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Antiviral Research, 3 (1983) 121–136
Elsevier

An effective dosage regimen for prophylaxis against rhinovirus infection by intranasal administration of HuIFN-α_2*

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(Received 25 February 1983; accepted 14 March 1983)

Before the prophylactic effect of human interferon α_2 (HuIFN-α_2) can be tested against naturally acquired rhinovirus infection in a large-scale field trial, it is desirable to show that self-administration of the drug is practical, and to determine the smallest well-tolerated dose likely to produce a worthwhile effect. Here we report that self-administered intranasal interferon can be effective, and show how prophylaxis against rhinovirus infection is affected by both the quantity of interferon, and the interval between a dose and virus challenge. Finally, the medication regimen suggested for use in field trials (3.85 MU 3 times/day) was tested in a double-blind, placebo-controlled trial in volunteers. Although virus challenge was at a time when those being treated with interferon would be most susceptible, a substantial protective effect was still demonstrated.

interferon; prophylatis; rhinoviruses infection; volunteer studies

Introduction

Most people experience 1 to 3 colds each year, and some patients may develop severe lower respiratory tract disease with a cold, for example children with wheezy bronchitis and sufferers from chronic bronchitis [4, 6]. Up to 50% of colds are caused by rhinoviruses [5], and a means of preventing rhinovirus colds would be of considerable value in clinical practice. Volunteer trials at the Common Cold Unit have shown that human interferon α_2 (HuIFN-α_2) produced by recombinant DNA techniques in

* This work was supported by the Medical Research Council of Great Britain, and the Schering-Plough Corporation.

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Escherichia coli, when administered by a physician, is highly effective in protecting against rhinovirus infection [8].

In a large-scale field trial of prophylaxis against naturally acquired rhinovirus infection administration by physician would not be practicable, so that before such a trial is undertaken, the interferon must be shown to be effective after self-administration by intranasal spray. In addition, the minimal dose likely to produce a worthwhile prophylactic effect must be determined both in the interest of economy, and to minimise the likelihood of side effects. Here we report a series of experiments in which the protective effect of various dose regimens of HuIFN-α_2 against experimental rhinovirus infection was examined.

Materials and methods

The studies were approved by the Ethical Committee of Northwick Park Hospital, Harrow.

Study design

Results were accumulated from a series of 10 day trails, each involving 20 to 30 volunteers. Healthy volunteers of both sexes, aged 18 to 50 yr were recruited, screened for suitability, and housed in isolation in groups of 2 to 3 at the Common Cold Unit according to our usual procedure [2]. Initial blood samples were taken for haematological and biochemical tests, including estimation of electrolytes, and to provide serum for the determination of neutralising antibody to human rhinovirus types 9 (HRV9) and 14 (HRV14). Volunteer accomodation units (flats) were divided into 2 groups so that the occupants were matched for age and sex. One group was allocated to interferon treatment, and the other to placebo administration. This procedure reduced the risk of treatment error by ensuring that only one treatment schedule was represented in each flat. On every trial, the occupants of 1 or 2 flats in each group were challenged with saline; the remaining volunteers were given nasal drops containing HRV9, followed 1 h later by HRV14 (geometric mean doses calculated from back titration were 50 $TCID_{50}$ and 190 $TCID_{50}$, respectively).

Interferon or placebo treatment started on the day before virus (or saline) challenge, and continued for 4 days. A further blood sample was obtained for haematology and biochemistry at the end of the 10-day period to look for any changes which could be attributed to medication.

The clinical effects were monitored by an observer unaware of the allocation of the volunteers. Each volunteer was assessed daily, and given a daily score on the basis of signs and symptoms [2]. Clinical responses were graded as nil, doubtful, very mild, mild, moderate or severe colds. Paper handkerchiefs used by volunteers were weighed in order to estimate daily nasal secretion [2]. Nasal washings for virus isolation were collected 2 days prior to, and on days 2 to 6 after virus challenge. Further serum samples were requested from the volunteers 2 wk after leaving the Unit. These were titrated in parallel with the initial samples for the estimation of neutralising antibodies

to HRV9 and HRV14. Volunteers were excluded from the trial if they developed signs of a cold before virus challenge, or if an external rhinovirus was recovered from their pre-challenge nasal wash sample.

