Treatment of childhood asthma for 13 months and longer with beclomethasone dipropionate aerosol

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Godfrey, S., and König, P. (1974). *Archives of Disease in Childhood*, 49, 591. **Treatment of childhood asthma for 13 months and longer with beclomethasone dipropionate aerosol.** Twenty-six children with asthma were treated with beclomethasone dipropionate aerosol in a dose adjusted to their symptoms for 13 to 20 months. 18 children in the group had been taking systemic steroids at the start of the trial and all were successfully weaned off them, mostly within 2 months. All but 1 of the children were satisfactorily controlled by beclomethasone, but 15 children needed short courses of oral steroids at times of severe exacerbations.

There was no evidence of either suppression or acceleration of growth, nor was there any adrenal suppression as assessed at intervals by the estimation of the resting level of plasma cortisol and the response to tetracosactrin. No other side effects were encountered apart from exacerbations of eczema or rhinitis in some children previously on systemic steroids.

Treatment with the steroid aerosol beclomethasone dipropionate has been reported to be beneficial in asthma, both in children (Dickson *et al.*, 1973; Godfrey and König, 1973; Morrison Smith, 1973) and adults (Lal *et al.*, 1972; Morrow Brown, Storey, and George, 1972; Clark, 1972). The trials carried out in children so far have been short term in the main and were unable to provide evidence about long-term efficacy and side effects, especially on growth and on adrenal function. Morrow Brown and Storey (1973) reported a resumption of growth on the drug, but only 4 of the 15 subjects for whom data are given were followed up for a year or more, and since no data are given on the expected growth of these children it is difficult to draw valid conclusions. As pointed out elsewhere (Silverman *et al.*, 1972), it is unwise to draw long-term conclusions about asthmatic children from short-term studies and so we have now followed up a group of children who have been treated with beclomethasone dipropionate for a minimum of 13 months.

Subjects and methods

Twenty-six patients aged 4 to 15 years (mean 9.1 ± 2.7 SD) with severe perennial asthma were treated with

beclomethasone for 13 to 20 months (mean 15.8 ± 2.7 SD). There were 7 girls and 19 boys whose clinical details, including height centiles, are given in Table I. Of these children, 19 had taken part in a short trial of the drug (Godfrey and König, 1973) and were then followed up on an open basis. The remaining 7 children were similar in all ways and were therefore included in the long-term assessment. All the children had failed to be controlled by sodium cromoglycate and 18 of them were receiving systemic steroids at the start of the trial. The other 8 children would have been started on systemic steroids in conformity with our normal policy, had beclomethasone not been available for trial.

The patients were examined monthly or more often at the beginning of the trial and at longer intervals afterwards, as dictated by their clinical condition. The assessment of the clinical control was based on the opinion of the parent and doctor with the help of a daily diary card (Connolly and Godfrey, 1970). Particular attention was paid to time off school, attendance at hospital, and drug usage. In cases where there was any doubt, the child was provided with a peak flow meter and recorded his peak flow every morning and evening at home. The initial short-term trial (Godfrey and König, 1973) was carried out in single-blind fashion, but once the efficacy of the drug was established the follow-up observations were made on an open basis. We have shown previously (Silverman *et al.*, 1972) that the symptomatic response to placebo usually becomes distinguishable from a sustained therapeutic improvement after 8 to 12 weeks. The overall clinical control

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TABLE I
Clinical data and growth

