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Assessment of echinocandin regimens by pharmacokinetic/pharmacodynamic analysis against *Candida* spp. in paediatric patients

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ABSTRACT

This study aimed to investigate the cumulative fraction of response of various echinocandin (caspofungin, micafungin and anidulafungin) dosing regimens against *Candida* spp. in paediatric patients with invasive fungal infections (IFIs). Monte Carlo simulations were performed using previously published pharmacokinetic parameters and pharmacodynamic data to evaluate the ability of each echinocandin regimen in terms of *f*AUC/MIC (free drug area under the concentration–time curve/minimum inhibition concentration ratio) targets of caspofungin, micafungin and anidulafungin. Pharmacodynamic targets were attained in paediatric patients by both caspofungin regimens as well as by a high micafungin dosing regimens against *Candida albicans* and *Candida glabrata*. However, the results for anidulafungin suggested that the dosing regimens recommended were not optimal for paediatric patients. In addition, the predicted efficacy of all of the echinocandins against *Candida parapsilosis* was low. This is the first study to assess caspofungin, micafungin and anidulafungin therapy using Monte Carlo simulation. These results rationalise and optimise the dosage regimens of caspofungin, micafungin and anidulafungin against *C. albicans*, *C. glabrata* and *C. parapsilosis* for paediatric patients with IFIs.

1. Introduction

Invasive fungal infections (IFIs) remain life-threatening in premature infants/toddlers and immunocompromised children. These diseases cause considerable mortality and morbidity in paediatric patients [1,2]. *Candida* and *Aspergillus* spp. are the fungi most frequently responsible for IFIs [3]. However, many antifungal agents (such as the azoles and liposomal amphotericin B) have a number of important limitations in their spectrum of activity, pharmacokinetics, risk for pharmacokinetic drug interactions, and unusual toxicities associated with long-term use [4]. The echinocandins (including caspofungin, micafungin and anidulafungin), which were discovered in the 20th century, are the final milestone of antifungal agent discovery. Members of this class of antifungal agents act by inhibiting the synthesis of β-(1,3)-D-glucan, an essential component of the cell wall of many pathogenic fungi, including *Candida* and *Aspergillus* spp. [4]. The echinocandins are associated with few adverse effects and drug interactions, making them safe to administer [5].

However, dosage regimens of echinocandins in paediatric patients cannot be extrapolated from adult data because of the different IFI pathophysiology, immune response and drug disposition compared with adults. Especially in young infants, maturation of renal and metabolic function occurs rapidly and can significantly influence drug exposure [2]. Thus, despite better evidence on antifungal therapy, dosing adjustment is necessary for echinocandins in paediatric patients to maximise favourable outcomes for treating IFIs.

Therefore, a pharmacokinetic/pharmacodynamic (PK/PD) analysis should be used to assess for various echinocandin regimens in paediatric patients with IFIs. In the present study, Monte Carlo simulations were used to calculate the probability of target attainment (PTA) and the cumulative fraction of response (CFR) against three most commonly encountered *Candida* spp., namely *Candida albicans*, *Candida glabrata* and *Candida parapsilosis*, in order to rationalise and optimise the commonly used echinocandin regimens.

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2. Materials and methods

2.1. Pharmacokinetics

Three previously described multicentre, open-label studies conducted with paediatric patients were employed. In the study of caspofungin, all paediatric patients received caspofungin at 50 mg/m^2 daily, with a daily maximum dose of 70 mg [6]. Patients in each age group receiving micafungin and anidulafungin were designed using sequential-group escalating dose [7,8]. All of the echinocandins were administered intravenously once daily as a 1-h infusion. The pharmacokinetic profiles for these agents were computed from the drug concentration–time data using non-compartmental methods. The population pharmacokinetic parameter values for each echinocandin determined following the first dose and at steady-state for each paediatric patient were gathered and are presented in Tables 1–3.

Using the population pharmacokinetic model, Monte Carlo simulations were undertaken to estimate the PTAs for various dosing regimens of each echinocandin (all of the dosing regimens are also displayed in Tables 1–3). The following process was repeated from the first to the 10 000th subject performed using commercially available risk analysis software (Crystal Ball 2000 v.2.2; Decisioneering Corp.; http://www.crystalball.com).

For evaluation of free (*f*) drug levels, the area under the concentration–time curve from time zero to the end of 24-h dosing interval ($AUC_{0–24}$) was multiplied by 0.03 for caspofungin, 0.0025 for micafungin and 0.01 for anidulafungin in all simulations, respectively [9], which are the approximate free fractions of the antibiotics. For each individual, the concentration–time profile provided the following metrics: *f*AUC following the first dose and at steady-state.

2.2. Minimum inhibition concentration (MIC) distributions of Candida *spp.*

The MIC data for *Candida* spp. were obtained from Pfaller et al. [10]. Caspofungin, micafungin and anidulafungin were assessed against a recent (2011) global collection of 1358 isolates of *Candida* spp. using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods in previous study. The frequency of MIC distributions of the three echinocandins against *C. albicans*, *C. glabrata* and *C. parapsilosis* were gathered and were used for each simulation to calculate the CFR.

2.3. Pharmacodynamic targets for Candida *spp.*

Previous pharmacodynamic studies were employed that used in vivo candidiasis models to determine the 24-h AUC/MIC targets for a stasis endpoint to identify a free-drug 24-h AUC/MIC of echinocandins against *C. albicans*, *C. glabrata* and *C. parapsilosis*. The 24-h *f*AUC/MIC associated with the stasis endpoint for the echinocandin group against *C. albicans* was 20.6 ± 32 (mean ± S.D.). Similar values for *C. glabrata* and *C. parapsilosis* were 7.0 ± 8.3 and 7.6 ± 7.1, respectively [9]. The pharmacodynamic target indexes of *f*AUC/MIC for caspofungin, micafungin and anidulafungin are displayed in Table 4.

2.4. Monte Carlo simulation

Echinocandin activities against *Candida* spp. are concentration-dependent and correlate with the AUC/MIC and the maximum plasma concentration over the MIC ratio (C_{max}/MIC). For *Candida* spp., the free-drug 24-h AUC/MIC (*f*AUC/MIC) at the specific value of two-fold diluted MIC was calculated.

Table 1
Caspofungin pharmacokinetics in paediatric patients receiving 50 mg/m^2 once daily and adults receiving 50 mg or 70 mg once daily.

Parameter	Infants/toddlers (age 3–24 months)		Children (age 2–11 years)		Adolescents (age 12–17 years)		Adults (50 mg daily)		Adults (70 mg daily)	
	n [a]	LSM (95% CI) [b]	*n*	LSM (95% CI)	*n*	LSM (95% CI)	*n*	LSM (95% CI)	*n*	LSM (95% CI)
Day 1										
$AUC_{0–24}$ (μg h/mL)	7	120.2 (88.39–163.45)	9	96.40 (73.51–126.42)	7	77.58 (57.05–105.50)	32	70.60 (65.06–76.61)	29	97.13 (89.14–105.84)
Day 4 or 3–14 time-averaged[c]										
$AUC_{0–24}$ (μg h/mL)	8	130.29 (105.26–161.26)	9	115.23 (94.24–140.89)	8	117.19 (94.68–145.04)	38	103.38 (94.63–112.93)	35	153.65 (140.13–168.47)

LSM, least-squares mean; CI, confidence interval; $AUC_{0–24}$, area under the concentration–time curve from time zero to the end of 24-h dosing interval.
[a] Number of patients included in the analysis.
[b] LSM for $AUC_{0–24}$.
[c] Time-averaged parameters were determined as the geometric mean of all values obtained between Days 3 and 14.