

DEXAMETHASONE AEROSOL THERAPY FOR BRONCHIAL ASTHMA

Carl E. Arbesman, M.D., Herbert S. Bonstein, M.D., and Robert E. Reisman, M.D.,
Buffalo, N. Y.*

THE value of systemic corticosteroids for the symptomatic relief of bronchial asthma has become a well-established fact. However, the well-known side effects stemming from the hyperphysiologic effects of hydrocortisone have often complicated therapy. Even the many synthetic corticosteroids developed to retain anti-inflammatory activity, while minimizing mineralocorticoid activity, have failed to resolve these difficulties. Hence, methods of administration other than systemic (oral, intravenous, or intramuscular) have been studied to produce a more effective local anti-inflammatory action without the development of significant generalized absorption and subsequent reduction of the side effects. The known effectiveness of the hydroxyl substitution at C11 of cortisone and prednisone, hydrocortisone, and prednisolone, when applied locally to the skin and mucous membranes, warranted investigation of their action on the bronchial mucosa for the relief of asthma.

Hydrocortisone in the form of powders and/or the hemisuccinate salt solution has been used in aerosols for the relief of asthma since 1954. The general consensus of many investigators¹⁻⁵ indicated that this mode of administration was effective if given in sufficient dosage (15 to 30 mg. per day) and if there were no infection or excessive amount of secretions present. Whether the beneficial action was due to systemic absorption (mouth, gastrointestinal tract, or respiratory tract) or due to local effect has not yet been clearly elucidated. However, in one report⁶ it was estimated that 18 mg. of hydrocortisone by aerosol was equivalent to 40 mg. administered orally.

Comparable results on the effectiveness of aerosol prednisolone when given in sufficient dosage have been published.^{4, 5}

In March, 1960, we had the opportunity to start a study of the effectiveness of an aerosol of one of the newer corticosteroids, dexamethasone.† This was supplied as dexamethasone phosphate in an inert freon propellant. This salt of dexamethasone is extremely water soluble.

From the Allergy Research Laboratory, Buffalo General Hospital, Departments of Medicine and of Bacteriology and Immunology, State University of New York at Buffalo, School of Medicine.

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*Training Fellow in Allergy now in Lausanne, Switzerland.

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We wish to study this type of therapy in the symptomatic relief of asthmatic patients and compare its efficacy to that of systemic steroids.

METHODS AND MATERIALS

1. *Patients*.—Asthmatic patients from the Allergy Clinics of the Buffalo General and Children's Hospitals, as well as from private practice, were used in this study. All of these patients had had complete medical and allergy work-ups, and they had been receiving indicated symptomatic medication and specific hyposensitization therapy. Only those patients who failed to respond to conventional therapy or those who were on maintenance oral corticosteroid medication were incorporated in this investigation. The ages of the patients varied from 6 to 75 years. The duration of symptoms was from one to 30 years. A total of 123 patients treated over a period of 2 to 30 months was finally available for analysis. Sixty-four of these patients had been on oral maintenance corticosteroid therapy from 2 to 120 months.

2. *Double-Blind Study*.—An additional 10 patients were studied exhaustively. Pulmonary function studies which included total vital capacity, timed vital capacity, and maximum breathing capacity were performed at the start of the study. All tests were performed on a 9 liter Collins apparatus and supervised by one of the authors (H. B.). Patients were then given either the dexamethasone aerosol or a placebo aerosol, and were advised to take the spray for a 3 week period. They were allowed to use other ancillary medication. A daily record of symptoms and type and amount of medication was kept by the patient. At the end of this 3 week interval, the pulmonary function tests were repeated, the symptom cards reviewed, the patients examined, and the other aerosol prescribed. This routine was repeated several times with each patient. Neither the physician nor the patient knew which medication was prescribed first!

3. *Materials*.—Several formulations of dexamethasone with different salts and different concentrations were available to us in the course of this study. The earlier materials were quite irritating and produced coughing and often initiated wheezing. Likewise, the taste was often not agreeable. However, with continued improvements, it was found that dexamethasone phosphate, freon propelled, was very effective and nonirritating. Sixty-nine per cent of the particle size delivered was between 0.5 to 2 microns and approximately 0.084 mg. of dexamethasone was propelled with each valve release.

