Safety and Efficacy of Intranasal Pirodavir (R77975) in Experimental Rhinovirus Infection

FREDERICK G. HAYDEN,1* KOEN ANDRIES,2 AND PAUL A. J. JANSSEN2

University of Virginia School of Medicine, Charlottesville, Virginia 22908;1 and Janssen Research Foundation, B-2340 Beerse, Belgium2

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Pirodavir (R77975) is a capsid-binding, antipicornaviral agent with in vitro activity against most rhinovirus (RV) serotypes. We conducted four double-blind, controlled trials to assess the efficacy of intranasal pirodavir in experimentally induced RV infection of susceptible volunteers. Intranasal pirodavir (2 mg per dose) or the hydroxypropyl-β-cyclodextrin vehicle as a placebo was given by metered pump spray. In three prophylaxis trials, subjects were inoculated with RV within 10 min of the second and third doses. When sprays were given six times per day for a total of 25 doses, infection, detected by either virus shedding or seroconversion, developed in 100% of the 13 placebo-treated subjects and 58% of the 12 pirodavir-treated subjects (P = 0.015). Clinical colds developed in 54% of placebo-treated subjects and 8% of pirodavir-treated subjects during drug administration (efficacy = 85%, P = 0.03), although late-developing colds developed in several subjects in both groups. Significant reductions in morning symptom scores and in the frequency of abnormal middle-ear pressures were also found in the pirodavir group. In contrast, in two prophylaxis studies using three doses daily, no significant antiviral or clinical benefits were observed. When frequent sprays were initiated at 24 h after RV challenge, significant reductions in virus shedding but no clinical benefits were found. Intranasal pirodavir was generally well tolerated but was associated with an excess rate of transient unpleasant taste. The findings indicated that frequent intranasal sprays of pirodavir were effective in preventing experimentally induced RV illness.

A number of synthetic antiviral agents with diverse chemical structures have been found to inhibit the in vitro replication of human rhinoviruses (16, 17). These agents appear to bind into a specific hydrophobic pocket within the capsid protein VP1, beneath the canyon floor of rhinoviruses, and prevent viral attachment and/or uncoating, depending on the serotype involved (13, 15). However, clinical trials in which several of the agents were administered orally or intranasally yielded negative results (2, 3, 14, 18). The first of these agents to show clinical activity in studies with humans was the pyridazinamine R61837 (1, 7). In a series of trials with a highly sensitive rhinovirus serotype (HRV9), intranasal sprays of R61837 showed significant protection against experimentally induced rhinovirus illness when frequent sprays (six times per day) were begun either before virus inoculation (1) or during the incubation period (7).

However, capsid-binding antihinoviral compounds vary considerably in their activity against different rhinovirus serotypes, and R61837 is much less active against most rhinovirus serotypes than against HRV9 (4). Andries and coworkers (6) have previously described two distinct groups (designated A and B) of rhinoviruses on the basis of their susceptibility profiles to a range of representative capsid-binding antiviral compounds. R61837 is almost exclusively active against serotypes belonging to antiviral group B, whereas disoxaril (12) is preferentially active against serotypes from antiviral group A. Subsequent work led to the development of pirodavir (R77975), a substituted phenoxypyridazinamine which has high activity against serotypes from both antiviral groups (5). Compared with its predecessor R61837, pirodavir has a greater than 500-fold improvement in potency in vitro and inhibits the replication of 80% of serotypes, at concentrations of 0.1 μg or less per ml. This paper describes the results of four clinical trials designed to assess the safety and effectiveness of this new agent in experimentally induced human rhinovirus infection.

MATERIALS AND METHODS

Participants. Previously healthy adults between the ages of 18 and 50 years with screening serum neutralizing antibody titers of ≥1:2 to one of two challenge rhinovirus serotypes (type 39 or a currently unnumbered serotype, designated Hank’s) were recruited for participation (10). Written informed consents in a form approved by the University of Virginia Human Investigation Committee were obtained from all participants. Subjects were compensated for participation.

