Pharmacokinetics of Anidulafungin in Pleural Fluid during the Treatment of a Patient with Candida Empyema

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Candida empyema is a serious complication of disseminated candidiasis. However, little is known about the intrapleural pharmacokinetics of echinocandins. We report the penetration of anidulafungin into the pleural fluid of a patient with Candida tropicalis empyema. The anidulafungin ratio for the area under the concentration-time curve from 0 h to the last measurement between pleural fluid and serum values was only 0.125 (12.5%), with pleural fluid concentrations ranging between 0.67 and 0.88 μg/ml.

Echinocandins are a novel class of antifungal agents with activities against Candida spp. (4). Candida species are a common cause of fungal empyemas (6). However, management of Candida empyema is not well defined (11), and there are limited data on the penetration of echinocandins into human pleural fluid (9). We therefore report the pharmacokinetics and penetration of anidulafungin into the pleural fluid of a patient with Candida tropicalis empyema.

Case description. A 44-year-old male recipient of a sibling-matched peripheral blood stem cell transplant for acute myeloid leukemia was admitted to the intensive care unit with septic shock. The patient’s course had been complicated by graft-versus-host disease of the gastrointestinal tract with colonic perforation and colostomy placement, multiple bacterial infections requiring broad-spectrum antibiotics, and chronic dialysis-dependent, end-stage renal failure. Blood cultures grew C. tropicalis, and treatment with caspofungin was initiated. Computed tomography showed findings consistent with a loculated left pleural effusion. A diagnostic thoracentesis was performed, and a size 8 French chest tube was placed, which was subsequently replaced with a size 16 French chest tube. The pleural fluid chemistries revealed an exudative effusion with a total protein level of 2.1 g/dl. Pleural fluid cultures grew C. tropicalis. The MICs at 24 h showed that the C. tropicalis isolate was resistant to antifungal triazoles (fluconazole MIC, >256 μg/ml; voriconazole MIC, >8 μg/ml; posaconazole MIC, >8 μg/ml) but susceptible to micafungin (MIC, 0.03 μg/ml), caspofungin (MIC, 0.12 μg/ml), and anidulafungin (MIC, 0.12 μg/ml). The MIC of amphotericin B was 1 μg/ml. Paradoxical growth occurred above the MIC for both micafungin and caspofungin, but not for anidulafungin at 48 h. Although the clinical significance of this phenomenon is unknown (1), caspofungin was discontinued and anidulafungin was initiated with a loading dose of 200 mg intravenously (i.v.) followed by a maintenance dose of 100 mg i.v. every 24 h. Intrapleural recombinant tissue plasminogen activator successfully broke down all visible loculations, but the lung did not fully expand.

Anidulafungin concentrations in serum and pleural fluid were measured to assist in the management of the patient’s C. tropicalis empyema. Serum and pleural fluid drug concentrations were obtained after 10 doses of anidulafungin (100 mg i.v. every 24 h). Serum and pleural fluid samples were drawn into plain red-top tubes via a venous catheter and from the chest tube, respectively. Samples were immediately placed on ice, centrifuged at 3,500 × g for 10 min, and stored at −70°C. Samples were shipped on dry ice to the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio, San Antonio, TX. Concentrations of anidulafungin were measured by an internally validated assay using high-performance liquid chromatography with fluorescence detection.

The anidulafungin values for the areas under the concentration versus time curves from 0 h to the last measured concentration in serum (AUCserum) and in pleural fluid (AUCpleural fluid) were determined using standard noncompartmental methods with the WinNonlin Professional computer program (version 5.0; Pharsight Corporation, Mountain View, CA). The AUCpleural fluid was 16.33 μg · h/ml, and the AUCserum was 130.08 μg · h/ml, with an AUCpleural fluid/AUCserum ratio of 12.5% (Fig. 1). The pleural fluid/serum anidulafungin concentration ratios for individual time points are presented in Table 1.

