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CHAPTER 4

Limited-sampling strategies for anidulafungin in critically ill patients

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ABSTRACT

Efficacy of anidulafungin is driven by the area under the concentration-time curve (AUC)/MIC ratio. Determination of the anidulafungin AUC along with MIC values can therefore be useful. Since obtaining a full concentration-time curve to determine an AUC is not always feasible or appropriate, limited sampling strategies may be useful in adequately estimating exposure. The objective of this study was to develop a model to predict the individual anidulafungin exposure in critically ill patients using limited-sampling strategies. Pharmacokinetic data were derived from 20 critically ill patients with invasive candidiasis treated with anidulafungin. These data were used to develop a two-compartment model in MW\Pharm using an iterative 2-stage Bayesian procedure. Limited sampling strategies were subsequently investigated using two methods; a Bayesian analysis and a linear regression analysis. The best possible strategies for these two methods were evaluated by a Bland-Altman analysis for correlation of the predicted and observed AUC from 0 to 24 h (AUC_{0-24}) values. Anidulafungin exposure can be adequately estimated with the concentration from a single sample drawn 12 h after the start of the infusion either by linear regression ($R^2 = 0.99$; bias, 0.05%; root mean square error [RMSE], 3%) or using a population pharmacokinetic model ($R^2 = 0.89$; bias, -0.1%; RMSE, 9%) in critically ill patients and also in less severely ill patients, as reflected by healthy volunteers. Limited sampling can be advantageous for future studies evaluating the pharmacokinetics and pharmacodynamics of anidulafungin and for therapeutic drug monitoring in selected patients.

INTRODUCTION

Echinocandins are a valuable addition for the treatment of invasive fungal infections, as they are efficacious, demonstrate low toxicity, and have limited drug-drug interactions (1).

The area under the concentration-time curve (AUC) divided by the MIC appears to be a good predictor of the efficacy of echinocandin drugs in a neutropenic murine disseminated candidiasis model (2, 3). No data are available on the influence of the AUC/MIC ratio on efficacy and mortality of anidulafungin in daily practice. More information is necessary to elucidate this relation. Determination of the anidulafungin AUC along with MIC values is therefore advisable for future research and possibly also in specific clinical situations, since anidulafungin exposure can be low in critically ill patients (4). Lack of response to the standard dose in the situation of an anidulafungin-susceptible tested isolate may prompt measurement of the anidulafungin concentration to detect whether drug exposure is too low.

Obtaining a full concentration-time curve to determine an AUC is not always feasible, since this can be a burden to the patient, is time consuming, and is relatively expensive. To overcome this problem, limited sampling strategies may be useful in adequately estimating exposure with one or only a few samples. However, no limited sampling strategy is available for anidulafungin at this moment.

The objective of this study was to develop a model to predict the individual anidulafungin exposure in critically ill patients using limited-sampling strategies.

METHODS

Study population. Pharmacokinetic data were derived from patients that participated in an open-label prospective study on the pharmacokinetics of anidulafungin in critically ill patients (4). This study was performed in the University Medical Center Groningen (The Netherlands). Patients were eligible for inclusion if they were at least 18 years old, admitted to an intensive care unit, and diagnosed with invasive candidiasis. The study protocol was approved by the local institutional ethics committee. The trial was registered at clinicaltrials.gov (NCT01047267). Written informed consent was obtained from each patient or his or her legal representative.

The 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, blood samples were drawn to measure anidulafungin plasma concentrations 3 and 12 h after the start of the 3-h infusion of the loading dose. A concentration-time curve was obtained at day 3 (± 1 day) after the start of anidulafungin. Blood samples were obtained prior to the start of the 1.5-h infusion of anidulafungin and at 1.5, 2, 3, 4, 6, 8, 12, and 24 h after the start of the infusion. In addition, blood samples for measuring anidulafungin trough concentrations were collected every three days during the continuation of anidulafungin treatment in the intensive care unit. All samples were determined with a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method that was validated according to FDA guidelines for bioanalytical method validation (5).

