Assessment of micafungin regimens by pharmacokinetic–pharmacodynamic analysis: a dosing strategy for *Aspergillus* infections

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**Objectives:** A pharmacokinetic (PK)–pharmacodynamic (PD) analysis was conducted to assess various micafungin regimens for *Candida* and *Aspergillus* infections, as appropriate regimens have not been established, especially for *Aspergillus* infections.

**Methods:** Plasma drug concentrations (48 samples from 10 adult patients with haematological malignancies) were determined chromatographically, and used for population PK modelling and Monte Carlo simulation to evaluate the ability of regimens (1 h infusions) to attain genus-dependent PK–PD targets, namely fungistatic and fungicidal targets against *Candida* spp. ([area under the plasma unbound (1%) drug concentration–time curve over 24 h/MIC (fAUC/MIC)] = 10 and 20) and an effective concentration target against *Aspergillus* spp. (plasma unbound drug concentration = 0.05 mg/L).

**Results:** Mean (variance) values for two-compartment PK model parameters were: clearance, 0.762 L/h (15.4%); volume of central compartment, 9.25 L (24.6%); intercompartmental clearance, 7.02 L/h (fixed); and volume of peripheral compartment, 8.86 L (71.8%). The Monte Carlo simulation demonstrated that 50 mg once daily and 100 mg once daily for the fungistatic and fungicidal targets achieved a >95% probability of target attainment against *Candida* spp. To achieve such probability against *Aspergillus* spp., 250 mg once daily or 100 mg twice daily was required.

**Conclusions:** These results rationalize the approved micafungin dosages for *Candida* infections (50 mg once daily for prophylaxis and 100–150 mg once daily for treatment), and on the basis of these results we propose a PK–PD-based dosing strategy for *Aspergillus* infections. A regimen of 200–250 mg/day should be initiated to ensure the likelihood of a favourable outcome. The regimen can be optimized by decreasing the dosing interval.

Keywords: echinocandins, population pharmacokinetics, Monte Carlo simulation
glabrata infection. Nevertheless, a PK–PD approach has not yet rationalized the approved once-daily regimens for Candida infections nor optimized the regimens for Aspergillus infections.

Therefore, in this study we conducted a PK–PD analysis to assess various micafungin regimens for the two fungal infections. PK data were obtained from adult patients with haematological malignancies because they represent the major patient group for micafungin therapy. Two types of targets (an AUC/MIC ratio for Candida and an effective concentration for Aspergillus) were used because earlier studies revealed genus-dependent PK–PD relationships for micafungin.3–5

Methods

This study was approved by the Institutional Review Board of the Kyoto Prefectural University of Medicine. The inclusion criteria were adult patients who had neutropenia (<1000 neutrophils/µL) and fever (>38°C); who were refractory for antibacterial therapy with broad-spectrum agents; who were suspected of fungal infections from laboratory and radiographic findings; and who provided their written informed consent. Micafungin was repeatedly infused and venous blood samples were drawn. Each plasma sample was removed after centrifugation and stored at −40°C until assay.

The total concentrations of micafungin in plasma were assayed using HPLC as reported previously.6 In brief, 50 µL of plasma sample was mixed with ethanol, acetonitrile and internal standard (FR195743) solution, and the mixture was centrifuged. Next, the supernatant was mixed with 0.02 M potassium dihydorgen phosphate/acetonitrile (50:50, v/v; the mobile phase for HPLC), and 20 µL of the mixture was injected onto a chromatograph. HPLC was performed using a C18 column at 40°C, a fluorescence detector at 273 nm for excitation and 464 nm for emission, and the mobile phase at a flow rate of 1 mL/min. The calibration curve was linear from 0.05 mg/L (lower limit of quantification) to 50 mg/L, and the coefficients of variation were within 7.3%.

Drug concentration data were analysed by population PK modeling using NONMEM VI (ICON Development Solutions, Ellicott, MD, USA). A standard two-compartment model was used because it described the data better than a standard one-compartment model. Therefore, the structural PK parameters were clearance (CL), it described the data better than a standard one-compartment model.

