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Ineffectiveness of Postexposure Prophylaxis of Rhinovirus Infection with Low-Dose Intranasal Alpha 2b Interferon in Families

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Past studies conducted in Australian and American families have demonstrated that alpha 2b interferon (IFN) is effective in preventing rhinovirus-associated illnesses in exposed family members. IFN had been used by intranasal application for 7 days after exposure (5×10^6 IU/day). We used the same approach but with only 5 days of spraying (5×10^6 IU on day 1 and 2.5×10^6 IU on each subsequent day). This amount has been effective in studies involving seasonal prophylaxis. During the study period, a total of 178 rhinoviruses were isolated from the 199 enrolled families in Tecumseh, Mich. There were 434 courses of IFN use and 434 courses of placebo use. Although rhinoviruses were less frequently isolated from those using IFN than those using the placebo, no differences favoring IFN treatment could be found in any of the symptomatic episodes. In fact, more episodes were observed in IFN recipients than in placebo recipients, although the differences were not statistically significant. Additionally, there was no evidence of modification of the severity of episodes of illness. It was concluded that prevention of rhinovirus illness episodes postexposure requires a dosage of at least 5×10^6 IU of IFN-α_{2b}.

A number of studies have demonstrated that when given in adequate dosages, intranasal alpha interferon (IFN-α) can prevent experimental or natural rhinovirus infection (6, 7, 10, 15–17). The major problem today with use of the drug is the occurrence of side effects which are often associated with its administration. These side effects are generally mild, but their presence has made recognition of clinical efficacy difficult, if not impossible, in evaluations lasting over periods of weeks (2, 14). Since many respiratory infections are acquired, at least in part, following intrafamilial transmission, the strategy of using IFN to prevent infection after the occurrence of an index case in the family has been developed. Duration of spraying can then be restricted to the period of risk (9). Two studies, one American, involving 60 families, and the other Australian, involving 97 families, demonstrated a significant reduction in rhinovirus colds during and for a period after use of the intranasal spray of a recombinant IFN-α_{2b} (3, 5). The dosage was 5×10^6 IU daily for 7 days. In seasonal prophylaxis studies, IFN-α_{2b} has been effective in preventing rhinovirus infection at a dosage of 2.5×10^6 IU daily (11). Thus, it seemed appropriate to evaluate use of the drug at a lower dose and during a period of expected high rhinovirus prevalence. We report results of this trial conducted among families living in Tecumseh, Mich., during an autumn rhinovirus season.

MATERIALS AND METHODS

The evaluation was conducted among families of the community of Tecumseh, Mich. That community has been the site of prior trials of prophylactic or therapeutic agents for respiratory infections, but IFN had never been tested in this population. Families were contacted and asked whether they wished to participate in a study in which IFN would be used in an attempt to interrupt rhinovirus transmission. The medication could potentially be used by children as young as 5 years old; pregnant and lactating females were excluded. For a family to be eligible, it was required that it contain at least two members who could use the spray, as well as at least two children under the age of 12 years. Families were recruited according to size and were stratified. They were assigned randomly as a whole on a 1:1 basis to receive either a spray containing a drug or a placebo. This assignment lasted throughout the trial. Informed consent was obtained. Members were given instructions on when and how to use the spray and were further instructed to inform the study office that an illness episode had started so that specimens could be collected by the study staff. The spray canisters were left in the home at the time of initial contact, and they were replaced after use. At the time of this visit, the participating families were questioned concerning spray use, as well as possible side effects, and the level of spray was visually checked to monitor compliance. A diary card on which the participants had been instructed to record symptoms graded from 1 to 3 in severity was also collected at this time.

When the study office was notified that an illness in any family member had occurred, a specimen for virus isolation was collected by nasal and throat swab. Eligible family members who were not ill began to use the spray; the spraying cycle could not begin unless all family members had been free of symptoms for 2 days or more. The dose was 5×10^6 IU of IFN-α_{2b} on day 1 and 2.5×10^6 IU daily for four more days. If additional illnesses occurred in the family, specimens were collected from those individuals on subsequent home visits. Thus, the family was visited whenever there was an illness and at the end of a cycle of spraying. A new cycle of prophylaxis could begin only after 7 days had passed; again, all family members were required to be symptom free for 2 days. If a family had not used the spray for a month, that family was visited and the material was replaced.