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Pharmacokinetics. The area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) was calculated using the log-linear trapezoidal rule from 0 up to 24 hours using KINFIT (MW\Pharm 3.80; Mediware, The Netherlands).

Potential factors that contribute to the pharmacokinetic variability of anidulafungin were previously investigated (4). A multiple linear regression analysis provided a significant correlation between anidulafungin exposure and total body water and bilirubin concentrations. MW\Pharm is straightforward software which is user-friendly but lacks the ability to include an extensive set of influencing factors in the model. The total body water was incorporated in the model by basing the model on fat-free mass (FFM), but it was unfortunately not possible to include the bilirubin concentration. A two-compartment model based on the observed anidulafungin concentrations was created using an iterative 2-stage Bayesian procedure (6), starting with estimates (Clearance [CL], 1.216 ± 0.250 L/h/56kg FFM; central volume of distribution [V_1], 0.170 ± 0.041 L/kg lean body mass corrected [LBMc]; intercompartmental clearance [Q], 21.6 ± 2.29 L/h/56kg FFM; peripheral volume of distribution [V_2], 0.392 ± 0.043 L/kg LBMc) based on those in literature (7). Interindividual variability of the pharmacokinetic parameters was assumed to be log-normally distributed. The residual error was assumed to be normally distributed and was modeled as a combination of additive and proportional error. The residual error parameters were estimated during the analysis. The initial value of both parameters was 0.1.

Limited sampling strategies. Limited sampling strategies were investigated with two methods: a Bayesian analysis and a linear regression analysis.

The optimal sampling times were determined with the limited-sampling module of MW\Pharm based on a Monte Carlo simulation of 1,000 patients randomly drawn from the population model using Bayesian analysis for parameter estimation. The performance of a strategy was considered acceptable if the prediction bias was <5% and the precision (root mean square error [RMSE]) was <15%. For the most suitable strategy, the AUC_{0-24} was predicted using the developed pharmacokinetic model.

For the other method, linear regression analyses were performed in IBM SPSS Statistics 20 (IBM Corp., Armonk, NY, USA) for the measured concentrations at every sampling time of the concentration-time curve versus the AUC_{0-24} . The performance of a strategy was considered acceptable if the prediction bias was <5% and the precision (RMSE) was <15%. The AUC_{0-24} was predicted using the equation of the regression line of the most suitable strategy.

Data analysis. The validation of the population pharmacokinetic model and the linear regression analysis was performed by a cross-validation in which one patient was left out (n-1). The AUC_{0-24} of the patient left out from the developed model was subsequently predicted using this n-1 model (8). The AUC_{0-24} predicted with the developed model was subsequently compared with the AUC_{0-24} predicted with the n-1 model using a Wilcoxon matched-pair signed-rank test. Means with 90% confidence intervals (CIs) for the ratios of AUC_{0-24} predicted with the developed model and the n-1 model were also calculated.

The best possible limited sampling strategies for these methods were evaluated by a Bland-Altman analysis for correlation of predicted and observed AUC_{0-24} and by determining the mean with 90% confidence interval for the ratio of the predicted versus the observed anidulafungin exposure as used in bioequivalence tests.

Numerical variables are summarized with medians and interquartile ranges unless stated otherwise.

External dataset. To evaluate if the best possible strategies were also applicable in

less-ill patients receiving anidulafungin, we used data from healthy volunteers from drug interaction studies (9, 10).

Possible implications for clinical practice. Since the AUC/MIC ratio is a good predictor of the efficacy (2, 3), information about the distribution of AUCs and MICs is necessary to gain more insight in clinical situations in which it can be appropriate to determine the anidulafungin exposure. Data about AUC distribution were available (4). The distribution of MICs and AUC/MIC ratio were based on EUCAST data (11). The exposure of the general patient population to 110 mg*h/L (12) is accepted to be sufficient for treating infections with susceptible *Candida* species (11). A *Candida* species was considered susceptible if its MIC was not higher than the EUCAST clinical breakpoint. Hence, the AUC/MIC target value is the exposure of the general patient population divided by the clinical breakpoint. Subsequently, the percentage of patients who achieve the AUC/MIC ratio target was calculated per MIC.

