PAPERS AND ORIGINALS

Beclomethasone Dipropionate: A New Steroid Aerosol for the Treatment of Allergic Asthma

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Summary

Beclomethasone dipropionate was used in pressurized aerosols for the treatment of 60 cases of chronic allergic asthma for up to 15 months. Twenty-eight out of 37 cases were transferred to this treatment after being dependent on oral steroids for up to 16 years. Nineteen out of 23 other asthmatics not dependent on steroids were also completely controlled. No biochemical evidence of adrenal suppression was found. Steroid withdrawal symptoms were often a problem, suggesting absence of systemic absorption. The precise mode of action and metabolic fate of this corticosteroid are not yet known.

Introduction

It has been obvious since the very early days of steroid therapy for allergic asthma that the deposition of the active drug directly on to the bronchial mucosa by means of an aerosol could be an advantageous method of treatment. The drug would be delivered only at the site where it was required. The local concentration could be high, yet systemic absorption minimal and the side effects of steroid therapy avoided.

Attempts to establish this method have been the subject of reports by many investigators from Gelfand (1951) onwards, including studies by Brockbank *et al.* (1956), Brockbank and Pengelly (1958), Helm and Heyworth (1958), Herxheimer *et al.* (1958), Smith (1958), Bickerman and Itkin (1963), Brown (1963), and a further publication, including a review of nine others, by Kravis and Lecks (1966). Hydrocortisone was used as powder by early investigators, and later dexamethasone phosphate in pressurized aerosols by others, with varying degrees of success. However, systemic absorption of dexamethasone with

typical steroid side effects was noted by Siegel *et al.* (1964), Novey and Beall (1965), and Toogood and Lefcoe (1965). Biochemical evidence of adrenal suppression was reported by Linder (1964). Systemic absorption of dexamethasone thus proved an insuperable problem which rendered administration of this steroid by aerosol rather pointless.

Beclomethasone dipropionate, which has already been used for some years as a topical ointment for eczema, does not suffer from this defect. This compound was used in aerosol form for the present trial.

Case Selection

Sixty patients were selected for the trial from both National Health Service and private practices. All except one were stable perennial asthmatics, as shown by observation over a period of from six months to 16 years. Sputum examination in 59 cases showed a significant excess of eosinophil cells. Intensive investigation of allergic factors and treatment, when indicated, using the methods described by Brown (1970) had been ineffective or unhelpful. Thirty-seven of the patients had been continuously dependent on steroid therapy for from 1 to 16 years, taking total daily doses of from 0.5 to 1.5 mg of betamethasone or 5 to 15 mg of prednisolone. Repeated attempts at steroid withdrawal had resulted in relapse. Thirty-five of the steroid-dependent group had previously taken part in a trial (unpublished) of disodium cromoglycate but only four had improved.

The cases were not classified as intrinsic or extrinsic, but simply as perennial allergic asthma. The extent of the reversibility of the airways obstruction in each case varied widely, and steroid-dependent patients were well indoctrinated to take the minimum dose possible. As shown in Table I 14 patients were

TABLE I—Steroid-dependent Group (37 Patients)

Steroid withdrawal symptoms		Response to Aerosol	
Worsening of eczema	17	Peak flow	
Unmasking of allergic rhinitis	4	Better	25
Disodium cromoglycate	5	No change	7
Not tried	2	Worse	4
Ineffective	31	Successful transfer to aerosol	28
Helpful	4	Occasionally needed short-term	
Steroid therapy side effects		steroids	13
evident	28	Failed transfer	9
Ineffective (200 units)	14	Failed on account of frequent	
Corticotrophin		infections	2
Responsive	10		
Not known	13		

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known not to respond to doses of 200 units of corticotrophin gel because of adrenal suppression. They were considered almost certainly steroid-dependent for life and this fact influenced their selection for a trial of a new mode of treatment.

The patients were therefore a miscellaneous group of proved allergic asthmatics. In 37 there was serious anxiety regarding their future because of dependence on steroid therapy and in 23 control by bronchodilators was regarded as inadequate and steroid therapy was considered inadvisable on a long-term basis.

The importance of sputum examination for eosinophils was brought home to us by the patient (Case 60) who did not have this investigation before entry to the trial. He was a 36-year-old ex-marine commando who gave a history so suggestive of mild allergic asthma of several years' duration that a search for causative allergens lasted over six months. It was then decided to give up attempts to find a cause and, as he was already using a peak flow meter, he was given the aerosol steroid. Two weeks later one of us (H. M. B.) was surprised to find that the expected increase in peak flow had not occurred. The sputum was belatedly examined and the cytological examination showed typical bronchitis with no eosinophils. The true diagnosis was, of course, early chronic bronchitis.