4. *Dosage*.—Patients were carefully instructed as to the proper use of the aerosol and those who had not been on maintenance oral steroid therapy were started on four inhalations four times a day. This is roughly equivalent to 1.3 mg. of dexamethasone delivered by the nebulizer. Some of the material is lost in the surrounding atmosphere and some gets deposited on the oral adapter. Hence, the starting daily dosage of 16 inhalations has been calculated to be in the neighborhood of 0.75 mg. daily.

The number of inhalations would be reduced each week until the minimal amount which would still produce effective results was determined. As little

as one to two inhalations per day could keep many of the patients comfortable as a maintenance dosage.

Many different methods of transferring patients from maintenance oral steroids to the aerosol were employed. In some instances, the oral steroids were abruptly stopped and the calculated equivalent dosage of the aerosol substituted. For example, a patient on 5 mg. oral prednisone daily would receive four inhalations four times a day. This dosage was gradually reduced each week. In most cases, however, the oral corticosteroid dosage was lowered by one-half tablet per week and the corresponding amount of aerosol prescribed in its place.

RESULTS

One hundred and twenty-three chronic asthmatic patients were finally available for evaluation of the efficacy of the dexamethasone aerosol. There were 67 males and 56 females, ranging in age from 6 to 75 years.

1. *Effectiveness.*—A. *Sex and age:* Of the 67 male patients, 43, or 64 per cent, were improved, whereas 57 per cent of 56 females were benefitted.

The highest percentage of patients given relief occurred in children under 15 years of age (Table I). Twenty of these 24 patients had a dramatic response and furthermore they required relatively small dosages of the aerosol. Eleven of 15 asthmatics between 26 and 35 years of age had a good therapeutic effect. The results were not nearly as beneficial in those patients over 55 years of age.

B. *Duration of symptoms:* Twenty-four of 32 patients who had asthma for 5 years or less prior to being given this type of therapy had favorable results (Table II). Roughly 60 per cent of those patients with symptoms from 6 to 15 years had benefit. It is interesting to note that 9 of 13 patients who had suffered from asthma for over 25 years were appreciably helped.

TABLE I. RELATION OF AGE AND SEX TO EFFECTIVENESS OF DEXAMETHASONE AEROSOL

AGE RANGE (YR.)	NUMBER OF PATIENTS	NUMBER IMPROVED	TOTAL PER CENT IMPROVED
6-15			
Male	18	16	83
Female	6	4	
16-25			
Male	8	6	80
Female	2	2	
26-35			
Male	7	5	73
Female	8	6	
36-45			
Male	10	6	57
Female	11	6	
46-55			
Male	14	6	55
Female	13	9	
56-65			
Male	8	3	31
Female	11	3	
Over 65			
Male	2	1	42
Female	5	2	

TABLE II. RELATION OF DURATION OF ASTHMA TO CLINICAL RESPONSE WITH DEXAMETHASONE AEROSOL

DURATION (YR.)	NUMBER OF PATIENTS	NUMBER IMPROVED
0-5	32	24
6-15	52	31
16-25	26	11
26-35	8	5
Over 36	5	4

C. *Classification of asthma:* The patients were divided simply into the so-called extrinsic and intrinsic groups. The former had strong significant positive skin reactions and the latter all had negative skin tests.

Fifty-nine of 75 patients with extrinsic asthma had excellent symptomatic relief with the dexamethasone aerosol, whereas only 16 of 48 patients of the intrinsic type responded well (Table III).

TABLE III. EFFECT OF DEXAMETHASONE AEROSOL THERAPY ON VARIOUS TYPES OF ASTHMA

TYPE	NUMBER OF PATIENTS	NUMBER IMPROVED	PER CENT IMPROVED
Extrinsic	75	59	79
Intrinsic	48	16	33
Pulmonary emphysema	17	1	
Aspirin-sensitivity	13	6	

Of these 48 "intrinsic" asthmatics, 17 had pulmonary emphysema. Only one of these 17 had some benefit with this additional medication. Six of 13 aspirin-sensitive asthmatics were adequately controlled by the corticosteroid aerosol.

2. *Side Effects.*—With the use of the newer sprays, only 15 patients had undesirable reactions (Table IV). Two developed an aggravating cough, and another 2, oral herpes. Three patients had a marked weight gain, and another 3, a ravenous appetite without weight gain. A 74-year-old man complained of precordial pain after using the dexamethasone aerosol and one patient with hypertension stated that he developed substernal burning after inhalation.

