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Pharmacokinetics of extended dose intervals of micafungin in haematology patients: optimizing antifungal prophylaxis

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Background: Extended dosing intervals for micafungin could overcome the need for hospitalization for antifungal prophylaxis.

Objectives: This multicentre, open-label, randomized trial compared the pharmacokinetics of 300 mg of micafungin given twice weekly with 100 mg once daily as antifungal prophylaxis in adult haematology patients at risk of developing invasive fungal disease. Secondary objectives were assessment of adequate exposure with an alternative dosing regimen of micafungin (700 mg once weekly) through Monte Carlo simulations and assessment of safety in this patient population.

Patients and methods: Twenty adult patients were randomized to receive either 300 mg of micafungin twice weekly or 100 mg once daily for 8 days. Blood samples were drawn daily and pharmacokinetic curves were determined on days 4/5 and 8. Monte Carlo simulations were performed for both investigated regimens as well as a frequently proposed alternative regimen (700 mg once weekly).

Results: The predicted median AUC_{0-168h} (IQR) for a typical patient on the investigated regimens of 100 mg once daily and 300 mg twice weekly and the hypothetical regimen of 700 mg once weekly were 690 (583–829), 596 (485–717) and 704 (585–833) mg·h/L, respectively.

Conclusions: We observed comparable exposure with 300 mg of micafungin twice weekly and 100 mg of micafungin once daily. We provide the pharmacokinetic proof for an extended dosing regimen, which now needs to be tested in a clinical trial with hard endpoints.

Introduction

The incidence of invasive fungal disease in patients with AML and HSCT patients not receiving antifungal prophylaxis may be as high as 30% and is associated with high mortality rates.[1,2] Primary antifungal prophylaxis with azoles (depending on local epidemiology) is a recommended strategy in these haematological patients, usually presenting with prolonged neutropenia and mucosal barrier injury. Alternatively, prophylaxis with an echinocandin can offer a solution in the setting of unmanageable interactions or toxicity due to azole therapy.[3–5]

Micafungin, one of three currently available echinocandins, inhibits the synthesis of 1,3-β-D-glucan, a structural component of the fungal cell wall. The licensed dose of micafungin is 100–200 mg intravenously once daily, although lower doses have been tested in prophylaxis.[4] Extended dosing intervals could overcome the need for hospitalization or daily outpatient visits in the ambulatory care of haematological patients, especially for antifungal prophylaxis.

From a pharmacokinetic/pharmacodynamic (PK/PD) point of view, extended dosing intervals are only applicable to antimicrobial drugs for which the PK/PD index is best described by either C_{max}/MIC or AUC/MIC. For micafungin, the *f*AUC/MIC ratio has been found to be the best descriptive PK/PD index for *Candida* infections.[6–8] Furthermore, echinocandins display a prolonged post-antifungal effect against *Candida* spp.[9]

