

Treatment of ragweed hay fever with an intranasal spray containing flunisolide, a new synthetic corticosteroid

Paul C. Turkeltaub, M.D., Philip S. Norman, M.D., and Seymour Crepea, M.D. *Baltimore, Md., and Palo Alto, Calif.*

Flunisolide, a new synthetic fluorinated corticosteroid, was administered as a nasal spray via a squeeze bottle to patients with ragweed hay fever for 4 wk during the hay fever season. Fifty-one patients, paired on the basis of similar skin sensitivity to intradermal ragweed ($\leq 10^{-1}$ PNU/ml), were randomly assigned in a double-blind manner either an aerosol-containing flunisolide dissolved in vehicle (a mixture of polyethylene glycol and propylene glycol) or vehicle alone. Flunisolide was sprayed as a 0.025% solution two times in each nostril twice a day. Forty-eight patients completed the study. Three patients dropped out for reasons unrelated to flunisolide usage. On the basis of physician interviews and daily symptom diary scores, patients receiving flunisolide showed significant improvement of hay fever symptoms when compared to their counterparts receiving vehicle. No systemic steroid side effects were observed. Morning plasma cortisol levels measured prior to and after 3 wk of flunisolide therapy showed no significant difference between the treatment groups. Adverse local effects were minor and were noted less frequently with flunisolide than with vehicle. Flunisolide's topical efficacy and lack of adrenal suppression provide distinct advantages over other steroid preparations available in the United States for treatment of seasonal allergic rhinitis.

Well-controlled studies have previously demonstrated the efficacy of dexamethasone applied intranasally in the treatment of ragweed hay fever.^{1, 2} The therapeutic dose of dexamethasone shown to suppress hay fever symptoms, however, resulted in significant, though only partial suppression of adrenocortical function.³

In order to avoid the systemic effects of corticosteroid therapy, several more potent topical steroids have been synthesized and subjected to clinical evaluation. Both beclomethasone dipropionate and betamethasone 17-valerate administered via nasal aerosol have been shown to suppress symptoms of allergic rhinitis without adrenocortical suppression.^{4, 5}

The present study was undertaken to test the efficacy and safety of another new, potent corticosteroid, flunisolide, in the treatment of allergic rhinitis.

From The Johns Hopkins University School of Medicine at The Good Samaritan Hospital, O'Neill Research Laboratories, Baltimore, and Syntex Corporation, Palo Alto.

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Reprint requests to: Dr. Paul C. Turkeltaub, Good Samaritan Hospital, Baltimore, Md. 21239.

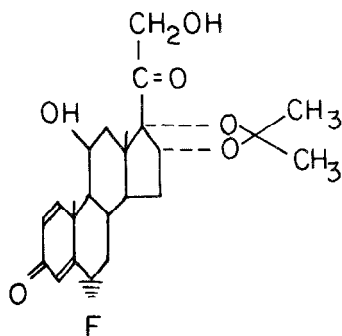


FIG. 1. Structure of flunisolide (6 α -fluoro-11 β , 16 α , 17 α , 21 tetrahydroxypregna-1,4-diene-3, 20 dione, 16,17-acetonide).

MATERIALS AND METHODS

Flunisolide aerosol

Flunisolide, (6 α -fluoro-11 β , 16 α , 17 α , 21 tetrahydroxypregna-1,4-diene-3,20 dione, 16,17-acetonide), provided by Syntex Corporation, Palo Alto, Calif., and shown in Fig. 1, was supplied in plastic squeeze bottles containing 0.025% flunisolide dissolved in vehicle (a mixture of polyethylene glycol and propylene glycol). Indistinguishable squeeze bottles containing only the vehicle were provided for the control group.

Patients were instructed to administer two sprays in each nostril in the morning and at bedtime, by placing the tip of the vial in each nostril, squeezing the bottle, and inhaling the spray simultaneously.

Selection of patients

Patients were drawn from a group of individuals previously known to the Center for Allergic Diseases at The Good Samaritan Hospital, as well as from a large group that responded to a newspaper article calling for volunteers to try new methods of hay fever therapy.

