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Alternate-Day Micafungin Antifungal Prophylaxis in Pediatric Patients Undergoing Hematopoietic Stem Cell Transplantation: A Pharmacokinetic Study

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Disseminated fungal infection is a major cause of morbidity and mortality in children undergoing hematopoietic stem cell transplantation (HSCT). Prophylaxis with amphotericin B can be limited by renal toxicity. Oral triazoles can be limited by poor absorption, large interindividual pharmacokinetic (PK) variability, and hepatic toxicity, leading to interruptions in therapy and breakthrough infections. Intravenous (i.v.) micafungin has potential advantages, because of its better safety profile, specifically in terms of hepatic and renal toxicity, and lack of drug-drug interactions with common medications used in the HSCT setting. We hypothesized that higher dose micafungin (3 mg/kg) every other day will provide drug exposure similar to standard dosing (1 mg/kg) given daily, and improve patient compliance in very young children in whom oral medications can be challenging, at reduced administration costs. Both animal and adult patient data support the use of this approach. Fifteen children (M/F = 11/4, aged ≤10 years; mean: 3.9 years, range: 0.6-10 years) with various hematologic, metabolic, and immune deficiency disorders undergoing HSCT received a single dose of micafungin (3 mg/kg) i.v. over 1 hour. Dose selection was based on published PK data in pediatric patients, and exploration of different dosing regimens using Monte Carlo PK/PD simulation. Blood samples were drawn around this dose and PK analysis was conducted using standard noncompartmental methods. Micafungin at 3 mg/kg dose was well tolerated in all patients. Measurable plasma concentrations were present in all cases at 48 hours. Half-life and clearance observed were comparable to previous pediatric PK data, with clearance being higher than adults as expected. Volume of distribution was higher in our patients compared to published pediatric data, likely because of a larger proportion of very young children in our study cohort. After correction for protein binding, concentrations at the end of the dosing interval during maintenance treatment remain above the minimum inhibitory concentration (MIC) of highly susceptible fungal pathogens. These data suggest that alternate day micafungin dosing, as described here, may provide an attractive alternative for antifungal prophylaxis in HSCT patients and merits further evaluation.

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INTRODUCTION

Disseminated fungal infection causes significant morbidity and mortality in immunocompromised children. Children with leukemias (eg, acute myelogenous leukemia [AML], relapsed acute lymphoblastic leukemia [ALL]), bone marrow failure syndromes, or immune deficiencies, and those undergoing allogeneic hematopoietic stem cell transplantation (HSCT) are at highest risk [1-3]. Graft-versus-host disease (GVHD) after allogeneic HSCT requires further immunosuppression, and in turn, increases the risk of invasive fungal infections. The leading causes of opportunistic fungal infections in these patients are *Candida* and *Aspergillus* species [1,4].

The life-threatening nature of invasive fungal infections warrants prophylaxis. A number of options are available for prophylaxis, but none have been found to be ideal. Oral triazoles are limited by poor absorption of some products, interindividual variation in metabolism, and hepatic toxicity, leading to reports

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of breakthrough infections [5]. Prophylaxis with amphotericin B has been shown to reduce the frequency of invasive fungal infections in some populations [6]. but widespread and long-term use is limited because of associated infusional toxicity and long-term nephrotoxic side effects [7].

An alternative approach to prophylaxis is the use of every other day intravenous (i.v.) micafungin. Micafungin is an i.v. antifungal compound of the echinocandin class. Micafungin acts by inhibiting the production of 1,3-β-D-glucan, a key component in fungal cell wall synthesis [8]. A semisynthetic lipopeptide, micafungin possesses in vitro and in vivo activity against a broad spectrum of *Candida* and *Aspergillus* species, including activity against azole-resistant *Candida* [9-13]. The safety and plasma pharmacokinetics (PK) of micafungin have been well studied in animal models [12,14] and in adult patients [15]. Although micafungin has the most pediatric data of the 3 echinocandins, data are still limited about the properties of this echinocandin in pediatric patients. This is in large part because of the fact that most of the pediatric studies have been performed in neonates and very low birth weight babies [15-18].

