Intravenous Pentamidine-Induced Bronchospasm*

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A 41-year-old man with AIDS developed a recurrence of Pneumocystis carinii pneumonia and was treated with intravenous pentamidine. This was associated with a significant bronchospastic reaction requiring treatment with an antihistamine and an aerosolized β-agonist therapy. To our knowledge, this is the first report of bronchospasm induced by intravenous pentamidine. (Chest 1992; 102:1891-92)

More than 80 percent of patients with the acquired immunodeficiency syndrome (AIDS) will develop Pneumocystis carinii pneumonia (PCP) with a recurrence rate within one year as high as 45 percent. Standard therapy with either trimethoprim-sulfamethoxazole or parenteral pentamidine is effective but unfortunately associated with a significant incidence of toxic reactions as well as a failure rate as high as 25 percent. Hypotension, dysglycemia, and nephrotoxicity are common adverse reactions to intravenous pentamidine. The need to develop a less systemic toxic treatment for PCP in AIDS patients prompted the investigation with inhaled pentamidine. However, similar to intravenous pentamidine, aerosolized pentamidine is also associated with disconcerting side effects ranging from dysglycemia, pancreatitis, renal insufficiency, and significant respiratory disturbances. Bronchospasm has been reported to occur in as many as 34 percent of the patients after aerosolized pentamidine therapy. Proposed mechanisms of this drug-induced bronchospasm include a direct effect of the nebulized particles as well as histamine-mediated reaction. Interestingly, intravenous pentamidine has not been associated with bronchospasm. An extensive Medline literature search dating back to 1965 did not reveal any reports of drug-induced bronchospasm after intravenous pentamidine administration. In addition, only one patient has been identified by the manufacturer as experiencing bronchospasm after intravenous pentamidine. We present what appears to be the first published case report of intravenous pentamidine-induced bronchospasm in an AIDS patient being treated for PCP. A treatment recommendation to alleviate this side effect is also included in this report.

**CASE REPORT**

A 41-year-old HIV-positive man presented to our community teaching hospital with complaints of progressive shortness of breath (SOB), intermittent fever and chills, and a slight cough for two weeks prior to hospital admission. His medical history was significant for PCP 2½ years ago. His infection responded to standard treatment with trimethoprim-sulfamethoxazole that resulted in resolution of the infection, but he had a severe cutaneous reaction as well. He had been receiving aerosolized pentamidine prophylaxis for one year. This was tolerated reasonably well except for chest tightness and wheezing with aerosolized pentamidine that resolved with bronchodilator therapy. Other significant history included esophageal candidiasis one year prior to hospital admission that was treated successfully with itraconazole. The patient stated that he had quit smoking two years ago.

At the time of hospital admission, the physical examination revealed an alert and oriented man in no acute distress. Vital signs included blood pressure of 130/96 mm Hg, pulse rate of 109 beats/min, respirations of 20/min and temperature 38.3°C. Chest examination revealed bibasilar rales that were more significant on the right side. Admission laboratory values included the following: arterial blood gas on room air: pH, 7.47; PaCO2, 34.2 mm Hg; PaO2, 71 mm Hg. Complete blood cell count included the following: white blood cell count, 4,500/μL; hemoglobin, 11.4 gm/dl; hematocrit, 32.6 percent; and platelets, 287,000/μL. Results of serum chemistry studies were normal: sodium, 141 mEq/L; potassium, 4.3 mEq/L; chloride, 103 mEq/L; bicarbonate, 29 mEq/L; serum urea nitrogen, 18 mg/dl; and creatinine, 1.0 mg/dl. Chest roentgenography revealed diffuse bilateral interstitial reticulonodular pattern, which was a new finding as compared with a previous examination from 1990. The patient was admitted to the hospital for presumed recurrent PCP. Blood cultures were obtained as well as sputum specimens sent for routine culture and sensitivity, acid-fast bacilli (AFB) stain and culture, fungal smear and culture, and P carinii silver stain.

Intravenous pentamidine 4 mg/kg/day infused over 1 h was empirically initiated for PCP. Shortly after the beginning of the first infusion, the patient complained of increased SOB, dyspnea on exertion (DOE), and wheezing. Lung examination revealed diffuse bilateral rhonchi in addition to the bibasilar rales originally present. Oxygen therapy as 2 L per naso cannula was given during the final minutes of the infusion without eliminating the patient's symptoms. The patient's symptoms slowly resolved without any additional therapy. Due to the severity of the reaction, diphenhydramine 50 mg orally was ordered to be given before the next infusion. If necessary to relieve the symptoms, aerosolized albuterol was also ordered as needed after the infusion.

