Intralun Pharmacokinetics and Pharmacodynamics of Micafungin in Adult Lung Transplant Patients

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Invasive pulmonary aspergillosis is a life-threatening infection in lung transplant recipients; however, no studies of the pharmacokinetics and pharmacodynamics (PKPD) of echinocandins in transplanted lungs have been reported. We conducted a single-dose prospective study of the intrapulmonary and plasma PKPD of 150 mg of micafungin administered intravenously in 20 adult lung transplant recipients. Epithelial lining fluid (ELF) and alveolar cell (AC) samples were obtained via bronchoalveolar lavage performed 3, 5, 8, 18, or 24 h after initiation of infusion. Micafungin concentrations in plasma, ELF, and ACs were determined using high-pressure liquid chromatography. Noncompartmental methods, population analysis, and multiple-dose simulations were used to calculate PKPD parameters. $C_{\text{max}}$ in plasma, ELF, and ACs was 4.93, 1.38, and 17.41 μg/ml, respectively. The elimination half-life in plasma was 12.1 h. Elevated concentrations in ELF and ACs were sustained during the 24-h sampling period, indicating prolonged compartmental half-lives. The mean micafungin concentration exceeded the MIC$_{90}$ of *Aspergillus fumigatus* (0.0156 μg/ml) in plasma (total and free), ELF, and ACs throughout the dosing interval. The area under the time-concentration curve from 0 to 24 h (AUC$_{0–24}$/MIC$_{90}$) ratios in plasma, ELF, and ACs were 5,077, 923.1, and 13,340, respectively. Multiple-dose simulations demonstrated that ELF and AC concentrations of micafungin would continue to increase during 14 days of administration. We conclude that a single 150-mg intravenous dose of micafungin resulted in plasma, ELF, and AC concentrations that exceeded the MIC$_{90}$ of *A. fumigatus* for 24 h and that these concentrations would continue to increase during 14 days of administration, supporting its potential activity for prevention and early treatment of pulmonary aspergillosis.

Postoperative invasive pulmonary aspergillosis is a frequent clinical problem among patients who have undergone lung transplantation (13, 23, 38–42). Strategies for management of invasive pulmonary aspergillosis in lung transplant recipients are not well defined. While voriconazole is indicated for the primary treatment of invasive aspergillosis, not all patients are able to tolerate this triazole, and drug interactions may be complicated. The role of echinocandins in treatment and prevention of invasive aspergillosis in lung transplant recipients is unknown. Although most lung transplant centers administer some form of antifungal prophylaxis, these regimens vary widely from center to center, and the optimal strategy for prophylaxis is unknown. Aerosolized amphoterin C, either alone or with systemically administered antifungal agents, may be used for prevention of invasive aspergillosis in lung transplant recipients (13).

Micafungin, a member of the echinocandin class of antifungal agents, has *in vitro* as well as *in vivo* activities against *Candida* spp. and *Aspergillus* spp. in treatment of experimental disseminated candidiasis (3, 5, 6, 33–35) and invasive pulmonary aspergillosis (33). Micafungin is licensed for the treatment of patients with esophageal candidiasis and candidemia (5, 12, 15, 30, 32, 36, 49). Micafungin also is approved for prevention of candidemia in neutropenic hematopoietic stem cell transplant recipients (44). Micafungin has been studied alone or in combination with other antifungal agents for treatment of invasive aspergillosis in hematopoietic stem cell transplant recipients (22). Although studies of micafungin for treatment and prevention of invasive pulmonary aspergillosis in animal models and in patients have demonstrated activity against this serious infection (8, 26, 33, 45), little is known about its intrapulmonary pharmacokinetics in patients at risk for invasive aspergillosis (28). We therefore studied the simultaneous intrapulmonary and plasma pharmacokinetics and pharmacodynamics of micafungin in adult lung transplant recipients.

**MATERIALS AND METHODS**

**Study design and subjects.** Participation of patients in this prospective study was conducted under a clinical protocol approved by the University of California, San Francisco. Participation was voluntary and expressed through written informed consent. All subjects had undergone lung transplantation at the University of California, San Francisco. The median transplant-to-study time was 14 days, with a range of 5 to 280 days prior to participation in the study. Nineteen subjects received a single 150-mg intravenous dose, administered either in the...
outpatient infusion center (n = 9) or in the inpatient unit (n = 10), and one received a 150-mg dose once daily for four consecutive days, administered in the intensive care unit. Subjects were assigned to five groups of four subjects each, with bronchoscopy at 3, 5, 8, 18, or 24 h after the single or last dose. Subjects were 21 years of age or older. Exclusion criteria included known hypersensitivity or intolerance to micafungin or other echinocandin drugs, pregnancy or breast-feeding, or concurrent treatment with nifedipine. If applicable, enrolled subjects confirmed that they were using contraception. Prior to enroll-
ment, clinical laboratory test results (complete blood count with differential, platelet count, blood urea nitrogen, serum creatinine, alkaline phosphatase, total bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and albumin), completed in the course of routine posttransplant care, were recorded into the research record.