Case no.	Sex	Age (yr)	Systemic steroids before the trial	Height at start of trial (cm)	Height centile at start of trial	No. of courses of systemic steroids during trial	Time of follow-up in trial (mth)	Growth in 1 year of beclomethasone treatment	
								Measured (cm)	Expected (cm)
1	M	8	+	138.0	90-97	—	20	5.0	5.0
2	F	9	—	137.0	75-90	1	19	3.0	4.7
3	F	5	+	102.0	10	1	19	6.5	5.5
4	M	11	+	141.5	50	—	18	6.0	4.5
5	M	4	+	105.0	25-50	1	18	6.5	6.5
6	M	9	—	127.0	10-25	—	18	4.0	4.3
7	F	15	+	151.5	3-10	—	17	3.0	2.0
8	M	10	+	146.0	75-90	—	18	5.0	5.5
9	M	9	+	130.5	25-50	—	18	6.0	5.0
10	F	8	+	130.0	50-75	> 3	19	4.5	5.5
11	F	10	+	129.0	10-25	2	15	6.5	5.0
12	M	6	+	120.0	50-75	2	15	5.5	5.8
13	M	7	+	115.5	10-25	5	15	6.5	5.0
14	M	13	+	131.5	<3	1	15	6.9	5.0
15	M	13	+	138.0	3-10	2	15	3.5	5.0
16	M	13	+	139.5	3-10	—	14	3.9	5.5
17	M	11	—	151.0	90	—	14	4.0	4.5
18	M	8	—	133.0	50-75	—	14	3.4	5.3
19	F	7	+	131.5	90-97	1	14	7.5	6.0
20	M	11	—	131.0	<3	—	13	4.5	4.2
21	M	8	—	129.0	50-75	—	13	5.0	5.2
22	F	7	—	126.5	50-75	1	14	5.0	5.5
23	M	9	+	131.5	50-75	1	15	3.0	5.0
24	M	9	—	127.0	10-25	2	14	3.5	4.0
25	M	11	+	129.5	3-10	1	14	4.0	4.0
26	M	5	+	104.0	<3	1	14	5.5	5.5
Mean		9.1					15.8	4.9	5.0
SD		2.7					2.2	1.3	0.9

was graded as good if it was better than on the treatment the child received before the trial, adequate if it was the same, and poor if it was worse than before the trial.

The dosage of beclomethasone was varied between 100 to 800 µg/day, according to the clinical response. The mothers were instructed to vary the dose at approximately weekly intervals according to the child's condition, with the overall intention that he remain free of symptoms.

Measurements of height were made on each visit to the clinic by a trained nurse using standard paediatric apparatus and were plotted on a growth chart (Tanner, 1958). The measured growth during the first year of beclomethasone therapy was compared with the expected growth, assuming the child would have continued along his initial centile line.

Adrenal function was assessed by measuring plasma cortisol between 9.00 and 10.00 a.m. An injection of 1 mg depot tetracosactrin was then given and the plasma cortisol was remeasured 2 hours later. Because of practical difficulties, adrenal function was only studied in 14 children before starting beclomethasone, in 21 children after 3 months on the drug, and in 14 children after 1 year of treatment. A blood chemistry screen for liver function, urea, and electrolytes and a haematological screen were carried out routinely after 3 months and 1 year of treatment in 18 children, and as clinically

indicated in all cases. Blood pressure measurement and urine analysis were carried out frequently in all cases.

In statistical comparisons, differences were not considered to be significant unless $P < 0.05$.

Results

Clinical response. All 18 children who were receiving systemic steroids at the start of the trial were weaned off them, 13 children (72%) by the end of 1 month and 4 children (22%) by the end of 2 months. In 1 severely affected child with gross iatrogenic Cushingoid features, it was only possible to wean him off systemic steroids after 9 months on beclomethasone, and his Cushingoid features have now gone. The clinical control was considered to be good in 19 children and adequate in 6, but 1 child who had been satisfactorily controlled for almost a year deteriorated later and her control was therefore considered poor.

From time to time exacerbations of asthma were encountered and these were treated by additional bronchodilators, usually aerosol salbutamol taken 10 minutes before the beclomethasone, together with an increase in the dosage of beclomethasone up to

800 μg daily (4 puffs q.d.s.). If this was not successful, the child was given a short course of additional oral prednisone for about a week in most cases. In all, 15 children (58% of the total) needed additional oral prednisone at some stage, 9 of them (35%) only once, 4 of them (15%) twice, and 2 (8%) three or more times during the whole period of follow-up (Table I). 1 of these 2 children needed two prolonged courses of prednisone and is still taking this drug at the time of writing. She has been the only major failure encountered so far in the trial. It should also be noted that 42% of children have never required systemic steroids since starting beclomethasone between 13 and 20 months ago, and 77% have required one such course at most. In 3 cases in which the children were very well on low doses of beclomethasone an attempt was made to withdraw the drug after 3 to 8 months, but this invariably resulted in exacerbations of asthma and the treatment had to be resumed.