Patients having seasonal or perennial rhinitis with distinct exacerbations during the local ragweed season, for at least the past two seasons, who also gave 2+ intradermal skin reactions to crude ragweed extract containing $\leq 10^{-1}$ protein nitrogen units (PNU)/ml, were selected for inclusion in the study. The low ragweed pollen extract used for skin testing contained 28 μ g of antigen E per 10,000 PNU.

Patients with underlying nasal pathology or who were receiving medication which might mask symptoms of allergic rhinitis were excluded from further consideration.

Of the patients selected, one had received preseasonal immunotherapy for the prior ragweed season with unsatisfactory results and had not received further treatment.

All patients selected gave informed consent.

METHOD OF STUDY

Fifty-one patients were selected for study. Patients were paired on the basis of similar skin reactivity to crude ragweed extract. One patient of each pair was randomly assigned to receive flunisolide and one to receive vehicle alone. Neither patient nor physician knew the contents of the squeeze bottles assigned.

The resulting two treatment groups were comparable with respect to age, sex, and duration of hay fever symptoms.*

The study was divided into three segments: a pretreatment period that included the time

*Data available on request.

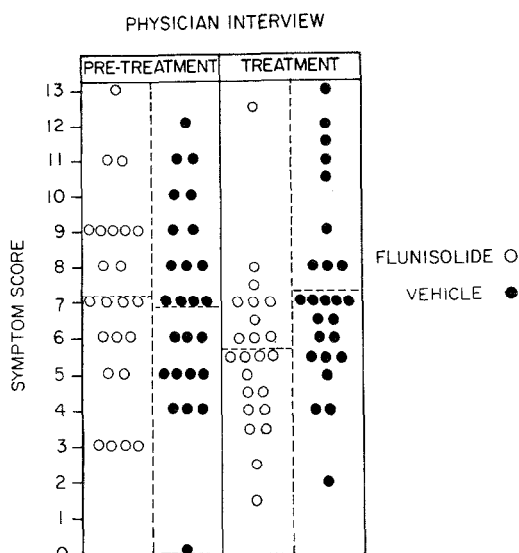


FIG. 2. Symptom scores derived from physician interviews for each patient prior to and during nasal aerosol treatment. Horizontal bars represent the average score of the group of patients in each vertical column.

of initial ragweed pollination; a treatment period which encompassed the time of peak ragweed pollination; and a posttreatment period which coincided with the end of the local ragweed season. On Aug. 12, 1974, each patient was supplied with symptom diary sheets, to be filled out twice daily, and antihistamine tablets, brompheniramine maleate, 4 mg, to be taken only if needed. On Aug. 26, 1974, patients received plastic squeeze bottles with instructions for their use. On Sept. 22, 1974, nasal aerosol was discontinued. From Aug. 12 to Oct. 7, 1974, patients returned at biweekly intervals for physician evaluation.

Evaluation of results

Symptom evaluation

This was carried out by the technique previously reported.⁶ Patients were requested to fill out symptom diaries in the morning and at bedtime, recording the duration of sneezing, rhinitis, conjunctivitis, and cough, for the preceding 12 hr. Symptom duration was ranked from 0 to 3 depending on whether the particular symptom was not present (0), present less than 30 min (1), present 30 min to 2 hr (2), or present more than 2 hr (3). The number of antihistamine tablets used in the same 12-hr period was also recorded and added to the symptom duration scores to derive a symptom score for each patient (or each group of patients) for each day of the ragweed season.

Physician evaluation

At 2-wk intervals each patient was seen by a physician and asked to rate the intensity of nose, eye, and throat symptoms for the preceding 2-wk period. Symptom intensity was ranked from 0 to 3 depending on whether symptoms were absent (0), mild (1), moderate (2), or severe (3). Nasal symptoms were also ranked from 0 to 3 based on the degree of interference with daily activity; i.e., no interference (0), less than 30 min interference (1), 30 min to 2 hr interference (2), and more than 2 hr interference (3). Scores for each patient were combined to yield a single physician interview score reflecting the intensity of symptoms for the two preceding weeks.

