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Safety and Pharmacokinetics of Rimantadine Small-Particle Aerosol

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The safety and pharmacokinetics of rimantadine administered by small-particle aerosol were assessed in healthy adults and adults with acute influenza virus infection. Aerosolized rimantadine delivered at a concentration of 40 μg/liter of air was associated with nasal burning and irritation in normal volunteers. A concentration of 20 μg/liter of air was well tolerated for up to 12 h by normal volunteers and was not associated with any changes in pulmonary function, as measured by routine spirometry, plethysmography, or diffusion capacity of carbon monoxide. Mean peak levels of drug in serum were approximately 10-fold lower after 12 h of aerosol administration than they were after oral administration of 200 mg (29.7 versus 255 ng/ml, respectively), while mean nasal wash levels were approximately 100-fold higher (6,650 versus 66.6 ng/ml, respectively). Elimination half-lives were similar after both aerosol and oral administration (24.1 and 25.2 h, respectively), and rimantadine urinary excretion was <1% per 24 h in both groups. Twenty micrograms of aerosolized rimantadine per liter of air given 12 h daily for 3 days to nine adults with acute influenza virus infection was well tolerated. Levels in plasma after 12 h of aerosol inhalation were similar to those in normal volunteers, but were higher at the end of the third treatment than they were at the end of the first treatment (88.3 versus 47.9 ng/ml, respectively). Thus, rimantadine delivered via small-particle aerosol at a dose of 20 μg/liter of air was well tolerated in normal volunteers and in those with acute influenza and was associated with high local concentrations.

Small-particle aerosol (SPA) delivery of antiviral agents was evaluated for the treatment of viral respiratory tract infections. This method of drug administration usually results in higher concentrations of drug at the site of infection than systemic administration does, may decrease or ameliorate systemic toxicities seen after systemic administration, and has been more effective than the systemic administration of antiviral agents in murine (31) and ferret (9) animal models of acute influenza virus infection. SPA delivery of antiviral agents has also been effective in the treatment of human respiratory viral diseases (13, 14, 17, 22, 24, 28).

Rimantadine has better antiviral activity against some influenza A virus strains than amantadine does (5), is better tolerated when taken orally (8), and is effective as a prophylactic (8, 35) and therapeutic (20, 26, 30, 34, 35) agent in influenza A virus infections. Hayden et al. (22) have previously reported the use of rimantadine delivered by ultrasonic nebulizer in subjects given an attenuated influenza A virus; except for minor complaints, the drug was well tolerated. No pharmacokinetic data were reported.

Although the combination of amantadine or rimantadine with ribavirin has been shown to have additive or synergistic activity in vitro (6, 21) and when administered systemically in a murine model of acute influenzal pneumonia (11, 33), only the combination of ribavirin and amantadine administered via SPA has been examined in an animal (murine) model and has been found to be more effective than single-agent therapy (33). Similar studies have not yet been done in humans. Because of its greater activity in vitro, rimantadine would be a logical choice for study in combination with ribavirin in humans. However, before the evaluation of SPA delivery of combined ribavirin and rimantadine therapy for acute influenza can be tested, the safety of rimantadine SPA delivery needs further evaluation. The purpose of this study was to evaluate the safety, tolerability, and pharmacokinetics of rimantadine when delivered by SPA.

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MATERIALS AND METHODS

SPA delivery of rimantadine. The SPA was generated from a continuous-flow, modified Collison nebulizer of the Fort Detrick design which has been described in detail previously (23). Sterile water was used as the placebo aerosol. For most studies, rimantadine was dissolved in sterile water at concentrations of 4 or 2 mg/ml; aerosols of 40 or 20 μg of rimantadine per liter of air, respectively, were generated from these reservoirs. In one group of volunteers, the rimantadine was dissolved in phosphate-buffered saline (PBS). The aerosol was delivered to the volunteers via Puritan Benefit masks at 12.5 liter/min. The masks covered each volunteer's mouth and nose. A delivered dose was calculated by using a quadratic equation for tidal volume and by estimating a 70% retention rate (25). The distribution of deposition of an aerosol generated from this nebulizer was determined previously; approximately 62% of the delivered dose would be deposited in the nasopharynx, 18% would be deposited in the tracheobronchial tree, and 20% would be deposited in the alveoli (25).

Safety evaluation in normal healthy adults. Twenty-one normal, healthy volunteers (ages, 22 to 31 years) participated

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in the first part of the study, after giving written informed consent. Before enrollment, history, physical examination, and pulmonary function testing were performed. Female volunteers had negative serum pregnancy tests. No volunteer gave a history of asthma, lung disease, or other chronic disease.