This case illustrates the value of examination of the sputum for eosinophils, so long as the methods described by Brown (1958) are strictly adhered to. It must be emphasized that the routine laboratory examination for eosinophils is not worth while unless the technician has been shown the simple method described.

Material and Methods

Beclomethasone dipropionate was administered by means of a metered aerosol delivering 50 µg of micronized powder per puff. The average size of the particles delivered is 5 µm, so they will penetrate to the smaller bronchi. The structural formula of this compound is:

9-α-chloro-11β,17α,21-trihydroxy-16-β-methylpregna-1,4-diene-3,20-dione, 17,21-dipropionate

Two puffs four times daily, giving a total of 400 µg, was the usual dose, occasionally increased to three puffs four times a day. In 56 cases 400 µg was the optimum dose but four remained well controlled on 150 to 200 µg daily. This dosage regimen is empirical, and may not be optimal. Three patients changed to 200 µg twice a day and had a gradual decrease in peak flow rate, suggesting that it is best to use the aerosol at least four times daily.

Most of the patients had used pressurized aerosols for long periods. Nevertheless, it was felt necessary to give practical instruction on their use before beginning the trial. Particular emphasis was placed on preliminary complete expiration and on firing the aerosol at the very beginning of inspiration, ensuring that particles of steroid are carried on the airstream as far down the bronchi as possible. It soon became obvious that many patients had never been instructed properly.

Each patient was supplied with a Wright Peak Flow Meter for personal use four times a day, fully instructed in its use, and shown how to keep a graph of the results. In addition, a very comprehensive symptoms diary was kept which included a daily record of all types of therapy. This is shown in Fig. 1. A control

DERBY CHEST AND ALLERGY CLINIC, GREEN LANE, DERBY

Allergy Symptoms Chart, 1971

This is a new type of symptoms diary and we hope you will help us to help you by filling it up every day with great care.

We want you to decide how severe your symptoms are on a number scale from 0, meaning no symptoms, to 9, meaning very, very severe symptoms. As long as you do not change your mind every day, it should make sense when it is analysed by the laboratory.

For example, 1 or 2 would be slight, 3 or 4 moderate, 5 or 6 severe and 7, 8 or 9 very severe. This rating is deliberately biased to exaggerate the bad patches.

Put a cross in the correct square every night before bed, and please remember to mark the '0' squares if you have no symptoms or are having no medicines. Please keep on filling it up on holiday. The NOTES section at the end is for entering where you are or if you have a cold, bronchitis, etc. Please ask your doctor to enter name of tablets if not known.

MONTH	SNEEZING					BLOCKAGE					EYES					ASTHMA					STEROIDS					AEROSOL				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
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FIG. 1—Child aged 9 years. This symptoms and treatment chart was introduced two years ago. It has been found that most patients are surprisingly careful in filling it in, and that the correlation with the daily counts of airborne seasonal allergens with either symptoms or treatment requirements is often remarkably close. In this case the transfer from oral steroids to aerosol is well documented. Only half the chart is shown here, other symptoms, treatment, and weather also being provided for.

ALWAYS BRING THIS CHART ON EVERY VISIT TO THIS CLINIC

period of at least two weeks preceded the introduction of the aerosol. Many patients had already been keeping peak flow records for long periods as part of an intensive investigation. When the patient was seen again, if record-keeping was good aerosol therapy was started, but if record-keeping was inadequate the case was rejected as unsuitable.

In steroid-dependent patients the aerosol, 100 µg four times a day, was added to the usual daily dose of oral steroids for four days, after which the oral steroid was gradually phased out over the next three to four days. For example, a patient taking 10 mg of prednisolone daily would reduce the dose by 2.5 mg/day, or if on betamethasone 1 mg daily, by 0.25 mg/day.

Peak flow readings were averaged over at least two weeks before the aerosol was introduced, readings over periods of many months being available in those patients who were being studied intensively. The average readings after the introduction of the aerosol were taken from a two-week period beginning from two weeks after the transfer to the aerosol or from the point at which the peak flow rate had become stabilized.

