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SUMMARY

A health hazard evaluation (HHE) was conducted in the AIDS Clinical Trial Unit at the George Washington University (GWU) Medical Center to evaluate exposures to pentamidine isethionate. This work was performed in response to a request submitted by a management representative at the facility. Aerosolized pentamidine (AP) had been administered to AIDS patients for prophylaxis against *Pneumocystis carinii* pneumonia (PCP) since January 1989. A case of interstitial fibrosis had been diagnosed in one of the health care workers (HCWs) responsible for administering the drug. A few other HCWs working in the area of administration were reported to have abnormal pulmonary function tests (PFTs), but baseline PFTs were not available for these workers.

Prior to the NIOSH evaluation, changes in the pentamidine administration procedure had been made. These changes included the administration of pentamidine in a small room (rather than in an open area within the clinic), an increase in the number of room air changes per hour, the establishment of negative air pressure with respect to surrounding areas, and the provision of a glass panel on the door through which observations of the patients could be made while the health care worker remained outside.

Environmental measurements made in May 1991 revealed a concentration of 0.04 microgram per cubic meter ($\mu g/m^3$) pentamidine isethionate in a personal breathing zone air sample obtained on the nurse involved in AP administration, and 0.09 and 0.13 $\mu g/m^3$ in area air samples obtained outside the treatment room. These air concentrations are more than 100-fold lower than those measured in the AP treatment room during six AP treatments given over the course of approximately three hours. There are presently no occupational exposure criteria for pentamidine isethionate.

The medical evaluation consisted of employee interviews and a review of available medical records including pulmonary function test results for 11 employees. Of 4 employees interviewed, two reported occasional symptoms of mild chest tightness associated with exposure to AP; one reported experiencing these symptoms occasionally, while the other reported only a single episode. This may reflect mild, reversible bronchospasm, which has been reported in both patients and workers exposed to pentamidine. There were also reports of mucosal irritation; however, both the irritative symptoms and chest tightness resolved or decreased after the changes (noted above) in work practices and ventilation were instituted. Eight employees were reported to have abnormally low pulmonary diffusing capacity. Only one employee reported symptoms of dyspnea. Retesting of four employees at another site indicated that their pulmonary diffusing capacities ($D_{L_{CO}}$) were within limits of normal, using different comparison populations. A test of pentamidine-induced lymphocyte stimulation was performed using blood from 8 of the 11 employees; although all 8 employees showed some degree of lymphocyte stimulation to pentamidine, no association was found between the degree of stimulation and the $D_{L_{CO}}$ values.

Although the medical significance of exposure to aerosolized pentamidine is unclear, the recognized irritant effects of pentamidine, its potential to cause bronchospasm, and the risk of tuberculosis (TB) transmission in these settings justify continued efforts to minimize worker exposures through engineering and administrative controls.

KEYWORDS: SIC 8069 (Hospitals, specialty), pentamidine, pentamidine isethionate, aerosolized pentamidine, tuberculosis, health care workers, AIDS, *Pneumocystis carinii* pneumonia.

INTRODUCTION

In the fall of 1989, there were nine employees who worked in the AIDS Clinical Trial Unit (ACTU) of the George Washington University (GWU) Medical Center and had potential exposure to aerosolized pentamidine. Concerns about potential health effects were raised by the publication of a case report of reduced pulmonary diffusing capacity (DL_{CO}) in a health care worker,[1] and the subsequent diagnosis of idiopathic pulmonary fibrosis in one of the workers administering pentamidine at this facility. In response to these concerns, employees who had occupational exposure to pentamidine underwent DL_{CO} testing by both single-breath and steady-state techniques; in subsequent consideration of the DL_{CO} values in this population, the single breath values were considered. No previous (baseline) DL_{CO} tests were available. Some employees were initially reported to have DL_{CO} less than predicted for their gender, age, and height; the prediction equations used were those of the Intermountain Thoracic Society, and are based on work by Crapo and Morris.[2] Several employees were retested at a facility in the National Heart, Lung and Blood Institute on the National Institutes of Health campus in Bethesda, Maryland; all had DL_{co} above 75% of their predicted values. Because of concerns of employer and employee representatives, management representatives requested a National Institute for Occupational Safety and Health (NIOSH) Health Hazard Evaluation. NIOSH personnel conducted on-site investigations on July 24-25, 1990, and a follow-up environmental survey May 8, 1991.