All subjects were blinded and assigned to receive placebo or rimantadine SPA. They were subsequently crossed over to receive the other SPA (usually on the following day). Before and after each aerosol exposure, volunteers were questioned and examined for possible side effects by a nonblinded observer (R.L.A.). Symptom scores were calculated as the presence of a symptom (score of 1) multiplied by severity (mild = 1, moderate = 2, severe = 3, stopped inhalation = 4). The respiratory symptoms that were evaluated included sneezing, nasal obstruction, nasal discharge, nasal irritation, and sore throat. Nonrespiratory symptoms included tearing, dysgeusia, dizziness, sleepiness, headache, difficulty concentrating, and anxiety.

Two volunteers underwent 15-min exposures to aerosol at a rimantadine (in sterile water) concentration of 40 μg/liter of air, two others had 60-min exposures, two had 120-min exposures, and four had 4-h exposures. Four volunteers underwent 4-h exposures to SPA generated at a rimantadine (in PBS) concentration of 40 μg/liter of air. Because of significant local (nasal) side effects, the rimantadine aerosol concentration was decreased to 20 μg/liter of air, and four volunteers then inhaled aerosol for 4 h, four volunteers inhaled aerosol for 8 h, and five volunteers inhaled aerosol for 12 h.

For the five volunteers who received 12-h inhalations, pharmacokinetic studies were performed in the General Clinical Research Center at The Methodist Hospital. Plasma samples were obtained at 0, 2, 4, 6, 12, 18, 24, 48, and 72 h after the beginning of aerosol exposure. By using 5 ml of Ringer lactate solution per nostril, nasal wash specimens were obtained for determination of drug levels at 0 and 12 h. Twenty-four-hour urine collections (beginning at the initiation of aerosol exposures) were obtained for determination of drug excretion. All procedures were repeated several weeks later, when these five subjects were rehospitalized and given a 200-mg oral dose of rimantadine.

Pulmonary function testing was begun within 30 min after completion of 4-, 8-, and 12-h aerosol exposures. Routine spirometry was performed on a Medical Graphics pneumotachymeter; and forced expiratory volume (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and forced expiratory flow 25 to 75% (FEF_{25-75}) were measured. Spirometry and data collection were performed in accordance with the criteria outlined previously (2). Lung volumes and airway resistance were determined by the shallow panting technique on a Medical Graphics body plethysmograph. Single-breath diffusing capacity of carbon monoxide was determined with a PK Morgan Analyzer by using 9.70% helium, 0.294% CO, and 20.6% O_2 as a test gas.

Evaluation in volunteers with a febrile upper respiratory infection. Eighteen volunteers (ages, 18 to 24 years) participated in the evaluation of febrile upper respiratory infection after giving written informed consent. At the time of enrollment, all had symptoms and signs of acute, febrile (>38.3°C) upper respiratory viral infection (nasal congestion, sore throat) with a duration of less than 24 h; influenza A virus subtype H3N2 was subsequently isolated from 13 volunteers and influenza B virus was isolated from 5 volunteers by previously described methods (3). For each volunteer, baseline history, physical examination, complete blood count, blood chemistries, bacterial throat culture, and urinalysis were obtained. The complete blood count and chemistries were repeated at the time of discharge and at 1 and 4 weeks after enrollment. Female volunteers had a negative urine pregnancy test before enrollment. No volunteer gave a history of asthma, chronic lung disease, or other chronic disease.

After enrollment, all subjects were hospitalized for 3 days in the Beutel Health Center on the Texas A&M University campus and were blinded and randomized to receive placebo or rimantadine SPA. Volunteers inhaled aerosol (20 μg/liter of air) for 12 h on the day of enrollment and then for 12 h on a set schedule between 0730 and 2130 hours for the following 2 days. After discharge, they were seen at follow-up 1 and 4 weeks later.

The first six volunteers were evaluated for signs of toxicity by a nonblinded observer (R.L.A.) every 15 min during the first hour of SPA exposure and hourly thereafter. On the next 2 days they were examined every 2 h. The remaining 12 volunteers were evaluated for toxicity at 15 min and 1, 2, 4, 8, and 12 h on the first day and intermittently on the following days. Each volunteer was examined twice daily during the hospitalization by a blinded observer (B.T.) to assess his or her clinical status, and nonblinded evaluations (R.L.A.) were performed at the 1- and 4-week follow-up visits.

