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# Pharmacokinetic evaluation of twice-a-week micafungin for prophylaxis of invasive fungal disease in children with acute lymphoblastic leukaemia: a prospective observational cohort study

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**Objectives:** To determine the pharmacokinetics of twice-a-week micafungin prophylaxis in paediatric leukaemic patients to provide the rationale for this approach.

**Methods:** Twice-a-week micafungin at a dose of 9 mg/kg (maximum 300 mg) was given during the leukaemic induction treatment with at least one pharmacokinetic assessment. Non-linear mixed-effects modelling was used for analysis. For model building, our paediatric data were strengthened with existing adult data. Monte Carlo simulations were performed with twice-a-week dosing regimens of 5, 7 and 9 mg/kg and flat dosing per weight band. Simulated paediatric exposures were compared with the exposure in adults after a once-daily 100 mg regimen.

**Results:** Sixty-one paediatric patients were included with a median age and weight of 4.0 years (range 1.0–17) and 19.5 kg (range 8.60–182), respectively. A two-compartment model best fitted the data. CL and central $V_d$ were lower ($P < 0.01$) in paediatric patients compared with adults. Predicted exposures ($AUC_{0-168\,h}$) for the 5, 7 and 9 mg/kg and flat dosing per weight band regimens exceeded the adult reference exposure.

**Conclusions:** All twice-a-week regimens appeared to result in adequate exposure for *Candida* therapy, with simulated exposures well above the adult reference exposure. These findings provide the rationale for the pharmacokinetic equivalence of twice-a-week and once-daily micafungin regimens. The greater micafungin exposures seem to be caused by a slower-than-anticipated CL in our paediatric leukaemic patients. The generalizability of our results for *Aspergillus* prophylaxis cannot be provided without assumptions on target concentrations and within-class identical efficacy.

## Introduction

Invasive fungal disease is one of the most common causes of treatment-related mortality in paediatric haemato-oncology patients.[1] Fungal prophylaxis during the induction treatment for paediatric patients with ALL may be required depending on regional incidence of invasive fungal disease. There are limited antifungal drugs available that can be safely deployed in the early phase of ALL treatment. The preferred drugs of choice are the mould-active azoles, but they are relatively contraindicated due to their drug–drug interaction profile. The drug–drug interaction with the weekly administered chemotherapeutic agent vincristine is especially difficult to manage.[2] Echinocandins appear to be a safe choice in this setting. As their β-D-glucan synthase target is unique to fungi, echinocandins are generally well tolerated and show minimal drug–drug interactions. Echinocandins show activity against both *Candida* and *Aspergillus* species.[3] In a recent large randomized open-label trial in paediatric patients with AML, the efficacy of caspofungin for prophylaxis of invasive fungal disease, including invasive aspergillosis, was demonstrated.[4]

The drawback of a prophylactic strategy with echinocandins is the customary daily IV dosing. To overcome the need for daily

hospital visits, a twice-a-week dosing regimen might be a preferable strategy. Such a strategy was explored in adults based on a bio-equivalency approach for both anidulafungin and micafungin. A 3× higher dose of these drugs in a twice-a-week regimen resulted in a comparable exposure to the equivalent daily dose.[5,6] These results provide the pharmacokinetic rationale to study a twice-a-week micafungin regimen in paediatric patients.

Three studies have explored intermittent micafungin regimens of 3 mg/kg every 48 h, 3–4 mg/kg twice a week or 5 mg/kg twice a week in paediatric patients, either as a single dose or multiple doses.[7–9] In these studies, dose selections and recommendations were made based on targets that were directly translated from the minimum effective concentrations or minimum inhibitory concentrations, dependent on the species.[7–9] Although these studies provided valuable pharmacokinetic information, sample sizes were relatively small and the choices made for pharmacokinetic targets and dose recommendations can be debated. There remains a clinical need for population pharmacokinetic information from a large cohort of patients with multiple dosing to support a twice-a-week regimen in paediatric patients.