Subjects were observed during and for 1 h after infusion for adverse effects. Subjects were scheduled to receive bronchoscopy as a part of routine posttransplant-care; infusions were scheduled so that the elapsing time between infusion and bronchoscopy corresponded to the time determined by the study schedule. The results of clinical laboratory tests performed after bronchoalveolar lavage (BAL) were recorded in the research record.

Bronchoscopy and bronchoalveolar lavage. Bronchoscopy and BAL (9–11) were performed at the University of California, San Francisco Medical Center at 3, 5, 8, 18, or 24 h after the administration of the single or the last dose. Local anesthesia with topical lidocaine and systemic sedation with fentanyl and midazolam were used. Pulmonary epithelial lining fluid (ELF) and alveolar cells (AC) were collected by bronchoscopy and BAL in a lobe of the transplanted lung. The duration (mean ± standard deviation [SD]) of the lavage was 7.1 ± 6.0 min. BAL was performed by infusing, and promptly aspirating, 20-ml aliquots of sterile, saline-saturated buffer fluid over 10–12 min, by one 2-ml-capacity Varian C8 cartridges were washed, and elution was accomplished using 1.0 ml of a 90:10 mixture of methanol-AA. Eluent was evaporated under air by utilizing a Zymark Turbo Vap LV evaporator (American Laboratory Trading LLC, Niantic, CT) for plasma samples, and normal saline (1:5) with human BAL fluid for BAL samples. For plasma, the lower limit of quantification (LLQ) was 0.1 mg/liter with a coefficient of determination (r²) of ≥0.9992; for BAL, the LLQ was 0.075 mg/liter with an r² of ≥0.9999. The intra- and interday coefficients of variation were ≤9.4% for both plasma and BAL fluid.

Monocyte enumeration. Human monocytes (MNCs) were obtained from healthy adult volunteers by elutriation from the Transfusion Medicine Department of the National Institutes of Health Warren Grant Magnuson Clinical Center. Cells were initially washed in Hank's balanced salt solution (HBSS—) without Ca²⁺ and Mg²⁺. The cells were then centrifuged at 470 relative centrifugal force (RCF) for 10 min at 4°C and resuspended to a final concentration of 1 × 10⁶ cells/ml in normal saline. Viability was assayed by the trypan blue exclusion assay (2, 4).

Pellet extraction. Micafungin was extracted from the BAL fluid pellet by solid-phase extraction as described earlier. Monocyte cells at a concentration of 10⁶ cells/ml, spiked with micafungin, were used as the matrix for standards and quality controls (OCS), which were stored at −80°C for 24 h prior to processing. A 1,100-μl aliquot of ACN was added to 300 μl of thawed standard, QC, or pellet samples, vortexed, and incubated for 10 min at 4°C. Afterwards the samples were centrifuged at 600 RCF for 10 min. One milliliter of supernatant was mixed with 9 ml of AA pH 4 buffer and extracted employing the same assay as for plasma or BAL samples, except that 10-ml-capacity LRC Varian C8 SPE cartridges were used instead of 1-ml-capacity Varian C8 cartridges.

The concentration of unbound drug in plasma was calculated from the following formula: unbound fraction = 0.01 × total concentration. Unbound drug concentrations in ELF and AC were not calculated because the extent of protein binding in these compartments is unknown. The volume of ELF in bronchoalveolar lavage (BAL) was determined in the research record.

Pharmacokinetic analysis. For all compartments, the individual subject con-
centrations at each collection time point were averaged, and the mean data were used to calculate the Cmax and Tmax. Cmax was the maximum mean concentration from among the five time groups, and Tmax was the mean time from the last dose to the time of BAL for the group to which the subject was randomized. The terminal phase half-life in plasma was calculated using model-independent analysis with Kinetics, version 4.4.1 (Admet Scientific). The half-life was not calculated for ELF or AC because the concentration-time profile was flat in those compartments.