The median anidulafungin exposure of 65.7 mg*h/L in our critically ill patients (4) was lower than the exposure of the general patient population. An anidulafungin maintenance dose of 170 mg seems appropriate to achieve an AUC of 110 mg*h/L for a patient with this median anidulafungin exposure. This dose was calculated on the basis of the linear pharmacokinetics of anidulafungin (1) by dividing the AUC of the general patient population of 110 mg*h/L by the achieved AUC and then multiplying the result by the administered dose (100 mg). A simulation of this increased dose was made with the pharmacokinetic model in MW\Pharm.

RESULTS

Study population. Blood samples were obtained from 20 patients, 11 male and 9 female, with a median age of 71 (60 to 75) years and a body mass index (BMI) of 25.8 (23.4 to 36.4) kg/m². Patients received treatment with anidulafungin for 9 (7 to 15) days during their stay in the intensive care. Additional anidulafungin trough concentrations were measured in 15 patients, 2 (2 to 4) concentrations per patient, and they ranged from 1.2 mg/L to 4.7 mg/L. Figure 1 shows the obtained concentration-time curves. The measured anidulafungin maximum concentration in plasma (C_{max}) was 4.6 (3.6 to 5.7) mg/L, and the minimum concentration in plasma (C_{min}) was 2.1 (1.8 to 3.1) mg/L.

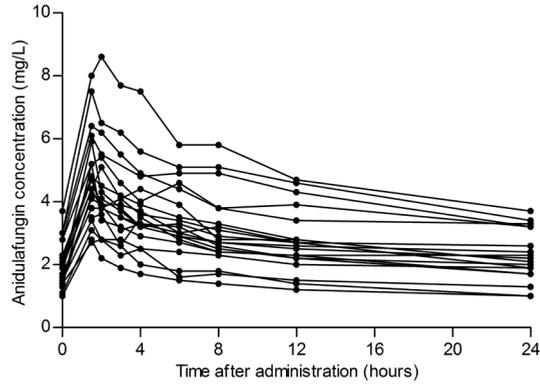


FIG 1 Concentration-time curves of the 20 critically ill patients receiving 100 mg anidulafungin once daily.

Pharmacokinetics. The observed AUC_{0-24} was 65.7 (57.3 to 85.0) mg^*h/L . The population pharmacokinetic parameters of the developed model were: CL , 1.39 ± 0.488 L/h/56kg FFM; V_1 , 0.426 ± 0.164 L/kg LBMc; Q , 7.94 ± 2.30 L/h/56kg FFM; V_2 , 0.514 ± 0.226 L/kg LBMc (each presented as population mean \pm the standard deviation). The median values of the pharmacokinetic parameters of the model and the model during cross-validation, based on all concentration-time curves, are presented in Table 1. The parameters of the cross-validation were not significantly different from the parameters of the model. The residual error parameters were 0.048 mg/L (additive error) and 0.111 (proportional error). The predicted AUC_{0-24} values during the cross-validation with the $n-1$ models were not significantly different ($P = 0.254$) from the values obtained with the developed model.

TABLE 1 AUC_{0-24} values and population pharmacokinetic model parameters from the developed model and from the $n-1$ models from the cross-validation

Parameter ^a	Model	Validation	<i>P</i> value
AUC_{0-24} (mg^*h/L)	64.0 (55.3 – 84.2)	64.0 (55.3 – 84.2)	0.254
CL (L/h/56 kg FFM)	1.26 (1.10 – 1.71)	1.26 (1.11 – 1.71)	0.062
V_1 (L/kg LBMc)	0.401 (0.338 – 0.529)	0.401 (0.335 – 0.530)	0.131
Q (L/h/56 kg FFM)	7.79 (7.32 – 8.45)	7.81 (7.48 – 8.39)	0.550
V_2 (L/kg LBMc)	0.514 (0.439 – 0.657)	0.520 (0.442 – 0.659)	0.334

^a AUC_{0-24} area under the curve over a 24-h dosing interval; CL , clearance; FFM, fat free mass; LBMc, lean body mass corrected; V_1 , central volume of distribution; Q , intercompartmental clearance; V_2 , peripheral volume of distribution.

