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# Intranasal Pirodavir (R77,975) Treatment of Rhinovirus Colds

FREDERICK G. HAYDEN,[1]* GLORIA J. HIPSKIND,[1] DIANE H. WOERNER,[1] GERALD F. EISEN,[2] MONIQUE JANSSENS,[2] PAUL A. J. JANSSEN,[2] AND KOEN ANDRIES[2]

*University of Virginia School of Medicine, Charlottesville, Virginia 22908,[1] and Janssen Research Foundation, B-2340 Beerse, Belgium[2]*

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**A randomized, double-blind, placebo-controlled trial assessed the therapeutic efficacy of intranasal pirodavir in naturally occurring rhinovirus colds. Adults with symptoms of ≤2 days' duration were randomly assigned to intranasal sprays of pirodavir (2 mg per treatment) or placebo six times daily for 5 days. In people with laboratory-documented rhinovirus colds (53 in the pirodavir group, 55 in the placebo group), no significant differences in the resolution of respiratory symptoms were apparent between the groups. The median duration of illness was 7 days in each group. Similarly, scores for individual symptoms found no differences in favor of pirodavir during or after treatment. In contrast, reduced frequencies of rhinovirus shedding were observed in the pirodavir group on day 3 (70 versus 23%; $P < 0.001$) and day 5 (38 versus 12%; $P = 0.002$) but not after the cessation of treatment, on day 7 (19 versus 21%). No pirodavir-resistant viruses were recovered from treated individuals. The pirodavir group had higher rates of nasal dryness, blood in mucus, or unpleasant taste on several study days. In summary, intranasal sprays of pirodavir were associated with significant antiviral effects but no clinical benefit in treating naturally occurring rhinovirus colds.**

Rhinoviruses are the most important etiologic agents causing common colds and are responsible for at least 30 to 50 percent of such illnesses. Although intranasal interferons have been shown to be protective against rhinovirus infection (8), no antiviral agent has been shown to be clinically effective in the treatment of established colds. A number of synthetic compounds have shown in vitro antirhinoviral activity mediated through binding into a hydrophobic pocket within the viral capsid protein VP1 and preventing viral attachment and/or uncoating (2, 4, 12). However, considerable serotype-related differences in potency exist among these agents.

Among these capsid-binding agents, pirodavir (R77,975) has been found to have a high level of potency and a broad spectrum of antirhinoviral activity (3). Inhibition of the replication of 80 percent of serotypes is found at concentrations of 1 μg/ml or less. Previous studies found that frequent intranasal sprays of pirodavir (six times daily) provided protection against experimental rhinovirus colds when administration was begun prior to viral exposure and continued afterward (9). Less frequent administration (three times daily) provided no protection, and early treatment with frequent spraying begun 24 h after rhinovirus challenge was associated with no obvious clinical benefits (9). However, the small number of subjects enrolled in that early treatment study precluded a definitive assessment of pirodavir's therapeutic potential. Consequently, we undertook a randomized, double-blind, placebo-controlled study to determine the efficacy and safety of intranasal pirodavir in treating naturally occurring rhinovirus colds.

## MATERIALS AND METHODS

**Participants.** The trial described here was conducted from August to October 1990. Previously healthy adults aged 18 to 65 years with common cold symptoms of ≤48 h in duration were recruited by advertisement from the University of Virginia community. Individuals with a recent history of wheezing or reactive airway disease, concurrent use of intranasal preparations, or recent severe epistaxis or those with medically important underlying conditions were excluded from participation. Women participants had to have a negative urine pregnancy test on the day of enrollment. The use of concurrent medications was discouraged, but rescue medication for the relief of severe cold symptoms was allowed and recorded. Volunteers provided written informed consent in a form approved by the University of Virginia Human Investigation Committee and were compensated for their participation.

**Drug administration.** Pirodavir at a concentration of 5 mg/ml was formulated in a 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 spray solution consisted of the same excipients. Both were supplied in multiple-metered pump sprayers designed to provide a volume of 100 μl per spray.