There are a number of potential advantages in the use of alternate day micafungin for fungal prophylaxis. This strategy is simple and convenient for patients, with little infusional toxicity and compliance is assured in young children in whom frequent oral medication can be a challenge. Alternate day dosing is less burdensome than the customary daily i.v. dosing for home therapy if prolonged prophylaxis after initial hospitalization is required. Micafungin has a more favorable safety profile compared with azoles and amphotericin B with low frequencies of hepatic and renal toxicity [19]. In addition, micafungin does not have drug interactions with tacrolimus, prednisone, cyclosporine, or mycophenolate mofetil, some of the common medications used in the HSCT setting [20].

Currently, children who receive micafungin are given daily dosing. To investigate the potential of alternate day prophylactic administration, we performed a PK study of micafungin (higher dose, 3 mg/kg every other day instead of standard dose, 1 mg/kg given daily) in young children undergoing HSCT.

METHODS

This study is a prospective opened-label single center observational clinical trial to establish the PK of alternate day micafungin therapy in young children. Patients receiving HSCT in whom antifungal prophylaxis was clinically indicated were eligible for the study. A total of 15 children with various hematologic disorders, metabolic disorders, and immune deficiency syndromes undergoing HSCT were enrolled (Table 1). The study included only children aged ≤10 years, because the goal of our study was to evaluate the pharmacokinetics of micafungin in young children, especially as in prior pediatric studies, the rate of clearance of micafungin increases at the ages of 8 years and under. The median age was 3.9 years (range: 0.6-10 years), and the male-to-female ratio was 11:4. None of the patients had a history of previous fungal infection.

Table 1. Patient Demographics

Patient No.	Age (Years)	Gender	Weight (kg)	Diagnosis
1	0.6	M	8.45	WAS
2	0.7	M	7.7	Marrow failure
3	1.6	M	10.4	WAS
4	2.0	M	12.7	WAS
5	2.4	M	14.9	WAS
6	2.5	M	13.8	NBL
7	2.6	M	10.5	FA
8	3.4	F	16.2	JMML
9	3.7	M	16.5	AML
10	4.0	M	15.9	WAS
11	4.8	F	26.5	FA
12	4.9	M	21	AA
13	6.3	F	18	FA
14	8.9	M	30.3	Ewing's sarcoma
15	10.4	F	32.1	FA

JMML indicates juvenile myelomomocytic leukemia; FA, Fanconi anemia; AML, acute myelogenous leukemia; NBL, neuroblastoma; WAS, Wiskott-Aldrich syndrome.

The study design was approved by the Cincinnati Children's Hospital Medical Center's institutional review board (IRB), and consent was obtained from each child's parents before the child was enrolled in the study. A separate Investigational New Drug (IND) was also obtained from the Food and Drug Administration (FDA).

Micafungin (Micamine®) (Astellas Pharma US, Inc., Deerfield, IL, USA) is a sterile, lyophilized product for i.v. infusion that contains micafungin sodium. The drug was reconstituted according to the manufacturer's instructions to give approximately 10 mg micafungin/mL solution. For infusion, this was added to 100 mL of 0.9% sodium chloride, and the final concentration for infusion was kept between 0.5 and 1.5 mg/mL. The diluted solution was protected from light. All patients received a single dose of micafungin (3 mg/kg) i.v. over 1 hour. Dose selection was based on published PK data in pediatric patients [17], and exploration of different dosing regimens using Monte Carlo PK/PD simulation (SimLab, Monte Carlo analysis tool, Medimatics, Maastricht, The Netherlands). Based on our simulation results, it was estimated that a 3 mg/kg dose administered every 48 hours will likely result in a similar micafungin trough concentration as the currently used 1 mg/kg every 24 hours.

