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Intranasal Recombinant Alfa-2b Interferon Treatment of Naturally Occurring Common Colds

FREDERICK G. HAYDEN,[1,2]* DONALD L. KAISER,[1] AND JANICE K. ALBRECHT[3]

Departments of Internal Medicine[1] and Pathology,[2] University of Virginia School of Medicine, Charlottesville, Virginia 22908, and Schering Corporation, Kenilworth, New Jersey 07033[3]

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In a double-blind, placebo-controlled study, patients with naturally occurring common colds of ≤48 h duration were randomly assigned to receive nasal sprays of recombinant alfa-2b interferon at 10 or 20 MU/day or placebo four times per day for 5 days. The 10-MU (n = 74), 20-MU (n = 74), and placebo (n = 72) groups had comparable frequencies of documented rhinovirus colds (50 to 65%) and mean durations of pretreatment symptoms (26 to 27 h). The median duration of colds tended to be longer in the 20-MU group (10 days) than the 10-MU group (8 days) or placebo group (8 days) (P = 0.06). In those with proven rhinovirus colds treated within 24 h, the median duration was significantly longer in the 20-MU group (9 days) than in the placebo group (6 days). No differences favoring interferon treatment were found in respiratory symptom scores or resolution of specific symptoms. On days 5 and 7, nasal washings from compliant subjects with proven rhinovirus colds yielded rhinoviruses more often in placebo (47 and 48%, respectively) than in interferon (15 and 16%, respectively) recipients (P < 0.02), but no differences in new respiratory illness occurrence were observed in household contacts. Interferon recipients had significantly higher frequencies of blood in nasal mucus (16 to 18%) than did placebo recipients (4%) during treatment. Antibiotics for presumed secondary infections were given more often in the 20-MU group (11%) than in the placebo group (0%) (P < 0.01). Nasal sprays of recombinant alfa-2b interferon were not an effective treatment for natural colds and were associated with toxicity.

Intranasal administration of recombinant alfa-2 interferon has been shown to be effective in the prevention of both experimentally induced (6, 13) and naturally acquired (1–3, 8, 11) rhinovirus colds. Prophylactic efficacy against natural rhinovirus colds has been observed at recombinant alfa-2b interferon (rIFN-α_{2b}) doses of 3 to 10 MU/day administered for 3 to 4 weeks during periods of rhinovirus activity in the community (1, 3, 11) and at doses of 5 MU/day administered for 1 week after exposure to common colds in the family setting (2, 8). Earlier we assessed the possible therapeutic effectiveness of rIFN-α_{2b} in a volunteer challenge model in which subjects infected with rhinovirus type 39 were randomly assigned to receive treatment with rIFN-α_{2b} (9 MU) or placebo three times daily for 5 days beginning 28 h after inoculation (7). When administered by nasal drops, rIFN-α_{2b} was associated with significant reductions in the duration and quantity of virus shedding in nasal secretions, as compared with the placebo. Treatment was also associated with approximately 40 to 50% reductions in peak nasal symptom scores and quantities of nasal mucus produced. Since treatment was begun during the incubation period of rhinovirus infection, this study did not assess the value of therapeutic administration after symptoms were established. In addition, an antiviral effect, such as that observed in the challenge study, could be potentially associated with a reduced risk of transmitting infection to contacts or perhaps of secondary complications, such as sinusitis or otitis media. Consequently, a placebo-controlled, double-blind, randomized trial was conducted to evaluate the therapeutic effectiveness of rIFN-α_{2b} in reducing the duration and severity of naturally occurring common colds.

* Corresponding author.

MATERIALS AND METHODS

Study population. This study was conducted from August to October 1985 in facilities of the University of Virginia Student Health Service, the Employee Health Service of the University of Virginia Medical Center, and the Eastern Regional Office of the State Farm Insurance Co. Previously healthy adults aged 18 to 65 years were included if they presented within 48 h of the onset of an upper respiratory tract illness (sneezing, rhinorrhea, nasal congestion, sore throat, hoarseness, cough) which they considered to be a common cold. A history of severe or recurrent nose bleeding, active allergic rhinitis or asthma, pregnancy, and concurrent use of intranasal medications were exclusion criteria. Patients were allowed to enroll in the study only once. Participants were recruited through advertisement and were compensated for participation. Written informed consent in a form approved by the University of Virginia Human Investigation Committee was obtained from all subjects.

