The Effect of Dexamethasone Aerosol on Airway Obstruction in Bronchial Asthma*

A Study Using the Forced Expiratory Volume for One Second

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THERE HAS BEEN RECENT INTEREST IN the use of aerosolized corticosteroid drugs in patients with chronic bronchial asthma. The hope is that a local effect on the bronchial mucosa will occur, thereby reducing the total daily steroid dose required and obviating some of the undesirable side effects of oral steroid administration.

The first report, by Gelfand1 in 1951, showed a favorable response in four of five patients with bronchial asthma after four days of therapy with aerosolized cortisone acetate solution in a total daily dose of 50 mg. Subsequent trials with aerosolized hydrocortisone hemisuccinate solution failed to confirm such success.4** However, clinical evaluation of relatively insoluble hydrocortisone acetate as an aerosolized powder was reported to show definite improvement in 50 to 82 per cent of asthmatics,10 comparable clinical results have been reported with aerosolized prednisolone phosphate by some authors.11*6

There have been only a few objective studies of aerosolized steroids using pulmonary function tests. Morrison Smith,5 using the forced expiratory volume for 0.75 second, was unable to find a significant benefit in asthmatic children with hydrocortisone hemisuccinate solution as compared with placebo. Langlands and McNeill12 evaluated ten chronic asthmatics on hydrocortisone acetate powder and placebo. They were unable to demonstrate improvement in the lung volumes, forced expiratory spiroms or distribution of inspired air in the treated group over the placebo group. Franklin et al13 utilized spiroms in addition to clinical evaluation of their patients. They concluded that their patients demonstrated marked improvement, but did not present their ventilatory function data.

The present study attempts to evaluate the bronchodilator effect of aerosolized dexamethasone phosphate in 26 patients with chronic asthma, utilizing the forced expiratory volume for 1.0 second (FEV1.0), also known as the one second vital capacity, and the peak expiratory flow rate (PEFR) as indices of ventilatory function. The peak expiratory flow rate is the maximum instantaneous velocity of air flow attained during a forced expiration following a full inspiration.

MATERIALS AND METHODS

Studies were performed on 26 patients with chronic asthma selected from the allergy clinics at Mt. Sinai Hospital and Michael Reese Hospital. They had been known to the clinics for at least one year. They were free of diabetes, hypertension and other illnesses contraindicating the use of steroid therapy. None was on oral steroid therapy at the time of the study, nor had any received steroid therapy during
the preceding three months. There were four men and 22 women with ages ranging from 14 to 72 years. There was one with allergic bronchial asthma, four with infectious asthma and 21 with mixed asthma. Six produced no sputum, four small amounts (less than 15 ml./day), and 16 produced more than 15 ml. of sputum daily.

The vital capacity (VC) and FEV\(_{1.0}\) were determined using the Gaensler-Collins Vitalometer. The PEFR was determined using the Wright Peak Flowmeter.\(^{14}\) All determinations were repeated until there was close agreement between the two highest, and the maximum value was used for study. The standard error of estimate of 143 replicate measurements of PEFR made in 12 patients on 12 days was ±5.5 L./min. The standard error of estimate of 143 replicate measurements of the FEV\(_{1.0}\) made in 12 patients on 12 days was ±0.041 L. Normal values for the VC and FEV\(_{1.0}\) were predicted from the nomograms of Kory et al.\(^{13,14}\)

At the first visit, 14 patients were studied before and after the inhalation of 0.3 ml. of one-half per cent isoproterenol aerosol. All 26 returned to the pulmonary function laboratory on Mondays, Wednesdays, and Fridays for ventilatory function tests for a total of six visits. This two-week period of observation constituted control period I (Fig. 1). On three or more occasions during this two-week period, each patient was asked about the amount of medication taken and the nature and severity of the asthma.

