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Concentrations of Aerosolized Pentamidine in Bronchoalveolar Lavage, Systemic Absorption, and Excretion

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Pentamidine pulmonary pharmacokinetics were studied in 13 patients receiving once-daily inhaled therapy and 4 patients receiving low-dose intravenous treatment for *Pneumocystis carinii* pneumonia. Twenty-four hours after inhaled or intravenous therapy, the mean (± standard deviation) concentrations of pentamidine in serial bronchoalveolar specimen fluid ranged from 28.6 ± 10 to 177.5 ± 28 ng/ml and 6.05 ± 2.29 to 21.4 ± 15.7 ng/ml, respectively. Pentamidine concentrations in brochoalveolar fluid were generally higher after 2 weeks than after day 1 of therapy; however, the differences were not statistically different ($P > 0.05$). The pulmonary half-life after inhaled therapy is long; pentamidine was detectable in bronchoalveolar fluid at 33 (one patient), 69 (one patient), and 115 (one patient) days following the completion of 2 weeks of therapy. Systemic absorption of pentamidine was minimal; the mean (± standard deviation) plasma concentration at the completion of inhalation was 13.84 ± 11.8 ng/ml, or 5% of the mean peak plasma concentration achieved after intravenous administration. Accumulation in the plasma did not occur with repeated inhalation as has been described with multiple intravenous dosing. Cumulative urinary excretion 24 h after the first dose was 5% of that observed with intravenous administration. These data may have importance in designing dosage regimens for the further investigation of inhaled pentamidine for treatment or prophylaxis of *P. carinii* pneumonia.

In a pilot study, we reported that either inhaled pentamidine, 4 mg/kg per day, or reduced-dose intravenous pentamidine, 3 mg/kg per day, might be effective therapy for mild *Pneumocystis carinii* pneumonia (2). In addition, the rate of major adverse reactions with both modes of administration was reduced to approximately 20%. During that study, serial plasma, urine, and bronchoalveolar lavage fluid (BAL) specimens were collected for the determination of pentamidine concentration in the 13 patients who received inhaled therapy, 2 who received intravenous treatment, and 2 subsequent patients not included in the original study who also received intravenous treatment. This report describes the pulmonary pharmacokinetics of pentamidine in these patients.

MATERIALS AND METHODS

The clinical characteristics of the patients are summarized in Table 1.

Inhaled pentamidine was administered once daily by nebulizer (Ultravent; Mallinckrodt, Inc., St. Louis, Mo.), using a 12-liter/s compressed airflow. The dose of pentamidine was 4 mg/kg dissolved in 8 ml of sterile water. Four-milliliter aliquots of this solution were introduced into the nebulizer so as not to exceed the reservoir capacity and potentially interfere with particle generation. While wearing nose clips, patients inhaled aerosolized pentamidine via a mouthpiece utilizing comfortable tidal volume breathing in the upright body position. The time required to inhale the total amount of solution (two 4-ml aliquots) was approximately 30 to 45 min.

Intravenous pentamidine, 3 (patients 14 to 16) or (patient 17) 4 mg/kg was administered once daily as a 2-h timed infusion.

From six patients (no. 1, 2, 3, 4, 11, and 12), blood samples were drawn prior to and at the completion of inhalation and at 0.17, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, and 24 h following initiation of the inhalation on day 1. Samples were then drawn at the completion of inhalation (peak) on day 2 and prior to (trough) and at the completion of inhalation (peak) on days 3 to 5 (patients 1, 2, 3, 4, 11, and 12), day 8 (patients 2 and 12), day 9 (patient 11), day 13 (patient 3), and day 14 (patients 2, 4, 11, and 12). The mean (± standard deviation [SD]) time of inhalation for these six patients was 0.63 ± 0.16 h.

Patients 1, 2, 3, 4, 11, 12, 14, 15, and 16 were admitted to the General Clinical Research Center for the first 24 h of therapy. Blood samples were drawn into heparinized tubes, placed immediately into ice, and centrifuged, and the plasma was frozen at −70°C until analysis. Accumulating urine was placed on ice during the collection period. The total volume was then measured, and aliquots were frozen at −70°C for analysis.

From seven patients (patients 5 to 10 and 13), trough and peak plasma samples were collected daily for the first 3 days and then weekly during therapy.

Urine was collected from 0 to 24, 24 to 48, and 48 to 72 h for patients 1 to 4, 14, and 15, respectively, and from 0 to 24 h only for patients 11, 12, and 16. Urine specimens were not collected from patient 17. Because it contained peaks that interfered with the high-pressure liquid chromatography assay, the urine from patient 3 was omitted from the analysis.