Subjects were instructed to avoid the use of other medications which could potentially modify their illness (antihistamines, decongestants) or the action of interferon (aspirin, nonsteroidal antiinflammatory drugs). They were allowed to use acetaminophen for fever or pain relief.

Drug administration. Patients were randomly assigned to receive treatment with rIFN-α_{2b} at 10 or 20 MU/day or placebo for 5 days. Study medications (Schering Corp., Kenilworth, N.J.) were packaged in individual vials containing lyophilized rIFN-α_{2b} (1×10^8 or 2×10^8 IU per vial) stabilized with human albumin (USP) and buffers. When the medications were reconstituted with sterile water, the final concentrations of interferon were 1.25×10^7 or 2.5×10^7 IU/ml, respectively. Thimerosal at a final concentration of 0.002% was included as a preservative. The reconstituted

solutions were previously shown to be stable at room temperature for 1 month (unpublished data, Schering Corp.).

Study medications were administered with a metered pump sprayer (0.05 ml per spray), and the subjects were instructed to use two sprays per nostril four times day (8 a.m., 12 p.m., 4 p.m., 8 p.m.) for a total of 5 days (20 doses). Patients were instructed to clear their nasal passages prior to each dose by blowing their noses. The interferon doses were 2.5 and 5.0 MU per application, and the projected total study doses were 50 and 100 MU per subject, respectively. Compliance was monitored by asking the subjects to record each use of the sprayer on a symptom record card. In addition, the residual volume of study medication was measured when the spray vials were returned.

Symptom assessment. At the initial visit, an assessment of patient symptoms during the previous 3 days was made, and only patients reporting symptoms of less than 48 h duration were admitted to the study. The subjects were asked to record the presence and severity of symptoms (fever, chills, muscle aches, sneezing, runny nose, stopped-up nose, sore or scratchy throat, hoarseness, cough) and an overall subjective assessment of whether or not they had a cold (yes or no) on a daily basis. The severity of specific symptoms was rated on a four-point scale as follows: 0, absent; 1, mild—symptom was minor; 2, moderate—symptom caused noticable discomfort; and 3, severe—symptom caused considerable discomfort and interfered with usual activities. The subjects were also asked to rate the effect that the cold had on their daily activities as follows: no effect; mild effect; moderate effect, indicating difficulty in performing activities; and severe effect, indicating missed work, school, or social activities because of the illness.

On study day 5, the subjects were asked whether they had experienced blood in nasal mucus, nasal burning, or nasal dryness, symptoms which had been associated with interferon toxicity in earlier studies. Nasal exams were performed by the nursing staff on enrollment and on study day 5. The subjects returned to the study center on study days 3, 5, and 7 to have symptom recording monitored and nasal washes collected for viral isolation. Symptom records were maintained for 14 days or longer if the patient continued to report having a cold.

On study days 7 and 14, the subjects were asked to indicate their total number of household contacts (persons sharing the same dwelling) and the number of well contacts who had developed colds.

Viral cultures. On enrollment, nasal washes were collected by instilling approximately 5 ml of lactated Ringer solution per nostril and collecting the effluent in a plastic cup. Four milliliters of nasal wash was combined with 1 ml of fourfold-concentrated beef heart infusion broth containing 5% bovine albumin, 80 μg of vancomycin per ml, 40 μg of gentamicin per ml, and 4 μg of amphotericin B per ml. Throat cultures were collected with cotton-tipped wooden swabs and combined with the nasal washes. Specimens were kept under refrigerated conditions until receipt in the laboratory. After vortexing and removal of the swab, 0.2-ml aliquots were inoculated onto duplicate monolayers of MRC-5 human embryonic lung fibroblast, human embryonic kidney, primary rhesus monkey kidney, and HEp-2 cells. After adsorption for 60 min at 33°C, the monolayers were washed once with Hanks balanced salt solution and refed with appropriate maintenance media. Cell cultures were observed every other day for cytopathic effects for 2 weeks. Hemadsorption testing with guinea pig erythrocytes was performed at 7 and 14 days on the rhesus monkey kidney cells. Rhinoviruses were identified on the basis of typical cytopathic effects and acid sensitivity.

