Exposure of Health Care Workers to Ribavirin during Therapy for Respiratory Syncytial Virus Infections

JOHN S. BRADLEY,1* JAMES D. CONNOR,3 LISA S. COMPOGIANNIS,2 AND LEONARD L. EIGER3

Department of Pediatrics, University of California, San Diego, La Jolla, California 920311; Children's Hospital–San Diego, San Diego, California 921232; and Zenith Insurance Company, Woodland Hills, California 913653

Received 27 September 1989/Accepted 28 December 1989

Health care workers (HCW) are exposed to ribavirin aerosol during therapy of infants with respiratory syncytial virus infections. To assess the degree of HCW exposure, we analyzed air samples from patient rooms and HCW personal breathing zones during ribavirin aerosol delivery by ventilator (two samples), oxygen hood (two samples), and a new vacuum exhaust hood (four samples). HCW exposure to ribavirin during aerosol delivery by ventilator or vacuum exhaust hood system was substantially lower than HCW exposure during aerosol delivery by oxygen hood in rooms with adequate ventilation.

Ribavirin, a synthetic nucleoside antiviral agent, is used for the treatment of respiratory syncytial virus infections in infants (2–4, 8, 9). Ribavirin aerosol is created by a small-particle aerosol generator, with delivery of aerosol by mist tent, hood, or ventilator. Toxicity data regarding teratogenicity and embryolethality in certain small animals dosed systemically with ribavirin were cited at the time this drug was approved for use in pediatrics in the United States in 1986 (Virazole package insert, January 1986, ICN Pharmaceuticals Inc., Irvine, Calif.). Concerns over health care worker (HCW) exposure to aerosolized ribavirin led to a clinical study by Rodriguez et al. (7) of 18 hospital personnel in whom neither plasma nor erythrocytes (RBC) contained detectable ribavirin. Harrison and co-workers (5) raised questions regarding HCW exposure to ribavirin aerosol at the conclusion of a similar study in which ribavirin was detected in a single RBC sample in 1 of 10 personnel tested. In addition to biological sampling, room air concentrations of ribavirin were also measured (5). Harrison et al. chose to evaluate HCW exposure limits based on a rabbit model of toxicity, with embryolethality as the outcome, to ascertain the highest oral dose causing no damage (the nonobserved adverse effect level [NOAEL]). A 1986 U.S. Environmental Protection Agency recommendation (10) for human exposure to agents, on the basis of limited data for experimental animals, suggested a value 1,000-fold less than the NOAEL as a safe exposure level. For the rabbit model, the ribavirin NOAEL was determined to be 0.3 mg/kg of body weight; therefore, Harrison et al. (5) felt that a dose theoretically safe for humans would be 0.3 µg/kg. The calculations of Harrison et al. suggest that HCW exposure to aerosol delivered by hood exceeded this level.

To extend the observations of Rodriguez et al. (7) and Harrison et al. (5) and, in addition, to test the efficacy of a new aerosol delivery device which incorporates a vacuum exhaust system to prevent ribavirin aerosol from leaving the hood of the infant and entering room air, we studied exposure of HCW to ribavirin in a clinical setting.

Ribavirin (ICN Pharmaceuticals) was reconstituted per instructions of the manufacturer and nebulized over a period of 12 h each day. The aerosol was delivered by oxygen hood (Care Cube, Goss Manufacturing Co., Alsip, III.), Aerosol Delivery Hood (ADH) (ICN Pharmaceuticals), or ventilator depending on the size of the patient and the severity of the underlying respiratory disease. Because of the small size of the hood, the ADH was used primarily for children weighing less than 5 kg. Room air levels of ribavirin were measured by the methods of Harrison et al. (5). Air samplers were placed either at the head of the bed (1 ft [30.48 cm]) away from the head of the infant or at the foot of the bed (approximately 3 to 4 ft away from the head of the infant). Monitoring also occurred at the opposite end of the room, approximately 8 ft away from the bed. Air samplers were worn on the lapels of HCW to measure personal breathing zone (PBZ) air levels. The time (in minutes) that HCW were present in the room while a child was receiving ribavirin was recorded, and interventions with the aerosol delivery device of the child were noted.

The sampling of blood from HCW for determination of levels of ribavirin in plasma and RBC was voluntary. Standard methods for ribavirin assay were used (1). Samples were obtained within 3 to 14 days after aerosol exposure.

Concentrations of ribavirin in room air at sampling sites at the bedside and across the room from the delivery device are given in Table 1 for children treated by oxygen hood, ADH, and ventilator. The hospital ventilation system, which provides HEPA-filtered recirculating air in these rooms, provided air changes per hour as noted in Table 1. The room ventilation systems were inadvertently turned off during the sampling periods for ADH 3 and ADH 4.

During oxygen hood administration of ribavirin in rooms with single or multiple hoods, the ribavirin levels at the bedside ranged from 303 to 1,383 µg/m³, with an average of 807 µg/m³. Room air levels varied from 218 to 969 µg/m³, with an average of 638 µg/m³, and PBZ concentrations ranged from 26 to 1,692 µg/m³, with an average of 485 µg/m³.