Recombinant IFN-α_{2b} was provided as a lyophilized powder containing human serum albumin. It was reconstituted with sterile distilled water before distribution. The placebo

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similarly contained albumin. Both preparations contained 0.002% thimerosal as a preservative. The metered spray device delivered 0.05 ml per spray into each nostril, or a total of 2.5×10^6 IU of active preparation of IFN. The participants were instructed to activate the spray twice in each nostril on day 1, and once in each nostril on each subsequent day.

For analytic purposes, each family cycle of prophylaxis was considered an independent event. An index individual was that person(s) whose illness initiated the prophylaxis cycle in the family but who did not use prophylaxis. Other family members were usually on prophylaxis if eligible, and if an illness occurred during this period, the participants were encouraged to continue spraying for the full course of 5 days. Each family cycle was characterized as to etiology by the agents isolated from the index individual or from any other member during that period. If only a single type of agent (rhinovirus or parainfluenza virus) was isolated from the index individual or from secondary cases, the cycle was identified by that agent. If two different types of agents were isolated, the cycle was placed in the "other virus associated" category. A number of measures of illness were examined, and because the results were consistent, the one used was a positive response for two successive days to the question, "Do you think you have a cold?" Standard parametric and nonparametric tests were used for data analysis.

For isolation of respiratory viruses, techniques previously used in the Tecumseh study were employed (11). Both nasal and throat swabs were collected and placed in the same tube of veal infusion broth. Specimens were collected once from each ill individual, provided that that individual could be seen within 48 h of illness onset. The specimens were sent to the laboratory as quickly as possible and were inoculated into cell cultures usually within 24 h of collection. For isolation of rhinoviruses, two tubes each of WI-38 and FT cells were used; two tubes each of primary cynomolgus monkey kidney and HL cells were also used. As in previous studies involving IFN, sheep antibody was added to the original specimen at a final concentration of 10,000 IFN-α_{2b} neutralizing units per ml. Viruses were identified by standard methods (acid tests, hemadsorption inhibition, and neutralization) (11).

RESULTS

Participating families and virus isolations. Since the clearest effect of IFN nasal spray has been against rhinovirus infection, the trial was timed to coincide with the autumn rhinovirus peak (12). Recruitment took place in late August 1985, and the trial was discontinued in mid-November 1985. The weekly patterns of rhinovirus and parainfluenza virus isolations from the group under study are shown in Fig. 1. As can be seen, most of the rhinovirus activity did take place during September, but activity continued throughout the remainder of the period. A total of 178 rhinovirus isolates were made from all participants. Parainfluenza viruses were the next most frequent isolate, becoming nearly as common as rhinoviruses in the last part of the study. The parainfluenza viruses were typed as follows: for type 1, $n = 41$; for type 2, $n = 29$; and for type 3, $n = 16$.

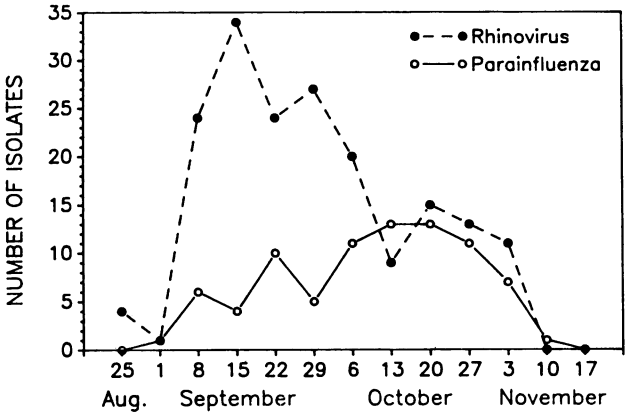

FIG. 1. Total number of rhinovirus and parainfluenza viruses isolated per week in Tecumseh, Mich., during 1985.

A total of 199 families participated in the trial; 100 were assigned to receive IFN and 99 received the placebo. Of these two groups 87 and 89 families, respectively, used spray at some time. The mean number of family members was 4.6, with similar distributions in both groups. The median number of treated members per family was three, with up to six in the IFN group and seven in the placebo group. Age, race, sex, and smoking status were also similar in the two groups.

