HETA 93-0582-2359
OCTOBER 1993
HCA WESLEY MEDICAL CENTER
WICHITA, KANSAS

NIOSH INVESTIGATOR:
STEVEN W. LENHART, CIH

SUMMARY

A management request was received from the respiratory therapist educator of HCA Wesley Medical Center in Wichita, Kansas, for a health hazard evaluation of the effectiveness of revised procedures for administering ribavirin via hood. The method used for administering ribavirin via hood at HCA Wesley was modified to resemble a previously described double-hood containment system. A twelve-inch cubical care-cube disposable hood and a Viratek Small Particle Aerosol Generator are used for ribavirin administration. The second hood of the double-hood system is an eighteen-inch, cubical, clear-vinyl hood that was placed over the care-cube hood. This outer hood was connected to an Emerson scavenging system which exhausted aerosol that might escape from the inner care-cube hood during ribavirin administration; the exhaust flow rate was estimated to be 200 l/min. This final report describes the activities, findings and recommendations associated with area air sampling for ribavirin and ventilation measurements performed during a two-day site visit.

Air samples were collected within the care-cube disposable hood, and area air samples were also collected at five locations within the room. A respiratory therapist simulated the activities that would normally have been necessary if a patient was actually receiving care, but did so with an infant mannequin for the purposes of this site visit. Exhaust and supply air flow measurements were made at ventilation system ceiling exhaust and supply grilles located in the room where area air sampling for ribavirin was conducted, and two patient rooms located in the pediatric intensive care unit that have also been used as ribavirin treatment rooms. Area air sampling showed either nondetectable or trace concentrations of ribavirin. In-hood concentrations of ribavirin ranged from 33 to 92 mg/m^3. The air exchange rate of each room exceeded the minimum of six air changes per hour recommended by the American Association for Respiratory Care.

Provided that the simulated ribavirin administrations conducted during this study are representative of actual administrations to patients, the double-hood system was found to be effective for preventing the release of ribavirin aerosol into the work environment. To ensure the effectiveness of the double-hood system, personal breathing zone and area air sampling for ribavirin should be conducted during the activities associated with ribavirin administration to actual patients. The ventilation system of each room where ribavirin is administered at HCA Wesley Medical Center should continue to be monitored on a routine basis to ensure that optimal operation is maintained.

Keywords: SIC 8062 (General Medical and Surgical Hospitals), CAS number 36791-04-5, double-hood containment system, health-care workers, and ribavirin.

INTRODUCTION

A management request was received by the National Institute for Occupational Safety and Health (NIOSH) from the respiratory therapist educator of HCA Wesley Medical Center in Wichita, Kansas, for a health hazard evaluation (HHE) of the effectiveness of revised procedures for administering ribavirin via hood. This was a follow-up project to a previous NIOSH HHE.[1, 2] Air sampling conducted during the previous NIOSH HHE found that health-care workers (respiratory therapists and nurses) were exposed to ribavirin during administration via hood despite the use of a scavenging system. As a result, NIOSH investigators recommended continuance of the hospital's 1987 policy that required health-care workers to wear respiratory protection in rooms where ribavirin was being administered.[1] NIOSH investigators further recommended that the use of respirators be considered an interim measure that would remain until technically feasible devices and/or procedures were developed and implemented for the administration of ribavirin that would alone reduce exposures of health-care workers at HCA Wesley Medical Center. In response to the latter recommendation, the method for administering ribavirin via hood at HCA Wesley was modified to resemble a previously described double-hood containment system.[3] This final report describes the activities, findings and recommendations associated with area air sampling for ribavirin and ventilation measurements performed during the site visit at HCA Wesley on March 9 and 10, 1993.

