Aerosol Pentamidine-induced Bronchoconstriction*
Predictive Factors and Preventive Therapy

Jean Quiéffin, M.D., John Hunter, M.D.; Martin T. Schechter, M.D.; Lindsay Lawson, M.D., F.C.C.P.; John Ruedy, M.D.; Peter Paré, M.D.; and Julio S. G. Montaner, M.D., F.C.C.P.

Objective: To determine the frequency of aerosol pentamidine-induced bronchoconstriction, its relationship to nonspecific airway responsiveness, and its response to preventive therapy using salbutamol, ipratropium bromide, or sodium cromoglycate.

Methods: Consecutive HIV-infected individuals starting prophylactic AP were eligible if they had not been previously treated with this agent. Simple spirometry was performed before and 10 min after a single 60-mg dose given through an ultrasonic nebulizer. Methacholine challenge was performed in all subjects 24 h to four days after the initial AP dose. Subjects with a change in FEV1 (ΔFEV1) >10 percent decrease after the initial AP dose were restudied on three separate occasions (>24 hours apart) after premedication with two puffs of salbutamol (200 μg), ipratropium bromide (40 μg), or sodium cromoglycate (2 mg), in random order.

Results: Fifty-three subjects were studied. The median ΔFEV1 after a single dose of AP was −7.0 percent (range: −47 percent, 1.8 percent). The ΔFEV1, following AP was only partially predicted by the degree of nonspecific bronchial responsiveness as measured by a standard methacholine challenge. Age, current smoking, history of asthma, baseline FEV1, or a prior episode of PCP failed to predict the ΔFEV1, following AP. Eighteen subjects (34 percent) had a ΔFEV1 ≥10 percent decrease (median: −17.0 percent). In these subjects, after premedication with salbutamol, ipratropium bromide, and sodium cromoglycate, the median ΔFEV1 was 1.0, 0.8, and −9.6 percent, respectively. Conclusion: Aerosol pentamidine produced a decrease in FEV1 ≥10 percent in 34 percent of subjects. This was not accurately predicted by the methacholine response. The bronchoconstriction induced by AP was effectively prevented by either salbutamol or ipratropium, whereas cromoglycate was only partially effective.

Pneumocystis carinii pneumonia remains the most common serious opportunistic infection among HIV-infected individuals. The risk of developing PCP has been shown to be markedly increased when the CD4 + T-lymphocyte count decreases below 250/cu mm. Recently, aerosol pentamidine has been shown to effectively reduce PCP relapse by as much as 85 percent over a six-month period, and therefore, its use as prophylaxis against PCP has been recommended.

Cough and/or bronchoconstriction have been reported to occur with varying frequency with AP therapy. Previous reports have suggested that these adverse reactions are more frequent among smokers and asthmatics, and it has been speculated that this could be indicative of underlying bronchial hyperresponsiveness. We undertook the present study to characterize the frequency and magnitude of AP-induced bronchoconstriction, its relationship to nonspecific bronchial responsiveness as measured with methacholine, and the effect of commonly used preventive medications.

Methods

Patient Selection

HIV-infected subjects are eligible for our AP program if they have had an episode of PCP and/or have CD4 cell counts below 300/cu mm. Consecutive individuals entering the program were eligible for this study if they had not been previously treated with AP. Consenting volunteers were asked to withhold any β2 agonists or anticholinergic agents for 24 hours prior to the study. Those currently receiving cromoglycate or chemotherapy were excluded from the study.

Protocol

Aerosol pentamidine was administered following a previously described protocol. Briefly, 60 mg of pentamidine isethionate diluted in 3 ml of sterile water was delivered over 15 to 20 min through a mouthpiece. This nebulizer generates particles of a mass mean aerodynamic diameter of 2.0 to 2.5 μm. Patients received five loading doses of 60 mg AP during the first two weeks of therapy, followed by one maintenance dose every two weeks.

Simple spirometry was performed prior to and 10 min after the completion of the first AP dose. Spirometric measurements were obtained using a portable bellows spirometer. Forced expiratory volume in one second was measured from the best of the forced expiratory efforts. Patients who showed a ≥10 percent decrease in

*From St. Paul's Hospital, University of British Columbia, Vancouver, Canada. Manuscript received October 16; revision accepted January 31. Reprint requests: Dr. Montaner, 200 1033 Davie Street, Vancouver, BC, Canada V6E 1M7

Aerosol Pentamidine-Induced Bronchoconstriction (Quiéffin et al)
FEV1, following AP administration were termed responders, and those with <10 percent decrease were termed nonresponders. A decrease in FEV1 ≥ 10 percent was considered significant based on the individual coefficient of variation of FEV1 in normal subjects reported to be 3 and 7 percent within a day and from week to week, respectively. All subjects were restudied 24 h to 4 days after the first AP dose. At that time, a standard methacholine challenge was performed, as previously described. Briefly, after completion of a baseline spirometry and using a Bennett twin nebulizer, subjects inhaled through a face mask first saline and then doubling concentrations of methacholine for 2 min. The methacholine challenge was stopped when the FEV1 decreased ≥ 20 percent of the initial value or when a methacholine concentration of 32 mg/ml was reached. The concentration of methacholine necessary to produce a 20 percent fall in FEV1 (PC20) was calculated by linear interpolation between the last two concentrations using a semilogarithmic scale.

