Utility of Inhaled Pentamidine Prophylaxis in Lung Transplant Recipients*

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The incidence of Pneumocystis carinii pneumonia (PCP) has been shown to be high posttransplantation in the absence of prophylaxis. For this reason, lung transplant recipients routinely receive prophylaxis. We report on our results using aerosolized pentamidine prophylaxis in nine patients post-lung transplantation (eight single lung transplants, one double). The patients received monthly treatments of 300 mg of aerosolized pentamidine for a mean of 10.6 months (range, 4 to 21 months). Patients were routinely monitored with serial pulmonary function studies and bronchoscopy as clinically indicated. Two of the patients experienced bronchospasm in response to the therapy. None of the patients experienced any episodes of PCP during the period of inhaled pentamidine prophylaxis. Inhaled pentamidine is a safe and effective form of PCP prophylaxis and may be used instead of sulfamethoxazole-trimethoprim in patients who have a sulfa allergy or other untoward sulfa side effects.

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PCP = Pneumocystis carinii pneumonia

The incidence of Pneumocystis carinii pneumonia (PCP) posttransplantation in the absence of prophylaxis has been shown to be in the order of 3 to 15 percent.1 In heart-lung recipients, a prevalence as high as 88 percent has been reported, although only 43 percent of these patients had symptomatic disease.2 The preferred form of prophylaxis for PCP is oral administration of trimethoprim-sulfamethoxazole.3 Other forms of prophylaxis are available, one of which is inhaled pentamidine. This modality gained favor and was used extensively in AIDS patients in the late 1980s and early 1990s. Subsequent reports of reduced efficacy as well as higher costs and logistical problems with its administration have resulted in this form of prophylaxis falling into disfavor. Despite the efficacy of orally administered trimethoprim-sulfamethoxazole, there is still a need for alternate forms of prophylaxis for the occasional patient with a sulfa allergy or other untoward inhale sulfa-related side effects. We report on our results using inhaled pentamidine as prophylaxis for PCP in a group of patients post-lung transplantation.

**Materials and Methods**

**Subjects**

We retrospectively analyzed the charts of nine patients who have received inhaled pentamidine as part of their postoperative management. The underlying disease entities for which these patients received lung transplants included COPD (4), pulmonary fibrosis (3), primary pulmonary hypertension (1), and lymphangiolymphomatosis (1). There were three right single, five left single, and one double lung transplants. Five of the patients were female and four were male.

**Immunosuppression**

All patients received induction immunosuppression in the immediate postoperative period with either OKT 3 (Ortho), 5 mg/d (n = 8), or Minnesota anti-lymphocyte globulin (n = 1), 5 mg/kg/d for five to seven days. All patients have received maintenance immunosuppression therapy with cyclosporin A, azathioprine, and prednisone. Rejection episodes were treated with intravenous methylprednisolone administered as a bolus of 1 g daily for 3 days, followed by an increase in orally administered prednisone that was tapered slowly over periods of between 3 and 6 weeks.

**Prophylaxis Regimen**

The patients received 300 mg of aerosolized pentamidine on a monthly basis via a Respigard II nebulizer unit (Marquest Products, Colorado). The pentamidine was dissolved in 5 ml of sterile water. The nebulizer unit was powered by compressed oxygen at a flow rate of 6 to 8 L/min. Delivery was terminated when the nebulizer was empty. The patients were instructed to breathe normally through the mouthpiece with vital capacity maneuvers every four to five breaths. All patients received their treatments in the seated position. All patients were premedicated prior to treatments with albuterol administered via a metered dose inhaler or hand-held nebulizer.

**Surveillance**

Episodes of PCP were excluded by Comori methenamine silver staining of bronchoalveolar lavage fluid specimens obtained at bronchoscopy. Bronchoscopy was performed as clinically indicated.

Serial pulmonary function studies (spirometry) also were routinely obtained for all patients as part of their clinical management. For each patient, the spirometry test with the maximum FEV1, from the three spirometry tests done immediately preceding the drug change was used to represent the pentamidine period; likewise, the spirometry test with the maximum FEV1, from the three spirometries immediately succeeding the drug switch were used to represent the post-pentamidine period.