Results

STERIOD-DEPENDENT GROUP (37 CASES)

These 37 cases are summarized in Fig. 2 and Table I, which also shows the "side effects" encountered in introducing the aerosol. Seventeen steroid-dependent patients experienced withdrawal symptoms to a greater or lesser degree. These consisted of tiredness, lassitude, headache, aches and pains, depression, and occasionally emotional instability, lasting for a week or longer. All but three were already known not to respond to cortico-

FIG. 2—Steroid-dependent group. The steroid usually preferred was betamethasone but the dosage has been expressed as an equivalent dose of prednisolone to render evaluation easier; 0.5 mg of betamethasone has been taken to equal 5 mg of prednisolone. Cases treated with prednisolone are indicated by an asterisk. Comparative averages of peak flow readings taken from two-week periods before and for two weeks after established on aerosol.

trophin. This was so common that we soon began to warn patients in advance that they might have to endure all the discomforts of relative adrenal insufficiency even though their peak flow meter readings might be the same or even much better than before. No serious episodes of adrenal insufficiency occurred in any case.

Five patients complained bitterly of allergic rhinitis and four of a worsening of eczema after transfer to the aerosol steroid. This surprising finding suggests that lack of exogenous oral corticosteroid in the blood stream, contrasting with local suppression of the bronchial allergy, had unmasked latent allergic symptoms in the nasal mucosa or skin. This finding contrasts markedly with the reports of Novey and Beall (1965) and of Toogood and Lefcoe (1965), who observed (and photographed) pronounced Cushingoid effects from dexamethasone phosphate aerosols. Moonface became less evident in those in whom this side effect was prominent. One patient who had been on steroids for 10 years was delighted by the fact that many of her friends failed to recognize her in the street. On their own these effects suggest that systemic absorption of the steroid is negligible, quite apart from the results of tetracosactrin and insulin tests shown in Fig. 3.

FIG. 3—Adrenal function tests in 29 patients, at up to over a year on aerosol steroid, showing the rise in plasma cortisol achieved as a result of direct and of indirect adrenal stimulation. There is no evidence of decrease in response with duration of treatment. Twelve patients had serial tests at wide intervals, again with no evidence of adrenal suppression.

We are particularly interested in this surprising effect because nasal provocation tests can still be carried out without the usual difficulty of the masking of positive results by oral steroids. Previously it had been necessary to omit steroids on the day of a provocation test.

If the patient cannot inhale enough air it follows that he cannot inhale enough aerosol of any kind for it to be effective. This simple fact should be obvious, but surprisingly this is not always so. Thus if a patient had severe airways obstruction, whether on or off steroids, it was essential to use high-dosage steroid therapy for a short time to clear the bronchi and thus allow the aerosol to become fully effective.

The best example of this type of case is illustrated in Fig. 4 which refers to a case of late-onset asthma of three years' duration in a man aged 45. During the control period he became progressively worse. As shown, the aerosol was first introduced in an attempt to gain control without using oral steroids, but it had an irritant effect, causing severe bronchospasm lasting half an hour or more, and it became obvious that oral steroids were essential. However, once his peak flow had risen markedly on oral steroids

Figs. 6 and 7. This is the virtual abolition of the violent diurnal variations in peak flow which commonly occur in the labile asthmatic.

Many cases are certainly much better controlled by this aerosol than by oral steroid, a surprising finding that is possibly related to the effects of this compound on the bronchial mucosa. It should be clear that the increases in average peak flow are in many cases surprisingly great, suggesting that the local effect of the aerosol was much greater than that of their usual dose of oral steroid. The dosage which would have been required to maintain an equivalent peak flow could not have been continued on a long-term basis without serious side effects.

FIG. 6—Boy aged 14. Perennial asthma since age of 3. Steroid therapy for five years and transferred to corticotrophin (ACTH) two years previously. Example of abolition of diurnal variation on aerosol. Known allergens—penicillium and aspergillus. Desensitization only partly successful.

FIG. 7—Married woman aged 28. Severe chronic perennial asthmatic. Frequent episodes of status asthmaticus. Steroid-dependent six years. Usual maintenance dosage 1-1.5 mg of betamethasone. Moonface, osteoporosis, and bruising. Marked withdrawal symptoms and no response to 200 units of corticotrophin gel. Allergens unknown, but coal-tar derivatives strongly suspect. Swings of peak flow from 60 l./min at 6 a.m. to 600 l./min at 6 p.m. were a constant feature of this patient on oral steroids. Subsequently proved difficult to maintain on aerosol alone because of frequent infections.