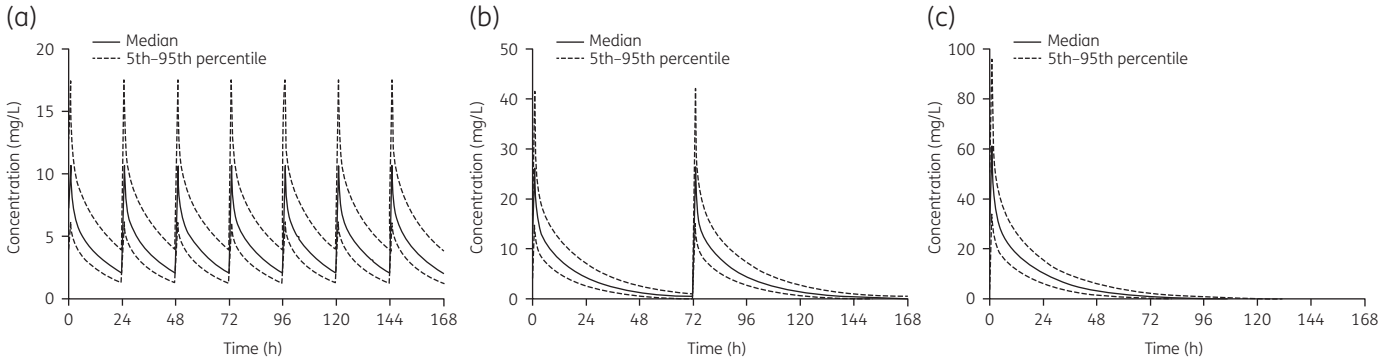

Figure 1. Simulation of micafungin at 100 mg once daily (a), 300 mg twice weekly, administered every 3 or 4 days, alternately (b), and 700 mg once weekly (c). Solid line shows median concentration; dotted lines show 5th and 95th percentiles.

Clinical data supporting a specific dose, frequency and duration for optimal prophylaxis are insufficient. Preclinical data have shown that once- or twice-weekly high-dose micafungin increased fungal decline compared with standard daily dosing.[10,11] PK data supporting extended dosing intervals in adults are limited to just one study.[8] Nevertheless, the combination of preclinical and PK studies provides a rationale for extended dosing intervals of micafungin in humans. Safety concerns are very limited as high dosages up to 8 mg/kg (896 mg) daily have been demonstrated to be well tolerated in multiple clinical trials.[12–14] To justify the use of extended dosing intervals of micafungin, preclinical and clinical data have to be combined and complemented with clinical pharmacological data[15] before putting this idea into practice. In selected cases the concept of extended dosing intervals is already used in different dose regimens.[16] A knowledge gap remains regarding what the best dose, interval and duration for optimal antifungal prophylaxis are for micafungin. We conducted a clinical PK study to provide the PK rationale for extended dosing regimens of micafungin.

Patients and methods

Study subjects

The included patients were receiving immunosuppressive therapy for acute graft-versus-host disease (aGVHD) grade II–IV, undergoing reduced-intensity conditioning regimens for allogeneic HSCT, or receiving first remission-induction chemotherapy for AML/myelodysplastic syndrome (MDS), who were at least 18 years of age, if female were not pregnant or nursing an infant, had no signs or symptoms of invasive fungal disease and were managed with a central venous catheter (CVC). Exclusion criteria were a documented history of sensitivity to (excipients of the formulation of) micafungin and a history or current abuse of drugs or alcohol. There were no exclusion criteria related to laboratory assessment.

Ethics

The study was approved by the local ethics committees of the Radboud University Medical Center, Nijmegen, the Netherlands (reference number 2013/493) and the University Hospital Leuven, Belgium (reference number S57173). The trial was registered at the European Clinical Trials Database Registry (EudraCT number 2013-002848-93) and at ClinicalTrials.gov (identifier NCT02172768). All subjects provided written informed consent.

Study design

This study was a prospective, multicentre, open-label, randomized trial determining the PK of 300 mg of micafungin given twice weekly compared with 100 mg of micafungin daily in patients at risk of developing an invasive fungal disease. Secondary objectives were (i) assessment of adequate exposure of micafungin to provide a PK rationale for dosing strategies other than 100 mg daily in the prophylactic setting, and (ii) assessment of safety in this patient population.

We chose a pragmatic twice-weekly regimen with a similar cumulative dose as being feasible and more patient friendly. Ultimately, a once-weekly regimen would be even more beneficial, but would require very high doses.

Patients were randomized 1:1 to receive either 300 mg of micafungin twice weekly for 8 days (Group A, receiving 900 mg in total) or 100 mg of micafungin once daily for 8 days (Group B, receiving 800 mg in total). The 300 mg dose was administered intravenously over 3 h and the 100 mg dose was administered intravenously over 1 h.

Patients were intensively sampled for full PK curves on day 4 or 5 (after the second dose in Group A, after the fourth or fifth dose in Group B) and on day 8, as shown in Figure 1. Blood samples were drawn pre-dose ($t = 0$) and at $t = 0.5$, 1, 2, 3, 4, 6, 8, 10, 12, 18 and 24 h after start of infusion. Samples taken from the infusion line were discarded. Additional samples were taken at $t = 36$, 48, 60, 72 and 96 h post-infusion in Group A, and daily just before administration in Group B. After stopping micafungin therapy, washout was determined during 3 days of follow-up.

