Respiratory Effects of Occupational Exposure to Aerosolized Pentamidine

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To determine the respiratory effects on health care workers of occupational exposure to aerosolized pentamidine (AP) used for the prophylaxis of Pneumocystis carinii *pneumonia, we designed a clinical prospective study using subjects as their own controls. Sixteen health care workers whose job duties included administration of AP at one or more of nine San Francisco Bay Area medical centers participated in the study. Pentamidine concentrations ranged in breathing zone samples from <0.03 to 62.2 $\mu g/m^3$. Pentamidine was not detected in the urine of any of the subjects. There were no significant increases in symptoms on days when AP was administered. Cross-workshift spirometry on days when AP was administered showed a statistically significant mean decrease (0.14 liter) in forced expiratory volume in 1 second. There was no statistically significant difference in mean diurnal variation of peak expiratory flow rate on days when AP was administered. Methacholine inhalation challenge testing did not show a statistically significant mean change in airway responsiveness across the workweek. The ambient concentrations of pentamidine that we measured document that detectable occupational exposure to AP can occur in poorly ventilated treatment rooms. The cross-workshift decrement in forced expiratory volume in 1 second that we observed in association with AP administration supports the respiratory tract irritant potential of inhaled pentamidine. We recommend that steps be taken to minimize health care worker exposure to AP.*

Pentamidine is an antiprotozoal diamidine that has been used for many years to treat infections with *Pneumocystis carinii*.[1,2] The traditional route of administration of pentamidine has been by intravenous infusion. In an effort to decrease systemic toxicity, aerosolized pentamidine (AP) administration was developed as a treatment modality for patients with HIV-related immunocompromise.[3–6] Although there is gradual systemic absorption, most of an inhaled AP dose is deposited in the respiratory tract, and bronchoalveolar lavage fluid concentrations may be at least two orders of magnitude higher than those achieved after intravenous administration.[7] Not surprisingly, the primary toxicity of AP is on the respiratory tract, with cough and bronchoconstriction occurring in many patients.[8–10]

Until recently,[11–17] little attention was paid to the possibility of secondary occupational exposure to AP among the health care workers (HCWs) required to administer this therapy. The design of the nebulizing system most commonly used in the United States (Respirgard II, Marquest Medical Products, Inc, Englewood, CO) allows continued output of aerosol into the treatment room environment when patients remove the mouthpiece to talk or cough. Because AP is often administered in treatment rooms that can accommodate more than one patient, the potential for significant occupational exposure seemed likely. We designed a prospective study to measure ambient concentrations of pent-

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amidine in San Francisco Bay Area treatment rooms and to assess the potential for adverse respiratory effects from occupational exposure to these concentrations.

Methods

Subjects

The study population included HCWs who gave scheduled AP therapy to patients with HIV infection for prevention of *P. carinii* pneumonia in San Francisco Bay Area medical centers during 1990 to 1991. At that time, there were approximately 30 HCWs administering AP therapy at 25 Bay Area centers.

Under a study protocol approved concurrently by the Committee on Human Research at the University of California at San Francisco (UCSF) and the institutional review boards of the participating medical centers, we recruited 16 subjects at 9 facilities. Subjects were directly contacted by the investigators and asked to participate in the study. At this time, a medical history was obtained. A history of any upper respiratory infection within the 6 weeks preceding the study was cause for exclusion, as was a history of personal AP treatments for prophylaxis of *P. carinii* pneumonia.

Characteristics of the HCWs studied are listed in Table 1. The amount of time administering AP ranged from 2 to 40 hours per week, and the number of patients treated ranged from 2 per week to 37 per day. Two workers administered pentamidine at more than one work site.