Demographic and pathophysiological parameters of the study patients (n=10) are summarized in Table 1.

Results

Forty-eight plasma concentrations were obtained from 10 patients 1–71.5 h after the first infusion of 50–300 mg of micafungin and were used for population PK modelling. The characteristics of the patients are summarized in Table 1.

The population PK modelling (Table 2) evaluated Q as a fixed value without any interindividual variability because its η was <0.0001. Each parameter estimate, for which the standard error was <4.5%, was in the range of the 95% confidence interval using the bootstrap method, which indicates reliability and stability of the model. The observed drug concentration (X; range 2.16–29.84 mg/L) was almost identical to the individual predicted concentration (Y) with a regression line of Y=0.998X+0.007 (n=48; r2=0.995), and other diagnostic scatter plots also indicated that the model adequately described the data. In this model, the 10000th subject using Crystal Ball 2000 (Oracle, Redwood Shores, CA, USA). For the ith subject, a set of four interindividual variable η values (CL, V1, Q and V2) was randomly generated according to each normal distribution (mean 0, variance η2) of the population PK model. The set of η values determined a set of four fixed-effects parameter θ values as θ=δθexp(η). Then, the curve of the free-drug concentration in plasma versus time from 144 to 168 h after the drug administration (i.e. at steady state) was simulated using the set of θ values, where a value of 99% protein binding was employed.7 (i) For Candida species, the free-drug 24 h AUC/MIC (fAUC/MIC) at a specific value of 2-fold diluted MIC was calculated. The probability of target attainment (PTA, %) was determined as the fraction of 10000 estimates that achieved at least fAUC/MIC=10 or 20. The PTA at a specific MIC was then multiplied by the fraction of a population of Candida albicans and C. glabrata clinical isolates (n=3616, range 0.007–1 mg/L, MIC50=0.015 mg/L, MIC90=0.03 mg/L) at each MIC. The sum of the individual products was finally defined as the expected population PTA (%). (ii) For Aspergillus species, the number of subjects whose free-drug plasma concentration remained above an effective concentration of 0.05 mg/L2,6,10 was counted. The proportion of the count to 10000 subjects was finally defined as the PTA (%).

Table 1. Demographic and pathophysiological parameters of the study patients (n=10)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD (range)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>63.5 ± 16.2 (30–79)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>55.4 ± 10.3 (46.0–77.4)</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>47.2 ± 56.1 (15–131)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>48.0 ± 30.1 (23–88)</td>
</tr>
<tr>
<td>Blood urea nitrogen (mmol/L)</td>
<td>6.8 ± 4.7 (1.5–12.1)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>55.8 ± 31.8 (23.9–99.1)</td>
</tr>
<tr>
<td>Sex, n</td>
<td>4 female, 6 male</td>
</tr>
<tr>
<td>Haematological malignancy, n</td>
<td>leukemia 4 lymphoma 4 others 2</td>
</tr>
</tbody>
</table>
a good correlation ($n=10$, $r^2>0.5$) was not found between the demographic and pathophysiological parameter values (Table 1) and the individual PK parameter values (CL, $V_1$ and $V_2$ each).

The Monte Carlo simulation (Table 3) demonstrated that 50 mg once daily and 100 mg once daily for the fungistatic and fungicidal targets achieved an expected population PTA of >95% against Candida spp. Each once-daily regimen was similar to the corresponding twice-daily regimen. However, in the case of Aspergillus spp., the minimum regimen needed to achieve a >95% PTA was 250 mg once daily (250 mg/day), which was equivalent to 100 mg twice daily (200 mg/day).

**Discussion**

Results of this PK–PD analysis in adult patients with haematological malignancies show a rationale for micafungin regimens for Candida and Aspergillus infections.