METHODS

A twelve-inch cubical care-cube disposable hood and a Viratek Small Particle Aerosol Generator (model SPAG-2, 6000 series, ICN Pharmaceuticals, Inc., ICN Plaza, 3300 Hyland Avenue, Costa Mesa, California 92626) are used for administration of Virazole® aerosol (ribavirin) at HCA Wesley Medical Center. The drug manufacturer's recommended concentration of 20 milligrams of ribavirin per milliliter of sterile USP water (mg/ml) is used as the starting solution for the drug reservoir of the SPAG-2. This drug concentration is expected to produce an aerosol concentration of 190 mg per cubic meter (mg/m^3) inside a ribavirin administration hood for a 12-hour period.[4] The operating parameters of the SPAG-2 used at HCA Wesley Medical Center during this study were a regulator pressure of 26 pounds per square inch gauge (psig), a nebulizer air flow rate of 7.5 to 8.0 liters per minute (l/min), and a drying air flow rate of 7.5 l/min. These values are within the ranges of the operating parameters recommended by the manufacturer and should result in the expected ribavirin concentration of 190 mg/m^3.[5] Bulk samples of ribavirin solutions were collected in small glass vials on both days of sampling and were analyzed to confirm that the solutions contained the recommended concentration of ribavirin.

The second hood of the double-hood system is an eighteen-inch, cubical, clear-vinyl hood that was placed over the care-cube hood. This outer hood was connected to an Emerson post-op scavenging system which exhausted aerosol that might escape from the inner care-cube hood during ribavirin administration. The exhaust flow rate was estimated to be 200 l/min. Air was exhausted from the Emerson scavenging system into the room environment after passing through model BB-50T Pall breathing circuit filters (Pall Biomedical Products Corporation, East Hills, New York). On the second day of testing, water vapor was continuously added to the space between the two hoods because a researcher had hypothesized "that because ribavirin is highly water soluble, suspended particles of the drug inside the (outer) tent would be captured by the high-density water aerosol particles and ultimately either rain out inside the tent or be exhausted through the vacuum system."[3]

Air samples were collected within the care-cube disposable hood used for the administration of ribavirin. Air samples were not collected in the space between the care-cube hood and the outer containment hood. Area air samples were collected in the room at two locations at the foot of the bed upon which the care cube was located, between the bed and the room divider, on the room divider, and on a chair beside the door to the hallway. A respiratory therapist simulated the activities that would normally have been necessary if a patient was actually receiving care, but did so with an infant mannequin for the purposes of this site visit.

Equipment for each in-hood and area air sample consisted of a closed-face 37-millimeter (mm) cassette containing a glass fiber filter (type A/E, Product Number 61652, Gelman Sciences Inc., Ann Arbor, MI 48106-9990) and a cellulose backup pad. Each cassette was connected by flexible tubing to a personal sampling pump operated at 1.0 liter per minute (l/min) for samples collected inside the care-cube hoods and at 2.0 l/min for all other samples. Field blanks were prepared and submitted for analysis along with the sample cassettes.

Samples were analyzed in accordance with NIOSH analytical method 5027 issued May 15, 1989.[6] Each filter sample was extracted with deionized water adjusted to a pH of 2.5 with concentrated sulfuric acid. Each sample was shaken for 30 minutes and then sonicated for 15 minutes. An injection volume of 30 microliters (µl) of each filter sample solution or each bulk sample of ribavirin solution was analyzed using a high performance liquid chromatograph equipped with an ultraviolet detector.

Exhaust and supply air flow measurements were made at ventilation system ceiling exhaust and supply grilles located in the patient room where area air sampling for ribavirin was conducted (room 509), and two patient rooms located in the pediatric intensive care unit that have also been used as ribavirin treatment rooms (room 511-7 and room 511-8). Air flow measurements were made with a Shortridge model 8405 SPL flow hood assembly equipped with a model ADM-860 Airdata Multimeter electronic micromanometer (Shortridge Instruments, Inc., 7855 East Redfield Road, Scottsdale, Arizona 85260-3430). Room volumes were calculated from room measurements so that the number of air changes per hour could be determined for each potential ribavirin treatment room.