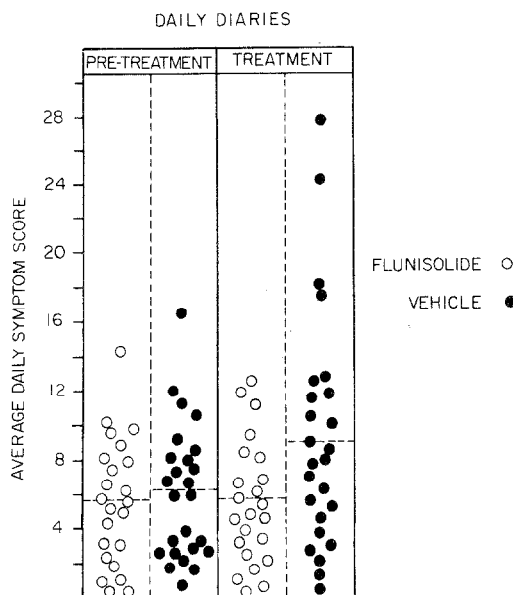


FIG. 3. Symptom scores derived from the daily diaries of each patient for the pretreatment and treatment period. Horizontal bars represent the average score of the group of patients in each vertical column.

Patients were also questioned as to the occurrence of unusual or unpleasant symptoms associated with nasal aerosol use in the preceding 2-wk period.

In addition to interviews, each patient was examined at 2-wk intervals for signs or systemic steroid effect and adverse effect of the nasal aerosol on the mucous membranes of the nose and throat.

Laboratory evaluation

Blood samples for plasma cortisol determinations were obtained from each patient on three successive mornings before 9 A.M. prior to and after 3 wk of nasal aerosol use. Plasma specimens were frozen immediately, stored, and mailed en bloc to Syntex Laboratories, Palo Alto, Calif., for cortisol determination.

RESULTS

Of the 51 patients originally selected for study, data were obtained from 48 (23 pairs). Of these patients, 23 were in the flunisolide-treated group and 25 were in the vehicle-treated group.

Physician evaluation

Fig. 2 shows a scattergram of the symptom scores of each patient derived from physician interviews in the pretreatment and treatment periods. By the Mann-Williamson U test, the symptom scores of the flunisolide and vehicle-treated groups were not different in the pretreatment period ($p = NS$), demonstrating both groups to be well matched with respect to the intensity of their hay fever symptoms. During the treatment period, however, a significant differ-