BACKGROUND

Pentamidine isethionate is an aromatic diamidine compound. It was synthesized in the 1930's and subsequently used as a pharmaceutical treatment for protozoal diseases resulting from infections with *Trypanosoma rhodesiense* and *Leishmania donovani*. More recently, it has been found to be effective in the treatment and prophylaxis of *Pneumocystis carinii* pneumonia (PCP), a common opportunistic infection in patients with compromised immune function.[3] Although pentamidine was originally administered by the intravenous or intramuscular route, in 1989 the Food and Drug Administration approved the administration of aerosolized pentamidine (AP) for prophylaxis against PCP.[4] Since that time, concern has been expressed over the risk which exposure to AP may pose to health care workers.

Reports have been published citing the occurrence of ocular irritation and acute bronchospasm among health care workers administering AP.[5,6] These effects have also been reported in patients receiving AP.[7,8] A single case of reduction in pulmonary diffusing capacity in a health care worker has been described.[1] However, this is contrasted by the absence of effects on pulmonary diffusing capacity in a recent year-long study of immunocompromised patients receiving monthly treatments with AP.[9] Pancreatitis, hypoglycemia, and hyperglycemia have usually been associated with intravenous administration of pentamidine, but several cases have been reported in patients receiving AP.[10,11] Although a significant association between pneumothorax and aerosolized pentamidine therapy has been shown, the incidence of PCP in the affected patients was high enough to suggest the possibility that the occurrence of pneumothorax might result from a synergistic effect between AP and PCP.[12]

Concerns have also been expressed about the potential teratogenicity of pentamidine.[13] In studies of pregnant rats administered pentamidine by injection, pentamidine transfer across the placenta and accumulation in fetal tissues was demonstrated; litter size was decreased but the rate of malformation was not increased compared to the offspring of unexposed rats, suggesting embryocidal but not teratogenic effects.[14,15] An Ames test did not yield any responses suggesting

mutagenicity, and a Chinese hamster ovary test for chromosomal aberration was negative.[16]

Only one report of an investigation of health care workers' exposures has been published to date; in that report the investigators detected a mean airborne pentamidine concentration of 0.045 microgram per cubic meter ($\mu g/m^3$).[17] A report of biological monitoring for pentamidine revealed detectable levels of pentamidine in the urine of health care workers who administered the aerosol treatment to patients. In this study, the high end of the range of urine pentamidine levels found in workers overlapped the low end of the range measured in patients receiving the drug.[18]

In addition, concerns have been expressed regarding the risk of health care workers' exposure to *Mycobacterium tuberculosis* while caring for HIV-infected patients.[19] In one investigation, there was an association between being in a room where aerosolized pentamidine was delivered and an increased rate of tuberculosis Purified Protein Derivative (PPD) skin-test conversion.[20] The risk is thought to be significant enough that recent CDC guidelines for preventing TB transmission in health care facilities have included recommendations to be followed when administering pentamidine therapy. These include screening for tuberculosis infection, administering pentamidine therapy in rooms with adequate ventilation, and use of personal respirators by health care workers under certain conditions.[21]

METHODS

Pentamidine Use in the ACTU

The ACTU has administered aerosolized pentamidine for PCP prophylaxis since January 1989. Changes in the administration procedure were made prior to the initial NIOSH evaluation, which was conducted in July 1990. These changes included the administration of AP in a small room, dedicated to this purpose, and which was under negative pressure with respect to surrounding areas. A glass panel on the door was added so that observations could be made while the health care worker remained outside, and an increase in the number of room air changes per hour (ACH) was made from 9, as reported by an outside consultant, to 33, as calculated by NIOSH investigators (based on exhaust airflow measurements).

