

## EFFECTIVENESS AND COMPLICATIONS OF AEROSOL DEXAMETHASONE PHOSPHATE\* IN SEVERE ASTHMA

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AEROSOLIZED corticosteroids have been applied topically to the bronchi of asthmatic patients since 1951.<sup>1-4</sup> This method was chosen to take advantage of the superior efficiency of these drugs when applied directly at the site of desired action, thereby reducing the harmful side effects while reducing the total dosage. The earlier necessity for elaborate equipment and close technical supervision of this form of therapy has been overcome; the use of a commercially available dexamethasone phosphate aerosol has been reported upon favorably.<sup>5, 6, 7</sup> The purpose of this article is not only to report the effectiveness of this aerosol in a group of hospitalized adult patients suffering from severe asthma but also to describe a previously unreported serious complication.

### METHOD

Patients of the Adult Asthma-Allergy Ward undergo routine pulmonary function tests weekly or biweekly for an objective measure of their asthmatic state. These measurements are used clinically to control medication doses and to determine response to treatment. The forced expiratory volume in the first second (FEV<sub>1</sub>) is taken as the most convenient sensitive measurement of the intermittent airway obstruction occurring in asthma. We therefore have had in these routine tests of airway function an objective baseline, in addition to daily clinical observation over periods of 3 to 18 months prior to the start of aerosol corticosteroid therapy. This baseline period in most cases included prior attempts to reduce corticosteroid medication.

Criteria for selection of patients for study included either (1) failure to achieve reduction of oral corticosteroid dosage despite repeated attempts, (2) continued low and unstable airway function (FEV<sub>1</sub>), or (3) side effects from the administration of oral steroids. All patients included in this study had diagnoses of severe perennial asthma, based on the need for chronic moderate-to-high oral corticosteroid treatment or for daily parenteral administration of epinephrine or theophylline. Following the selection of patients, semiweekly

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airway function observations were made for several weeks to insure determination of a baseline oral corticosteroid dose and to stabilize all other medications (theophylline, epinephrine, ephedrine, etc.) for the duration of the study. All patients were then reassessed by means of semiweekly measurements of FEV<sub>1</sub> and daily clinical observation, for at least 6 weeks of aerosol corticosteroid therapy and at least 2 weeks of placebo aerosol. For a patient to be considered significantly improved, a decrease of over 50 per cent was required in oral corticosteroid dose while pulmonary function remained stable or improved. All patients "improved" were followed for at least 4 months.

Dexamethasone was self-administered in four inhalations four times daily, after preliminary trials with lower doses were found to be ineffective. While the maximum recommended dose is twelve inhalations, sixteen inhalations daily were found to be the smallest effective dose in these patients. This dose is identical with that used by Arbesman and associates to begin therapy in patients not on oral corticosteroids.<sup>7</sup> As a control, placebo aerosols were substituted during the course of therapy. These were identical in appearance and ingredients with the steroid-containing nebulizer, except for the absence of dexamethasone phosphate, and were used by the patient in a similar fashion. No preparations containing isoproterenol were used.

#### RESULTS

Twenty-five patients, fourteen female and eleven male, were studied before, during, and in some cases after, aerosol corticosteroid therapy. Thirteen patients were less than 20 years old, and the average age of the group was 31.1 years. Of the twenty-five patients, ten improved (including eight teen-agers) as measured by the previously noted standard; fifteen showed no improvement or became worse. Twenty-one patients had been receiving 10 to 24 mg. daily of oral methylprednisolone before the beginning of the study. Of these 21, eight improved in response to aerosol dexamethasone, with a coincident reduction in oral methylprednisolone dosage from a daily average of 15.4 mg. before treatment, to an average of 4.6 mg. after. In only one patient was complete discontinuance of oral corticosteroid possible. The greater incidence of response in the adolescent group, compared to those over age 21, and the failure to completely withdraw the oral corticosteroids confirm the results of a previous report.<sup>7</sup> Six of the eight patients who had improved demonstrated features of hypercorticism prior to aerosol dexamethasone; there was little change in these features even after 4 to 6 months of the greatly reduced oral dose.