Treatment protocol and supportive care

Reduced-intensity conditioning chemotherapy consisted of fludarabine, busulfan and antithymocyte globulin (ATGI).[17] Patients who underwent an HSCT started cyclosporine A on the day of HSCT as aGVHD prophylaxis. Remission-induction chemotherapy consisted of idarubicin or daunorubicin in combination with cytarabine (i.e. '3+7') or high-dose cytarabine (3000 mg/m^2 twice daily for 4 days). Patients received supportive care measures, such as antibacterial prophylaxis, CVC management and a diagnostic-driven approach for managing invasive fungal disease. No other antifungal prophylaxis was allowed.

Clinical and laboratory assessments

Micafungin concentrations were quantified with a validated UPLC fluorescence method. After pretreatment with a protein precipitation solution (50% acetonitrile, 50% methanol and 0.1% formic acid), analysis was performed with a validated UPLC method, using a fluorescence detector [dynamic range for micafungin, 0.01–32.40 mg/L; concentration-dependent

Table 1. Baseline characteristics

Characteristic	Group A ($n = 10$), 300 mg twice weekly	Group B ($n = 10$), 100 mg once daily	Total ($n = 20$)
Age (years), median (range)	59.0 (38–66)	63.0 (49–68)	59.5 (38–68)
Weight (kg), median (range)	76.2 (59.3–110.1)	87.1 (53.5–95.2)	86.6 (53.5–110.1)
Height (cm), median (range)	173 (152–188)	179 (166–189)	178 (152–189)
BMI (kg/m^2), median (range)	25.6 (19.0–27.6)	28.0 (20.7–33.2	25.7 (19.0–33.2)
Sex, female (*n*)	4	4	8
Haematological disease (*n*)			
AML/MDS	8	7	15
other	2	3	5
Treatment (*n*)			
allogeneic HSCT	6	4	10
remission-induction chemotherapy	4	6	10

accuracy range ($n = 15$), 97.61% to 101.64%].[18] Intraday precision ranged between 1.41% and 5.14% ($n = 5$).[18] In addition, interday precision varied between 0.69% and 2.20% ($n = 15$). A stability analysis of micafungin in whole blood confirmed that micafungin was stable for a minimum of 7 days at 4°C (mean concentration ± SD, 98.56% ± 1.91%, $n = 4$).[18]

Clinical and laboratory assessments were performed at baseline and on days 1, 4 or 5 and 8. Clinical assessments consisted of monitoring of body temperature, pulse, oxygen saturation and blood pressure immediately before starting the infusion and hourly until 4 h after the infusion. Laboratory assessments consisted of determination of sodium, potassium, calcium, inorganic phosphorus, chloride, total protein, albumin, total cholesterol, triglycerides, blood urea nitrogen, glucose, creatinine, uric acid, AST, ALT, GGT, alkaline phosphatase, conjugated and total bilirubin, lactate dehydrogenase, haemoglobin, leucocyte differential counts and platelet counts. These laboratory parameters were determined for safety purposes but not for a covariate analysis. An electrocardiogram was recorded on baseline and day 1. Use of co-medication was recorded throughout the study.

Pharmacokinetic model

PK analysis was performed by non-linear mixed-effect modelling using the software program NONMEM® version 7.3 with PiranaJS as an interface for NONMEM, Perl Speaks Nonmem and R statistics.[19] The relative standard errors of the estimates (RSEs) were calculated using sampling importance resampling.[20] A previously developed model for micafungin in critically ill patients[21] was used as a starting point for the analysis. All flow and volume parameters in the PK model were allometrically scaled to total body weight, normal fat mass or fat-free mass[22] as described earlier. As inter-individual variability in CL and *V* are often correlated, this was tested by investigating the presence of the physiologically plausible correlation between CL and *V*. Model evaluation was performed in line with best practice.[23]

Simulation study

After development of the PK model of micafungin in haematology patients, we performed a Monte Carlo simulation study of the studied dosing regimens 100 mg once daily and 300 mg twice weekly (every 3 or 4 days, alternately). For the Monte Carlo simulation, we simulated 500 virtual patients for each dose group based on the final model. For the body size distribution in the simulations, we assumed a mean fat-free mass of 57.18 kg with an inter-individual variability of 20%. A fat-free mass of 57.18 kg corresponds to a typical man of 1.80 m with a total body weight of 70 kg.