Here, the feasibility of a patient-friendly prophylactic regimen for invasive fungal disease was explored by giving micafungin in a twice-a-week regimen at a dose of 9 mg/kg/administration during the induction treatment of childhood ALL. During this period we evaluated the pharmacokinetics of this micafungin dosing strategy, developed an integrated population pharmacokinetic model for children and adults, and simulated various dosing regimens that could be used as prophylactic regimens for invasive fungal disease.

## Methods

### Patients and study

All paediatric patients aged <18 years and diagnosed with childhood ALL received micafungin prophylaxis as part of standard care during the first 5 weeks of their induction treatment in the Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands. This study was an observational, prospective pharmacokinetic cohort study, which was conducted between September 2018 and April 2019. Patients who signed consent for the Dutch Childhood Oncology Group (DCOG) ALL-11 protocol were eligible for this evaluation. The evaluation protocol was approved by the Medical Ethics Committee Erasmus MC of Rotterdam (MEC-2018-1684).

### Micafungin dosing and sampling

As part of clinical practice in the Princess Máxima Center for Pediatric Oncology, a twice-a-week prophylactic micafungin regimen at a dose of 18 mg/kg/week (9 mg/kg/administration; maximum 300 mg) was chosen based on a bio-equivalence approach.[5,6] The dose was chosen as follows: the paediatric micafungin dose for treatment of invasive candidiasis or candidaemia is 2–4 mg/kg/day.[10] Hence, a dose between 14 and 28 mg/kg/week divided over two administrations could be a logical approach. The pragmatic decision was made to choose a dose of 18 mg/kg/week and thus a dose of 9 mg/kg/administration in a twice-a-week regimen. Regarding the toxicity profile of micafungin, once-daily doses of up to 8 mg/kg were well tolerated in adults and once-daily doses of up to 15 mg/kg were administered in the neonatal populations without signs of severe toxicity.[11–13] The chosen micafungin dose of 9 mg/kg/administration was therefore expected to be well tolerated. The infusion time was 2 h per dose. The twice-a-week dosing schedule was chosen at the discretion of the physician. As part of routine care, patients were monitored for micafungin exposure to prevent unexpected toxic exposures. Pharmacokinetic samples were obtained as early in the treatment as possible, after patients had a venous indwelling catheter inserted. A five-point micafungin curve was obtained from patients via indwelling venous catheter sampling. Venous blood samples (2.0 mL) were obtained at $t = 0$ (before start of the micafungin infusion), $t = 2$ h (at the end of infusion) and $t = 4$, 5 and 24 h after the start of micafungin infusion.

### Clinical and laboratory assessments

Baseline characteristics such as sex, age, height and total body weight were extracted from the electronic health record system. Micafungin-related data such as dose, infusion time, dosing interval, dose adjustments, times of blood sampling and micafungin concentrations were extracted from the electronic health record system and by means of a dedicated laboratory form.

### Bioanalysis

Micafungin concentrations were measured with a validated UPLC fluorescence method. This method was validated over a concentration range of 0.01–32 mg/L. The accuracy of the assay ranged from 97.6% to 101.6%, interday precision ranged from 0.7% to 2.2% and intraday precision ranged from 1.4% to 5.1%.

### Pharmacokinetic analysis

The collected paediatric pharmacokinetic data were combined with previously collected pharmacokinetic data of micafungin in adult haematology patients, from our group, for the purposes of data enrichment and improvement of model robustness.[5] This allowed for a direct comparison of pharmacokinetics between paediatric ALL patients and adult haematology patients.

The pharmacokinetics of micafungin were analysed using non-linear mixed-effects modelling (NONMEM) with the software package NONMEM v7.4.1. The covariate model included *a priori* allometrically scaled CL and volume of distribution ($V_d$) to a fat-free mass (FFM) of 57.2 kg, corresponding to the mass of a typical male patient of 1.80 m.[14] Furthermore, a binary covariate was added for paediatric and adult patients. Model evaluation was assessed by standard goodness-of-fit plots and prediction-corrected visual predictive checks. The details of the analysis and model evaluation are described in the Supplementary data, available at *JAC* Online.