Bronchoscopy for collection of lavage fluid (6) was performed 24 h after an inhaled or intravenous dose of pentamidine. Following topical anesthesia and with the patient in the supine position, the brochoscope (Pentax FB-19D) was advanced and wedged into a subsegmental bronchus of the right middle lobe. Serial 20-ml boluses of normal saline at room temperature were instilled and aspirated into four consecutively numbered (lavage 1 through lavage 4) 30-cm^3 suction traps. Aliquots of 15 ml were removed from each and then frozen at −70°C until analysis. Bronchoscopy, with

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TABLE 1. Patient characteristics[a]

Patient no.	Age (yr)	Ht (cm)	Wt (kg)	Duration of symptoms (wk)[b]	CR_s (mg/dl)	PaO_2 (mm Hg)[c]	$PaCO_2$ (mm Hg)	Duration of therapy (days)
1	35	184	65.1	3	0.9	81	34	5
2	35	178	62.3	2	0.8	67	ND	15
3	38	165	58.9	2	1.0	74	42	15
4	36	174	61.5	1	0.9	82	39	14
5	35	165	54.0	1	0.6	73	22	3
6	38	170	52.0	1	0.8	75	33	13
7	37	175	70.0	3	0.9	62	36	1
8	35	183	70.0	1	1.0	60	36	14
9	49	172	60.0	1	1.0	57	36	3
10	36	174	64.0	2	0.8	64	36	14
11	46	169	62.3	3	0.9	95	34	14
12	28	170	57.7	9	0.8	68	36	14
13	31	177	70	1	0.9	73	34	14
14	31	160	56	2	0.8	67	38	12
15	45	168	67	1	0.9	60	37	18
16	49	168	63	7	0.7	63	38	14
17	34	ND	59	0.5	0.8	50	29	17

[a] All of the patients were men. PaO_2 and $PaCO_2$ are partial pressure of oxygen and carbon dioxide, respectively, in arterial blood while breathing room air. CR_s is serum creatinine. ND, Not done. Some of the data have been published previously (2).
[b] Rounded to the nearest week.
[c] 1 mm Hg = 133.3 Pa.

collection of BAL for pentamidine assay, was performed 24 h after the first dose (patients 2 and 8), after the second dose (patient 14), after the third dose (patient 4), after the fourth dose (patient 3), after the fifth dose (patient 16), after the sixth dose (patient 15), after the seventh dose (patient 18), after the 11th dose (patient 16), after the 12th dose (patient 2), after the 14th dose (patient 6), and after the 15th dose (patients 3, 8, 10, 11, and 13). In patients 10, 2, and 8, bronchoscopy was repeated on days 33, 69, and 115, respectively, following completion of the original course of inhaled therapy.

The high-pressure liquid chromatography assay used to measure concentrations of pentamidine in plasma, urine, and BAL has been reported previously (4, 5).

The statistical analysis was performed with the Prophet computer resource (Division of Research Resources, National Institutes of Health, Bethesda, Md.).

RESULTS

Relationship of BAL pentamidine concentration and lavage sequence number. Eleven BAL sets of four lavages were analyzed in eight patients (no. 2, 3, 4, 6, 8, 10, 11, and 13) receiving inhaled therapy. The concentrations (mean ± SD) of pentamidine were 43.0 ± 52.0, 80.5 ± 71.6, 77.9 ± 42, and 110 ± 63 ng/ml in lavages 1 to 4, respectively, regardless of day of therapy. Only the difference in concentration between lavages 1 and 4 was significant ($P < 0.05$).

In the four patients receiving intravenous therapy, the concentrations (mean ± SD) of pentamidine in lavages 1 to 4 were 6.05 ± 2.29, 17.0 ± 10.9, 18.8 ± 15.9, and 21.4 ± 15.7 ng/ml, respectively, regardless of day of therapy. Although there was a trend toward increasing concentrations with each lavage, the differences were not significant ($P > 0.05$).

Relationship of BAL pentamidine concentration and day of therapy. In patients receiving inhaled therapy, the mean (± SD) concentrations (nanograms per milliliter) of pentamidine in the serial lavages were 38.8 ± 24.3 on day 1 (two patients), 66.8 ± 16 (one patient) on day 3, 28.6 ± 10 (one patient) on day 4, 177.5 ± 28 (one patient) on day 12, and 29.0 ± 2.2 (one patient) and 89.7 ± 71.3 (five patients) on day 15. The mean BAL pentamidine concentration on day 15 of therapy was not significantly ($P > 0.05$) greater than that measured on day 1 of therapy.