Effect of IFN on family episodes of illness. For the purpose of assessing the overall effect of IFN, episodes in which spray was used were first considered without respect to etiology. In view of the predominant role of rhinoviruses during this period, any effect, even one limited to these viruses, should have been evident. Periods examined for illness onsets, timed from the start of the index case, were the 5 days of spraying, that period plus 2 days, and finally the prophylactic period plus 7 days. Results compiled are from the 344 cycles or times families were being treated, of which

TABLE 1. Symptomatic cold episodes in groups on IFN prophylaxis or placebo

Type of cycle	Treatment	No. of cycles		No. (%) of courses with cold episodes		
		Family[a]	Individual[b]	During therapy	During and 2 days after therapy	During and 7 days after therapy
All	IFN	172	434	33 (7.6)	49 (11.1)	79 (18.2)
	Placebo	172	434	21 (4.8)	35 (8.1)	60 (13.8)
Rhinovirus only	IFN	58	141	16 (11.3)	23 (16.3)	33 (23.4)
	Placebo	54	140	13 (9.2)	20 (14.2)	31 (22.0)
Parainfluenza viruses only	IFN	18	46	0	2 (4.3)	9 (19.5)
	Placebo	21	49	0	3 (6.1)	4 (8.2)
All other virus associated	IFN	13	30	4 (13.3)	6 (20.0)	9 (30.0)
	Placebo	11	27	1 (3.7)	2 (7.4)	5 (18.0)

[a] Number of times a family group was involved in spraying.
[b] Number of times individual family members used spray.

172 were IFN cycles and 172 were placebo cycles (Table 1). There were 434 individual courses of prophylaxis in each prophylaxis group, and results are given for these courses. No prophylactic effect of IFN can be observed in the overall results, even in the period when the drug was being administered or with the two added postprophylaxis days, a period of known continuing efficacy against rhinoviruses (14) (Table 1). In fact, there was a tendency for more frequent cold episodes to occur in the IFN group, although those differences were not statistically significant. Similar results were observed in those episodes in which rhinoviruses only, parainfluenza viruses only, and other viruses or combinations of viruses were isolated. Not shown are results by day of prophylaxis; evidence of a drug effect could be not detected with any combination of days. Additionally, an analytic model was employed to examine the frequency of secondary cases in the two groups, and no differences were found. A detailed report of these findings will appear elsewhere (9).

While in the past side effects have been observed when intranasal IFN has been administered over a period of weeks, no evidence of sensitization has been identified with repeated use. Since 168 of the individual courses in the IFN group and 165 of the individual courses in the placebo group represented second or subsequent treatment, the first courses alone were examined to see if a higher illness rate among IFN users was also found. Among the 266 first courses with or without virus isolation in the IFN group results similar to those in "all cycles" in Table 1 were found, i.e., illness onsets occurred for 8.3% (22 patients) during the 5 days on prophylaxis, for 10.5% in the first 7 days, and for 18.4% in the 2 weeks. Figures for the placebo group (269 courses) were all somewhat lower: 4.8, 8.9, and 15.2%, respectively. This indicates that the greater illness rate in the IFN group seen in Table 1 occurred both in those using the spray for the first time and in those on repeated prophylaxis; thus, there was no evidence of sensitization.

The higher illness rates in persons using IFN instead of placebo, while consistent, were in no case statistically significant. It is possible that the mild side effects so commonly observed in persons using IFN over prolonged periods might be responsible for the difference (4, 11). Evidence for this possibility was sought by examining occurrence of those side effects which in the past were associated with IFN use. Only twice was nasal stuffiness observed in the IFN group, compared with once in the placebo group; for blood-tinged mucus, the numbers were five in the IFN group against none in the placebo group. Frank epistaxis was seen three times in the IFN group and once in the placebo group. None of these differences are statistically significant. While much lower in frequency than side effects encountered in seasonal prophylaxis, these results suggest that even at this low and short-term dosage, symptoms related to IFN, while unlikely, might have occurred.

Virus isolation and symptoms during cycles of prophylaxis. During and immediately after a course of prophylaxis, 30 rhinoviruses were isolated from those using the spray. There were 13 isolates during the 5 days of medication; 3 of 24 cultures (12.5%) came from those on IFN, and the remaining 10 of 17 cultures (58.8%) came from those on placebo ($P < 0.005$). With the addition of the 2 days postprophylaxis, the number of isolates increased to 20; 6 of 40 cultures (15%) were from the IFN groups, and 14 of 30 cultures (46.7%) were from the placebo group ($P < 0.01$). For the full 14 days, the number of isolates reached 30, with 12 of 73 cultures (16.4%) from IFN recipients and 18 of 57 cultures (31.6%) from the placebo group ($P > 0.05$). Other isolates, mainly parainfluenza viruses, were equally distributed between the IFN and placebo groups. Thus, even though there was clearly no protection by IFN from rhinovirus-associated illness, there was evidence of protection from rhinovirus infection, at least as manifested by the present isolation techniques.

