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Environmental Exposure of Primary Care Personnel to Ribavirin Aerosol When Supervising Treatment of Infants with Respiratory Syncytial Virus Infections

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The potential exposure to ribavirin aerosol in the environment was assessed in nurses caring for infants and children with severe lower respiratory tract infections due to respiratory syncytial virus. Ribavirin aerosol was administered via a ventilator, oxygen tent, or oxygen hood. Participants worked directly with infants receiving ribavirin for 20.0 to 35.0 h over a 3-day period. No toxic or adverse effects of ribavirin aerosol were observed in any of the 19 nurses studied, and ribavirin was not detected in erythrocytes, plasma, or urine collected after the potential exposure period.

Ribavirin (1-β-D-ribofuranosyl 1,2,4-triazole-3-carboxamide) is a synthetic nucleoside with in vitro and in vivo activity against a variety of RNA and DNA viruses. Aerosolized ribavirin is reported as valuable in the treatment of hospitalized infants and children with severe lower respiratory tract infections due to respiratory syncytial virus (7, 9). The aerosol, produced by a Collison generator, has particles of approximately 1.3 μm in mass median diameter and is administered at a rate of 12.5 liters/min into an infant oxygen hood, oxygen tent, or the inhalation tubing of a ventilator.

One vial of ribavirin (ICN Pharmaceuticals Inc., Costa Mesa, Calif.), to be used for 18 to 24 h of aerosol treatment, contains 6.0 g of lyophilized drug. Because the pattern of small-particle deposition in infants is not known, the exact dose of ribavirin delivered to a child cannot be determined. In adults with an estimated 0.7 retention factor, the dose to the pulmonary area was calculated to be 0.82 mg/kg of body weight per h of exposure to the aerosol (6). The balance of the ribavirin used is found in the leftover fluid in the small-particle aerosol generator (SPAG) reservoir, in tubing, or on the tent, hood, or bed sheets, and some is expelled into the room air. Ribavirin has been reported to induce cell transformation in an in vitro mammalian system (BALB/c 3T3 cell line) at an intermediate dose (15 μg/ml) but not at the low or high doses (7.5 or 60 μg/ml) (11). An increase in the mutation rate at the thymidine kinase locus was seen in the presence of this drug in cultured mouse lymphoma (L5178Y) cells. However, in the presence of liver metabolic activation, only the suggestion of a weak mutagenic response was seen. No evidence of mutagenicity was found in microbial and dominant lethal rat and mouse assays (5).

Although no teratogenic effects of ribavirin were observed in one study in nonhuman primates, the drug was teratogenic in most rodent species tested (5). Thus, ribavirin is contraindicated in pregnant women because of its unassessed teratogenic potential.

In humans, the most sensitive indicator for the presence of ribavirin is the erythrocyte, which concentrates the drug at a level 100 times greater than the level in plasma and has a slow excretory rate (half-life, 40 days) (3–5).

Because many nursing professionals are women of potential child-bearing age, it was deemed important to assess the degree of environmental exposure to ribavirin by primary care personnel, to identify potential hazards, and if required, to institute prophylactic measures for handling and administering this drug.

Participants and methods. Nonpregnant female nurses engaged directly in the care of patients receiving ribavirin aerosol treatment via an oxygen hood, oxygen tent, or ventilator were invited to participate in the study. To enter this trial, it was required that nurses care for patients undergoing ribavirin aerosol treatment for a minimum of 20 to 24 h within 5 consecutive days. Additionally, nurses not engaged in the care of patients on ribavirin but who were in the vicinity were asked to participate as controls.

The study objectives, procedures, and possible associated risks and discomforts were explained and discussed with all participants, and a written informed consent was obtained from each participant. The study was approved by the Institutional Review Board of each hospital.

Aerosolized ribavirin typically is administered for at least 3 to 5 days to infants with proven respiratory syncytial virus infections and acute lower respiratory tract disease. Direct care givers most often are exposed to ribavirin during 3 consecutive days (an average of 8 h/day).

A pregnancy test on participating nurses was performed before the study, and negative test results were recorded in the study charts.