Responders were then restudied with each of three premedications given in random order 24 h to 7 days apart. The premedications consisted of two puffs of either salbutamol, ipratropium bromide, or sodium cromoglicate given via a metered dose inhaler (corresponding to 200 µg, 40 µg, and 2 mg, respectively). Premedication was given 10 min before AP administration in a single blind fashion. Spirometry was measured before each premedication and 10 min after the AP. In the final ten patients, additional spirometric tests were performed 10 min after each premedication immediately prior to the administration of AP.

Because several variables did not appear normally distributed, continuous data were compared using the nonparametric Wilcoxon signed rank test. Categoric data were analyzed using the chi-square test. A significance level of 0.05 was used unless otherwise indicated. The effect of each premedication was tested by comparing the change in FEV1 (ΔFEV1) associated with AP alone with the ΔFEV1 associated with AP following premedication using a Wilcoxon signed rank test.

Results

A total of 53 consecutive subjects entering the AP program at St. Paul's Hospital were studied; 52 of them were men. Risk factors for HIV infection included homosexual/bisexual (n = 49), hemophilia (n = 2), and blood transfusion (n = 1). As shown in Table 1, the median age of participants in the study group was 38 years (range 21 to 53), 21 subjects were current smokers, five had a history of asthma during childhood, and one had current asthma treated with salbutamol and topical corticosteroids. The AP was indicated for primary PCP prophylaxis in 42 subjects and for secondary PCP prophylaxis in the remaining 11. The median ΔFEV1 after AP administration was −7.0 percent (range: −47 percent, 1.8 percent). Eighteen of the 53 subjects (34 percent) had a decrease in FEV1 ≥ 10 percent (responders) with a median ΔFEV1 of −17.0 percent.

Methacholine challenge could not be performed in two subjects who developed rapidly progressive cytomegalovirus retinitis. Table 2 shows the distribution of PC20 among responders and nonresponders in the 51 remaining subjects; overall, there was a statistically significant association (chi-square p = 0.002). Using cutoff values for PC20 of 8, 16, and 32 gave rise to positive predictive values of 60, 70, and 77 percent, respectively, and negative predictive values of 67, 73, and 79 percent. Among the 13 subjects with a measurable PC20 (≤32 mg/ml), the degree of ΔFEV1 post AP was not correlated with the PC20. In addition, neither age, baseline FEV1, current smoking habit, history of asthma, nor prior PCP episode were associated with ΔFEV1 in univariate comparisons.

Figure 1 illustrates the effect of the preventive

### Table 1—Baseline Characteristics and Spirometry Results Before and After the First Administration of Aerosol Pentamidine in 53 Subjects

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Responders</th>
<th>Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>53</td>
<td>38 (21, 53)</td>
<td>15 (25, 53)</td>
</tr>
<tr>
<td>Age*</td>
<td>38 (21, 53)</td>
<td>37 (21, 50)</td>
<td>39 (25, 53)</td>
</tr>
<tr>
<td>Current smokers, n</td>
<td>21</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Asthma history, n</td>
<td>6</td>
<td>3†</td>
<td>3</td>
</tr>
<tr>
<td>Secondary PCP prophylaxis, n</td>
<td>11</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>FEV1 pre AP (I)*</td>
<td>3.8 (2.5, 4.8)</td>
<td>3.5 (2.5, 4.4)</td>
<td>3.9 (2.5, 4.8)</td>
</tr>
<tr>
<td>FEV1 post AP (I)*</td>
<td>3.4 (1.5, 4.7)</td>
<td>3.0 (1.5, 3.9)</td>
<td>3.6 (2.5, 4.7)</td>
</tr>
<tr>
<td>ΔFEV1, %*</td>
<td>−7 (1.8, −47)</td>
<td>−17 (−10, −47)</td>
<td>−4.1 (−7.5, −9)</td>
</tr>
</tbody>
</table>

*Median (range).
†One had current asthma.

### Table 2—Distribution of PC20 Among Responders and Nonresponders

<table>
<thead>
<tr>
<th>PC20 mg/ml</th>
<th>Responders, n</th>
<th>Nonresponders, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤8</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>&gt;8, ≤16</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>&gt;16, ≤32</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>&gt;32</td>
<td>8</td>
<td>30</td>
</tr>
</tbody>
</table>

*Chi square p = 0.002.
regimens studied among the 18 responders using box plots. All three preventive regimens offered some degree of protection against AP-induced bronchoconstriction. The median ΔFEV₁ was –17.0 percent for AP alone compared to 1.0 percent, 0.8 percent, and –9.6 percent for salbutamol, ipratropium bromide, and sodium cromoglycate, respectively. Each of these was significantly different from AP alone (p<0.001). Comparisons among the premedications revealed that both salbutamol and ipratropium bromide were superior to sodium cromoglycate (p = 0.0002 and 0.0108, respectively) but were not significantly different from one another (p = 0.102). It should be noted that in one subject, none of the three regimens used was able to prevent the development of severe bronchoconstriction after AP with a decrease in FEV₁ of 28 percent in all three instances. This subject, who was a smoker with no past history of asthma, was unable to tolerate any further AP treatments.