They were then placed on dexamethasone aerosol inhalations, administered from a pressurized inhaler containing dexamethasone as a finely divided suspension in fluorochlorohydrocarbon propellant containing two per cent ethanol and sorbitan trioleate. The latter is a wetting agent used to provide better dispersal of the suspension. The inhaler delivered approximately 0.084 mg. of dexamethasone free alcohol for each actuation of its valve. They were instructed to take three inhalations four times daily, regardless of the severity of symptoms, for a total daily dose of 1.0 mg. They were also instructed not to take additional inhalations of the drug even if symptoms became worse. Ephedrine orally, isoproterenol aerosol and aminophylline rectally were used as indicated throughout the period of study. An attempt was made to keep a careful record of all medication used during the various study periods. The treatment period with dexamethasone aerosol was continued for a minimum of two weeks. During this time they were seen by a physician on at least three occasions, and a record was made on a standard form of the amount of bronchodilator drugs taken since the last visit. The severity of asthma was also recorded on the basis of patient's statements and physical examination of the chest.

A second control period of one week, or three to four observation periods, was then carried out in 12 patients after dexamethasone aerosol was discontinued (control period II, Fig. 1). This was followed by a second period of treatment using a pressurized inhaler containing isoproterenol sulfate in addition to dexamethasone. This inhaler delivered .084 mg. of dexamethasone free alcohol and approximately 0.10 mg. of isoproterenol sulfate for each actuation of its valve. Clinical and ventilatory function observations were made three times weekly as noted above. Following this second period of treatment with dexamethasone and isoproterenol aerosol, nine

<table>
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<tr>
<th>DAYS</th>
<th>CONTROL I</th>
<th>DEXAMETHASONE AEROSOL</th>
<th>CONTROL II</th>
<th>DEXAMETHASONE - ISOPROTERENOL AEROSOL</th>
<th>CONTROL III</th>
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**Figure 1:** Schematic representation of experimental design. Vital capacity, forced expiratory volume for 1.0 second and peak expiratory flow rate were measured three times weekly during the course of the experiment.
were studied during a third control period (control period III, Fig. 1). 

Results

Severity of Asthma

Severity of airway obstruction was graded by analysis of the FEV₁₀ during control period I. Obstructive disease was considered to be mild if the FEV₁₀ was greater than 75 per cent of predicted, moderate if it was from 51 to 75 per cent, severe if it was from 26 to 50 per cent, and very severe if it was less than 25 per cent of predicted. In the total group of 26 patients, there were five who were classified as mild, nine moderate, ten severe and two very severe.

Criteria of Significant Change

Significant change in the severity of airway obstruction was considered to have occurred, as judged by physiologic measurements, if the mean FEV₁₀ during one study period showed a change of 0.2 L. or more as compared with the mean data of another period. Significant change of the PEFR was considered to have occurred if there was a difference of 25 L./min. or more between the mean data of two periods. These values were arbitrarily chosen, but represent five times the standard error of estimate for both measurements. They also represent more than 20 per cent of the control value of PEFR and FEV₁₀ in those classified as severe and very severe. A significant change in VC without a change in either the PEFR or FEV₁₀ was not considered indicative of bronchodilation.

Potential Ability to Respond to Bronchodilator Therapy

Potential ability to respond to bronchodilator therapy was judged on the basis of two criteria: the ability to respond acutely to bronchodilator aerosol and the day to day variation in severity of asthma during the control and treatment periods (Figs. 2 and 3).

Nine of the 14 patients who were studied after the administration of isoproterenol aerosol in the first control period showed significant improvement in airway obstruction. The five who did not respond significantly and 11 of the 12 not studied after isoproterenol aerosol showed a 20 per cent variation or greater in the FEV₁₀ or the PEFR with or without changes in VC.

![Figure 2: L.M. Graphic representation of peak expiratory flow rate (PEFR), vital capacity (VC), and forced expiratory volume for one second (FEV₁₀) determined three times weekly during 52-day observation period. Asthma was classed as very severe because the FEV₁₀ on day 0 was less than 25 percent of predicted. Note the considerable day to day variation of severity of asthma during the entire study period, the roughly parallel course of all three indices and the improvement while on dexamethasone and dexamethasone isoproterenol aerosol.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21393/)
during the control or treatment periods. One patient showed a change in VC only. Since there was a language barrier and since he demonstrated almost no variation in his FEV1.0 or PEFR, his data are excluded in the final analysis of the bronchodilator effect of dexamethasone aerosol.

