Pulmonary Tolerance of Prophylactic Aerosolized Pentamidine in Human Immunodeficiency Virus-Infected Patients*

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The effects of primary and secondary long-term prophylaxis of Pneumocystis carinii pneumonia with aerosolized pentamidine on pulmonary function in HIV+ patients were evaluated. Eighty-one patients, none of whom were drug addicts or had pulmonary Kaposi’s sarcoma, were studied. Fifty patients were receiving AP as secondary prophylaxis, 36 monthly and 14 twice-monthly; eight patients with a history of PCP served as control subjects. Twenty-three patients were receiving AP as primary prophylaxis, 12 monthly and 11 twice-monthly. Pulmonary function tests, including spirometry, lung transfer capacity for carbon monoxide (Tlco) and alveolar-arterial oxygen gradient (P(A-a)O2) were evaluated at M1, ie, one month after the diagnosis of PCP, or at the beginning of the AP prophylaxis, and then at three-month intervals (M4 to M13). No differences were observed in the results of spirometry or P(A-a)O2. Among the patients receiving secondary prophylaxis, a significant increase (paired Student’s t-test) in Tlco occurred at M7 compared to M1 in the group receiving monthly administrations (p<0.01) and in the untreated control group (p<0.05); there was no significant difference in Tlco at M13 compared to M1 in the 12 patients who received monthly administrations for this period or at M7 in the 14 patients receiving AP twice-monthly. No significant difference in Tlco was observed at M7 in the primary prophylaxis groups. These results indicate that pulmonary tolerance of AP, as reflected by pulmonary function tests, is good.

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Aerosolized pentamidine is effective prophylaxis for PCP in HIV+ individuals. This recent mode of administration initially was mainly in the prevention of PCP relapse (secondary prophylaxis), but since the definition of predictive factors of PCP, it has also been extensively used for primary prophylaxis, ie, prevention of the first episode. Along with co-trimoxazole, AP is now recommended in the guidelines of the US National Institutes of Health.

The lack of systemic side-effects using this route of administration is a major advantage over systemic regimens, notably oral co-trimoxazole. However, data on the long-term pulmonary tolerance of AP are scarce. The aim of this study was to investigate pulmonary function in HIV+ patients receiving AP.

PATIENTS AND METHODS

This prospective study involved patients in the Hôpital Claude Bernard Zidovudine Study Cohort.**

Patient Population

Patients were required to meet the following criteria: (1) HIV infection documented by the presence of serum antibodies; (2) symptomatic HIV infection (grade IVc, IVc1, or IVc2, Centers for Disease Control classification); (3) no clinical, radiologic or biologic evidence of pneumonia at enrollment or during follow-up.

Exclusion criteria were as follows: (1) intravenous drug abuse; (2) diagnosis of pulmonary Kaposi’s sarcoma.

No anti-Pneumocystis carinii agent other than aerosolized pentamidine was prescribed.

Eighty-one patients were included and were divided into two groups, as follow: group 1, 23 patients receiving AP as primary prophylaxis; and group 2, 58 patients with history of at least one episode of PCP. Fifty patients received AP, while the remaining eight patients received no anti-Pneumocystis carinii prophylaxis and served as control subjects.

Aerosolized Pentamidine Regimen

Prophylaxis was initiated with pentamidine mesylate (Lomidine) for 50 of 73 (79 percent) of the patients at the dose of 4 mg/kg (200 to 280 mg) of pentamidine base. Between the second and fifth month of prophylaxis, pentamidine mesylate was replaced by an isethionate salt (Pentacarinat), at the dose of 300 mg, equivalent to 172.5 mg of pentamidine base. Fifteen patients (21 percent) received only the isethionate salt. Pentamidine was delivered using an ultrasonic nebulizer. The mass median aerodynamic diameter of the particles was 4.6 μ, with a geometric standard deviation of 1.9.

Administration took place in the day-care unit under medical supervision. Salbutamol was inhaled, when required, for wheezing and/or cough.

The AP was administered every two weeks during the first month, then every two weeks in 12 group 1 and 14 group 2 patients and every month in 11 group 1 and 36 group 2 patients.

Pulmonary Function Tests

Patients underwent PFT at month 1 (M1) and every three months until M13. M1 was defined as the time of the initiation of the primary prophylaxis in group 1 patients and of secondary prophylaxis.
Spirometric data remained within predicted values. With regard to Tlco (Table 4), there was no significant difference in values between the control subjects and the monthly and fortnightly treatment groups at M1. The Tlco values in the control group were significantly increased at M7 compared to M1 (p<0.05). When AP was administered fortnightly, Tlco values did not vary significantly between M1 and M7, whereas in the group receiving monthly AP (n=36), Tlco values were significantly higher (p<0.01) at M7 than at M1. In the 20 patients of the later group who underwent PFT at M10 and in the 12 who underwent PFT at M13, Tlco values were similar to those at M1.

The P(A-a)O2 values did not vary significantly during the course of the study (Table 3).

**Discussion**

In this study, no deterioration in pulmonary function parameters (spirometry, Tlco and P(A-a)O2) was observed after seven months of treatment in 50 patients receiving AP as primary or secondary PCP prophylaxis, or after 13 months in 12 patients receiving secondary prophylaxis. Thirty-six patients receiving monthly administrations of AP as secondary prophylaxis showed a recovery of Tlco values (p<0.01) similar to that observed in the untreated control group. The significant difference (p<0.05) in Tlco values between M1 and M7 in the control group resulted from the relatively small standard deviation.

