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Aerosolized Ribavirin—Exposures and Controls

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Case Report by John Decker

Introduction

The administration of pharmaceutical aerosols is rapidly expanding in medicine. Asthma, chronic obstructive pulmonary disease, and pulmonary infections are frequently treated with aerosols of sympathomimetics, beta-agonists, corticosteroids, and antimicrobials. The advantages to the patient include rapid onset of therapeutic action, optimized delivery of the drug to the site of action, and reduction in unwanted systemic side-effects. Aerosol delivery, however, results in increased exposure to the health care worker (HCW), compared with other administration routes. The difficulty in controlling the spread of aerosols, along with their small particle size, contributes to the risk of occupational exposure.

Much of the concern about occupational exposure to pharmaceutical aerosols has centered around the use of ribavirin. In response to a request for a Health Hazard Evaluation, National Institute for Occupational Safety and Health (NIOSH) investigators conducted an evaluation of HCW exposure to ribavirin in relation to engineering controls, work practices, and method of administration.

Background

Ribavirin is a synthetic nucleoside used to treat severe respiratory syncytial virus (RSV) pneumonia in infants and children.[1] Aerosolized ribavirin (AR) is produced by the drug manufacturer's Small Particle Aerosol Generator® (SPAG-2®). The aerosol can be delivered to the patient by a variety of methods, including head-hood, mist or croup tent, oxygen hood, or direct coupling to tracheotomy. The small particle size (1.0–1.3 μm mass median diameter) of the aerosol permits deep penetration of the drug into the patient's lungs.[2] Treatment is carried out for 12 to 24 hours per day, generally for 3 to 5 days.

Ribavirin has known teratogenic activity in several species. Ribavirin was teratogenic and embryolethal in rats, mice, and hamsters, and it was embryolethal in rabbits.[3–6] A single primate study, however, did not show teratogenic effects.[7] Three studies in rats showed degenerative or histopathologic testicular effects. Eight other studies in rats, mice, dogs, and monkeys induced no testicular effects.[8] Ribavirin has not been linked to fetal abnormalities in humans; however, given the wide spectrum of teratogenic potential in several animal species, avoidance of ribavirin prior to pregnancy, during pregnancy, and during lactation has been recommended.[9] Eye irritation and contact lens damage have been reported in employees administering the drug.[10]

The adverse reproductive effects seen in animal studies have raised concerns among HCWs who administer ribavirin; many of these workers are in their reproductive years. At present, the potential health effects of long-term occupational exposure to ribavirin are unknown. The toxicological data available for AR are currently insufficient to conduct an assessment of occupational health risks.[11] No exposure standard for AR has been recommended by NIOSH, the Occupational Safety and Health Administration (OSHA), or the American Conference of Governmental Industrial Hygienists (ACGIH).

Experimental Methods

Personal air monitoring for AR was conducted in conjunction with the following administration methods: ICN Aerosol Delivery Hood® (ADH®) with ICN evacuation device in operation, ADH enclosed by the Demistifier® scavenging tent, croup tent, and direct coupling to a ventilator. The ADH is the administration device supplied by the drug manufacturer. The Demistifier scavenging tent exhausts air out of a plastic tent through a high-efficiency particulate air (HEPA) filter into the room.

Personal samples were collected in the workers' breathing zone. Full-shift samples were generally collected from nurses who provided care continually throughout their shift. Short-term samples were generally collected from respiratory therapists (RTs), who provided intermittent care, approximately four times per shift. Since most of the HCWs wore disposable respirators, actual exposures were probably less than the breathing zone concentrations.

Air sampling for ribavirin was conducted according to NIOSH Method 5027, utilizing 37-mm diameter, 1.0 μm pore glass fiber filters.[12] Ribavirin was collected on the filters at a flow rate of 2.0 L/min for full-shift personal and area samples. A flow rate of 3.0 L/min was utilized for the short-term samples.

The glass fiber filters containing ribavirin were extracted with 3 ml sulfuric acid (pH = 2.5) in an ultrasonic bath and analyzed by high-performance liquid chromatography (HPLC) using a cation exchange resin column. The HPLC was equipped with an ultraviolet detector set at 210-nanometers wavelength. Two sets of samples were submitted to the laboratory. The reported limits of detection were 0.3 and 1 μg/sample; the limits of quantitation were 0.8 and 3.1 μg/sample.