Under double-blind conditions, the participants were randomly assigned to receive intranasal sprays of pirodavir or placebo. Treatments consisted of two sprays per nostril (2 mg per treatment) given six times daily at approximately 3-h intervals while the participant was awake for a total of 30 doses. On the first study day, a variable number of doses (three to five doses) was administered depending on the time of enrollment. Consequently, dosing was continued on study day 6 to reach a total of 30 doses over the 6-day period. Study drugs were self-administered by the subjects after receiving instructions on the use of the spray device.

**Clinical monitoring.** The patients recorded symptoms on a diary card which was filled out on a twice-daily basis just prior to the morning and evening doses during the treatment period. Symptoms of upper respiratory tract illness (sneezing, runny nose, nasal stuffiness, dry or sore throat, cough) and cold-associated symptoms (headache, chills, muscle aches, fatigue, malaise, feverishness, and hoarseness) were scored on a 10-point scale. The scores were defined as mild (score of 1, 2, or 3), being noticeable but not bothersome; moderate (score of 4, 5, or 6), being occasionally bothersome but not interfering with daily activities; severe (score of 7, 8, or 9), being frequently bothersome and interfering with daily activities; or very severe (score of 10), being always bothersome and disruptive of daily activities.

Each evening, patients also indicated in their diaries whether or not they felt that they had a cold on that particular study day and assessed the overall severity of the illness and its effects on their daily activities. Subjects were seen at the study center on enrollment and on study days 3, 5, and 7 to check their diary records and to obtain nasal washings for virus isolation. Patients continued to record the presence of cold symptoms up to day 21 or until they indicated that they did not have a cold for at least 2 consecutive days.

Middle ear pressures in each ear were measured prior to treatment initiation on day 1 and again during patient visits on days 3, 5, and 7. This was done with a digital tympanometer as described previously (7, 11). Abnormal middle ear pressure was defined as those ≥+100 or ≤−100 mm of $H_2O$.

Nasal tolerance of topically applied pirodavir was assessed by recording in the diary the occurrence of symptoms of nasal dryness, nasal burning, nasal soreness, blood in mucus, and unpleasant taste. Rhinoscopic examinations for the detection of mucosal erythema or bleeding, erosions, or ulcers were performed at entry into the study and again on study day 7.

**Viral diagnosis and monitoring.** Nasal washings (5 ml of phosphate-buffered saline per nostril) and throat swabs were collected for virus isolation and were combined with chilled viral transport medium. On enrollment these samples

* Corresponding author. Mailing address: Department of Internal Medicine, University of Virginia Health Sciences Center, Box 473, Charlottesville, VA 22908. Phone: (804) 924-5059. Fax: (804) 924-9065.

TABLE 1. Characteristics of rhinovirus-positive patients at enrollment

| Characteristic or outcome | Placebo group | Pirodavir group |
|---|---|---|
| No. of enrolled subjects[a] | 55 | 53 |
| Age (yr [mean ± SD]) | 21 ± 5 | 20 ± 1 |
| % Female | 69 | 64 |
| Time (h) since onset of illness | | |
| Mean ± SD | 24 ± 10[a] | 27 ± 8 |
| Median | 24 | 24 |
| Illness severity (mean symptom score [% of subjects])[b] | | |
| Nasal stuffiness | 2.1 (94) | 2.3 (98) |
| Runny nose | 2.5 (100) | 2.2 (94) |
| Sneezing | 1.7 (91) | 1.7 (98) |
| Cough | 1.3 (81) | 1.6 (94) |
| Sore throat | 1.5 (87) | 1.8 (83) |
| Earache or pressure | 0.7 (50) | 0.9 (64) |
| Headache | 1.1 (68) | 1.1 (70) |
| Chills | 0.4 (31) | 0.5 (36) |
| Muscle ache | 0.4 (52) | 0.8 (49) |
| Fatigue or malaise | 1.5 (93) | 1.7 (92) |
| Feverishness | 0.6 (43) | 0.5 (30) |
| Hoarseness | 1.2 (81) | 1.4 (83) |

