

# Suppression of hay fever symptoms with intranasal dexamethasone aerosol

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Dexamethasone phosphate aerosol was tried intranasally in a dose of 1 mg. daily in 40 patients with seasonal ragweed hay fever, with the use of a double blind crossover plan of study. By three methods of evaluation applied independently, significant improvement of hay fever symptoms was obtained in about 75 per cent of patients. No steroid side effects were observed; some patients complained of nasal irritation immediately after spraying.

**I**ntranasal application of a variety of steroid preparations has been reported to alleviate the symptoms of allergic rhinitis, both seasonal and nonseasonal. The hydrocortisone-free alcohol in solution,<sup>1</sup> 9  $\alpha$ -fluorohydrocortisone spray,<sup>2</sup> prednisone aerosol,<sup>3</sup> powdered hydrocortisone,<sup>4-6</sup> and cortisone acetate spray<sup>7</sup> apparently have shown good results in uncontrolled studies. Godfrey, Maunsell, and Pearson<sup>8</sup> reported that prednisone snuff suppressed symptoms of hay fever in 16 to 20 treated patients, whereas only 7 of 18 control patients responded to placebos. None of these preparations, however, has gained widespread use in therapy. More recently, uncontrolled clinical trials have suggested that dexamethasone phosphate in aerosol form sprayed intranasally is effective therapy for nasal polyps<sup>9</sup> and pollen hayfever.<sup>10, 11</sup>

The current study, with appropriate controls, was undertaken to assess further the possible efficacy of intranasal dexamethasone aerosol in seasonal hay fever. Clinical evaluation of results in ragweed-sensitive hay fever patients, with a carefully controlled double blind crossover plan of study, confirms the earlier reports of the efficacy of this preparation. Steroid side effects were not detected.

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## MATERIALS AND METHODS

### Dexamethasone aerosol

Cartridges of dexamethasone aerosol for intranasal application (Turbinaire\*) were used. Each unit contained 18 mg. of dexamethasone phosphate as the free acid, 252 mg. of anhydrous ethanol, and sufficient Freon propellant to make 12.6 gm. total. The metered value was calibrated to deliver 0.10 mg. dexamethasone phosphate (equivalent to 0.08 mg. dexamethasone alcohol) with each actuation. The dose was two inhalations in each nostril three times a day (12 inhalations) for total daily dose (at the nozzle) of about 1.0 mg. dexamethasone. Indistinguishable placebo units which contained the same amount of alcohol and Freon without dexamethasone phosphate were also provided.

Patients were instructed to shake the unit vigorously, insert the nozzle into the nostril with the vial upside down, and to sniff in when the aerosol was delivered.

### Selection of patients

Adult patients were selected from a large group of individuals who responded to a newspaper story calling for volunteers to try new methods of treatment for hay fever. Patients with a definite history of ragweed hay fever (some also had hay fever during tree and grass seasons) who, except for 4 patients, had not been desensitized for at least 4 years, were selected for further

\*Provided by Merck Sharp & Dohme Research Laboratories, West Point, Pa.

