Hospital Topics

Beclomethasone Dipropionate Steroid Aerosol in Treatment of Perennial Allergic Asthma in Children

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British Medical Journal, 1973, 3, 161-164

Summary

Thirty-one chronic perennial asthmatics aged from 2½ to 16 years were treated with beclomethasone dipropionate pressurized aerosols for up to 20 months. Of these, 16 patients dependent on oral corticosteroid or corticotrophin for up to 11 years were successfully transferred to this treatment, with one exception. Steroid withdrawal symptoms were slight. Loss of weight, disappearance of Cushingoid features, and resumption of growth indicated lack of systemic side effects. Fifteen others inadequately controlled on bronchodilators or disodium cromoglycate, were also effectively treated, and no clinical evidence of adrenal suppression was noted.

Introduction

In 1972 Brown *et al.*¹ showed that beclomethasone dipropionate aerosol was a satisfactory alternative to long-term oral corticosteroids in 28 out of 37 perennial allergic asthmatics, and was highly effective in 19 out of 23 others who were not steroid-dependent. The main problems were steroid withdrawal symptoms and the unmasking of hitherto suppressed allergic manifestations. Severe asthma in childhood seemed an obvious indication for a further trial of any remedy which could afford relief without iatrogenic side effects, as recently confirmed by Lal *et al.*² and Clark.³ One group of 16 children had been dependent on corticosteroids or corticotrophin for long periods, while 15 others were inadequately controlled by antispasmodics or disodium cromoglycate (DSCG).

Selection of Patients

All patients were either stable perennial asthmatics, as shown by observation over periods of six months to 10 years, or had perennial plus superadded seasonal asthma treated in the winter months. Sputum or nasal smears had been shown in all cases to contain excessive numbers of eosinophil cells using the method described by Brown.⁴ Intensive investiga-

tion of allergic factors, and desensitization treatment when indicated by nasal provocation tests, had already been carried out using the approach described by Brown,⁵ but had been unhelpful or ineffective. Patients chosen were those to whom nothing further could be offered by way of specific therapy or avoidance, or who had become dependent on corticosteroids or corticotrophin.

Material and Methods

Beclomethasone dipropionate (Becotide inhaler) was administered by metered aerosol delivering 50 µg per puff of micronized powder of average size 5 µm so as to penetrate to the smaller bronchi. The usual initial dose was two or three puffs four times daily, but when fully controlled it was often possible to decrease the dose to one puff four times daily. As with adults, it was absolutely essential to ensure correct use of the aerosol so that the active powder could reach the bronchi. Preliminary complete expiration, followed by firing the aerosol to coincide with the very beginning of a deep, sudden inspiration, has to be taught patiently to both parents and child. In very young children who do not have the necessary strength it is mother who must trigger the aerosol. Any trace of "smoke" at nostrils and mouth indicates improper use.

Each patient was supplied with a personal Wright peak flow meter and instruction was given both in its use and in the graphing of results. A comprehensive symptoms and treatment chart was also kept. Sometimes children will acquire the habit of puffing out the cheeks like a trumpeter, this achieving a false high reading. The presence of obvious bronchospasm on examination despite a constant reading of 200 litres per minute led to the detection of this unconscious trick in two cases.

A control period of at least two weeks preceded the introduction of the aerosol. Many children already had continuous records of their peak flow for a year or more. The average of peak flow readings for at least two weeks was taken as the baseline, regardless of steroid or other therapy being given during this period. As the aerosol usually produced a stable peak flow within one or two weeks the average after introduction of the aerosol was taken from two weeks after the start of aerosol therapy, over a period of two weeks. In the steroid-dependent cases the aerosol was added to the usual daily dose for four days, after which oral steroids were gradually phased out. In corticotrophin-dependent cases it was possible to stop after one extra dose, the aerosol taking over smoothly thereafter.

Adrenal function tests were not carried out, being considered unnecessary in view of the data already obtained in adults showing lack of adrenal suppression by Brown *et al.*,¹ Lal *et al.*,² and Clark.³

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Results

Important data on both groups of patients are summarized in tables I and II, and figs. 1 and 2 show the increases in average peak flow readings and the predicted peak flow readings for height, according to Godfrey *et al.*⁵ As the stature of many children was below normal it was thought best to predict the peak flow rate for their *actual* height because of the close relation between height and respiratory function. As shown in figs. 1 and 2, all except seven remained well below the predicted figure. Improvement was *relatively* good, but complete reversal of airways obstruction seldom occurred.

