High Incidence of Bronchospasm with Regular Administration of Aerosolized Pentamidine*


A systematic evaluation of changes in pulmonary status by objective spirometric assessment and subjective rating using visual analog scale was performed in a cohort of 134 patients receiving aerosolized pentamidine (AP) for the prevention of Pneumocystis carinii pneumonia. Significant bronchospasm defined as ≥15 percent reduction in the forced expiratory volume in 1 s was noted in 26 of 100 (26 percent) of patients receiving AP alone. Despite the use of salbutamol (albuterol) as concurrent aerosolized treatment in 34 subjects, bronchospasm developed in 9 of 34 (26 percent) of the patients. The subjective respiratory status rating scale was found to be unreliable in correctly predicting the development of bronchospasm. We conclude that a high incidence of bronchospasm is present in patients receiving regular AP administration using an ultrasonic nebulizer as studied, and concurrent administration of salbutamol is not fully protective of this acute adverse pulmonary reaction. (Chest 1992; 101:79-81)

AP = aerosolized pentamidine; VAS = visual analog scale

Pneumocystis carinii pneumonia is the most common pulmonary infection in patients infected with the human immunodeficiency virus. Aerosolized pentamidine has recently been proven in clinical trials to be effective as secondary prophylaxis of PCP. The efficacy of AP as sole treatment regimen for episodes of PCP is somewhat questionable. Since 1989, PCP prophylaxis program using AP has been widely established throughout the world. United States centers tend to use the jet nebulizer system, whereas most Canadian patients are using the ultrasonic nebulizers. The AP may not be the most effective prophylactic agent, but it is currently the best tolerated regimen for both primary and secondary prevention of PCP in HIV patients. However, AP is not completely free of complications. The most prevalent complication is related to an acute pulmonary reaction resulting in cough and wheezing. This reaction was recently shown to be attributable to pentamidine, and can occur in up to 24 percent of patients receiving AP as demonstrated in prior placebo-controlled, randomized study.

The pragmatic approach in handling cough and bronchospasm in patients undergoing regular prophylactic AP therapy ranges from the use of various bronchodilators such as beta-agonists or anticholinergics as a premedication for AP treatment in all patients, or as symptomatic therapy after AP treatment for those patients with subjective symptoms, to objective surveillance using spirometry prior to AP and post-AP treatment for the detection of significant bronchospasm and then provide bronchodilator therapy. No standard approach for the detection and treatment of bronchospasm has been established to date.

The purpose of this prospective study is to define the incidence of significant bronchospasm in a heterogeneous population of HIV patients who are receiving AP for both primary and secondary prophylaxis of PCP at our centralized AP clinic. Some of these patients are receiving bronchodilators as concurrent medication hoping to prevent bronchospasm, and it is also the intention of this study to define the incidence of bronchospasm despite the use of bronchodilator as co-intervention. The second objective of this study is to determine whether clinically significant bronchial reactivity can be detected subjectively by either the patients or nurses who supervise the treatment.

METHODS

Patient Population

From December 1989 to January 1990, 134 HIV-infected patients receiving regular AP for primary and secondary prophylaxis of PCP at our centralized AP clinic in Toronto were enrolled in this study. One hundred patients received AP only. The remaining 34 patients, had either a past history of asthma or prior severe cough and wheezing with AP, received AP plus salbutamol (albuterol) as concurrent aerosolized treatment.

AP Administration

Pentamidine isethionate, 300 mg, was reconstituted in 15 ml of sterile water to establish a final concentration of 20 mg/ml of pentamidine solution. Three milliliters of this pentamidine solution was then withdrawn via a syringe and placed in a nebulizer. In the group receiving salbutamol (albuterol), 1.25 mg of salbutamol was added to the pentamidine solution in the nebulizer. The ultrasonic nebulizer was then set up with the face mask and mouthpiece in place. The patient, under supervision, inhaled the solution through
the mouthpiece via a self-administration process over a 15- to 30-minute period.

Pulmonary Function - Objective Detection of Bronchospasm

Pulmonary mechanics were measured using a Vitalograph model 42.000 (Vitalograph Ltd., Buckingham, England). Spirometric testing was performed both pre-AP and post-AP treatment, and the best effort of three expiratory maneuvers was recorded.