EVALUATION CRITERIA

General Guidelines

As a guide to the evaluation of the hazards posed by workplace exposures, NIOSH investigators employ environmental evaluation criteria for assessment of chemical and physical agents. These criteria are intended to suggest levels of exposure to which most workers may be exposed up to 10 hours/day, 40 hours/week for a working lifetime without experiencing adverse health effects. It is important to note, however, that not all workers will be protected from adverse health effects if their exposures are maintained below these levels. A small percentage may experience adverse health effects because of individual susceptibility, a preexisting medical condition, and/or a hypersensitivity (allergy). In addition, some hazardous substances may act in combination with other workplace exposures, the general environment, or with medications or personal habits of the worker to produce health effects even if the occupational exposures are controlled at the levels established by the evaluation criteria. Also, some substances are absorbed by direct contact with the skin and mucous membranes, and thus the overall exposure may be increased

above measured airborne concentrations. Evaluation criteria typically change over time as new information on the toxic effects of an agent become available.

The primary sources of evaluation criteria for the workplace are: NIOSH Criteria Documents and Recommended Exposure Limits (RELs),[7] the American Conference of Governmental Industrial Hygienists' (ACGIH) Threshold Limit Values (TLVs),[8] and the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs).[9] These values are usually based on a time-weighted average (TWA) exposure, which refers to the average airborne concentration of a substance over an entire 8- to 10-hour workday. Concentrations are usually expressed in parts per million (ppm), milligrams per cubic meter (mg/m^3), or micrograms per cubic meter ($\mu g/m^3$). In addition, some substances have only a ceiling limit, a concentration that should not be exceeded during any part of a workday. Other substances have a short-term exposure limit (STEL) to supplement a TWA limit where there are recognized toxic effects from short-term exposures. A STEL is a 15-minute TWA concentration which should not be exceeded at any time during a workday even if the 8-hour TWA is less than the exposure limit. The ACGIH recommendation for a substance without a STEL is that "excursions in worker exposure levels may exceed 3 times the TLV-TWA for no more than a total of 30 minutes during a workday, and under no circumstances should they exceed 5 times the TLV-TWA, provided that the TLV-TWA is not exceeded."[8] The basic concept is that excursions above a substance's 8-hour TWA exposure limit should be maintained within reasonable limits in well-controlled processes.

NIOSH RELs are based primarily on the prevention of occupational disease. In contrast, PELs and other OSHA standards are required to take into account the economic feasibility of reducing exposures in affected industries, public notice and comment, and judicial review. In evaluating worker exposure levels and NIOSH recommendations for reducing exposures, it should be noted that employers are legally required to meet OSHA standards.

Ribavirin

Ribavirin (1-beta-D-ribofuranosyl- 1,2,4-triazole-3-carboxamide) is a synthetic nucleoside analogue which is licensed in the United States for the short-term treatment of respiratory syncytial virus (RSV) infection.[10] Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to RSV.[4] Because ribavirin has been found to be teratogenic and/or embryolethal in most animal species in which it has been tested,[4, 10, 11] there is concern about its potential reproductive effects in humans. However, health hazard assessment data available for ribavirin aerosol are currently insufficient to assess accurately the health risk to exposed health care workers.[11] Ribavirin has not been linked to fetal abnormalities in humans; but, given the wide spectrum of teratogenic potential in most animal species, avoidance of ribavirin prior to pregnancy, during pregnancy, and during lactation has been recommended by the author of a review of the toxicology of antimicrobial aerosols.[10]

Occupational exposure criteria have not been established or recommended for ribavirin by NIOSH, the Occupational Safety and Health Administration (OSHA), or the American Conference of Governmental Industrial Hygienists. The California Department of Health and the Massachusetts Department of Labor and Industries have defined an occupational exposure limit for ribavirin of 2.7 micrograms ($\mu g)/m^3$.[12] This concentration is the same as the provisional exposure limit derived in 1988, by the California Occupational Health Program as a working guideline, representing a concentration unlikely to produce adverse reproductive effects.[13-15] Among other assumptions, the concentration of 2.7 $\mu g/m^3$ was calculated assuming that 70% of

inhaled drug is retained and that 100% of retained drug is absorbed. Others have substituted the percent absorbed of 100% with an absorption of 0.2% and reported that the acceptable exposure concentration for ribavirin should be 1359.4 µg/m^3.[16]