The use of the peak flow meter also produced individual data of great interest which were obscured by mean averages, illustrative examples being shown in figs. 3 and 4. These show very clearly the dramatic changes which took place on the introduction of aerosol therapy, but cannot illustrate the even more striking improvement which occurred in psychological adjustment to the disease and in athletic performance. Individual records also showed the immense value of the personal peak flow meter in the study of asthma over long periods.

In the steroid-dependent group withdrawal symptoms were a much less common problem than in adults, the only complaints being headache and lassitude in six children for no longer than a week. Unmasking of allergic rhinitis and eczema was also less frequent. Oral and faucial candidiasis occurred in four cases but responded to antifungal agents.

TABLE I—Steroid-dependent Group

Case No.	Sex	Months on Aerosol	Total Hospital Admissions	Total Daily Dose (μ g)		Growth Since Transfer (cm)	Percentage of Peak Flow for Height	
				Initial	Maintenance		Before	After
1	M.	18	29	600	600	7	39	62
2	M.	9	2	600	400	10	28	63
3	M.	4	2	400	300	5	44	49
4	F.	7	1	600	400	5	40	89
5	M.	11	6	600	400	3.5	45	73
6	F.	8	12	400	400	0	40	45
7	M.	15	6	400	400	6	47	67
8	F.	9	12	400	300	10	63	77
9	M.	5	15	600	600	2.5	37	74
10	F.	20	8	400	300	10	37	57
11	M.	10	2	400	400	5	35	57
12	M.	20	4	400	400	5	35	61
13	F.	5	8	600	400	1.5	89	100
14	M.	4	8	600	400	10	62	96
15	M.	5	4	600	600	2.5	50	63

In this group of 10 boys and 5 girls growth had been retarded in 13, chest deformity was severe in 4 and moderate in 9, and occasional oral steroids were still required in 7. Osteoporosis was present in 1, while 6 had withdrawal symptoms of headaches and lassitude, 3 had unmasking of allergic rhinitis, and 1 had worsening of eczema. DSCG had been helpful in 1 and ineffective in 12, and corticotrophin had also been used in 4.

TABLE II—Non-steroid-dependent Group

Case No.	Sex	Months on Aerosol	Total Hospital Admissions	Total Daily Dose (μ g)		Percentage of Peak Flow for Height	
				Initial	Maintenance	Before	After
16	M.	4	—	400	400	63	68
17	F.	16	—	400	300	55	92
18	F.	20	2	400	200	26	59
19	M.	11	—	400	200	50	79
20	M.	2	—	400	400	42	62
21	M.	3	—	400	400	30	50
22	F.	3	1	600	400	49	75
23	F.	5	2	400	400	30	36
24	F.	8	1	400	400	21	35
25	F.	11	1	400	200	45	77
26	M.	5	4	600	400	26	56
27	F.	5	4	400	300	58	84
28	M.	17	3	400	300	54	67
29	M.	7	—	600	400	43	100
30	M.	15	6	600	300	58	82

In this group of 8 boys and 7 girls 14 had required steroids for exacerbations, and 5 had severely, and 5 moderately deformed chests. Although hospital admission was much less frequent the severity of the airways obstruction was not necessarily less. DSCG had been ineffective in 11 and helpful in 4 cases.

In no case was there any evidence of pulmonary candidiasis. DSCG was disappointing in most of the children, as detailed in the footnotes to tables I and II. Children with various problems are illustrated in the following selected case reports.

CASE 26

This patient, born in 1962, had severe asthma from infancy. He was treated intermittently with oral steroids from an early age, continuously with up to 10 mg prednisolone daily in his third and fifth years, and

FIG. 1—Steroid-dependent cases. Average peak flow readings before and after establishment on inhaled steroid in place of oral steroid therapy, and also as compared with predicted peak flow for actual height.

FIG. 2—Non-steroid-dependent cases. Average peak flow readings before and after establishment on inhaled steroid, and also as compared with predicted peak flow for actual height.

FIG. 4—Male aged 15 years. Daily minimum peak flow readings. Severe chronic perennial asthma since infancy, subject to sudden dangerous attacks, and with serious interference with education. Dramatic improvement well illustrated. Patient now able to play football and completed 3-mile (4.8-km) cross-country run, coming 23rd out of 30 boys.