Medication

HuIFN-α_2 (Schering-Plough) purified to >100 mega units (MU)/mg protein was dissolved in phosphate buffered saline (PBS), stabilised with 2 mg/ml of human serum albumin, and lyophilised; the placebo was lyophilised human serum albumin in PBS. Both were reconstituted with distilled water. The Schering-Plough intranasal spray was used, which delivers 50–60 µl/activation. Both interferon and placebo were kept for a maximum of 48 h at +4°C, except in the final trial when interferon was given 3 times/day. On this occasion merthiolate, 0.05 mg/ml was added as a preservative, and both the interferon and placebo preparations were kept for the whole period of medication in the dark at room temperature. Volunteers were familiarised with the sprays (containing PBS) on the day before medication began. The volume of solution delivered during medication was determined by weighing the sprays before and after use, and this information was used to calculate the mean quantity of interferon in each dose. One dose always consisted of 2 activations of the spray/nostril, and when the frequency of medication was <4 times/day, each dose was supervised by a physician.

Virological procedures

The nasal wash samples collected were tested for the presence of rhinoviruses in HeLa Cells (0 strain). All virus-negative washes were re-tested after the addition of an equal volume of anti-human leucocyte interferon antibody diluted to contain 10^4 neutralising U/ml (kindly supplied by Dr. K. Fantes of the Wellcome Research Laboratories, Beckenham, Kent). At least one isolate from each infected volunteer was tested using a mixture of antisera to HRV9 and HRV14, and neutralisation was demonstrated; external rhinoviruses were recognised by the characteristic cytopathic effect, and acid lability. Serum neutralising antibodies to HRV9 and HRV14 were estimated using a micromethod previously described [7].

Statistical methods

Differences in the frequency of colds, virus isolations and antibody rises were tested for significance using the χ^2 test with Yates' correction. Clinical score, nasal secretion and virus excretion data were evaluated using the Mann-Whitney U test.

Results

Virus challenge studies

In pharmacokinetic studies the Schering-Plough spray produced intranasal levels

TABLE 1

Clinical and laboratory findings in volunteers treated with intranasally, self-administered interferon (2.28 MU/dose; 4 doses daily for 4 days) and challenged with rhinoviruses 9 and 14, 2 and 3 h after fifth interferon dose

Treatment	Stratification of volunteers by pre-challenge immune status		Number of volunteers with clinically diagnosed colds		Number of volunteers with positive laboratory findings		
	Antibody titre[a]	Number	Mild or worse	Very mild or none	Rise in antibody titre to HRV9 and/or HRV14	Virus isolation	Either or both
Interferon	<2	8	0	8	1	6	6
	2–8	2	0	2	2	1	2
	>8	1	0	1	0	0	0
	Total	11	0	11	3	7	8
Placebo	<2	4	2	2	3	4	4
	2–8	6	1	5	5	5	5
	>8	4	3	1	3	4	4
	Total	14	6 (< 0.05)[b]	8	11 (< 0.05)	13 (> 0.05)	13 (> 0.05)

[a] Neutralising antibody titre to HRV9 or HRV14, whichever was lower.

[b] *P*-level for statistical significance between interferon and placebo-treated groups.

of interferon similar to those achieved with the Risdon gun (Davies et al., in press). We therefore chose this spray to examine the protective effect of interferon self-administered by volunteers. In a placebo-controlled trial, medication was given 4 times/day (8 a.m., 1, 6 and 10 p.m.) for 4 days. Virus challenges were given 2 and 3 h after the 5th dose. The mean quantity of HuIFN-α_2 in each dose was 2.28 MU.

The results of virus challenge are summarised in Table 1. There were no mild, moderate or severe colds amongst 11 interferon recipients, as compared to 6 mild or worse colds in 14 placebo recipients ($P < 0.05$). The number of volunteers who produced one or more virus-positive nasal wash samples (virus shedders) was reduced in the interferon as compared to the placebo group (but not significantly). However, the incidence of antibody rises was reduced significantly ($P < 0.05$). There were also large and significant reductions in clinical score and nasal secretion; the proportion of volunteers excreting virus was reduced significantly on days 2 to 4 after challenge (Fig. 1).