Limited sampling strategies. Table 2 shows the results of the limited-sampling module of MW\Pharm using Bayesian analysis for parameter estimation. The anidulafungin concentration measured 12 h after the start of the infusion seemed to be the most suitable time point for predicting the AUC_{0-24} with an acceptable bias and precision. The predicted AUC_{0-24} values during the cross-validation with the $n-1$ models were not significantly different ($P = 0.422$) from the values obtained with the developed model. The mean ratio (90% CI) of the predicted exposures was 100.04% (99.67 to 100.40%).

Data from the limited-sampling strategies based on linear regression analyses are presented in Table 2. The sampling time of the most suitable strategy for predicting the AUC_{0-24} using linear regression was also 12 h after the start of the infusion with anidulafungin. The equation of the corresponding regression line, which is illustrated in Fig. 2, was $AUC_{0-24} = 3.8 + 24.1 * C(12)$. The predicted AUC_{0-24} values during the cross-validation with the $n-1$ regression were not significantly different ($P = 0.772$) from the values obtained with the complete regression. The mean ratio (90% CI) of the predicted exposures was 99.97% (99.76 to 100.19%).

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TABLE 2 Limited sampling strategies from the pharmacokinetic model in MW\Pharm and the linear regression.

Sampling times (h)	MW\Pharm			Linear regression		
	R ²	Bias (%)	RMSE (%)	R ²	Bias (%)	RMSE (%)
12	0.89	-0.1	9	0.99	0.05	3
8	0.80	0.8	12	0.97	0.7	6
24	0.79	1.3	12	0.91	0.7	10
1.5, 12	0.93	-1.2	7	0.99	0.04	3
8, 12	0.93	-0.9	7	0.99	0.1	3
1.5, 12, 24	0.97	-1.3	5	0.99	-0.02	3
1.5, 8, 12, 24	0.98	-1.5	4	0.99	0.1	2

The Bland-Altman analyses of the correlation between the observed AUC_{0-24} and the predicted AUC_{0-24} using the pharmacokinetic model and the linear regression equation are shown in Fig. 3A and 3B, respectively. The mean ratios (90% CIs) of the predicted versus the observed anidulafungin exposure was 99.03% (96.56 to

101.50%) for the pharmacokinetic model and 100.05% (98.97 to 101.12%) for the linear regression analysis.

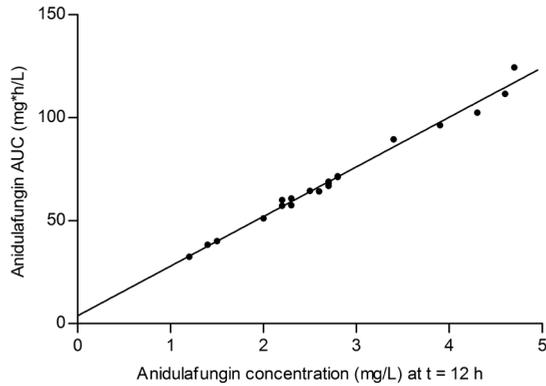


FIG 2 The observed AUC_{0-24} versus the concentration measured 12 h after the start of the infusion of anidulafungin.