The AUC over the dosing interval (AUC(0–24)) was calculated using the population methods described below.

Pharmacodynamic analysis. The Cmax, AUCC(24), and the concentration-time data were used to calculate the following pharmacodynamic parameters: Cmax/MIC90 ratio, AUCC(24)/MIC90 ratio, and time above MIC in plasma, ELF, and AC. The pharmacodynamic parameters in plasma were derived from the free (i.e., unbound) drug concentrations as well as total (i.e., unbound plus bound) drug concentrations. Although the presence of protein increases the MIC of micafungin (29), the effect of protein binding on clinical outcomes is unknown (1, 23, 29). The MIC90 value for A. fumigatus was obtained from the recent literature (43).

Population analysis and multiple-dose simulations. A population PK analysis using the exact concentration-time data for all 20 patients was carried out using the nonparametric adaptive grid (NPAG) algorithm implemented in the MM-USC Pack software (24). In the first step, various compartmental models were fit to plasma drug concentrations only. In the second step, all plasma, ELF, and AC drug concentrations were modeled simultaneously. The final model was a linear four-com-
partiment model with first-order processes for all transfers. The model was de-
scribed by the following system of ordinary differential equations:

\[
\frac{dC_1}{dt} = -K_{12}C_1 + K_{21}C_2 + \frac{\psi}{AUC_{0–24}}\left(C_1 - C_2\right) + k_{in}\mu \left[C_{in} - C_1\right];
\]

\[
\frac{dC_2}{dt} = -K_{21}C_2 + K_{12}C_1 - \frac{\psi}{AUC_{0–24}}\left(C_2 - C_1\right) + k_{in}\mu \left[C_{in} - C_2\right];
\]

\[
\frac{dC_3}{dt} = -k_{out}C_3 + \psi\left[C_{in} - C_3\right];
\]

\[
\frac{dC_4}{dt} = -k_{out}C_4 + \psi\left[C_{in} - C_4\right];
\]

[where $C_1$ and $C_2$ are concentrations of drug in the central (plasma), peripheral, peripheral, and peripheral, compartments, respectively; $AUC_{0–24}$ is the area under the concentration-time curve for the given drug dose; $k_{in}$ is the rate constant for drug administration; $\psi$ is the rate constant for drug absorption; $k_{out}$ is the rate constant for drug elimination; and $C_{in}$ is the concentration of drug in the inlet compartment (in mg/h).]

In addition, there were three output equations, defined as follows: $Y_1 = X_1/V; Y_2 = X_2/V; Y_3 = X_3/V; Y_4 = X_4/V$ (where $Y_1$, $Y_2$, and $Y_3$ are the micafungin concentrations in mg/liter in the central [plasma], peripheral, AC, and ELF compartments, respectively. The goodness of fit was assessed using the log-likelihood criterion during the model building. A graphical analysis of predicted versus observed concentration...
TABLE 1. Recovery of cells and ELF from BAL fluid