In a further placebo-controlled trial, we investigated the protective effect of a lower daily dose. A calculated dose of 2.28 MU (or placebo) was given once a day at 8 a.m. starting on the day before virus challenge and continuing for 4 days. Volunteers were challenged with virus 2 and 3 h after the second dose.

There were no mild or worse colds amongst 9 interferon recipients, as compared to 8

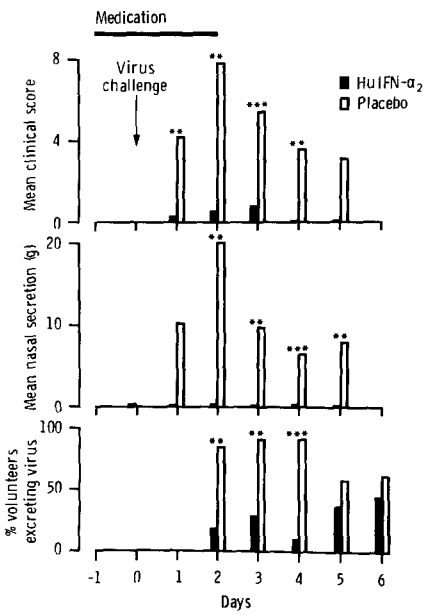

Fig. 1. Clinical score, nasal secretion and virus excretion in volunteers treated intranasally with interferon and challenged with HRV9 and 14. HuIFN-α_2, 2.28 MU was self-administered 4 times/day for 4 days. Virus challenges were given 2 and 3 h after the fifth dose. Asterisks indicate level of statistical significance between interferon and placebo-treated groups: * = $P <$ 0.05; ** = $P < 0.01$; *** = $P < 0.001$.

TABLE 2

Clinical and laboratory findings in volunteers treated with intranasally, self-administered interferon (2.28 MU/dose; 1 dose daily for 4 days) and challenged with rhinoviruses 9 and 14, 2 and 3 h after the second interferon dose

Treatment	Stratification of volunteers by pre-challenge immune status		Number of volunteers with clinically diagnosed colds		Number of volunteers with positive laboratory findings		
	Antibody titre[a]	Number	Mild or worse	Very mild or none	Rise in antibody titre to HRV9 and/or HRV14	Virus isolation	Either or both
Interferon	<2	4	0	4	3	4	4
	2–8	1	0	1	0	1	1
	>8	4	0	4	1	2	2
	Total	9	0	9	4	7	7
Placebo	<2	6	5	1	6	6	6
	2–8	3	3	0	2	3	3
	>8	2	0	2	2	2	2
	Total	11	8 (< 0.01)[b]	3	10 (> 0.05)	11 (> 0.05)	11 (> 0.05)

[a] Neutralising antibody titre to HRV9 or HRV14, whichever was lower.

[b] *P*-level for statistical significance between interferon and placebo-treated groups.

in 11 placebo recipients ($P < 0.01$; Table 2). Although there were fewer volunteers with antibody rises, and virus shedders in the interferon than in the placebo-treated group, these reductions did not reach statistical significance. However there were large and significant reductions in clinical score and nasal secretion, which were accompanied by a significant reduction in the proportion of volunteers excreting virus on day 2 after challenge (Fig. 2).

That prophylaxis was successful in this trial, in spite of the reduced dose of interferon may have been because virus challenge closely followed the second dose. To investigate this possibility, we repeated the study with an interval of 13 to 14 h between the second interféron dose and the virus challenge. There was a similar response to challenge with HRV9 and HRV14 in both the interferon and placebo-treated groups (Table 3). Although there were fewer colds and antibody rises in the interferon-treated group, these reductions were not significant. There was no significant difference between the two groups in either clinical score, nasal secretion or virus excretion, nor was there a consistent trend in any variable to suggest a prophylactic effect of interferon (Fig. 3). We therefore concluded that the treatment had no detectable protective effect in this trial.