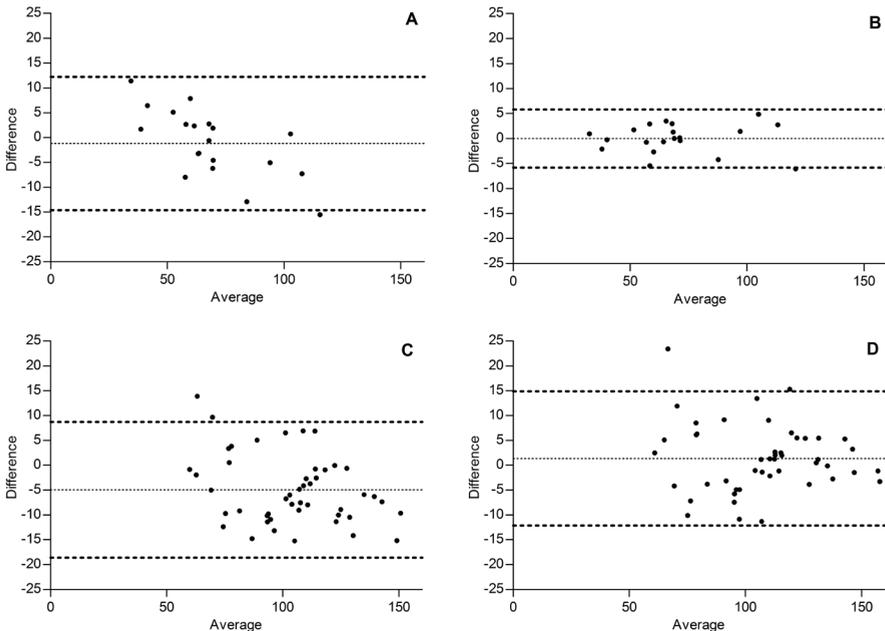


FIG 3 Bland-Altman plots of the observed anidulafungin AUC_{0-24} versus the predicted AUC_{0-24} with MW\Pharm (A) or regression analysis (B) for critically ill patients ($n = 20$) and Bland-Altman plots of the observed anidulafungin AUC_{0-24} versus the predicted AUC_{0-24} with MW\Pharm (C) or regression analysis (D) for the healthy volunteers ($n = 47$).

External dataset. Data were obtained from 47 healthy volunteers, 38 male and 9 female, with a median age of 24 (22 to 33) years and a BMI of 24.2 (21.5 to 26.2) kg/m². The observed anidulafungin AUC₀₋₂₄ was 109.8 (86.7 to 122.4) mg*h/L. The Bland-Altman analyses of the correlation between the observed AUC₀₋₂₄ and the predicted AUC₀₋₂₄ using the pharmacokinetic model and the linear regression equation are shown in Fig. 3C and 3D. The mean ratios (90% CIs) of the predicted versus the observed anidulafungin exposure were 95.39% (93.75 to 97.03%) for the pharmacokinetic model and 101.62% (99.89 to 103.35%) for the linear regression analysis.

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Possible implications for clinical practice. Figure 4 illustrates the specific clinical situations in which it can be necessary to determine the anidulafungin exposure. In most patients, anidulafungin exposure will be sufficient after receiving the standard dose (i.e., a loading dose of 200 mg on day one and continuing with a maintenance dose of 100 mg once daily). The anidulafungin AUC of approximately one-quarter of the patients infected with a *Candida* species with MICs of 0.016 mg/L for *C. albicans* and 0.03 mg/L for *C. glabrata* is expected to be insufficient. For the very few patients with *Candida* species with MICs of 0.03 mg/L for *C. albicans* and of 0.06 mg/L for *C. glabrata*, the exposure in most critically ill patients may be insufficient.

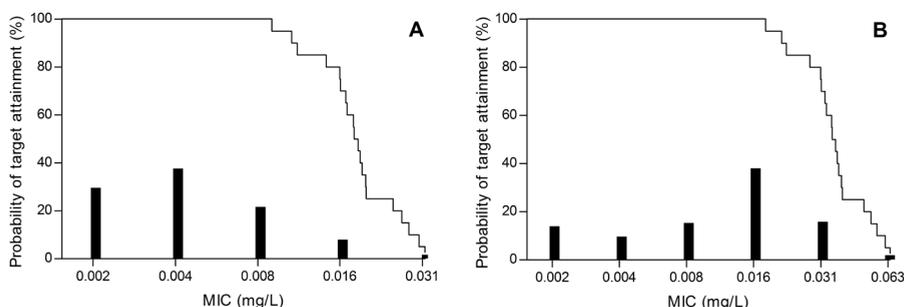


FIG 4 The probability of target attainment versus the MIC for *C. albicans* (A) and *C. glabrata* (B) for critically ill patients. The bars represent the distribution of MICs based on EUCAST data.

