Ribavirin Small-Particle-Aerosol Treatment of Influenza B Virus Infection

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In a randomized double-blind trial of aerosolized ribavirin for the treatment of influenza B virus infection, no significant difference was found in the febrile course or symptom score of the ribavirin-treated versus placebo-treated patients. The apparent lack of efficacy in this study as compared with that in previous studies is unexplained.

Although several agents, including ribavirin, amantadine, and rimantadine, have antiviral activity against influenza A viruses in vitro, only ribavirin is effective against influenza B viruses in vitro (4). In 1981 a successful trial of small-particle-aerosolized ribavirin was reported for the treatment of influenza A virus infections (5), and in 1983 effectiveness for influenza B virus infections was reported (6). An additional study was equivocal after evaluation of a small number of influenza B-infected patients (3). In 1984 and 1986 outbreaks of influenza B illness occurred in Cincinnati, Ohio. We report the results of a double-blind, randomized, placebo-controlled evaluation of small-particle-aerosolized ribavirin treatment of acute influenza B in otherwise healthy young adults.

College students, as well as others who responded to advertisements, had an influenza-like illness of less than 30 h duration and a temperature of 38.5°C or higher, and were otherwise in good health, were eligible for the study. All patients denied previous influenza vaccination. In both 1984 and 1986 five ribavirin and five placebo recipients had documented influenza B infections (influenza B isolation) (Table 1) and are the subject of this report.

Small-particle-aerosolized ribavirin was produced by Colison generators operated at a flow rate of 12.5 liters/min with drug diluted to 20 mg/ml in sterile water to yield a concentration of 190 ng/ml of ribavirin per liter of air, as previously reported (2, 5, 6, 8). Placebo-treated patients were administered an aerosol of sterile water. In 1984 patients received medications for alternating periods, 8 h on aerosol and 4 h off aerosol, during the initial 48 h, followed by alternating periods, 6 h on aerosol and 6 h off aerosol, for the remaining 24 h. In 1986, patients received continuous aerosol for the first 18 h, followed by alternating periods of 4 h for the remaining observation period of 72 h.

After a detailed double-blind clinical assessment of signs and symptoms of the eyes, ears, throat, and upper and lower respiratory tracts and of systemic illness was made, the physician graded patients for rhinitis, pharyngitis, tracheobronchitis, pneumonia, and systemic illness twice daily on a scale of 0 to 3. Oral temperatures were recorded every 4 h. Because aerosolized ribavirin was deposited in the perioral area, this area was washed prior to examination. The Wilcoxon rank-sum test and the Fisher exact test were used to compare groups. Using the mean and standard deviation of the time to afebrility for our control patients and our sample size, we calculated that there was a power of 90% to detect a 50% reduction, as previously reported (6), given an alpha of 0.05 (one sided). Our power to detect a 0.5-point reduction in a symptom score was 50 to 80% with the same parameters. Viral isolation was performed by inoculation of a Madin-Darby canine kidney tissue culture (5) with nasal wash specimens obtained on admission, twice daily for the 3 days during therapy, and at the initial follow-up visit on day 5. Cultures positive by hemadsorption were identified as influenza B by immunofluorescence. Virus titrations were performed by a modification of the method of Knight et al. (5), while antibody titers for paired specimens were determined by hemagglutination inhibition (1) with the H1N1, H3N2, and B antigens supplied by Alan Kendal (Centers for Disease Control) for 1984 and 1986. The susceptibility of influenza B isolates obtained on admission to ribavirin was measured by the method of Hayden et al. (4). No significant differences were found in the mean age or sex of the two groups or in the duration of illness prior to treatment when both 1984 and 1986 were combined (Table 1). Similarly, the temperature and severity of symptoms in the ribavirin and placebo groups were nearly equal upon entry into the study (Fig. 1 and 2). Patients who received ribavirin became afebrile (sustained temperature, less than 37.8°C) an average of 34.2 ± 20.8 h after starting ribavirin therapy, as compared with 45.0 ± 24.2 h for the placebo group (not significant). Because patients in the ribavirin