USE OF AEROSOL STEROID IN CHILDREN

We are most impressed with the results in nine children who were trained to use a pressurized aerosol from the age of 6. Five had been on oral steroids, with serious effects on growth, for periods of some years before referral, and attempts to identify the responsible allergens were unsuccessful so that there was no prospect of cessation of steroids. Resumption of growth was remarkable, two children gaining 2 in (5 cm) in six months and another 3 in (7.5 cm) in a year. Measurements on the others were unfortunately omitted but growth had obviously been resumed. Control of the asthma was complete in four of the cases; the other child was liable to frequent infections. Unmasking, or increase in, atopic manifestations such as eczema has been troublesome in two cases.

The four children who were not steroid-dependent were all markedly improved and completely controlled. One of the striking examples is illustrated in Fig. 8, where serial records of

FIG. 8—Boy aged 12. Chronic perennial asthma five years. Never required steroids but seemed likely to do so just before aerosol began. Allergens unknown in spite of extensive investigation. Wright Respirometer used for serial vital capacity measurements. Peak inspiratory flow obtained by use of peak flow meter modified according to Nairn and McNeill (1963). Note the effects of the aerosol on the peak expiratory flow which soon becomes almost equal to the peak inspiratory flow.

peak inspiratory and expiratory flow, using a meter modified according to Nairn and McNeill (1963), and also vital capacity, using a Wright Respirometer, were obtained, thanks to the very high degree of co-operation from his mother. The relationships of these measurements as shown are of great interest.

EVIDENCE OF LACK OF SYSTEMIC ABSORPTION

Tetracosactrin tests and insulin hypoglycaemia stress tests, as described by Landon *et al.* (1963), were carried out in 27 cases and the results are presented in Fig. 3. Plasma cortisol was estimated by the method of Mattingly (1962). Two or more serial adrenal function tests were carried out at intervals of from 6 to 14 months in 12 patients. We would have preferred to do more serial tests, but for a multiplicity of reasons this was impossible. However, in none, whether steroid-dependent or not, was there any evidence of adrenal suppression with either type of test.

Apart from the biochemical data, the steroid withdrawal symptoms and the unmasking of allergic manifestations can be reasonably assumed to indicate absence of significant absorption

of the aerosol steroid. Serial liver function and full blood examinations have disclosed no abnormality in any of the cases.

In order to obtain further evidence regarding possible adrenal suppression three volunteer subjects inhaled excessive quantities of the aerosol daily for two days, following several daily basal cortisol estimations. The results are shown in Fig. 9, and from

FIG. 9—Effects of inhaled beclomethasone dipropionate on the morning basal cortisol. An aerosol delivering 250 μ g per puff was used eight times a day, for two days, in one healthy volunteer (X-X) and a patient (●-●), who had already been on 400 μ g daily for six months. Another volunteer (O---O) took 4 mg daily for two days.

this it is clear that in at least three subjects there is no evidence whatever of the occurrence of adrenal suppression in higher dosages than have been used normally in the treatment of patients.

Conclusions and Discussion

Beclomethasone dipropionate aerosol would seem to provide an alternative to long-term oral steroid therapy in many cases of chronic perennial asthma. Effective control of the asthma is achieved with no evidence of systemic absorption or of steroid side effects. The exact mode of action of this compound remains to be fully elucidated.

The best results are in the younger and more reversible cases. The abolition of diurnal fluctuation is a surprising feature. It is possible to substitute this therapy for long-term oral steroids even when taken for many years. Steroid withdrawal symptoms, and unmasking of hitherto suppressed allergic manifestations, have presented interesting problems.

Selection of pure allergic asthmatics, or cases where the allergic factor is dominant, is a sine qua non of this, or any other,

trial of a steroid preparation in allergic asthma. Care has been taken to exclude seasonal cases, where daily fluctuations of airborne allergens can cause wide variation in peak flow.

It cannot be overemphasized that these patients are in a precarious condition in the event of trauma or infection. It is essential that they be instructed to resume oral steroids in high dosage without delay, when obviously necessary, without waiting for medical advice. They must carry warning cards clearly indicating their potentially dangerous situation.

Such serious problems do not arise in relation to patients who have had only occasional steroid therapy, or have never required it. On the data presented here there seems to be no contra-indication to the use of this preparation by mild asthmatics who would not normally be considered for the use of corticosteroids. As many of them had already failed to respond to disodium cromoglycate this new therapeutic approach may have much to offer, especially in paediatrics. In all types of case considerable clinical expertise and experience of the management of allergic asthma may be required during the transfer period.

This method of treatment has no place whatever in status asthmaticus. Those unable to inhale air surely cannot inhale enough aerosol to have any effect. The presence of excess bronchial mucus and often pus must also form a barrier the aerosol cannot penetrate. The future role of aerosol therapy is clearly confined to maintenance of airway patency and prevention of attacks.

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