

Occupational exposures to aerosolized pharmaceuticals and control strategies

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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. Compared with other administration routes, aerosol delivery, however, results in increased exposure to the health care worker. The difficulty in controlling the spread of aerosols, along with their small particle size, contributes to the risk of occupational exposures.

Concerns about occupational exposures to pharmaceutical aerosols have centered around the use of two antibiotics, ribavirin and pentamidine isethionate. In response to these concerns, scientists at the National Institute for Occupational Safety and Health (NIOSH) have conducted several health hazard evaluations concerning occupational exposures of health care workers during the administration of these drugs.

Materials

Aerosolized ribavirin. Ribavirin is a synthetic nucleoside used to treat severe respiratory syncytial virus pneumonia in infants and children (1). Aerosolized ribavirin can be delivered to the patient by a variety of methods, including face mask, mist or croup tent, oxygen hood, or direct coupling to tracheotomy. The small particle size (1.0–1.3 μm mass median aerodynamic diameter) of the aerosol permits deep penetration of the drug into the patient's lungs (2). Treatment is conducted for 12–24 h per day, generally for 3 to 5 d.

Ribavirin has been shown to be teratogenic and embryolethal in rats, mice, and hamsters, and em-

bryolethal in rabbits (3–6). A single primate study, consisting of a small number of animals, did not show teratogenic effects (7). The teratogenic potential of ribavirin in humans has not been extensively studied. Ribavirin has not yet 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 (8). Eye irritation and contact lens damage have been reported in workers administering the drug (9).

Aerosolized pentamidine isethionate. Pentamidine isethionate is an antiprotozoal agent used predominantly for the prevention and treatment of *Pneumocystis carinii* pneumonia, an infection occurring in immunocompromised patients, including those with human immunodeficiency virus (HIV) infection. In the United States, pentamidine is usually self-administered via a handheld nebulizer. Treatments last from 20 to 60 min.

The administration of aerosolized pentamidine raises two concerns related to occupational health, nosocomial transmission of *Mycobacterium tuberculosis* and passive exposure to the pentamidine aerosol. One of the most common side-effects reported by patients receiving aerosolized pentamidine isethionate is coughing. Because coughing generates respirable aerosols, and since HIV-infected patients have an increased prevalence of tuberculosis (TB), there is an increased chance of exposure to the TB microorganism among health care workers. Occupational exposure to aerosolized pentamidine isethionate has been associated with several acute symptoms, including eye, nose, throat, and respiratory irritation and metallic taste (10). Other reported health effects on health care workers have included bronchospasm, asthma, and decreased pulmonary carbon monoxide diffusion capacity (11–13).

Results and observations

Ribavirin. Air sampling for aerosolized ribavirin was conducted according to NIOSH method 5027, utilizing 37-mm diameter, 1.0- μm glass fiber filters at a flow rate of 2–3 l $\cdot$ min⁻¹ (14). The analysis was per-

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formed by high-performance liquid chromatography (HPLC) using a cation exchange column and an ultra-violet detector. The limits of detection and quantitation were 0.7 µg per filter and 2.0 µg per filter, respectively. The analytical precision was 5.7%, the relative standard deviation being in the range of 20–110 µg per sample. HPLC and radioimmunoassay were used to measure the urinary ribavirin levels (performed at a contract laboratory) (15). Personal and area air monitoring for aerosolized ribavirin was conducted in conjunction with the following administration methods: Aerosol Delivery Hood® (ADH®), 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 the tent through a high-efficiency particulate air filter into the room. Full-shift samples were generally collected from nurses who provided care continually throughout their shift. Short-term samples were generally collected from respiratory therapists who provided treatment approximately four times per shift.

