Oral Rimantadine Hydrochloride Therapy of Influenza A Virus H3N2 Subtype Infection in Adults

FREDERICK G. HAYDEN and ARNOLD S. MONTO

Departments of Internal Medicine and Pathology, University of Virginia School of Medicine, Charlottesville, Virginia 22908; and Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan 48109

Received 3 June 1985/Accepted 8 November 1985

In a randomized, double-blind trial involving patients with uncomplicated influenza A H3N2 subtype virus infection, rimantadine treatment (200 mg/day for 5 days) was associated with significant reductions in nasal secretion viral titers (days 2 through 4), maximal temperature (days 2 and 3), time until defervescence (mean, 37 h shorter), and systemic symptoms compared with placebo treatment.

Rimantadine hydrochloride (α-methyl-1-adamantanemethylamine hydrochloride) is an amantadine analog that has shown greater activity than amantadine against some influenza A viruses in vitro, and in experimental influenza A virus infection in mice (2, 5, 6). Previous studies have found similar therapeutic activity, reflected by faster defervescence and resolution of symptoms as compared with placebo treatment, when the drugs have been given to patients with uncomplicated influenza (4, 8, 9). However, patients tolerate rimantadine significantly better than amantadine when these drugs are administered in equivalent doses (200 or 300 mg/day) to healthy (1, 3) or influenza virus-infected (8) adults. The differences in toxicity relate to differences in plasma concentrations and pharmacokinetics between the drugs (3, 3a, 7). Although in earlier studies rimantadine was administered in divided doses, its long plasma elimination half-life (30 to 40 h) suggests that single daily doses should be adequate for treatment or prophylaxis. The treatment was started within 48 h of the onset of symptoms. If any subjects were enrolled during the morning or early afternoon, then an additional single 100-mg dose was given on the evening of treatment day 1 (four of seven rimantadine recipients). The treatment was initiated in the seven rimantadine recipients (four female, three male; mean age, 28 years) at a mean ± standard deviation 33 ± 12 h after the onset of symptoms. Treatment in the seven placebo recipients (three female, four male; mean age, 23 years) was initiated at 29 ± 10 h after the onset of symptoms.

The virological effects of treatment were assessed by measuring virus recoverable in nasal secretions (Table 1). At the University of Virginia (two placebo and two rimantadine patients), nasal washings were collected by putting 5-ml volumes of lactated Ringer solution into each nostril and collecting the effluent. Titers of the virus were determined by culturing serial 10-fold dilutions of once-frozen (−70°C) and thawed specimens in monolayers of Madin-Darby canine

<table>
<thead>
<tr>
<th>Treatment (n)</th>
<th>Mean (±SD) log_{10} TCID_{50}/0.2 ml on treatment day*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo(7)</td>
<td>2.4 (±1.1) 3.2 (±0.9) 2.5 (±1.8) 2.1 (±1.4) 0.3 (±0.6)</td>
</tr>
<tr>
<td>Rimantadine (7)</td>
<td>3.0 (±0.8) 0.3 (±1.1) 0.5 (±1.2) 0.1 (±1.1) −0.3 (±0.3)</td>
</tr>
<tr>
<td>* Specimens were collected at enrollment before drug administration on treatment day 1. TCID_{50}, 50% tissue culture infective dose.</td>
<td></td>
</tr>
<tr>
<td>* Only three placebo (three positive) and five rimantadine (two positive) recipients were cultured for virus on day 5.</td>
<td></td>
</tr>
<tr>
<td>* Statistical analysis by two-tailed t test. For calculation purposes, negative cultures were assigned a value of −0.5 log_{10} TCID_{50}/0.2 ml.</td>
<td></td>
</tr>
<tr>
<td>* NS, Not significant.</td>
<td></td>
</tr>
</tbody>
</table>

The current study was a randomized, placebo-controlled, double-blind trial designed to determine the therapeutic activity of oral rimantadine given once daily in uncomplicated influenza A H3N2 subtype infection. This study was conducted at the University of Michigan and the University of Virginia from January to February 1983. A total of 14 adults with culture-proven influenza A infection caused by an A/Bangkok/1/79 (H3N2)-like virus were randomly chosen to receive either 200 mg of oral rimantadine or placebo once daily for 5 days. The treatment kidney cells incorporating 2 μg of trypsin per ml in the medium (2). At the University of Michigan (five placebo and five rimantadine patients), nose and throat swabs were combined in 4-ml portions of veal infusion broth, and titers were determined in monolayers of cynomolgus monkey kidney cells. Both treatment groups had similar concentrations of virus recoverable in nasal secretions before the treatment was initiated, and placebo recipients continued to shed high concentrations of virus 4 days after enrollment (Table 1). By contrast, the rimantadine recipients had a prompt reduction in virus titers by treatment day 2 and had significantly lower titers than did placebo recipients on days

* Corresponding author.

339
2 through 4. During treatment days 2 through 5, 23 of the 24 (96%) specimens from placebo recipients yielded the virus, compared with 16 of the 26 (62%) specimens from rimantadine recipients ($P < 0.01$, Fisher’s exact test). An earlier study (7) documented that oral rimantadine (100 mg twice daily for 5 days) had significant antiviral effects in influenza A/USSR/77/H1N1-infected students compared with those of placebo recipients. The results of the current study extend this observation to H3N2 subtype influenza A virus-infected adults. This correlates with the in vitro observation that contemporary strains of influenza A viruses have been susceptible to inhibition by rimantadine (2).