#### Alternative dose evaluation

The final pharmacokinetic model was used to explore different dosing regimens by means of Monte Carlo simulations. For this purpose, extraction of demographic data of paediatric ALL patients from the database of the DCOG was performed. Four different dosing regimens were simulated: micafungin twice-a-week regimens of 5, 7 and 9 mg/kg, with a maximum of 300 mg per dose, and a flat dosing regimen per weight band. The 5 and 7 mg/kg dosing regimens were chosen based on earlier studies and at the discretion of the researchers, respectively.[7,9] Additionally, we chose an allometric dosing strategy with a flat dose for each weight band to take optimal benefit of vial sizes (50 mg per vial) and allow a practical dosing strategy. The doses per weight band were categorized as follows: <20 kg received 100 mg, 20–40 kg received 150 mg and >40 kg received 300 mg.

Predicted paediatric micafungin exposures of all four regimens were compared with a reference micafungin exposure in adult haematology patients after daily administration of 100 mg micafungin given for either *Candida* prophylaxis or treatment.[5] The pragmatic decision was made to at least attain the adult reference exposure for *Candida* infections in the absence of clinical breakpoints for *Aspergillus* infections.

## Results

### Patient characteristics

A detailed description of patient characteristics of our paediatric population and the adult population,[5] as presented earlier, is given in Table 1. A total of 61 paediatric ALL patients were evaluated in this study, of which 55.7% were male. Median age and weight were 4.0 years (range 1.0–17) and 19.5 kg (range 8.60–182), respectively, for the paediatric cohort. The median micafungin dose was 175 mg (range 77–300). Pharmacokinetic samples were obtained after first and multiple administrations (range 1–8 administrations) of micafungin. In total, 73 micafungin sampling occasions occurred. A full four- or five-point pharmacokinetic curve was taken on 49 sampling occasions, and ≤3 concentrations were taken on 24 sampling occasions.

### Pharmacokinetic analysis

Data of 61 paediatric patients and 20 adult patients were used for pharmacokinetic analysis. Combining both paediatric and adult cohorts resulted in a total of 760 paired observations of time and micafungin plasma concentrations. In short, the pharmacokinetics of micafungin were best described using a two-compartment linear pharmacokinetic model. The details of the analysis can be found in the Supplementary data (including Table S1 and Figures S1–S3b). It was found that the allometrically scaled CL and $V_d$ of micafungin in paediatric patients were significantly lower ($P < 0.01$) compared with adult haematology patients, with a respective $CL_{paediatrics}$ of 0.678 (95% CI 0.634–0.725) versus $CL_{adults}$ of 1.02 L/h (95% CI 0.913–1.13) and $V_{d,\ paediatrics}$ of 7.91 (95% CI 6.51–9.27) versus $V_{d,\ adults}$ of 11.6 L (95% CI 9.45–13.9).

### Alternative dose evaluation

Details on the demographics of the real-life paediatric ALL cohort are given in Table 2. The predicted micafungin exposures are presented in Figure 1. The median predicted micafungin exposures ($AUC_{0-168\,h}$) of twice-a-week 5, 7 and 9 mg/kg regimens and a flat dosing regimen were, respectively, 800 (IQR 652–987), 1069 (IQR 882–1293), 1311 (IQR 1071–1576) and 979 mg·h/L (IQR 802–1191). All four regimens showed an above-median exposure compared with the median exposure of 690 mg·h/L (IQR 583–827) in adult haematology patients after a daily dose of 100 mg.

**Table 2.** Demographics of a real-life cohort of paediatric patients with ALL used for dose exploration simulations

| Demographic | |
|---|---|
| Number of patients, *N* | 590 |
| Sex (%) | |
| Male | 59.3 |
| Female | 40.7 |
| Age, years; median (range) | 5.0 (1.0–17) |
| Weight, kg; median (range) | 20.0 (8.70–105) |
| Height, cm; median (range) | 114 (75.0–196) |