Nasal wash specimens were also collected on subsequent study visits (days 3, 5, and 7) and kept at −70°C. For selected subjects whose initial cultures yielded rhinoviruses, the follow-up specimens were later thawed and cultured on duplicate MRC-5 fibroblast monolayers by using modifications of the method described above. A 1.0-ml sample was combined with 50 to 200 μl of sheep antibody to rIFN-α_{2b} at a final concentration of 10,000 to 40,000 neutralizing units per ml (5). After the specimen was mixed and kept for 30 min at room temperature, 0.2-ml aliquots were inoculated onto the MRC-5 monolayers. After an adsorption period, the monolayers were washed three times with Hanks balanced salt solution prior to the addition of maintenance media. The amount of antibody to rIFN-α_{2b} which was added was based in part on the results of interferon assays on the nasal specimen collected from the patient on that day.

Interferon assay. Interferon concentrations in nasal washes were determined by a previously described bioassay (15) in the laboratory of L. Westreich (Schering Corp.).

Data analysis. Analysis of side effects was conducted for all evaluable subjects. Analysis of efficacy was done for all evaluable subjects, as well as for subsets of subjects in whom a treatment benefit might have been expected. These groups included all subjects with rhinovirus colds, all subjects with rhinovirus colds treated within 24 h of symptom onset, compliant subjects with rhinovirus colds treated within 24 h, and all compliant subjects treated within 24 h of symptom onset. In addition to reviewing the drug administration record for each subject, compliance was defined by a residual measured volume of ≤4.0 ml. The time to resolution of a cold was defined by the number of days between enrollment and the first day on which the subject reported that he or she felt that the cold was no longer present for at least 2 days. The time to resolution of specific symptoms was the number of days from enrollment until the first day the symptom was no longer present for at least 2 days.

Statistical analysis was conducted by using the statistical analysis system on a Digital Equipment Corp. VAX 8300. Means were compared among the three treatment groups by using analysis of variance (in a general linear model), followed by a Duncan multiple-range test. In cases in which additional power was required to minimize type II error, Kruskal-Wallis analysis of variance was used. Analysis of differences in proportions used a chi-square statistic and a Fisher exact test when expected values were <10. For analysis of timed events (e.g., resolution of a symptom), Kaplan-Meier tables were used, followed by either a Gehan-Wilcoxon or log rank statistic, depending on the nature of the distribution of events over time. All P values were two tailed.

RESULTS

Study population. A total of 228 patients, 78 in the placebo group and 75 in each of the interferon groups, were enrolled (Table 1). Eight subjects (six placebo and two interferon) prematurely stopped dosing with the study medication and did not return for the scheduled visits. Consequently, 74 patients in the 10-MU and 20-MU rIFN-α_{2b} groups and 72 patients in the placebo group were evaluable for efficacy. The treatment groups were comparable with respect to sex distribution, age, proportion of smokers, duration of cold symptoms, initial severity of cold symptoms at enrollment, proportion of rhinovirus-positive colds, and volume of resid-

TABLE 1. Demographic characteristics of the study population

Parameter	Data for indicated treatment group:		
	rIFN-α_{2b}		Placebo
	10 MU/day	20 MU/day	
Total no. enrolled	75	75	78
No. of dropouts	1	1	6
No. of evaluable subjects	74	74	72
No. of males/females	21/53	26/48	25/47
Age (yr, mean ± SD)	25 ± 8	26 ± 9	25 ± 9
No. (%) of smokers	15 (20)	10 (14)	17 (19)
Duration of colds prior to therapy (h, mean ± SD)	27 ± 10	27 ± 9	26 ± 11
Symptom score on enrollment (mean ± SD)	10 ± 4	11 ± 4	10 ± 5
No. (%) rhinovirus positive	37 (50)	48 (65)	44 (61)
Residual volume (ml, mean ± SD)	3.1 ± 1.2	3.0 ± 1.1	3.0 ± 1.1
No. of subjects taking concurrent medication:			
Acetaminophen	23	23	26
ASA, NSAIDS	6	8	8
Antihistamines	3	3	2
Decongestants	6	4	3