Drug administration. Pirodavir at a concentration of 5 mg/ml was formulated in an aqueous solution containing 10% hydroxypropyl-β-cyclodextrin as a solubilizing agent and saccharin as a sweetening agent to mask the taste of the drug. The placebo solution consisted of the same excipients. Drugs were supplied in multiple-use metered pump sprayers. Each treatment (or dose) consisted of two sprays per nostril (100 μl per spray), so that a single treatment administered 2 mg of pirodavir.

Virus inoculation. The viral inoculum was administered by nasal drops (0.1 ml per nostril) on two separate occasions to supine subjects by previously described techniques (10). The challenge virus was a safety-tested pool of serotype Hank’s for all subjects, except for three participants (two pirodavir recipients and one placebo recipient) who were inoculated with serotype 39 in the first prophylaxis study. In a multicycle cytopathic-effect inhibition assay (4), the minimal inhibitory concentrations of pirodavir for Hank’s and type 39 were 0.002 and 0.006 μg/ml, respectively.

Experimental procedures. Four randomized, double-blind, placebo-controlled trials were conducted to assess the pro-
phyllactic (three trials) and therapeutic activities (one trial) of intranasal pirodavir. In the three prophylaxis studies, virus challenge was given within 10 min after the second and third drug doses. In the first prophylaxis trial, four doses (6 p.m., 9 p.m., 12 a.m., and 4 a.m.), beginning on the evening of the first day of the study, were given and continued six times daily at 3-h intervals (8 a.m. to 11 p.m.) over the next three days, with three doses on the fifth day (total of 25 doses). The total inoculum was \(-4,000\) TCID\(_{50}\) per volunteer. In the second prophylaxis trial, three doses (2 p.m., 8 p.m., and 2 a.m.), beginning on the afternoon of the first treatment day, were given and followed by treatments three times daily (7 a.m., 3:30 p.m., and 11 p.m.) over the next five days, with one dose on the morning of the seventh day (total of 19 doses). The inoculum was \(~400\) TCID\(_{50}\) per volunteer. The third study had a design similar to that of the second study, but the inoculum was reduced to \(-20\) TCID\(_{50}\) per volunteer and the treatment period was shortened by one day (total of 16 doses).

In the therapy trial, subjects were inoculated with \(-4,000\) TCID\(_{50}\) as outpatients and sequestered 12 h later. Treatment with the study drugs was initiated at 24 h after viral challenge and was given as six doses daily while the subjects were awake (8 a.m. to 11 p.m.) for four days, with one additional dose on the fifth day of treatment (total of 25 doses).

**Clinical monitoring.** The occurrence of clinical colds, the weights of nasal secretions, and the use of tissue were determined during the isolation period by previously described methods (10). Subjects rated the severity of cold-associated symptoms twice daily, in the morning and evening, during the period of isolation and then each morning for 3 to 7 days following discharge from the hotel (10). Total symptom scores were determined by adding the morning and evening scores for the 5- to 6-day isolation period. Middle-ear pressures (MEP) were tested daily with a digital tympanometer before and during treatment (11). Abnormal MEP were defined as those greater than +20 or less than \(-50\) mm of H\(_2\)O.

Tolerance to the nasal sprays was assessed by recording adverse symptoms (nasal dryness, nasal burning or soreness, blood in mucus, unpleasant taste, and unpleasant odor) on a daily basis by rhinoscopic examinations before and on the last day of treatment and by laboratory testing (complete blood count and standard blood chemistry) before treatment and on the last treatment day. All treated subjects were included in the analysis of drug tolerance.

**Virologic monitoring.** Pretreatment nasal washings (5 ml per nostril) were obtained for detection of preexisting viral infections. Postinoculation nasal washings were collected each morning for the isolation of rhinovirus on human embryonic lung (strain WI-38 or MRC-5 cells) (HEL). Samples were held on wet ice and inoculated fresh onto triplicate monolayers of HEL cells. After a 1-h absorption period, the monolayers were washed three times and observed every other day for development of cytopathic effect.