TABLE 1
Subject Characteristics

Characteristic	Population
Number of subjects, n (%)	16 (100)
Female subjects, n (%)	3 (19)
Ethnicity, n (%)	
Filipino	1 (6)
Hispanic-American	2 (12)
African-American	2 (12)
Caucasian, non-Hispanic	11 (69)
Median age, years (range)	38 (30–48)
Median years at current job (range)	4.1 (0.4–13.7)
Median years of AP administration (range)	2.4 (0.2–4.5)
Smoking status, n (%)	
Current	8 (50)
Former	1 (6)
Respiratory history, n (%)	
Asthma	4 (25)
Hay fever	8 (50)

Exposure Assessment

During the workweek, the subjects performed their regular duties as respiratory therapists or nurses, which included administering AP to patients. On days when AP was administered, none of the subjects was occupationally exposed to other known respiratory tract irritants, such as glutaraldehyde or ethylene oxide. Pentamidine concentrations in the work environment and urine of the subjects were measured to assess exposure.[13]

The personal breathing zone was sampled for each participant for at least one full workshift. Ambient air samples were collected at each facility for each entire workshift for which personal sampling was performed.

Personal breathing zone and area samples were collected on glass fiber filters (Type AE, Gelman Sciences, Ann Arbor, MI) at a flow rate of 2 liters/min. Opaque cassettes were used to guard against potential photodecomposition of the collected material. The aerosol particle size was determined using a Marple personal cascade impactor (Model 298, Anderson Instruments, Inc, Atlanta, GA). Mylar substrate was placed on four stages of the eight-stage impactor. The stages used corresponded to aerodynamic cutoffs of 20, 15, 10, and 2 gmm diameters. A glass fiber back-up filter captured all remaining particles <2 μm in diameter. Samples were kept in the dark and refrigerated until analysis was performed.

A spot urine sample was obtained at the start and again at the end of the workweek. Urine samples were kept frozen at -90 °C until analyzed for pentamidine concentration.

A high-performance liquid chromatography method developed by the National Institute for Occupational Safety and Health (NIOSH), based on the earlier work of Lin and coworkers,[18] was used in the NIOSH laboratory to analyze for pentamidine in ambient air samples collected at the work site. The urine pentamidine concentrations were determined by a laboratory at UCSF that routinely performed these analyses using the high-performance liquid chromatography method of Lin and coworkers.[18]

Respiratory Effects

Symptoms and Peak Expiratory Flow. On day 1, a log book for the recording of symptoms and serial peak expiratory flow rate (PEFR) measurements and a peak flow meter were issued to the subject with instructions in their use. Symptoms, including respiratory symptoms, headache, and eye irritation, were recorded twice daily (7 AM and 5 PM) for 3 weeks. Peak flow measurements (best of three efforts) were recorded by subjects four times daily (7 AM, 12 PM, 5 PM, and 10 PM), for 3 weeks, both during workdays and days off.

Spirometry. During the third week (the study week), spirometry was performed before and after a workshift in which AP was administered and again later on a day when no AP

was administered. Spirometry was performed on a dry, rolling seal spirometer (S400, Spirotech Division, Anderson Instruments, Inc, Atlanta, GA) in accordance with American Thoracic Society criteria. The predicted values used were those of Knudson and coworkers.[19]

Nonspecific Airway Responsiveness. Nonspecific airway responsiveness was measured by generating a methacholine dose-response curve before the first workshift of the study week and again before the last workshift of the study week. We used a modified version of the short protocol designed by O'Connor and coworkers for application to epidemiologic studies.[20]

Statistical Analysis

For each subject, the change in forced expiratory volume in 1 second (FEV_1) across a workshift with AP exposure was calculated by subtracting the postshift value from the preshift baseline value. The change in FEV_1 across a comparable 8-hour period on a day without AP exposure was similarly calculated. The mean changes in FEV_1 for days with and without AP exposure were compared with a paired *t* test. Diurnal variation in PEFR was calculated for each day as follows: maximum value − minimum value/maximum value × 100%. Mean diurnal variations in PEFR for days with and without AP exposure were compared with a paired *t* test.