Blood samples were drawn from each participant for erythrohematology and base-line ribavirin determination no more than 1 day prior to exposure. A urine sample was obtained at the same time. A second blood sample was obtained within 1 h after completion of the final exposure period. A third blood sample and a second urine sample were collected 3 to 5 days later.

During the exposure period, participants kept a log indicating whether any protective clothing was used (gloves or mask); they also noted the frequency and duration of ribavirin treatment and when and why treatment was inter-

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TABLE 1. Opportunity for exposure of nurses to aerosolized ribavirin[a]

Study group	Subject location[b]	Total h of exposure
SPAG-ventilator	W	24.0
	W	24.0
	W	24.0
	W	24.0
	CA	24.5
	CA	26.5
	CA	29.5
	CA	25.0
Mean		25.2
Oxygen tent	W	20.0
	W	25.2
	W	21.2
	CA	24.2
	CA	26.2
Mean		25.3
Oxygen hood	CA	24.0[c]
Control	W	24.5
	W	19.0
	W	29.2
	CA	25.5
Mean		24.5

[a] Ribavirin levels in erythrocytes were assayed preexposure and at 1 h and 3 to 5 days postexposure. All erythrocyte values were negative with assays that would have detected ribavirin at levels of 0.020 μg/ml (confidence level of 99.9%).

[b] W, Washington, D.C.; CA, Loma Linda, Calif.

[c] Cared for patient 2.5 h on day 4.

rupted. Four nonpregnant primary care nurses working within the study area but not caring for patients receiving aerosolized ribavirin participated as controls.

During the study period, most of the nurses who worked directly with ribavirin patients, as well as the control nurses who did not, had assignments to areas where another patient, not under their direct care, was receiving ribavirin. Information was collected from each nurse participant so that the potential for incidental exposure that might add to the primary exposure could be evaluated.

Blood samples were drawn in a 3-ml sodium heparin VACUTAINER tube (45 USP; Becton-Dickinson Vacutainer Systems), cold centrifuged at 1,500 × *g* for 5 min, and immediately separated into erythrocyte and plasma components. Urine samples and blood components were frozen at −20°C and shipped in dry ice, overnight and under code, to the University of California, San Diego, for ribavirin analysis by using a radioimmunoassay that has a reported sensitivity of approximately ±0.002 μg/ml (0.01 μM) (1). The standard curves for the assay that used ribavirin, ribavirin monophosphates, and ribavarin triphosphates are virtually identical (J. D. Connor, unpublished data). Following the take-down procedures for the sample tubes in this radioimmunoassay, 100 μl of 4 N HCl and 2 ml of Aquasol-2 were added to each tube. The tubes were then vortexed and placed into the carrier racks of a Beckman LS 250 scintillation counter. Each tube was counted for 5 min by using the wide channel for ^3H. The counts were computer averaged and reported as mean counts per minute.

Direct exposure to ribavirin. A total of 19 nonpregnant female nurses, 22 to 41 years old (mean age, 30.2 years), participated in this evaluation. Of the 19 participants, 8 cared for patients receiving aerosolized ribavirin with the SPAG unit connected to a ventilator (SPAG-ventilator). Six other nurses cared for children being treated via an oxygen tent. One participant cared for an infant receiving aerosolized ribavirin via an oxygen hood. Four nurses not engaged in the care of a patient receiving ribavarin acted as controls. The daily hours of potential exposure for each participant in the study are shown in Table 1. Eight participants worked near the SPAG-ventilator (mean duration, 25.5 h; range, 24.0 to 29.5 h), six worked near an oxygen tent (mean duration, 25.3 h; range, 20.0 to 35.0), and one worked near the only child being treated by using an oxygen hood (24 h). Four control nurses were near the area where ribavirin was being administered, for a mean of 24.5 h (range, 19 to 29.2).

SPAG-ventilator group. On day 1, participants in the SPAG-ventilator group disconnected the aerosol generator from the inhalation tubing an average of six times, with a mean duration of 5.4 min each time. On day 2, the system was again disconnected approximately six times (mean duration, 4.6 min each time). Day 3 involved only three participants; the system was then disconnected nine times, for a mean duration of 5.9 min each. Participants in this group were potentially exposed to aerosolized ribavirin for a mean of 25.2 h over 2 to 3 days. During this period, the SPAG was disconnected from the ventilator tubing an average of 16 times, for an overall mean duration of 68 min.