AP treatments last approximately 20-30 minutes and are given every weekday at this clinic. A 300-milligram dose of pentamidine isethionate is nebulized using the Marquest Respirgard II nebulizing system which has been reported to deliver an aerosol with a mass median aerodynamic diameter (MMAD) of 0.8 micron (μm).[22] Four employees are directly involved in AP administration or preparation, including three nurses and a pharmacist. At the time of the follow-up evaluation conducted in May 1991, management reported that one nurse was responsible for approximately 75-80% of all treatments given. The number of treatments given at this clinic ranged from 2 to 15 per day, with 6 to 10 per day being most common. Two patients may be treated at the same time. In an effort to minimize health care workers' (HCWs') exposures to pentamidine, patients are instructed to turn on the nebulizer after the HCW leaves the treatment room and to turn it off prior to leaving the room. No protective equipment or clothing is worn by the HCWs with the exception of a lab coat.

To minimize side effects such as bronchospasm and coughing, a bronchodilator is administered to each patient before the person receives AP. The health care worker obtains a recent medical history from the patient and measures weight, blood pressure, and temperature. Patients with symptoms suggestive of tuberculosis or pneumonia are referred to a physician for evaluation

prior to receiving pentamidine treatments. In addition, patients receive initial and periodic (every 6 months) chest radiographs and PPD skin tests as part of their tuberculosis screening procedure. HCWs involved in AP administration also receive periodic PPD skin tests. As of December 1991, HCWs receive baseline and annual PPD screening, and annual pulmonary function tests are planned.

Data Collection

Air monitoring for pentamidine isethionate was performed on the initial evaluation; however, these data are not reported due to problems encountered during the analysis. Environmental monitoring was again conducted in May 1991 to characterize workers' pentamidine exposures during aerosol administration. Only one HCW was involved in the AP administrations on the day of the survey. A personal breathing zone air sample was obtained on this worker. Area air samples were obtained to assess potential contamination of surrounding areas and to determine the concentration of pentamidine in the treatment room. Air samples were collected over the course of the AP treatments (which lasted approximately three hours), or over the entire workshift, as appropriate. Because the HCW administering AP did not remain in the clinic after the treatments were completed, this air sample was collected only during the treatment period. Conversely, the air sample obtained on the secretary/receptionist desk was collected over the entire workday since the employee at that workstation could potentially be exposed to stray aerosol for a longer period of time.

Air samples were collected on 37 millimeter, 5 µm pore size polyvinyl chloride (PVC) membrane filters (in opaque closed-face cassettes) using sampling pumps calibrated to two liters per minute (Lpm). Pentamidine isethionate was recovered from the filters using three milliliters of a solution containing 97.5% methanol, 0.5% sodium-1-heptane sulfonate, 0.02% (10%) tetramethylammonium chloride, 0.1% phosphoric acid and water. Analysis of the resulting solutions was performed using high-performance liquid chromatography (HPLC) with fluorescence detection. HPLC conditions were a variation of those described by Lin *et al*.[23]

Additionally, a Model 294 Marple Personal Cascade Impactor was used to obtain an air sample for particle size characterization. This sample was collected in the pentamidine treatment room during the course of six AP treatments. A flowrate of 2 Lpm was used giving rise to cut-points of 21, 15, 10, and 3.5 µm for this four-stage impactor. Personal breathing zone air sampling was not attempted using this sampling device, as the exposures were anticipated to be too low to enable an accurate size distribution. Mylar substrates were used on the impaction stages, and a 5-µm pore size PVC filter was used as the back-up filter. Recovery and analysis of the pentamidine isethionate was performed as described above.

Medical Evaluation

The medical evaluation consisted of employee interviews, a review of available medical records, and discussions with physicians involved in prior medical investigations of these workers.