Figure 2 displays the data for the final ten subjects in whom additional spirometric tests were performed after premedication, just prior to AP. These data suggest that the beneficial effect of the premedication is largely due to a true prevention of the bronchoconstriction rather than to a pre-AP bronchodilation.

**DISCUSSION**

Our data confirm that some degree of bronchoconstriction occurs in most subjects after a single dose of AP. The decrease in FEV₁ in our study was as great as 47 percent, with a median ΔFEV₁ of –7 percent. A decrease in FEV₁ ≥10 percent from baseline occurred in 34 percent of subjects and six subjects (11 percent) had a decrease in FEV₁ ≥20 percent. The magnitude of AP-induced bronchoconstriction in our study would appear to be different from that previously reported. Chan et al. found a 15 percent FEV₁ decrease in 4 of 17 subjects (24 percent) after administration of AP. Ghedira et al. reported a decrease in FEV₁, greater than 60 percent of the predicted FEV₁ in 8 of 15 subjects. Smith et al. reported a mean decrease in peak expiratory flow rate of 25.5 percent in eight subjects, and Ong et al. reported a post-AP peak expiratory flow ranging from 21 to 91 percent of the pretreatment value in six patients. The apparent discrepancy between these reports and our results is most likely attributable to their small sample size, their varying doses and delivery systems, as well as their varying selection criteria. Our data, derived from a large sample of unselected subjects studied in a prospective fashion, likely provide a more accurate estimate of the true occurrence of AP-induced bronchoconstriction.

AP-induced bronchoconstriction has been previously reported to occur with increased frequency among smokers and asthmatics. Our data, however, fail to confirm this association. A number of recent reports have suggested a relationship between non-specific bronchial hyperresponsiveness as measured using methacholine challenge and AP-induced bronchoconstriction. Indeed, we observed a statistical association between AP-induced bronchoconstriction and response to methacholine. However, this did not translate, in our view, into a clinically significant relationship. The positive and negative predictive values, even at the optimal threshold of 32 mg/ml for the PC₂₀, were not sufficiently high to warrant the use of methacholine challenge as a clinical predictor of the response to AP.

A number of recent reports have suggested that AP-induced bronchoconstriction can be alleviated using salbutamol, ipratropium bromide, or sodium cromoglycate. Our data demonstrate that both salbuta-
mol and ipratropium can effectively prevent AP-induced bronchoconstriction in most subjects. Sodium cromoglycate, on the other hand, is only partially effective to this end. It must be noted, however, that at least one subject in our series could not tolerate AP therapy because of severe bronchoconstriction that could not be satisfactorily prevented by any of the three prophylactic regimens used. This highlights the need of initiating AP in a supervised setting. Furthermore, since bronchoconstriction impairs aerosol delivery to the lung, it could be argued that premedication with bronchodilators will improve the protective effect of AP while preventing bronchoconstriction for a minimal cost, making screening of subjects unnecessary. Use of bronchodilators prior to aerosol pentamidine has, therefore, become routine practice in several centers including our own.

Having selected responders on the basis of their greater decrease in FEV₁ following AP, one might anticipate that with repeated measurements, the magnitude of this response would lessen, so-called “regression toward the mean.” We cannot rule out entirely that this phenomenon is, in part, responsible for the lesser degree of bronchoconstriction seen with the subsequent premedications. However, the fact that the ΔFEV₁ following premedication with salbutamol and ipratropium bromide was much less than the median ΔFEV₁ of the entire population prior to preselection, strongly supports that the preventive effect of these premedications is real. At any rate, given that the testing of the preventive medications was performed in random order, “regression toward the mean” cannot explain the statistically significant differences observed between these regimens.

We conclude that a decrease in FEV₁ occurs frequently with AP. This is usually mild and well tolerated. Although AP-induced bronchoconstriction tends to occur more frequently in subjects with enhanced nonspecific bronchial responsiveness, this is not always the case. Finally, AP-induced bronchoconstriction can be effectively prevented by premedication with salbutamol or ipratropium bromide, while sodium cromoglycate appears to be only partially effective. Routine use of bronchodilators prior to aerosol pentamidine treatments may represent a valid clinical strategy to enhance tolerance and probably even efficacy.

REFERENCES

17 Ong ELC, Hanley SF, Mandal BK. Bronchoconstriction, nebulized pentamidine, and mast cells. Lancet 1989; 1:956
18 Heley A. Aerosolized pentamidine treatment at home. Lancet 1987; 2:1092