Plasma for drug level determinations was obtained at 0, 2, 4, 8, and 12 h during the first SPA exposure. Drug levels in plasma were also obtained at the end of treatment, on the last day of SPA exposure, and on the following morning prior to discharge. Nasal washes and urine collections for drug levels were not done in this group of volunteers.

Environmental sampling. Environmental (room air) sampling for rimantadine levels was done while the first two ill volunteers were receiving therapy. Paired 5-min collections with all glass impingers were collected in 20 ml of sterile water at 15 min and 2, 4, 8, and 12 h on the first day and at 0, 2, 4, 8, and 12 h on the following 2 days. Two investigators kept logs of the time spent in the volunteers' rooms, and drug levels in plasma were measured daily at the end of each day's aerosol inhalation. Thereafter, drug levels in plasma were determined in one investigator weekly for 2 weeks.

Drug levels. Plasma, urine, and nasal wash specimens were assayed for rimantadine by gas chromatography plus mass spectrometry (TexMS Analytical Services, Houston, Tex.) by previously described methods (10). Deuterated rimantadine served as an internal standard. The ratio of peak heights and concentrations of known calibration standards were used to generate a standard curve by using weighted ($1/y^2$), nonlinear regression; drug concentration of unknown samples could be calculated from these ratios. Drug concentrations were assayed over a range of 5 to 500 ng/ml. The interassay variability for plasma levels was 1.2% relative standard deviation, and the intraassay variability was 4.5% relative standard deviation.

Pharmacokinetic analysis. The elimination rate constant (k_{el}) was calculated from the slope of the log-linear portion of the decay of the rimantadine plasma concentration-versus-time curve. All slopes were calculated by linear regression of the natural logarithm of concentration against time. The area under the curve from initiation of the dose (time zero) to infinity ($AUC_{0-\infty}$) was calculated by the LaGrange method by using the LAGRAN computer program (27). From k_{el} and $AUC_{0-\infty}$, the following parameters were calculated for rimantadine disposition for each subject: elimination half-life = $0.693/k_{el}$; total plasma clearance (CL) = $F \cdot \text{dose}/AUC_{0-\infty}$,

TABLE 1. Symptom scores associated with rimantadine SPA inhalation in normal volunteers

Aerosol group (concn)	Symptom score (mean)[a]		
	Respiratory	Nonrespiratory	Total
Rimantadine in H_2O (40 μg/liter of air)[b]	3.0[c,d]	0.7	3.7[e]
Placebo[b]	0.5[c]	0.7	1.2[e]
Rimantadine in PBS (40 μg/liter of air)[f]	3.9[e]	1.0	4.9
Placebo[f]	0.8[e]	1.5	2.3
Rimantadine in H_2O (20 μg/liter of air)[g]	1.5	0.3	1.9
Placebo[g]	0.9	0.5	1.4

[a] Symptom scores were calculated as the presence of the symptom (score of 1) multiplied by its severity (mild, 1; moderate, 2; severe, 3; stopped inhalation, 4). Respiratory symptoms included sneezing, nasal obstruction, nasal discharge, nasal irritation, and sore throat. Nonrespiratory symptoms included tearing, dysgeusia, dizziness, sleepiness, headache, difficulty concentrating, and anxiety.

[b] Duration of inhalation was 15 min to 4 h; placebo was sterile water (n = 10).

[c] $P < 0.01$ for rimantadine versus placebo by the Wilcoxon rank sum test.

[d] Nasal irritation was the only symptom that occurred significantly more often in the rimantadine group than in the placebo group (9 of 10 versus 0 of 10 volunteers, respectively; $P = 0.0001$ by the Fisher two-tailed exact test).

[e] $P < 0.05$ for rimantidine versus placebo by the Wilcoxon rank sum test.

[f] Duration of inhalation was 4 h; placebo was sterile water (n = 4).

[g] Duration of inhalation was 4 to 12 h; placebo was sterile water (n = 13).

where F represents the fraction of drug reaching the systemic circulation; and volume of distribution (V) = $F \cdot CL/k_{el}$. The bioavailability of the aerosol dose compared with that after oral administration was calculated from the relationship: bioavailability$_{SPA/Oral}$ (F) = $AUC_{0-\infty,SPA}/AUC_{0-\infty,Oral}$. These values were corrected for dose and half-life differences (12). Peak drug levels were considered to be the highest levels measured.

Statistical methods. Unpaired and paired Student's t tests, chi-square with the Yates correction, the Fisher two-tailed exact test, and the Wilcoxon rank sum test were used for statistical analysis.