Figure 5 shows a pharmacokinetic simulation of the increased maintenance dose of 170 mg for a 75-year-old patient (BMI, 24.7 kg/m²) with an AUC of 64.5 mg*h/L after the standard dose of 100 mg after a loading dose of 200 mg. The predicted AUC₀₋₂₄

after 5 doses of 170 mg is 109.7 mg*h/L.

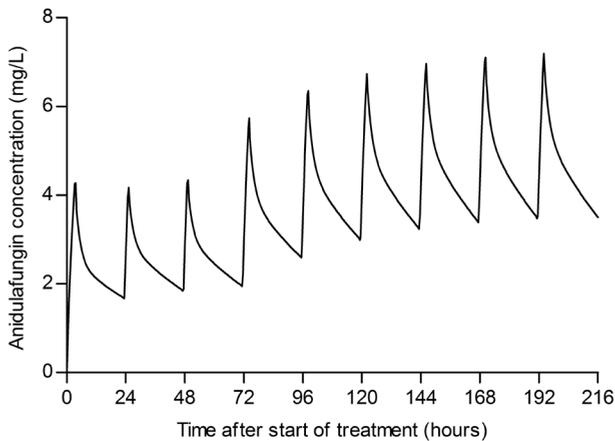


FIG 5 Simulation of an increased anidulafungin dose of 170 mg in a patient with an AUC_{0-24} of 64.5 mg·h/L after a loading dose of 200 mg on day 1 and 100 mg anidulafungin once daily on day 2 and 3.

DISCUSSION

We demonstrated here that limited-sampling strategies can be used to predict anidulafungin exposure with acceptable precision and bias. Anidulafungin exposure can be estimated with the concentration from a single sample drawn 12 h after the start of the infusion either by linear regression or using a population pharmacokinetic model.

This limited-sampling strategy can be advantageous for future research, including investigating the AUC/MIC ratio in daily practice and in specific clinical situations when the MIC is unknown or close to the clinical breakpoint since only one sample is required instead of a complete concentration time-curve. In the case of possible insufficient exposure, anidulafungin doses can be increased in a linear manner since anidulafungin exposure increases proportional to the dose (1). Simulation of a linearly increased anidulafungin dose in our pharmacokinetic model supports this. Deviating from the standard dose is not included in the summary of product characteristics, however. There has been limited experience with increased anidulafungin doses in patients with *Candida* endocarditis. A double anidulafungin dose seemed to be well

tolerated (13). A decrease of the anidulafungin dose seems currently unnecessary because adverse events are uncommon, but might be considered in the future to decrease costs when more information is available about the AUC/MIC ratio in daily practice.

We used cross-validation for our pharmacokinetic model and linear regression analysis because this is an efficient method for reliable validation and evaluation of the accuracy and precision of limited-sampling strategies without the need for additional patients (14).

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For anidulafungin it appeared feasible to develop a limited-sampling strategy based on linear regression, which has some advantages. This method is easy to use without extensive knowledge or pharmacokinetic modeling software. The time point 12 h after the start of the infusion appeared to be the optimal sampling time for accurately estimating the anidulafungin exposure based on the linear regression analysis and the Bayesian analysis in MW\Pharm. This time point is convenient for daily practice in our intensive care units since this time point coincides with the time for routine sampling in most cases.

The strength of this study is that the developed limited-sampling strategies in critically ill patients were also investigated with data from healthy volunteers. Accurately estimating the anidulafungin exposure appeared possible using linear regression and the pharmacokinetic model in critically ill patients and in healthy volunteers. The two methods have their own advantages. Linear regression analysis is simple and easy to use and does not require pharmacokinetic software. However, limited sampling based on a pharmacokinetic model is more flexible regarding sampling times, and other data that can improve the predictive performance can be incorporated.

In conclusion, this study shows that anidulafungin exposure can be estimated accurately using a single blood sample drawn 12 h after the start of the infusion by using either linear regression or a pharmacokinetic model in critically ill patients and in less-ill patients, as reflected by healthy volunteers.

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