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# Comparison of the probability of target attainment of anidulafungin against *Candida* spp. in patients with acute leukaemia☆

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ABSTRACT

This study aimed to investigate the probability of target attainment (PTA) of various anidulafungin dosing regimens against *Candida* spp. in patients with acute leukaemia. A Monte Carlo simulation was performed using a previously published population pharmacokinetic model. The following dosing scenarios were evaluated: 200 mg loading dose (LD) on Day 1 then 100 mg daily (manufacturer's recommended dosing regimen); 200 mg LD on Day 1 then 100 mg every 48 h (q48 h); and 200 mg q48 h, 200 mg every 72 h (q72 h) and 300 mg q72 h. For each dosing regimen, free drug concentrations were calculated to evaluate the effect of 99% protein binding. The PTA at various pharmacodynamic (PD) targets was determined as the percentage of subjects who achieved a free drug area under the plasma concentration–time curve over the minimum inhibitory concentration ratio ($f$AUC/MIC) or a free drug maximum plasma concentration over the minimum inhibitory concentration ratio ($fC_{max}$/MIC) above the PD targets. PTA expectation values were then calculated for each dosing regimen. The currently recommended dosing regimen of anidulafungin was not optimal for invasive candidiasis in patients with acute leukaemia. Alternate dosing strategies with higher doses and extended dosing intervals (intermittent dosing) achieved better target attainment. This is the first study to optimise therapy with anidulafungin using Monte Carlo simulation. These results provide a rationale in support of future clinical investigation of intermittent dosing of anidulafungin.



## 1. Introduction

Patients with acute leukaemia, including acute lymphoblastic leukaemia and acute myeloid leukaemia, are at high risk of developing invasive fungal infections (IFIs) [1]. In these patients, invasive candidiasis (IC) is an important cause of IFIs and is associated with considerable morbidity and mortality [1]. The azoles (e.g. voriconazole and posaconazole) and liposomal amphotericin B (L-AmB) are widely used for the management of IC in this patient population [2]. However, the use of azoles is associated with hepatotoxicity, gastrointestinal intolerance, unpredictable bioavailability, drug interactions and resistance [2,3], whilst the clinical utility of L-AmB is limited by nephrotoxicity [4] and high drug acquisition cost [5]. As the treatment of acute leukaemia involves chemotherapy agents that are predominantly metabolised by the liver [6], ideally the antifungal agents used should be those that are not hepatically metabolised and have favourable safety profiles.

The echinocandins are a new class of antifungals that act by inhibiting the synthesis of (1,3)-β-D-glucan of the fungal cell wall, ultimately causing cell death [7]. Anidulafungin (Eraxis®; Pfizer) is the latest echinocandin with fungicidal activity against *Candida* spp., including strains resistant to the azoles and L-AmB [8]. It is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of IC and candidaemia in non-neutropenic adults at a daily dose of 100 mg based on proven efficacy and safety profiles [9,10]. Unlike the azoles, anidulafungin is not metabolised by the liver [9]. As such, it is currently thought to have a very low propensity for drug interactions

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[9]. This suggests that anidulafungin might be an attractive option for the management of IFIs in patients with acute leukaemia.

Previous studies have demonstrated that anidulafungin has predictable pharmacokinetics characterised by dose-proportional exposure and low between-subject variability (BSV) [9,11]. Only one study has investigated the pharmacokinetics of anidulafungin in patients with acute leukaemia [12]. This study demonstrated that anidulafungin is well tolerated and has pharmacokinetic (PK) parameter values that are comparable with those in healthy adults and critically ill patients with IC [12]. The antifungal activity of anidulafungin against *Candida* spp. is concentration dependent and correlates with the area under the plasma concentration–time curve over the minimum inhibitory concentration ratio (AUC/MIC) and the maximum plasma concentration over the minimum inhibitory concentration ratio ($C_{max}$/MIC) [13]. This pharmacodynamic (PD) property suggests that intermittent dosing strategies with the administration of large infrequent doses (i.e. intermittent dosing) of anidulafungin will not compromise efficacy [14]. Intermittent dosing of the drug would obviate the need for long-term intravenous (i.v.) catheterisation and would minimise the risk of complications such as mechanical and bleeding complications and microbial infections [15,16]. Furthermore, intermittent dosing would result in cost savings due to reduction in the time and resources consumed with daily preparation and administration of the drug. However, intermittent dosing regimens of anidulafungin have not been evaluated, nor has the currently approved once-daily regimen.

Monte Carlo simulation is a valuable tool for evaluating, rationalising and optimising antimicrobial therapy [17]. It can be used to estimate the probability of attaining optimal PD targets, i.e. the probability of target attainment (PTA), of a dosing regimen of an antimicrobial agent against a specific organism by incorporating the variability in pharmacokinetics and MICs [17]. The present study used such an approach to investigate the PTA against *Candida* spp. with intermittent dosing regimens of anidulafungin in adult patients with acute leukaemia.