Two children developed mild moon facies on a relatively small dosage (four to six inhalations daily), and one patient developed mild hirsutism.

TABLE IV

SIDE EFFECTS	NUMBER OF PATIENTS
Irritating throat	2
Herpes	2
Weight gain	3
Excessive appetite	3
Precordial pain (74-year-old man)	1
Substernal burning (hypertensive)	1
Hirsutism (mild)	1
Moon facies	2
Total	15

3. *Double-Blind Study.*—It soon became obvious which substance the patient was using. Eight of the 10 patients in this study, when placed on placebo therapy, required more symptomatic medication. Five of these patients were much worse within 24 to 48 hours. Hence, in many instances it was necessary to cut short the time on placebo and return to the medicated aerosol. Almost all patients responded well following dexamethasone aerosol therapy. Although the clinical response was quite evident, the change in the pulmonary function tests did not vary significantly. However, one patient (Fig. 1) showed a strong

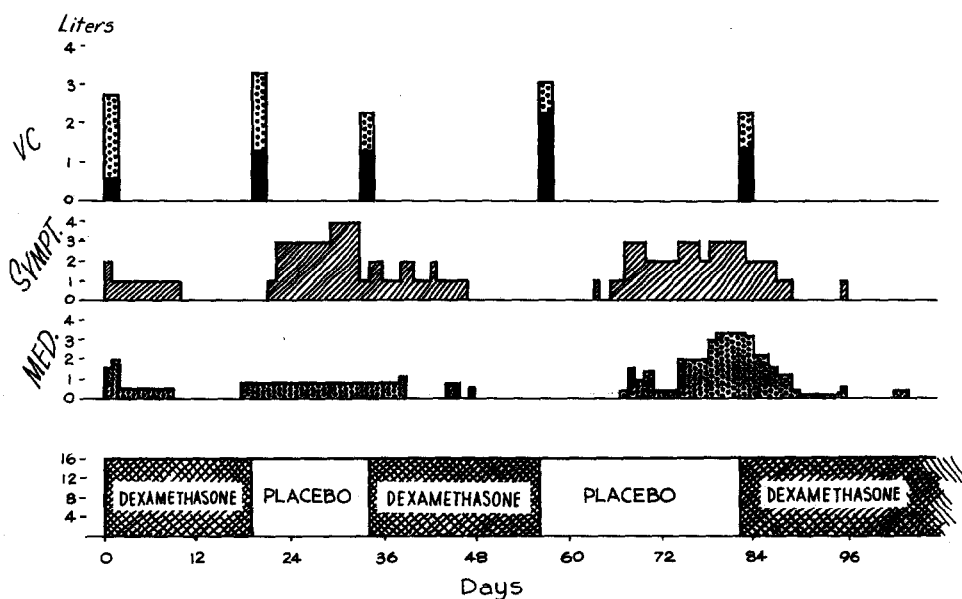


Fig. 1.—Effect of dexamethasone aerosol and placebo on total and timed vital capacity, degree of symptoms, and amount of ancillary medication.
Top row: Entire bar indicates total vital capacity. Solid bar indicates 1 second volume.
Second row: Demonstrates degree of symptoms.
Third row: Reveals amount of other symptomatic medication (exclusive of steroids) necessary to keep the patient comfortable.
Bottom row: Demonstrates when the medicated and placebo aerosols were administered.

correlation between subjective symptoms and objective measurements of respiratory function. It can be seen that after 3 weeks of the corticosteroid aerosol, there was a definite increase in the total and timed vital capacity, a decrease in symptoms, and much less ancillary medication was necessary. During the placebo period, symptoms increased, symptomatic medications increased, and the total vital capacity decreased. When dexamethasone aerosol was again administered the reverse procedure occurred. This test was repeated several times.

We had an additional group of 15 patients of whom 11 responded well to the dexamethasone aerosol. Ten of these 11 immediately relapsed when switched to a placebo spray. One patient claimed benefit by the placebo. None of the 4 patients who did not respond to the corticosteroid nebulizer were improved on the placebo.

4. *Transfer From Oral Corticosteroids to Dexamethasone Aerosol.*—Sixty-four of our 123 patients were on maintenance oral corticosteroid therapy in daily dosages ranging from the hydrocortisone equivalent of 10 to 60 mg., or an average of about 30 mg. They had been on this dosage from 2 to 120 months.