We next examined how well volunteers were protected against rhinovirus challenge by various doses of HuIFN-α_2. In this experiment all volunteers were given interferon (mean quantity in each dose 0.0218, 0.223 or 2.37 MU) twice daily at 8 a.m. and 8 p.m. Interferon given either before or after virus challenge might be expected to protect. If

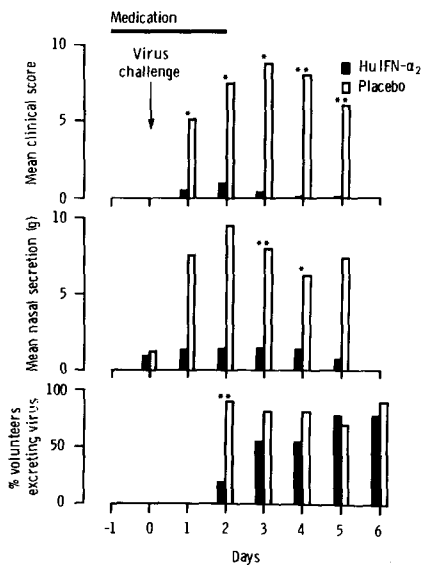

Fig. 2. Clinical score, nasal secretion and virus excretion in volunteers treated intranasally with interferon and challenged with HRV9 and 14. HuIFN-α_2, 2.28 MU was self-administered once/day for 4 days. Virus challenges were given 2 and 3 h after the second dose. Asterisks indicate levels of statistical significance between interferon and placebo-treated groups: * = $P <$ 0.05; ** = $P < 0.01$.

TABLE 3

Clinical and laboratory findings in volunteers treated with intranasally, self-administered interferon (2.28 MU/dose; 1 dose daily for 4 days) and challenged with rhinoviruses 9 and 14, 13 and 14 h after the second interferon dose

Treatment	Stratification of volunteers by pre-challenge immune status		Number of volunteers with clinically diagnosed colds		Number of volunteers with positive laboratory findings		
	Antibody titre[a]	Number	Mild or worse	Very mild or none	Rise in antibody titre to HRV9 and/or HRV14	Virus isolation	Either or both
Interferon	<2	7	1	6	4	7	7
	2–8	1	0	1	1	1	1
	>8	0	0	0	0	0	0
	Total	8	1	7	5	8	8
Placebo	<2	7	3	4	5	7	7
	2–8	1	0	1	1	1	1
	>8	1	0	1	1	0	1
	Total	9	3 (> 0.05)[b]	6	7 (> 0.05)	8 (> 0.05)	9 (> 0.05)

[a] Neutralising antibody titre to HRV9 or HRV14, whichever was lower.

[b] *P*-level for statistical significance between interferon and placebo-treated groups.

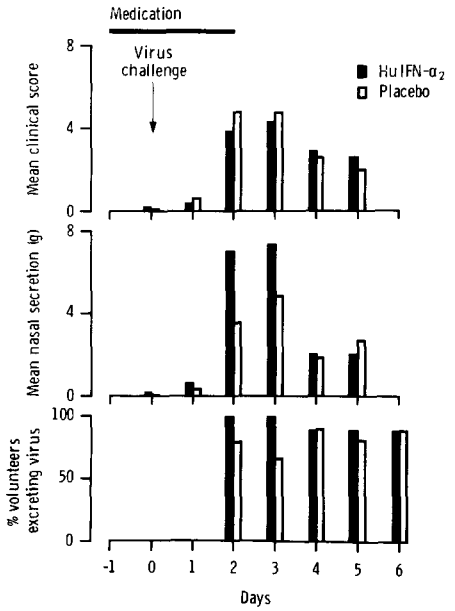

Fig. 3. Clinical score, nasal secretion and virus excretion in volunteers treated intranasally with interferon and challenged with HRV9 and 14. HuIFN-α_2, 2.28 MU was self-administered once/day for 4 days. Virus challenges were given 13 and 14 h after the second dose. None of the observed differences were statistically significant.

each dose was equally effective, the time of greatest susceptibility to virus infection would be half way between them. However, if interferon given before virus challenge produced a greater protective effect than that given afterwards, susceptibility would increase with the interval between an interferon dose, and exposure to virus. To identify the time of greatest susceptibility to virus infection, volunteers in these experiments were challenged with virus 6 and 7 h or 10 and 11 h after the third dose of interferon.