### TABLE 1. Study population

<table>
<thead>
<tr>
<th>Group (subject no.)</th>
<th>No. of patients from whom influenza B virus was isolated</th>
<th>No. of patients with seroconversiona</th>
<th>Mean age (yr)b</th>
<th>No. of females/no. of males</th>
<th>Mean duration of illness prior to therapy (h)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984</td>
<td></td>
<td></td>
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<tr>
<td>Placebo (7)</td>
<td>5</td>
<td>2</td>
<td>24.0</td>
<td>2/3</td>
<td>23.3ab</td>
</tr>
<tr>
<td>Ribavirin (9)</td>
<td>5</td>
<td>5</td>
<td>27.0</td>
<td>4/1</td>
<td>16.4ab</td>
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<tr>
<td>1986</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (11)</td>
<td>3</td>
<td>5</td>
<td>29.8</td>
<td>1/4</td>
<td>22.8</td>
</tr>
<tr>
<td>Ribavirin (10)</td>
<td>5</td>
<td>3</td>
<td>23.6</td>
<td>2/3</td>
<td>22.8</td>
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<tr>
<td>Combined</td>
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<tr>
<td>Placebo (18)</td>
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<td>26.9</td>
<td>3/7</td>
<td>23.6</td>
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<tr>
<td>Ribavirin (19)</td>
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<td>8</td>
<td>25.3</td>
<td>6/4</td>
<td>19.6</td>
</tr>
</tbody>
</table>

* Includes only patients with laboratory-confirmed influenza B infections.
ab P < 0.05, as determined by Student’s t test.
FIG. 1. Mean temperatures ± standard deviations in placebo- and ribavirin-treated patients. Temperatures were obtained orally every 4 h. Temperatures were only significantly ($P < 0.05$) different at one time, 12 h after therapy.

FIG. 2. Mean symptom scores ± standard deviations in placebo- and ribavirin-treated patients. A study physician evaluated patients at admission and between 8:00 and 9:00 a.m. and 5:00 and 7:00 p.m. each day. The scores are based on the physician evaluation of signs and symptoms as discussed in the text.
FIG. 3. Mean viral titers in nasal washes obtained at admission and at 8:00 a.m. and 5:00 p.m. each subsequent day. TCID_{50}, 50% Tissue culture infective dose.

group entered the study earlier in their disease, we also compared the time to afebrility from the onset of symptoms, but again the difference was not significant. The temperature curves (Fig. 1) for both groups were similar, and at only one time (12 h after therapy) was the temperature in the treated group significantly lower ($P < 0.05$) than that in the placebo group.

No significant differences were found between the ribavirin and placebo groups in clinical scores for systemic symptoms, rhinitis, tracheobronchitis, or pharyngitis during any evaluation period (Fig. 2).

Mean viral titers were also not significantly different at any time (Fig. 3). Since the mean viral titer of the ribavirin group at admission was almost one log_{10} 50% tissue culture infective dose higher than that of the placebo group (not significant), we also examined the change in titer from admission for each evaluation period. No significant difference occurred, although between admission and the third evaluation period, viral titers in the placebo group had increased, while the treated group showed a consistent decline in viral titers.

Because the results of this study differed from those previously published, we examined the susceptibility of viral isolates to ribavirin. The 50% inhibitory doses ranged from 1.8 to 5.2 μg/ml in 1984 and from 0.5 to 4.2 μg/ml in 1986, values similar to those reported previously (4).

This study involved low numbers of patients, so it is possible that a significant effect of ribavirin may have been missed. In addition, no drug level determinations were performed. However, in a previously reported study of influenza B infection (6) consisting of 11 ribavirin-treated and 10 placebo-treated patients, there were significant differences in time to afebrility, disappearance of systemic illness, and reduction in viral shedding. Our evaluation did reveal trends for a more rapid reduction in viral excretion and a decreased duration of fever in the ribavirin group but no trend towards an earlier reduction in other symptoms. Patients in the previous study (6) received an average of 39.2 h of therapy, as compared with 44 and 42 h in our 1984 and 1986 subjects, respectively. Thus, the disparate results of these studies could not be attributed to a shortened treatment schedule in our study. The susceptibility of our influenza B isolates to ribavirin was similar to that previously reported (4), and it is unlikely that placebo recipients treated in the same room as ribavirin recipients received ribavirin through the spread of the aerosol (7).

Our study is based on data pooled from two different outbreaks. We feel that pooling these data is valid because little antigenic variation occurred among influenza B viruses from 1984 to 1986 and because isolates from both outbreaks had similar susceptibilities to ribavirin. Since both the ribavirin-treated and placebo-treated groups included five patients from each year, it is unlikely that differences between the virulence of strains from year to year contributed to study bias. In only one reported study (2) aerosolized ribavirin was reported to be ineffective against influenza viruses. In that study, the investigators believed that the short duration of illness and limited virus shedding of the influenza A (H1N1) virus were the principal bases for the failure to detect the efficacy of ribavirin. These factors were not pertinent in our study.

Further evaluation of aerosolized ribavirin is important because of its potential for treating both influenza A and B infections and should concentrate on patients severely affected by influenza infections, so that more dramatic differences between treated and control patients may be found. In addition, drug levels within the respiratory tract should be assayed and correlated with the clinical and virological results.

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LITERATURE CITED