RESULTS

Safety evaluation in normal, healthy adults. Ten volunteers inhaled rimantadine SPA at a concentration of 40 μg/liter of air for 15 min to 4 h; mean respiratory symptom scores were significantly higher after rimantadine SPA than after placebo inhalation (Table 1). Nasal irritation was the only symptom that occurred significantly more often after rimantadine inhalation than after placebo inhalation (9 of 10 versus 0 of 10 subjects, respectively, $P = 0.0001$; Fisher two-tailed exact test). The irritation increased in severity with increasing duration of inhalation, with three of four volunteers in the 4-h group reporting severe irritation. One volunteer ceased aerosol exposure after 50 min because of nasal irritation.

When PBS was used as a diluent at the same rimantadine aerosol concentration (40 μg/liter of air), the mean respiratory symptom scores remained higher compared with the scores obtained with placebo (Table 1). Nasal irritation was still a prominent complaint, with three of four volunteers experiencing nasal irritation.

With the delivery of aerosol at a concentration of 20 μg/liter of air, the SPA inhalations were well tolerated (Table 1). Of the 13 volunteers who received SPA exposures with durations of 4 to 12 h, only two noted mild irritation during rimantadine SPA inhalation, whereas one subject noted mild irritation during sterile water (placebo) SPA inhalation.

There were no changes in mean FEV_1, FVC, FEV_1/FVC, FEF_{25-75}, diffusing capacity of carbon monoxide, or airways resistance following rimantadine or placebo SPA inhalation (Table 2). One volunteer had a significant decrease in FEV_1 after both rimantadine and placebo SPA inhalation; however, the volunteer had no subjective complaints, and no wheezing was noted on auscultation of the lungs.

Safety evaluation in adults with acute influenza. Three-day SPA inhalations of rimantadine from a reservoir concentration of 2 mg/ml were well tolerated by the nine volunteers with acute influenza. There was more nasal irritation in the rimantadine treated group than in the placebo group (6 of 9 versus 0 of 9 subjects, respectively; $P = 0.009$, Fisher two-tailed exact test). However, the irritation was mild and short-lived (duration of less than 15 min); no volunteer discontinued aerosol treatment.

Six volunteers with proven influenza A virus infection received rimantadine SPA and seven volunteers received placebo. The treated group had significantly lower influenza virus titers 24 h after the study was begun and significantly fewer positive cultures, but carry-over of rimantadine in secretions as an explanation for the reductions could not be excluded. Duration of fever was shorter in the treated group, but the reduction was not significant. No significant differences in complete blood counts or chemistries occurred among the treated volunteers compared with those among the volunteers given placebo.

Pharmacokinetic data. Pharmacokinetic parameters for each of the normal, healthy subjects are presented in Table 3. The mean rimantadine half-life was 24.1 ± 10.9 h for the SPA dose and 25.2 ± 3.7 h for the oral dose. The bioavailability of the aerosol dose of rimantadine compared with oral administration was 45.6 ± 10.6% for the five subjects studied. Individual bioavailabilities ranged from 36.7 to 60.8%. If it is assumed that the oral bioavailability of rimantadine is close to 1 (19), then pharmacokinetic parameters of total clearance and volume of distribution can be calculated from these data and are given in Table 3. Similar data for the aerosol dose were obtained by correcting the parameters for the fraction of rimantadine reaching the systemic circulation by the aerosol route of administration (bioavailability).

Rimantadine levels in plasma were significantly higher after oral compared with those after SPA administration at each of the time points that levels were measured (Fig. 1), and mean peak levels in serum were 8.6-fold higher after oral administration (255.0 ± 30.0 versus 29.7 ± 10.8 ng/ml, respectively). Levels of rimantadine in nasal washings at 12 h were almost 100-fold higher after SPA than after oral administration (6,650 ± 2,860 and 66.6 ± 20.4 ng/ml, respectively); rimantadine was still present in nasal secretions 12 h after completion of SPA inhalation in the three volunteers tested (259 ± 45 ng/ml). The percentage of rimantadine excreted unchanged in the urine in the first 24 h was <1% in both groups.

