Ribavirin Aerosol in the Elderly*

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Ribavirin aerosol is effective in treating respiratory syncytial virus and influenzal infections in children and young adults. It has not been studied in elderly patients. We evaluated the safety of ribavirin aerosol in eight elderly volunteers at high risk for influenza. Their mean age was 64 years; seven subjects had chronic obstructive pulmonary disease (COPD). Subjects received ribavirin aerosol for two or six hours with six hours between treatments. Regimens were continued for 96 hours. The drug was well tolerated.

Ribavirin (1-β-D-ribofuranosyl-1,2,4, triazole-3-carboxamide) is an antiviral drug with a broad spectrum of activity. It has been successfully used to treat infants with respiratory syncytial virus infections1 and in college students and young adults with respiratory syncytial virus and influenza infections.2,4 Experience with ribavirin in elderly patients has been limited, especially in patients with underlying chronic obstructive pulmonary disease (COPD). In this study, we administered a ribavirin aerosol using two different protocols to elderly volunteers without acute viral infections to investigate the effect of aerosolized ribavirin on pulmonary function.

METHODS

Eight subjects were recruited from the Dayton Veterans Administration Medical Center domiciliary. The study was approved by the Human Studies Committee of Wright State University, and all volunteers signed informed consent. The subjects were eligible to participate in the study if they were more than 60 years of age or were at high risk for influenza (eg, if they had COPD). Seven men and one woman were enrolled in this trial (mean age, 64 years; range, 45 to 72 years; only one patient was less than 60 years of age). Seven of the eight subjects had COPD, as defined by standard criteria.†

Ribavirin was dissolved in sterile water and delivered through a tight-fitting face mask using a small particle aerosol generator (SPAG-2; ICN Pharmaceuticals Inc, Costa Mesa, CA). This produced particles with a mass median diameter of 1.3 μm. One group of four subjects received ribavirin aerosol (40 mg/ml) for six hours followed by a six-hour interval off the medication (12 hours of aerosol therapy per day). A second group of four subjects received ribavirin aerosol (60 mg/ml) for two hours, with a six-hour interval between treatments (six hours of aerosol therapy per day). Both treatment protocols were continued for 96 hours.

Pulmonary function tests were done before and after the first treatment on each study day on a Gould Pulmonary Analysis Computer (Gould, Inc, Dayton, OH). Measurements included forced vital capacity (FVC), forced expiratory volume in one second (FEV1), the ratio of FEV1 to FVC expressed as a percentage (FEV1/FVC), the highest forced expiratory flow measured with a peak flow meter (PEF), and the mean forced expiratory flow during the middle half of the FVC (FEF25-75%).

Oral medications were taken by subjects at their regularly scheduled times. Inhaled bronchodilators (metaproterenol or albuterol) were used as needed. The times when inhaled medication were used were recorded.

Statistical analysis was done using the 1-tailed Student t-test. A p value <0.05 was accepted as significant.

RESULTS

Pulmonary function data before and after treatment for the two groups are found in Tables 1 and 2. In the 6-hour treatment group, there were no significant differences in any of the measured pulmonary functions during the period of the study (Table 1). In the 2-hour treatment group, however, there were signifi-

Table 1—Pulmonary Function Data in the 6-Hour Group before and after Treatment*

<table>
<thead>
<tr>
<th>Test†</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>3.22 ± 0.82</td>
<td>3.23 ± 0.78</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1</td>
<td>1.89 ± 0.76</td>
<td>1.93 ± 0.82</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1/FVC%</td>
<td>56.30 ± 15.20</td>
<td>56.40 ± 16.30</td>
<td>NS</td>
</tr>
<tr>
<td>PEF</td>
<td>4.91 ± 2.25</td>
<td>4.93 ± 2.10</td>
<td>NS</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>1.11 ± 1.07</td>
<td>1.16 ± 1.18</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Each number is the mean ± standard deviation for all values before and after treatment from all patients from all four study days.
†FVC = forced vital capacity (liters); FEV1 = forced expiratory volume in one second (liters); FEV1/FVC% = the ratio of FEV1 to FVC expressed as a percentage; PEF = highest forced expiratory flow measured with a peak flowmeter (liters per second); and FEF25-75% = mean forced expiratory flow during the middle half of the FVC (liters per second).

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Table 2—Pulmonary Function Data in the 2-Hour Group before and after Treatment

<table>
<thead>
<tr>
<th>Test†</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>2.45 ± 1.13</td>
<td>2.40 ± 1.12</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁</td>
<td>1.43 ± 0.67</td>
<td>1.33 ± 0.64</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>FEV₁/FVC%</td>
<td>56.10 ± 5.40</td>
<td>54.60 ± 5.00</td>
<td>NS</td>
</tr>
<tr>
<td>PEF</td>
<td>3.08 ± 1.28</td>
<td>2.80 ± 2.16</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>0.76 ± 0.39</td>
<td>0.66 ± 0.29</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Each number is the mean ± standard deviation for all values before and after treatment from all patients in the 2-hour study group.
†FVC = forced vital capacity (liters); FEV₁ = forced expiratory volume in one second (liters); FEV₁/FVC% = the ratio of FEV₁ to FVC expressed as a percentage; PEF = highest forced expiratory flow measured with a peak flow meter (liters per second); and FEF25-75% = mean forced expiratory flow during the middle half of the FVC (liters per second).