**Table 1.** Patient characteristics of the paediatric ALL cohort and the adult haematology cohort

| Characteristic | Paediatric patients | Adult patients[a] |
|---|---|---|
| Number of patients, *N* | 61 | 20 |
| Sex (%) | | |
| Male | 55.7 | 60.0 |
| Female | 44.3 | 40.0 |
| Age, years; median (range) | 4.0 (1.0–17) | 59.5 (38–68) |
| Weight, kg; median (range) | 19.5 (8.60–182) | 86.6 (53.5–110.1) |
| Height, cm; median (range) | 107 (75.0–200) | 178 (152–189) |
| Underlying malignancy, *n* | | |
| ALL | 61 | — |
| AML/MDS | — | 15 |
| Other | — | 5 |
| Treatment, *n* | | |
| Induction chemotherapy | 61 | — |
| Allogeneic HSCT | — | 10 |
| Remission-induction chemotherapy | — | 10 |
| Micafungin dose, mg; median (range) | | |
| Once daily | — | 100 |
| Twice weekly | 175 (77–300) | 300 |
| Number of samples, *N* | 262 | 498 |
| Number of occasions with a full 4- or 5-point PK curve, *n* | 49 | — |
| Number of occasions with ≤3 micafungin concentrations, *n* | 24 | — |

MDS, myelodysplastic syndromes; PK, pharmacokinetics.
[a]Data from Muilwijk *et al.*[5]

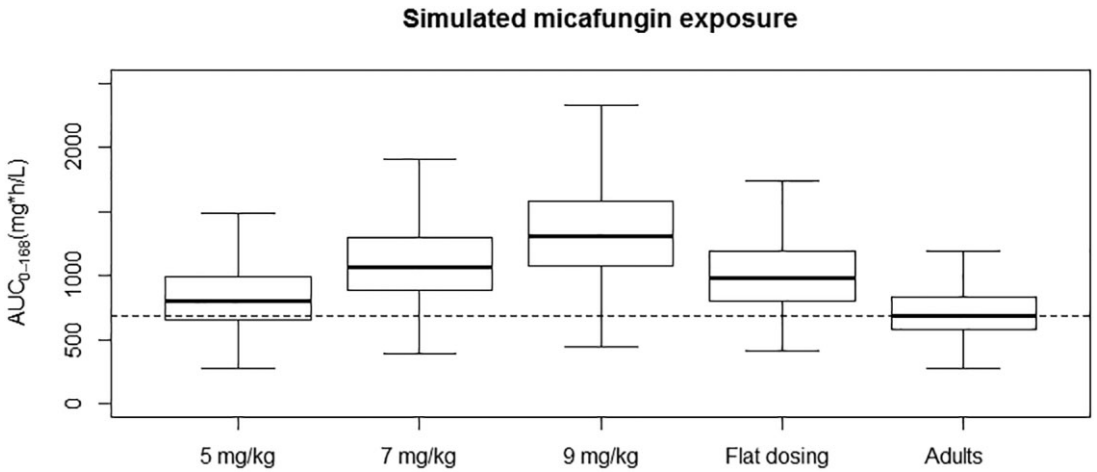


**Figure 1.** Predicted micafungin exposure of four twice-a-week paediatric regimens compared with a once-daily regimen in adult patients. The dashed line represents the median exposure in adult haematology patients. Flat dosing per weight band: weight bands were categorized as follows: <20 kg received 100 mg, 20–40 kg received 150 mg and >40 kg received 300 mg. Adult haematology patients received a daily dose of 100 mg micafungin.

## Discussion

In this study the pharmacokinetics of micafungin were evaluated in the largest cohort to date and at multiple doses in a twice-a-week regimen for the purpose of fungal prophylaxis in paediatric ALL patients.

Interestingly, significantly lower micafungin CL and $V_d$ were found in paediatric ALL patients compared with adult haematology patients, despite allometric scaling. Very little information to explain this observation was found in the literature. Four earlier studies reported the population pharmacokinetics of micafungin in paediatric patients.[9,15–17] As these studies used different covariates and scaling methods, we could not directly compare their parameter estimates with the parameter estimates found in our model. Three of these studies combined or compared their paediatric data with adult data. Neither of these studies reported any differences in pharmacokinetic parameters or exposures between paediatric patients and adults after adjustment for weight, with or without allometric scaling.[15–17] A non-compartmental analysis reported a significantly higher weight-adjusted CL in paediatric patients aged <8 years compared with paediatric patients aged >8 years and adult patients.[18] This study did not take allometry into account, which could explain the higher weight-adjusted CL reported in the younger group of patients.