ual study drug at the end of the dosing period. One subject in the placebo group had a parainfluenza virus isolated. Compliance with the dosing regimen was comparable in each group; 82 to 84% of each group had residual volumes of ≤4.0 ml, and 85 to 88% reported using at least 20 doses of the study drug.

Concurrent use of medications which could alter symptom reporting was common. Acetaminophen-containing products were used by approximately one-third of the subjects. Other symptom treatments were used much less commonly and by similar proportions in each of the groups (Table 1).

Duration of colds. The effect of treatment on the duration of colds was assessed by comparing the proportion of each group who indicated that they felt that they had a cold on each treatment day and by determining the time to disappearance of the colds (Table 2). No significant differences favoring interferon were found when the proportions of patients with colds on each day were compared for all enrolled subjects and for those with rhinovirus-positive colds (Fig. 1). For each comparison, the 20-MU interferon group did less well than the placebo group. For all subjects, the median time to the subjective resolution of the colds was 8 days in the 10-MU and placebo groups, as compared with 10 days in the 20-MU group ($P = 0.06$ versus the placebo), and significantly more 20-MU recipients reported colds on days 5, 8, and 9 than did placebo recipients. Similar differences in the median time to disappearance of the colds were seen in the selected patient groups who would be expected to benefit from treatment (Table 2). The subjects most likely to benefit would be those who had rhinovirus-proven colds of ≤24 h duration and who complied with the drug regimen. Even in this subset of patients, the median time to resolution was 3 days longer in 20-MU recipients (9 days) than in placebo recipients (6 days) ($P = 0.02$).

Symptom resolution. The average symptom scores for each study day during the 2 weeks following enrollment were compared between the treatment groups for all recorded symptoms and for nasal symptoms (sneezing, runny nose, stopped-up nose). No significant differences indicative of a treatment benefit were observed (data not shown). The 10-MU recipients had values similar to those of the placebo recipients, whereas the 20-MU recipients had higher total symptom scores on study days 6 through 9. In compliant subjects treated within 24 h, the scores for sore throat (days 6 to 8) and stopped-up nose (day 5) were significantly higher in the 20-MU group than in the placebo group. No beneficial treatment effect was found when activity levels were compared (data not shown).

Similarly, no treatment benefit was observed when the times to disappearance of individual respiratory symptoms were compared for groups of subjects who would likely benefit from treatment (Table 2). The time to disappearance of runny nose, stopped-up nose, and particularly sore throat tended to be longer in the 20 MU-group than in the corresponding placebo group. Symptoms of sneezing, cough, or hoarseness did not appear to be adversely affected or benefited by interferon administration.

Adverse reactions. On study day 5, nasal exams detected mucosal abnormalities of punctate bleeding or erosion in similar proportions of subjects in each of the treatment groups (Table 3). The only ulceration observed was in a 20-MU rIFN-α_{2b} recipient. When subjects were directly

TABLE 2. Time to resolution of colds and specific respiratory tract symptoms in selected patient groups

Group	Treatment (MU/day)	No. of patients[a]	Median no. of days to disappearance of:						
			Cold	Sneezing	Runny nose	Stopped-up nose	Sore throat	Cough	Hoarseness
Rhinovirus colds, all subjects	10	37	9.0	4.0	6.0	8.0	5.0	6.0	5.0
	20	48	10.0[b]	5.0	7.0	9.0	5.5	6.0	5.0
	0	44	6.5	4.0	6.0	6.0	5.0	8.0	5.0
Colds, ≤24 h, compliant subjects	10	39	6.0	4.0	5.0	7.0	4.5	6.0	5.0
	20	34	9.0	5.0	8.0	9.0	8.5[c]	6.0	5.0
	0	38	6.5	4.0	6.0	5.0	4.5	7.0	5.0
Rhinovirus colds, ≤24 h, compliant subjects	10	18	6.5	4.0	5.0	7.5	4.5	6.0	5.0
	20	24	9.0[d]	4.0	6.5	8.5	8.0[e]	6.0	5.0
	0	22	6.0	4.0	4.0	5.0	3.0	7.0	5.0