In addition, a frequently proposed once-weekly schedule of 700 mg was also simulated. Dose linearity over this dose range was assumed, as linear PK have been shown over a dose range of 0.15–8 mg/kg/day.[24]

Safety

Monitoring for adverse events was performed daily by medical and nursing observations; additionally, patients were asked to report any adverse experiences. Any potential causal relationship with micafungin was determined by the local investigator.

Results

Subject characteristics

Twenty haematology patients (12 men and 8 women) participated in this trial. Subjects had a median (range) age of 59.5 (38–68) years and a median (range) weight of 86.6 (53.5–110.1) kg. Details of the demographic characteristics are presented in Table 1.

Nineteen patients completed the trial; one patient receiving 100 mg of micafungin once daily had no PK curve taken on day 8 owing to removal of the CVC on day 8.

Micafungin PK

The population PK of micafungin were best described as disposition in one central compartment and two peripheral compartments of the same volume. Fat-free mass as a body size descriptor best explained the inter-individual variability in CL and *V* of micafungin, when compared with total body weight or normal fat mass, as observed in the largest decrease in the Akaike information criterion and greatest reduction in unexplained PK variability (data not shown). Therefore, all flow and volume parameters were scaled to a fat-free mass of 57.18 kg, corresponding to a typical male of 1.80 m and 70 kg. Estimation of *V* with three separate parameters did not result in better model fit than when the volumes were estimated with a single parameter. Estimating a single parameter instead of three resulted in higher parameter precision. The volume of each compartment was estimated to be 6.26 L with an RSE of 3.4%. The inter-

Table 2. Pharmacokinetic parameter estimates of the final model

Description	Parameter[a]	Estimate	RSE[20]
Structural model			
V	Θ_1 (L)	6.26	3.42%
CL	Θ_2 (L/h)	1.01	4.61%
inter-compartmental CL V_1-V_2	Θ_3 (L/h)	10.3	3.27%
inter-compartmental CL V_1-V_3	Θ_4 (L/h)	2.04	11.3%
Inter-individual variability (%CV)			
V	Ω_V	48.1	36.5%
CL	Ω_{CL}	21.3	31.5%
correlation between inter-individual variability in *V* and inter-individual variability in CL		0.809	37.6%
Intra-individual variability			
CL (%)		9.78	23.0%
Residual error			
additive error (mg/L)	σ_a	0.0878	18.3%
proportional error (%)	σ_p	7.71	8.72%

[a]All volume and flow parameters are scaled to a typical man of 1.80 m and 70 kg, corresponding to a fat-free mass of 57.18 kg.

compartmental CL parameters describing exchange between the central and peripheral compartments were 10.3 L/h (RSE 3.3%) and 2.04 L/h (RSE 11.3%), scaled to a fat-free mass of 57.18 kg. The inter-individual variability in volume of the central compartment was 48.1% (RSE 36.5%) and the inter-individual variability in CL from the central compartment was 21.3% (RSE 31.5%) and the parameters' correlation was 0.809 (RSE 37.6%). An intra-individual variability in central CL of 9.8% (RSE 23.0%) was observed. The residual error model consisted of a combined additive (0.0878 mg/L, RSE 18.3%) and proportional (7.71%, RSE 8.7%) error. The mass transport between the three compartments and elimination from the central compartment in the final model was described with the following rate constants: $k_{10} = CL/V$, $k_{12} = Q_1/V$, $k_{21} = Q_1/V$, $k_{13} = Q_2/V$ and $k_{31} = Q_2/V$.