Ventilation measurements indicated that the treatment rooms, which were exhausted directly to the outside, ranged from 10 to 19 air changes per hour. Smoke tests indicated that the

rooms varied from negative to positive pressure with respect to the adjacent hallway.

Hospital policy for ribavirin administration mandated that the aerosol generator was to be turned off 5 minutes prior to opening the administration hood or tent. Employees were also required to wear isolation gowns, shoe covers, latex gloves, and high-efficiency disposable respirators while working in the treatment rooms. Adherence to these procedures was variable. Some HCWs wore surgical masks instead of the hospital-supplied respirators. Some of the staff had not been fit-tested or trained in the use of respirators.

Results and Observations

Table I shows the personal air monitoring results for AR. The use of the scavenging tent, which enclosed the ADH, lowered personal exposures for both nurses and RTs. The full-shift, mean time-weighted average personal exposure for nurses was 4.4 $\mu g/m^3$ with the use of the scavenging tent, versus 24.9 $\mu g/m^3$ without the scavenging tent. The full-shift sample for RTs was below the limit of detection with the scavenging tent, versus 5.9 $\mu g/m^3$ without the scavenging tent. An RT also had comparatively low exposures (<7.4–<12.1 $\mu g/m^3$) in conjunction with the ADH alone. This individual was in the habit of turning off the aerosol generator and leaving the room for 10 to 15 minutes before starting his work. During the 10- to 15-minute time period, a large percentage of AR was probably removed by the room ventilation system, which provided a measured 19 air changes per hour.

Comparatively low exposures (full-shift mean of 4.3 $\mu g/m^3$ for nurses) occurred with the ventilator administration. This finding was not unexpected since the pediatric ventilator was essentially a closed system with a filter on the exhalation circuit.

The highest full-shift personal exposure (78.0 $\mu g/m^3$) was collected from a nurse caring for two children, one child treated with the ADH alone and one in the ADH enclosed by the Demistifier scavenging tent. The nurse spent proportionally more time in the treatment rooms and did not always turn off the aerosol generator 5 minutes before opening the head hood. The highest short-term exposures (means of 58.1 and 77.0 $\mu g/m^3$) occurred with the croup tent, which was reasonable to expect since a substantial amount of ribavirin remained inside the relatively large tent when opened by the HCW.

Two 5-minute samples collected inside the ADH were less than the expected concentration of 190 mg/m^3 AR, specified by the drug manufacturer.[13] The concentrations were 64 and 78 mg/m^3 AR with the nebulizer air flow set at 7 L/min. Other investigators have found that AR concentrations within the administration hood vary as a function of time and nebulizer air flow.[2] Measured AR concentrations within the administration hood might also vary depending on the sampling method and location of the sampling probe within the administration hood.

When the treatment rooms were under positive pressure, ribavirin was detected at the nurses' station located across the hallway from the ribavirin treatment rooms. The HCWs wore respirators only while working in the treatment room.

Conclusions

Variables that can affect health care workers' exposure to AR include the method of administration, use of scavenging devices, and implementation of certain work practices, such as turning off the SPAG-2 before opening the administration device. Although patient care considerations typically determine the route of ribavirin administration, hospital staff should be aware that in this study, exposures to personnel were greatest when ribavirin was administered by croup tent, less by ADH, and least with the ventilator or ADH in conjunction with a scavenging tent. Full-shift breathing-zone concentrations among nurses appeared to be related to the amount of time spent in the treatment room, which is dependent on the severity of the patient's illness and the number of children treated at a time. The RTs generally spent less time than the nurses providing treatment to the children, and the two full-shift samples collected from RTs were less than the corresponding mean breathing-zone concentrations from nurses. Other factors that may affect exposure (not fully evaluated here) include the concentration of AR generated by the SPAG-2 and room ventila-