The clinical effects of rimantadine treatment were assessed by measuring oral temperatures four times per day (Table 2) and by the subjective scoring of systemic and respiratory symptoms by the infected students (Table 3). The two treatment groups had similar maximum oral temperatures (Table 2) and symptom scores (Table 3) on enrollment in the study. Placebo recipients experienced a gradual reduction in mean temperature, whereas rimantadine-treated patients defervesced rapidly and had significantly lower mean maximum temperatures on treatment days 2 and 3 (Table 2). On treatment day 3, all seven rimantadine recipients were afebrile (with a maximum oral temperature of $\leq 99°F$), compared with none of the seven placebo recipients ($P < 0.01$). The mean ± standard deviation duration of the fever (temperature, $>99°F$) from the onset of therapy was 31 ± 22 h in the rimantadine group, compared with 68 ± 8 h in the placebo group ($P < 0.01$, Mann-Whitney U test). Similarly, the resolution of both respiratory and systemic symptoms tended to be more rapid in rimantadine than in placebo recipients (Table 3). Rimantadine recipients had significantly lower systemic symptom scores on treatment days 3 and 4.

During the treatment period, one subject in each of the rimantadine and placebo groups reported insomnia, and one in each of the groups reported dizziness. These complaints resolved despite continued drug administration. One rimantadine recipient, a 30-year-old female, developed unilateral galactorrhea 3 days after stopping rimantadine treatment. Detailed studies failed to determine a cause, and she continued to experience unexplained mild galactorrhea for over 1 year, after which she was lost to follow-up.

Earlier placebo-controlled studies documented that rimantadine (150 mg twice daily for 10 days) was associated with a reduction in the duration of fever and symptoms in H3N2 subtype influenza A virus-infected prisoners (4, 9). At equivalent doses (100 mg twice daily for 5 days), rimantadine was associated with a somewhat slower defervescence and resolution of symptoms compared with amantadine, although both drugs were significantly more effective than placebo (8). Since rimantadine is associated with significantly lower plasma concentrations than amantadine, and has an approximately twofold longer plasma elimination half-life (3a), the current study used a single daily dosage regimen with a modified loading scheme, in which the majority of rimantadine recipients received 300 mg on day 1 and 200 mg/day thereafter. The results indicated a prompt improvement in the rimantadine group with significant de-

### Table 2. Maximal daily temperatures in influenza A (H3N2) virus-infected students treated with rimantadine or placebo

<table>
<thead>
<tr>
<th>Treatment (n)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (7)</td>
<td>102.0 (±1.2)</td>
<td>100.3 (±1.5)</td>
<td>100.0' (±0.4)</td>
<td>98.7 (±0.8)</td>
<td>98.2 (±0.1)</td>
</tr>
<tr>
<td>Rimantadine (7)</td>
<td>101.7 (±1.1)</td>
<td>98.9 (±0.6)</td>
<td>98.4 (±0.3)</td>
<td>98.4 (±0.4)</td>
<td>98.0 (±0.5)</td>
</tr>
<tr>
<td>$P^a$</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*a Based on six placebo and six rimantadine recipients.
*b Based on four placebo and six rimantadine recipients.
*c Statistical analysis by two-tailed $t$ test.
*d NS, Not significant.

### Table 3. Systemic and respiratory illness symptom scores in influenza A (H3N2) virus-infected students

<table>
<thead>
<tr>
<th>Symptom$^a$</th>
<th>Treatment</th>
<th>1$^b$</th>
<th>2$^b$</th>
<th>3$^b$</th>
<th>4$^b$</th>
<th>5$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>Placebo</td>
<td>14 (±4)</td>
<td>11 (±5)</td>
<td>10 (±4)</td>
<td>9 (±4)</td>
<td>3 (±2)</td>
</tr>
<tr>
<td></td>
<td>Rimantadine</td>
<td>13 (±3)</td>
<td>7 (±5)</td>
<td>4 (±3)</td>
<td>4 (±2)</td>
<td>3 (±3)</td>
</tr>
<tr>
<td></td>
<td>$P^c$</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Placebo</td>
<td>9 (±3)</td>
<td>10 (±2)</td>
<td>7 (±3)</td>
<td>6 (±3)</td>
<td>2 (±2)</td>
</tr>
<tr>
<td></td>
<td>Rimantadine</td>
<td>9 (±4)</td>
<td>8 (±4)</td>
<td>4 (±2)</td>
<td>4 (±1)</td>
<td>4 (±2)</td>
</tr>
<tr>
<td></td>
<td>$P^c$</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*a Systemic: headache, chills, malaise/fatigue, nausea, diarrhea, anorexia, and eye pain. Respiratory: nasal stuffiness/discharge, sneezing, sore throat, cough, chest pain, and hoarseness.
*b Rated absent (0) to severe (3) on each treatment day.
*c Data from only six placebo recipients.
*d Data from only five placebo recipients.
*e Statistical analysis by two-tailed Mann-Whitney U test.
*f NS, Not significant.
creases in fever by treatment day 2. The average decrease in the duration of fever (37 h) compared with the deviation in the placebo group was similar to observations reported previously (28 h) for oral rimantadine (150 mg twice daily for 10 days) in treating adults with uncomplicated H3N2 subtype influenza A virus infection (9).

In summary, oral rimantadine given once daily was generally well tolerated and associated with significant clinical benefits in uncomplicated H3N2 subtype influenza A virus infection. Because of its therapeutic efficacy and lower potential for side effects (1, 3, 8), rimantadine may be preferable to amantadine for treating influenza A virus infections.

This study was supported by grants from E. I. Du Pont de Nemours & Co., Inc.

We thank Katherine Adams, Lisa Kennan, and personnel at the Student Health Services of the University of Michigan and the University of Virginia for help in conducting the study, and Doris Pinson for help in manuscript preparation.

LITERATURE CITED