In patients receiving intravenous therapy, the mean (± SD) concentrations (nanograms per milliliter) of pentamidine in the serial lavages were 10.90 ± 2.89 on day 2 (one patient), 3.40 ± 0.15 (one patient) on day 6, 27.0 ± 14.4 on day 7 (one patient), and 21.07 ± 0.87 (one patient) on day 11. These differences are not significant ($P > 0.05$).

Pentamidine concentration in BAL following inhaled therapy. The mean (± SD) pentamidine concentrations in BAL were 3.0 ± 5, 5.6 ± 0.8, and 0.2 ± 0.5 ng/ml at 33 (patient 10) 69 (patient 2), and 115 (patient 8) days following the completion of 2 weeks of therapy.

Systemic absorption of inhaled pentamidine. Table 2 depicts the concentrations of pentamidine in plasma measured during the first 2 h of observation in patients 1, 2, 3, 4, 11, and 12. The highest concentration measured at the completion of inhalation (0.67 h) in any patient was 35.1 ng/ml (patient 10). Pentamidine was not detectable in any plasma samples from 2 to 24 h following initiation of the inhalation.

The mean (± SD) pentamidine concentration in plasma at the completion of the first inhalation for all 13 patients was

TABLE 2. Pentamidine concentrations in plasma during and shortly after the first dose of pentamidine by inhalation

Time (h)	No. of observations	Pentamidine concn (ng/ml)[a]
0.17	5	3.41 ± 3.60
0.5	6	9.27 ± 6.87
0.53[b]	1	0
0.67[b]	2	24.88 ± 14.47
0.92[b]	1	30.91
1	6	7.99 ± 11.57
1.5	6	1.78 ± 2.84
2	6	0.44 ± 1.07

[a] Data given are means ± 1 SD (where indicated).
[b] These four patients completed the inhalation at the indicated times; the remaining two completed the inhalation at 0.5 h. The mean (± SD) time of inhalation for the six patients was 0.63 ± 0.16 h.

TABLE 3. Pentamidine concentrations in plasma at completion of inhalation on various days during therapy

Day of therapy	No. of observations	Pentamidine concn (ng/ml)[a]
2	12	13.1 ± 12.6
3	12	11.2 ± 16.7
4	6	10.9 ± 11.5
5	6	16.4 ± 16.3
8	4	13.7 ± 32.9
9	3	5.3 ± 6.3
13	3	15.4 ± 18.3
14	6	23.2 ± 24

[a] Data given are means ± 1 SD.

13.84 ± 11.89 ng/ml. The pentamidine concentrations in plasma at the completion of inhalation from days 2 to 14 are summarized in Table 3. Pentamidine was not detectable in any plasma samples drawn prior to inhalation (trough). There was no significant ($P > 0.05$) increase or decrease in the peak concentrations with time (linear regression analysis; $P > 0.05$).

There were no significant differences among the peak plasma concentrations when all days were compared ($P > 0.05$).

Three (patients 14, 15, and 16) of the four patients treated intravenously had pentamidine concentrations in plasma measured at the completion of infusion (peak). The values were 267, 169, and 345 ng/ml, respectively (mean ± SD, 260 ± 88.2 ng/ml).

The renal excretion of pentamidine during the first 3 days of therapy is summarized in Table 4.

DISCUSSION

The precise quantity of pentamidine that was deposited in the alveolar space in the patients we studied is unknown. Deposition of aerosolized pentamidine in the lung depends upon particle size as well as respiratory variables found in patients with *P. carinii* pneumonia.

Aerosol deposition in the alveolar space is judged to be maximal at a mass median aerodynamic diameter particle size of about 2 μm (9). For radionuclide aerosols, the ultravent nebulizer used in this study generates a mass median aerodynamic diameter particle size of 0.25 μm (12).