The amount of data on drug concentrations to characterize micafungin PK thoroughly was not large. Moreover, the current PK modelling did not examine the effect of covariates on the PK of micafungin as did earlier PK modelings for echinocandins. Nevertheless, the developed model (Table 2) was validated by both the bootstrap method and diagnostic scatter plots.
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In addition, each 95% confidence interval included reported mean values for a two-compartment model (CL, 0.78 and 1.165 L/h; V₁, 11.2 and 10.430 L; Q, 5.79 L/h; V₂, 9.4 L), which indicates consistency of the current model with the reported models. Therefore, the developed model is considered to be acceptable for subsequent Monte Carlo simulation.

The antifungal effects of micafungin on Candida spp. have been best explained by AUC/MIC ratios. Gumbo et al.³ reported that the free-drug 168 h AUC/MIC ratios for stasis and 2 log decline were 23.0 and 138.3 (which correspond to 3.3 and 19.8 per 24 h, respectively) against a C. glabrata infection. Supporting these in vivo findings, Andes et al.⁴ demonstrated that the free-drug 24 h AUC/MIC ratios for stasis and killing were near 10 and 20, respectively, against both C. albicans and C. glabrata infections. In contrast, the antifungal effects of micafungin on Aspergillus spp. are generally regarded as concentration-dependent. In adult patients with aspergillosis, the plasma drug concentration required to obtain positive responses was suggested to be a total concentration of 5 mg/L,⁶,¹⁰ which corresponds to a free concentration of 0.05 mg/L when the protein binding is 99%. Providing a microbiological explanation for these clinical findings, Antachopoulos et al.⁵ reported that effective micafungin concentrations, which produce 95% of the maximum inhibitory effect on the metabolic activity of Aspergillus spp., were 0.04 mg/L for non-germinated Aspergillus fumigatus and 0.05 mg/L for both germinated A. fumigatus and non-germinated Aspergillus flavus. Therefore, the PK–PD target values used in the Monte Carlo simulation are considered to be the best ones currently available.

The results (Table 3) suggest that the usual micafungin dosages for Candida infections in the USA and the EU (50 mg once daily for prophylaxis and 100–150 mg once daily for treatment) are reasonable. For Aspergillus infections, the results suggest that 200–250 mg/day (which was higher than the usual 50–150 mg once daily but was within the maximal 300 mg once daily in Japan) should be initiated to ensure the likelihood of a favourable outcome. In clinical studies,¹⁴,¹⁵ 75 mg/day was initiated and then escalated with a maximum of 225–292 mg/day for positive responses in adult patients with aspergillosis. However, de-escalation therapy starting with a higher dosage has been administered without dose-limiting toxicity (Mycamine package insert; Astellas Pharma, Deerfield, IL, USA). Therefore, the PK–PD-derived 200–250 mg/day regimen is considered to be a clinically significant and acceptable dosage for Aspergillus infections.

Gumbo et al.³ examined the influence of increasing the dosing interval on PK–PD target attainments of micafungin (against C. glabrata). Conversely, we examined the influence of decreasing the dosing interval. Switching a once-daily regimen to the corresponding twice-daily regimen increased the PTA only against Aspergillus spp. (Table 3) because the switching increased the average drug concentration but did not change the AUC. Therefore, decreasing the dosing interval can be a useful method to maximize outcomes in Aspergillus infections, unless frequent administration is unacceptable due to the increase in both the patient’s burden and the medical workload.

In conclusion, the PK–PD analysis in adult patients with haematological malignancies rationalizes the approved micafungin dosages for Candida infections (50 mg once daily for prophylaxis and 100–150 mg once daily for treatment). For Aspergillus infections, a regimen of 200–250 mg/day should be initiated to ensure the likelihood of a favourable outcome; the regimen can be optimized by decreasing the dosing interval. This PK–PD-based dosing strategy for Aspergillus infections provides a theoretical rationale for dosage choice in daily practice and dosage design for further clinical trials.

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Transparency declarations

None to declare.

References