Invasive aspergillosis has drawn serious attention because of its high mortality and increasing prevalence within immunocompromised patients since the 1990s (13, 19, 20). Because most invasive aspergillosis infections occur in the respiratory tract (20), it is fundamentally important to provide adequate antifungal exposure to this difficult-to-reach infection site. As a result of the recent success of echinocandins combined with other first-line agents, the idea of combination therapy for invasive aspergillosis has been given serious consideration (16, 21). Micafungin, a member of the echinocandin class, has potent in vitro activity against Aspergillus species and is considered an acceptable salvage therapy option for invasive pulmonary aspergillosis (4, 22). While the pharmacokinetics of micafungin in plasma have been well described, the bronchopulmonary disposition is largely unknown, aside from data from animal studies (7). Bronchoscopy and bronchoalveolar lavage (BAL) studies with uninfected volunteers have become a useful approach for determining intrapulmonary pharmacokinetics for antimicrobials (3, 5, 6). To our knowledge, we describe the first investigation to determine the bronchopulmonary disposition of an echinocandin in healthy volunteers.

This prospective phase I pharmacokinetic study was reviewed and approved by the Hartford Hospital institutional review board. The trial included 15 nonsmoking, healthy adults (20 to 46 years old) who met eligibility requirements based on a comprehensive medical evaluation and provided written informed consent prior to the study. Included participants received three 150-mg doses of micafungin (Astellas Pharma US, Inc., Deerfield, IL) administered intravenously over 1 h every 24 h.

Blood samples were collected at 0 h (before the third dose), 1 h (at the end of the infusion of the third dose), and 4, 12, and 24 h after the third dose. As described previously, single bronchoscopy and BAL procedures for each participant were performed at either 4, 12, or 24 h after the third dose (five participants per time point) (3). After the initial aspirate was discarded, the remaining BAL aspirates were pooled (mean volume ± standard deviation, 95 ± 19 ml) and small portions were separated for complete cell count (mean value, 1.1 × 10⁷ cells/liter) and urea concentration determination. The remaining BAL fluid was centrifuged to separate the cell pellet. Urea concentrations in BAL fluid and plasma were analyzed with a colorimetric enzymatic assay (urea nitrogen diagnostic kit no. 640; Sigma, St. Louis, MO) by a detection method employing a spectrophotometer (Cary 50 series; Varian, Walnut Creek, CA). Micafungin concentrations in plasma, BAL fluid, and the lysed cell pellet were measured by a modified and validated high-pressure liquid chromatography method (8, 20) at the Fungal Testing Laboratory (San Antonio, TX). The standard curves for each of the matrices were linear over a range of 0.05 to 25.0 μg/ml (r² = 0.99), while the interday and intraday coefficients of variation were ±11.3% and <18%, respectively.

Concentrations in plasma and AC differed significantly from those in ELF (P = 0.009 and 0.008, respectively, by analysis of variance and Student's Newman-Keuls test for multiple comparisons of repeated measurements).

Concentrations in AC differed significantly from those in plasma and ELF (P = 0.015 and 0.005, respectively, by analysis of variance and Student's Newman-Keuls test for multiple comparisons of repeated measurements).

<table>
<thead>
<tr>
<th>Collection time (h)</th>
<th>Plasma (μg/ml)</th>
<th>ELF (μg/ml)</th>
<th>AC (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentration (mean ± standard deviation)</td>
<td>Concentration (mean ± standard deviation)</td>
<td>Concentration (mean ± standard deviation)</td>
</tr>
<tr>
<td>4</td>
<td>14.8 ± 1.6</td>
<td>0.52 ± 0.1</td>
<td>10.4 ± 5.6</td>
</tr>
<tr>
<td>12</td>
<td>7.4 ± 1.4</td>
<td>0.44 ± 0.1</td>
<td>8.4 ± 5.5</td>
</tr>
<tr>
<td>24</td>
<td>4.8 ± 0.6</td>
<td>0.43 ± 0.2</td>
<td>14.6 ± 8.6</td>
</tr>
</tbody>
</table>

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By way of bronchoscopy and bronchoalveolar lavage, intrapulmonary steady-state concentrations of micafungin administered at 150 mg daily to 15 healthy volunteers were determined at 4, 12, and 24 h after the third dose. The micafungin disposition was predominantly intracellular, with approximately 100% penetration into alveolar macrophages and 5% penetration into epithelial lining fluid.
unclear, it is suggested that the invading host defense (9, 11, 14). Although the exact pathogenesis is ciliary clearance, AC along with neutrophils are the primary concentration/MEC ratio of 10. While this exposure target was against

These antifungals display concentration-dependent activities in all matrices, including projected concentrations of free drug in plasma, were above the median minimum effective concentration (MEC) of 0.06 µg/ml for conidial strains of Aspergillus fumigatus throughout most of the dosing interval (Fig. 1) (2).

In summary, micafungin at 150 mg once daily in healthy volunteers concentrates predominately within AC, with complete (106%) penetration relative to the total plasma drug exposure. These data provide encouraging support for clinical investigations determining the role of micafungin in the treatment or prophylaxis of invasive pulmonary aspergillosis.

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REFERENCES