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD value at indicated time point (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cells/liter</td>
<td></td>
</tr>
<tr>
<td>3 h (4)</td>
<td>4.2 (±2.4) \times 10^8</td>
</tr>
<tr>
<td>5 h (4)</td>
<td>7.7 (±6.5) \times 10^8</td>
</tr>
<tr>
<td>8 h (4)</td>
<td>3.6 (±3.0) \times 10^8</td>
</tr>
<tr>
<td>18 h (4)</td>
<td>4.2 (±1.1) \times 10^8</td>
</tr>
<tr>
<td>24 h (4)</td>
<td>3.8 (±1.3) \times 10^8</td>
</tr>
<tr>
<td>PMNs (%)</td>
<td></td>
</tr>
<tr>
<td>3 h (4)</td>
<td>5.5 ± 6.4</td>
</tr>
<tr>
<td>5 h (4)</td>
<td>18.2 ± 12.1</td>
</tr>
<tr>
<td>8 h (4)</td>
<td>14.8 ± 20.3</td>
</tr>
<tr>
<td>18 h (4)</td>
<td>12.0 ± 20.0</td>
</tr>
<tr>
<td>24 h (4)</td>
<td>7.0 ± 10.8</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td></td>
</tr>
<tr>
<td>3 h (4)</td>
<td>3.0 ± 2.2</td>
</tr>
<tr>
<td>5 h (4)</td>
<td>2.0 ± 2.3</td>
</tr>
<tr>
<td>8 h (4)</td>
<td>1.2 ± 1.5</td>
</tr>
<tr>
<td>18 h (4)</td>
<td>2.0 ± 2.2</td>
</tr>
<tr>
<td>24 h (4)</td>
<td>6.8 ± 5.1</td>
</tr>
<tr>
<td>Monocytes/macrophages (%)</td>
<td></td>
</tr>
<tr>
<td>3 h (4)</td>
<td>74.0 ± 41.4</td>
</tr>
<tr>
<td>5 h (4)</td>
<td>78.8 ± 12.3</td>
</tr>
<tr>
<td>8 h (4)</td>
<td>82.5 ± 19.9</td>
</tr>
<tr>
<td>18 h (4)</td>
<td>85.8 ± 20.2</td>
</tr>
<tr>
<td>24 h (4)</td>
<td>84.2 ± 17.3</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td></td>
</tr>
<tr>
<td>3 h (4)</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>5 h (4)</td>
<td>0.5 ± 1.0</td>
</tr>
<tr>
<td>8 h (4)</td>
<td>0.2 ± 0.5</td>
</tr>
<tr>
<td>18 h (4)</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>24 h (4)</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>Other cells (%)</td>
<td></td>
</tr>
<tr>
<td>3 h (4)</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>5 h (4)</td>
<td>0.5 ± 1.0</td>
</tr>
<tr>
<td>8 h (4)</td>
<td>0.2 ± 0.5</td>
</tr>
<tr>
<td>18 h (4)</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>24 h (4)</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>Degenerated cells (%)</td>
<td></td>
</tr>
<tr>
<td>3 h (4)</td>
<td>17.5 ± 35.0</td>
</tr>
<tr>
<td>5 h (4)</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>8 h (4)</td>
<td>1.2 ± 2.5</td>
</tr>
<tr>
<td>18 h (4)</td>
<td>0.2 ± 0.5</td>
</tr>
<tr>
<td>24 h (4)</td>
<td>2.0 ± 4.0</td>
</tr>
<tr>
<td>ELF volume (ml)</td>
<td></td>
</tr>
<tr>
<td>3 h (4)</td>
<td>1.1 ± 1.0</td>
</tr>
<tr>
<td>5 h (4)</td>
<td>2.0 ± 1.5</td>
</tr>
<tr>
<td>8 h (4)</td>
<td>1.3 ± 1.2</td>
</tr>
<tr>
<td>18 h (4)</td>
<td>1.0 ± 0.6</td>
</tr>
<tr>
<td>24 h (4)</td>
<td>0.8 ± 0.1</td>
</tr>
</tbody>
</table>

* No significant differences were found between time groups for cell recovery or ELF volume. PMNs, polymorphonuclear leukocytes; other cells, other unrecognizable cells.

RESULTS

Twenty subjects were enrolled in the study. The primary pulmonary diagnoses included idiopathic pulmonary fibrosis (15 patients), chronic obstructive pulmonary disease (3 patients), bronchiolitis obliterans (1 patient), pulmonary agenesis (1 patient), right heart failure (1 patient), and unspecified end-stage lung disease (1 patient). Eighteen of the 20 underwent bilateral and 2 underwent unilateral lung transplantation. In all cases, the BAL was performed in the transplanted lung, and all 20 subjects who were enrolled in the study completed the bronchoscopy procedure. BAL was performed in the lingula in 10, the right middle lobe in 5, the right upper lobe in 2, and the left upper lobe in 3 of the 20 patients.

The mean age (± SD) of the patients was 59.0 ± 9.8 years; 10 were men and 10 were women; 15 were Caucasian, 1 was Hispanic, 2 were African-American, and 2 were multiracial. The weight (mean ± SD) of the subjects was 123.6 ± 12.3 kg. Prior to drug administration, serum creatinine, AST, ALT, alkaline phosphatase, and total bilirubin were 0.95 ± 0.28 mg/dl, 36.1 ± 27.1 IU/liter, 34.1 ± 37.4 IU/liter, 89.9 ± 47.6 IU/liter, and 0.75 ± 0.34 mg/dl, respectively.

Seventeen of the 20 subjects reported no adverse effects of the study drug. One subject experienced burning at the site of the intravenous infusion, which resolved with a change of the site. Two subjects experienced episodes of altered mental status, one of which was self-limited and required no intervention and the other for which the altered status lasted for 3 days and was considered unrelated to the study drug.