[a] All subjects in a group were evaluable for time to resolution of the cold. Subjects not reporting a particular symptom were dropped from the analysis for that symptom.
[b] $P = 0.02$ versus placebo (Wilcoxon test).
[c] $P = 0.06$ versus placebo (log rank test).
[d] $P = 0.02$ versus placebo (Wilcoxon test).
[e] $P = 0.01$ versus placebo (log rank test).

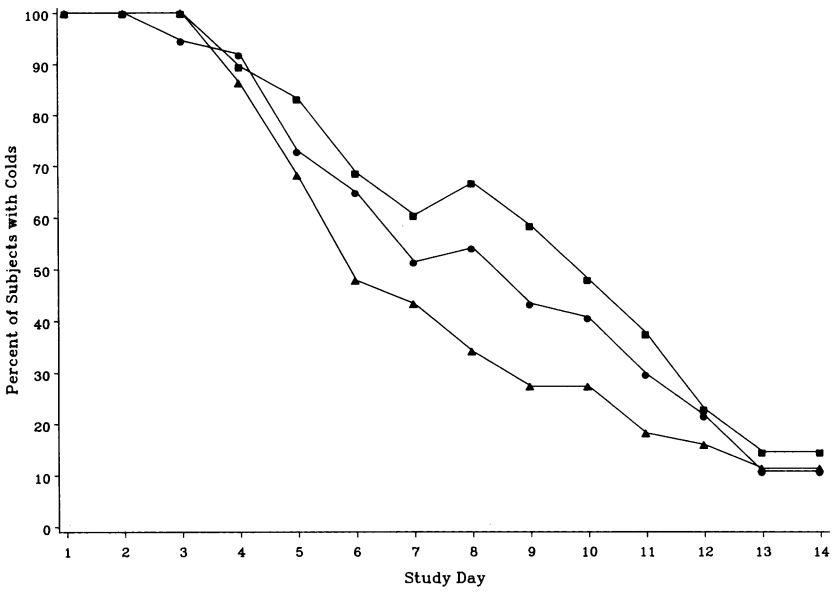

FIG. 1. Resolution of colds based on the subjects' assessments. The percentages of subjects indicating that they had colds are indicated for each study day by treatment group for those with documented rhinovirus colds. The 20-MU rIFN-α_{2b} group differed significantly from the placebo group on days 6, 8, and 9. Symbols: ●, 10 MU/day; ■, 20 MU/day; ▲, placebo.

questioned on day 5 about the occurrence of irritative symptoms during the treatment period, no differences in the proportions of subjects with complaints of nasal dryness or nasal burning were found (Table 3). In contrast, the proportions of subjects reporting blood in nasal mucus in the 10-MU rIFN-α_{2b} group (16%) and in the 20-MU rIFN-α_{2b} group (18%) were significantly higher than in the placebo group (4%). During the 2 weeks after enrollment, blood in nasal mucus or nasal bleeding was reported by 19% of 10-MU and 24% of 20-MU interferon recipients, as compared with 6% of placebo recipients ($P < 0.02$ versus either interferon group).

Provoked or spontaneous epistaxis developed in one 10-MU, seven 20-MU, and two placebo recipients. In contrast to the other groups, four of the 20-MU interferon recipients had epistaxis that occurred after the end of the treatment period. These episodes were usually rated as mild in severity and generally resolved on the same day, except for three 20-MU interferon recipients who had one or more recurrences.