RESULTS

Environmental Monitoring

Six of the eight scheduled patients reported to the clinic for treatment. Results of the air monitoring are shown in Table I. Results are reported as micrograms of pentamidine isethionate

per cubic meter of air (µg/m^3). Pentamidine isethionate was present in all samples, at concentrations ranging from 0.04 to 19.6 µg/m^3. The personal air sample obtained on the HCW administering pentamidine had a concentration of 0.04 µg/m^3. This sample and the area air samples obtained outside the treatment room had concentrations more than 100 times below the concentration detected in the treatment room. Occupational exposure criteria are not available for pentamidine isethionate

TABLE I. Pentamidine isethionate air sampling data

Job/Location	Sampling Time (minutes)	Pentamidine Isethionate (µg/m^3)
Nurse AP Administration	183	0.04
Inside AP treatment room: 2' from nebulizer	198	18.6
Inside AP treatment room: 2' from nebulizer, side-by-side with above sample (using cascade impactor)	198	19.6
Outside AP treatment room: On table 3' from door (near chair)	400	0.13
Outside AP treatment room: Sec/Recpt desk	405	0.09

Results of the particle size selective air sampling were plotted on a log-probability graph (particle diameter vs. cumulative mass fraction [%]) to enable determination of the mass median aerodynamic diameter (MMAD). A MMAD of less than 1 micron (µm) was determined for the air sample collected in the AP treatment room over the course of six AP treatments. This sample was collected at a distance of two feet from the nebulizer. Approximately 94% of the pentamidine isethionate was detected on the final (back-up) filter. This sample had an air concentration of 19.6 µg/m^3 when the mass of pentamidine isethionate from the four stages and the back-up filter was combined. This compares favorably with the filter cassette sample obtained side-by-side, which had 18.6 µg/m^3.

Smoke tubes used to determine the direction of airflow confirmed that the room was under negative pressure with respect to the rest of the clinic on the day of the survey. Airflow measurements indicated an exhaust airflow of 220 cubic feet per minute (CFM), which corresponds with an air change rate of 33 air changes per hour (ACH) (assuming perfect mixing). The clinic staff reported that air from this room was exhausted directly to the outside, with no recirculation into other areas of the clinic.

Interviews

Four employees directly involved in the preparation or administration of AP were interviewed during the initial NIOSH visit on July 25, 1990. One employee reported no symptoms, but was not involved in AP administration. Three of the employees reported occasional to rare symptoms of mucosal irritation while administering treatments. One employee reported a single episode of mild chest tightness on a day when more patients than usual were treated, while another employee reported "occasional" mild chest tightness while administering treatments. These symptoms had mainly occurred while giving treatment before the ACTU was remodeled to contain exposures. These three employees did not report shortness of breath during exertion or at rest.

The fourth employee had been diagnosed as having pulmonary fibrosis. After working in the ACTU for about a year, the employee developed complaints of shortness of breath and dyspnea on exertion, and following transbronchial lung biopsy was diagnosed as having "idiopathic" pulmonary fibrosis. At the time of the NIOSH visit, this employee had not administered pentamidine treatments for 8 months. The employee indicated that the pulmonary symptoms were resolving.

During a follow-up visit on May 8, 1991, a new employee who had been involved in pentamidine administration for approximately 4 months was interviewed with respect to administration procedures and possible work-related symptoms. No symptoms were reported by this worker.

Record review

Pulmonary diffusing capacity

TABLE 2. Medical laboratory results.

SUBJ ECT	DLCOsb measured (GWU)	DLCOsb predicted (GWU)	DLCOsb measured (NIH)	DLCOsb predicted (NIH)	LSI
FEMALES					
1	23.06	27.8			11.3
2	18.11*	31.52	17.68	22.65	
3	17.81*	30.33	18.54	22.3	3.1
4	18.36*	31.34	18.71	23.59	7.2
5	13.69*	26.63			6.6
6	18.19*	31.43			8.5
7	22.76*	27.38			17
MALES					
8	26.62*	42.36			13.8
9	30.85	38.62			10.7
10	27.77*	42.46	27.11	31.68	
11	19.4*	29.65			

DLCOsb= single breath pulmonary diffusing capacity
LSI= lymphocyte stimulation index
*DLCOsb was less than 80% of predicted and was below the lower boundary of the 95% confidence interval (Crapo and Morris, 1981)