The rimantadine levels in plasma were consistently, but not significantly, higher during the first 12 h of aerosol administration in the volunteers with an acute febrile upper respiratory illness compared with those in the normal volunteers (Fig. 1). Levels of drug in plasma were significantly higher at the end of the third 12-h SPA treatment compared with those at the end of the first 12-h treatment (88.3 ± 44.4 versus 47.9 ± 23.7 ng/ml, respectively; $P < 0.01$), but they were still one-third of the peak levels seen after oral admin-

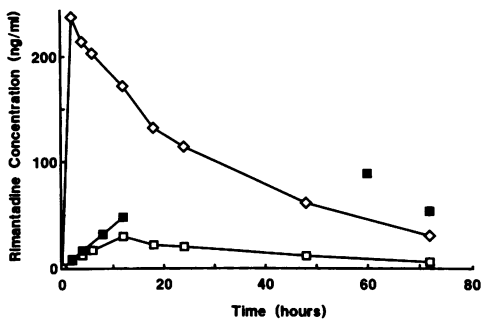

FIG. 1. Mean rimantadine concentrations in plasma of healthy volunteers after aerosol (□) or oral (◇) administration and volunteers with an acute febrile upper respiratory illness after aerosol administration (■).

istration of 200 mg to normal volunteers. The estimated delivered aerosol dose was approximately 68 mg per day.

Environmental sampling. Rimantadine was detected at very low concentrations in air samples from the rooms of the first two treated and infected individuals (Table 4). There were 15 air changes per hour in these rooms. No rimantadine was detected in the plasma of two investigators who were in the patients' rooms for 40 to 160 min/day during the environmental sampling.

DISCUSSION

We reported on the safety, tolerability, and pharmacokinetics of rimantadine SPA generated from a modified Collison nebulizer in normal volunteers and volunteers with acute influenzal illness. This method of SPA delivery was chosen because of the well-characterized nature of the aerosol generated by this nebulizer, our previous experience with this system in studies with ribavirin, and our goal of evaluating rimantadine in combination with ribavirin for SPA treatment of influenza A virus infection.

When delivered in a concentration of 40 μg/liter of air for up to 4 h, rimantadine SPA was associated with local (nasal) toxicity in normal volunteers. However, at the lower concentration of 20 μg/liter of air, rimantadine SPA was well tolerated both by normal volunteers for up to 12 h and by volunteers with acute influenza for 36 h of administration over 3 days. Nasal burning or irritation was the most common side effect associated with rimantadine SPA administration, but at the dose of 20 μg/liter of air, it was minimal. Unpleasant smell or taste, which was reported as a common side effect in a previous study (22), was uncommon.

The pharmacokinetics of an oral dose of 200 mg of rimantadine were similar to those previously reported by Hayden et al. (19). The half-life, clearance, and volume of distribution of rimantadine reported by those investigators were in good agreement with similar parameters obtained from the present investigation. For example, parameters from the previous work (19) for half-life, clearance, and volume of distribution were 36.5 h, 20.4 liter/h, and 986 liters, respectively, compared with our values of 25.2 h, 25.3 liters/h, and 904 liters, respectively. Following SPA administration of rimantadine, only 45.6% of the dose reached the systemic circulation, and mean peak levels in serum were 8.6-fold lower. Whether this was due to a lower fraction of dose available for absorption or to first-pass lung metabolism requires further study, but the lower levels in serum are potentially important since central nervous system and gas-

TABLE 2. Pulmonary function testing in normal volunteers inhaling rimantadine and placebo SPAs[a]

Parameter	FEV_1		FVC		% FEV_1/FVC	FEF_{25-75}		TLC		DL_{CO}		R_{AW} (cm of H_2O/liter/s)
	Liters	% Predicted	Liters	% Predicted		Liters	% Predicted	Liters	% Predicted	ml/min/mm Hg	% Predicted	
Base line	4.22 ± 0.91	116 ± 10	5.03 ± 1.31	110 ± 10	85 ± 6	4.47 ± 0.79	113 ± 26	6.42 ± 1.58	107 ± 9	28 ± 9	98 ± 20	1.45 ± 0.28
Following administration of:												
Rimantadine[b]	4.15 ± 1.01	113 ± 13	4.95 ± 1.35	108 ± 11	84 ± 6	4.32 ± 1.03	108 ± 27	6.64 ± 1.56[c]	108 ± 8	27 ± 7	93 ± 13	1.44 ± 0.36[c]
Placebo	4.20 ± 1.00	115 ± 12	5.00 ± 1.33	109 ± 10	85 ± 5	4.47 ± 0.96	112 ± 26	6.35 ± 1.56	107 ± 9	27 ± 8	93 ± 12	1.40 ± 0.36

[a] Thirteen subjects were tested: four after 4-h inhalations, four after 8-h inhalations, and five after 12-h inhalations. Abbreviations: FEV_1, forced expiratory volume; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow 25 to 75%; TLC, total lung capacity; DL_{CO}, single-breath diffusing capacity of carbon monoxide; R_{AW}, airways resistance. Values are means ± standard deviations.