Our initial assumption was that paediatric patients have reduced CL due to concomitant hepatotoxic chemotherapy and subsequently reduced hepatic enzyme function. Micafungin is metabolized by arylsulfatase and catechol-*O*-methyltransferase and altered enzyme function might lead to changes in micafungin metabolism and CL.[19] Yet, in adult patients with mild to severe hepatic impairment no changes in pharmacokinetic parameters were observed.[20,21] This makes our hypothesis less likely and a final explanation for this observation remains to be unravelled.

A twice-a-week regimen can be considered at least comparable to a daily regimen in terms of exposure, as the predicted median micafungin exposure in all simulated dosing regimens exceeded the reference median micafungin exposure in adult haematology patients.

Although the place of a twice-a-week micafungin regimen for *Candida* prophylaxis seems appropriate given the chosen target exposure, the place of this micafungin regimen in the setting of *Aspergillus* prophylaxis can be debated. Recently, caspofungin was reported to be effective for prophylaxis of invasive aspergillosis in paediatric patients.[4] We are of the opinion that micafungin will likely have similar efficacy as caspofungin. These thoughts are supported by the report that 50 mg micafungin therapy resulted in a trend towards a lower incidence of *Aspergillus* infections.[22] We could hypothesize that aiming for a target exposure of a twice-a-week micafungin regimen that is at least similar to a 100 mg daily exposure would mark comparable clinical efficacy of these regimens. Evidently, more knowledge on the pharmacodynamics of micafungin for prophylaxis of *Aspergillus* infections will be needed to substantiate our hypothesis. Caution should be exercised to interpret our findings, as it remains challenging to recommend a specific dosing regimen in the absence of these clinical targets for *Aspergillus* infections. The efficacy of the twice-a-week 9 mg/kg regimen is currently under evaluation for *Aspergillus* prophylaxis.

The twice-a-week regimens of 5 and 7 mg/kg and flat dosing by weight band might be alternative strategies as these regimens result in analogous exposure compared with the adult reference daily regimen (Figure 1). These assumptions only hold their strength when linear pharmacokinetics are foreseeable. So far, no evidence is available supporting non-linear pharmacokinetics of micafungin. The efficacy of either regimen remains a topic of investigation.

In conclusion, the pharmacokinetic data obtained from this large combined paediatric and adult population will support the rationale of a twice-a-week micafungin regimen. Our analysis proved that a twice-a-week micafungin regimen is at least pharmacokinetically equivalent to a daily regimen. Understanding the underlying mechanism of the lower CL in paediatric ALL patients and the clinical targets of micafungin for *Aspergillus* infections will

help to improve this twice-a-week micafungin dosing strategy for prophylaxis of invasive fungal disease.

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## Transparency declarations

No conflicts of interest/competing interests are applicable for this work. Disclosures outside of this work: R.J.M.B. has served as a consultant to Astellas Pharma, Inc., F2G, Amplyx, Gilead Sciences, Merck Sharp & Dohme Corp., Mundipharma and Pfizer, Inc., and has received unrestricted and research grants from Astellas Pharma, Inc., Gilead Sciences, Merck Sharp & Dohme Corp. and Pfizer, Inc. All contracts were through Radboudumc and all payments were invoiced by Radboudumc. None of the other authors have any conflicts to declare.

### *Author contributions*

D.B., W.J.E.T., T.F.W.W. and R.J.B. designed the research; D.B. performed the research; D.B., R.t.H. and R.J.B. analysed data; D.B. and R.J.B. wrote the manuscript; R.t.H., W.J.E.T., T.F.W.W. and E.W.M. provided critical revision of the manuscript. All authors provided approval of the final version.

## Supplementary data

Table S1 and Figures S1 to S3 are available as Supplementary data at *JAC* Online.

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