[a] $P = 0.05$; placebo versus pirodavir group.
[b] No significant differences in scores at the time of entry existed between the two groups.

were inoculated onto monolayers of human embryonic lung fibroblast (WI-38 strain), A549, primary rhesus monkey kidney, and Ohio HeLa cell monolayers for the recovery of a range of respiratory viruses. Aliquots of nasal washings from days 3, 5, and 7 were frozen at −70°C for later detection of rhinovirus in WI-38 cells from patients whose sample obtained at enrollment was positive by culture. For these samples, the washings were subjected to extraction by dichloromethane (Sigma) to remove residual pirodavir (3, 9).

**In vitro susceptibility testing.** The in vitro susceptibilities of the rhinovirus isolates to pirodavir were determined by an end point dilution assay in the presence of increasing concentrations of pirodavir. Serial fivefold dilutions of pirodavir (final concentrations, 0.003 to 1.950 μg/ml) in HEPES (*N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid)-buffered cell culture medium were added to semiconfluent monolayers of WI-38 cells in 24-well plates. Serial 10-fold dilutions of viral isolates, passaged two or three times in WI-38 cells, were inoculated thereafter. The monolayers were then monitored microscopically for the development of a cytopathic effect for up to 5 days. The lowest concentration of pirodavir that reduced the viral titer by at least 2.0 $\log_{10}$ units compared with that for the nontreated virus control was considered the inhibitory end point.

The results of the assay were compared with the MICs obtained in a previously described cytopathic effect inhibition assay for the selected serotypes (3). The corresponding MICs and the inhibitory end point concentrations averaged 0.026 and 0.015 μg/ml (HRV9), 0.054 and 0.078 μg/ml (HRV9H), 0.587 and 1.95 μg/ml (HRV9M), 0.006 and 0.010 μg/ml (HRV39), and 0.002 and 0.003 μg/ml (HRV Hanks'), respectively. The isolates selected for assay were from patients who continued to shed rhinovirus on days 3, 5, and/or 7. Paired isolates from day 1 and the last day of shedding were tested in parallel under blinded conditions.

**Data analysis.** The study specified that the primary analysis would be restricted to those patients who were positive for rhinovirus infection at enrollment, although secondary analyses were performed on all enrolled subjects for whom data were available (intent to treat). Categorical variables were analyzed by the Cochran-Mantel-Haenszel test, and continuous variables were analyzed by the Wilcoxon rank sum test. For analysis the symptom scores were condensed to a five-point scale consisting of none (score of 0), mild (score of 1), moderate (score of 2), severe (score of 3), and very severe (score of 4). To incorporate changes across time during the treatment period, the area under the curve was calculated for each respiratory symptom and each cold-associated symptom by using the symptom assessment at the time of enrollment as the baseline value. For between-group comparisons, the areas under the curve over the treatment period for each of these symptoms were analyzed by the Wilcoxon rank sum test on the basis of the difference from the baseline score. Two-sided *P* values were used for all analyses.

## RESULTS

**Participants.** No clinically important differences were found in the demographic characteristics of the treatment groups at enrollment (Table 1). Of the 201 participants initially enrolled in the study, symptom data were not available for two subjects in each group because of loss to follow-up and so data for those subjects were not included in the intent-to-treat analysis.

Slightly more than one-half of the subjects with illnesses in each of the placebo and pirodavir groups were positive for rhinovirus at entry into the study (Table 1). The median time from the onset of illness until treatment was administered was 24 h in both groups. Illness severity, as assessed by average total (means, 15 to 16) and individual symptom scores (Table 1) on enrollment, was comparable in the two groups. The frequencies and severity scores for individual symptoms were highest for complaints of nasal stuffiness, runny nose, sneezing, cough, sore throat, hoarseness, headache, and malaise at enrollment (Table 1). The proportions of affected subjects were also comparable between the two treatment groups.