Hospital policy for ribavirin administration mandated that the aerosol generator be turned off 5 min prior to the opening of the administration hood or tent. Health care workers were required to wear isolation gowns, shoe covers, latex gloves, and 3M 9970 high-efficiency disposable respirators while working in the treatment rooms. The use of the scavenging tent, which enclosed the ADH®, lowered personal exposures for both the nurses and the respiratory therapists. The full-

shift mean time-weighted average (TWA) personal exposure for nurses was 4.4 (range <3.3–4.8) µg · m⁻³ with the use of the scavenging tent versus 24.9 (range 18.7–31.0) µg · m⁻³ without the scavenging tent (table 1). The full-shift respiratory therapist sample was below the limit of detection with the scavenging tent, versus 5.9 µg · m⁻³ without the scavenging tent. Another respiratory therapist also had comparatively low exposures (below the limit of quantitation <12.1 µg · m⁻³) in conjunction with the ADH® alone.

Comparatively low exposures (full-shift TWA mean of 4.3 µg · 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 TWA personal exposure (78.0 µg · 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 did not always turn the aerosol generator off 5 min before opening the head hood. The highest short-term exposures (means of 58.1 and 77.0 µg · m⁻³) occurred with the croup tent, and this finding was reasonable to expect since a substantial amount of ribavirin probably remained inside the relatively large tent when it was opened by the health care worker.

Postshift urine samples for ribavirin were collected from nine nurses (mean 0.044 µmol · g⁻¹ creatinine, range not detected to 0.136 µmol · g⁻¹) and eight respiratory therapists (mean 0.010 µmol · g⁻¹, range not detected to 0.036 µmol · g⁻¹). Despite the use of

Table 1. Concentrations of aerosolized ribavirin in personal exposure.

Administration method ^a	Job category	Number of samples	Sample type	Ribavirin concentration (µg · m ⁻³)	
				Mean ^{b, c}	Range ^{c, d}
ADH® + tent	Nurse	8	Full-shift	4.4	ND–13.2 ^d
ADH® + tent	Nurse	2	Short-term	12.9	11.9–13.9
ADH® + tent	Respiratory therapist	1	Full-shift	ND	ND
ADH® + tent	Respiratory therapist	6	Short-term	22.0	8.3–55.5
Croup tent	Nurse	4	Full-shift	22.9	12.0–28.2
Croup tent	Nurse	2	Short-term	77.0	58.8–95.2
Croup tent	Respiratory therapist	4	Short-term	58.1	33.3–83.3
ADH® alone & ADH® + tent	Nurse	1	Full-shift	78.0	78.0
ADH® alone	Nurse	2	Full-shift	24.9	18.7–31.0
ADH® alone	Respiratory therapist	2	Short-term	<12.1	<12.1
ADH® alone	Respiratory therapist	1	Full-shift	5.9	5.9
Bear Cub® ventilator	Nurse	3	Full-shift	4.3	<3.3–4.8
Bear Cub® ventilator	Respiratory therapist	3	Short-term	ND	ND

^a ADH + tent refers to an Aerosol Delivery Hood® (ADH®) 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.

^b Mean refers to the mean of the individual samples.

^c ND means not detected. ND concentrations were treated as zero for calculating the mean.

^d Range refers to the range in concentrations of the individual samples.

high-efficiency particulate respirators, ribavirin was detected in the urine of 11 of 17 health care workers. The urinary ribavirin concentrations of the nurses were statistically greater than those of the respiratory therapists.

Pentamidine isethionate. Air sampling for aerosolized pentamidine isethionate was conducted according to NIOSH method 5032, utilizing 37-mm, 5- μ m pore polyvinyl chloride membrane filters at 1 to 2 l $\cdot$ min⁻¹ (14). The pentamidine isethionate is extracted with 3-ml quantities of 50:50 ethanol:water with 0.085% phosphoric acid and 0.04% tetramethylammonium chloride in an ultrasonic bath. The analysis was performed by HPLC using fluorescence detection. The HPLC conditions were a variation of the conditions of Lin et al (16). The limits of detection and quantitation were 8 and 50 ng, respectively, for the polyvinyl chloride filters.