In these equations, k_{ab} denotes the first-order mass transport from compartment a to b. The PK parameters in these rate constants were calculated with the following equations:

$$V = \Theta_1 (FFM/57.18)^1 \quad (1)$$
$$CL = \Theta_2 (FFM/57.18)^{0.75} \quad (2)$$
$$Q_1 = \Theta_3 (FFM/57.18)^{0.75} \quad (3)$$
$$Q_2 = \Theta_4 (FFM/57.18)^{0.75} \quad (4)$$

where FFM is the individually calculated fat-free mass.[22]

Parameter estimates of the final model are provided in Table 2. Shrinkage was <20% for all random variability parameters. The plots and data of the model evaluation showing the adequacy of the PK model are shown in Figures S1 and S2 (available as Supplementary data at *JAC* Online).

Simulation study

Higher doses of micafungin with extended dosing intervals showed a dose-related linear increase in observed exposure. The median (IQR) predicted cumulative AUC_{0-168h} for the tested and licensed doses of 100 mg once daily (1 h infusion), tested and experimental 300 mg twice weekly (3 h infusion) and hypothetical 700 mg once weekly (3 h infusion) were 690 (583–829), 596 (485–717) and 704 (585–833) mg·h/L, respectively. C_{max} and AUC increased linearly with dose. PK of the simulated regimens are displayed in Table 3 and Figure 1.

Table 3. Modelling and simulation of 1500 patients (three cohorts)

Parameter	100 mg once daily	300 mg twice weekly	700 mg once weekly
Cumulative AUC_{0-168h} (mg·h/L)	690 (583–829)	596 (485–717)	704 (585–833)
C_{max} (mg/L)	10.8 (8.84–13.0)	26.8 (21.2–32.8)	61.9 (49.0–75.1)
C_{min} (mg/L)	2.02 (1.65–2.51)	0.13 (0.07–0.21)	0.008 (0.003–0.021)

All values shown are median (IQR).

Safety

Six patients experienced a total of eight (serious) adverse events (AEs) during or within 30 days after stopping the study. Six were reported as serious: respiratory insufficiency resulting in ICU admission; death due to neutropenic enterocolitis; probable pulmonary *Rhizomucor* infection; hospitalization owing to fever and CVC-related thrombosis; hospitalization for treatment of Epstein–Barr virus reactivation and renal insufficiency; and hospital admission owing to painful arthritis of the wrist. All serious AEs were reported to be (likely) unrelated to micafungin. Of the two reported AEs, neither was reported to be related to micafungin. None of the above AEs resulted in discontinuation of the study treatment.

Breakthrough infections

One patient was diagnosed 7 days after cessation of micafungin with a probable pulmonary mucormycosis.

Discussion

This study investigated, for the first time, the PK of twice-weekly micafungin versus daily dosing in adult haematology patients. With our study, we provide the missing PK data on exposure of micafungin when administered at doses of 100 mg once daily, 300 mg twice weekly and simulated 700 mg once weekly.

We demonstrated that 300 mg of micafungin, administered as a 3 h infusion twice weekly, provides exposure over time comparable to that provided by 100 mg administered as a 1 h infusion once daily. These data provide a pharmacological rationale for twice-weekly dosing of micafungin.

A three-compartment model best fitted our data, in contrast to other population PK studies in which two-compartment models were used.[21,25,26] A third compartment can only be identified when the sampling time frame after dosing is long enough to detect it. A three-compartment model showing lower CL and therefore higher exposure later in a dose interval is of value for extending dosing intervals. We found a comparable *V* and CL in our