## 2. Materials and methods

### 2.1. Pharmacokinetics

A previously described two-compartment model with a zero-order i.v. infusion input and first-order elimination was implemented [12]. The PK parameters in the final model were total serum clearance (CL), volume of distribution of the central compartment ($V_1$), volume of distribution of the peripheral compartment ($V_2$) and intercompartmental clearance ($Q$). BSV was included on CL and $V_1$ using a log-normal distribution. The population PK parameter values with associated BSV are shown in Table 1.

For the above model, no covariates were identified for CL, $V_2$ and $Q$; however, lean body mass (LBM) was found to be an informative covariate on $V_1$ [12]. This covariate was included in the Monte Carlo simulation platform using the following equation:

$$V_1(\mathrm{L}) = 22 \times (\mathrm{LBM}/\mathrm{LBM}_{\mathrm{median}})$$

where LBM was calculated using the following formulae and $\mathrm{LBM}_{\mathrm{median}}$ was 40 kg [12]:

LBM = (9270 × BW)/[6680 + (216 × BMI)] for males [18]; and

LBM = (9270 × BW)/[8780 + (244 × BMI)] for females [18],

where BW is total body weight (kg) and BMI is body mass index calculated as BW/height$^2$ (kg/m$^2$).

Monte Carlo simulations were undertaken using the above covariate model with a typical patient who had a 40, 55 and 70 kg LBM. These values represent the median LBM of a patient with acute leukaemia [12], the general population [19] and an obese patient [20], respectively. The simulations were performed in Berkeley–Madonna v.8.3.18 (Macey R & Oster G, Berkeley, CA) utilising the stochastic variability coding options.

Concentration–time profiles were simulated for 10 days for the following dosing regimens: manufacturer's recommendation for IC in non-neutropenic subjects [200 mg loading dose (LD) on Day 1 followed by 100 mg daily] [9]; 200 mg LD on Day 1 followed by 100 mg every 48 h (q48 h); and 200 mg q48 h, 200 mg every 72 h (q72 h) and 300 mg q72 h.

An infusion rate of 2 mg/min was used for all dosing regimens as has been used previously with no increased toxicity [12]. To calculate free drug ($f$) concentrations, a protein binding value of 99% was used in all simulations [9]. For each individual, the concentration–time profile provided the following metrics: $f$AUC and $fC_{max}$ following the first dose and at steady state.

### 2.2. Pharmacodynamic targets for Candida species

The PD targets were derived from Andes et al. [13]. In this study, the PD indices evaluated were $f$AUC/MIC and $fC_{max}$/MIC ratios for *Candida* spp., *Candida albicans* and *Candida glabrata* [13]. MICs were determined using both complete and partial inhibition endpoints. For complete inhibition, the MIC endpoint was defined as the lowest concentration of anidulafungin that resulted in no visual growth, whilst for partial inhibition the MIC endpoint was defined as the lowest concentration of anidulafungin that caused a significant (≥50%) reduction in turbidity compared with the controls [13]. The mean PD targets for the complete inhibition MICs for *Candida* spp. were 13 and 0.7 for $f$AUC/MIC and $fC_{max}$/MIC, respectively [13]. The mean (range) $f$AUC/MIC targets for *C. albicans* and *C. glabrata* were 16 (3.2–41.3) and 11 (6–23.8), respectively [13]. The mean (range) $fC_{max}$/MIC targets for the two species were 1 (0.14–2.55) and 0.6 (0.24–1.29), respectively [13]. The mean PD targets for the partial inhibition MICs for *Candida* spp. were 39 for $f$AUC/MIC and 2 for $fC_{max}$/MIC [13]. The mean (range) targets for *C. albicans* were 58 (12.5–165) for $f$AUC/MIC and 3 (0.56–10.2) for $fC_{max}$/MIC [13]. The corresponding values for *C. glabrata* were 27 (10.6–47.7) and 1.4 (0.48–2.58) [13]. For comparative purposes, the $f$AUC/MIC targets reported in another study by Andes et al. for *C. albicans* ($f$AUC/MIC ≥ 91), *C. glabrata* ($f$AUC/MIC ≥ 32) and *Candida parapsilosis* ($f$AUC/MIC ≥ 22) were also considered [21].

### 2.3. Minimum inhibitory concentration distributions for Candida species

The MIC data for *Candida* spp. were obtained from Pfaller et al. [22]. In summary, the study included 17,817 clinical isolates obtained from 15 medical centres worldwide [22]. Table 2 displays the percentage of isolates that are susceptible at each MIC. The susceptibility rates of *Candida* spp. were used as a measure of the MIC distribution for the PTA analysis.

**Table 1**
Population pharmacokinetic (PK) parameter values of anidulafungin in haematological patients [12].

| PK parameter | Value | BSV (%CV) |
|---|---|---|
| CL (L/h) | 1.12 | 26% |
| $V_1$ (L) | 22 × (LBM/$\mathrm{LBM}_{\mathrm{median}}$) | 10% |
| Q (L/h) | 0.953 | |
| $V_2$ (L) | 23.4 | |

BSV, between-subject variability [expressed as percent coefficient of variation (%CV)]; CL, total serum clearance; $V_1$, volume of distribution of the central compartment; LBM, lean body mass ($\mathrm{LBM}_{\mathrm{median}}$ was 40 kg); $Q$, intercompartmental clearance; $V_2$, volume of distribution of the peripheral compartment.