The 1991 Aerosol Consensus Statement of the American Association for Respiratory Care, contains guidance that patient rooms where ribavirin is administered should have a minimum of six air changes per hour.[17]

RESULTS

The pre- and post-administration concentrations of the ribavirin solutions used on both days of testing are presented in Table I. Both pre-administration ribavirin concentrations were slightly less than the recommended starting concentration of 20 mg/ml. The results of area air sampling in room 509 and in-hood air sampling for ribavirin are presented in Tables II and III. Area air sampling showed either nondetectable or trace concentrations of ribavirin. The area air sampling results for the two days of sampling are essentially the same. In-hood concentrations of ribavirin ranged from 33 to 92 mg/m^3. All of the in-hood concentrations were much less than the expected ribavirin concentration of 190 mg/m^3. The results of air flow measurements made in rooms 509, 511-7, and 511-8 are presented in Table IV. The air exchange rate of each room exceeded the minimum of six air changes per hour recommended by the American Association for Respiratory Care.[17]

TABLE I

Concentrations of Ribavirin Solutions
Prepared for Reservoir of SPAG
HCA Wesley Medical Center
Wichita, Kansas
March 9 and 10, 1993

Ribavirin Concentration (mg/ml)	
Pre-administration	Post-administration
March 9, 1993	
18	21
March 10, 1993	
19	25

Limit of Detection: 0.0001 mg/ml
Limit of Quantitation: 0.00033 mg/ml

TABLE II

Results of Area Air Sampling for Ribavirin in Room 509
[Water Vapor Not Added to Air Between Tents]
HCA Wesley Medical Center
Wichita, Kansas
March 9, 1993

Sampling Location	Sampling Period	Sampling Duration (minutes)	Ribavirin Concentration ($\mu g/m^3$)
Two samples at foot of bed	0858 - 1058	120	ND
	1058 - 1115	17	ND
	1118 - 1318	120	ND
	1319 - 1334	15	ND
	1337 - 1503	86	ND
	1505 - 1535	30	ND
44 inches from side of bed	0858 - 1158	180	(0.6)
	1200 - 1500	180	ND
	1505 - 1535	30	ND
90 inches from side of bed (on divider)	0858 - 1158	180	(1.0)
	1200 - 1500	180	ND
	1505 - 1535	30	ND
Beside door to hall	0858 - 1158	180	(0.8)
	1200 - 1500	180	ND
	1505 - 1535	30	ND
Inside "care-cube"	0930 - 0940	10	75 mg/m^3
	1145 - 1156	11	64 mg/m^3
	1407 - 1417	10	44 mg/m^3

Note: Values in ( ) represent a quantity of ribavirin between the Limit of Detection [0.2 µg/sample] and the Limit of Quantitation [0.66 ug/sample], and should be considered trace concentrations with limited confidence in their accuracy. Minimum detectable concentrations were 0.6 $\mu g/m^3$ for a 210-minute air sample and 3.0 $\mu g/m^3$ for a 30-minute air sample.