Table 1. Pairing of patients

| Group I     |     |     |                              |                           | Group II    |     |     |                              |                           |
|-------------|-----|-----|------------------------------|---------------------------|-------------|-----|-----|------------------------------|---------------------------|
| Patient No. | Sex | Age | Duration of symptoms (years) | Previous desensitization* | Patient No. | Sex | Age | Duration of symptoms (years) | Previous desensitization* |
| 1           | M   | 23  | 18                           | No                        | 2           | M   | 23  | 14                           | No                        |
| 4           | M   | 25  | 22                           | No                        | 3           | M   | 26  | 22                           | No                        |
| 6           | M   | 31  | 25                           | Yes, 20                   | 5           | M   | 30  | 23                           | Yes, 15                   |
| 8           | M   | 32  | 15                           | No                        | 7           | M   | 30  | 20                           | No                        |
| 9           | M   | 35  | 14                           | No                        | 10          | M   | 35  | 15                           | No                        |
| 12          | M   | 37  | 3                            | Yes                       | 11          | M   | 38  | 4                            | No                        |
| 14          | M   | 39  | 25                           | No                        | 13          | M   | 40  |                              | No                        |
| 15          | M   | 43  | 8                            | No                        | 16          | M   | 44  | 7                            | No                        |
| 18          | M   | 47  | 40                           | Yes, 15                   | 17          | M   | 49  | 37                           | Yes, 6                    |
| 19          | M   | 52  | 26                           | No                        | 20          | M   | 55  | 33                           | No                        |
| 22          | F   | 23  | 14                           | No                        | 21          | F   | 20  | 14                           | Yes, 1                    |
| 23          | F   | 24  | 12                           | No                        | 24          | F   | 25  | 12                           | Yes, 4                    |
| 26          | F   | 31  | 12                           | No                        | 25          | F   | 32  | 10                           | Yes, 5                    |
| 27          | F   | 31  | 26                           | Yes, 15                   | 28          | F   | 32  | 20                           | Yes, 12                   |
| 29          | F   | 39  | 15                           | Yes, 4                    | 30          | F   | 37  | 14                           | Yes, 13                   |
| 31          | F   | 37  | 9                            | No                        | 32          | F   | 38  | 11                           | Yes, 5                    |
| 34          | F   | 42  | 23                           | Yes, 3                    | 33          | F   | 42  | 18                           | Yes, 13                   |
| 36          | F   | 43  | 10                           | Yes, 5                    | 35          | F   | 42  | 9                            | No                        |
| 37          | F   | 48  | 22                           | No                        | 38          | F   | 47  | 24                           | No                        |
| 39          | F   | 49  | 23                           | Yes, 15                   | 40          | F   | 52  | 23                           | Yes, 15                   |

\*Desensitization treatment with specific antigens. The number of years since the last injection is shown.

study. Of the 24 patients who had been desensitized previously, none reported a satisfactory result. Thirty-seven of the patients selected had a positive intradermal skin test to short ragweed extract containing 10 PNU per milliliter or less. One was positive to 100; one to 1000, and one to 10,000 PNU per milliliter. The age, sex, duration of symptoms, and prior desensitization treatment of the patients are shown in Table I.

### **Method of study**

Forty patients were selected for study. Pairs of patients were matched as closely as possible as to sex, age, and duration of symptoms (Table I). Initially, one patient of each pair was assigned at random to receive dexamethasone aerosol and one to receive placebo. Neither patient nor physician knew the contents of the aerosol. Each patient was given an aerosol unit on August 21. Each was also supplied with tablets of an antihistamine, dimethpyridine maleate (Forhistal) 1 mg., with instructions to take only if needed. The patients returned two weeks later, on September 4, for evaluation of results. At that time, they received a new unit containing the alternate medication; i.e., the dexamethasone group was switched to placebo and vice versa. The patients returned for a second evaluation after two more weeks (September 18), at which time all patients received a dexamethasone unit to complete the hay fever season.

### **Evaluation of results**

*Physician evaluation.* At each two-week visit each patient was interviewed by one of us and asked to rate each symptom—sneezing, stuffy nose, rhinorrhea, and red itchy eyes—as severe, moderate, slight, or none. The nose was examined, and the edema of the mucous membranes and amount of secretion were rated on the same scale. The color of the membranes was described as pale, very red, slightly red, or normal. The patient's ratings of each symptom were numerically scored on basis of 0 for no symptom, 1 for slight, 2 for moderate, and 3 for severe. The physician's examination was rated separately on a similar scale. Each antihistamine taken was counted as 1 on the rating scale. These symptoms scores and physical examination scores were then totaled and tabulated for statistical analysis.

*Patient evaluation.* Patients were also asked to compare their symptoms for each two-week period with their symptoms during the previous year's hay fever season and rate their symptoms as worse, the same, or 25 per cent, 50 per cent, 75 per cent, or 100 per cent improved.

*Symptom diaries.* A daily symptom diary card was also supplied to each patient and he was asked to rate at bedtime his symptoms for the previous 24 hours. Separate ratings were given for (1) sneezing, (2) stuffy or runny nose, (3) red, itchy eyes, and (4) cough, each being scored as none (0), occasionally part of the day (1), occasionally all day (2), or steadily all day (3). The number of antihistamine tablets taken daily was also listed and the degree of relief obtained was scored as complete, partial, or none. These data were converted to numerical scores and each patient's total symptom score for each day was derived for statistical analysis.