Twenty-nine of these 64 patients were able to be taken off the oral corticosteroids and maintained on the aerosol. There was no correlation between the level of maintenance oral dosage and/or the duration of receiving oral steroids to the ability to switch satisfactorily to the aerosol. However, with a severe flare-up of the asthma (usually due to infection), 4 of these 29 patients had to resort to oral corticosteroids to get them "over the hump" and then were again controlled on the aerosol alone.

Of the 35 patients who could not be controlled on the aerosol and needed systemic corticosteroids, 2 had disseminated lupus erythematosus, 3 were aspirin-sensitive, 5 had severe pulmonary emphysema, and 12 were chronic intrinsic asthmatics.

Nine patients who had had no previous corticosteroids were given dexamethasone aerosol without benefit. Eight of these asthmatics did respond favorably, however, when placed on oral corticosteroids. We found only one patient who failed to respond to the systemic steroids who was benefitted by the aerosol.

5. *Duration of Treatment.*—Patients who have responded beneficially to dexamethasone aerosol therapy were able to be adequately controlled from one month to as long as 30 months without undue effects. The dosage started at four inhalations four times daily (1.3 mg. delivered) and was gradually reduced. Some patients could be adequately controlled with as little as one to two inhalations once or twice daily.

DISCUSSION

In our group of patients, children under the age of 15 years responded most dramatically to dexamethasone aerosols and those with the extrinsic type did much better than those with the intrinsic type of asthma. The average maintenance dosage was about eight inhalations daily. This is calculated to be 0.64 mg. of dexamethasone delivered from the nebulizer. It has been shown that only about 50 per cent of this amount gets into the tracheobronchial tree. The rest is either in the mouth or exhaled. Hence, one could roughly estimate that from 0.3 to 0.5 mg. daily of dexamethasone could keep patients with moderate asthma fairly comfortable along with other adjunct therapy. Whether the beneficial effects obtained by aerosol are due to its local action or perhaps are due to better systemic absorption from the mouth and respiratory tract than from the gastrointestinal tract has yet to be determined. It has been shown, however, that minimal doses of corticosteroid (dexamethasone) by aerosol are more effective than a comparable dose ingested orally and without the dangers of the side effects of systemic steroid therapy. Franklin and his co-workers⁶ reported similar results with hydrocortisone aerosol.

It was interesting to note that although patients responded subjectively to the medication and not to the placebo, the objective findings of the respiratory

function tests did not change appreciably. In 1960 Langlands and his associates⁷ also found that patients had favorable subjective reactions to a nebulizer of hydrocortisone but they, too, found no change in respiratory function. Recently, Crepea and his colleagues⁸ reported excellent therapeutic control in 28 or 29 severely asthmatic children and a marked decrease in hyperphysiologic hormonal effects as compared to oral steroids.

A few patients who responded favorably also had a definite shrinking of nasal polyps while on dexamethasone aerosol. This also would indicate that there is a certain amount of systemic absorption. Forsham⁹ studied the effect of aerosol dexamethasone on ACTH suppression. He found that 12 inhalations (approximately 1.1 mg.) caused the urinary corticoid level to fall approximately 40 per cent. This is equivalent to an effect of 15 mg. of hydrocortisone. Therefore, 0.4 mg. of dexamethasone was absorbed to produce that amount of ACTH depression. Hence, roughly 33 per cent of the amount delivered from the nebulizer is absorbed systemically.

One of the disadvantages of this method of administration of steroids is the finding that patients with severe asthma and those with superimposed infection do not react favorably. This could be due to the thick tenacious exudate which will not allow local effects on the mucous membranes and prevent the systemic absorption of the medication. In addition, the individual with severe asthma perhaps cannot inhale the aerosol deep enough for it to be effective.

SUMMARY AND CONCLUSIONS

1. Dexamethasone aerosol is effective in relief of symptoms of mild to moderately severe asthma, particularly in children and those with asthma of the extrinsic type.
2. Patients with severe asthma and those with associated infection respond more favorably to oral steroids.
3. Many patients may be gradually weaned from maintenance steroid therapy by use of the dexamethasone aerosol.
4. The side effects are minimal from this mode of administration of steroids.
5. The exact mechanism of action, whether due to better absorption from the respiratory tract or due to its local action on the tracheobronchial tree, has not yet been determined.

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