Poststudy laboratory testing was performed at 10.7 ± 17.6 days following infusion. There was no significant difference between the pre- and postdrug serum creatinine levels (1.11 ± 0.38 mg/dl; P > 0.05). The AST following drug administration (28.6 ± 22.4 IU/liter) was less than (P < 0.05) the predrug AST determination. The mean ALT and total bilirubin levels stayed within the normal ranges (41.6 ± 62.3 IU/liter and 0.74 ± 0.39 mg/dl, respectively). The poststudy alkaline phosphatase exceeded the normal range (160.0 ± 258 IU/liter). This elevated poststudy mean value was due to a single patient with underlying cirrhosis whose alkaline phosphatase was not measured until 2.5 months after the end of the study.

AC and ELF recovery. The number (mean ± SD) of AC recovered from BAL fluid ranged from 3.8 × 10^8 to 7.7 × 10^8 to 6.5 × 10^8 for the five time groups (Table 1). Alveolar cell recovery was not significantly different among the time groups (P > 0.05). The majority of the cells in all time groups consisted of monocytes and macrophages (range, 74.0 ± 41.4% to 85.8 ± 20.2%). The calculated volume (mean ± SD) of ELF recovered was 1.2 ± 0.1 ml. ELF recovery was not significantly different among the time groups (P > 0.05) (Table 1). The cell counts and differential cell counts obtained in these patients were similar to those previously reported in normal subjects (10, 11).

Mycfungin concentrations and pharmacokinetics. The concentrations of micafungin in plasma, AC, and ELF and the AC/plasma and ELF/plasma ratios at the time of BAL are summarized in Fig. 1 and Table 2. The Cmax in plasma, ELF, and AC was 4.93 ± 0.97, 1.38 ± 1.93, and 17.41 ± 24.25 pg/ml, respectively. The Tmax in plasma, ELF, and AC was 4.0 ± 0.5, 24.2 ± 1.8, and 17.9 ± 1.4 h, respectively. The elimination half-life in plasma was 12.1 h.
tion parameter distribution. The means, medians, and standard deviations of the probability distribution are presented in Table 3. Population predictions calculated using these means correlated well with observed concentrations, and predictive performance was good (Fig. 2A). The goodness of fit for Bayesian posterior predictions was also very good (Fig. 2B). Body weight was tested as a covariate on clearance and also on volume of distribution. However, this did not result in any significant increase in the log likelihood, which indicated no improvement in the fit. Thus, body weight was not included in the model.

(ii) Final model. A 10-parameter, four-compartment linear model best fit the data. The model structure assumed a linear diffusion of micafungin from the peripheral compartment into both the ELF and the AC compartments. The model also included a possible transfer between ELF and AC compartments.

A 14-support point grid was provided by the NPAG algorithm as a population parameter distribution. Parameter values of the final model are summarized in Table 4. Pharmacokinetic variability, especially concerning intercompartmental clearances, was high. Based on median clearance values, micafungin penetration into the ELF was approximately eight times slower than in AC.

Overall, population predictions correlated quite well with observed concentrations except for the four highest micafungin levels measured in AC. As a result, the predictive performance of the population model was heavily biased (data not shown). However, individual predictions obtained after the Bayesian step showed better agreement with observed concentrations (Table 5).

Predictive performance of the final model is presented in Table 5 (individual predictions). Overall results were acceptable but varied according to the type of concentration and also according to the measure considered. Weighted measures were better than nonweighted measures for AC drug concentrations because of the lower credibility given to the higher concentrations by the assay error pattern. The opposite tendency was observed for ELF drug concentrations, due to a large number of undetectable and low micafungin concentrations observed, which were given a high credibility in the modeling framework.

The statistical analysis did not find any significant relationship between the tested covariates and the pulmonary diffusion PK parameter values of the final model except for BAL location and

![FIG. 1. Concentrations of micafungin in plasma, AC, and ELF.](image)

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Drug concn or ratio between compartments at indicated sampling point (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 h (4)</td>
</tr>
<tr>
<td>Plasma</td>
<td>4.93 ± 0.97</td>
</tr>
<tr>
<td>ELF</td>
<td>0.04 ± 0.07</td>
</tr>
<tr>
<td>ELF/plasma</td>
<td>0.01</td>
</tr>
<tr>
<td>AC</td>
<td>7.17 ± 13.21</td>
</tr>
<tr>
<td>AC/plasma</td>
<td>1.53</td>
</tr>
</tbody>
</table>

*The subject who received four doses was excluded from the time-group analysis. His plasma, ELF, and AC drug concentrations were 5.38 µg/ml, 0.69 µg/ml, and 33.31 µg/ml, respectively.*
the volume of distribution in the ELF compartment ($V_4$). $V_4$ was significantly higher ($P = 0.0084$) in individuals sampled in the lingula (mean volume, 15.69 ± 0.33 liters; n = 11) than in those sampled in other sites (mean volume, 7.47 ± 6.25 liters; n = 9).