PK Sampling

Serial blood samples were drawn around the single dose of micafungin. Venous blood samples (2.0 mL)

were obtained from an indwelling catheter immediately before the micafungin infusion (ie, time = 0) and then at 1 hour (ie, at the end of the infusion), 1.5, 2, 4, 6, 8, 10, 24, 36, and 48 hours after the start of the micafungin infusion. In accordance with standard practice, all specimens were drawn from the lumen where the micafungin was not infused.

Micafungin Assay

The concentration of micafungin in plasma was determined by a modified validated high-performance liquid chromatography (HPLC) assay [17] in the Fungus Testing Laboratory, Antifungal Levels Lab, Department of Pathology, University of Texas Health Science Center, San Antonio, Texas. The lower limit of detection for this assay was 0.05 μg/mL. The intraday coefficients of variation (CV) ranged from 1.28% to 9.87%. Interday CV for controls 0.5, 7.5, and 18.75 μg/m$ were 8.10%, 5.44%, and 5.58%, respectively.

PK Analysis

PK analyses of data were conducted using standard noncompartmental methods (WinNonlin Professional version 5.2.1; Pharsight, Mountain View, CA, USA). Individual plasma trough concentrations were determined using the 48-hour plasma concentration data. The apparent terminal elimination rate constant (λz) for micafungin was estimated for each subject by nonlinear regression analysis. The area under the plasma concentration-time curve ($AUC_{0-\tau}$; AUC_{0-INF}) was determined using the log linear trapezoidal method. Total body clearance (CL), volume of distribution at steady state (V_{ss}), and terminal half-life ($T^1/_2$) were calculated using standard equations.

Statistical Analysis

Data are presented as mean ± standard deviation (SD). A P value < .05 was considered significant. Associations between pharmacokinetic measures and patient data (eg, age, height [Ht], body weight [Wt], body surface area [BSA], body mass index) were evaluated using Spearman's correlation coefficient at the 0.05 significance level. Statistical analyses were performed using SPSS version 11.5 for Windows (SPSS, Chicago, IL, USA).

RESULTS

All 15 patients completed the PK study. Micafungin at a 3 mg/kg dose was well tolerated in all patients. The Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was used to evaluate adverse events. One patient developed nonspecific abdominal pain on day 1 that resolved without therapy (grade 1). Two patients had mild hypocalcemia, and 1 patient developed mild hypocalcemia, hypokalemia, and had low albumin (all grade 1). The mean serum creatinine level was similar to the pretreatment level when measured at 48 hours. Mean liver function tests at the end of study were similar to the starting levels, except in 2 patients, who had modestly elevated alanine aminoaspartate (from 36 to 93, and 39 to 114) and alanine aminotransferase levels (from 18 to 49, and 9 to 71), and 1 of these also developed elevated GGT (all grade 1). Additionally, 1 patient each had increase in alanine aminoaspartate, alanine aminotransferase, and GGT level (grade 1 again).

The mean concentration-time profiles of micafungin in plasma after single dose are shown in Figure 1. Peak concentrations observed at the end of the micafungin infusion ranged from 8.3 to 18.7 mg/L. The elimination half-life ranged from 9.5 to 16.8 hours, comparable to previous pediatric PK data [17]. PK parameter estimates after a single dose (3 mg/kg) of micafungin for all 15 patients are summarized in Table 2. Measurable plasma concentrations were present in all cases at 48 hours (Figure 1 and Table 2).

Clearance was comparable to previous pediatric PK data [17], but was higher than adults, as expected. Volume of distribution was higher in our patients compared to published pediatric data, likely because of a larger proportion of very young children in our study cohort (<2 years, n = 3; 2-5 years, n = 9; 5-10 years, n = 3), and correlated well with body weight (R^2 = 0.76). Body weight explained 30% of the variability observed in the estimates for micafungin clearance (R^2 = 0.30).