Nasal wash samples which were negative on initial isolation were subjected to extraction by dichloromethane (Sigma) to remove residual pirodavir (5). Briefly, equal volumes of nasal wash and dichloromethane were vortexed for 1 min at room temperature and then centrifuged at 500 \(\times\) g for 5 min. The aqueous phase was removed and mixed with an equal volume of dichloromethane, and the process was repeated twice, for a total of three extractions. An aliquot of the resulting aqueous phase was diluted 1:10 in cell culture medium and used for repeat culture at two dilutions (undiluted and \(10^{-1}\)) on duplicate monolayers of HEL cells.

Samples yielding virus by conventional culture or by culture following extraction were considered positive. Eighty-two (13\%) of 648 initially negative specimens, including 58 from pirodavir-treated subjects and 24 from placebo-treated subjects, were positive after extraction and repeat culture.

Sera were collected before and at 3 weeks following virus inoculation for measurement of serum neutralizing antibody titers to the challenge virus by standard techniques. Only sera with at least a titer of 1:8 (dilution of virus to 50\% tissue culture). The inoculum was \(\sim\)400 TCID\(_{50}\) per volunteer. The three prophylaxis studies, virus samples (10 ml of heparanized blood) were collected pretreatment and just after the last dose for determination of concentrations of pirodavir and its major metabolite R80044 in plasma by high-pressure liquid chromatography (17a). Nasal wash aliquots were also collected at each time that samples were collected for virus isolation.

**Data analysis.** The significance of differences was calculated for categorical variables by Fisher's exact test, for symptom scores by Mann-Whitney U test, and for other variables by Student's t test. All P values are those for two-tailed testing. Efficacy (percent) was calculated as \(100 \times (\text{frequency in the placebo group} - \text{frequency in the active group}) / \text{frequency in the placebo group}.

**RESULTS**

**Prophylaxis studies.** A total of 29, 38, and 33 subjects were enrolled in the first, second, and third prophylaxis studies, respectively. The mean ages (20 to 22 years) of the treatment groups were comparable. Only males were enrolled in the first two studies; in the third study, more females were enrolled in the pirodavir group (9 of 16) than in the placebo group (5 of 16) (\(P > 0.1\)). One subject was dropped from the third prophylaxis study after receiving one drug dose, because leukopenia was detected at baseline testing. A total of 11 subjects (six pirodavir recipients and five placebo recipients) were considered nonevaluable for efficacy because of infection with nonchallenge rhinoviruses (four pirodavir recipients and three placebo recipients) and other viruses (one from each group) or because of seropositivity in the acute-phase sample (one from each group).

**Virologic effects.** In the first prophylaxis study, in which there were six spray doses daily, there were significant reductions in the proportion of pirodavir recipients who shed virus or who became infected compared with that of the placebo group (Table 1). However, the rates of seroconversion did not differ significantly between the groups. The calculated efficacy of pirodavir in preventing infection was 42\%. Similarly, the overall number of days of virus shedding was reduced in the pirodavir group, and significant differences in the proportion of virus-positive subjects in the pirodavir and placebo groups were found on days 2 (0 versus 69\%, \(P < 0.001\)), 3 (17\% versus 85\%, \(P = 0.005\)), and 4 (17\% versus 62\%, \(P = 0.04\)) of drug administration. At 48 or 72 h after cessation of drug administration, 33\% of pirodavir-treated subjects and 69\% of placebo-treated subjects continued to shed virus on one or both days (\(P = 0.12\)).

In contrast, in the second and third prophylaxis studies, which utilized three sprays daily, no significant reductions in overall virus shedding, seroconversion rates, or infection rates were observed (Table 1). At 48 or 72 h after drug administration was stopped, the percentage of subjects who continued to shed virus on one or both days was comparable in both treatment groups during the second (26\% of the pirodavir group and 31\% of the placebo group) and third
(77% of the pirodavir group and 67% of the placebo group) studies.