Subjective Detection of Bronchospasm

A 10-cm visual analog scale was used in this study to determine whether the patient or the nurse supervising the AP treatment could detect the development of significant bronchospasm with the treatment. Prior to this study, a pilot project on 20 patients undergoing AP treatment was undertaken to pretest this simple VAS. In the pilot project, we found that the instrument with the two anchor points labelled as "breathing is just fine" as the zero mark and "having trouble breathing" at the 10 cm mark was comprehensible to both the patients and the nurses. We also assessed whether spirometric maneuvers performed by the patient had any effect on scoring on VAS. The results indicated that prespirometry and postspirometry values were, on the average, within 2 mm out of 100 mm of each other. The spirometric maneuvers, therefore, did not result in deterioration of the patients' subjective pulmonary status based on VAS.

During the actual study, the patients scored on the VAS both prior to as well as after the AP treatment. The change in the scoring of the VAS was compared to the changes on the objective testing, ie, spirometry. The nurses, on the other hand, only scored on the VAS after the patients had completed the AP treatment.

Study Protocol

Before receiving AP treatment, each patient was asked to rate his respiratory status by making a mark along the 10 cm VAS scale. That scoring was used as the baseline pre-AP respiratory status.

The patient then performed the spirometric maneuvers under the supervision of a respiratory therapist who was blinded to the VAS scoring.

The AP treatment was then administered as described previously under the supervision of a nurse.

After the AP treatment, the patient was asked to rescore his respiratory status using a blank VAS. The patient was blinded to the original scoring pre-AP. Meanwhile, the patient's nurse was asked to independently assess the patient's respiratory status after AP using a blank VAS as well.

The patient then went on to perform spirometry, and the result of the spirometry was used as the post-AP spirometric data.

Data Analysis

Continuous variables such as spirometry results are expressed as means ± SD. Baseline spirometric data of the group receiving AP alone and the group receiving AP and salbutamol were compared using unpaired Student's t-test. The diagnostic utility of VAS was computed using the conventional methods for calculating sensitivity, specificity, positive and negative predictive values.7 The gold standard for clinical significant bronchospasm was defined as a 15 percent or greater reduction in the FEV1, as measured by spirometry.

RESULTS

The mean FEV1 of the group receiving AP alone was 93 percent with a range from 61 to 131 percent compared to the mean FEV1 of the 34 patients who received salbutamol with the AP treatment being 83 percent with a range from 58 to 108 percent (p<0.001). This significantly lower flow rate in the group receiving

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<th>Table 1 — Spirometry Data*</th>
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<tr>
<td>Patient No.</td>
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<tr>
<td>Pre-AP FEV1†</td>
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<tr>
<td>(61-131%)</td>
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<td>Number with bronchospasm‡</td>
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<td>Reduction in FEV1, post-AP</td>
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<td>(15-52%)</td>
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*NS, nonsalbutamol; S, salbutamol; AP, aerosolized pentamidine; FEV1, forced expiratory volume in one second.
†Expressed as percentage predicted.
‡Definition of bronchospasm: [pre-AP FEV1 - post-AP FEV1] / pre-AP FEV1 ≥15% concurrent salbutamol merely reflects a history of either asthma or difficulties with cough and wheezing with prior AP treatments. Despite the use of bronchodilator as concurrent therapy, 26 percent of the 34 patients who received salbutamol together with AP developed bronchospasm. Coincidentally, 26 percent of those who did not receive salbutamol also developed bronchospasm (Table 1). Therefore, the overall incidence of significant bronchospasm in this heterogeneous group of patients receiving ongoing AP treatment is 26 percent.

Various cutoffs of VAS were analyzed to achieve the highest negative predictive value associated with a reasonable positive predictive value. For the patients' scale, a post-AP increase of 15 ml or greater from the pre-AP value provides the optimal diagnostic utility. For the nurses' scale, which was a one-time assessment, a rating of 25 mm from the zero mark also offered the best negative value in excluding patients with significant bronchospasm as defined based on the spirometry.

