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Prophylactic efficacy and tolerance of low-dose intranasal interferon-alpha$_2$ in natural respiratory viral infections

Frederick G. Hayden*, Jack M. Gwaltney, Jr. and Michael E. Johns**

Departments of Internal Medicine, Pathology, and Otolaryngology, University of Virginia School of Medicine, Charlottesville, Virginia 22908, U.S.A.

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Summary

The prophylactic activity of intranasal human interferon-alpha$_2$ (HuIFN-α_2) was determined in a randomized, double-blind, placebo-controlled study. Healthy, working adults self-administered sprays of HuIFN-α_2(1.25×10^6 IU; $n = 142$) or placebo ($n = 145$) twice daily. Drug administration was stopped after 12 days because of the frequent occurrence of nasal irritation manifested by blood-tinged nasal mucus (44% HuIFN-α_2 versus 15% placebo, $P < 0.001$) and associated nasal mucosal abnormalities. Over 80% of volunteers had participated in a similar field trial conducted 7 months earlier; no evidence of cumulative toxicity was detected. HuIFN-α_2 administration did not decrease the occurrence of illnesses associated with rhinorrhea, cough, or feverishness as compared to placebo, but the number of laboratory-documented respiratory viral infections was small (6 HuIFN-α_2, 3 placebo). Intranasal HuIFN-α_2 1.25×10^6 IU twice daily was associated with significant local intolerance.

interferon; topical administration; tolerance; respiratory infection

Experimental

In previous studies it has been found that either human leukocyte-derived interfe-

* To whom all correspondence should be addressed: Box 473, Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville, VA 22908, U.S.A.

** Present address: Chairman, Department of Otolaryngology – Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, U.S.A.

ron (HuIFN) [3,10] or recombinant DNA-produced human IFN-alpha$_2$ (HuIFN-α_2) [5,9,11] are effective in preventing experimental rhinovirus colds. In two recent field trials it was found that intranasal administration of HuIFN-α_2 10×10^6 IU/day was effective in preventing naturally occurring rhinovirus colds in adults [1,2]. However, tolerance studies [7,9] and field trials [1,2] have revealed unacceptable rates of nasal side effects after several weeks of HuIFN-α_2 administration at this dosage. In an effort to improve tolerance, the current study was undertaken to assess the prophylactic efficacy and acceptability of intranasal HuIFN-α_2 at a dosage of 2.5×10^6 IU/day for prevention of naturally occurring respiratory viral infections. This randomized, placebo-controlled, double-blind study was conducted in the volunteer population used in an earlier field trial [2], which enabled us to determine the effects of repeated HuIFN-α_2 exposure.

The study was conducted in April 1983, in 287 adult volunteers working in an insurance company. The methods used for drug administration, illness surveillance, and virologic studies have been detailed previously [2,4,6]. The treatment groups were comparable with respect to sex distribution (male/female ratio 46/96 IFN, 48/97 placebo), age (mean 34.5 years IFN, 35.8 years placebo), and number of smokers (36 IFN, 35 placebo). Eighty percent of the HuIFN-α_2 group (previous exposure – 43% IFN, 37% placebo) and 86% of the placebo group (40% IFN, 46% placebo) had participated in the first study involving this population (September 1982). Although originally planned for 4 weeks, the treatments were stopped after 12 days because of the frequent occurrence of nasal irritation (see below). Eight HuIFN-α_2-treated volunteers (1 for noncompliance, 2 for concurrent illness, 5 for adverse experience) and 2 placebo-treated (2 for adverse experience) were dropped during the treatment period ($P = 0.10$).

Lyophilized HuIFN-α_2 (Schering Corp., Bloomfield, NJ) and an identical appearing placebo were reconstituted in a phosphate-buffered solution containing the preservative thiomerosal (0.002%). Volunteers were randomized to receive 2 sprays per nostril (0.05 ml/spray) of HuIFN-α_2 (1.25×10^6 IU/treatment) or placebo twice daily between 8 a.m. and 12 noon and at 4 p.m. Sprays were self-administered under the observation of a study nurse on 5 of 7 mornings of each week. Afternoon and weekend dosing was not supervised.