The results of virus challenge are summarised in Table 4. Clinical and laboratory parameters of infection were similar for the 0.0218 MU and 0.225 MU treatment groups, but both were consistently reduced in the 2.37 MU 7 h virus challenge group. Time of virus challenge had no consistent effect on clinical or laboratory evidence of infection in the 2 lower dose treatment groups, but there was a consistent reduction in all variables in the 6 and 7 h as compared to the 10 and 11 h challenge group when 2.37 MU/dose was given. The significance of these trends was determined by an analysis of variance. The categorical variables (frequency of colds, virus isolations on days 2 and 3 after virus challenge and antibody rises) were tested by rank analysis, and the continuous variables (total clinical score and mean daily nasal secretion for each volunteer from the time of virus challenge) by analysis of covariance, with pre-challenge serum neutralising antibody titre as covariate.

TABLE 4

Clinical and laboratory findings in multiple dose study

Dose of HuIFN-α_2 (MU)	Time of virus challenge (h)[a]	Volunteers excreting virus on days 2 and 3 after challenge	Volunteers with fourfold or greater antibody rises to HRV9 and/or HRV14	Volunteers with mild or worse colds	Geometric mean clinical score
0.0218	6 and 7				
	$n = 8$	7	6	2	6.63
	10 and 11				
	$n = 8$	7	4	1	2.74
	Total				
	$n = 16$	14	10	3	4.31
0.223	6 and 7				
	$n = 12$	9	10	1	2.45
	10 and 11				
	$n = 12$	11	9	4	5.15
	Total				
	$n = 24$	20	19	5	3.58
2.37	6 and 7				
	$n = 12$	3	4	1	0.98
	10 and 11				
	$n = 13$	6	8	2	1.73
	Total				
	$n = 25$	9	12	3	1.33

[a] n = number of volunteers.

The frequency of virus isolations and antibody rises was significantly reduced in the 2.37 MU treatment group ($P < 0.01$, Scheffé's test); the reduction in the incidence of colds did not reach significance. Virus challenge at 6 and 7 h or 10 and 11 h did not have a significant effect on clinical or laboratory parameters of infection.

The continuous variables were transformed, $y = \log_e (x + 0.5)$, to overcome a skew distribution. There was a significant effect of interferon concentration on total clinical score ($P < 0.05$), but this effect did not reach significance for nasal secretion weight. The difference in clinical scores was largely the result of a low score in the 2.37 MU treatment group. Time of virus challenge did not have a significant effect on any variable.

The results of these experiments led us to conclude that an intranasal dose of at least 2.37 MU, given 3 times/day, might be necessary to produce a substantial protective effect against naturally acquired rhinovirus infection. Therefore in a final placebo-controlled trial HuIFN-α_2 was given in a suitable formulation and presentation (see Materials and Methods) for prophylactic efficacy against rhinovirus challenge. Medication was given 3 times/day, (at 8 a.m., 2 and 8 p.m.) for 4 days, and volunteers were challenged with virus when those receiving interferon might be expected to be most susceptible to infection, that is 4 to 5 h after the fourth dose. The mean quantity of HuIFN-α_2 in each dose was 3.85 MU.

One volunteer was excluded from the analysis because an external rhinovirus was recovered from her pre-challenge nasal wash; two further volunteers (one interferon, the other placebo-treated) had pre-challenge neutralising antibody titres of $\geqslant$ 1:128 to both viruses. These were excluded as being resistant to infection. The results of virus challenge in the remaining 36 volunteers are summarised in Table 5. There were 2 mild or worse colds amongst 17 volunteers receiving interferon as compared to 5 amongst 19 placebo recipients (not statistically significant). The number of virus shedders, and antibody rises were also slightly reduced in the interferon-treated group (not statistically significant). However, the proportion of volunteers excreting virus (on days 2 and 4 after virus challenge), nasal secretion and clinical scores (days 3, 4 and 5 after virus challenge, both variables) were significantly reduced (Fig. 4).