Bacterial complications. Subsequent to enrollment in the study, a total of 18 subjects had antibiotics prescribed by their personal physicians for presumed bacterial infections. Three subjects in the 20-MU group, two in the 10-MU group, and two in the placebo group had antibiotics prescribed for proven or suspected streptococcal pharyngitis. Oral antibiotics were prescribed for other indications in eight (10%) patients in the 20-MU group (bronchitis, four; sinusitis, two; otitis media, one; conjunctivitis, one) and in four (5%) patients in the 10-MU group (otitis media, one; bronchitis, one; bronchitis and otitis media, one; possible sinusitis, one) but in no subjects in the placebo group ($P < 0.01$ for placebo versus interferon at 20 MU) (Table 4). In the majority of suspected bacterial superinfections in both the 10-MU and 20-MU interferon groups, rhinoviruses were isolated from the initial specimens (9 of 12), and the superinfections were identified during the week following the completion of interferon administration (7 of 12) (Table 4).

Virus shedding. Follow-up specimens from rhinovirus-positive subjects who initiated treatment within 24 h of symptom onset and who were compliant with the dosing regimen were available for 17 of the 10-MU, 24 of the 20-MU, and 22 of the placebo recipients. Approximately one-half of the placebo group continued to have recoverable virus on follow-up cultures through day 7 (Fig. 2). Approximately one-third of the subjects in either interferon group were virus positive on day 3, but less than one-fifth were virus positive on day 5 or 7. No dose-related differences were apparent between the two interferon groups, and so they were combined for analysis. Overall, 6 of 40 interferon-treated subjects (15%) and 9 of 19 placebo-treated subjects (47%) were virus positive on day 5 ($P < 0.02$). On study day 7, 6 of 38 interferon-treated subjects (16%) and 10 of 21 placebo-treated subjects (48%) were virus positive ($P < 0.02$).

Since residual interferon in nasal wash samples can inhibit the in vitro recovery of rhinoviruses (5, 12), samples of nasal

TABLE 3. Adverse nasal reactions during the treatment period

Reaction	% of subjects[a] with indicated reaction to:		
	rIFN-α_{2b} at:		Placebo (n = 72)
	10 MU/day (n = 74)	20 MU/day (n = 74)	
Symptom (days 1 to 5)			
Blood in mucus	16[b] (6)	18[c] (7)	4 (1)
Nasal dryness	16 (9)	18 (8)	21 (10)
Nasal burning	12 (8)	14 (9)	10 (3)
Nasal exam abnormality (day 5)			
Mucosal bleeding	9	8	6
Erosion	5	4	4
Ulcer	0	1	0

[a] Numbers in parentheses represent the percent of treatment days 1 to 5 on which the volunteer reported a specific symptom.
[b] $P < 0.02$ versus the placebo.
[c] $P = 0.02$ versus the placebo.

TABLE 4. Use of antimicrobial drugs for suspected bacterial complications

Group	Diagnosis	Days after enrollment	Rhinovirus isolation	Antibiotic
Placebo	None			
rIFN-α_{2b} at 10 MU/day	Bacterial upper respiratory tract infection or sinusitis	6	+	Ampicillin
	Otitis media or bronchitis	4	+	Trimethoprim-sulfamethoxazole
	Bronchitis	15	−	Erythromycin
	Otitis media	7	+	Ampicillin
rIFN-α_{2b} at 20 MU/day	Sinusitis	7	+	Amoxicillin
	Sinusitis[a]	9	+	Erythromycin
	Bronchitis	3	+	Amoxicillin
	Bronchitis	9	+	Tetracycline
	Otitis media	5	−	Ampicillin
	Bronchitis	9	+	Erythromycin
	Bronchitis	12	−	Erythromycin
	Conjuctivitis	16	+	Sulfacetamide

[a] Self-diagnosis and medication.

washings from the patients described above were assayed for interferon. In placebo recipients, interferon activity was detected in 3 of 21 samples on day 3 and in no samples on day 5 or 7. The levels in the three positive nasal washes were 38, 38, and 75 U/ml. Interferon at ≥75 U/ml was demonstrable in all but two samples collected from interferon recipients on days 3 and 5. In the 17 subjects receiving 10 MU/day, the median (range) interferon concentrations in the nasal wash samples were 11,600 (150 to 38,400) U/ml on day 3, 2,400 (75 to 38,400) U/ml on day 5, and <75 (<75 to 4,800) U/ml on day 7. In the 24 subjects receiving 20 MU/day, the median (range) interferon concentrations were 19,200 (<75 to 153,600) U/ml on day 3, 19,200 (<38 to 153,600) U/ml on day 5, and 75 (<38 to 38,400) U/ml on day 7.