Four patients were not on oral corticosteroid when started on aerosol dexamethasone. Two of these improved, but they also manifested mild features of hyperadrenocorticism following 6 weeks of sixteen inhalations daily. Studies of urinary corticosteroid levels before and during the aerosol treatment confirmed previous reports of decreased excretion of corticosteroid in the urine with aerosol dexamethasone.<sup>5</sup> In the two clinical failures, no signs of hyperadrenocorticism appeared; subsequently, both received oral methylprednisolone with good clinical response, except for exacerbation of acne. All four patients were under 20 years of age.

None of the more serious side effects of continuous oral corticosteroid therapy were found in the patients followed on this study, whether improved or not improved. Side effects reported were of the minor variety (edema, moon-face, striae, hirsutism, etc.).

The previously reported side effects of aerosol steroid therapy, such as nausea, irritation of the throat, and depression of airway function, were not marked and necessitated early discontinuance of therapy in only three patients, who are therefore not included in this study. Throat irritation and nausea were reported by five of the patients studied, including three in the "improved" group, but all were able to continue the use of aerosol. However, a more serious and previously unreported side effect did appear: clinical infection of the oropharynx with *Candida albicans* developed in five patients, and in two of the five *Candida* laryngitis developed as well. The lesions of the oropharynx responded well to nystatin mouth washes and local applications of gentian violet; however, in two patients, when aerosol dexamethasone was reinstituted following the clearing of lesions, these lesions quickly recurred despite continued nystatin therapy. Laryngeal lesions proved refractory for several months despite treatment with oral and aerosol nystatin and aerosol gentian violet. Aerosol sodium caprylate (10 per cent), as suggested by Keeney,<sup>8</sup> unfortunately provoked severe wheezing in our patients. No increase in the frequency of bacterial infections of the oropharynx or bronchi was noted, despite the inclusion in this study of several patients with chronic bronchitis. (The case histories of the five patients with *Candida* infections are appended).

Use of the placebos produced a decline in airway function in the improved patients; this fall was identical with that produced when aerosol dexamethasone was abruptly discontinued. In the unimproved patients, the use of placebos produced no change in airway function. The incidence of minor side effects was the same whether aerosolized placebo or steroid were used; however, no candidiasis occurred when the placebo was used.

#### DISCUSSION

The use of aerosol dexamethasone promotes effective reduction of dosage of oral steroids in the treatment of some adults (including adolescents) with severe asthma. Absorption from the respiratory and alimentary tract does take place, and the systemic effect cannot be discounted. Also, in six of the ten patients whose condition was improved, conventional hyposensitization injections to known allergens were begun at about the same time as institution of aerosol therapy. However, it would still appear that in at least some patients aerosol corticosteroid is several times as effective as an equivalent dose of oral corticosteroid. A further impression gained from this study was that if improvement does not occur within the first week of aerosol dexamethasone treatment none will occur, because no further improvement was found in the succeeding five weeks. This finding is not supported by other reports.<sup>5, 6</sup>

A decreased incidence of minor corticosteroid side effects was not observed with this form of treatment, and there does appear to be the additional hazard

of clinical candidiasis of the pharynx and larynx. All five patients in whom candidiasis developed had previously shown persistently positive *C. albicans* cultures of sputum and throat (in random cultures repeated at intervals), but in many months of observation clinical fungal disease was not seen, despite continued corticosteroid therapy as well as treatment with antibiotics. The last case of clinical candidiasis noted on the asthma ward had occurred 12 months before. A high incidence of positive *Candida* cultures from the upper respiratory tract is not uncommon in patients with severe asthma who have been on prolonged treatment with corticosteroids and antibiotics.<sup>9</sup> The increase of both the carrier state and of the virulence of *C. albicans* following the use of systemic antibiotics or corticosteroids, and the possible potentiating effect of both used together, has been reported extensively and requires no further discussion here.<sup>10-13</sup> One may postulate that the aerosol form of therapy deposits increased amounts of corticosteroid in the pharynx and larynx, providing an environment for *Candida* many times more fertile than that produced by systemic corticosteroids. It would seem that cultures persistently positive for *C. albicans* are a definite contraindication to the use of aerosol corticosteroids in these patients. Before institution of aerosol steroid therapy for any severely asthmatic patient, sputum cultures for *C. albicans* should be collected.