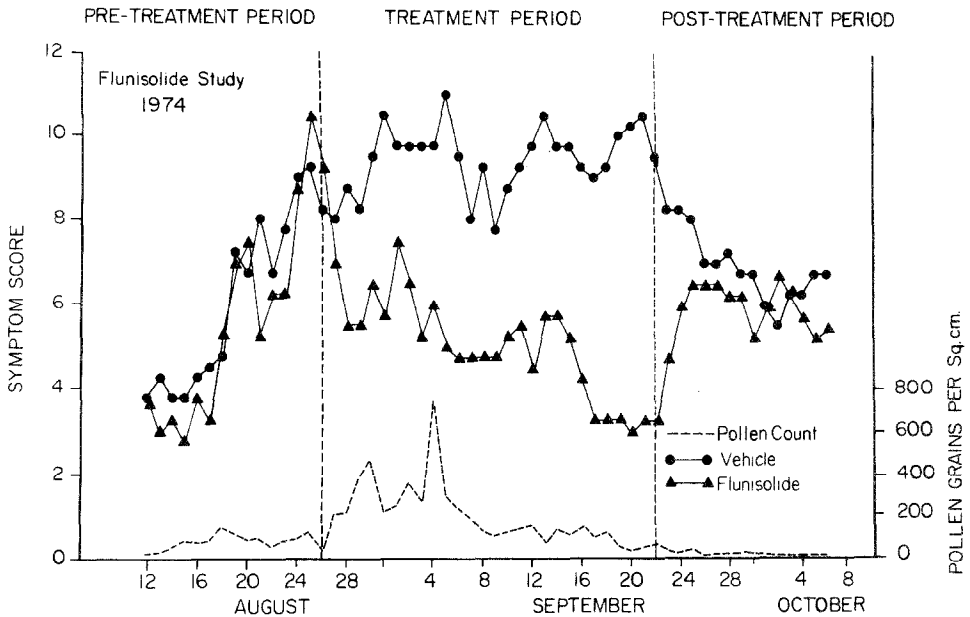


FIG. 4. Average daily symptom scores of each treatment group and the daily ragweed pollen count for the entire study period.

ence between the symptom scores of the two treatment groups is found ($p < 0.001$), with the flunisolide-treated group reporting less severe hay fever symptoms.

Symptom diaries

A scattergram of the average symptom scores for each patient computed from their diaries during the pretreatment and treatment periods is shown in Fig. 3. No difference between the symptom scores of the two treatment groups was found in the pretreatment period ($p = \text{NS}$), whereas a significant difference was found between the flunisolide and vehicle groups during the treatment period ($p < 0.01$), once again demonstrating the beneficial effect of flunisolide in suppressing hay fever symptoms.

The average symptom scores for each group of patients receiving treatment and the pollen count were computed daily for the entire study period and are shown in Fig. 4. In the pretreatment period, both treatment groups responded to the inhalation of ambient ragweed pollen by a comparable increase in the level of hay fever symptoms. Following administration of flunisolide, a prompt diminution in the level of hay fever symptoms was noted in the flunisolide-treated group followed by a sustained, progressive decrease in symptom scores for the remainder of the treatment period. This is in distinct contrast to the level of hay fever symptoms reported by the vehicle-treated group. After the treatment aerosols were discontinued, both groups rapidly approached similar posttreatment symptom score levels, without any observable persistence of steroid effect on the

TABLE I. Adverse effects of aerosol therapy*

	Flunisolide	Vehicle
Nasal irritation	2	10
Nasal dryness	2	1
Sore throat	1	
Sneezing	1	2
Unpleasant residual taste	2	
Dry mouth		1
Stomatitis		1
Total	8	15

*Numbers of responses tabulated include multiple unpleasant reactions reported by individual patients.

hay fever symptoms of the flunisolide-treated group. The graphed data demonstrate the comparability of both groups, in the pre- and posttreatment periods, as well as the improvement of the hay fever symptoms of the flunisolide-treated group when compared to the vehicle-treated group.

Adverse effects

Unusual or unpleasant symptoms that appeared to be related to aerosol use are tabulated in Table I. Unpleasant reactions were described by 6 patients receiving flunisolide and 13 patients receiving vehicle.

Unpleasant symptoms usually occurred within the first weeks of therapy, rapidly disappeared, and were of minor intensity and duration, lasting no longer than several minutes. However, 3 patients noted transient nasal irritation following inhalation of the vehicle throughout the treatment period, and 1 additional patient developed this symptom in the last 2 wk of treatment. Among patients inhaling flunisolide, 2 complained of transient nasal dryness and 1 noted transient nasal irritation throughout the entire treatment period. In the last 2 wk of flunisolide treatment, 1 patient complained of residual unpleasant taste and 1 patient who had initially noted nasal dryness also began complaining of transient nasal irritation.

Nevertheless, none of the adverse effects reported, whether noted at the beginning, end, or throughout the treatment period, approached the intensity to even consider limiting nasal aerosol use. The disparity in the incidence of nasal irritation between the two treatments appears related to a transient, local, irritant property of the vehicle which is suppressed by flunisolide.

Examination of the mucous membranes of the nose and throat failed to reveal any apparent adverse effect related to treatment, nor was any sign of systemic steroid effect noted on physical examination.