ND: none detected

TABLE III

Result of Area Air Sampling for Ribavirin in Room 509
[Water Vapor Added To Air Between Tents]
HCA Wesley Medical Center
Wichita, Kansas
March 10, 1993

Sampling Location	Sampling Period	Sampling Duration (minutes)	Ribavirin Concentration ($\mu g/m^3$)
Two samples at foot of bed	0806 - 1136 1139 - 1509 1510 - 1540	210 210 30	ND ND ND
44 inches from side of bed	0806 - 1136 1139 - 1509	210 210	ND ND
90 inches from side of bed (on divider)	0806 - 1136 1139 - 1509 1510 - 1540	210 210 30	ND ND ND
Beside door to hall	0806 - 1136 1139 - 1509 1510 - 1540	210 210 30	ND ND ND
Inside "care-cube"	0836 - 0846 1045 - 1056 1400 - 1410	10 11 10	92 mg/m^3 51 mg/m^3 33 mg/m^3

ND: none detected

Note: The minimum detectable concentration for a 210-minute sample was 0.5 $\mu g/m^3$. The minimum detectable concentration for a 30-minute sample was 3.0 $\mu g/m^3$.

TABLE IV

Results of Air Flow Measurements
HCA Wesley Medical Center
Wichita, Kansas
March 9, 2993

Room Number	Room Volume (ft3)	Mean Exhaust Air Flow Rate (CFM)	Air Changes per Hour	Supply Air Flow Rate (CFM)
509	1250	160	8	60 (AC off) 205 (AC on low) 230 (AC on Med) 260 (AC on High)
511-7	1190	160	8	160
511-8	1160	190	10	210

CFM: cubic feet per minute
AC: Air conditioner fan setting

DISCUSSION

The use of exhausted containment systems to control the release of ribavirin into the work environment of health-care workers during the administration of this drug has been reported previously.[3, 18-21] However, the results of air sampling (during simulated activities and during actual administration) have shown that not all of these systems completely eliminate the potential for exposures to aerosolized ribavirin. Because the vast majority of RSV cases treated with ribavirin at HCA Wesley Medical Center occur in the late fall and winter months, ribavirin administration was simulated for the purposes of this study, as was successfully done for previous NIOSH visits.[1, 2]

The highest ribavirin concentration measured inside the care-cube hood (92 mg/m^3) was essentially one-half the expected concentration of 190 mg/m^3. While lower than expected ribavirin concentrations have been measured inside delivery hoods,[1, 20] the reasons for this happening here are unknown. Perhaps more importantly, the effects of these lower concentrations on the recovery of an RSV patient are unknown as well.

According to the ventilation data presented in Table IV, the ventilation systems for room 511-8 and room 509, when the air-conditioning fan setting is on low, medium, or high, tend to be under positive pressure. This situation would suggest that ribavirin aerosol might be released outside these treatment rooms. Room 511-7 is essentially neutral.

CONCLUSIONS AND RECOMMENDATIONS

Provided that the simulated ribavirin administrations conducted during this study are representative of actual administrations to patients, the double-hood system was found to be effective for preventing the release of ribavirin aerosol into the work environment of health-care workers. These results suggest that the policy of HCA Wesley Medical Center requiring health-care workers to wear respiratory protection in rooms where ribavirin is being administered could be safely discontinued. To further ensure the effectiveness of the double-hood system, personal breathing zone and area air sampling for ribavirin should be conducted during the activities associated with ribavirin administration to actual patients.

The ventilation system of each room where ribavirin is administered at HCA Wesley Medical Center should continue to be monitored on a routine basis to ensure that optimal operation is maintained. The ventilation system of each room should also be maintained at a slight negative pressure to prevent aerosolized ribavirin from escaping to other occupied areas.[17, 20] Also, room air should be exhausted to the outside rather than recirculated to other areas of the hospital.[20]

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AUTHORSHIP AND ACKNOWLEDGEMENTS

Principal investigator:	Steven W. Lenhart, CIH Industrial Hygienist Industrial Hygiene Section
Field assistance provided by:	Gregory A. Burr, CIH Industrial Hygienist Industrial Hygiene Section
	Debra Fox, RRT HCA Wesley Medical Center 550 North Hillside Wichita, Kansas 67214
Report formatted by:	Donna M. Pfirman Office Automation Assistant Industrial Hygiene Section
Originating office:	Hazard Evaluations and Technical Assistance Branch Division of Surveillance, Hazard Evaluations and Field Studies

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