Side effects

Twenty-four volunteers were challenged with saline; 10 were given placebo, and 14 HuIFN-α_2. There were no haematological or biochemical abnormalities in any of the blood samples from 128 volunteers given interferon. Other reactions to medication are summarised in Table 6. The proportion of volunteers with increased nasal secretion was similar in both the interferon and placebo-treated groups and there was no obvious relationship between the quantity of nasal secretion produced and the dose of interferon. Clinical symptoms (mainly mild nasal symptoms) were reported more frequently by interferon than placebo recipients, and the mean total clinical score of the interferon-treated group was higher than that of the placebo-treated group. Again there was no obvious relationship with dose. One volunteer receiving the lowest dose of interferon (0.0436 MU) had a very mild cold, and accumulated a total clinical score of 15.5.

TABLE 5

Clinical and laboratory findings in volunteers treated with intranasally, self-administered interferon (3.58 MU/dose; 3 doses daily for 4 days) and challenged with rhinoviruses 9 and 14, 4 and 5 h after the second interferon dose

Treatment	Stratification of volunteers by pre-challenge immune status		Number of volunteers with clinically diagnosed colds		Number of volunteers with positive laboratory findings		
	Antibody titre[a]	Number	Mild or worse	Very mild or none	Rise in antibody titre to HRV9 and/or HRV14	Virus isolation	Either or both
Interferon	<2	6	1	5	4	5	5
	2–8	5	1	4	3	3	3
	>8	6	0	6	2	2	2
	Total	17	2	15	9	10	10
Placebo	<2	8	4	4	4	7	7
	2–8	6	1	5	4	4	5
	>8	5	0	5	3	3	4
	Total	19	5 (> 0.05)[b]	14	11 (> 0.05)	14 (> 0.05)	16 (> 0.05)

[a] Neutralising antibody titre to HRV9 or HRV14, whichever was lower.

[b] *P*-level for statistical significance between interferon and placebo-treated groups.

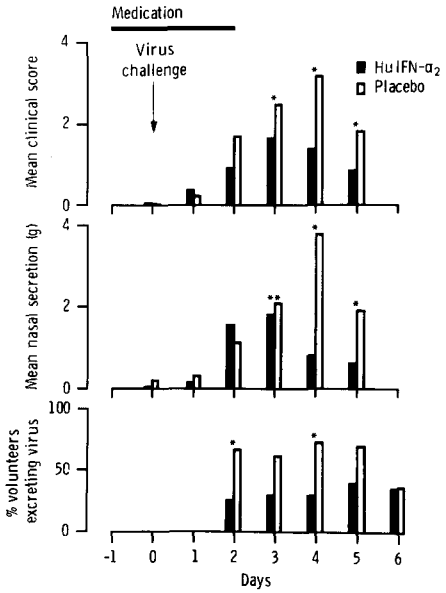

Fig. 4. Clinical score, nasal secretion and virus excretion in volunteers treated intranasally with interferon and challenged with HRV9 and 14. HuIFN-α_2, 3.85 MU was self-administered 3 times/day for 4 days. Virus challenges were given 4 and 5 h after the fourth dose. Asterisks indicate levels of statistical significance between interferon and placebo-treated groups: * = $P <$ 0.05; ** = $P < 0.01$.

TABLE 6

Tolerance of volunteers for intranasally administered HuIFN-α_2

Daily dose of interferon (MU)	Number of volunteers in group	Number of volunteers with:				Mean total clinical score
		Increased nasal secretion[a]	Sore throat	Nasal stuffiness	Sneezing	
0.0436	2	1	1	1	1	7.25
0.446	3	0	0	0	1	0.67
2.28	2	1	1	0	0	0.75
4.74	2	1	0	1	0	0.25
9.12	2	2	0	1	1	3.00
12.6	3	0	0	0	0	0
All doses	14	5	2	3	3	1.73
Placebo	10	4	0	7	0	0.40

[a] $\geqslant$ double the daily quantity produced on the 2 days preceding the start of the medication.

Discussion

In these experiments various dosage schedules of HuIFN-α_2 were evaluated for their protective effect against challenge with virulent rhinoviruses. Two strains, type 9 and type 14, were used in order to increase the frequency of infection and clinical symptoms. The object of our experiments was to arrive at a regimen suitable to be tested in large-scale prophylactic trials. HuIFN-α_2 was apparently well tolerated for 4 days at all the dosage levels given. However, there was some evidence of mild local inflammation in a few volunteers. The mild nasal symptoms produced were not obviously dose-related, nor were they of sufficient magnitude to obscure the beneficial effect of interferon treatment.