**Clinical effects.** In the first study, drug administration was associated with a significant reduction in the proportion of pirodavir recipients who developed clinical colds during the period of drug administration compared with that of placebo recipients (Table 2). The single individual in the pirodavir group meeting the criteria for a cold did not have laboratory evidence of infection. The calculated efficacies of pirodavir were 85% in preventing colds and 100% in preventing laboratory-documented rhinovirus-induced illness. This effect was associated with a trend toward reductions in total symptom scores, which were reduced by 50%, but with no reductions in mucus weights or tissue use (Table 2). Significantly lower symptom scores were observed on the mornings of days 3 to 5 for the pirodavir group than for the placebo group (Fig. 1). In addition, late colds developing after subjects were discharged from the hotel were reported by three of the four pirodavir-treated subjects who shed virus and also by two placebo-treated subjects.

In the two prophylaxis studies employing thrice daily dosing, no reductions in the proportions of subjects developing colds, in symptom scores, or in mucus weights were observed for the pirodavir groups compared with those for the corresponding placebo groups (Table 2). The relatively high mean symptom score for the pirodavir group in the third trial was due, in part, to three subjects with high scores (36, 56, and 84) who also experienced complicated clinical courses (one tracheobronchitis and two otitis media).

**MEP.** In the first study, the percentages of subjects or ears (Fig. 2) with abnormal MEP before virus challenge were comparable for the two groups. Following challenge, subjects in the placebo group showed increased proportions of ears with abnormal MEP on days 3 to 5, but these changes occurred significantly less often in the pirodavir group (Fig. 2). Similarly, the proportion of subjects with one or more

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**TABLE 1. Rates of infection and virus shedding in subjects given intranasal pirodavir or placebo for prophylaxis or treatment of experimentally induced rhinovirus infection**

<table>
<thead>
<tr>
<th>Study (dosage)</th>
<th>Treatment</th>
<th>No. of subjects</th>
<th>No. (%) of subjects with:</th>
<th>Days of virus shedding (% of observation days)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Virus shedding</td>
<td>Seroconversion</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (6 times/day)</td>
<td>Pirodavir</td>
<td>12</td>
<td>4 (33)*</td>
<td>7 (58)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>13</td>
<td>11 (85)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>2 (3 times/day)</td>
<td>Pirodavir</td>
<td>19</td>
<td>10 (53)</td>
<td>13 (68)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>16</td>
<td>11 (69)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>3 (3 times/day)</td>
<td>Pirodavir</td>
<td>13</td>
<td>11 (85)</td>
<td>11 (85)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>15</td>
<td>13 (87)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Treatment (6 times/day)</td>
<td>Pirodavir</td>
<td>13</td>
<td>10 (77)</td>
<td>12 (92)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>11</td>
<td>11 (100)</td>
<td>10 (91)</td>
</tr>
</tbody>
</table>

* Infection is defined as shedding virus, seroconversion, or both.

*a* Expressed as mean ± standard deviation number of days of virus shedding + days of observation for each subject. The numbers of postchallenge days of observation were 7, 9, and 8 in the first, second, and third prophylaxis studies, respectively. In the treatment study, these were 7 days of observation after initiation of treatment at 24 h postchallenge.

*P* = 0.015 versus placebo.

*P* = 0.01, two-tailed t test, versus placebo.

*P* = 0.004 versus placebo.