FIG. 3—Male aged 10 years. Severe perennial and seasonal steroid-dependent asthmatic. Chart shows dramatic result of initial introduction of steroid aerosol. With advent of seasonal allergens, patient had to have oral steroids intermittently from May to November 1972.

thereafter for severe episodes only. DSCG was tried without success, and just after his eighth birthday he required 30 mg prednisolone daily in hospital. Glycosuria appeared and a random blood sugar was 325 mg/100 ml. Four months later he again required steroid therapy. Fasting blood sugar was 240 mg/100 ml, and a peak of 910 mg/100 ml was reached during a glucose tolerance test. He was treated with insulin temporarily and the prednisolone was withdrawn. The asthma worsened, however, and a month later an injection of triamcinolone acetonide (Kenalog) again caused glycosuria.

At the beginning of his ninth year the asthma entered a severe phase and the aerosol steroid seemed the only possible compromise. The first attempt to introduce the aerosol elsewhere, however, was unsuccessful. He was then admitted to Derby Children's Hospital when it was found that failure was due to incorrect use of the aerosol. Full allergy investigations yielded nothing except a blood eosinophilia of 17%. Great difficulty was experienced in obtaining co-operation and co-ordination in a disturbed and difficult child, but finally he was established on the aerosol at a dosage of 600 µg daily. His asthma became moderately well controlled and remained so, but the mild diabetes required daily insulin.

This case, as in the adult series which will be reported elsewhere, illustrates how the aerosol can provide an alternative to oral steroids in diabetic asthmatics.

CASE 1

This patient, born in 1959, developed asthma when he was aged 2 years, after recovery from eczema, and in all had had 29 admissions for severe life-threatening asthma. From the age of 5 he was treated almost continuously with oral steroids or corticotrophin, and Cushingoid features and obesity became prominent. In September 1971 he was transferred to aerosol steroid, initially with success, but later had to revert to oral steroids in heavy dosage on account of frequent infective exacerbations. In November he was admitted for reassessment and found to have developed partial collapse of the third, fourth, and fifth dorsal vertebrae. Aerosol was restarted at 600 µg daily and he was intensively desensitized using pure dust mite extract (*Dermatophagoides farinae*) to a top dose of 1 ml of 0.2% extract. The peak flow rose to over 300 l./minute, and on one occasion reached 425 l./min. He had no oral steroids for four months and grew 10 cm, but in March 1972, for no obvious reason, he again went out of control and has had oral steroids or corticotrophin intermittently to date.

This case illustrates the problems in management of a difficult case, which is to date our only failure in children. The fact that practically normal peak flow levels were achieved indicates potential reversibility, but how to maintain this level remains an unsolved problem.

CASE 13

This girl, born in January 1955, developed asthma at 18 months, began oral corticosteroids when aged 4, and had six emergency admissions for acute asthma. By age 11 her height then being 4 ft 3 in (123 cm), she was transferred to zinc corticotrophin 30 units alternate days but with an increase in Cushingoid features and weight. In February 1971 she was changed to tetracosactrin zinc (Synacthen Depot) 0.5 mg twice weekly, with further increase in weight and also depression. DSCG since 1968 had been ineffective.

In September 1971 she was transferred to prednisolone stearoylglycolate 6.75 mg thrice daily. In February 1971 her height was 4 ft 6½ in (138 cm), weight 7 st 10 lb (49 kg), and a tetracosactrin test showed basal cortisol 13.9 µg, and at one hour 17.6 µg.

Transfer to aerosol was quite smooth, and apart from depression, headaches, and two episodes of infection requiring oral steroids and antibiotics for a few days she remained well. Growth occurred by ½ in (1.3 cm) and she lost 24 lb (11 kg) after five months on the aerosol. Allergy studies yielded no clue, but the banishment of dog and cat resulted in further improvement in peak flow readings. Provocation tests with likely allergens were in progress at the time of writing, particularly as allergic rhinitis had been unmasked. The difference in appearance is well illustrated in fig. 5, but the improvement in personality and the disappearance of self-consciousness and introversion is even more striking.

FIG. 5—Case 13. Difference in appearance at age 16 after five months on aerosol steroid alone, after having been dependent on oral steroids or corticotrophin for 11 years. Weight loss 24 lb (11 kg).