TABLE 2. Severity of symptoms in cold episodes occurring during IFN prophylaxis and on 2 subsequent days

Type of cycle	Aspect measured	Intensity with[a]:			
		IFN		Placebo	
		Avg	Maximum	Avg	Maximum
All[b]	Cold severity	1.34	1.75	1.32	1.74
	Effect on activities	1.04	1.47	1.10	1.67
	Total symptom severity	3.81	6.13	4.11	6.31
Rhinovirus associated[c]	Cold severity	1.33	1.78	1.23	1.60
	Effect on activities	1.06	1.48	1.05	1.63
	Total symptom severity	3.32	6.13	3.67	6.00

[a] Patients scored themselves on a scale of 1 to 3, with 1 being lowest intensity. Symptom severity is a calculation in which reported symptoms are summed.

[b] In the IFN group, 48 people had colds and 434 people used the spray. In the placebo group, 35 people had colds and 434 used the placebo.

[c] In the IFN group, 23 people had colds and 141 people used the spray. In the placebo group, 20 people had colds and 140 used the placebo.

In a previous low-dosage study of postexposure prophylaxis, while no protection was found, the illnesses that did occur were of reduced severity among IFN users (8). Therefore, the severity of cold episodes in all cycles and in rhinovirus-associated cycles were examined. Results are shown in Table 2. Cold severity is a summary in which patients scored themselves as to the intensity of the overall episode; in contrast, symptom severity is a calculation in which the reported symptoms are summed. For each of these variables, both an average severity over the episode and a maximum severity were calculated. Neither for all episodes nor for those that were rhinovirus-associated was there evidence of an effect on any variable. Similar results were observed for episodes associated with other virus isolates and for other symptom variables, including illness duration.

DISCUSSION

Control of common respiratory disease has been a long-term goal because of the frequency of these illnesses and their impact on the population (12). However, except for influenza, no methods have been available for specific prevention (1, 13) despite many encouraging leads from the laboratory, sometimes confirmed by initial studies in volunteers. Thus, the observation made independently in two studies that IFN-α_{2b} at an intranasal dosage of 5×10^6 IU for 7 days had a prophylactic effect on respiratory illnesses when used post-familial exposure was greeted with great excitement (3, 5). The effect was confined exclusively to rhinoviruses, and efficacy was highest when they were the primary circulating agents. The strategy of using IFN in postexposure prophylaxis rather than seasonally was in part developed to lessen the problem with side effects experienced during prophylaxis lasting for 2 weeks or more (4, 11).

Because of the concern about side effects and the general principle that active drugs should be used at the lowest effective dosage, it was decided to reevaluate the strategy of

using 5×10^6 IU on day 1 and 2.5×10^6 IU on each subsequent day to a total of 5 days. This represented a 2-day-shorter course and nearly half the dosage used in the previous evaluations. Since it was known that the effect was confined to rhinoviruses, the trial was limited to the autumn season; to compensate for the smaller number of episodes which would occur during a shortened period, the number of families was more than doubled. The method of conducting the trial in Tecumseh and of identifying episodes was similar to that employed in the previous two studies, although the method of analysis was slightly different in each study. It was anticipated that even if the effect was less than that previously observed, there still would be some residual efficacy demonstrable. This was based on the past studies of seasonal prophylaxis in which an effect on viral isolation had been present at 2.5×10^6 IU. It was thus very surprising to find no evidence of a protective efficacy of IFN, even for a limited period during prophylaxis. When analyzed by the current technique, the two prior studies still gave similar positive results, indicating that methodological differences were not responsible for the current findings (3, 5). The only evidence of a positive effect was not in reducing illness but in reducing the likelihood of detecting rhinovirus infection by standard isolation techniques. This finding suggests that lack of compliance was not responsible for the inability to demonstrate effect on illness. In a prior family study in which 0.3×10^6 or 1.5×10^6 IU of IFN-αA was used, no effect on illness frequency was seen, but there was an effect on symptoms of the illnesses and especially on duration (8). Even that evidence of a positive outcome was lacking in this study.

Not only were illnesses not prevented in the IFN group, but they were actually more frequent. These differences were not statistically significant and probably occurred by chance. However, even during the short period of prophylaxis, there was a slight excess in IFN recipients of the events which have been associated in the past with drug use. Thus, it now appears that while a gradual response to dose reduction is seen when rhinovirus isolation is used as an endpoint, the end effect is more abrupt when illnesses are the endpoint (11). No less than 5×10^6 IU of IFN-α_{2b} can be used per day to achieve acceptable postexposure protective efficacy to rhinovirus infection.

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