Records of pulmonary function tests, including pulmonary diffusing capacity, for 11 employees were reviewed and are presented in Table 2. All 11 employees (7 women and 4 men) were initially tested at GWU. Eight of the 11 showed DL_{CO} test results which were below 80% of predicted and below the lower 95% confidence interval predicted from the reference normal population; the predicted scores were derived from prediction equations derived by Crapo and Morris.[2] Although the prediction equations used were for DL_{CO} which had been normalized to a standard hemoglobin concentration, hemoglobin correction was not performed in the calculation of the predicted DL_{CO}. When the lower 95% confidence interval were recalculated using the prediction equations of Crapo and Morris without hemoglobin correction, 9 employees' DL_{CO} values were below the lower 95% confidence interval.[2] Four of the employees were subsequently retested at a facility in the National Heart, Lung and Blood Institute (NHLBI). In the GWU tests, these four had DL_{CO} values from 59% to 65% of predicted; in the NHLBI laboratory, the DL_{CO} values were 78% to 86% of predicted.

The actual values of DL_{CO} were similar at the two pulmonary laboratories. In all 4 cases, the difference between the values was less than 4%, calculated as:

(GWU value - NHLBI value)/(NHLBI value) x 100% = % difference.

The difference between the GWU results and those from the NHLBI can be attributed to the use of different predictive equations; in all 4 cases the NIH predicted values were lower than the predicted values used by the GWU laboratory. The NHLBI predicted values were calculated using predictive equations supplied by the manufacturer of their testing apparatus; these were based upon equations published by Gaensler and Wright.[24,25]

Spirometry

All employees received spirometric testing at the time of their pulmonary diffusing capacity tests. We examined the forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), the ratio of FEV_1 to FVC, and the forced expiratory flow between 25% and 75% of FVC ($FEF_{25-75\%}$). Eight of the 11 employees scored at or above 80% of the predicted value for almost all these tests (one individual had an $FEF_{25-75\%}$ which was 76% of predicted; this person's FEV_1, FVC, and FEV_1/FVC were above 80% of the predicted value). The remaining three employees had initial $FEF_{25-75\%}$ below 65%. They were retested after administration of the bronchodilating drug isoproterenol; all post-drug values were improved, and (except for one employee's $FEF_{25-75\%}$, which was still below 70%) were greater than 80% of predicted.

Lymphocyte stimulation test

An immunologist at GWU performed a test of pentamidine-induced lymphocyte stimulation on 8 of the 11 employees whose DL_{CO} had been tested.[26] In the lymphocyte stimulation test, lymphocytes obtained from a person by drawing a blood specimen are exposed in the laboratory to the substance being tested (pentamidine in this case). If the lymphocytes respond by proliferating, the test indicates that the lymphocytes were previously sensitized to this substance.[27] All 8 employees tested showed some degree of lymphocyte stimulation to pentamidine, ranging from "medium" to "very high" responses; 7 of 8 controls showed no evidence of stimulation, and 1 showed a "low" response. Low response was interpreted as indicating exposure, medium was interpreted to mean early reactivity or exposure to pentamidine, and high or very high response suggested allergic reactions. However, the individual with "very high" reactivity had a DL_{CO} over 80% of predicted.

We examined a hypothetical relationship between the lymphocyte stimulation test, as an indicator of a possible immunologically mediated effect, and DL_{CO} by testing for a correlation between the lymphocyte stimulation index (the numeric measure of stimulation) and the percent of DL_{CO} as predicted by the equations of Crapo, et al.[2] If the presence of sensitized lymphocytes was related to an adverse pulmonary effect (as indicated by a less than predicted), a significant negative correlation would be expected. However, two nonparametric tests for correlation showed positive correlations between the lymphocyte stimulation index and the percent of predicted DL_{CO} as calculated at GWU (Spearman's rank correlation R=0.76, p=0.03; Kendall Tau-b correlation R=0.57, p=0.05).

Hypersensitivity pneumonitis panel

As part of the evaluation of abnormal DL_{CO} tests among employees, the hospital tested 14 GWU employees for antibodies to common antigens involved in hypersensitivity pneumonitis. We examined the records of these tests during the NIOSH investigation. Ten of the employees had current or past pentamidine exposures; they had received DL_{CO} testing and 8 employees had previously undergone lymphocyte stimulation tests. The other four worked in an adjacent laboratory on the same air handling system. Table 3 shows the number of employees who had demonstrable antibodies in their sera.

