Micafungin Concentrations from Brain Tissue and Pancreatic Pseudocyst Fluid[∇]

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We report the attainment of micafungin concentrations from brain tissue and pancreatic pseudocyst fluid from two patients with invasive candidiasis. Micafungin was present in low levels at both body sites, indicating limited penetration into central nervous system (CNS) tissue and pancreatic fluid. Further studies are needed to fully characterize its pharmacokinetics at these locations, as micafungin may potentially serve as an alternative antifungal therapy for CNS or pancreatic candidal infections for which the currently recommended first-line therapy fails.

Micafungin is an echinocandin widely used for the treatment of invasive candidiasis (2, 6, 7, 8, 10). Little information exists regarding its penetration into human brain tissue and pancreatic fluid. We report the measurement of micafungin levels from these sites in 2 patients during treatment of invasive candidiasis.

Patient 1. A 79-year-old male with a history of dysphagia secondary to cricopharyngeal achalasia was transferred from an outside hospital with an esophageal rupture, pneumomediastinum, and left pneumothorax. He was initiated on antimicrobial therapy with ciprofloxacin, fluconazole, piperacillin-tazobactam, and vancomycin, and bilateral pleural catheters were placed. Cultures from the pleural catheters on hospital day (HD) 9 grew fluconazole-resistant *Candida glabrata* (MIC = 64 µg/ml). Echinocandin susceptibility was not determined. Fluconazole was discontinued, and micafungin (100 mg daily; 1.69 mg/kg of body weight) was initiated. Computed tomographic (CT) imaging was consistent with an esophageal-pleural fistula and mediastinitis. The patient underwent a left thoracotomy and decortication on HD 13, and pleural tissue cultures also grew fluconazole-resistant *Candida glabrata*. He subsequently developed left hemiparesis, and CT imaging of the head revealed a frontal lobe lesion concerning for an abscess on HD 29. Brain tissue specimens were obtained on HDs 31 and 53 via craniotomy and tissue biopsy. Bacterial, myco-

bacterial, and fungal cultures were negative, and pathology was inconsistent with malignancy. Micafungin plasma and brain tissue levels were obtained simultaneously during the second neurosurgical procedure, 23 h after the previous dose. Micafungin concentrations were assayed (lower limit of quantification, 0.05 µg/ml; Beckman Coulter, Fullerton, CA) using high-performance liquid chromatography (11). The plasma level was 1.58 µg/ml, and the corresponding brain tissue level was 0.28 µg/ml (0.26 µg/g). The patient was stabilized and eventually discharged to a long-term care facility on HD 81.

Patient 2. A 31-year-old male with a history of biliary pancreatitis and pancreatic pseudocysts was readmitted for further management of an enlarging pancreatic pseudocyst. Upon admission, his renal function and nutritional status were within normal limits, but liver function tests demonstrated an elevated aspartate aminotransferase level, total bilirubin, and alkaline phosphatase. A culture of pancreatic pseudocyst fluid from the pseudocyst catheter on HD 1 revealed heavy growth of *Candida albicans* and *C. glabrata*, both fluconazole susceptible (echinocandin susceptibility was not determined). He was initially treated with fluconazole, but antifungal therapy was changed to micafungin therapy on HD 3 due to elevated transaminase levels (8 times the upper limit of the normal range). The micafungin pancreatic pseudocyst fluid level obtained from the pseudocyst catheter on HD 10 was 0.38 µg/ml 24 h after the previous dose. The patient subsequently underwent pancreatic necrosectomy and cholecystectomy on HD 21 and was discharged home on HD 53.

The pharmacokinetics of micafungin are similar to those of other echinocandins, with a low volume of distribution and extensive protein binding (5). However, its high molecular weight, water solubility, and pharmacokinetics may potentially limit drug availability at sequestered sites. Unfortunately, there is a paucity of data regarding its disposition in various tissues and fluids. To our knowledge, this is the first report of the

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assessment of micafungin concentrations in brain tissue and pancreatic fluid in humans.

Brain tissue penetration has previously been reported to occur in rabbit models. Groll et al. evaluated the plasma pharmacokinetics and tissue distribution of micafungin in healthy rabbits (4). In rabbits administered micafungin doses of 0.5, 1, and 2 mg/kg/day intravenously for a total of 8 days, micafungin was detectable in brain tissue at concentrations of 0.08, 0.10, and 0.18 $\mu\text{g/g}$, respectively, 30 min after the eighth dose. In contrast, concentrations in the lungs ranged from 2.26 to 11.76 $\mu\text{g/g}$ and 1.40 to 6.12 $\mu\text{g/g}$ in the kidneys. This model resulted in an area under the concentration-time curve in rabbits receiving the maximum dose that was approximately one-fifth that seen in humans administered the 100-mg daily dose routinely used in clinical practice, due to a considerably shorter half-life in rabbits. Though micafungin concentrations in brain tissue were diminished in comparison to those in other tissues, they were evaluated at only one time point after administration and in the absence of tissue inflammation.

In a neutropenic rabbit model of disseminated candidiasis, rabbits receiving micafungin at doses of 0.25, 0.5, 1, and 2 mg/kg/day for a maximum of 10 days were compared to untreated controls (9). Micafungin doses of 0.5, 1, and 2 mg/kg were effective in significantly reducing the *C. albicans* burden from brain tissue, compared to the level for the untreated control animals ($P < 0.001$). Interestingly, only the highest micafungin dose completely eradicated *C. albicans* from brain tissue, while lower doses were effective in fully clearing other tissues. While this study did not evaluate brain tissue concentrations of micafungin, it does suggest a dose-response relationship in the clearance of central nervous system (CNS) candidiasis. Similar data for pancreatic micafungin concentrations in animals have not been reported.

CNS *Candida* infections are a rare consequence of disseminated candidiasis or neurosurgical procedures (8). Current treatment guidelines recommend a lipid formulation of amphotericin B as initial therapy but do not recommend echinocandins as treatment for CNS candidiasis (7). The available animal data indicate that micafungin penetrates brain tissue and reduces candidal burden in a dose-dependent manner. Thus, micafungin may potentially be considered in clinical situations where guideline-recommended therapy is failing, but further human data are required to verify its efficacy in this setting.

The use of prophylactic antibiotics in necrotizing pancreatitis is a widespread practice (1, 12). Broad-spectrum antibiotics for prolonged periods may increase the risk of fungal infections of the necrotic pancreas or peripancreatic tissue, necessitating treatment with antifungals, and fluconazole is often utilized in this setting (3, 13). Micafungin may be an alternative to fluconazole, but it has not been evaluated clinically for this purpose.

Our data were obtained for 2 patients as trough levels. Though a firm conclusion cannot be made regarding micafungin pharmacokinetics in brain tissue and pancreatic fluid on the basis of this information, it is notable that active drug was present in low levels after several days of therapy. Taken in combination with the animal data cited above, this raises the possibility that micafungin may have limited penetration into CNS tissue and pancreatic fluid and warrants further characterization of its pharmacokinetics in these body sites in humans.

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