0.5$  to  $10.0$  mg/L for anidulafungin.

The AUC from 0 to 24 h ( $\text{AUC}_{0-24}$ ) was calculated using the log-linear trapezoidal rule from 0 up to 24 hours using KINFIT (MWPharm 3.60; Mediware, the Netherlands) (28). The clearance (CL) was estimated by dividing the dose administered by the  $\text{AUC}_{0-24}$ .

**Microbiology.** MIC values were determined with the Etest (bioMérieux, Marcy l'Etoile, France). Etest assays were performed using RPMI glucose agar and inoculum density adjustment with a 0.5 McFarland Standard. The plates were incubated at  $35^{\circ}\text{C}$  and were read after 24 h. If no growth was detected, the plates were incubated for another 24 h. The drug concentration shown on the Etest strip at the outer border of the elliptical inhibition halo was recorded as the MIC.

**Pharmacokinetics/pharmacodynamics.** For the assessment of sufficient exposure, the calculated anidulafungin AUC in proportion to the MIC ( $\text{AUC}_{0-24}$  for the free, unbound fraction of drug [ $f\text{AUC}_{0-24}$ ]/MIC ratio) for each patient was compared with a target value based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) data (29). Exposure for the general patient population of  $110$  mg\*h/L (11) is accepted to be sufficient to treat infections with susceptible *Candida* species (29).

A *Candida* species was considered susceptible if its MIC was not higher than the EUCAST clinical breakpoint. The free fraction of anidulafungin is assumed to be 1% (11). Therefore the target value for *Candida albicans*  $[(110 \text{ mg}^* \text{h/L} * 1\%) / 0.03 \text{ mg/L}]$  was 36.7. For *Candida glabrata*, the target value  $[(110 \text{ mg}^* \text{h/L} * 1\%) / 0.06 \text{ mg/L}]$  was 18.3.

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**Statistics.** Based on a large variation in disease severity and the consequent expectation of a large variation in pharmacokinetics, a sample size of 18 patients is needed to detect a clinically relevant correlation of 60% with 80% power and significance level of  $\alpha = 0.05$  (two-sided). We planned to recruit 20 patients to cover a dropout rate of 10%. The Mann-Whitney U test was used to assess whether the continuous data from two groups was significantly different. Correlations were determined with the Spearman correlation coefficient ( $r_s$ ) in SPSS version 20 (IBM, Armonk NY).

Multiple linear regression analysis was performed using a backward elimination strategy, keeping variables with  $P$  values of  $<0.1$  in the model. The variables that were included in the multiple linear regression analysis were gender (11), age (11), total body water (11), albumin (13), total bilirubin (30, 31), and the disease severity score with the lowest  $P$  value for the correlation.

## RESULTS

Twenty patients were included; nine were female. Most patients were admitted after abdominal surgery with complications or severe abdominal infections. An overview of patient characteristics is shown in Table 1.

At day 28 after the start of treatment with anidulafungin, five of the patients were deceased. These patients died while on treatment with anidulafungin; at 4, 6, 7, 15, and 16 days after the start of treatment. All five patients died after withholding and withdrawing of therapy because of progressive multiple organ failure and lack of treatment options for the underlying disease. All patients suffered from infections when they died, but because no autopsies were performed, it remains uncertain whether they died because of infection or with infection and whether the *Candida* infection was still present.

**TABLE 1** Patient characteristics

Characteristic	Median value (IQR <sup>a</sup> )
Age (yr)	71 (60 - 75)
Weight (kg)	81 (72 - 102)
Height (cm)	175 (165 - 181)
BMI (kg/m <sup>2</sup> )	25.8 (23.4 - 36.4)
Total body water (L)	41 (35 - 45)
Underlying condition (no. of patients)	
Abdominal surgery	12
Pancreatitis	3
Infected prosthesis	2
Stomach perforation	1
Abdominal abscess	1
Pneumococcal sepsis	1
Diagnosis (no. of patients)	
Candidemia	3
Candida peritonitis	13
Candidemia and candida peritonitis	4

<sup>a</sup> IQR, interquartile range.