**Side Effects of Dexamethasone Aerosol**

Untoward symptoms were observed on three occasions. Two patients vomited immediately after taking the aerosol. However, they had previously had similar symptoms after taking other medication and the emesis was not considered to be drug-induced. One of them completed five of the six observations on dexamethasone aerosol and is included in the analysis; the other is not. The third complained of increased obstructive dyspnea after dexamethasone aerosol on two separate trials of therapy; he is not included in the analysis of the results.

**Bronchodilator Effect of Dexamethasone Aerosol**

Ten of the 23 patients (43 per cent) remaining for analysis from the original 26 showed a significant response while on dexamethasone aerosol as compared with control period I. In two, the results were striking. Of the ten responding to therapy, three were graded as moderate, six as severe and one as very severe. Thus, of the ten in the severe and very severe group (Table 1), more than half showed a significant response while on dexamethasone aerosol.

Evaluation of ventilatory function data on 12 patients during control period II showed one improved, two worse, and nine un-
Figure 4: The mean forced expiratory volume for 1.0 second in liters and peak expiratory flow rate in L./min. for each study period is plotted on the indicated vertical lines for 23 patients. The lines connect the mean points for individual patients. See text for discussion.

Table 1—Relation Between Response to Dexamethasone Aerosol and Severity of Bronchial Asthma

<table>
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<tr>
<th>Severity of Asthma:</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
<th>Total</th>
</tr>
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<tr>
<td>No. of Patients*</td>
<td>4</td>
<td>9</td>
<td>9</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>No. Responding</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>10</td>
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*Three of the original 26 patients were not included in this analysis because of failure to complete the study in two instances and lack of evidence of reversible airway obstruction in one patient.

changed as compared with control period I. Control period II, when compared with the dexamethasone period, showed none improved, six worse and six unchanged (Fig. 4).

A comparison of dexamethasone-isoproterenol aerosol with dexamethasone aerosol in 11 showed two patients improved, one worse, and eight unchanged. However, in comparison with control period II, seven were improved, none was worse and five were unchanged. Comparing control period III with control period II in nine patients, five were improved, none was worse and four were unchanged. Comparing control period III with dexamethasone-isoproterenol aerosol in nine, two were worse and seven were unchanged.

Clinical Impression of the Medication

It was exceedingly difficult on the basis of clinical criteria to reach a precise and satisfying evaluation of the patients' response to drug therapy. This was due in part to marked day to day variation in the severity of asthma and in part to great difficulty in determining precisely how much medication patients had taken from week to week. Of 21 who could be evaluated, 11 were classified as better, eight as the same and two as worse.

Discussion

Quantitative methods are essential in evaluating the effect of drugs in bronchial
asthma unless the response to a particular agent is dramatic. The problem is further complicated with corticosteroid drugs, because clinical improvement may frequently be related to a systemic or tonic action rather than to a specific effect on the bronchi.

In choosing a method of evaluating airway obstruction in asthma, the striking day-to-day variations must be borne in mind. It seems unreasonable to expect once-weekly testing to be representative of the entire preceding period. In an attempt to overcome these difficulties, we decided to base our evaluation of dexamethasone aerosol primarily on objective tests of ventilatory function, using thrice weekly observations of $FEV_{1.0}$ and PEFR.

The $FEV_{1.0}$ and PEFR are simple to perform and have been shown to increase after the administration of known bronchodilator drugs. Previous studies have shown that it may be misleading to rely on a single test in evaluating a bronchodilator agent, since one test may show bronchodilation while another does not. An evaluation was made of the relative direction of change of 461 paired observations of PEFR and $FEV_{1.0}$. In 81 per cent of observations, the direction of change was the same, in 19 per cent it was different. The use of at least two physiologic indices in objectively evaluating bronchodilator drugs has thus been confirmed.