### TABLE 3. Population PK parameter values of the plasma micafungin concentration model

<table>
<thead>
<tr>
<th>Statistic</th>
<th>CL_{10} (liters/h)</th>
<th>$K_{12}$ (h$^{-1}$)</th>
<th>$K_{21}$ (h$^{-1}$)</th>
<th>$V_1$ (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.309</td>
<td>3.068</td>
<td>6.795</td>
<td>17.617</td>
</tr>
<tr>
<td>Median</td>
<td>1.411</td>
<td>1.625</td>
<td>7.096</td>
<td>16.750</td>
</tr>
<tr>
<td>SD</td>
<td>0.262</td>
<td>2.766</td>
<td>2.034</td>
<td>5.109</td>
</tr>
</tbody>
</table>

**Drug exposure simulation.** The simulated time-concentration profiles in plasma, ELF, and AC of the 20 individuals over the first 72 h of micafungin therapy (150 mg intravenously once daily; 1-h infusion) are depicted in Fig. 3. AUC and AUC ratios predicted in the 20 individuals during 14-day micafungin therapy administered once daily (150 mg) are presented in Table 6. The simulation indicated that micafungin exposure in plasma increased from day 1 to day 7 but not significantly from day 7 to day 14. Significant drug accumulation over the 14 days was predicted in the two lung compartments, especially in the ELF compartment, but interindividual variability in drug exposures was high. The median value of AUC$_{AC}$/AUC$_{plasma}$

![Graph](http://aac.asm.org/)

**FIG. 2.** Plot of predicted versus observed concentrations for the plasma drug concentration model. (Top) Population predictions; (bottom) individual predictions (calculated using the means of the individual Bayesian posterior parameter joint densities).
with micafungin have been performed in healthy and hospital-
intravenous administration. Plasma pharmacokinetic studies 
elevated and sustained intrapulmonary concentrations in ELF 
PKPD findings indicate that micafungin achieves sufficiently 
13,340, respectively. Concentrations of micafungin in ELF and 
total AUC0–24/MIC90 ratios in ELF and AC were 923 and 
martly 0.3 and 3.5. Consistent with these observations, the 
time above MIC 90 was 24 h in all compart-

Measures of bias 

Mean 0.279 0.0067 0.362 5.407 1.607 12.024 1.309 3.068 6.795 17.617
Median 0.0903 0.0118 0.0143 3.519 0.851 15.361
SD 0.772 0.0236 0.708 4.992 1.455 5.712

a Subscript numeral correspond to compartments as follows: 1, central (plasma) compartment; 2, peripheral compartment; 3, AC compartment; 4, ELF compartment. 

AUC0–24 in ELF and AC were 10.2 and 233.6 

<table>
<thead>
<tr>
<th>Statistic</th>
<th>CL23</th>
<th>CL24</th>
<th>CL34</th>
<th>V2</th>
<th>V1</th>
<th>V4</th>
<th>CL10</th>
<th>K12</th>
<th>K31</th>
<th>V1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
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<td>0.0143</td>
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<tr>
<td>SD</td>
<td>0.772</td>
<td>0.0236</td>
<td>0.708</td>
<td>4.992</td>
<td>1.455</td>
<td>5.712</td>
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<td></td>
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</table>

The plasma drug free and 
total Cmax/MIC90 ratios were 3.2 and 316.0, respectively. Cmax/ 
MIC90 ratios were 88.5 and 1,115.4 in ELF and AC, respec-
tively. The mean time above MIC90 was 24 h in all compart-
ments (Fig. 1). AUC0–24/MIC90 ratios were 5,077, 923.1, and 
max/MIC90 ratios were 3.2 and 316.0, respectively.

Increased from 0.98 on day 1 to 2.13 on day 7 and 2.26 on day 
14. Over the 14-day therapy course, the median value was 
about 2. The median AUCELF/AUCplasma value was very low 
on day 1 (0.07) but greatly increased to 0.66 and then 1.12 on 
day 7 and day 14, respectively. The median value of this ratio 
was 0.68 over the 14-day period.