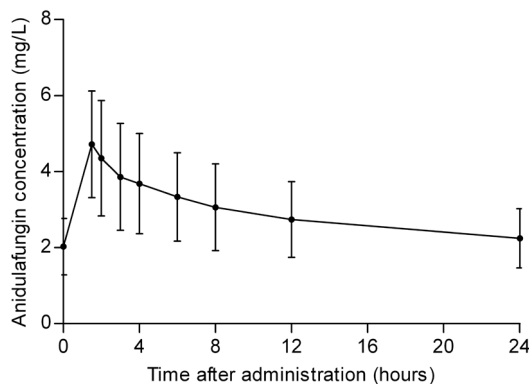
**Anidulafungin pharmacokinetics.** The mean concentration-time curve of anidulafungin with standard deviation (SD) is presented in Fig. 1. The mean ( $\pm$  SD) AUC<sub>0-24h</sub>, maximum concentration of drug in plasma ( $C_{\max}$ ), and minimum concentration of drug in plasma ( $C_{\min}$ ) were  $69.8 \pm 24.1$  mg\*h/L,  $4.7 \pm 1.4$  mg/L, and  $2.2 \pm 0.8$  mg/L, respectively. Both the anidulafungin  $C_{\max}$  and  $C_{\min}$  showed a significant correlation with the anidulafungin exposure ( $C_{\max}$ ,  $r_s = 0.854$ ,  $P < 0.001$ ;  $C_{\min}$ ,  $r_s = 0.884$ ,  $P < 0.001$ ). The mean ( $\pm$  SD) estimated clearance was  $1.6 \pm 0.6$  L/h.

The anidulafungin trough concentrations ranged from 1.0 mg/L to 4.7 mg/L during treatment.

On the first day of treatment with anidulafungin, the mean ( $\pm$  SD) anidulafungin

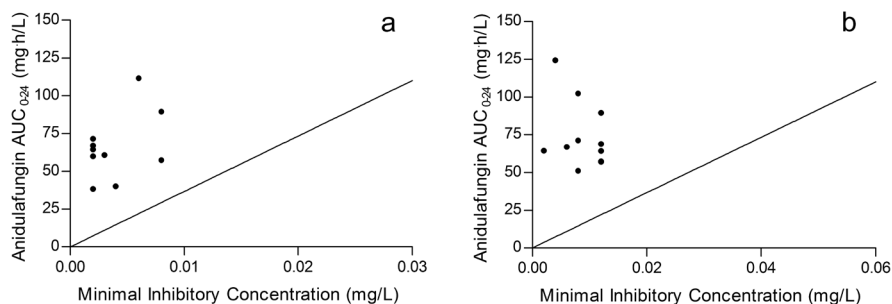


plasma concentration at the end of the infusion was  $4.9 \pm 1.4$  mg/L. Twelve hours after start of the infusion, the mean anidulafungin concentration was  $2.3 \pm 0.6$  mg/L. For logistical reasons, it was not possible to obtain samples from 4 patients on the first day of treatment.



**FIG 1** Mean anidulafungin concentration-time curve with standard deviations.

**Microbiology.** Blood cultures for *Candida* were positive in 7 patients and for 17 patients, intra-abdominal fluid cultures were positive. In 13 patients, *C. albicans* was cultured, and in 11 patients, *C. glabrata*. No other *Candida* species were recovered. The MIC values for *C. albicans* ranged from  $<0.002$  to  $0.008$  mg/L, all below the EUCAST anidulafungin MIC breakpoint of  $0.03$  mg/L. The MIC values for *C. glabrata* were also lower than the EUCAST MIC breakpoint of  $0.06$  mg/L, ranging from  $0.002$  to  $0.012$  mg/L. The distribution of the MICs can be seen in Fig. 2.