#### CONCLUSIONS

1. The daily use of sixteen inhalations of aerosol dexamethasone phosphate will permit effective reduction of oral corticosteroid dosage in some adult patients with severe asthma.
2. Candidiasis of the oropharynx and larynx would appear to be a hazard consequent on the use of dexamethasone aerosol in the minimum effective dose in patients suffering from severe asthma who have been treated with oral corticosteroids for long periods.
3. Persistently positive *C. albicans* cultures of the sputum and pharyngeal secretions should be regarded as a definite contraindication to therapy with aerosolized corticosteroid.

#### REFERENCES

1. Gelfand, M. D.: Administration of Cortisone by the Aerosol Method in the Treatment of Bronchial Asthma, *New England J. Med.* **245**: 293, 1951.
2. Brockbank, W., Brebner, H., and Pengelly, C. D. R.: Chronic Asthma Treated With Aerosol Hydrocortisone, *Lancet* **2**: 807, 1956.
3. Brockbank, W., and Pengelly, C. D. R.: Chronic Asthma Treated With Powder Inhalations of Hydrocortisone and Prednisolone, *Lancet* **1**: 187, 1958.
4. Franklin, W., Lowell, F. C., Michelson, A. L., and Schiller, I. W.: Aerosolized Steroids in Bronchial Asthma, *J. ALLERGY* **29**: 214, 1958.
5. Crepea, S. B.: Inhalation Corticosteroid (Dexamethasone PO<sub>4</sub>) Management of Chronically Asthmatic Children, *J. ALLERGY* **34**: 119, 1963.
6. Bickerman, H. A., and Itkin, S. E.: Aerosol Steroid Therapy and Chronic Bronchial Asthma, *J. A. M. A.* **184**: 533, 1963.
7. Arbesman, C. E., Bonstein, H. S., and Reisman, R. E.: Dexamethasone Aerosol Therapy for Bronchial Asthma, *J. ALLERGY* **34**: 354, 1963.
8. Keeney, E. L.: Candida Asthma, *Ann. Int. Med.* **34**: 223, 1951.
9. Weinraub, R. W., Dennis, M., and Itkin, I. H.: Unpublished data.
10. Seligmann, E.: Virulence Enhancement of *Candida albicans* by Antibiotics and Cortisone, *Proc. Soc. Exper. Biol. & Med.* **83**: 778, 1953.

11. Winter, W. D., and Foley, G. E.: Candida Infections in Children With Neoplastic Disease, *Pediatrics* **18**: 595, 1956.
12. Bendel, W. L., and Race, G. J.: Acute Disseminated Candidiasis in Aplastic Anemia, *A. M. A. Arch. Int. Med.* **108**: 916, 1961.
13. Torack, R. M.: Fungus Infections Associated With Antibiotic and Steroid Therapy, *Am. J. Med.* **22**: 872, 1957.

## APPENDIX

*Case Report No. 1, B. H.*—A 39-year-old Caucasian female had severe asthma for 8 years, progressive over the past 2 years, requiring four to twelve tablets of oral corticosteroid daily. She also had chronic recurrent bronchitis and received antibiotics frequently.