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**TABLE 2. Frequency and severity of colds in subjects receiving intranasal pirodavir or placebo for prevention of experimentally induced rhinovirus illness**

<table>
<thead>
<tr>
<th>Prophylaxis study no. (dosage)</th>
<th>Treatment</th>
<th>No. of subjects</th>
<th>No. (%) of subjects with*:</th>
<th>Total symptom score Mean ± SD*</th>
<th>Nasal mucus (g) Mean ± SD*</th>
<th>No. of tissues used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical colds</td>
<td>Infection + colds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (6 times/day)</td>
<td>Pirodavir</td>
<td>12</td>
<td>1 (8)*</td>
<td>0 (0)*</td>
<td>6 ± 8*</td>
<td>13.0 ± 9.2</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>13</td>
<td>7 (54)</td>
<td>7 (54)</td>
<td>12 ± 10</td>
<td>12.6 ± 10.9</td>
</tr>
<tr>
<td>2 (3 times/day)</td>
<td>Pirodavir</td>
<td>19</td>
<td>10 (53)</td>
<td>8 (42)</td>
<td>13 ± 13</td>
<td>10.7 ± 8.6</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>16</td>
<td>7 (44)</td>
<td>7 (44)</td>
<td>13 ± 16</td>
<td>17.1 ± 24.9</td>
</tr>
<tr>
<td>3 (3 times/day)</td>
<td>Pirodavir</td>
<td>13</td>
<td>9 (69)</td>
<td>9 (69)</td>
<td>26 ± 23</td>
<td>18.8 ± 17.5</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>15</td>
<td>10 (67)</td>
<td>10 (67)</td>
<td>17 ± 15</td>
<td>15.6 ± 13.2</td>
</tr>
</tbody>
</table>

* All colds and those associated with laboratory evidence of rhinovirus infection during the period of drug administration are indicated. Colds developing after discharge from the hotel were considered separately.

*b* The duration of observation was 5 days for the first and third prophylaxis trials; it was 6 days for the second prophylaxis trial.

*P* = 0.03 versus placebo.

*P* = 0.005 versus placebo.

*P* = 0.1, Wilcoxon two-sample test, versus placebo.
abnormal MEP in the pirodavir group was reduced on the evenings of days 3 (17% of the pirodavir group versus 62% of the placebo group, $P = 0.04$) and 4 (8% versus 50%, $P = 0.07$) and on the morning of day 5 (17% versus 69%, $P = 0.02$).

In contrast, no differences favoring pirodavir were found in either of the two prophylaxis studies using three doses daily (Fig. 2). However, the second trial was confounded by a higher frequency of MEP abnormalities at enrollment and on the second day of the study for the pirodavir group than for the placebo group.

**Drug levels in blood and nasal washing.** In the first and second prophylaxis studies, plasma samples collected at the end of the dosing period had no detectable pirodavir (<0.005 μg/ml) and low concentrations (mean ± standard deviation, 0.023 ± 0.009 μg/ml in the first trial and 0.016 ± 0.009 in second trial) of its major deesterified metabolite (R80044).

In the first study, levels of pirodavir in nasal washings averaged -4.5 μg/ml on the second day 3 h after a preceding dose and 1.3 to 2.3 μg/ml on days 3 to 5 when samples were collected 7 to 8 h after a preceding dose. Concentrations averaged 0.12 μg/ml on day 6 - 15 h after the last dose and were nondetectable in nasal washings (≤0.01 μg/ml) of 10 of 14 subjects on day 7 and of 13 of 14 subjects on day 8. Levels of R80044 in nasal washings showed a similar pattern (data not shown). In the second prophylaxis trial, levels of pirodavir in the morning nasal washings collected 7 to 8 h after a preceding dose averaged 0.7 to 2.3 μg/ml on days 2 to 7 and 0.03 μg/ml on day 8 at approximately 24 h after a preceding dose and were nondetectable in 19 of 20 subjects on days 9 and 10.

**Treatment study.** Thirty-two subjects were enrolled, but eight (three pirodavir recipients and five placebo recipients) were considered nonevaluable because of preexisting infection with nonchallenge rhinoviruses (three in each group) or with parainfluenza viruses (two in the placebo group). The remaining subjects (all males) had similar ages (mean, 21 years for both groups) and symptom scores (mean ± standard deviation, 3 ± 2 for the pirodavir group and 3 ± 3 for the placebo group) at the time of initiation of drug treatment at 24 h postchallenge. Most subjects in both groups shed virus, and over 90% of the subjects seroconverted to the challenge serotype (Table 1). The mean number of days of virus shedding following initiation of drug treatment was significantly less for the pirodavir group than for the placebo group (Table 1), and the fraction of subjects who were positive for virus on the final observation day, eight days after challenge and two days after cessation of the study drug, tended to be lower in the pirodavir group (17%) than in the placebo group (55%) ($P = 0.08$).