CASE 31

This patient was born in August 1969 and his asthma began at 6 months. When first seen at 21 months he had already been in hospital five times with acute asthma, and was admitted thrice more within the next few months, once requiring intensive care. No possible clues to the cause were found, but a nasal smear was loaded with eosinophils. Finally, he was established on 20 units of corticotrophin twice a week, but after six months was still liable to sudden and serious attacks requiring hospitalization and large doses of oral steroids. He became grotesquely Cushingoid in appearance but at the age of 30 months there seemed no alternative. His mother, however, also asthmatic, pointed out that he could take DSCG effectively, so it was decided to try aerosol therapy.

For the past nine months, thanks to the boy's intelligence and mother's co-operation, he has been well controlled on the aerosol, with disappearance of the Cushingoid features. In the beginning oral steroids were required on occasion but have not been needed for the past six months. As he was unable to blow a peak flow meter he is not included in fig. 1, but the case seems well worth reporting. The improvement has been very obvious, and he now behaves like a normal child. Before aerosol treatment he often became cyanosed on running short distances in play.

Discussion and Conclusions

On the objective evidence presented here and in our previous publication there can be no possible doubt that this new compound has great promise in the treatment of perennial asthma in children from an age when they can be trained in its effective use. It is clearly far superior to DSCG in its ability to induce reversal of allergic airway obstruction, and, as in the adult series, the only side effects have been due to steroid withdrawal and unmasking of latent allergic symptoms, with the possible exception of occasional oral or faucial candidiasis. The absence of growth suppression and the effects of complete absence of asthma on the lives and exertional capabilities of these children have been dramatic, often

allied with marked improvement in emotional status and confidence. The reduction in the use of potentially dangerous aerosol bronchodilators is most gratifying in that their use is no longer necessary.

Our results in adults, and now in children are in acute contrast to those of Choo-Kang *et al.*,⁷ Grant,⁸ and Herxheimer,⁹ and are in broad agreement with Clark.³ No one, however, has given any details of case selection, sputum cytology, history, or skin reactions to indicate which of the selected cases might be allergic asthmatics. Excess of eosinophils in sputum or nasal smear is a clear indication that a response to corticosteroids can be expected⁴—provided that the sputum is examined using the techniques described by Brown,^{4,5} Knott and Bruce Pearson,¹⁰ or Sanerkin and Evans.¹¹

Treating no more than seven cases of "airways obstruction," Choo-Kang *et al.*⁷ used the aerosol in a dosage of 2,000 μ g daily. Their published data show that after seven days the FEV₁ in their cases 1 and 4 improved by 55% and 42%, and by a further 43% and 4% after the substitution of 20 mg prednisolone daily for a further week. The total improvement was 97% and 46% respectively, and both relapsed when steroid therapy was stopped. Their remaining five cases showed no improvement either on aerosol or on prednisolone. The marked difference in results between these two cases and the other five did not appear to have raised the very obvious suspicion that the causes of their "airways obstruction" could be different. This small clinical trial in unselected and unspecified "airways obstruction" seemed insufficient to justify criticism of our initial publication.⁸

The results reported in this paper are notably better than in our previous series. Presumably the greater reversibility and the lack of permanent damage explains this, also why the aerosol steroid was so often much more effective than oral corticosteroids alone. Nevertheless, complete reversal to the predicted peak flow is exceptional, even though comparison with the baseline averages shows remarkable improvement.

Objectively based evidence from this centre and also personal communication and pending publication from other investigators^{12,13} confirm our impression that beclomethasone aerosol is a safe and effective alternative to oral corticosteroids in many cases of chronic perennial asthma in children. For those who are poorly controlled on bronchodilators or DSCG, this treatment can give complete or comparative freedom from airways obstruction without risk of adrenal suppression or other side effects, provided patients and parents are fully instructed in its use, so that the substance is effectively inhaled.

Our thanks are due to Dr. D. M. Harris, of Allen and Hanbury's Limited, for supplying the Becotide inhalers and peak flow meters; to Dr. I. B. Burke, of the Royal Berkshire Hospital, who referred case 13; to Dr. R. H. Townsend, of the Sheffield Chest Clinic, who referred case 26; and to the Midlands Asthma and Allergy Research Association for facilities and help with the illustrations.

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