Growth. The distribution of height centiles of the children before the trial showed a preponderance of small children, and there was very little change after the trial (Fig. 1). Most children continued to

FIG. 1.—Distribution of height centiles of the children before and after the trial.

grow along their previous height centiles (Fig. 2) and there was no evidence of growth suppression or acceleration while on beclomethasone (Table I). The mean measured growth over a year for the whole group was $4.9 \text{ cm} \pm 1.3 \text{ (SD)}$, which is remarkably close to the mean expected growth of $5.0 \text{ cm} \pm 0.9 \text{ (SD)}$, the difference between them being nonsignificant. It was found that 13 children remained on the same centile or improved slightly, while the other 13 children moved to a slightly lower centile. The maximum discrepancies were an increased growth of 1.9 cm above expected and a decreased growth of 2.0 cm below expected (Table I).

FIG. 2.—Height of 3 children, whose case numbers are circled, in relation to steroid therapy. The arrows indicate the onset of treatment with daily prednisone (PD), alternate day prednisone (PA), or beclomethasone (B). Only one type of regimen was used at any one time.

Adrenal function. The results of the adrenal function tests are given in Table II and are summarized in Fig. 3. In most cases the adrenals were not suppressed before the trial because the majority of the children had been treated with alternate-day oral prednisone or corticotrophin, but the relatively large SDs before the trial reflect the fact that some children had diminished responses. There was no evidence of adrenal suppression by treatment with beclomethasone either at 3 months or

FIG. 3.—Resting plasma cortisol and response to tetracosactrin stimulation at various stages.

TABLE II
Results of adrenal function studies

Case no.	Before trial		After 3 mth on beclomethasone		After 1 yr on beclomethasone	
	Resting cortisol ($\mu\text{g}/100\text{ ml}$)	After tetracosactrin ($\mu\text{g}/100\text{ ml}$)	Resting cortisol ($\mu\text{g}/100\text{ ml}$)	After tetracosactrin ($\mu\text{g}/100\text{ ml}$)	Resting cortisol ($\mu\text{g}/100\text{ ml}$)	After tetracosactrin ($\mu\text{g}/100\text{ ml}$)
1	—	—	20.0	34.0	12.0	36.0
2	—	—	14.0	50.0	29.0	52.0
3	—	—	6.4	56.0	15.0	48.0
4	1.0	6.0	10.0	38.0	—	—
5	—	—	11.0	47.0	12.0	48.0
6	—	—	16.0	43.0	21.0	48.0
7	1.0	0.6	10.0	43.0	10.0	36.0
8	—	—	9.0	40.0	—	46.0
9	—	—	13.0	42.0	10.0	50.0
10	—	—	10.0	36.0	10.0	42.0
11	14.0	29.0	15.0	24.0	—	—
12	16.0	34.0	18.0	44.0	—	—
13	11.0	40.0	9.0	45.0	20.0	48.0
14	6.0	30.0	—	—	8.0	27.0
15	18.0	69.0	11.0	58.0	14.0	44.0
16	19.0	42.0	17.0	45.0	—	—
17	18.0	57.0	15.0	46.0	—	—
18	10.0	34.0	16.0	43.0	12.0	42.0
19	10.0	45.0	9.0	41.0	9.0	37.0
20	3.0	6.0	17.0	30.0	—	—
21	13.0	46.0	10.0	38.0	—	—
22	8.0	53.0	14.0	38.0	—	—
Mean	10.6	35.1	12.9	42.0	14.0	43.1
SD	6.2	20.0	3.7	7.8	6.0	7.0
Total	14	14	21	21	13	14

at 1 year, and none of the differences in plasma cortisol levels were significant. The pattern of adrenal function was also more uniform. It can be seen that 3 children were relatively suppressed before starting beclomethasone (Cases 4, 7, and 20), but all had normal function by 3 months.

Side effects. Blood chemistry and haematological investigations revealed no abnormalities and the blood pressure and urine analysis remained normal throughout. The only side effect encountered so far has been the tendency to exacerbations of hay fever, perennial rhinitis, and eczema in children previously treated with systemic steroids. In 8 children there was a worsening of eczema, and in 2 a worsening of hay fever or perennial rhinitis. These complications were not severe enough to warrant systemic steroid treatment. No clinical evidence of oral monilial infection nor any increase in the frequency of respiratory infections has been noted.