Student's t-test was used to compare the mean percentage of predicted DL_{CO}, and the mean lymphocyte stimulation index, between the employees who did or did not have antibody to each antigen. There were no significant differences seen at the p=0.05 level. However, the number of subjects in these groups is very small, making it unlikely that a difference would be identified as significant. A physician who had seen the employees indicated that none reported symptoms of hypersensitivity pneumonitis.

TABLE 3. Number of employees with demonstrable antibodies to antigens in the hypersensitivity pneumonitis screening panel.

Antigen	Number of employees with antibodies (14 tested)
Micropolyspora faeni	0
Cephalospora acremonium	0
Thermoactinomyces vulgaris #1	0
Aspergillus flavus	5
Aspergillus fumigatus #1	5*
Aspergillus niger	3
Aureobasidium pullulans	1
Pigeon serum	1

*Includes one partially reactive

DISCUSSION

One employee in this workplace reported occasional symptoms of mild chest tightness associated with occupational exposure to AP, while a second employee reported a single episode of chest tightness. This may reflect mild, reversible bronchospasm, which has been reported in both patients and workers exposed to pentamidine. However, the infrequency of these reports makes it difficult to be certain that these are truly work-related. It is reassuring that the GWU employees reported a decrease in symptoms after the delivery area was redesigned and work practices changed. Unfortunately, there are no data available on airborne concentrations of pentamidine prior to the time when these changes were made. Environmental monitoring conducted during this survey revealed that air concentrations outside the patient treatment room and in the personal air sample obtained on the nurse were more than 100 times lower than the concentrations measured in the treatment room. The provision of good general ventilation, the establishment of negative air pressure with respect to surrounding areas, and procedures requiring HCWs to remain outside the treatment room during AP administration were effective in minimizing worker exposures.

The concerns in this investigation involved the report of reduced pulmonary diffusing capacity among health care workers who administer pentamidine. The reports are confused by the discrepancy in predicted normal values at two laboratories. The differences between the reference equations used for prediction of normal values of DL_{CO} have been discussed in the Record Review section, and it has been suggested that the differences result from variations in technique among the laboratories reporting the reference equations.[2] In this investigation, however, it is important to note that the actual values of DL_{CO} were similar in the GWU and NHLBI laboratories. Thus, differences between laboratories, or variation between tests in the same individual, do not contribute to the discrepancies in the interpretations of the DL_{CO} in these employees. Of the four employees interviewed, one had an abnormally low DL_{CO} compared to the predicted normal using the equations of Crapo, et al.; this employee experienced symptoms and was diagnosed as having pulmonary fibrosis. One employee had a normal DL_{CO} (compared to the predicted normal using equations of Crapo, et al.). Of particular interest in this context are the other two employees, both of whom had a DL_{CO} below 80% of predicted and below the 95% confidence interval of the reference normal population. Both of these denied symptoms of dyspnea on exertion or shortness of breath.

The account of a worker at this site who was diagnosed with pulmonary fibrosis after administering AP is of concern. Pulmonary fibrosis is a cause of reduced DL_{CO} due to thickening of the alveolar membrane in the lung, and this employee's DL_{CO} was the lowest, relative to predicted values, of all those tested. However, it is not clear that this condition was caused by exposure to pentamidine. If pentamidine was strongly associated with the development of pulmonary diseases which result in reduced DL_{CO}, such as pulmonary fibrosis, then higher exposures could be expected to produce either more severe disease or a higher incidence of disease. As evidenced by studies of urine measurements, patients receiving pentamidine treatment excrete much higher levels of pentamidine (1.3 to 247 nanograms of pentamidine per milliliter of urine [ng/ml]) than do exposed workers (0.15 to 8.19 ng/ml), suggesting higher exposures and greater absorption among patients.[18] Yet a study of drug efficacy in patients receiving AP for prophylaxis against *P. carinii* pneumonia did not show significant differences in DL_{CO} among patients receiving the drug, when compared to control patients receiving aerosolized distilled water.[9] A comparison between the patients in that study and exposed workers must be made with care, as the former were immunocompromised patients at risk for *P. carinii* and other pneumonias which would alter DL_{CO}. Still, given the concerns in this hazard evaluation, the absence of an effect in patients is worth noting. At least one clinical investigator

has studied possible associations between occupational pentamidine exposure and pulmonary function tests, including D_{LCO}. An early report suggested some statistically significant changes occurred in cross-shift FEV1 with exposure, but the investigators felt these changes were not clinically significant.[28] There were no significant changes in D_{LCO}.[29]