**FIG 2** AUC versus MIC of individual patients for *C. albicans* (a) and *C. glabrata* (b). The line represents the ratio of the AUC of the general patient population and the EUCAST MIC breakpoint of the *Candida* species.

**Pharmacokinetics/pharmacodynamics.** The mean ( $\pm$  SD)  $fAUC_{0-24}/MIC$  ratio was  $229 \pm 105$  for *C. albicans* and  $118 \pm 101$  for *C. glabrata* and appeared to be above the target value for all patients based on EUCAST data. Figure 2 shows the  $AUC_{0-24}$  that was determined versus the MIC of the *Candida* species isolated.

**Evaluation of possible variables of anidulafungin exposure.** Table 2 provides the median disease severity scores and data regarding a possible correlation with the anidulafungin exposure, reflected by the  $AUC_{0-24}$ . None of the disease severity scores showed a significant correlation with the anidulafungin exposure.

**TABLE 2** Disease severity scores and correlation with anidulafungin exposure.

Score	Median (IQR)	Spearman correlation	
		coefficient	P value
Apache II	14 (11-15)	0.078	0.743
LODS	4.50 (3.25-7)	0.317	0.174
MODS	4 (3-8)	0.374	0.105
ODIN	3 (2-4)	0.150	0.527
SAPS II	41 (31.5-51.5)	0.202	0.394
SAPS 3	74.50 (63.25-77.75)	-0.094	0.695
SOFA	7 (4-9)	0.153	0.520

The plasma protein concentrations were low in these patients. As expected, all 20 patients had albumin concentrations below the lower limit of normal (35 g/L). The mean albumin concentration was 19 g/L (range 14 to 31 g/L). The total protein concentration of most patients was also below the lower limit of normal (60 g/L). Total protein concentrations ranged from 29 to 62 g/L, with a mean of 46 g/L. Neither albumin nor total protein concentration showed a significant correlation with the anidulafungin exposure ( $AUC_{0-24}$ ) ( $r_s = 0.009$ ,  $P = 0.677$  and  $r_s = 0.092$ ,  $P = 0.700$ ).

No significant correlation was observed between the anidulafungin exposure and the body weight of patients ( $r_s = -0.282$ ,  $P = 0.229$ ). The correlation with total body water did not reach statistical significance ( $r_s = -0.427$ ,  $P = 0.061$ ). A possible correlation between anidulafungin exposure and total bilirubin concentrations also could not be established ( $r_s = 0.312$ ,  $P = 0.181$ ).

In the multiple linear regression analysis, total body water and bilirubin concentration showed a significant correlation with anidulafungin exposure (Table 3). The adjusted *R* square of the model is 0.345.

**TABLE 3** Multiple linear regression analysis for anidulafungin exposure

Variable	$\beta$ (95% CI) <sup>a</sup>	<i>P</i> value
Total body water	-2.566 (-4,192 to - 0.941)	0.004
Total bilirubin	0.232 (0.036 to 0.428)	0.023

<sup>a</sup> $\beta$ , regression coefficient of the population; 95% CI, 95% confidence interval.

The deceased patients did not seem to have a different anidulafungin exposure than the surviving patients; the respective median exposures were 68.9 mg\*h/L (range: 64.2 – 89.5 mg\*h/L) and 60.8 mg\*h/L (range 32.4 – 124.4 mg\*h/L).

## DISCUSSION

We found low exposure to anidulafungin in our critically ill patients. Although the exposure was low, the MICs of *Candida* species isolates were also low, and therefore, none of our patients received inadequate antifungal treatment. No correlation was observed between anidulafungin exposure and disease severity or plasma proteins concentrations in this group of critically ill patients.