Patients were initially given prophylaxis with aerosolized pentamidine after transplantation and were subsequently switched over to orally administered trimethoprim-sulfamethoxazole. The reason for this change in our protocol was the growing body of literature that attested to the occurrence of breakthrough episodes of Pneumocystis infections in patients receiving inhaled pentamidine prophylaxis.4,5

**Statistical Analysis**

The paired Student's t test was used to compare the mean differences of the forced vital capacity (FVC), FEV1, and mean forced expi-
Results

The patients received the aerosolized pentamidine for a mean of 10.2 months (range, 4 to 21 months). Only one of the patients, because of a sulfa allergy, has not subsequently been switched to orally administered trimethoprim-sulfamethoxazole prophylaxis. The mean interval after the transplant to the administration of the first pentamidine treatment was 37 days (range, 21 to 72 days). Two of the patients developed cough or bronchospasm as a result of the treatments. In one of these patients, who also had a pretransplant history of asthma, this side effect was averted by pretreatment with a nebulized β₂ agonist. In the remaining patient, recurrent bronchospasm was due to discontinuation of the inhaled pentamidine after four doses. There were no episodes of pneumothorax or other clinically evident local or systemic complications (eg, pancreatitis or hypoglycemia).

None of the patients developed an episode of PCP or disseminated pneumocystosis during the period of prophylaxis with inhaled pentamidine.

During the time that the patients were receiving the inhaled pentamidine, they underwent bronchoscopy a mean of 10.6 times as part of their clinical course. This high bronchoscopy rate was due to patients who developed bronchial anastomotic stenoses and underwent numerous bronchoscopic procedures (Nos. 24 and 26, respectively) as part of their management. Excluding these two patients, the mean number of times bronchoscopy was performed was 6.6 (range, 3 to 15).

There were a total of seven episodes of rejection treated with augmented immunosuppression in six of the patients. In addition, there was one episode of bronchiolitis obliterans organizing pneumonia treated with augmented immunosuppression. The patients had pulmonary function studies performed a mean of 22 times while receiving the inhaled pentamidine treatments. Comparison of the patients’ pulmonary function studies during and after pentamidine prophylaxis are summarized in Table 1. In general, the spirometry test results chosen from the three spirometry tests done prior to the switch over to trimethoprim-sulfamethoxazole yielded results that were higher than or equal to results of any other spirometry tests done during the period of inhaled pentamidine prophylaxis.

Discussion

This retrospective analysis suggests that aerosolized pentamidine is an effective and well-tolerated form of PCP prophylaxis in patients post-lung transplantation. The incidence of symptomatic PCP in lung transplant recipients in the absence of prophylaxis has been reported to be 26 to 43 percent.2,6 In these studies, there was only a 4 to 5 percent incidence of symptomatic PCP in patients who had been exposed to trimethoprim-sulfamethoxazole prophylaxis because of complications. Nonetheless, it still underscores that there may be unique local features that make the lung transplant patient more susceptible to PCP compared with other solid organ recipients. Despite the small number of patients in our study, the high incidence of PCP in patients who did not receive prophylaxis lends credence to inhaled pentamidine as an effective form of prophylaxis. Furthermore, seven of our nine patients had at least one episode of augmented immunosuppression without the subsequent development of PCP. It has been shown that there is an association between augmented immunosuppression for episodes of rejection and the subsequent development of PCP.3 Although our patients only received inhaled pentamidine for a mean duration of 11.5 months after transplantation, this correlates with the period of highest incidence of the disease. It has been recommended that patients should only receive prophylaxis for the first 12 to 18 months post-transplantation and during periods of augmented immunosuppression.3

There are theoretical concerns that aerosolized pentamidine may place patients at higher risk for the development of rejection. First, it has been hypothesized that airway inflammation may result in upregulation of bronchial epithelium class II major histocompatibility complex antigen expression.7 This upregulation may result in a greater propensity for the development of rejection. It also has been shown that inhaled pentamidine results in increased macrophage recruitment which could result in augmented antigen processing.8 Our incidence of rejection is not abnormally high compared with historic controls, and thus there is no evidence to suggest that inhaled pentamidine results in the development of rejection.8