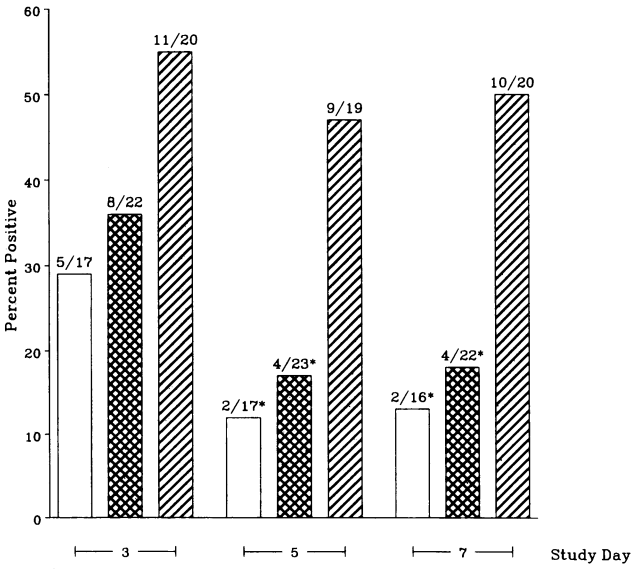

FIG. 2. Recovery of rhinoviruses from the respiratory secretions of compliant subjects who initiated treatment within 24 h of symptom onset. All of these subjects were rhinovirus positive on enrollment. The percentage of virus-positive subjects was significantly ($P < 0.05$) lower on day 5 or 7 in either interferon group than in the placebo group (indicated by asterisks). Symbols: ▭, 10 Mu/day; ▩, 20 MU/day; ▨, placebo.

Illness in contacts. At the time of enrollment, the proportions of household contacts with acute respiratory illness were similar in the 10-MU (30 of 131, 23%), 20-MU (31 of 140, 22%), and placebo (22 of 125, 18%) groups. The proportions of well contacts who developed respiratory illnesses were comparable in the three treatment groups on day 7 (12, 13, and 16%, respectively) and day 14 (3, 3, and 4%, respectively). When analyzed by household, respiratory illnesses developed during the 2-week period in one or more well contacts in 22% of 54 households of 10-MU recipients, 28% of 53 households of 20-MU recipients, and 19% of 57 households of placebo recipients. Similar results were found when the data from only college student participants were analyzed (data not shown).

DISCUSSION

This study found that intranasal rIFN-α_{2b} treatment of naturally acquired common colds was not associated with significant symptom benefit when compared with placebo treatment. Even in the subjects most likely to benefit from interferon therapy, specifically, those treated early in the course of proven rhinovirus infections, no reductions in symptom severity or duration favoring interferon were recognized. Indeed, the 20-MU/day interferon recipients had a more prolonged duration of colds and more pronounced respiratory symptoms, especially sore throat and stopped-up nose, than did placebo recipients. As discussed below, these findings are probably related to local interferon intolerance. In compliant subjects with proven rhinovirus colds of short duration, an antiviral effect of interferon was demonstrated by a decreased frequency of virus shedding at 5 and 7 days after the onset of treatment, as compared with the frequency of virus shedding in the placebo group. The frequency of virus isolation on day 5 could have been artificially reduced by the very high interferon concentrations present in some samples, despite the processing measures used (5). In contrast, the day-7 samples generally had low interferon concentrations, which should have been removed by the anti-rIFN-α_{2b} antibody. However, the observed antiviral effect was incomplete, and some interferon recipients remained virus positive during and after treatment. Although a decrease in the frequency of virus recovery could indicate a reduced risk of transmitting infection to contacts, no decrease in episodes of respiratory illnesses were recognized in

healthy household contacts of interferon recipients. However, this analysis was limited by the fact that the day of onset and the etiology of respiratory illnesses in the household contacts were not established. It is possible that their illnesses represented coprimary infections, were acquired in other settings, or were due to other causes.