The reported presence of antibodies against antigens implicated in hypersensitivity pneumonitis suggests that the employees have been exposed to these antigens. It is beyond the scope of this evaluation to determine whether the exposures occurred in this workplace. In addition, detecting the antibodies does not conclusively prove that disease exists; up to 50% of individuals who were exposed to these antigens but do not have symptoms may have moderate to high titers of serum precipitating antibodies.[30]

The discovery that pentamidine-exposed health care workers developed pentamidine sensitization of lymphocytes is significant, and raises the possibility that reduced D_{LCO} might be a manifestation of an immunologically mediated response to pentamidine exposure. However, the positive correlation between the lymphocyte stimulation index and the percent of predicted D_{LCO} argues against this hypothesis. Further, the employee with confirmed pulmonary disease had the second lowest stimulation index of the eight employees tested. It is possible that the development of sensitized lymphocytes is a biological marker of exposure, unrelated to pulmonary diffusing capacity. Further research may be useful to discern whether the lymphocyte populations involved are B-cells or T-cells, and whether anti-pentamidine antibodies are formed.

CONCLUSIONS AND RECOMMENDATIONS

The low D_{LCO} values in this exposed population do not appear to be consistently "low" when compared to different reference populations. The absence of symptoms in most of the workers interviewed, and the failure of a clinical study to detect adverse effects of pentamidine on D_{LCO}, do not provide support for concerns that occupational pentamidine exposure is the cause of work-related interstitial lung disease. However, there are still unanswered questions regarding the interpretation of the D_{LCO} results in these employees, the applicability of the patient-related studies, and the implications of the lymphocyte stimulation tests.

Even with the uncertainty regarding significance of the D_{LCO} results in GWU employees, the irritant effects of pentamidine, its potential to cause bronchospasm, and the risk of tuberculosis transmission (due to the coughing that results from AP therapy) justify efforts to minimize HCW's exposures. The engineering controls and work practices currently in place serve to minimize pentamidine exposure as well as potential exposure to droplet nuclei from patients who may have unrecognized tuberculosis. Future consideration should, however, be given to the use of a booth, hood, tent, or other local exhaust system, with exhaust air either directed to the outside or filtered using a high efficiency particulate air (HEPA) filter. These local exhaust systems contain the contaminants at their source, a practice which is preferable to controls which rely on later removal of the contaminants from the pathway between the source and the worker. These local exhaust systems would also serve to minimize the potential for tuberculosis transmission among patients undergoing simultaneous AP therapy.

The performance of the engineering controls should be evaluated periodically through scheduled maintenance and testing. Surveillance of all workers potentially exposed to pentamidine isethionate and TB should continue. Air sampling for pentamidine isethionate should be performed periodically, particularly when changes in engineering controls, work practices, or

administration procedures are made which may affect worker exposures. A NIOSH air sampling and analytical method for pentamidine isethionate has been developed (NIOSH Method No. 5032).[31] The NIOSH method is a modification of the method described in this report.

A recently completed clinical trial suggested that aerosolized pentamidine is not as effective as oral trimethoprim/sulfamethoxazole in preventing recurrent *Pneumocystis carinii* in persons with AIDS.[32] Aerosolized pentamidine therapy also may not adequately protect all recipients from extrapulmonary *Pneumocystis carinii* infection.[33,34,35] Because of these considerations fewer patients are being treated with aerosolized pentamidine.[27] However, some patients still require pentamidine therapy because they have adverse reactions to other drugs. When pentamidine therapy is indicated, appropriate measures should be taken to protect health care workers from associated exposures.

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