The result of those two cutoffs provides the diagnostic utility values shown in Table 2. Thirty-five patients developed significant bronchospasm as defined by spirometry. The patient's VAS using a change of 15 mm in the scale as a significant change produces a sensitivity of 51 percent and specificity of 76 percent. The corresponding positive and negative predictive values are 43 percent and 82 percent, respectively. Similarly, using a post-AP score of 25 mm from the zero mark scored by the nurses yields a sensitivity of 43 percent, a specificity of 78 percent, positive predictive value of 41 percent, and a negative predictive

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<th>Table 2 — Spirometry</th>
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<td>≥15% Drop in FEV1</td>
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<td>Patient's VAS</td>
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<td>≥15% Increase in VAS</td>
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<td>&lt;15% Increase in VAS</td>
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<td>Nurses' VAS</td>
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<td>≥25% Score on VAS</td>
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<td>&lt;25% Score on VAS</td>
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High Incidence of Bronchospasm with Aerosolized Pentamidine (Katzman et al)
value of 79 percent (Table 2).

Conclusions

Previous studies have demonstrated that when subjects are exposed to AP for either treatment or prophylaxis of PCP, 11 to 26 percent of patients developed cough and bronchospasm.1-5 The lower incidence of bronchospasm with the jet nebulizer4 in contrast with the somewhat higher incidence of bronchospasm with the ultrasonic nebulizer may reflect the particle size of aerosol. However, to date, no direct in vivo comparative study has been done. The current investigation included a relatively heterogeneous group of patients, where about one quarter of the patients receiving AP had previous adverse reaction to AP in terms of cough and wheezing or past history of asthma, and for that reason, they were receiving salbutamol as concurrent treatment to prevent bronchospasm. Despite the use of salbutamol, 26 percent of the patients receiving bronchodilator as concurrent therapy with AP developed significant bronchospasm. For those who did not have a past history of asthma or who on prior treatments tolerated AP well without subjective deterioration in their pulmonary status, 26 percent also had a significant reduction in the flow rates, up to 52 percent reduction in the FEV1 post-AP.

The diagnostic utility of the VAS evaluated in this study suggests that the VAS is not satisfactory to be used as a simple and sensitive indicator of significant bronchospasm to AP. In the study, bronchodilator was administered concurrently with AP because it reduced the time commitment for each AP treatment for the patients. Whether premedication with a beta2-agonist would completely eliminate bronchospasm due to AP is not addressed in our study. However, preliminary data from other centers suggest that premedication may eliminate airflow obstruction.8

The frequency of bronchospasm as evaluated by objective spirometric assessment in this and other studies1-5,8 is certainly high enough to warrant some form of surveillance or monitoring procedure for patients receiving AP treatments. Especially because the natural history and clinical implication of bronchospasm to regular AP administration is yet undefined as most of the data reported to date have a median follow-up of only 6 to 12 months.1,2 From an efficacy standpoint, untreated bronchospasm during AP administration may lead to poor distribution of AP throughout the lungs, and thus, contribute to some of the upper lobe breakthrough episodes of PCP. Also, there is the question of whether regular sensitization to AP causing bronchospasm may result in a “chronic asthma” condition in some of these patients. Whether the 26 percent frequency of bronchospasm is sufficient to justify routine administration of bronchodilator as either premedication or concurrent aerosol treatment to all recipients of AP remains controversial.

An alternative approach to universal premedication with beta2-agonist pre-AP is to prescreen patients at risk of bronchospasm. In theory, methacholine challenge test may be quite suitable. Unfortunately, preliminary study by Montaner et al.6 would suggest that methacholine challenge test is not reliable in that role. In terms of routine surveillance strategies, both for natural history study and to alleviate bronchospasm with AP, an alternative to the unreliable subjective scale such as the VAS evaluated in this study and to the cost of spirometry is to use a simple device like a peak flowmeter for peak flow measurement both pre-AP and post-AP treatments. In those patients where a significant reduction in peak flow is observed post-AP administration, bronchodilator can be given. Those subjects with no deterioration in their peak flow readings post-AP would then avoid the unnecessary intake of the beta2-agonist and its associated side effects. This approach can be generalized to both clinic-treated and home-treated patients, and it may offer a safe yet inexpensive method for monitoring and alleviating some of the unpleasant acute pulmonary effects of AP.

Acknowledgment: This study was done in collaboration with Kim Favell, R.N.; Margaret Moore, R.N.; Carmen Lewis, R.N.; and Lesley Lee-Pack. The authors wish to thank Mrs. May Chan and Mrs. Fehimda Nurmohamed for preparing the manuscript.

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