For children treated by means of the ADH, ribavirin levels at the bedside averaged 214 µg/m³ (range, 21 to 464 µg/m³), room samples averaged 124 µg/m³ (range, 7 to 286 µg/m³), and PBZ levels averaged 34 µg/m³ (range, 1 to 91 µg/m³). The child being treated in ADH 2 developed respiratory distress and required intubation during the sampling period. During aerosol delivery by ADH 3 and 4, respiratory therapy personnel stopped nebulization prior to entering the hoods, whereas nursing personnel did not, as they had not been instructed to perform this maneuver. For children treated through ventilators, average ribavirin levels at the bed,
across the room, and in the PBZ were 3, 4, and 3 \( \mu g/m^3 \), respectively.

Of 14 exposed HCW, 7 consented to give plasma and RBC for ribavirin assay. One of the seven personnel wore a face mask that was considered capable of filtering ribavirin during contact with the aerosol. Ribavirin was not detected in plasma and RBC samples of any personnel tested.

We evaluated the effectiveness of the ADH in decreasing room air levels of ribavirin in a clinical setting. Other vacuum exhaust aerosol delivery devices are currently under study (National Institute for Occupational Safety and Health, Centers for Disease Control, Atlanta, Ga., 30 June 1989). We found that concentrations of ribavirin in room air generally corresponded to those published by Harrison et al. (5) for delivery of ribavirin either by oxygen hood or by ventilator. The ADH was shown to reduce room air levels of ribavirin substantially, although wide variations in room and PBZ levels were seen. These variations were likely to be due to several factors: (i) inadequate room ventilation, (ii) HCW entering the ADH without first stopping aerosol delivery into the hood, (iii) air sampler exposure to aerosol streams, or (iv) position of the hood with respect to room ventilation outlets.

These data confirm, in a clinical setting, that ribavirin concentrations in room air can be substantially lowered when the delivery of aerosol is accompanied by a system designed to remove and filter the aerosol during treatment. However, such devices may prove to be more effective if education for HCW includes specific instructions to stop the nebulizing airflow prior to opening the hood. Lower concentrations of ribavirin in room air will decrease the risk of absorption of ribavirin by HCW as well as other people present in the room of a child being treated with aerosol.

A safe level of ribavirin aerosol exposure among HCW is yet to be determined. Harrison et al. chose to follow a convention established by the Environmental Protection Agency in 1986 (10). However, in a more recently published guideline by this agency (11), a factor of 10 for intraspecies variation (human) was suggested, as well as a factor of 10 for interspecies variation, with an additional factor “for scientific uncertainties that may exist in the available data base.” Because substantial experimental animal data exist, it may be more appropriate to use a total 100-fold reduction below the NOAEL. Other standards, such as that proposed by Johnson (6), support a total uncertainty factor of 100 as being more appropriate for evaluating human exposure to potentially toxic agents. Given these assumptions, controlling exposure to ribavirin during aerosol delivery by ventilator or by ADH will result in a total environmental exposure which would be considered acceptable by these standards.

As any model is at best a theoretical predictor of toxicity, it is still appropriate to reduce environmental exposure to potentially toxic drugs to the lowest possible level. Our limited data suggest that the ADH and mechanical ventilation are both effective in reducing environmental levels of ribavirin significantly compared with oxygen hood administration. Further studies on HCW exposure to ribavirin aerosol delivered by the ADH vacuum exhaust system, as well as by systems designed for children who weigh more than 5 kg and who do not require mechanical ventilation, are clearly needed.

### Table 1. Concentrations of ribavirin in room air at various sampling sites

<table>
<thead>
<tr>
<th>Method of ribavirin delivery</th>
<th>Ribavirin concn (( \mu g/m^3 )) in:</th>
<th>HCW</th>
<th>Room ventilation (air changes/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Environmental sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bed</td>
<td>Room*</td>
<td>PBZ</td>
</tr>
<tr>
<td>Ventilator 1</td>
<td>2.0d</td>
<td>1.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Ventilator 2</td>
<td>7.0d</td>
<td>4.7</td>
<td>4.2</td>
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<tr>
<td>2 Oxygen hoods</td>
<td>1,383d</td>
<td>969</td>
<td>1,328</td>
</tr>
<tr>
<td>2 Oxygen hoods + ADH</td>
<td>278d</td>
<td>287f</td>
<td>116</td>
</tr>
<tr>
<td>Oxygen hood 1</td>
<td>735d</td>
<td>727</td>
<td>76.7</td>
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<td>Oxygen hood 2</td>
<td>303d</td>
<td>218</td>
<td>212.0</td>
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<tr>
<td>ADH 1</td>
<td>89.7d,a</td>
<td>6.6h</td>
<td>49.1h</td>
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<td>ADH 2</td>
<td>20.8d</td>
<td>14.9</td>
<td>8.95</td>
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<tr>
<td>ADH 3</td>
<td>464.0d,l</td>
<td>286d</td>
<td>90.8</td>
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<tr>
<td>ADH 4</td>
<td>283d,l</td>
<td>189d</td>
<td>63.7</td>
</tr>
</tbody>
</table>

* Length of exposure of HCW to ribavirin aerosol.
* RN, Registered nurse; RT, respiratory therapist.
* Sample taken 8 ft (1 ft = 30.48 cm) from head of bed.
* Sample taken at foot of bed, 4 ft from head of child.
* ND, Not sampled.
* Measured 8 ft from and equal distance between two oxygen hoods.
* Sample taken at head of bed, 1 ft from head of child.
* Infant developed respiratory distress and required intubation during this sampling period.
* Room ventilation system was inoperative.
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LITERATURE CITED