## RESULTS

Of the 40 patients originally selected for study, data were obtained from 38. Of the 38, two patients were unable to use the aerosol because of irritation immediately after spraying. One of these tried only the placebo aerosol and the other tried the dexamethasone aerosol. A third patient did not use the placebo aerosol during the first period because of irritation but at the next period she received the dexamethasone aerosol, found it acceptable, and was able to use it with good results. Adequate data for evaluation were obtained from 36 patients or 17 pairs (two patients unpaired) during the first period of treatment and from 36 patients or 18 pairs during the second period.

### Physician evaluation

Table II shows the distribution of patients according to the physician score obtained from both interview and examination. The scores tended to be higher among patients receiving placebos than among patients receiving dexamethasone, particularly during the second two-week period.

Table III shows the result of comparing paired patients and shows that the treated patient was better in 13 of 17 pairs during the first period, and that, likewise, the treated patient was better in 16 of 18 pairs during the second period.

The differences in symptom and physical examination scores were evaluated statistically by the standard method of testing for crossover analysis of variance designs.<sup>12</sup> This method of analysis adjusts for variations due to innate differences among individuals other than the differences ascribable to treatment. It also adjusts for differences in exposure to pollen occurring in the two different time periods. Sufficiently complete data from both patients of a pair for both periods were available from 16 pairs of patients. The average physician score during placebo administration was 13.3, whereas the average score during dexamethasone treatment was 8.3. The difference between these scores was highly significant ( $p < 0.0005$ ).

The two treatment periods of each patient, one placebo and one Turbinaire, were also compared, thus allowing each patient to act as his own control (Table IV). Of the 35 patients from whom there were data, 27 were better, i.e., had lower scores; one reported no difference; and 7 were worse during dexamethasone treatment. Five of the 7 patients who were listed as being worse on dexamethasone had such small differences in scores between the dexamethasone and the placebo treatment periods that they should probably be classified as "unchanged" rather than worse. Similarly, 4 of the 27 patients classified as improved might be considered as unchanged. Consequently, it may be more accurate to say that 23 patients were improved by dexamethasone, 10 were unchanged, and 2 were worse.

### Patient's evaluation

Patient evaluation of improvement compared to the previous season is illustrated in Table V. Twenty-eight of 37 reported improvement of 50 per cent

**Table II.** *Patient scores obtained from physician interview and examination*

| <i>Total score</i> | <i>Period 1</i>      |                | <i>Period 2</i>      |                |
|--------------------|----------------------|----------------|----------------------|----------------|
|                    | <i>Dexamethasone</i> | <i>Placebo</i> | <i>Dexamethasone</i> | <i>Placebo</i> |
| 0-5                | 7 patients           | 2 patients     | 10 patients          | 1 patient      |
| 6-10               | 4                    | 4              | 4                    | 3              |
| 11-15              | 5                    | 7              | 3                    | 7              |
| 16-20              | 1                    | 3              | 0                    | 4              |
| 21-25              | 2                    | 1              | 1                    | 1              |
| 26-30              | 0                    | 0              | 0                    | 2              |
| Total patients     | 19                   | 17             | 18                   | 18             |
| Average score      | 9.6                  | 12.2           | 6.2                  | 14.8           |

**Table III.** *Distribution of differences in physician interview and examination scores in paired patients*

| <i>Score differences</i>                     | <i>Period 1<br/>(17 pairs)</i> | <i>Period 2<br/>(18 pairs)</i> |
|----------------------------------------------|--------------------------------|--------------------------------|
| + 9 to + 5                                   | 3                              | 2                              |
| 0                                            | 1                              | 0                              |
| Total worse or unchanged<br>on dexamethasone | 4                              | 2                              |
| - 1 to - 4                                   | 7                              | 2                              |
| - 5 to - 8                                   | 3                              | 4                              |
| - 9 to - 12                                  | 2                              | 5                              |
| - 13 to - 15                                 | 1                              | 2                              |
| - 16 to - 19                                 | 0                              | 2                              |
| - 23                                         | 0                              | 1                              |
| Total better on dexametha-<br>sone           | 13                             | 16                             |