This study was designed without the use of a placebo for several reasons. First, we have been unable to obtain a satisfactory placebo which could be used in a blind study since the distinctive bitter taste of the steroid used is difficult to reproduce. In all of the papers reporting the use of placebo in blind studies, either the type of placebo used was not mentioned or it consisted of merely the vehicle without the steroid. Only Hajos attempted to reproduce this bitter taste by adding quinine. Second, most of the patients admitted to this study were quite ill and it was considered that the use of a placebo in this group might entail risk. Needless to say, we recognize that in the present study there were many variables in addition to the administration of steroid aerosol.

We obtained striking physiologic improvement in only two of 23 patients, with less striking improvement seen in eight additional patients. It seems significant that of 12 patients studied after dexamethasone aerosol was discontinued, six became worse, while none improved. The proportion of patients responding to dexamethasone-isoproterenol aerosol (seven of 12) was not appreciably larger than the proportion responding to dexamethasone aerosol (10 of 23). The degree of improvement was also the same in the two groups. Rebound worsening following cessation of steroid aerosol apparently is not of major concern since in only two instances out of 21 compared, did a control period following steroid aerosol show worsening when compared with a control period preceding it.

Most of our patients were of the "wet" type, that is, producing daily sputum; many had an infectious component. Helms and Heyworth have pointed out that their results were disappointing in chronic asthma and in patients with bronchial infection. Herxheimer et al. also feel that the infectious type is less likely to respond than the allergic type and that hypersecretion is a handicap, possibly because of obstruction to the inhalation of the aerosol by bronchial exudate. Hajos attempted to circumvent this difficulty by first aspirating secretions with a bronchial catheter and by the use of aerosolized hyaluronidase. We were unable to find a relationship in this study between quantity of sputum produced and a response to dexamethasone aerosol.

Side effects of dexamethasone aerosol were minimal. However, in addition to the one patient reported in this series, we have seen several patients who developed exacerbation of airway obstruction immediately after the aerosol. Others have also noted similar effects. This manifestation has not
been observed with the dexamethasone-isoproterenol mixture. In addition, we have observed one case of thrush after prolonged administration of dexamethasone-isoproterenol aerosol.

While there is no doubt that much of the steroid administered by aerosol reaches the blood stream, and may well exert a systemic effect, most authors feel that the total daily dose used in the aerosolized form is considerably less than that effective orally. Our patients received about one unit of dexamethasone (one unit is equivalent to 25 mg. of cortisone) which is less than the oral maintenance dose usually required in such patients.

Helm and Heyworth observed their best results in acute asthma with symptom-free intervals and suggested that a prime use of steroid aerosol was in this situation. It is our feeling that the need for aerosolized steroids arises because of the toxicity of prolonged oral corticosteroid therapy in chronic asthma. If this form of treatment is to assume an important role in our armamentarium, it must prove its usefulness on a maintenance basis rather than as intermittent therapy; that is, either as a substitute for prolonged oral therapy or as an adjunctive agent in withdrawing patients from oral steroid maintenance.

The results of aerosol dexamethasone therapy were not dramatic in this study, but most of the patients responding had the more severe degrees of airway obstruction. Although a limited role seems likely for this form of therapy, further controlled clinical trial appears to be warranted.

**Summary**

1. The bronchodilator effect of dexamethasone aerosol was evaluated in a controlled study in 26 patients with chronic asthma. The forced expiratory volume for one second and the peak expiratory flow rate were used as indices of airway obstruction. Measurements were made three times a week for periods of four to eight weeks.

2. Ten of 23 patients (43 per cent) showed a significant response while on dexamethasone aerosol; there was no rebound worsening after cessation. Most of the patients responding had the more severe degrees of airway obstruction.

3. The only significant side-effect was exacerbation of airway obstruction in one patient. This was not seen with a dexamethasone-isoproterenol mixture.

These results appear to warrant further controlled clinical trial of dexamethasone aerosol.