**Micafungin pharmacodynamics.** The plasma drug free and 
total Cmax/MIC90 ratios were 3.2 and 316.0, respectively. Cmax/ 
MIC90 ratios were 88.5 and 1,115.4 in ELF and AC, respec-
tively. The mean time above MIC90 was 24 h in all compart-
ments (Fig. 1). AUC0–24/MIC90 ratios were 5,077, 923.1, and 
13,340 in plasma, ELF, and AC, respectively.

**DISCUSSION**

This single-dose prospective study of the intrapulmonary 
and plasma PKPD of 150 mg intravenous micafungin in adult 
lung transplant recipients found distribution into the ELF and 
AC of this echinocandin that substantially exceeded the re-
ported MIC90 of *A. fumigatus*. At concentrations near the 
Cmax, the ELF/plasma and AC/plasma ratios were approxi-
mately 0.3 and 3.5. Consistent with these observations, the 
total AUC0–24/MIC90 ratios in ELF and AC were 923 and 
13,340, respectively. Concentrations of micafungin in ELF and 
AC were sustained throughout the 24-h dosing interval. These 
PKPD findings indicate that micafungin achieves sufficiently 
elevated and sustained intrapulmonary concentrations in ELF 
and AC to support activity for prevention and early treatment 
of invasive aspergillosis.

Micafungin is not absorbed orally and can only be given by 
intravenous administration. Plasma pharmacokinetic studies 
with micafungin have been performed in healthy and hospital-
ized adults (16–20). In healthy subjects receiving a 150-mg 
intravenous dose, the Cmax, half-life (*t*1/2), clearance, and AUC 
are 8.7 ± 2.9 μg/ml, 14.8 ± 1.7 h, 10 ± 1.6 ml/h/kg, and 120.9 ± 
16.7 μg · h/ml. Steady state is achieved in approximately 4 to 5 
days. Moderately reduced liver function and moderate to se-
vere impaired renal function have no significant effects on the 
pharmacokinetics of micafungin and therefore require no dos-
age adjustment. A study of the intrapulmonary PKPD in 
healthy subjects found that micafungin concentrates in AC; the 
AUC0–24 in ELF and AC were 10.2 and 233.6 μg · h/ml, re-
spectively (28). The half-life, Cmax, and Tmax have not been 
reported for pulmonary compartments. Protein binding of 
micafungin in humans is 99%, predominantly to albumin and 
independent of circulating drug concentrations over the range 
of 10 to 100 μg/ml.

Three of 20 subjects (15%) had treatment-emergent adverse 
events during the course of the study. Among these adverse 
events, the episode of altered mental status was considered to 
be unrelated to the study drug. This relatively well-tolerated 
safety profile is consistent with the observations of the ran-
domized trial of micafungin in prevention of invasive fungal 
infestions in neutropenic hematopoietic stem cell transplant 
recipients, in which its safety profile was comparable to that 
of fluconazole (44).

The intrapulmonary distribution of micafungin into AC and 
ELF has important implications for lung transplant recipients 
and other immunocompromised host populations. As pulmo-
nary alveolar macrophages ingest conidia of *Aspergillus spp.* as 
the first line of phagocytic host defense (46, 47), the high 
intracellular concentrations of micafungin may further aug-
ment its properties when used as prophylaxis. The effects of
denervation and lack of bronchial circulation on the pharmacology of echinocandins in the transplanted lung have not been studied. Laboratory and clinical observation studies of immunocompromised hosts have demonstrated impairment of pulmonary alveolar macrophages and monocyte-derived macrophages (7, 37). Given the intrinsic and pharmacological immunosuppression associated with lung transplantation and other transplant conditioning regimens, the high intracellular drug concentrations may be particularly advantageous in this population. These findings also warrant several questions as to the mechanism of intracellular drug uptake and the possible immunomodulatory effects on the host response.

Distribution of micafungin into the ELF may be particularly beneficial in lung transplant recipients, where bronchial anastomotic aspergillosis can be a catastrophic complication (40). Such devastating complications include loss of the transplanted lung, bronchopleural fistula, and bronchial-pulmonary artery fistula. Sustained drug concentrations in the ELF, as demonstrated in the study reported herein, may reduce the development of anastomotic aspergillosis. A prospective study investigating micafungin in prevention of invasive aspergillosis in lung transplant recipients is warranted to confirm this hypothesis.