SPAG-oxygen tent group. Nurses caring for patients receiving ribavirin treatment via an oxygen tent lifted the oxygen tent flap an average of four times on day 1, for a mean duration of 14 min each time, six times for 14.7 min each on day 2, and four times for 16.8 min each on day 3. In total, over the 2 to 3 days of the study, participants were potentially exposed to aerosolized ribavirin for an average of 25.3 h, and the oxygen tent flap was lifted 13 times, for a mean duration of 182 min.

Reasons for interruption of ribavirin treatment included suctioning, position change, checking of vital signs, chest pulmonary therapy, diaper change, feeding, and administration of medication.

SPAG-oxygen hood. The nurse caring for the child who used an oxygen hood did not remove the patient from treatment during the entire 4-day duration of the study. Note that, with the exception of day 2, daily exposure for that nurse was less than 5 h.

Four participants from the SPAG-ventilator group (intensive care service) and five from the group supervising patients receiving ribavirin aerosol via an oxygen tent always used gloves and a gown. One nurse in the SPAG-ventilator group wore a mask during day 2 of the study while the SPAG was disconnected from the inhalation tube. One nurse in the oxygen tent group wore a mask on all 3 study days.

Eleven nurses wore some sort of protective covering: gown and gloves (eight), gown alone (one), mask alone (one), gloves alone (one). One participant wore a mask on day 1; another was instructed to use a mask on the 2 days she participated in the study because the patient had been exposed to chicken pox. Controls used no protective clothing.

Total exposure to ribavirin. In a 1,910 ft^2 (ca. 177.4 m^2) intensive care unit (ICU) (Children's Hospital National Medical Center), four patients received ribavirin via a respirator from 4 to 9 days during a 3-week period. Four nurses giving direct care and a control nurse were assigned to the ICU area from 2 to 3 weeks prior to the last blood drawing (for a total of 91 person-days of potential exposure). The 2- to 3-week period also included the period of direct adminis-

TABLE 2. Ventilation in patient care rooms

Room[a]	Area (ft^2) (m^2)	Vol (ft^3) (m^3)	Air flow (ft^3/min) (m^3/min)	Minimum outside air changes/h[b]	Total air changes/h[c]	Minimum total air changes/h[d]
A (ward room)	262 (24.33)	2,227 (63.02)	270 (7.64)	7.3	7.3	6
B (ward room)	262 (24.33)	2,227 (63.02)	200 (5.66)	1.1	5.4	2
C (ICU-isolation)	255 (23.68)	2,168 (61.35)	650 (18.4)	3.4	18.0	6
D (ICU)	1,910 (177.44)	16,235 (459.45)	6,600 (186.78)	4.9	24.0	6

[a] Rooms A, B, and D are served by separate air conditioning units that provide, respectively, 100%, 20% (minimum), and 20% (minimum) outside air. All air from room C is exhausted outside.
[b] Minimum air changes with outside air per hour are based on the amount of outside-air intake to the unit.
[c] Total air changes are based on the total air flow to the room.
[d] Calculations are based on published guidelines (12).

tration of ribavirin by the participant nurse. In the general pediatric ward, in rooms averaging 262 ft^2 (ca. 24.3 m^2) each, two patients received ribavirin for a period of 3 to 8 days, and the six study nurses (including two control nurses) were in the immediate vicinity for 1 to 1.5 weeks (a total of 54 person-days of potential exposure for the whole group). Overall total exposure in both units ranged from 1 to 3 weeks, with a median of 1.5 weeks.

At Loma Linda University Medical Center, all patients were in the pediatric ICU (size, 1,380 ft^2 [ca. 128.2 m^2]), and the total exposure time, including both direct and indirect exposure, ranged from 1.5 to 2.7 weeks (median, 1.7 week), a total of 41 person-days of potential exposure.