The slope of the methacholine dose-response slope was selected as the measure of airway responsiveness rather than the provocative concentration of methacholine that causes a 20% decrease in FEV_1 from baseline (PC_{20} in micromoles) because only 11 subjects reached a 20% decrease in FEV_1 before termination of the test. The dose-response slope is defined as [(posttest FEV_1 − pretest FEV_1)/pretest FEV_1 × 100]/cumulative dose of methacholine in micromoles. The dose-response slope obtained in the last day of the study week was compared with that obtained on the first day of that week by a paired *t* test to assess whether these values were significantly different.

Because symptoms scores were not normally distributed, the Wilcoxon signed-rank test was used to compare scores for days with and without AP exposure.

The potential association of personal breathing zone concentrations of AP to cross-workshift change in FEV_1 was also evaluated by analysis of covariance.

TABLE 2
Personal Breathing Zone Concentrations of Pentamidine and Number of Treatments Administered

Number of Treatments on Day of Sampling	μ/m³	Subject
2	< 0.03	I
6	0.1	N
6	0.1	O
6	1.2	C
8	< 0.03	C
8	0.6	P
10	5.7	E
12	0.1	O
12	7.0	N
13	0.2	G
14	9.7	D
15	17.1	B
17	0.4	M
17	15.8	B
18	7.5	F
18	22.9	L
19	4.2	A
20	0.5	H
20	1.4	L
20	11.0	F
22	8.8	K
23	8.8	D
23	13.9	J
23	62.2	E
25	15.9	J
27	< 0.03	M
31	1.2	A

Results

Environmental and Biological Samples

Concentrations of AP in personal breathing zone samples from the nine work sites ranged from <0.03 to 62.2 μg/mg³. Table 2 shows the results of the personal breathing zone samples for each of the subjects. These results have been standardized for an 8-hour workday. For the Marple cascade impactor samples, most (median, 70%; range, 55 to 88%) of the pentamidine was collected on the backup glass fiber filter, with the largest portion of the remainder on stage 6 (cutoff of 2 μm), indicating a mass median aerodynamic diameter (MMAD) of less than 2 μm.

Various local exhaust ventilation and air movement controls were in place at the facilities at the time of the study. The HCWs wore no personal respiratory protective equipment except at one site, where a half-face mask respirator was used when HCWs attended patients receiving AP. The number of treatments for the days of the study ranged from two treatments per week to 31 treatments per workshift with a median of 17. Personal breathing zone concentrations of pentamidine were significantly associated with number of treatments administered ($P = .03$). Follow-up environmental sampling was conducted at one facility after a local exhaust system was installed. The results showed a substantial reduction in worker exposure to AP at this site after exhaust system installation (from 4.2 and 1.2 μg/m³ on two different occasions before this intervention down to <0.03 μg/m³). One of the sites had installed a commercially available booth. The exposure level at this location was also relatively low (0.6 μg/m³).

Pentamidine was not detected in the urine of any of the subjects (limit of detection = 0.23 μg/mL).

Respiratory Effects

Baseline pulmonary function data are shown in Table 3. The percent predicted values for baseline forced vital capacity and FEV_1 were normal for all but one subject (subject A). Changes in FEV_1 on days with and without AP exposures are shown for each subject in Table 4. Cross-workshift spirometric data on a nontreatment day were not available for

TABLE 3
Baseline Pulmonary Function Data*

Subject	FEV_1 (liters)	% Predicted	FVC (liters)	% Predicted	PC_{20} (μmol)	DRS
A	1.90	48	4.58	70	1.9	−0.0018470
B	2.27	90	2.65	87	>49.8	−0.0000286
C	4.05	100	4.86	97	>49.8	−0.0000124
D	3.52	94	3.98	85	>49.8	−0.0000088
E	3.53	89	5.94	121	3.6	−0.0004512
F	3.73	91	5.76	113	3.0	−0.0006030
G	3.82	91	4.71	92	>49.8	−0.0000074
H	4.38	107	4.89	97	>49.8	−0.0000357
I	3.30	127	3.90	126	3.9	−0.0003908
J	3.55	95	4.11	89	5.4	−0.0002692
K	3.89	91	4.53	86	18.6	−0.0000494
L	4.02	93	5.06	94	4.3	−0.0003011
M	4.00	101	5.57	113	5.9	−0.0002444
N	4.43	105	5.73	113	18.7	−0.0000510
O	2.90	91	3.81	98	9.2	−0.0002048
P	3.45	97	4.23	95	19.5	−0.0000410

* FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PC_{20}, the provocative concentration of methacholine that induced a 20% decrease in FEV_1 from the postsaline baseline value; DRS, [(posttest FEV_1 − pretest FEV_1)/pretest FEV_1 × 100]/cumulative dose of methacholine in micromoles.

TABLE 4
Changes in FEV_1 on Days with and without Aerosolized Pentamidine (AP) Administration

Subject	Days with AP Administration (liters)	Days without AP Administration (liters)
A	−0.47	−0.09
B	−0.03	−0.01
C	−0.07	−0.05
D	−0.08	−0.15
E	−0.59	−0.25
F	−0.10	−0.04
G	−0.22	−0.28
H	−0.12	−0.23
I	−0.30	−0.07
K	−0.09	−0.31
L	−0.15	−0.24
M	−0.49	−0.11
N	−0.27	−0.22
O	−0.01	−0.01
P	−0.01	−0.20
Mean ± SD	−0.1 ± 0.23	0.05* ± 0.18

* $P = .03$.

one subject; this subject was excluded from the statistical analysis of cross-workshift spirometry. Cross-workshift spirometry demonstrated a mean ± SD decrease in FEV_1 of 0.14 ± 0.23 liter on AP treatment days compared with a mean increase of 0.05 ± 0.18 liter on nontreatment days. This difference in cross-workshift FEV_1 between treatment and nontreatment days was statistically significant ($P < .03$). There was no statistically significant dose-response relationship between personal breathing zone pentamidine concentration and change in FEV_1 ($P = .19$). There also was no statistically significant difference in mean ± SD diurnal variation in PEFR between days when AP was administered (6.3 ± 3.4%) and days when AP was not administered (5.7 ± 4.2%) ($P = .4$). Methacholine inhalation challenge testing did not show a statistically significant mean ± SD increase in airway responsiveness across the workweek 0.0001 ± 0.0004 liter/μmol ($P = .4$). Finally, there were no significant increases in symptoms on days when AP was administered as compared with days when it was not administered. The median difference in symptom scores was 0 with a range from −4 to +4.

Discussion

In this study of the respiratory health effects of occupational exposure to AP in a variety of settings, we measured concentrations of pentamidine that ranged up to 10 times greater than those previously reported.

We are aware of four other studies in which measurement of ambient pentamidine concentrations in AP treatment rooms has been attempted. In the first of these studies, Montgomery and coworkers reported a mean pentamidine concentration of 0.045 μg/m^3 for a treatment room at San Francisco General Hospital[11] that was also later studied by us. We found considerably higher concentrations in this room, 4.2 and 1.2 μg/m^3 on two separate occasions, using a different sampling technique. The particle size data from the Montgomery study suggest that there may have been a problem with the area sampling strategy used.

Despite the fact that the AP nebulizer was designed to generate particles of respirable size, approximately 2 μm in diameter, the MMAD of the particles collected by Montgomery and coworkers was 8 μm. By comparison, the MMAD for the AP particles collected by us in the same room was <2 μm.

Two other published studies that measured ambient concentrations of pentamidine in treatment rooms re-

ported results that are closer to those described here. A study of an AP treatment facility in Toronto, which used a different nebulizer system (Fisoneb) and had an apparently effective ventilation system, found a mean pentamidine concentration of 0.23 $\mu g/m^3$ in personal samples and a mean concentration of 0.5 $\mu g/m^3$ in area samples.[14] Investigators at Johns Hopkins Medical Center reported that pentamidine concentrations in their institution's treatment room before the installation of engineering controls ranged up to 18 $\mu g/m^3$ for personal samples and 45 $\mu g/m^3$ for area samples.[15] The higher concentration that we report for one of the facilities we studied is consistent with the level of ventilation at the time of the study.