In the hospital, she had frequent attacks of asthma, necessitating elevation of methylprednisolone dose to 24 to 32 mg. per day. There were frequent courses of antibiotics for acute bronchitis. During this period sputum cultures repeatedly showed growth of *Candida albicans*, but there was no clinical evidence of candidiasis of the mouth or pharynx. She was started on a dexamethasone aerosol, four inhalations four times daily, on Dec. 7, 1962, continuing oral corticosteroid dosage of four tablets a day. On December 23 she complained of sore throat and developed white patches of the oropharynx. Culture of the lesions demonstrated heavy growth of *C. albicans*. The aerosol was discontinued for 1 week, and she was treated with nystatin and gentian violet, with complete clearing of the lesions. Aerosol dexamethasone was restarted on December 31, and oral nystatin was continued. Within 3 days, candidiasis of the mouth and pharynx recurred. Dexamethasone was discontinued for 2 more weeks and, when it was restarted on Jan. 24, 1963 (while nystatin therapy continued), recurrence of the candidiasis was noted on February 6. No antibiotics were given during the period of aerosol dexamethasone treatment.

After the aerosol dexamethasone and nystatin therapy was stopped, corticosteroid dosage varied between two to sixteen tablets daily, with frequent courses of antibiotics (including tetracycline, chloramphenicol, and penicillin) for chronic bronchitis. There was no recurrence of the candidiasis of the mouth and pharynx, despite persistently positive cultures of the sputum and throat for *C. albicans*.

*Case Report No. 2, T. W.*—A 16-year-old Caucasian male had severe asthma for 3 years. The average corticosteroid dosage was four tablets a day, and he required frequent intravenous infusions containing up to 200 mg. per day of methylprednisolone. Prior to and during hospitalization he had also received repeated courses of antibiotics (including tetracycline, penicillin, and erythromycin) for upper respiratory tract infections. He showed persistent growth of *C. albicans* in random sputum cultures during asymptomatic periods, with no history or evidence of clinical Candida infection.

On Dec. 6, 1962, the patient was started on aerosol dexamethasone, four inhalations four times a day. On December 17, he had hoarseness and a dry nonproductive cough, despite a low oral corticosteroid dose and no antibiotic medication. Over the next week he required intravenous infusions with added steroid, and so the aerosol was discontinued until Feb. 18, 1963. During this period the hoarseness and cough disappeared. On February 18 the aerosol dexamethasone was restarted, and once more progressive hoarseness appeared, along with a dry nonproductive cough. On March 21, examination of the larynx revealed a severe laryngitis with white patches over the lower pharynx and larynx. Culture swabs of the vocal cords grew *C. albicans*. After aerosol treatment was stopped there was gradual loss of hoarseness, and the appearance of the vocal cords slowly returned to normal. Despite attempts to hasten this process by nystatin orally, by gentian violet locally, and by aerosol, complete clearing did not occur until April 22. No antibiotics were given during the period of aerosol dexamethasone administration.

Following discontinuation of the aerosol dexamethasone, corticosteroid dosage has been elevated to as high as four tablets a day by mouth, and severe episodes of asthma have required intravenous infusions containing 200 to 400 mg. of methylprednisolone. He has had several further courses of antibiotics (chiefly tetracycline), with no recurrence of the hoarse-

ness or of the *Candida* laryngitis. There has been no evidence of *Candida* infection despite persistence of the positive throat and sputum cultures for *C. albicans*.

*Case Report No. 3, L. W.*—A 46-year-old Caucasian female had severe perennial asthma for 2 years and moderate asthma for 8 years. She had been on corticosteroid dosage ranging between eight to twenty tablets a day by mouth prior to hospital admission. She had also received frequent courses of antibiotics for chronic recurring bronchitis. There was no history of candidiasis, and during the present hospital stay no evidence of candidiasis occurred, despite repeatedly positive cultures for *C. albicans* on random sputum cultures.

The patient was started on aerosol dexamethasone, four inhalations four times daily, on Dec. 8, 1962. On December 22 she had a typical white patchy overgrowth on the mouth and tongue. At this time she was given gentian violet locally and nystatin orally, and by December 27 the candidiasis had cleared completely. Subsequent swabs of the mouth were negative for culture for *Candida*, although the sputum continued to show growth of *C. albicans*. On December 31 the aerosol dexamethasone was restarted, four inhalations twice a day. By Jan. 7, 1963, despite continuous nystatin therapy, the candidiasis of the oropharynx had recurred. The dexamethasone aerosol was then discontinued completely. No antibiotics were given during the period of aerosol dexamethasone administration.