[b] Aerosol concentration of 20 μg/liter of air.

[c] n = 11.

TABLE 3. Rimantadine pharmacokinetic data following oral or SPA administration[a]

Subject no.	Oral[b]				SPA[c]				$F_{SPA/Oral}$
	AUC (ng · h/ml)	$t_{1/2\beta}$ (h)	CL (liters/h)	V (liters)	AUC (ng · h/ml)	$t_{1/2\beta}$ (h)	CL (liters/h)[d]	V (liters)[d]	
1	7,559	19.6	26.5	747	1,436	18.6	27.9	750	0.608
2	5,929	23.4	33.7	1,136	690	18.1	43.5	1,135	0.431
3	8,091	27.7	24.7	987	1,393	26.1	26.3	989	0.516
4	10,462	28.8	19.1	794	1,915	42.3	13.0	794	0.357
5	8,924	26.5	22.4	857	607	15.3	38.9	860	0.367
Mean ± SD	8,193 ± 1,675	25.2 ± 3.7	25.3 ± 5.5	904 ± 158	1,208 ± 551	24.1 ± 10.9	29.9 ± 11.9	906 ± 157	0.456 ± 0.106

[a] Abbreviations: AUC, area under the curve; $t_{1/2\beta}$, elimination half-life; CL, total plasma clearance; V, volume of distribution; $F_{SPA/Oral}$, drug bioavailability for SPA versus oral administration.
[b] Oral dose was 200 mg.
[c] The mean estimated SPA dose was 68 mg (range, 64 to 71 mg).
[d] Corrected for drug bioavailability for SPA versus oral administration.

trointestinal side effects have been correlated with peak levels in serum (18). The mean concentration in nasal wash specimens after 12 h of treatment was 6,650 ng/ml. The 50% inhibitory concentration of rimantadine against several influenza A viruses by the plaque reduction assay has previously been reported to be 200 to 400 ng/ml (16), a concentration which was less than 10% that achieved in the nasal wash specimens after SPA delivery.

Exposure of health care workers to drug delivered by the aerosol route is a potential concern. Ribavirin has been reported to be present in the environment when administered by SPA to infants with respiratory syncytial virus infections (7). In addition, drug was detected in one specimen from a health care worker who was exposed to the aerosol (7). In our study, rimantadine was also found in the environment. However, it was not detected in multiple plasma specimens from the two investigators from whom samples were obtained. The number of room air changes per hour was higher than the minimum number (two) recommended for patient rooms (1), and drug levels in room air may be higher under other conditions. The importance of this level of drug exposure to health care workers remains to be determined in future studies.

Resistance to rimantadine after oral administration has been reported in several recent studies (4, 15, 29). The emergence of rimantadine resistance was not examined in this study. Although the clinical significance of rimantadine resistance remains to be determined, it is possible that the use of combination therapy (rimantadine plus ribavirin) may prevent resistance from emerging since strains that are resistant to ribavirin have not been reported (32).

Rimantadine SPA at a concentration of 20 μg/liter of air appears to be safe and well tolerated by both healthy volunteers and those with acute influenza. These studies suggest that an aerosol concentration of 20 μg/liter of air is near the maximal tolerable dose. The pharmacokinetics suggest that a lower reservoir concentration of rimantadine could be used to achieve levels in the mucosa greater than the 50% inhibitory concentration of most influenza A viruses; the mild local toxicity could then be decreased even further.

Because of its efficacy in animal models of pneumonia caused by influenza virus, rimantadine SPA deserves further evaluation for its efficacy in the treatment of naturally acquired influenza A virus infections in humans. Furthermore, evaluation of SPA delivery of the combination of rimantadine and ribavirin in humans should be considered.

TABLE 4. Rimantadine levels in room air[a]

Duration of aerosol (h)	Rimantadine concn (ng/liter of air [mean ± SD])
0[b]	<2
0.25[c]	7.0 ± 0.2
2	12.2 ± 4.9
4	16.8 ± 6.4
8	15.0 ± 10.1
12	17.0 ± 8.3

[a] Paired 5-min collections were made by using all glass impingers in two different rooms on each of 3 consecutive days of treatment.
[b] Collections were made on second and third days.
[c] Collections were made on the first day only.

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