The following day, the patient received pretreatment with diphenhydramine but still experienced significant SOB, DOE, and wheezing during the infusion. After two albuterol nebulization treatments, the patient stated that he could breathe easier.

Final results of blood and sputum cultures from hospital admission were released and were noncontributory. Consequently, the patient

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underwent bronchoscopy with lavage and biopsy that later was positive for P. carinii.

Intravenous pentamidine therapy was to continue for a complete three-week course. For the next five consecutive days, the patient received diphenhydramine pretreatment as well as aerosolized albuterol via nebulization on an "as needed" basis. The number of albuterol treatments required ranged from one to two usually 30 minutes apart. On hospital day 4 (day of bronchoscopy), data concerning times of nebulized treatments were unavailable but the patient did receive two aerosolized albuterol treatments following the infusion of pentamidine. The patient's response to pentamidine was slow and on hospital day 7, the patient developed significant azotemia most likely secondary to pentamidine therapy. Intravenous pentamidine therapy was discontinued on this day and combination therapy with clindamycin and pyrimethamine was begun. This therapy was tolerated well with improvement in symptoms and the patient was discharged from the hospital five days later. No complaints of wheezing, DOE, or SOB were voiced by the patient after the discontinuation of intravenous pentamidine therapy.

**DISCUSSION**

Intravenous pentamidine has been widely used for the treatment of PCP with no published reports of drug-induced bronchospasm. In this case, there was a clear temporal relationship between the administration of intravenous pentamidine and the patient's bronchospasm. Even at different administration times during the day, bronchospasm began on initiation of pentamidine therapy. In addition, the bronchospasm was significant enough to warrant therapy with a bronchodilator. An antihistamine alone did not appear to relieve the respiratory symptoms.

Aerosolized pentamidine (AP) has been associated with various pulmonary complications, including cough, bronchospasm, and less frequently spontaneous pneumothorax, and disseminated pneumocytosis.1-10 In a recent review, the Toronto Aerosolized Pentamidine Study (TAPS) Group assessed the efficacy and toxicity of AP as secondary prophylaxis for PCP. Results from this small study (n = 36) indicate the AP therapy is frequently associated with coughing, but the actual incidence of bronchospasm is only 24 percent and usually mild in severity.4 Similar to our patient, all bronchospastic episodes experienced by the subjects in this study responded favorably to bronchodilators. Quieffin et al6 studied the frequency of AP-induced bronchoconstriction and the response to preventative therapy with inhaled bronchodilators. After pentamidine, a decrease in forced expiratory volume in one second (FEV1) was seen in 34 percent of the subjects. Factors such as smoking, asthma, age, baseline FEV1, and prior episode of PCP failed to predict the change in FEV1 after AP. The bronchodilators salbutamol and ipratropium prevented the bronchoconstriction caused by AP. This differs from the previous study and in our patient in which bronchodilators were used as treatment and not prophylaxis of bronchospasm.

The mechanism by which intravenous pentamidine led to bronchospasm in our patient is not clear. A direct effect is unlikely, although this is reported for AP-induced bronchospasm.4 Histamine release has also been offered as an explanation for the bronchospasm and it has been suggested that pentamidine is a nonspecific histamine-releasing compound.7 If this were true, it would be anticipated that intravenous pentamidine would also cause bronchospasm. Clinically, this has not been observed. In addition, an antihistamine alone did not effectively resolve the bronchospasm in this case. Only with the addition of albuterol did the wheezing reverse. It appears that either prophylaxis or treatment with bronchodilators will be effective.4

In summary, AP has been frequently associated with bronchospasm. We present the first (to our knowledge) published intravenous pentamidine-induced bronchospasm that was successfully treated with diphenhydramine pretreatment and albuterol nebulized treatments after the infusion. The bronchospasm occurred shortly after the initiation of the infusion and lasted approximately 1 h after the end of the infusion. The underlying mechanism is not known and we suggest that further research be undertaken to elucidate the mechanism as well as the true incidence of intravenous pentamidine-induced bronchospasm. The purpose of this report is to alert physicians and other medical personnel responsible for the care of HIV-infected patients to the possibility of this reaction occurring with intravenous pentamidine therapy.

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**REFERENCES**