Airflow patterns in patient care areas. The area, volume in cubic feet and cubic meters, and pattern of air changes in four rooms representative of those where patients were treated and care was delivered in this study are given in Table 2. Table 2 is provided to allow environmental comparison with other institutions. Total air changes per hour of all areas at Children's Hospital exceeded the requirements for minimum total air changes per hour standard at Children's Hospital National Medical Center. At Loma Linda, ribavirin was administered in two rooms of 144 ft^2 (ca. 13.38 m^2) and 1,095 ft^3 (ca. 30.99 m^3) each. The two rooms communicate, and the entire volume for both rooms is 3,818 ft^3 (ca. 108.05 m^3). Air exchange took place 11 times every hour.

Subjective reports. Participants were questioned for evidence of clinical intolerance to ribavirin aerosol. There were no side effects or adverse reactions noted among participants in the study.

Plasma and urine samples obtained preexposure, immediately after completion of the exposure period, and 3 to 5 days postexposure had no detectable ribavirin (data not shown). The quantitative sensitivity of the ribavirin assay used in this study was about 0.1 μM (0.02 μg/ml) at 99.9% confidence during a series of 17 standard runs. Inspection of radioactivity counts per minute for individual specimens, however, revealed that qualitative sensitivity was perhaps 5 to 10 times greater. There were virtually no differences in the actual counts for pre- and postexposure erythrocytes from the participants. During two runs, counts were above the blank in a competitive binding assay (B_0) value for both runs (run 1, $B_0 = 4.7573 \times 10^3$ cpm; run 2, $B_0 = 5.3237 \times 10^3$ cpm); counts equal to or greater than the B_0 in the corresponding run would have indicated a lack of ribavirin in the sample. The detection limit of the method used in these assays is at least 0.02 μg/ml.

Unlike other human body tissues, erythrocytes have no ability to generate diphosphorylating enzymes (11). Ribavirin triphosphate concentrates in and is retained by these cells (2, 4). Approximately 3% of the administered dose of ribavirin (equivalent to 10 to 15% of the total retained dose) is incorporated in erythrocytes. Since erythrocytes account for only 3% of the body mass, there appears to be selected concentration of ribavirin in erythrocytes (10).

Furthermore, because body tissues other than erythrocytes have diphosphorylating enzymes, levels of ribavirin in tissue and plasma are equilibrated (11). In humans, 53% of the administered dose appears in the urine in 3 days. Ribavirin was not detected in any of the erythrocyte or urine samples obtained from participants in this study. These samples appeared to be the logical ones to assay for ribavirin.

Since we estimate that the radioimmunoassay used for detection of ribavirin in this study has a lower limit of sensitivity of 0.02 μg/ml, as little as 60 μg in a total erythrocyte mass of 2,500 ml can be detected. No data are available on levels of ribavirin in the blood of rats, rabbits, mice, and primates which have been used for teratologic studies. However, in pharmacokinetic studies conducted in rats receiving intramuscularly 10 mg of ribavirin per kg, a general approximation of comparable drug level can be derived. Levels in erythrocytes as high as 178 μg/mg at 0.5 h, 24.4 μg/kg at 24 h, and 5.71 μg/kg at 72 h were found. These rats weighed between 250 and 390 g.

The absence of detectable ribavirin in the erythrocytes of nurses participating in the study is reassuring. However, these negative data must be interpreted within their limitations. Finding neither detectable levels nor side effects with the sample size provides an approximate 84% probability of deriving the right conclusion. These data rule out any long-run risk rate higher than 16%, with 95% confidence or 5% limit of credibility (8). We should also note that the air exchange rates at the two institutions studied could have contributed to optimal environmental conditions. These factors should also be considered by those engaged in administering aerosol therapy.

It appears quite unlikely that personnel involved in the routine care of patients receiving ribavirin during a typical 3- to 5-day course will accumulate levels of ribavirin similar to those observed in animal teratogenic studies. However, since the basis of teratogenicity is not fully understood, one cannot exclude the possibility that cumulative low doses all below the limit of sensitivity of our assay could result in some teratogenicity or hematologic toxicity. The present data are from a pilot study which will require additional follow-up to support the observation that under normal circumstances, a 3- to 5-day exposure of care givers to ribavirin will not lead to the accumulation of clinically significant ribavirin levels in human cells, tissues, or fluids.

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