Laboratory evaluation

Averages of the three morning cortisol levels obtained prior to and after 3 wk of treatment are shown in Fig. 5. Both treatment groups tended to have slightly lower plasma cortisol levels after 3 wk of therapy when compared to their pretreatment levels. However, when subjected to analysis by *t* test, the cortisol levels of each treatment group were not significantly different from each other, either prior to or after 3 wk of treatment. Thus, no evidence of suppression

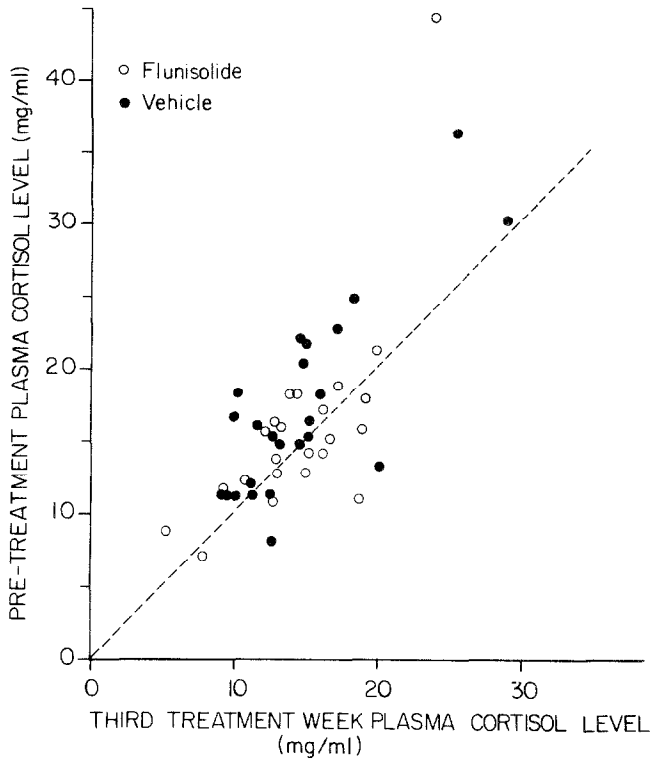


FIG. 5. Average plasma cortisol levels of each patient obtained prior to and after three weeks of aerosol treatment.

of adrenocortical function was found after inhaling the therapeutic dose of flunisolide.

Since flunisolide was administered via a squeeze bottle, dosages inhaled varied from patient to patient depending on the vigor of squeezing the plastic bottles. To determine the daily inhaled dose of flunisolide, the filled squeeze bottles were weighed prior to treatment and after final use, at the end of treatment. By this method from 20 to 200 μg of flunisolide were found to be inhaled daily, with 17 of 23 patients inhaling less than 100 μg per day. Correlation of the daily inhaled dose of flunisolide with each patient's rhinitis score failed to show a significant dose-response relationship.

DISCUSSION

The efficacy of flunisolide was demonstrated by comparing the effect of two treatment aerosols, one containing flunisolide dissolved in vehicle, the other vehicle alone, on the hay fever symptoms of two groups of patients. Differences in hay fever symptoms during treatment, therefore, could be due to either differences in the treatment aerosols received or to differences between the patients in the two groups.

The data presented demonstrate that the patients in the two groups were com-

parable. They were well matched as to age, sex, duration of symptoms, level of pretreatment symptom scores, and they responded similarly to exposure to ambient ragweed pollen. Consequently, the difference in hay fever symptoms during treatment was due to the two different treatment aerosols administered. Aerosolized flunisolide has been shown to significantly suppress hay fever symptom scores when compared to the vehicle-treated group. However, aerosolized vehicle has also been shown to produce unpleasant nasal symptoms in a small number of patients. A question is thus raised whether the difference in symptoms between the two groups was exaggerated by some adverse effect of the vehicle treatment. In the absence of an untreated control group of hay fever patients, this question cannot be answered directly. There are several lines of evidence, however, that suggest a lack of significant adverse effect of the vehicle treatment on hay fever symptom scores.