DISCUSSION

In this study we evaluated the PK of 3 mg/kg micafungin for 48 hours after a single dose given to young children (age ≤10 years). Our interest in alternate day administration of micafungin came from a couple of sources. Administering long-term oral antifungal

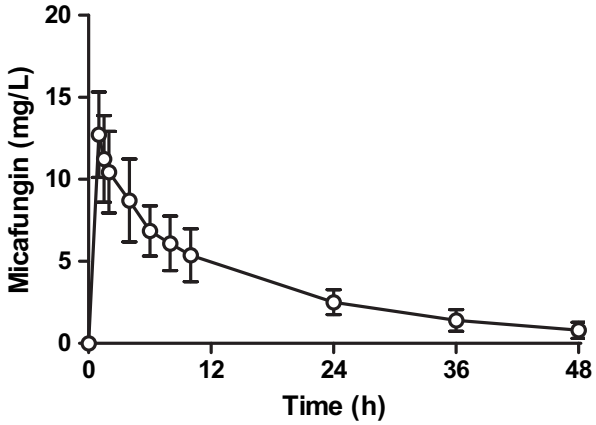

Figure 1. Mean concentration-time profiles of micafungin (3 mg/kg dose) in pediatric HSCT patients (mean data points ± SD).

Table 2. Mean (SD) Pharmacokinetic Parameter Estimates after Single-Dose Micafungin in 15 Patients

Parameters (Unit)	Mean	SD	Range
C_{max} (mg/L)	12.5	2.7	8.3-18.7
C_{min} (mg/L at 48 hours)	0.8	0.5	0.3-2.0
AUC_{0-24} (h*mg/L)	128.5	35.9	79.3-229.2
AUC_{0-48} (h*mg/L)	164.4	50.7	97.5-305.2
AUC_{0-INF} (h*mg/L)	180.8	62.2	104.2-352.9
CL (mL/h/kg)	17.7	5.8	7.9-29.6
$T^1/_2$ (h)	13.0	2.1	9.5-16.8
V_{ss} (L/kg)	0.3	0.1	0.2-0.5

C_{max} indicates peak plasma concentration; C_{min}, trough plasma concentration; AUC_{0-24}, $_{0-48}$ and $_{0-INF}$, area under the plasma concentration-time curve extrapolated from 0 to 24 hours, 0 to 48 hours, or or 0 to infinity; $T^1/_2$, elimination half-life; CL, total body clearance; V_{ss}, volume of distribution at steady state.

prophylaxis (eg, azoles) to small children can be both challenging and unreliable. In addition, hepatic toxicity is common, and may require dose interruption, for example, in a recent meta-analysis of tolerability and hepatotoxicity of different antifungals, 19.7% voriconazole users and 17.4% of itraconazole users had elevated serum liver enzyme levels in comparision to 9% for fluconazole and 3% for Micafungin users [21]. Long-term therapy with amphotericin B is associated with renal toxicity. In the setting of pediatric HSCT, it is not uncommon to have patients with both hepatic and renal insufficiency, making echinocandins a particularly appropriate option for prophylaxis. Currently, echinocandins require daily i.v. administration. The second impetus for the study was that both animal [22] and adult human data [23] have suggested that alternate day dosing schedule may be effective, and support the use of this schedule.