TABLE 4. Pentamidine renal excretion

Type of treatment	Time interval (h)	No. of observations	Pentamidine base concn (μg/ml)	Pentamidine base excreted during interval (mg)[a]
Inhaled	0–24	5	0.131 ± 0.083	0.214 ± 0.156
	24–48	3	0.220 ± 0.053	0.295 ± 0.108
	48–72	2	0.213 ± 0.021	0.172 ± 0.098
Intravenous	0–24	3	2.10 ± 0.493	4.23 ± 1.60
	24–48	2	6.51 ± 4.82	9.90[b]
	48–72	2	7.00 ± 4.80	10.6 ± 9.07

[a] The cumulative percentage (mean ± SD) of dose excreted at 24, 48, and 72 h was 0.15 ± 0.10, 0.14 ± 0.04, and 0.11 ± 0.01% for patients receiving inhaled therapy. Because of the incomplete urine collection at 48 h in the patients treated intravenously, cumulative percent urinary excretion for all three intervals could only be calculated for one patient (no. 14), and it was 1.7, 3.8, and 5.9% at 24, 48, and 72 h.

[b] The urine volume was not measured in one of the two patients; therefore, this value represents one patient only.

However, we have not measured particle size with pentamidine in this device. With a radionuclide, technetium-99m DTPA, the Ultravent nebulizer resulted in good pulmonary deposition in patients with *P. carinii* pneumonia (11).

Respiratory variables associated with *P. carinii* pneumonia include increased inspiratory airflow rate, increased respiratory rate, low tidal volume, and minimal time for breath hold (4, 8, 9). For example, increased inspiratory airflow will increase inertial impaction of particles in the upper airways and allow less time for peripheral sedimentation. Both of these effects will result in decreased alveolar deposition of aerosolized pentamidine. Inspiratory airflow rate and pentamidine concentration in the nebulizer will also influence the ultimate size of the particles in the airways by affecting the duration of and extent to which evaporation from the particle occurs.

Moreover, as pointed out by Raabe (8), aerosol is generated continuously even during exhalation. This results in an approximately 60% loss of the total dose. Approximately 16% of the medication available for inhalation is deposited in the lung, and only 6 to 8% of that will be deposited in the alveolar compartment for particles with mass median aerodynamic diameters of 1 to 2 μm (1, 8). Finally, there is no way to accurately determine the dilution effect of the saline used for lung lavage, and therefore the true alveolar pentamidine concentration in lung lining fluid is unknown (10).

Despite these theoretic issues regarding pentamidine deposition, the response to therapy (2) and the pharmacologic data suggest that administration of inhaled pentamidine with the Ultravent nebulizer is a potentially effective mode of therapy. Montgomery et al. have had similarly favorable results with a different nebulizer (7).

An unexpected finding was that pentamidine concentrations in lavage fluid increased with repeated washing of the same bronchopulmonary segment. Pentamidine concentrations in lavage 4 were approximately 2.5-fold those in lavage 1. If residual pentamidine remained in the distal tracheobronchial tree, one would expect the opposite; i.e., the concentration of pentamidine should have decreased with subsequent lavages. Further investigation will be necessary to clarify these findings.

As one would expect, inhaled pentamidine results in higher drug concentrations in BAL than parenterally administered pentamidine. In the four patients treated intravenously, BAL pentamidine concentrations were 14 to 19% of those in patients treated with inhaled pentamidine.

An important point demonstrated by these data is that systemic absorpton of inhaled pentamidine is minimal. The mean plasma concentration measured at the completion of inhalation for all 13 patients was 13.84 ± 11.89 ng/ml. This was approximately 5% of the concentration achieved in the three patients treated with 3 mg/kg intravenously and approximately 3% of the concentration previously reported with a 4-mg/kg dose (4). Trace amounts of pentamidine are excreted in the urine of patients receiving inhaled pentamidine. The mean (± SD) cumulative percentage of dose excreted at 24 h following the first inhalation was 0.15 ± 0.10%. This was 5% of the cumulative percentage of dose excreted at 24 h in three patients treated with 3 mg/kg intravenously.

The data also indicate that peak absorption of pentamidine into the systemic circulation occurs at, or near, the completion of inhalation. Pentamidine was not measurable in plasma for 2 to 24 h following initiation of the inhalation.

We were also concerned that systemic absorption of inhaled pentamidine would increase with repeated adminis-

tration. This might have occurred if progressive airway inflammation facilitated absorption. We found no evidence to support this idea. The mean peak plasma concentration following inhalation did not increase with multiple dosing. There also was no trough accumulation as we have observed in patients with normal (unpublished data) or impaired (3) renal function who receive multiple intravenous doses. Moreover, in our patients who underwent repeat bronchoscopy, macroscopic airway inflammation was not noted.

Since our original pilot study (2) contained only a small number of patients, we are unable to correlate these pharmacologic data with toxicity or outcome. However, this information may be useful in designing and interpreting future studies of inhaled or lower-dose pentamidine regimens for the treatment or prevention of *P. carinii* pneumonia.

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