Efficacy

In our first study on this population, which utilized a dosage of 10×10^6 IU/day, we found highly significant protection against rhinovirus infections, significant reductions in illnesses associated with cough, and trends toward fewer illnesses associated with rhinorrhea [3]. In contrast, in the current study we found that HuIFN-α_2 administration was not associated with fewer episodes of respiratory illness or laboratory-documented viral infection compared to placebo (Table 1). Forty-four percent of HuIFN-α_2 but only 27% of placebo recipients developed respiratory illness during the 12 day treatment period ($P = 0.004$). HuIFN-α_2 administration was associated with significantly more episodes in which rhinorrhea occurred on 3 or more days (Table 2) and with more episodes in which stopped-up nose (i.e. congestion or stuffiness) was the sole respiratory complaint (14 IFN versus 3 placebo, $P = 0.009$).

TABLE 1

Respiratory illness episodes and respiratory viral infections during intranasal administration of HuIFN-α_2 (2.5×10^6 IU/day) or placebo

	No. of episodes	
	HuIFN-α_2 ($n = 142$)	Placebo ($n = 145$)
Respiratory illnesses[a]	64[b]	40[b]
+ rhinorrhea ⩾3 days	27[c]	9[c]
+ cough ⩾3 days	10	10
+ feverishness	4	2
Illness + laboratory documented viral infection[d]	6	3
rhinovirus	1	0
parainfluenza virus	3	1
influenza B	1	1
adenovirus	1	1

[a] An episode of respiratory illness was defined according to previously used criteria: one respiratory symptom (excluding sneezing) on 2 or more consecutive days or at least 2 symptoms on the same day [2,4].

[b] $P = 0.003$, IFN versus placebo, Fisher's exact test, two-tailed.

[c] $P = 0.002$.

[d] Laboratory documentation was based on virus isolation (1 rhinovirus), serology (3 parainfluenza, 1 influenza B, 1 adenovirus), or both (1 parainfluenza, 1 influenza B, 1 adenovirus). Paired sera collected before treatment and approximately 2 weeks after the last treatment were tested for complement fixation antibodies to influenza A, influenza B, adeno-, respiratory syncytial, and parainfluenza type 1–3 viruses and to *M. pneumoniae* by standard methods. Serologic testing was performed by Dr. Frank W. Lambert, Virginia Division of Consolidated Laboratory Services, Richmond, Virginia.

Viral serologies (cultures) were performed in 83% (38%) of HuIFN-α_2 and 80% (45%) of placebo-associated illness episodes, but the abbreviated nature of this study resulted in few virologically confirmed respiratory illnesses (Table 1). No obvious protection against laboratory-documented viral infection was apparent (6 HuIFN-α_2, 3 placebo), and the only rhinovirus cold documented during the treatment period occurred in an HuIFN-α_2 recipient. However, the low prevalence of viral infections during this study did not allow for an adequate assessment of efficacy. Other workers have found that prophylactic administration of HuIFN-α_2(2.5×10^6 IU/day) significantly reduced the frequency of rhinovirus colds (T. Shope, personal communication), but that lower dosages of recombinant leukocyte A interferon did not appear to prevent colds in family contacts of persons with respiratory illness [8].

Tolerance

Volunteers recorded the presence of symptoms possibly related to local side effects (blood-tinged mucus, nasal dryness) each day. Overall, 79 (56%) HuIFN-α_2 and 37 (26%) placebo-treated volunteers reported at least one adverse symptom during the 12-day treatment period ($P<0.001$). The most commonly reported symptoms were

TABLE 2

Nasal mucosal abnormalities in volunteers receiving intranasal HuIFN-α_2(2.5×10^6 IU/day) or placebo for 12 days