Subsequently, the patient received between two to eight tablets a day of corticosteroid and several courses of antibiotics (including erythromycin, tetracycline, and chloramphenicol), with no recurrence of clinical candidiasis. Subsequent cultures of the sputum have been repeatedly positive for *C. albicans*.

*Case Report No. 4, M. D.*—A 39-year-old Caucasian female had severe perennial asthma for 5 years, requiring long-term corticosteroid therapy of two to three tablets per day. The patient had frequent courses of antibiotics (including erythromycin, chloramphenicol, penicillin, and tetracycline) in the past and during the hospital stay, with no clinical candidiasis, although cultures of the sputum have been persistently positive for *C. albicans*.

Dexamethasone aerosol, four inhalations four times a day, was started Nov. 15, 1962. On December 3 she showed an overgrowth of the mouth and pharynx with white patches which were positive on culture for *C. albicans*. Dexamethasone aerosol was discontinued, and she was started on nystatin and gentian violet, with clearing of the lesions. Following this, she was treated with various antibiotics for a *Staphylococcus aureus* bronchitis. After this cleared, the patient was restarted on dexamethasone aerosol on December 26. On January 3, 1963, she reported gradually increasing hoarseness of 1 week's duration and dry, hacking, nonproductive cough. Subsequent examination revealed laryngitis with laryngeal edema, hyperemia, and whitish material overlying the vocal cords. Cultures taken from this whitish material grew *C. albicans*. She had been taking nystatin since the last episode of candidiasis, but the dosage of this was increased, and further attempts to use aerosol nystatin and aerosol gentian violet were made. In addition, she was given aerosols of sodium caprylate, which unfortunately provoked wheezing and severe asthma. Dexamethasone aerosol was discontinued, but following this there was only gradual improvement, with complete clearing of the hoarseness and improvement in the appearance of the vocal cords in late March, 1963. No antibiotics were given during the period of aerosol dexamethasone administration.

Following complete clearing of the laryngeal lesions, oral corticosteroid doses have been as high as six tablets a day, and repeated courses of antibiotics have been given. There has been no recurrence of clinical candidiasis, although sputum cultures continue to be positive for *C. albicans*.

*Case Report No. 5, M. B.*—A 21-year-old Caucasian female had severe perennial asthma for 15 years. She had been hospitalized for 1½ years prior to the start of dexamethasone aerosol therapy. During this period there was a persistent growth of *C. albicans* in sputum cultures taken at random intervals. There was no clinical evidence of candidiasis of the tongue, oral cavity, or pharynx. She had had repeated courses of antibiotics for upper respiratory tract and urinary tract infections. Oral corticosteroid dosage had varied between four to sixteen tablets a day, and the patient had received intravenous infusions with over 400 mg. a day of methylprednisolone, with no clinical evidence of candidiasis in the oropharynx.

The patient was started on dexamethasone aerosol, four inhalations four times a day,

on Oct. 15, 1962. On November 12 she reported coating of the tongue and pain on swallowing, and white patches with ulcerations were noted over the oropharynx. *Candida albicans* was cultured from the ulcerations and the tongue. The aerosol was continued, and treatment with gentian violet locally and oral nystatin was started. While the dexamethasone aerosol was continued there was no clearing of the lesions, but with discontinuation the lesions cleared up fairly rapidly. Subsequently she received doses of corticosteroid up to 2000 mg. of methylprednisolone intravenously daily for acute asthmatic episodes and had frequent courses of antibiotics, with no recurrence of her candidiasis. No antibiotics were given during the period of aerosol dexamethasone administration.

In March, 1963, the patient received several courses of an antimetabolite (6-mercaptopurine). Subsequently, she developed agranulocytosis and anemia, with candidiasis of the oropharynx. With local treatment and gradual improvement of her agranulocytosis, the clinical *Candida* infection has cleared completely. Cultures of the sputum continue to be positive for *C. albicans*, but the oropharynx is now normal.