...cant decreases in the mean FEV₁, PEF, and FEF25-75% at the end of the treatment periods (Table 2).

In the 2-hour treatment group, all four subjects were receiving long-term bronchodilator therapy. Two subjects were receiving oral bronchodilators only; one subject was receiving oral and inhaled bronchodilators; and one subject was receiving inhaled bronchodilators only. There was no elective use of inhaled bronchodilators by any subject in this treatment group during the time the aerosol was being delivered.

In the six-hour treatment group, only two subjects were on long-term bronchodilator therapy. One subject was receiving oral and inhaled bronchodilators, and one subject was receiving only oral bronchodilators. In this treatment group, the subject receiving inhaled bronchodilators used the drug twice, once, not at all, and twice, respectively, during the first treatment on the four days of the study.

No subject in either treatment group complained of increased shortness of breath or wheezing associated with aerosol treatment. One subject in the 6-hour treatment group and three subjects in the 2-hour treatment group complained of increased sputum production.

The quantity of ribavirin solution aerosolized per treatment was approximately 100 ml in the 6-hour treatment group and 35 ml in the 2-hour treatment group. Crystallization of the drug was noted around the nares of all subjects in the 6-hour treatment group.

**DISCUSSION**

Both oral and aerosol preparations of ribavirin have been used to treat a broad range of both RNA and DNA virus infections. In the United States, the aerosol form of the drug is indicated for the treatment of respiratory syncytial virus infections. However, outside the United States, oral and parenteral forms of the drug are used and have been shown to be effective in the treatment of measles and Lassa fever. Most of the data on the aerosol form of the drug has been in children or young adults, not in elderly patients or patients with underlying lung disease.

This study demonstrated that an aerosol of ribavirin dissolved in water can be delivered safely to elderly people with COPD. While there was no significant decrease in the pulmonary function of any subject in our 6-hour treatment group (Table 1), there was a significant decrease in the FEV₁, PEF, and FEF25-75% of the subjects receiving the aerosol for 2 hours (Table 2). Two observations explain this difference between the study groups. First, baseline FVC, FEV₁, and PEF of the subjects in the two-hour treatment group were significantly worse than the baseline values of the subjects in the 6-hour treatment group. Ultrasonic nebulization of aerosols without bronchodilators can cause an increase in cough, chest tightness, and wheezing, a decrease in the FEV₁, FVC, and partial pressure of oxygen, and an increase in the airway resistance. It is conceivable that the subjects in the 2-hour treatment group were more likely to have worsened pulmonary function tests with bland aerosols. Secondly, the single subject in the six-hour treatment group receiving an inhaled bronchodilator used this medication during the study period; this might have reversed any decline in pulmonary function that occurred during administration of the aerosol.

The total dose of ribavirin administered to the subjects was difficult to determine precisely. During aerosol treatment, concentration of the drug occurs in solution. The delivered concentration of the drug is thus higher toward the end of the treatment period. In addition, crystallization of ribavirin was noted around the nares of subjects receiving the drug for 6 hours. For these reasons, it is impossible to know if the decrement in pulmonary function seen in the subjects receiving the drug for 2 hours was due to the higher initial concentration of the drug.

Precipitation of ribavirin can be troublesome when the aerosol is administered for a prolonged period. In one report, ribavirin precipitated in a ventilation tube of an intubated infant; at the present time, ribavirin is not recommended for use in patients on mechanical ventilation.

None of the studies cited carefully evaluated pulmonary function in their patients during treatment. Influenza A can produce reversible airway hyperreactivity and peripheral airway dysfunction. Whether these changes can be attenuated by treating the patients with ribavirin is not known. Additionally, a major concern of using this treatment in the elderly or in patients with underlying COPD is their tolerance to bland aerosols. In this study, the aerosols were tolerated very well in spite of the decline in pulmonary function in one study group. The only complaint was increased sputum in four of the eight subjects. We conclude that aerosol delivery of ribavirin is safe and effective in treating respiratory syncytial virus infection.
well tolerated in elderly patients with COPD as long as their regular bronchodilator drugs are used. Therapeutic trials with ribavirin aerosol can therefore proceed in this important population.

REFERENCES
2 Hall CB, Walsh EE, Hruska JF Betts RF, Hall WJ. Ribavirin treatment of experimental respiratory syncytial viral infection. JAMA 1983; 249:2666-70
3 McClung HW, Knight V. Gilbert BE, Wilson SZ, Quarles JM, Divine GW. Ribavirin aerosol treatment of influenza B virus infection. JAMA 1983; 249:2671-74
8 Malik SK, Jenkins DE. Alterations in airway dynamics following inhalation of ultrasonic mist. Chest 1972; 62:660-64
12 Hicks RA, Olson LC, Jackson MA, Burry VF. Precipitation of ribavirin causing obstruction of a ventilation tube. Pediatr Infect Dis 1986; 5:707-08