The proportion of subjects meeting the criteria for clinical colds was similar for the pirodavir (62%) and placebo (55%) groups, initiation of drug treatment. For all evaluable subjects, pirodavir administration was not associated with reductions in total symptom scores (mean ± standard deviation at 4 days, 15 ± 11 [pirodavir group] versus 14 ± 14 [placebo group] or nasal mucus weights (21.5 ± 28.2 versus 18.7 ± 20.1) during the four inpatient days of treatment compared with placebo administration. Similarly, no differences in favor of pirodavir were observed when only subjects developing colds were analyzed (data not shown). Treatment had no significant effect on reducing the frequency of subjects or ears (Fig. 2) with abnormal MEP.

**Tolerance.** All of the volunteers, except one receiving only one drug dose, completed drug administration, and no serious adverse events were recognized. Spraying was associated with a high frequency of nasal dryness for both groups (Table 3), but the degree of nasal dryness was generally mild. Unpleasant taste was reported at a higher frequency in the pirodavir groups in all four trials, and the difference in frequency was significant for two separate prophylaxis trials and for all subjects combined (Table 3). The unpleasant taste was reported as being generally mild and transient (lasting up to several minutes) and usually occurred at 5 to 15 min after application of spray. Symptoms of mucosal irritation were reported with similar frequencies for both treatment groups, although blood in mucus and rhinoscopic evidence of mucosal bleeding on the last treatment day were found about twice as often in pirodavir recipients as in placebo recipients ($P > 0.1$). Minor reversible elevations (less than two times the upper limit of normal) of serum glutamic oxalacetic transaminase. A peak of 220 HAYDEN ET AL.
transaminase (three pirodavir recipients and one placebo recipient) or serum glutamic pyruvic transaminase (two in each group) were detected during the four trials.

**DISCUSSION**

Our findings indicated that frequent intranasal sprays of pirodavir (six times daily) were effective in preventing the development of clinical colds and cold-associated abnormalities in MEP following experimentally induced rhinovirus infection. The results also found that frequent pirodavir applications were associated with significant antiviral effects and may have partially reduced the overall frequency of infection. The findings confirm the protective effect against clinical colds observed with frequent intranasal sprays (six times daily) of R61837 in studies of experimentally induced HRV9 infection (1, 7). Thus, pirodavir represents the second capsid-binding agent and the first one with a broad antirhinoviral spectrum (5) to provide protection against experimentally induced rhinovirus illness.

Previous studies of R61837 did not provide data on viral shedding because of concerns regarding artificial inhibition of virus recovery due to direct interaction between virus and drug in nasal washings (1). In vitro studies had previously established that the interaction between the drug and the particular challenge virus used in the studies (HRV9) was irreversible by dilution or organic solvent extraction (5). After in vitro studies had established that the infectivity of the challenge virus exposed to pirodavir was fully recoverable by repeated extraction of samples with dichloromethane, this technique was applied to all samples that were culture negative on initial isolation, and a substantial number of additional isolates were recovered. In addition, washings were collected for several days after cessation of drug, when pirodavir concentrations were shown to be negligible and unlikely to affect virus recovery. We observed that virus recovery was reduced significantly in the two trials in which six sprays daily were given but was not reduced in the two trials in which three doses daily were used.