An explanation for the lack of correlation could be that anidulafungin exposure is influenced slightly by several factors at the same time, making it difficult to correlate anidulafungin exposure with disease severity, plasma protein concentrations, or other contributing factors. Total body water, expected to be similar to the volume of distribution of anidulafungin (11), was also not significantly correlated to anidulafungin exposure. Based on studies with micafungin, which showed a reduced elimination clearance in the case of cholestatic hyperbilirubinemia (31) and a correlation of micafungin concentrations with total bilirubin (30), we explored a possible correlation between bilirubin concentrations and anidulafungin exposure. The expectation was that in patients with high bilirubin concentrations, the excretion of bilirubin and anidulafungin into bile would be decreased. No correlation could be established. As no correlation was observed between anidulafungin exposure and the individual contributing factors, a multiple linear regression analysis was

performed. The multiple linear regression analysis provided a significant correlation between anidulafungin exposure and total body water and bilirubin concentrations. No significant correlations were observed between anidulafungin exposure and disease severity or plasma protein concentrations.

The group of patients is on the one hand a limitation and on the other hand a strength of this study. The limitation is that our group of patients was relatively homogeneous with respect to their critical illness and plasma protein concentrations. Possibly, this could be another explanation for the lack of correlation between anidulafungin exposure and disease severity or plasma protein concentrations. The strength of this group is that these are the critically ill patients that are in need of treatment with an echinocandin.

The low anidulafungin exposure in our group of patients compared to the exposure in the general patient population was expected based on previously published data (12), as anidulafungin clearance appeared to be approximately 30% higher in the more severely ill patients with invasive candidiasis than in patients with esophageal candidiasis. The anidulafungin exposure also appeared to be significantly lower ( $P = 0.045$ , Mann-Whitney U test) than was evidenced by earlier data from other intensive care patients, i.e.  $69.8 \pm 24.1$  mg\*h/L (14) versus  $92.7 \pm 38.0$  mg\*h/L. From the data available for both groups, it appears that our patients were significantly older ( $P = 0.004$ ), heavier ( $P = 0.001$ ), taller ( $P = 0.032$ ) and had a higher total body water volume ( $P = 0.007$ ). Further analysis is required to determine other factors causing the apparent difference.

The observed lower exposure appeared to be not clinically relevant for our patients. To assess the clinical relevance of the observed lower anidulafungin exposure, the  $fAUC_{0-24}/MIC$  ratio was used because of the listed sample size and the complex pathology of critically ill patients. This could be advocated because the  $AUC/MIC$  ratio appeared to be a good predictor of anidulafungin efficacy (9, 10). We did not use the target values from these studies (9, 10) because the MICs used were measured with the CLSI method, whereas our MICs were determined with an Etest. MICs determined with an Etest are usually lower than those determined with the CLSI method (32) and were used in determining EUCAST breakpoints; therefore, we used target values based on EUCAST data. The observed lower exposure combined with

the low MICs of the *Candida* species that were isolated resulted in favorable  $fAUC_{0-24}/MIC$  ratios in our patients.

Further research is necessary on factors that contribute to the variability of anidulafungin exposure, because total body water and bilirubin only partly explain the variability in anidulafungin exposure. This is necessary in order to anticipate a lower exposure in patients before starting treatment with anidulafungin, as the MIC of the pathogen is usually not available at that moment. Besides, validation of target values for the  $fAUC_{0-24}/MIC$  ratio in clinical practice is needed. Investigation of limited sampling strategies for anidulafungin can be useful for future research and for specific clinical situations.

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No correlation could be established between anidulafungin exposure and disease severity or plasma proteins concentrations in this group of critically ill patients. In this population, we observed a lower anidulafungin exposure than in the general patient population. In patients infected with a susceptible *Candida albicans* or *glabrata* strain with a MIC well below the breakpoint, no problems are to be expected in the case of a lower exposure. However, in patients with less-susceptible *Candida albicans* or *glabrata* strains, a lower exposure can be a problem. If the MIC is high or unknown, we recommend considering determining the anidulafungin exposure to ensure the exposure is adequate.

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