The feasibility of self-administration was proved conclusively in a double-blind, placebo-controlled trial, in which HuIFN-α_2 was given 4 times/day. In these experiments, mild, moderate or severe colds were considered significant, as they were invariably accompanied by laboratory evidence of infection, either virus was isolated, an antibody rise demonstrated, or both; also they did not occur in saline-challenged volunteers. No significant colds were produced by virus challenge in any of the interferon-treated volunteers, and interferon protected against challenge with both HRV9 and HRV14 (data not shown). However, in further experiments the surprising degree of protection produced by a single daily dose decayed to undetectable levels within 13 to 14 h. In experiments in which the dose of interferon was varied, 2.37 MU twice a day had a significantly greater protective effect than 0.0218 MU or 0.223 MU. However 3 out of 25 volunteers treated with 2.37 MU, and challenged with virus 6 h or more after the third dose developed colds. There was a consistent (but not statistically significant) trend toward protection in the 2.37 MU treatment group when the interval between the third dose of interferon and virus challenge was 6 and 7 rather than 10 and 11 h. This suggests that HuIFN-α_2 given 6 h before virus challenge had a greater protective effect than when given only 1 to 2 h afterwards (this being the interval after which the fourth dose of interferon followed virus challenge in the 10 and 11 h challenge group).

Harmon et al. [3] have shown that the antiviral state induced by interferon may persist in nasal epithelial cells obtained by biopsy for at least 72 h after interferon treatment. These experiments were conducted in vitro using a sensitive technique (reduction in the yield of VSV). Experiments which measure a clinical response to rhinovirus challenge may be insufficiently sensitive to detect all but large effects on virus replication. We found that protection against clinical symptoms decayed rapidly, and that relatively large amounts of intranasally administered HuIFN-α_2 were necessary in order to prevent a cold. As protein solutions are rapidly cleared from the nose with a half-lifetime of approximately 20 min [1], high concentrations of interferon may be maintained with a smaller daily dose if the frequency of dosing, rather than the quantity in a dose is increased. An increase in dosing frequency might also lessen the interval by which medication with interferon is followed by natural exposure to virus.

However, frequency of dosing should not be increased to the detriment of compliance. Based on this practical consideration and the results of our volunteer experi-

ments, we concluded that a regimen of self-administered interferon of approximately 4 MU/dose 3 times/day would be appropriate for evaluation in large-scale field trials of prophylaxis against naturally acquired rhinovirus infection. A suitable formulation and presentation of HuIFN-α_2 was tested in a placebo-controlled trial in volunteers in which we sought to demonstrate the minimum protective effect of such a regimen. Although volunteers were challenged with rhinovirus at a time when those receiving interferon might be expected to be most susceptible to infection (4 and 5 h after the fourth dose) a substantial protective effect was still demonstrated. Interferon treatment produced significant reductions in both clinical and laboratory evidence of infection, although protection was not complete as there were 2 significant colds amongst 17 treated volunteers.

Natural exposure to rhinoviruses might be expected to occur as frequently just after a dose of interferon as just before; also the dose of virus used to challenge volunteers in our experiments may have been larger that normally encountered in nature. Therefore, we recognise that a less intensive medication regimen of HuIFN-α_2 could prove an effective prophylactic against naturally acquired rhinovirus colds. However, the beneficial effects of a drug may be less easily detected in field trials than in carefully controlled volunteer studies. By reproducing conditions in our experiments as unfavourable for prophylaxis as any which might be expected to occur in nature, we tried to ensure that the dosage regimen chosen would have a substantial protective effect against naturally acquired rhinovirus infection. Further studies are now in progress to determine whether the mild nasal symptoms experienced by some volunteers taking intranasal HuIFN-α_2 reach an unacceptable level during long-term administration.

Acknowledgements

We would like to express our gratitude to the volunteers who took part in these experiments, to the technical and ancilliary staff of the Common Cold Unit for their expert assistance, to Rosslynn Line for preparation of the typescript, and to Patrick Royston for his statistical help.

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