During the treatment phase, the use of medication for the relief of colds symptoms was common in both groups (42% of the placebo recipients and 49% of pirodavir recipients). Acetaminophen (25 and 40% of subjects, respectively) was used frequently but in comparable amounts (on 32 and 31 total days, respectively; for 40 and 41 total doses per group, respectively). Nonsteroidal anti-inflammatory agents (13 and 8% of subjects, respectively) were used more often in placebo recipients (15 and 4 days, respectively; 19 and 4 total doses per group, respectively).

**Compliance.** Compliance was assessed by daily recording of the number of doses used. Overall, 8% of placebo recipients and 3% of pirodavir recipients reported using less than the target number of 30 doses.

In addition, nasal washings from a randomly selected sample of 22 patients (12 in the pirodavir group, 10 in the placebo group) obtained on treatment days 3 and 5 were assayed for pirodavir and its major metabolite (R80044) by a high-performance liquid chromatographic method in the laboratory of R. Woestenborghs (Janssen Research Foundation, Beerse, Belgium). Neither compound was detectable (≤0.025 μg/ml) in the 10 placebo recipients. In contrast, pirodavir was not detectable in only 1 of the 24 samples from the 12 pirodavir recipients. The concentrations in the remaining samples ranged widely, from 0.07 to 35 μg/ml, likely because they were collected at various intervals in relation to the administration of the preceding doses.

**Effect on illness resolution.** In both the placebo and pirodavir groups, significant reductions in symptom severity scores occurred during the treatment period compared with those at enrollment (Fig. 1). Among subjects with rhinovirus-positive illnesses, the largest average reductions in scores occurred for symptoms of runny nose and sneezing and to a lesser extent for those of sore throat, nasal stuffiness, hoarseness, headache, and malaise. However, no differences in the magnitudes of these reductions or in their speed of resolution were apparent between the placebo or pirodavir groups for individual symptoms on any day during or after treatment (Fig. 1). Similarly, no differences favoring pirodavir were found in an intent-to-treat analysis of all subjects (data not shown).

For subjects with rhinovirus-positive colds, the duration of illness (mean ± standard deviation) was 7.3 ± 2.9 days in the patients receiving pirodavir and 7.5 ± 2.9 days in the patients receiving placebo. In addition, the volunteers' ratings of cold severity by day and of the cold's effect on daily activities did not differ between the treatment groups (data not shown). Compared with the mean values at enrollment (pirodavir group, 2.0; placebo group, 2.0), ratings of the cold's adverse effects on activity level had decreased by more than one-half in both groups (pirodavir group, 0.7; placebo group, 0.7) by the last treatment day.