TABLE I. Aerosolized Ribavirin Personal Exposure Concentrations

Administration Method	Job Category	Number of Samples	Sample Type	Range of Conc. ($\mu g/m^3$)[A]	Mean of Conc. ($\mu g/m^3$)[B]
ADH + tent[C]	Nurses	8	Full-shift	ND–13.2[D]	4.4
ADH + tent	Nurses	2	Short-term	11.9–13.9	12.9
ADH + tent	RT[E]	1	Full-shift	ND	ND
ADH + tent	RTs	6	Short-term	8.3–55.5	22.0
Croup Tent	Nurses	4	Full-shift	12.0–28.2	22.9
Croup Tent	Nurses	2	Short-term	58.8–95.2	77.0
Croup Tent	RTs	4	Short-term	33.3–83.3	58.1
ADH alone & ADH + tent	Nurse	1	Full-shift	78.0	78.0
ADH alone	Nurses	2	Full-shift	18.7–31.0	24.9
ADH alone	RTs	2	Short-term	<7.4–<12.1	<12.1
ADH alone	RT	1	Full-shift	5.9	5.9
Bear Cub® Ventilator	Nurses	3	Full-shift	<3.3–4.8	4.3
Bear Cub® Ventilator	RTs	3	Short-term	ND	ND

[A]"Range of Conc." refers to the range in concentrations of the individual samples, expressed in micrograms per cubic meter ($\mu g/m^3$).
[B]"Mean of Conc." refers to the mean of the individual samples.
[C]"ADH + tent" refers to an Aerosol Delivery Hood® enclosed by the Peace Medical Demistifier® Isolation tent. This scavenging tent was placed over the ADH. The ADH did not have the ICN evacuation apparatus connected.
[D]"ND" means nondetected. ND concentrations were treated as zero for calculating the "Mean of Conc."
[E]"RTs" signifies respiratory therapists.

tion rates.

Recommendations

Although reproductive effects have not been documented in humans, steps to reduce unnecessary HCW exposure are appropriate. The following recommendations are offered to minimize exposure of HCWs and other individuals who may enter rooms where ribavirin is administered.

1. Training programs should be developed to educate health care workers about potential risks of ribavirin exposure. Education should not be limited to direct care personnel but should include ancillary personnel such as phlebotomists, housekeepers, maintenance staff, and others who enter the room during treatment or who must clean contaminated rooms, waste, and bedding. The staff should be educated to recognize situations that could result in increased occupational exposure. Pregnant and lactating HCWs and HCWs who are not actively avoiding pregnancy should be counseled about risk reduction strategies. Family members and visitors should be notified of potential health effects.
2. Various ribavirin administration and scavenging systems result in different levels of environmental contamination. All administration systems should include a mechanism to reduce environmental exposures to ribavirin. It is the responsibility of hospital administration to implement more effective control measures as they become available. Administration and scavenging equipment should be maintained and visually inspected on a regular basis.
3. Rooms where ribavirin is administered should conform to the American Institute of Architects recommendations for isolation rooms.[14] Rooms should provide a minimum of 6 total air changes per hour and should be under negative pressure. Room air should be exhausted to the outside rather than recirculated to other areas of the hospital.
4. Air pressure in the ribavirin treatment rooms should be evaluated before therapy begins and daily thereafter. This can be accomplished by observing the direction of airflow at the doorway by holding a piece of tissue paper at the cracked doorway.
5. The aerosol generator should be turned off for a minimum of 5 minutes prior to the HCW entering the room to provide routine care. This could be accomplished by placement of a remote switch outside the room.
6. During aerosol therapy, ribavirin precipitate is deposited on the patient and on the surrounding area. Care should be taken when ribavirin-contaminated clothing, bedding, or equipment is handled to prevent the dust from becoming airborne. Although dermal absorption is not thought to be significant, dermal exposure should be avoided to prevent unintentional oral ingestion or ocular contact. The use of personal protective equipment, including gloves, gowns, and goggles, should be considered.
7. Ribavirin has been found to deposit on contact lenses; therefore, HCWs should be discouraged from wearing lenses when working with ribavirin.
8. Individual hospitals may choose to use respirators to further reduce HCW exposure to ribavirin. High-efficiency air-purifying respirators approved by NIOSH/MSHA (Mine Safety and Health Administration) and assigned to employees based on the results of quantitative fit tests have been found by in-mask sampling to reduce exposure to aerosolized ribavirin to the limit of detection of the analytical method.[15] By OSHA standard, respirator use must take place within the context of a respiratory protection program that includes evaluation of worker fitness to use a respirator, training, fit testing, and maintenance. Surgical masks should not be relied upon to provide personal protection from occupational exposure to ribavirin.[16]
9. In order to help reduce exposure of HCWs to ribavirin, medically unnecessary use of it should be avoided. Accordingly, medical staff should remain mindful of the American Academy of Pediatrics' recommendations and other current knowledge regarding ribavirin therapy.[17]

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