The findings in this study with respect to antiviral activity but lack of symptom benefit were predicted by the results of earlier volunteer model studies which utilized high rIFN-α_{2b} doses (27 MU/day) beginning during the incubation period of experimental rhinovirus infection (7). In these studies, reductions in virus shedding but no symptom relief were seen when interferon was given by nasal spray. When given by nasal drops, decreases in viral titers, in the duration of virus shedding, and in peak nasal symptoms were observed. Since the current study enrolled patients who were already symptomatic for 1 to 2 days, it is not surprising that the interferon nasal spray afforded no symptom benefit. Perhaps administration of interferon by nasal drops or in combination with other agents that may improve its distribution or retention in the nasal passages could alter its activity. However, the relationship between ongoing viral replication and the pathogenesis of cold symptoms is uncertain, and it remains an open question whether a more potent antiviral effect could reduce illness in established colds.

Intranasal rIFN-α_{2b} was also associated with discernible local adverse effects when used for short-term treatment of common colds. Intolerance was manifested in part by an increased frequency of reports of blood in nasal mucus in the interferon recipients as compared with the placebo recipients. In contrast to results in studies in which interferon was used for prophylaxis of healthy subjects (1–3, 8, 9, 11), bleeding episodes tended to occur earlier and with greater frequency in the current trial. Intranasal rIFN-α_{2b} induces chronic lymphocytic infiltration in the nasal mucosa of healthy adults (10). Such inflammatory changes occur as early as 4 days after the initiation of exposure and may relate to the immunomodulating effects of interferon (4). In the current study, it appears that the irritative effects of intranasal interferon were enhanced by concurrent infectious rhinitis. This interaction may relate in part to infection-mediated reductions in the mucociliary clearance (14) of interferon.

In addition, the 20-MU interferon group had a significant excess of apparent secondary complications for which antibiotics were prescribed (11% of subjects), as compared with the placebo group (0%). The reasons for this excess rate in interferon recipients are unclear, but the likelihood that these patients were simply allocated to the high-dose interferon group by chance was less than 1 in 100. Furthermore, most of the episodes occurred during the week after the completion of interferon administration. It is possible that effects on mucociliary clearance of the cold, in conjunction with the adverse mucosal effects of interferon, led to this apparent increased risk of complications. It is possible that interferon affected the colonization of the upper respiratory tract by potential pathogens. However, no bacteriologic studies were performed in this study, and prescription drug use cannot be construed as a specific measure of bacterial infection. The proportions of affected subjects in the two interferon groups with presumed sinusitis (2%) or otitis media (2%) were similar to the rates of sinusitis (~0.5%) or otitis media (~2%) reported in adults with common colds (4). Three of four high-dose interferon patients treated for bronchitis had rhinoviruses isolated from their initial specimens, and it is clear that intranasal interferon did not prevent the development of lower respiratory tract illnesses in these individuals. Thus, although it is uncertain whether interferon treatment caused an increased risk of secondary bacterial infections in the current study, the results clearly indicate that the treatment did not prevent such complications.

In summary, intranasal sprays of rIFN-α_{2b} were not associated with a reduced duration or severity of symptoms in naturally occurring rhinovirus colds. The failure to observe a therapeutic benefit did not appear to be due to a lack of compliance but was related in part to the local toxicity of intranasal interferon. Although an antiviral effect was demonstrable in subjects with proven rhinovirus colds, no reduced risk of illness was found in their household contacts. Furthermore, a significant excess of apparent secondary bacterial complications was found in the high-dose interferon recipients. Intranasal rIFN-α_{2b} was ineffective as single-agent therapy for common colds and was associated with clinically significant toxicity.

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