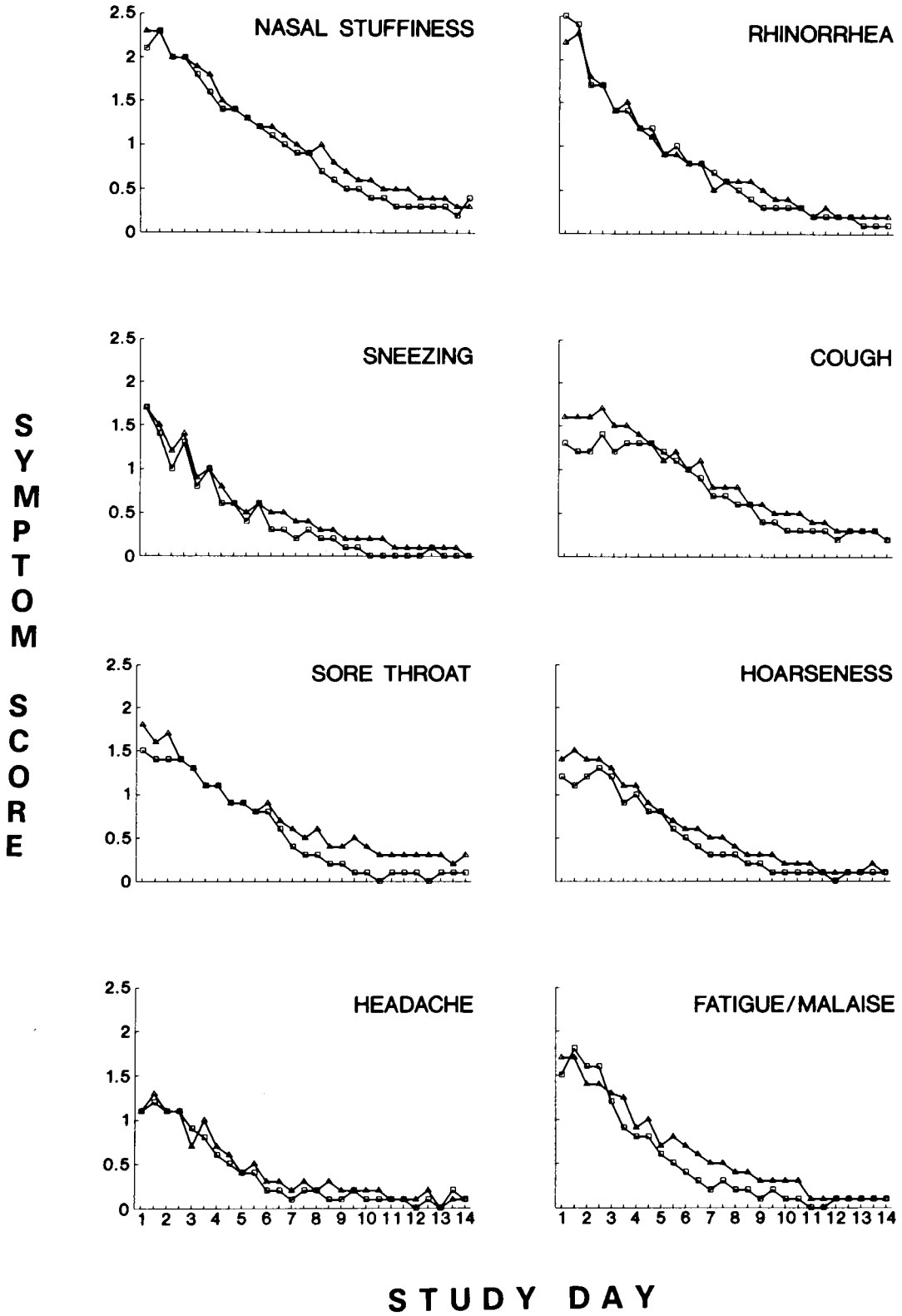


FIG. 1. Resolution of specific respiratory and cold-associated symptoms in subjects with rhinovirus-positive illnesses receiving intranasal pirodavir (△) or placebo (□). The mean score for each symptom is shown for each time point of data collection beginning with the time of entry into the study (day 1). No significant differences in favor of pirodavir were noted for any of these individual symptoms on any treatment day.

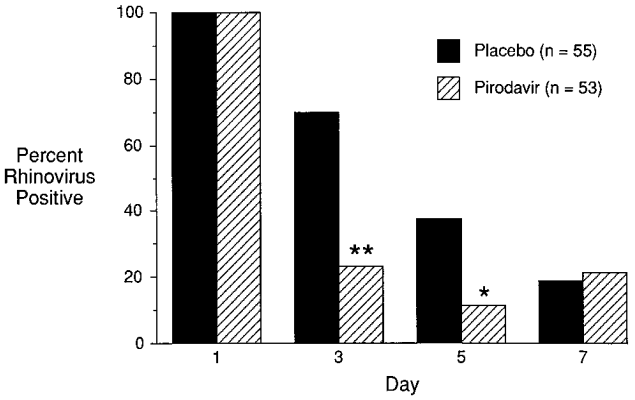


FIG. 2. Frequency of virus recovery from nasal washes in those with rhinovirus colds treated with intranasal pirodavir or placebo. Significant differences in the frequency of virus isolation were present on day 3 (**; $P < 0.001$) and day 5 (*; $P = 0.002$).