Personal and area air monitoring for aerosolized pentamidine isethionate was conducted in conjunction with the following controls: Emerson® chamber, Demistifier® tent, and no engineering controls. Sampling was conducted over the actual administration period. While the concentrations of aerosolized pentamidine isethionate within the Emerson® treatment chambers ranged from 63.5 to 122 μ g $\cdot$ m⁻³, all of the personal samples were below the limit of quantitation. All but two area samples collected outside the chambers were below the limit of quantitation. Concentrations outside the Demistifier® tent were below the limit of detection. Measurable exposures occurred when no engineering controls were used. One personal sample had an aerosolized pentamidine isethionate concentration of 9.8 μ g $\cdot$ m⁻³. Area measurements in the treatment room ranged up to 127 μ g $\cdot$ m⁻³. Particle size analysis using 11 Marple personal cascade impactors (models 294 and 296) indicated that the mass median aerodynamic diameter of the aerosolized pentamidine isethionate was less than 1.5 μ m (in the respirable range).

In NIOSH medical interviews, health care workers with pentamidine exposure often reported symptoms of mucosal or upper respiratory irritation. Chest tightness was rarely reported, and a single case of bronchospasm was reported in a worker with preexisting asthma.

Concluding remarks

NIOSH investigators found that exposure to aerosolized pentamidine isethionate and aerosolized ribavirin can be reduced substantially through the use of en-

gineering and administrative controls. Recommendations to the hospitals included the following measures: implementation of hazard communication programs for aerosolized pentamidine isethionate and aerosolized ribavirin, administration of the drugs in isolation rooms, modification of drug administration procedures, and potential use of personal protective equipment and aerosol scavenging devices to protect health care workers.

References

1. Food and Drug Administration. Ribavirin aerosol approved for severe cases of RSV in infants and young children. FDA Drug Bull 1986;16(1):7.
2. Arnold S, Buchan R. Exposure to ribavirin aerosol. Appl Occup Environ Hyg 1991;6(4):271-9.
3. Kilham L, Ferm VH. Congenital abnormalities induced in hamster embryos with ribavirin. Science 1977;195:413-4.
4. Hillyard IW. The preclinical toxicology and safety of ribavirin. In: Smith RA, Kirkpatrick W, ed. Ribavirin: a broad spectrum antiviral agent. New York, NY: Academic Press, 1980:59-71.
5. Ferm VH, Willhite C, Kilham L. Teratogenic effects of ribavirin on hamster and rat embryos. Teratology 1978;17:93-102.
6. Kochhar DM, Penner JD, Knudsen TB. Embryotoxic, teratogenic, and metabolic effects of ribavirin in mice. Toxicol Appl Pharmacol 1980;52:99-112.
7. Gallagher R, Givan N, Hazelden K, McGregor DB, Ridgway P, Wickramaratne GA. Teratogenicity testing in baboons of virazole: report from ICN Pharmaceuticals, March, 1977.
8. Waskin H. Toxicology of antimicrobial aerosols: a review of aerosolized ribavirin and pentamidine. Respir Care 36:1026-36.
9. Diamond SA, Dupuis LL. Contact lens damage due to ribavirin exposure [letter]. Drug Intell Clin Pharm 1989;23:428-9.
10. State of California/Occupational Safety and Health Administration. CAL/OSHA information bulletin. San Francisco, CA: State of California, Department of Industrial Relations, Division of Occupational Safety and Health, September 24, 1990.
11. Green ST, Nathwani D, Christie PR, Kennedy DR. Aerosolized pentamidine [letter]. Lancet 1989;2:1284.
12. Doll DC. Aerosolized pentamidine [letter]. Lancet 1989;2:1284-5.
13. Gude JK. Selective delivery of pentamidine to the lung [letter]. Am Rev Respir Dis 1989;139:1060.
14. National Institute for Occupational Safety and Health (NIOSH). NIOSH manual of analytical methods, 3rd ed., Cincinnati, OH: NIOSH, 1984. (DHHS (NIOSH) publication no 84-100).
15. Austin RK, Trefts PE, Hintz M, Connor JD, Kagnoff, MF. Selective radioimmunoassay for the broad-spectrum antiviral agent ribavirin. Antimicrob Agents Chemother 1983;24(5):696-701.
16. Lin JM, Shi RJ, Lin ET. High-performance liquid chromatographic determination of pentamidine in plasma. J Liq Chromatogr 1986;9:2035-46.