We studied the pulmonary tolerance of pentamidine in the light of the high pulmonary concentration reached after aerosol administration10 and the long half-life of elimination from the lung11,12. Pulmonary toxicity has previously been described with long-term administration of drugs such as bleomycin (prolonged inflammatory process characterized by fibrosis13,14) and amiodarone (hypersensitivity pneumonitis by an immunologic process and/or interstitial fibrosis?).15

Bronchial toxicity following long-term AP was also evaluated, given the frequent cough and bronchospasm observed during the inhalation. This may be due to thiol derivatives contained in the two pentamidine salts used in this context.16 In addition, the acidity of the pentamidine solution (pH = 4.50 to 6.50) may cause airway irritation.17
Pulmonary function tests are commonly used to evaluate pulmonary and bronchial drug toxicity. Lung gallium scans require specialized equipment and are not as reliable as TLco. Similarly, the measurement of lung mechanics has proved less sensitive and specific than TLco. Histologic studies are excluded for ethical reasons.

Patients with pulmonary Kaposi’s sarcoma were excluded from this study. This neoplasm involves the tracheobronchial tree and pulmonary parenchyma, with septal distribution of nodular lesions. The TLco is moderately to severely impaired and airway obstruction is often observed.\(^\text{19}\)

Intravenous drug abusers were also excluded, since intravenous injection of illicit drugs and dissolved tablets can cause foreign particle lung embolization. Particles may also induce granuloma formation, vasculitis, and interstitial fibrosis. Altered pulmonary function has been described in such subjects and includes reduction of TLco.\(^\text{19}\)

In the present study, FEV\(_1\)/VC was determined some days after the inhalations; after seven months’ treatment, no evidence of bronchoconstriction was observed in either the primary or secondary prophylaxis group, regardless of the frequency of AP administration. A previous study found a fall in FEV\(_1\) of between 15 and 60 percent of predicted values when measured immediately after the inhalations.\(^\text{20}\)

No prospective evaluation of pulmonary tolerance in terms of PFT in patients receiving pentamidine aerosols has previously been published, although a moderate decrease in TLco after 14 months’ exposure to pentamidine has been reported in a respiratory technician delivering aerosols.\(^\text{21}\) In the present study, no restrictive syndrome was observed. The TLco was not altered in the secondary prophylaxis group after 7 and 13 months’ treatment, or in the primary prophylaxis group after 7 months’ treatment.

The bronchopulmonary deposition of AP is known to vary according to the type of nebulizer used.\(^\text{22}\) The ultrasonic apparatus used in this study may give rise to low levels of alveolar deposition despite its proven efficacy in PCP prophylaxis.\(^\text{4}\)

In conclusion, the long-term administration of AP as primary or secondary PCP prophylaxis was not associated with alterations of pulmonary function. Further studies involving nebulizers inducing higher levels of alveolar deposition and longer follow-up periods may be warranted, particularly in the context of primary prophylaxis.

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### Table 3—Alveolar-Arterial Gradient for Oxygen

<table>
<thead>
<tr>
<th>Pentamidine Aerosols Dosage</th>
<th>Group 1: Primary Prophylaxis</th>
<th>Group 2: Secondary Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300 mg Monthly (n=36)</td>
<td>300 mg Monthly (n=14)</td>
</tr>
<tr>
<td></td>
<td>300 mg Fortnightly (n=14)</td>
<td>300 mg Fortnightly (n=11)</td>
</tr>
<tr>
<td></td>
<td>300 mg Monthly (n=12)</td>
<td>300 mg Monthly (n=12)</td>
</tr>
<tr>
<td>P(A-a)O(_2) mm Hg</td>
<td>M1</td>
<td>M7</td>
</tr>
<tr>
<td>14.4</td>
<td>15.9</td>
<td>14.6</td>
</tr>
<tr>
<td>±10.2</td>
<td>±14.4</td>
<td>±11.5</td>
</tr>
</tbody>
</table>

### Table 4—TLco (Percent of Predicted Values) in Patients Receiving AP as Secondary Prophylaxis

<table>
<thead>
<tr>
<th>AP Administration</th>
<th>M1</th>
<th>M7</th>
<th>M10</th>
<th>M13</th>
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</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=8)</td>
<td></td>
<td></td>
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<tr>
<td>Fortnightly (n=14)</td>
<td>64.8±9.6</td>
<td>p&lt;0.05</td>
<td>ns</td>
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<tr>
<td></td>
<td>70.1±24.7</td>
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<tr>
<td>(n=36)</td>
<td>66.2±15.9</td>
<td>p&lt;0.01</td>
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<tr>
<td>Monthly (n=20)</td>
<td>67.2±19.9</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>73.8±17.6</td>
<td>ns</td>
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<tr>
<td>(n=12)</td>
<td></td>
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<tr>
<td></td>
<td>74.2±16.4</td>
<td>ns</td>
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</tr>
<tr>
<td></td>
<td>75.0±19.4</td>
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7 Shafer RW, Seitzman PA, Tapper ML. Successful prophylaxis of Pneumocystis carinii pneumonia with trimethoprim-sulfamethoxazole in AIDS patients with previous allergic reactions. J Acq Imm Def Synd 1989; 2:389-93

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