Table 1—Summary of Paired t Tests for FVC, FEV₁, and FEF25-75%

<table>
<thead>
<tr>
<th></th>
<th>Pentamidine, Mean ± SD</th>
<th>Post-pentamidine, Mean ± SD</th>
<th>Difference, Mean ± SD</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L</td>
<td>3.10 ± 1.38</td>
<td>3.32 ± 1.39</td>
<td>0.22 ± 0.32</td>
<td>0.03</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>2.22 ± 0.81</td>
<td>2.29 ± 0.83</td>
<td>0.07 ± 0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>FEF25-75%, L/s</td>
<td>1.91 ± 1.01</td>
<td>1.80 ± 0.96</td>
<td>−0.11 ± 0.29</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Inhaled Pentamidine in Lung Transplant Recipients (Nathan et al)

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Although it has been shown that patients can have hyperreactive Airways post-lung transplant, the incidence of pentamidine-induced cough or bronchospasm was not higher than that reported in the literature in nontransplant patients. In only one patient did this side effect necessitate discontinuation of the medication. The incidence of asymptomatic decrements in spirometric flow rates secondary to the inhaled pentamidine was not assessed in our study. However, the similarity between the test results of the patients during and after the periods of pentamidine administration refute the occurrence of any significant long-term pulmonary sequelae secondary to the inhaled pentamidine treatments. The differences in the FVC values during and after pentamidine prophylaxis are most likely due to either inherent variability of the test or continued improvement in this parameter which typically occurs posttransplantation.

Atypical manifestations of PCP in human immunodeficiency virus patients receiving inhaled pentamidine prophylaxis have been reported. Most of these reports have been of cases of upper lobe PCP involvement. This presentation has been attributed to regional differences in the deposition of inhaled pentamidine with higher deposition rates occurring in the lower lobes compared with the upper lobes. Regional ventilation must play some role in the distribution of deposition, since particles must be carried to an area if they are to be deposited there. However, it has been shown that there is a poor correlation between regional ventilation and regional deposition of pentamidine, suggesting that other local factors are more important in determining deposition. In single-lung transplant recipients, with the inhomogeneity that exists between the two lungs, regional differences in deposition are apt to be more marked. In a prior study using quantitative krypton ventilation scanning after single-lung transplantation, we have shown that most of the ventilation is shifted to the transplanted side. Six of the seven single-lung transplant patients in our current study also participated in that study. The mean quantitative ventilation to the transplanted side in these patients was 72.5 percent (range, 58 to 88 percent). This inequity in distribution of ventilation could therefore have resulted in reduced deposition in the native lung. Another factor that may influence the nature of deposition is the primary disease process of the native lung. This could be a consequence in patients who receive transplants for obstructive lung disease, since a more central pattern of distribution has been shown to occur in patients with airflow obstruction. In the setting of chronic allograft rejection (obstructive bronchiolitis), deposition could similarly be adversely affected. The zero incidence of PCP in our patients suggests that regional differences in ventilation may only be of theoretical concern. The most important factors determining deposition are thought to be particle size and aerosol delivery. Optimization of these factors appears to be sufficient to nullify the clinical significance of the regional differences in deposition. Other measures that may be employed to enhance an equitable distribution include pretreatment with a bronchodilator, changes in breathing pattern, and changes in body position during the administration, specifically assumption of the supine position.

There are a few reasons that preclude recommendation of inhaled pentamidine as first-line prophylaxis for PCP. The most compelling reasons are the proven efficacy, ease of administration, and lower cost of orally administered trimethoprim-sulfamethoxazole. In addition, because of the small numbers of patients in our study, we would still caution against the occurrence of disseminated pneumocystosis or episodes of atypical PCP in patients receiving inhaled pentamidine.

In summary, we believe that inhaled pentamidine is a safe and effective alternate form of PCP prophylaxis in the subset of lung transplant patients with a sulfa-related side effect or sulfa allergy.

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