Similarly, no important effects were observed in the proportion of patients who had abnormal middle ear pressures during the treatment period. Major abnormalities ($\leq -100$ or $\geq +100$ mm $H_2O$) in middle ear pressures were detected in 24% of placebo recipients and 27% of pirodavir recipients with proven rhinovirus illness on the day of enrollment. The proportions affected did not differ significantly between the groups on day 3 (33% of placebo recipients and 23% of pirodavir recipients), day 5 (18 and 19%, respectively), or day 7 (13 and 10%, respectively). One pirodavir recipient was treated with oral antibiotics for otitis media beginning on study day 15.

**Effect on viral shedding.** In patients from whom rhinovirus was recovered from nasal washings at enrollment (55 in the placebo group, 53 in the pirodavir group), pirodavir was associated with significantly lower rates of rhinovirus recovery compared with that from the placebo group on treatment days 3 and 5 (Fig. 2). The proportion of pirodavir recipients who remained rhinovirus positive was reduced to about one-third of that observed in the placebo group on each of these days. By study day 7, 1 day after the cessation of therapy, approximately one-fifth of the subjects in each of the treatment groups remained rhinovirus positive.

**In vitro pirodavir susceptibility.** A total of 16 pairs of isolates from pirodavir-treated individuals and 34 pairs from placebo-treated individuals were able to be analyzed for their susceptibilities to pirodavir. Of 50 total isolates recovered before drug administration on day 1, 94% were inhibited at concentrations of 0.078 μg/ml and 100% were inhibited at concentrations of 0.39 μg/ml. No difference in the susceptibility distribution between isolates from placebo and pirodavir recipients obtained on study day 1 was apparent (Table 2). Furthermore, susceptibility testing of paired isolates from individual patients detected no instance in which resistant variants appeared to emerge. In each instance the inhibitory concentration for the isolate on the last day of shedding was within 1 fivefold dilution of the value on day 1 (Table 2).

Six pirodavir recipients shed virus persistently through day 7, and for four others recurrent virus was recovered on day 7, after the subjects were negative on days 3 and 5. No decreases in susceptibility were recognized in isolates from these participants obtained on test day 7.

**Tolerance.** Pirodavir administration was generally well tolerated but appeared to be associated with increased frequencies of irritative nasal symptoms and unpleasant taste on several study days (Table 3). The reported frequency of taste perversion was high in both groups, although it was significantly greater in the pirodavir group on 3 treatment days. This complaint decreased in frequency over the treatment period and was generally mild in severity. Blood-tinged nasal mucus was reported on treatment days 4 and 5 by approximately 10% of pirodavir recipients, a fivefold higher rate than that observed in the placebo group. However, the placebo group tended to have a lower frequency of this complaint on the first treatment day (Table 3). Three episodes of severe blood in mucus were recorded in the pirodavir group on the fifth treatment day.

However, nasal examinations detected minor abnormalities on day 7 in similar proportions of individuals in the two groups. Minor nasal mucosal abnormalities (crusting, erosion, punctate bleeding, friability) were detected at enrollment in 62% of placebo recipients and 55% of pirodavir recipients. On study day 7, 44% of placebo recipients and 50% of pirodavir recipients had one or more such abnormalities.

TABLE 2. In vitro susceptibilities of rhinovirus isolates from individuals continuing to shed virus during pirodavir or placebo administration

| Group | Day | Cumulative % of strains inhibited at concn (μg/ml) of: | | | | |
|---|---|---|---|---|---|---|
| | | ≤0.003 | 0.015 | 0.078 | 0.39 | 1.95 |
| Placebo ($n = 34$) | 1 | 9 | 74 | 94 | 100 | |
| | 3, 5, 7[a] | 6 | 68 | 94 | 97 | 100 |
| Pirodavir ($n = 16$) | 1 | 0 | 69 | 94 | 100 | |
| | 3, 5, 7[a] | 6 | 75 | 94 | 100 | |

[a] The last isolate recovered on day 3, 5, or 7 was tested in parallel with the isolate recovered on day 1.