**Resumen**

1. El efecto broncodilatador del aerosol de Dexametasona se estudió en un estudio controlado de 26 enfermos de asma crónico. El volumen de la espiración forzada por un segundo y el pico de la curva espiratoria se usaron como índices de la obstrucción de las vías aéreas. Se hicieron mediciones tres veces por semana durante períodos de cuatro a ocho semanas.

2. De 23 enfermos (43 por ciento) mostraron una respuesta de significación baja el aerosol de Dexametasona, no hubo fenómeno de rebote al suspenderse el tratamiento. La mayoría de los enfermos que mostraron respuesta tenían los grados más graves de obstrucción de las vías respiratorias.

3. El único fenómeno colateral fue la exacerbación de la obstrucción en un enfermo. Esto no se notó con la asociación Dexametasona-Isoproterenol.

4. Estos resultados autorizan a continuar el ensayo clínico controlado del aerosol de Dexametasona.

**Résumé**

1. L'effet broncodilatateur du dexaméthasone en aérosol a été évalué dans un groupe de 26 malades atteints d'asthme chronique. Le volume expiratoire forcé par seconde, et le débit expiratoire furent utilisés comme indices de l'obstruction aérique. Des mesures furent faites trois fois par semaine dans des périodes allant de 4 à 8 semaines.

2. Dix malades sur 23 (43%) montrèrent une réponse nette sous aérosol de dexaméthasone; il n'y eut aucun retentissement aggravant après cessation. La plupart des malades répondant à l'aérosol avaient les atteintes les plus graves d'obstruction aérienne.

3. Le seul effet secondaire net fut l'exacerbation de l'obstruction aérienne chez un seul malade. On ne constata pas le phénomène avec un composé de dexaméthasone-isoproterenol.

Dexamethasone Aerosol in Bronchial Asthma

ZUSAMMENFASSUNG

1. Der bronchiodilatatorische Effekt eines Dexamethason-Aerosols wurde an einer kontrollierten Untersuchungsreihe von 26 Patienten mit chronischem Asthma ermittelt. Es wurden das forcierte Expirations-volumen für eine Sekunde und die Spitzenwerte für die expiratorische Durchströmungsrate als Indikatoren der Verlegung der Luftwege benutzt. Die Messungen erfolgten dreimal wöchentlich während 4-8 Wochen.

2. 10 von 23 Patienten (43%) zeigten eine signifikante Reaktion während des Einsatzes von Dexamethason-Aerosol; nach Beendigung der Behandlung fand sich keine Verschlechterung als Gegenwirkung. Die meisten der günstig reagierenden Patienten hatten schwere Formen von Verlegung der Luftwege.


REFERENCES


For reprints, please write Dr. Snider at Mt. Sinai Hospital, Chicago 8.

SEGMENTAL INFILTRATIONS DUE TO BRONCHIAL OBSTRUCTION

Pathogenesis is summarized as follows: the bronchial wall becomes involved in the tuberculous inflammation of the hilar lymph nodes. The bronchial lumen becomes narrowed as a result of local swelling of the wall. Next, the lumen becomes blocked by polypoid masses of granulation tissue developing around a fistula when perforation of a caseated lymph node has actually taken place. The caseous debris of the lymph node expelled through the fistula becomes accumulated in the pulmonary segment (or lobe) as they cannot pass along the impediment in the bronchus in question. The caseous material contains both tubercle bacilli and nonbacterial noxae. In reaching the pulmonary parenchyma, the former cause true of tuberculous inflammation whereas the latter give rise to a non-tuberculous and nonbacillary pneumonia. Although obstruction infiltrations themselves do not seem to be influenced, it is imperative that patients suffering from them be treated with tuberculostatic drugs. Bronchoscopy is essential for making the diagnosis. Its regular repetition is, furthermore, all important for this treatment; the endoscopic treatment not only enables us to prevent the bronchial occlusion to a considerable extent, but at the same time prevents the accumulation of expelled caseous matter containing tubercle bacilli.