In the first 2 wk of treatment when 9 of 25 patients taking vehicle complained of adverse effects, hay fever symptom scores fluctuated with the ragweed pollen counts and did not significantly exceed the peak hay fever symptom scores recorded prior to treatment. No overriding adverse impact of the vehicle aerosol on hay fever symptoms was thus noted in the first 2 wk of treatment. In the last 2 wk of treatment, when only 4 of 25 patients complained of unpleasant nasal symptoms, symptom scores did not exceed the first 2 wk of treatment and were similar to the level of scores recorded by untreated patients followed in prior seasons.⁶ This sustained level of hay fever in late September at a time of decreasing pollen counts is typical of the local ragweed season and is thought to reflect some combination of inhalation of fragmented ragweed pollen, priming of the nasal mucosa from prior exposure, or nonallergic factors such as vasomotor influences. Although the drop in symptom scores appears temporally related to discontinuing vehicle, it also coincides with the end of the local ragweed season, documented in previous years by a decrease in the symptoms of untreated hay fever patients at a similar date.⁶

Since the unpleasant nasal symptoms associated with vehicle were distinct from the patient's typical hay fever symptoms, they were not directly recorded in the symptom diaries.

The symptom scores of the vehicle-treated group are thus seen to reflect their eye and nasal responses to the conditions of the local ragweed season, rather than any adverse effect due to the vehicle itself. Consequently, the significant difference between the hay fever symptoms of the two treatment groups accurately demonstrates flunisolide's efficacy in suppressing hay fever symptoms.

The two methods used in this study to determine the severity of hay fever symptoms were daily symptom diaries and physician interviews. Previous studies have shown symptom scores derived from daily diaries to correlate better with ragweed pollen counts and basophil sensitivity to ragweed allergen than do symptom scores obtained from physician interviews.⁷ Daily symptom scores, therefore, more accurately reflect the severity of hay fever symptoms, accounting for the discrepancy in the level of hay fever symptoms reported by the vehicle group during treatment. Whereas physician interview symptom scores (Fig. 2) indicate no significant increase in the level of symptoms during vehicle treatment, when

pollen counts were highest, symptom diary scores show the expected worsening of symptoms (Fig. 3). This difference is attributable to limitations in the interview technique due to less frequent reporting, biasing symptoms in favor of the most recent symptoms experienced, and to interviewer influence, generally biasing patients to minimize the intensity of symptoms reported.⁸ Since both treatment groups and the interviewing physicians were blinded to the treatments received, whatever bias existed in the reporting of symptom scores was reflected equally by both treatment groups. The limitations of interview technique, therefore, do not negate the significant improvement in hay fever symptoms reported by flunisolide-treated patients in their physician interviews and confirmed by their symptom diary scores.

The present study, in addition to showing flunisolide's efficacy in suppressing hay fever symptoms, also demonstrated that inhalation of the therapeutic dosage of flunisolide did not result in either signs of systemic absorption or adrenal suppression. Even the highest dose of flunisolide inhaled (200 $\mu\text{g}/\text{day}$) is still at least 4 to 5 times less than the daily dose required to suppress adrenocortical function in normal volunteers.⁹ Thus, flunisolide provides a wide margin of safety for patient use. This high topical to systemic activity ratio may be related to esterification at the C-17 position, for both beclomethasone dipropionate and betamethasone 17-valerate appear to have augmented topical activity compared to their non-C-17-esterified parent compounds.^{10, 11} Metabolic inactivation of the orally absorbed portion of the inhaled steroid may also contribute to the lack of systemic side effects.¹²

The long-term effect of flunisolide aerosol is as yet unknown. Experience with other potent steroid aerosols, e.g., dexamethasone, betamethasone 17-valerate, and beclomethasone dipropionate, on the nasal mucosa demonstrates the lack of significant adverse effects, other than nasal irritation in a small percentage of patients and nasal septal perforation in several dexamethasone-treated patients.¹³ There have been no reports to our knowledge of nasal mycosis following inhalation of nasal steroids.

The lack of systemic adrenocortical side effects suggests that the efficacy of flunisolide in the treatment of perennial rhinitis should be further assessed.

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