Pharmacokinetics of Liposomal Amphotericin B in Pleural Fluid

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We report the penetration of liposomal amphotericin B into the pleural fluid of a patient with pulmonary zygomycosis and empyema. The ratio of area under the concentration-versus-time curve in pleural fluid (AUCpleural fluid) to that in serum (AUCserum) for liposomal amphotericin B over 24 h was 9.4%, with pleural fluid concentrations of 2.12 to 4.91 µg/ml. Given the relatively low level of intrapleural penetration of liposomal amphotericin B, chest tube drainage may be warranted for successful treatment of zygomycotic empyema.

Invasion of the pleural space is a serious complication of fungal pneumonias (9). There is limited information on the penetration of liposomal amphotericin B (LAmB) into the pleural fluid of humans (20). We report herein a detailed pharmacokinetic sampling and analysis of the penetration of LAmB into the pleural fluid of a patient with pulmonary zygomycosis (mucormycosis) and empyema.

Case description. A 52-year-old female recipient of a myeloablative allogeneic hematopoietic stem cell transplant for mantle cell lymphoma was admitted to the intensive care unit with increasing dyspnea. Her course had been complicated by corticosteroid-induced diabetes mellitus and graft-versus-host disease involving the skin, liver, and gastrointestinal (GI) tract, necessitating high-dose corticosteroids, infliximab, and dactilumab. Computed tomography showed findings consistent with a cavitary right upper-lobe lesion and associated pleural effusion. Surgical wedge resection of the right-upper-lobe lesion was undertaken, pleural fluid was sampled, and two 32 French drainage chest tubes were placed, one inferiorly and one superiorly. A wet mount of the pleural fluid showed broad nonseptate hyphae morphologically consistent with a zygomycete. Pathological inspection of the surgical sample similarly showed broad nonseptate hyphae with nondichotomous branching within the lung tissue as well as infiltration of the vascular wall and intravascular thrombosis.

The patient was diagnosed with pulmonary zygomycosis and empyema. She received LAmB at an initial dose of 5 mg/kg of body weight (440 mg) intravenously (i.v.) every 24 h for 15 days. Thoracotomy, lung resection, and insertion of chest tubes were performed on day 13 of LAmB therapy. However, in light of a worsening renal function (serum creatinine peaked at 2.7 mg/dl), the dosage of LAmB was changed to 7.5 mg/kg (660 mg) i.v. every 48 h on day 17 of LAmB therapy. Immunosuppression was reduced by tapering high-dose methylprednisolone. Liposomal amphotericin B was administered for a total course of 27 days until the day of the patient’s expiration.

Liposomal amphotericin B serum and pleural fluid concentrations were measured to assist in the management of the patient’s zygomycotic empyema. Serum and pleural fluid concentrations were obtained starting on day 21 and ending on day 22 of LAmB therapy. Serum concentrations were drawn from an arterial line and collected in serum separator tubes, while pleural fluid concentrations were drawn from the patient’s inferior chest tube and collected in plain red-top tubes. The serum concentration at 24 h was drawn from a venous catheter due to removal of the patient’s arterial line. The samples were protected from light and centrifuged at 3,500 x g for 10 min. The samples were shipped on ice packs to the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio, TX. Liposomal amphotericin B concentrations were determined by a previously validated high-performance liquid chromatography (HPLC) assay (18).

Serum and pleural fluid concentrations were obtained starting on day 21 of LAmB infusion (Fig. 1). With recognition that samples were obtained for only the first 24 h, the LAmB area under the concentration-versus-time curve in serum (AUCserum) and that in pleural fluid (AUCpleural fluid) were calculated as previously described (17). The AUCserum was 802 µg·h/ml, and the AUCpleural fluid was 75 µg·h/ml, with an AUCpleural fluid/AUCserum ratio of 9.4% over the 24-h period. The pleural fluid-to-serum LAmB concentration ratios for individual time points are presented in Table 1. After 21 days of administration of a cumulative dose of 8,580 mg of LAmB, there was no evidence of intrapleural accumulation.

The patient’s respiratory status and renal function improved. Following discussion of the duration of chest tube placement, the drainage tubes remained in place, with output decreasing over time. The repeat pleural fluid wet mount and fungal culture remained negative. Unfortunately, on postoperative day 15, the patient died from fulminant Acinetobacter baumannii septic shock and multiorgan failure.

Discussion. Much has been written about the management of pulmonary zygomycosis, but little is reported about the treatment of zygomycotic empyema (3, 4, 14). Pleural effusions

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Little is known about the penetration of amphotericin B and its lipid formulations into the pleural space (1, 2, 11, 20). While the pleural fluid levels of amphotericin B deoxycholate were 25 to 70% of the serum levels in a patient with Blastomyces dermatitidis empyema, the trough concentration was only approximately 0.6 μg/ml (11). Based upon two time points, Weiler and colleagues reported that the penetration of LAmB into the pleural fluid of a critically ill patient ranged from 3 to 6% (20). We therefore performed a detailed pharmacokinetic sampling and analysis to further characterize penetration of LAmB into pleural fluid. The percentage of penetration of LAmB into pleural fluid was low, with an \( \text{AUC}_{\text{pleural fluid}}/ \text{AUC}_{\text{serum}} \) ratio of 9.4% and pleural fluid concentrations of 2.12 to 4.91 μg/ml. As the sampling in this report was conducted for the first 24 h postinfusion, the \( \text{AUC}_{\text{pleural fluid}}/ \text{AUC}_{\text{serum}} \) ratios may vary with a longer sampling time. However, as the 24-h sampling period captured the majority of the AUC, the ratios would be similar.

Medical therapy alone with liposomal amphotericin B may not be adequate for the management of zygomycotic empyema, considering that its achievable pleural fluid concentrations are unlikely to substantially exceed the minimal lethal concentrations of amphotericin B against zygomycetes (2 to 8 μg/ml) (6). Given the data presented above, continued pleural fluid drainage is an integral part of the management strategy for patients with zygomycotic empyemas. Similar to the management of bacterial empyemas, the drainage tubes may be placed to water seal and subsequently removed once the drainage is reduced to less than 50 ml per day.

In conclusion, the level of penetration of LAmB into pleural fluid may be relatively low for the treatment of zygomycotic empyema. Chest tube drainage is an important adjunct, with the duration of chest tube placement dictated by the volume of drainage.

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**REFERENCES**


### TABLE 1. Ratios of LAmB concentrations in pleural fluid to those in serum over 24 h

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Pleural fluid (μg/ml)</th>
<th>Serum (μg/ml)</th>
<th>Pleural fluid/serum concn ratio</th>
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<td>0</td>
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</tr>
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<td>2.12</td>
<td>7.75</td>
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