The pharmacodynamic parameters that best predict outcomes for treatment of invasive pulmonary aspergillosis with micafungin have not been defined (25). The $C_{\text{max}}$/minimally effective concentration (MEC) ratio has been reported to be the parameter best associated with efficacy for caspofungin (48), with an optimal range of 10 to 20 against experimental murine aspergillosis. However, Louie and colleagues found in a study of the pharmacodynamics of caspofungin in a murine model of disseminated candidiasis that the AUC/MIC ratio was a better predictor, possibly as a result of the echinocandin's slow elimination from tissues (27). Similarly, Andes et al. found that the in vivo pharmacodynamic target for micafungin against *Candida albicans* and *Candida glabrata* in a neutropenic murine model of disseminated candidiasis were free-drug AUC/MIC ratios for stasis and killing of approximately 10 and 20, respectively (3). Although the parameter that best predicts efficacy is not known, our results showed that even

![Graph](image1.png)

**FIG. 3.** Simulated concentration-time profiles of micafungin in plasma (top), AC (middle), and ELF (bottom) from 20 lung transplant patients.

<table>
<thead>
<tr>
<th>TABLE 6. Drug exposures predicted in lung transplant patients receiving micafungin administered intravenously once daily for 14 days</th>
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$^*$All data are given as mean ± SD.

**AUC ratio = AC AUC$_{0-24h}$/Plasma AUC$_{0-24h}$ and ELF AUC$_{0-24h}$/Plasma AUC$_{0-24h}$.
when estimated free drug levels are taken into account, the \( C_{\text{max}} \) and total exposure (AUC) were both high relative to the MIC\(_{90}\), indicating a strong likelihood of favorable outcomes for treatment of *Aspergillus* infections in lung transplant patients.

The intrapulmonary PKPD of micafungin in normal volunteers has been reported elsewhere (28). Those results, which are similar to our findings, demonstrate that micafungin achieves levels that are sustained above the MEC in all compartments, with significant concentration in AC. In that multiple-dose study (three doses), the AUC\(_{0-24}\) for plasma (219.7 ± 37.6 \( \mu \)g·h/ml) was approximately three times greater than that we observed (79.2 \( \mu \)g·h/ml) in this single-dose study. The AUC\(_{0-24}\) for ELF and AC were 10.2 \( \mu \)g/h/ml and 233.6 \( \mu \)g/h/ml, respectively, which were similar to those we observed (14.4 \( \mu \)g/h/ml and 208.1 \( \mu \)g/h/ml). These differences are relatively small and likely due in part to differences in study design (three doses versus one dose), lavage technique, specimen collection, and the populations studied.

Our population modeling suggests that steady state would be achieved in plasma by day 7 at an AUC\(_{0-24}\) of approximately 117 \( \mu \)g·h/ml, which is consistent with reports that plasma drug steady state is achieved within 3 to 6 days (21, 28). However, 24-h exposure in AC and especially ELF continued to increase from days 7 to 14. This suggests the possibility that the attainment of steady state may be delayed in pulmonary compartments and that the half-lives of micafungin in ELF and AC are greater than that in plasma. The model also predicts that exposure in ELF, which had the lowest drug concentrations of any compartment after a single dose, would continue to increase with repeated dosing and would exceed exposure in plasma over a 2-week dosing period. The drug accumulation, prolonged residence time, and high inhibitory ratios in pulmonary compartments further suggest that micafungin would be effective in prevention and early treatment of invasive pulmonary aspergillosis.

Once deeply invasive aspergillosis is well established as a pneumatic process, distribution into the AC and ELF compartments may not necessarily be predictive of response. Other physiological and compartmental factors affecting penetration of micafungin would then be relevant. These factors include penetration of micafungin into an infarcted lung in neutropenic hosts, local tissue hypoxia, and concentration of drug in circulating neutrophils in nonneutropenic hosts. The effects of other routes of delivery, such as aerosol administration, on these PKPD parameters have not been studied.

We conclude the following: (i) a single intravenous dose of 150 mg resulted in sustained plasma, ELF, and AC drug concentrations that were above the MIC\(_{90}\) for *Aspergillus fumigatus* during the entire 24-hour dosing interval; (ii) multiple-dose simulations indicate that ELF and AC concentrations of micafungin will continue to increase during 14 days of administration; (iii) the high intrapulmonary \( C_{\text{max}}/\text{MIC}_{90} \) and AUC\(_{0-24}^{	ext{MIC}_{90}} \) ratios and time above MIC\(_{90}\) observed in this study are favorable for the treatment or prevention of aspergillosis; (iv) cell counts, differential cell counts, and ELF recovered from transplanted lungs are similar to those observed in normal subjects; (v) intravenous micafungin was well tolerated in adult lung transplant recipients.

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