+sign used when *placebo*-treated member of the pair was better (had lower score).-sign used when *dexamethasone*-treated member of the pair was better (had lower score).**Table IV.** *Distribution of differences in physician interview and examination scores comparing dexamethasone and placebo periods in each patient\**

| <i>Score differences</i>                       | <i>No. of patients</i> |
|------------------------------------------------|------------------------|
| + 7 to + 3                                     | 2                      |
| + 2 to + 1                                     | 5                      |
| 0                                              | 1                      |
| Total unchanged or worse on dexametha-<br>sone | 8                      |
| - 1 to - 2                                     | 4                      |
| - 3 to - 7                                     | 9                      |
| - 8 to - 11                                    | 10                     |
| - 11 to - 14                                   | 4                      |
| Total better on dexamethasone                  | 27                     |

\*Patients serve as own controls.

+sign used if patient was worse during dexamethasone treatment.

-sign used if patient was better.

or more on dexamethasone therapy, whereas only 8 of 34 reported 50 per cent or more improvement on placebo.

### Symptom diaries

Thirty-two patients turned in adequately filled-out daily symptom diaries for evaluation. Fig. 1, top graph, illustrates the curve of the average daily symptom scores of the two groups, which shows that the dexamethasone-treated patients had lower scores than placebo-treated patients during both the first and second periods; this difference was greater during the second period. During the third period, when all patients were treated with dexamethasone, symptoms declined in the former placebo group, as the downward curve of the upper line illustrates. The middle and lower graphs show, interestingly, that eye symptoms as well as nose symptoms were improved during dexamethasone.

The average daily symptom scores of 14 pairs of patients were analyzed

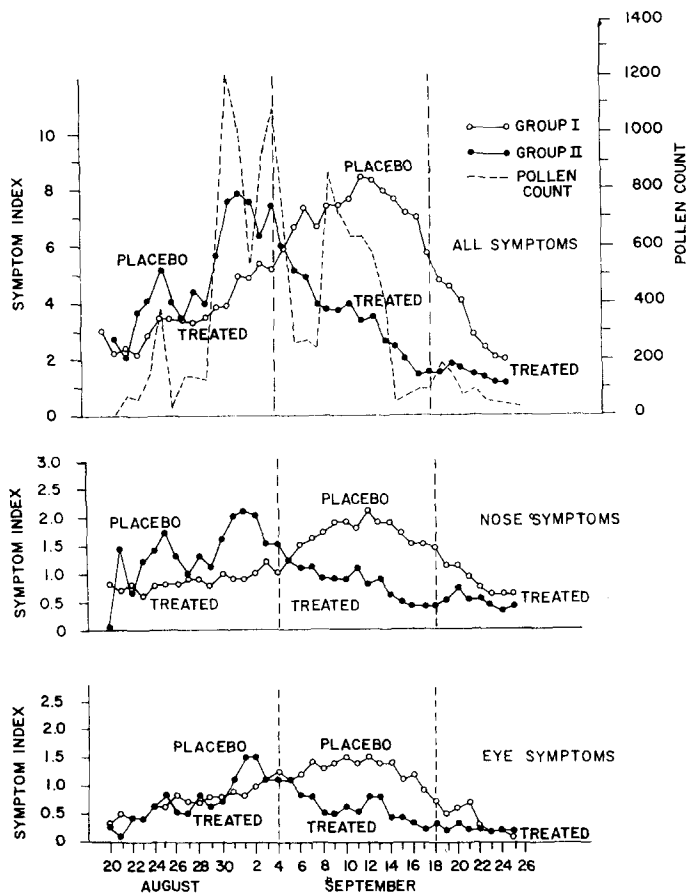


**Fig. 1**

Average daily symptom scores of hay fever from daily symptom diaries.

statistically by the same method used for the physician scores. The average score was 6.0 during placebo and 3.9 during treatment. The difference between these scores was highly significant ( $p < 0.001$ ).