## DISCUSSION

The present study represents the first trial of a capsid-binding antirhinoviral agent in patients with naturally occurring rhinovirus colds. The results indicated that intranasal pirodavir is associated with apparent antiviral effects but no clinical benefits in individuals with proven rhinovirus illness. The findings of the present study were predicted by results obtained in experimentally infected volunteers (9) and help to confirm the

TABLE 3. Symptoms of local intolerance in patients receiving intranasal sprays of placebo or pirodavir

| Symptom | Study day[a] | % of patients | |
|---|---|---|---|
| | | Placebo ($n = 99$) | Pirodavir ($n = 100$) |
| Unpleasant taste | 1 | 45 | 40 |
| | 2 | 51 | 61[b] |
| | 4 | 40 | 53[b] |
| | 5 | 33 | 48[b] |
| | 7 | 23 | 33[b] |
| Blood in mucus | 1 | 4 | 7 |
| | 4 | 2 | 11[c] |
| | 5 | 2 | 10[b] |
| Nasal dryness | 1 | 32 | 32 |
| | 7 | 19 | 33[b] |

[a] Day 1 refers to first day of treatment.
[b] $P \leq 0.05$; placebo versus pirodavir group.
[c] $P < 0.01$; placebo versus pirodavir group.

validity of the human challenge model with regard to the evaluation of antirhinoviral agents. Previous studies of pirodavir and its narrower-spectrum predecessor, R61,837, found that intranasal administration was protective against rhinovirus illness when it was begun prior to viral challenge with a susceptible serotype (1, 9) and, in the case of R61,837, when administration was begun during the incubation period before symptom onset (5). In contrast, when pirodavir (six sprays per day) administration was begun at 1 day after viral challenge, when the subjects were symptomatic, reductions in the frequency of viral shedding but no clinical benefits were found (9). Similarly, very frequent administration of R61,873 (up to 15 sprays per day) after the onset of symptoms was also ineffective and was associated with increased nasal symptoms compared with those after the administration of placebo (1).

The failure of pirodavir to suppress viral recovery completely was consistent with the results observed in the treatment of experimental rhinovirus colds (9). One explanation would be the lack of compliance among pirodavir recipients. However, the results collected from dosing records and from random assay of nasal washings found high rates of compliance. Differences in rhinoviral susceptibility to pirodavir's antiviral action might have accounted for a lack of inhibition of viral recovery in some participants. Studies of in vitro susceptibility by an end point dilution assay found no apparent differences in susceptibility among initial isolates from pirodavir recipients who continued to shed rhinovirus during or following treatment in comparison with that among those from placebo recipients. Importantly, no emergence of drug-resistant variants was found when pre- and posttreatment isolates were compared. This is in contrast to the findings reported for R61,837, in which experimentally infected volunteers often yielded drug-resistant virus (6). The broad antiviral spectrum of pirodavir may relate to binding to conserved amino acid residues within the hydrophobic pocket (1a), and this feature might reduce the likelihood of the emergence of resistance.

The possibility exists that the reduced frequency of virus isolation observed on several treatment days in the present study could have been artificially altered by residual pirodavir in nasal washings, despite the processing measures used to remove it. The reversibility of binding of pirodavir to rhinovirus is serotype dependent. Recovery of viral infectivity can be fully restored or significantly enhanced by dichloromethane extraction for certain rhinovirus serotypes (3), although this may not be true for all rhinovirus serotypes. Since the current study was conducted in subjects with naturally occurring rhinovirus colds, a wide range of serotypes was likely present in the population studied.

One explanation for the discrepancy between antiviral and clinical effects may be that local adverse effects of pirodavir could have masked some degree of clinical benefit. This was observed in a previous study of intranasal interferon treatment of naturally acquired colds (10). Although generally well tolerated, the minor local nasal irritation effects observed with pirodavir may have contributed to its lack of clinical benefit. Another issue is the adequacy of the sample size to detect differences in clinical outcomes. Given the observed changes in runny nose score from enrollment in the placebo group and a two-sided test with an $\alpha$ value of 0.05, the present study had an 80% power to detect a 30% difference with a sample size of 100 per group (intent to treat) and a 50% power for a sample of 50 per group (rhinovirus positive). In addition, the analyses of individual symptoms (Fig. 1) found no evidence of trends toward faster resolution of illness in the pirodavir group.