haematology patients compared with other haematology patients and critically ill patients (*V* of 18.8 versus 18.1, 19.5 and 17.6 L, CL of 1.01 versus 0.76, 1.34 and 1.10 L/h, respectively.[21,25–27]) The inter-individual variabilities in *V* and CL were small compared with those of critically ill patients (48.1% versus 73.2%, and 21.3% versus 40.1%, respectively),[21] making PK in haematology patients less variable than in critically ill patients. The exposure found in our study based on simulation was comparable to exposure achieved with 300 mg every 2 days (median AUC_{0-48} 275 versus 303 mg·h/L and median C_{max} 26.8 versus 23.4 mg/L).[8] Furthermore, a linear model fitted our PK data of micafungin up to 300 mg, which is in line with previous studies.[8,13] A limitation of our study is the sample size of only 20 patients. However, we performed extensive PK sampling for all patients. Furthermore, the only covariate included in the model was calculated fat-free mass. We did not search for other covariates, such as platelet count and albumin,[28,29] as this study was not designed for that purpose. Third, one may argue that estimating *V* with one parameter is a limitation of our study. We advocate the principle of parsimony: a PK model should always be as simple as possible, but not too simple. We found that estimating a single parameter for the three distribution compartments did not worsen model fit, as the objective function did not increase, yet it allowed more robust estimation of the other model parameters, as observed in the parameter precision. We therefore argue that a single parameter for the three distribution compartments is justified. Last, although fat-free mass was a fundamental part of the PK model, only a population with a relatively small weight range of 50–110 kg was included in our study. The prediction of PK in other weight groups should be done with caution. For obese patients, two recently proposed population PK models may be used.[30,31]

We observed no breakthrough fungal infections in our patient population during micafungin prophylaxis with the exception of one probable *Rhizomucor* infection 7 days after the end of the trial. Of note, micafungin does not display activity against *Mucorales* species.

Reduced-frequency dosing of micafungin seems more favourable than conventional dosing considering its PK/PD index. Animal studies have pointed us towards an optimal human dose through humanization of mouse experiment results.[10,11,32] Nevertheless the PK of these regimens have not been tested until now for micafungin. For anidulafungin these experiments have been conducted.[33]

Clinical studies have investigated the efficacy of higher doses of echinocandins, with mixed results. Dose increase of caspofungin from 50 mg once daily to 150 mg once daily did not result in better outcome,[34] but higher doses of 300 mg of micafungin every 2 days versus 150 mg once daily in patients with oesophageal candidiasis showed a trend towards better outcome with higher doses every 2 days.[8] A retrospective study including 104 patients receiving successive doses of 300 mg of micafungin two or three times weekly showed that this regimen was well tolerated, and a breakthrough fungal infection percentage of 6.0% in the prophylaxis group was observed, comparable with previously reported breakthrough percentages in antifungal prophylactic clinical trials. However, the study was not powered for this[16] and PK were not studied.

Two prospective studies in children analysing safety, efficacy and PK of a single-dose or twice-weekly high dose micafungin given as prophylaxis showed that reduced-frequency dosing was safe and there was linearity over a dose range of 1–4 mg/kg.[35,36] No breakthrough infections occurred.[36]

The optimal dosing interval and dose with respect to efficacy, toxicity and patient comfort remain unknown.

To assess whether alternative dosing strategies provide adequate exposure for prophylaxis with micafungin, several factors have to be accounted for. First, we showed that 300 mg of micafungin , infused over 3 h, was well tolerated in our study, without infusion-related reactions and attributable AEs. Safety of doses up to 896 mg has been described before, but unfortunately no PK data are available for doses >200 mg.[12–14]

Second, a possible downside of high dosing of echinocandins is the Eagle effect or paradoxical growth effect, in which higher concentrations seem less effective than lower concentrations. This has only been observed in *in vitro* and animal studies, with conflicting evidence, but has not been observed in human studies,[37–43] thus suggesting it would not compromise the efficacy of the high doses used in our study and needed for effective therapy with extended dosing intervals.

In conclusion, our study provides the PK rationale to support a twice-weekly 300 mg dosing regimen for micafungin in adults for both prophylaxis and therapy as compared with a once-daily 100 mg dosing scheme. The clinical relevance of extended dosing intervals becomes more pronounced in patients unable to tolerate azoles and liposomal amphotericin B, specifically in the outpatient setting.

Extending the dosing interval would improve patient comfort, reduce CVC manipulations and lower the costs of administration, thereby tackling the inherent downside of daily intravenous dosing with visits to the hospital, or, when available, daily parenteral home care. The next step needed for definite proof of an effective extended dosing interval with confirmation of the predicted PK is a prospective non-inferiority trial, with breakthrough infections as primary endpoint and patient experience as secondary endpoint.

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Supplementary data

Figures S1 and S2 are available as Supplementary data at *JAC* Online.

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