**Table V.** *Patient's evaluation of improvement (comparison with previous season)*

| <i>Evaluation</i>           | <i>Placebo</i> | <i>Dexamethasone</i> |
|-----------------------------|----------------|----------------------|
| Worse                       | 4              | 1                    |
| Same                        | 14             | 6                    |
| 25% improved                | 8              | 2                    |
| 50% improved                | 5              | 8                    |
| 75% improved                | 3              | 15                   |
| 100% improved               | 0              | 5                    |
|                             | 34             | 37                   |
| 50 % improvement or greater | 8/34           | 28/37                |

The average symptom scores from diary cards for each two-week period, one dexamethasone and one placebo, were also compared for individual patients, allowing each patient to serve as his own control. Of the 32 patients from whom there were data which could be evaluated by this method, 24 were improved, i.e., had lower scores, and 8 were worse. If minor differences in symptom scores are ignored, however, only 17 of the 32 patients reported definite and unquestioned improvement, whereas 1 reported worsening on dexamethasone, when results are measured by symptom scores. The remaining 14 should probably be considered essentially unchanged by treatment.

## DISCUSSION

In this study three methods of evaluation of therapy were used independently: (1) physician interview and examination; (2) patient's subjective opinion of severity of symptoms compared to the previous season; and (3) a daily symptom diary. All three methods of evaluation showed similar results. For example, the first method of evaluation indicated that 29 of 35 patients were improved; the second method, that 28 of 37 were improved; and the third method, that 24 of 32 were improved. One may conclude, therefore, that an aerosol of dexamethasone phosphate suppressed ragweed hay fever symptoms in approximately three quarters of patients at the dosage level used in this study.

Ten patients, however, showed little or no change in symptoms, and, in 2 patients, symptoms seemed to be intensified. Lack of symptom response in some of these 12 patients may be related to inadequate use of the aerosol. If the recommended dosage schedule was followed, the units should have been nearly exhausted in two weeks. Some units were returned after two weeks' use and weighed to determine how much medication remained. In the two periods, 80 aerosol units were distributed; 46 units were returned, of which 16 (5 placebo and 11 dexamethasone) still contained half or more of the aerosol, indicating that these (and perhaps other) patients failed to use the units as directed. Of the 11 patients who returned inadequately used dexamethasone units, 8 re-

ported symptomatic improvement, 2 were unchanged, and one was worse. These data raise the possibility that, in some patients, less than the recommended dosage may be effective in suppressing hay fever symptoms. On the other hand, only 3 of the 12 patients who were *not* improved on dexamethasone returned units, too few to determine whether this group used the units properly or not. Mechanically, the aerosol units were quite reliable. Of the 120 units furnished for this study, only one failed to function properly and had to be replaced.

Although no dexamethasone is deposited in the eye from the intranasal use of the aerosol, eye symptoms were suppressed similarly to nose symptoms (Fig. 1, middle and lower graphs). Two explanations are possible: Decrease of edema of nasal membranes may permit better drainage through the lachrymal ducts; or, more likely, systemic absorption of the dexamethasone was sufficient for suppression of allergic reactions elsewhere than in the nose. Indeed, the latter possibility may be invoked to explain the general improvement of hay fever symptoms in this study; i.e., systemic absorption of the steroid may be necessary to obtain improvement even of the nasal symptoms. Accurate data as to the amount of steroid absorbed systemically are not available and more study on this point would be desirable.

Less symptomatic improvement was reported by the patients (Group 1) treated with dexamethasone during the first period (see Fig. 1, top graph) than was reported by the patients (Group II) treated with dexamethasone during the second period. This finding may be due to imperfect matching of the groups, in that the patients in Group I might have tended to show more severe hay fever symptoms than those in Group II. If true, this would tend to make the dexamethasone appear less effective in the first period and more effective in the second period. It is also possible that the small difference in response between dexamethasone and placebo noted in the first period was due to minimal atmospheric pollen, thus producing symptoms so mild that little difference due to therapy could be observed. This possibility is supported by the definite differences in the symptom scores obtained when pollen counts rose rapidly during the last few days of the first period.

The crossover experimental design used in this study tends to correct for variations such as those just described. These include (1) inherent differences in experimental subjects, (2) differences due to time—in this study, differences in pollen exposure between the two periods—and (3) carryover effects of the specific treatment after switching to placebos.

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