Due to the relatively low anidulafungin concentrations in the patient’s pleural fluid, the anidulafungin dose was increased to 150 mg i.v. every 24 h, without apparent toxicity. Pleural fluid
from the chest tube subsequently remained negative for fungus by wet mount and culture over the next 35 days. Repeat computed tomography of the chest showed a unified pleural space without visible loculations but failure of the chest tube to fully expand the left lung. Blood cultures also remained negative for *C. tropicalis*. Unfortunately, due to multiple chronic intractable medical problems, medical care was eventually limited to comfort measures and the patient died 48 days after first presenting with candidemia.

**Discussion.** *Candida tropicalis* empyema is a relatively uncommon infection that has seldom been reported (2, 6, 8). Nonetheless, in a retrospective study of fungal empyema thoracis by Ko and colleagues, *C. tropicalis* and *Candida glabrata* were the second most common fungal pathogens isolated from pleural fluid specimens after *Candida albicans* (6). However, as *Candida* empyema is an uncommon infection, management recommendations are not specifically addressed in the Infectious Diseases Society of America guidelines for management of candidiasis (11).

Management of *Candida* empyema includes administration of an appropriate antifungal agent along with adequate drainage of the infected pleural space. Disruption of loculations may enhance pleural drainage and allow better antifungal penetration. Unfortunately, there are only limited data on penetration of antifungal agents into pleural fluid of humans (7, 9, 10, 12–14). The range of percent penetration of antifungal agents into pleural fluid is reported to be 3% to 9.4% for liposomal amphotericin B and 45.2% to 94.7% for voriconazole (10, 12–14). By comparison, little is known about the intrapleural pharmacokinetics of echinocandins. While caspofungin is FDA approved for *Candida* pleural space infections, to our knowledge there is only one published report describing echinocandin penetration into pleural fluid. Matsuda and colleagues recently reported that the penetration of micafungin at 22 h postdose into the pleural fluid of a patient with *Aspergillus* empyema...
ranged from 57 to 67% (9). However, as variations in intrapleural pharmacokinetics among the echinocandins may occur due to differences in polarity of the cyclic hexapeptide or substitutions in the N-acyl side chain, we characterized the penetration of anidulafungin into pleural fluid.

The anidulafungin AUC\textsubscript{serum} of 130.08 μg · h/ml was consistent with that of previous pharmacokinetic parameters reported for adults (5). Penetration of anidulafungin into pleural fluid was relatively low, with an AUC\textsubscript{pleural fluid}/AUC\textsubscript{serum} ratio of 12.5% and absolute pleural fluid concentrations from 0.67 to 0.88 μg/ml. Whether this isolate of \textit{C. tropicalis}, with a MIC of 0.12 μg/ml, might have been microbiologically cleared from the pleural fluid without increasing the anidulafungin dose to 150 mg i.v. every 24 h is uncertain. Nevertheless, \textit{Candida} species with a MIC of ≥1 μg/ml would likely not be eradicated from the pleural space, and alternative antifungal agents, such as liposomal amphotericin B (10) or voriconazole (12, 13), would be warranted based on susceptibility testing.

This study further enhances our understanding of the intrapulmonary pharmacokinetics of anidulafungin. The anidulafungin epithelial lining fluid and alveolar macrophage penetration ratios have been reported to be 0.22 and 14.2, respectively (3).

In conclusion, anidulafungin has a low percent penetration into the pleural fluid of humans. In this patient, anidulafungin and chest tube drainage cleared \textit{C. tropicalis} from the pleural space. Alternative antifungal agents should be considered in treatment of \textit{Candida} empyema caused by organisms with a MIC of ≥1 μg/ml to anidulafungin. Further pharmacokinetic and pharmacodynamic studies are needed to clarify echinocandin penetration into pleural fluid as a guide to treatment of \textit{Candida} empyema.

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REFERENCES