Reason for exam	Mucosal abnormality	Treatment group	No. (%) subjects with prior exposure to			
			HuIFN-α_2	Placebo	Neither	Total
Symptomatic[a]	Any[b]	IFN	10(48)[c]	8(62)	4(57)	22(54)
		Placebo	0(0)[c]	2(29)	3(75)	5(29)
	Bleeding	IFN	4(19)	3(23)	1(14)	8(20)
		Placebo	0(0)	1(14)	0(0)	1(6)
Routine (treatment day 12)	Any[b]	IFN	10(48)[d]	7(41)	1(33)	18(44)
		Placebo	2(12)[d]	8(36)	2(100)	12(29)
	Bleeding	IFN	2(10)	4(24)[e]	1(33)	7(17)[f]
		Placebo	0(0)	0(0)[e]	0(0)	0(0)[f]

[a] Overall 41/142 (29%) HuIFN-α_2 compared to 17/145 (12%) placebo recipients requested a nasal examination because of symptoms during the 12 day treatment period ($P = 0.005$).

[b] This category includes ulcers, erosions, punctate bleeding sites and dry, crusted, or erythematous mucosa.

[c] $P = 0.08$, IFN versus placebo.

[d] $P = 0.04$.

[e] $P = 0.06$.

[f] $P = 0.012$.

blood-tinged nasal mucus (IFN 44% versus placebo 15%, $P<0.001$) and nasal dryness (IFN 34% versus placebo 11%, $P<0.005$). The occurrence of blood-tinged nasal mucus was analysed with respect to previous exposure to HuIFN-α_2, placebo, or neither in the first field trial, and no differences were observed in the proportions of HuIFN-α_2 (48%, 38% and 43%, respectively) or placebo (17%, 13% and 15%) recipients who reported this symptom during the current study.

Nose and throat examinations were performed (M.E.J.) pretreatment on all subjects and also weekly (treatment days 5 and 12) on approximately one-third of the volunteers in a rotating fashion. Four percent of HuIFN-α_2 and 3% of placebo recipients had exam abnormalities before treatment. In addition to the scheduled examinations, 41 HuIFN-α_2 and 17 placebo recipients ($P<0.001$) had examinations because of nasal symptoms by the end of 12 days of treatment. The most frequently detected mucosal abnormalities were dry, crusted mucosa and punctate mucosal bleeding sites (Table 2). Overt ulceration developed in only 2 IFN recipients during treatment period (both had prior exposure to placebo). Mucosal abnormalities (54% versus 29%) and, specifically, punctate mucosal bleeding (20% versus 6%) tended to occur more often in symptomatic HuIFN-α_2 than symptomatic placebo recipients (Table 2). Similarly, routine examinations performed on treatment day 12 detected punctate mucosal bleeding significantly more often in HuIFN-α_2 (17%) than in placebo recipients (0%) (Table 2). No differences in regard to previous HuIFN-α_2 or placebo exposure were observed in examinations performed on volunteers in a prospective fashion or on those with symptoms (Table 2).

The study design incorporated daily reporting of nasal side effects and prospective monitoring for objective abnormalities, so that milder forms of nasal irritation were readily detected. The severity of the mucosal abnormalities was much less than observed in the previous study in this population, in which 28/40 (70%) symptomatic HuIFN-α_2 recipients had mucosal erosions or ulcerations by the end of 3 weeks exposure [2]. This was the first large-scale study to examine the tolerance to repeated courses of intranasal HuIFN-α_2, since over 80% of the volunteers in this study had participated in a similarly designed field trial conducted approximately 7 months earlier. No evidence of cumulative toxicity to a second HuIFN-α_2 exposure was found. However, the lack of clinical efficacy and the occurrence of local intolerance in this study suggest that intranasal HuIFN-α_2 at a dosage of 2.5×10^6 IU/day is not a feasible approach for long-term prophylaxis of respiratory viral infections in healthy adults. Alternative strategies, such as short-term use after recent exposure to a common cold [8], or other means to reduce the risk of local intolerance, such as alteration in dosage, methods of delivery, or formulation, should be considered for future studies.

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