The discrepancy observed between antiviral activity and clinical effects leaves open the question about the relationship between ongoing viral replication and the persistence of cold symptoms, and it remains unclear whether a more potent antiviral intervention could reduce the length and/or severity of illness in subjects with established colds. Alternative topical formulations of pirodavir or possibly combination therapy with other antirhinoviral agents might enhance the antiviral effects. The observation that symptom scores were highest at enrollment and decreased in both groups thereafter indicates that earlier intervention than is possible by the design of the present study would be desirable. If the participant estimates of the duration of symptoms prior to treatment are accurate (median, 1 day), then the natural history of rhinovirus colds would make this impractical without prospective surveillance.

## REFERENCES


1. **Al-Nakib, W., P. G. Higgins, G. I. Barrow, D. A. J. Tyrrell, K. Andries, G. V. Bussche, N. Taylor, and P. A. J. Janssen.** 1989. Suppression of colds in human volunteers challenged with rhinovirus by a new synthetic drug (R61837). Antimicrob. Agents Chemother. **33:**522–525.

1a. **Andries, K.** Unpublished data.

2. **Andries, K.** Antipicornavirus agents. *In* D. J. Jeffries and E. DeClercq (ed.), Antiviral chemotherapy, in press. John Wiley & Sons, Inc., Sussex, England.
3. **Andries, K., B. Dewindt, J. Snoeks, R. Willebrords, K. Van Eemeren, R. Stokbroekx, and P. A. J. Janssen.** 1992. In vitro activity of pirodavir (R 77975), a substituted phenoxypyridazinamine with broad-spectrum antipicornaviral activity. Antimicrob. Agents Chemother. **36:**100–107.
4. **Arruda, E., and F. G. Hayden.** Clinical studies of antiviral agents for picornavirus infection. *In* D. J. Jeffries and E. DeClercq (ed.), Antiviral Chemotherapy, in press. John Wiley & Sons, Inc., Sussex, England.
5. **Barrow, G. K., P. G. Higgins, D. A. J. Tyrrell, and K. Andries.** 1990. Review. An appraisal of the efficacy of the antiviral R 61837 in rhinovirus infections in human volunteers. Antiviral Chem. Chemother. **1:**279–283.
6. **Dearden, C., W. Al-Nakib, K. Andries, R. Woestenborghs, and D. A. J. Tyrrell.** 1989. Drug resistant rhinoviruses from the nose of experimentally treated volunteers. Arch Virol. **109:**71–81.
7. **Doyle, W. J., T. P. McBride, J. D. Swarts, F. G. Hayden, and J. M. Gwaltney, Jr.** 1988. The response of the nasal airway, middle ear, and eustachian tube to experimental rhinovirus infection. Am. J. Rhinol. **2:**149–154.
8. **Hayden, F. G.** 1988. Intranasal interferons for control of respiratory viral infections, p. 1–16. *In* M. Revel (ed.), Clinical aspects of interferons. Kluwer Academic Publishers, Boston.
9. **Hayden, F. G., K. Andries, and P. A. J. Janssen.** 1992. Safety and efficacy of intranasal pirodavir (R77975) in experimental rhinovirus infection. Antimicrob. Agents Chemother. **36:**727–732.
10. **Hayden, F. G., D. L. Kaiser, and J. K. Albrecht.** 1988. Intranasal recombinant alfa-2b interferon treatment of naturally occurring common colds. Antimicrob. Agents Chemother. **32:**224–230.
11. **McBride, T. P., W. J. Doyle, F. G. Hayden, and J. M. Gwaltney, Jr.** 1989. Alterations of the eustachian tube, middle ear, and nose in rhinovirus infection. Arch. Otolaryngol. Head Neck Surg. **115:**1054–1059.
12. **Sperber, S. J., and F. G. Hayden.** 1988. Chemotherapy of rhinovirus colds. Antimicrob. Agents Chemother. **32:**409–419.