The results of air sampling in a treatment room were reported by another group of investigators at the State University of New York at Stonybrook in terms of the amount of pentamidine sampled per day rather than per cubic meter.[17] Thus, no direct comparison with our results is possible. The pentamidine sampled per day in the Stonybrook study ranged from 79.7 to 200.2 μg, depending on the number of patients treated and the amount of coughing by the patients. The MMAD of the pentamidine aerosol was 1.85 μm, similar to the value obtained by us. Again similar to our results, no pentamidine was detected in the urine of the HCWs administering the treatments.

We observed a significant change in one measure of pulmonary function in association with AP administration, a cross-workshift decrement in FEV_1. Despite this observation, there was no statistically significant association between AP administration and diurnal variation in PEFR, and nonspecific airway responsiveness did not significantly increase with cumulative exposure to AP across a workweek. There was also no statistically significant increase in either acute irritative or respiratory symptoms associated with AP administration.

In addition to our study, respiratory health effects of occupational exposure to AP also have been assessed by both the Toronto and Johns Hopkins investigators cited above. The Toronto group, which measured relatively low pentamidine concentrations, found no significant exposure-related changes in peak expiratory flow rates, FEV_1, or diffusing capacity in association with AP exposure.[21] McDiarmid and coworkers[16] at Johns Hopkins, however, did find acute respiratory symptoms, decrements in cross-workshift PEFR and/or decrements in cross-workshift diffusing capacity for carbon monoxide (DL_{CO}) in 4 of 11 subjects who administered AP to inpatients in hospital rooms where no engineering controls were in place and where area pentamidine concentrations ranged from 0.036 to 30.774 $\mu g/m^3$.[16] In contrast to our finding, the Johns Hopkins investigators did not observe significant cross-workshift decrements in FEV_1. Although their data analysis revealed no statistically significant dose-response relationships for pentamidine exposure and symptoms or lung function outcomes, these investigators noted that all four of their subjects who experienced effects associated with AP exposure may have been susceptible because of a history of asthma and/or allergies.

The major weakness of the study is the small sample size. With only 16 subjects, even when serving as their own controls, the power of the study to detect small changes in lung function is limited. Despite this limitation, however, we did find one parameter of lung function, FEV_1, that was significantly associated with AP administration. The small number of subjects, although reflecting the "universe" of occupationally exposed persons in our region at the time of the study, also limits our ability to assess the potential confounding effects of smoking, asthma, and allergic rhinitis among our subjects.

Another potential weakness of our study is that we were unable to study naive subjects without previous occupational exposure to AP. It is possible that HCWs who experience the greatest irritative symptoms and adverse changes in lung function with AP administration leave positions in which they are required to give this therapy, consistent with the well-known healthy worker effect. It is also possible that tolerance to irritative effects of pentamidine develops among HCWs who continue to administer AP, similar to the adaptation that has been described for repeated daily exposure to ozone.[22] If either of these two possibilities actually were to occur among HCWs who administer AP, our study design would have been less likely to detect any potential adverse effects of occupational exposure to AP on lung function.

The ambient concentrations of pentamidine that we measured in the diverse facilities that participated in our study clearly document that significant occupational exposure to aerosolized pentamidine does occur, especially in less well ventilated treatment rooms. In the facility where booths with a local exhaust system were installed, repeated environmental monitoring documented a substantial reduction in ambient concentrations of pentamidine. Therefore, we recommend the use of appropriate engineering controls to reduce health care worker exposure to aerosolized pentamidine. Based on the postmarketing experience with both pentamidine and ribavirin,[23] we also recommend that greater attention be paid to occupational health and safety issues when new drugs are being developed for inhalational administration in the future. The level of occupational exposure and the potential for adverse health effects as the result of such exposure need to be assessed in the premarketing stage so that appropriate protective strategies can be developed.

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