Our data show measurable plasma levels at 48 hours after a single 3 mg/kg dose of micafungin. It is clearly important to consider whether the levels achieved are likely to have meaningful antifungal activity. Previous in vitro time-kill studies with micafungin have demonstrated fungicidal activity for most *Candida* strains. A postantifungal effect has also been shown, and may be enhanced with higher drug concentrations [24]. In addition, serum drug concentrations are used in general as a relatively good surrogate of tissue concentrations. In 1 study of 2000 *Candida* bloodstream isolates, most species (*C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. dubliniensis*) exhibited minimum inhibitory concentrations (MICs) of 0.03 to 0.06 μg/mL. The MICs for *C. krusei* and *C. lustitaniae* were slightly higher (0.6-2.0 μg/mL), with *C. parapsilosis* having the highest MIC (1-2 μg/mL) [25]. The Clinical and Laboratory Standards Institute (CLSI) has recently established susceptibility breakpoints for echinocandins against *Candida* spp. A MIC ≤2 μg/mL for all 3 echinocandin agents is classified as susceptible, and a value ≥2 μg/mL is considered nonsusceptible [26]. Micafungin also has potent in vitro activity against *Aspergillus* spp., including *A. fumigatus*, *A. flavus*, *A. niger*, *A. versicolor*, *A terreus*, and *A. nidulans*. MIC ranges of 0.0078-0.0156 μg/mL have been reported against these *Aspergillus* spp.; however, standard susceptibility breakpoints for the echinocandins against molds have not been established. The minimum effective concentration (MEC), which is the minimum concentration noted to produce short and aberrant hyphal branching under the microscope, has been proposed as an alternative measure, and has been reported as ≤0.125 μg/mL for several *Aspergillus* spp., including *A. fumigatus*, *A. flavus*, and *A. niger* [27]. These results were confirmed in a recent study from Japan, which evaluated in vitro antifungal activity of micafungin compared to caspofungin, fluconazole, itraconazole, voriconazole, and amphotericin B. Ninety-three *Candida* and 23 *Aspergillus* isolates recovered from pediatric patients with fungal infections were evaluated. Micafungin showed potent activity against *Candida* albicans, *Candida* tropicalis, and *Candida* glabrata, with an MIC range of ≤0.002 to 0.015 μg/mL. In contrast, micafungin demonstrated higher MIC levels against *Candida* parapsilosis with an MIC range of 0.12 to 2 μg/mL. Micafungin showed potent antifungal activity against *Aspergillus* species tested with an MIC range of 0.004 to 0.015 μg/mL [28].

The mean concentration of micafungin at 48 hours (the end of interval in this study) was 0.8 μg/mL (range: 0.3-2.0 μg/mL), which appears favorable considering the MIC distributions of most common strains (*Candida* , ≤0.06 μg/mL; *Aspergillus*, ≤ 0.016 μg/mL). However, after correction for the high protein binding (99%), free micafungin concentrations at the end of the dosing interval only exceeds the MIC of highly susceptible fungal pathogens. The implications of this observation and the potential contribution of postantifungal effects (ie, ongoing antifungal activity at concentrations below the MIC) will be explored in a future Monte Carlo Simulation PK/PD study using epidemiologic fungal MIC distribution data for common fungal pathogens, with the goal of finding the regimen that would provide adequate coverage based on the pharmacodynamic index parameters (eg, AUC/MIC ratio) [29]. Gumbo et al. [22] have demonstrated prolonged antifungal effects of micafungin in neutropenic mice with disseminated *C. glabrata.* This animal study showed that micafungin has a true in vivo postantifungal effect, which for doses of 3 mg/kg in mice (serum AUC_{0-INF} = 64 mg*h/L) lasted for around 5 days after decline of tissue concentrations below the *C. glabrata* MIC. Moreover, when the whole 10-day cumulative dose (30 mg/kg) was administered, micafungin's effect lasted for up to 7 days.

Our data, suggesting that alternate day dosing is an effective strategy are in agreement with a study in adults, published in abstract form in 2005. A multicenter, multinational, double blind, noninferiority trial of adult patients with esophageal candidiasis, evaluated

every other day dosing of micafungin (300 mg every other day) versus daily micafungin (150 mg) versus daily dosing of caspofungin. This study concluded that every other day dosing of micafungin was a safe and effective alternative to daily dosing of micafungin or caspofungin [23].

Our PK data, along with the fact that 3 mg/kg dosing was well tolerated, with no infusion toxicity and no renal, major hepatic, or other toxicities, suggests that alternate day micafungin dosing, as described here, may provide an attractive alternative for antifungal prophylaxis in HSCT patients. Although our study was not designed to prove the efficacy of this approach, the data provide support for a prospective clinical study of this prophylaxis strategy as a safe strategy for long-term use.

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