The fact that these agents exert antiviral activity through hydrophobic interactions with the virus capsid makes it difficult to administer adequate concentrations in an aqueous solution compatible with respiratory secretions. In the studies with R61837 and pirodavir, this administration was facilitated by using hydroxypropyl-β-cyclodextrin as a vehicle for these hydrophobic molecules. The viscous or sticky nature of this molecule probably contributed to the high frequency of subjective nasal dryness in both treatment groups (Table 3). In addition, frequent intranasal applications were used to overcome normal mucociliary clearance mechanisms. Because such frequent intranasal applications are not practical for prophylaxis, we tested the efficacy of less-frequent spraying. Despite administration of the viral inoculum within 10 min of the preceding drug dose, no protective effects were recognized. The differences between the results of the prophylaxis studies suggest that the protective effect observed with frequent spraying was not simply due to an interaction between the drug and virus at the time of inoculation and that antiviral activity is needed on a sustained basis in nasal secretions to provide protection against colds. Alternative formulations that may provide prolonged secretion concentrations warrant testing.

In both the first prophylaxis study and in several of the trials with R61837 (1, 7), late-developing colds developed in some recipients after the cessation of drug administration. Although late colds were also reported by several placebo recipients, the association of delayed onset of colds with persistent virus shedding in some pirodavir recipients suggests that this dose regimen only partially suppressed viral replication in these subjects. It is possible that a more prolonged course of drug administration might prevent late colds, perhaps by allowing effective host immune responses to control infection. In addition, the possible emergence of drug-resistant variants, already described for R61837 (8), needs consideration.

Recent studies have found a high frequency of subclinical Eustachian tube dysfunction and abnormal MEP during experimental rhinovirus colds (9, 11). Such abnormalities develop in the majority of persons experiencing colds but not in those with subclinical infection following virus challenge (11). The results of the current trials are consistent with these earlier observations. The finding that the frequency of

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**TABLE 3. Tolerance of intranasal sprays of pirodavir or placebo**

<table>
<thead>
<tr>
<th>Study (dosage)</th>
<th>Treatment</th>
<th>No. of subjects</th>
<th>No. (%) of subjects with symptom:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nasal dryness</td>
<td>Nasal burning</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Pirodavir</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>1 (6 times/day)</td>
<td>Pirodavir</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>2 (3 times/day)</td>
<td>Pirodavir</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>3 (3 times/day)</td>
<td>Pirodavir</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Treatment (6 times/day)</td>
<td>Pirodavir</td>
<td>66</td>
<td>43 (65)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>65</td>
<td>39 (58)</td>
</tr>
</tbody>
</table>

*Rhinoscopy was performed on last day of spray administration (day 5, 6, or 7).

\[ P = 0.05 \text{ versus placebo.} \]
\[ P = 0.003 \text{ versus placebo.} \]
\[ P < 0.001 \text{ versus placebo.} \]
abnormal MEP was significantly reduced in the pirodavir recipients in the first prophylaxis study is additional objective evidence of protection against colds. However, the results from our preliminary therapy study did not indicate evidence for protection against the development of abnormal MEP in subjects that were already symptomatic.

Intranasal sprays of pirodavir were generally well tolerated. However, the tendencies toward higher frequencies of reported blood in nasal mucus and observed mucosal bleeding with pirodavir spray than with placebo spray suggest that the compound may have some intrinsic irritating effect on the respiratory mucosa. Furthermore, the higher frequency of unpleasant taste in the pirodavir groups suggests that this effect may be directly related to the molecule. The timing of this complaint is consistent with the clearing of the nasal sprays through the posterior nasopharynx.

Earlier studies of R61837 found that its administration, when commenced during the incubation period, was partially protective against the development of colds (7) but that very frequent applications (up to 15 times per day) were therapeutically ineffective for established colds and likely associated with local irritation (1). The results of our small treatment study with less-frequent dosing also did not provide evidence of clinical benefit. Because of the uncertain link between active virus replication and symptom production in rhinovirus infections, it remains to be determined whether any antiviral intervention will provide symptom relief for established colds. The decreased infectiousness of nasal secretions could result in reduced transmission of infection. However, study of a much larger number of patients with naturally occurring rhinovirus colds would be needed to reliably address these questions.

REFERENCES