Discussion

The results of this study, summarized in Table III, have shown that the generally good response to beclomethasone observed during short-term trials in

TABLE III
Aerosol beclomethasone in 26 children

	No. of children	%
Age: 9.1 yr $\pm$ 2.7 (SD)		
Clinical success	25	96
Follow-up		
13-16 mth	16	62
17-20 mth	10	38
Additional prednisone courses		
0	11	42
1	9	35
2	4	15
3 to 5	2	8
Annual growth		
1-2 cm greater than expected	5	19
Expected $\pm$ 1 cm	16	62
1-2 cm less than expected	5	19

childhood asthma can be sustained for periods of up to 20 months without serious side effects.

The dose required by the children to give good control fluctuated from time to time, presumably due to variations in the severity of prevailing stimuli. Gaddie *et al.* (1973) came to the conclusion that a dosage of 800 μg or more of beclomethasone was no better than 400 μg daily in a comparative trial to determine optimal doses, but their patients received the fixed dosage irrespective of symptoms. It is

entirely conceivable that a patient who is well on 400 μg daily will not gain further benefit from 800 μg daily, while the same patient, when having an exacerbation, might still be improved by raising the dose to 800 μg . Likewise, adherence to a fixed (and possibly rather low) dose in the study by Dickson *et al.* (1973) may have accounted for the failures in some of their children. However, in contrast to systemic steroids there is an important limitation to the efficacy of beclomethasone in severe exacerbations of asthma because of the inability of the dyspnoeic patient to inhale the aerosol properly, and persistence with the aerosol alone in this situation could very well be dangerous. The fact that 58% of the patients in this study needed additional systemic steroids at some stage is in accordance with the experience of other authors. Thus Dickson *et al.* (1973) had to resort to this treatment in 3 out of 25 patients and Clark (1972) in 5 out of 17 patients, but in both these studies the follow-up was much shorter than in the present study. Morrow Brown and Storey (1973) mentioned the need for short courses of systemic steroids in 2 out of their 3 case reports, but gave no data for the rest of their patients.

There was no evidence that adrenal function was suppressed by prolonged administration of beclomethasone dipropionate and this confirms the results of short-term trials (Godfrey and König, 1973). On the contrary, there was evidence of a return to normal in previously suppressed children. The only side effects encountered in this study were recurrences of hay fever, allergic rhinitis, and eczema, but they were not severe enough to stop beclomethasone. No clinically obvious oral thrush was found in contrast to the four cases reported by others (Morrow Brown and Storey, 1973), but routine cultures were not carried out during our study and subclinical cases could have been missed. Subsequent to the conclusion of the trial, cultures were taken from the faeces of 24 children receiving beclomethasone and 33 matched control asthmatics not receiving the aerosol. *Monilia* was grown from 3 of the former and 2 of the latter group, the difference being insignificant.

Limitation of growth has been a major problem in the past when treating children with steroids. It has been shown that continuous treatment with oral steroids causes serious growth stunting (Falliers *et al.*, 1963), while the use of an alternate-day regimen (Zachmann, 1970; Soyka, 1967), or possibly of corticotrophin (Friedman and Strang, 1966), diminished this complication. However, severe asthma in itself tends to stunt growth (Falliers *et al.*, 1963) even without steroid therapy, and it might therefore have been expected that beclomethasone

would actually result in a growth spurt if it was truly free from systemic activity. Morrow Brown and Storey (1973) claimed that their children did show a growth spurt on beclomethasone, but it is likely that most of their children would have grown the amounts reported in the normal course of events as judged by their ages, and even 1 of the children growing 10 cm could well have done so in the 20 months available. Though several of their children did appear to grow more rapidly than expected, there was an equal number who clearly grew less rapidly, such as the boy of 13 years who only grew 5 cm in 20 months and should have grown approximately 10 cm. We did not find evidence of growth suppression by treatment with beclomethasone, but neither was there a dramatic acceleration of growth on stopping systemic steroid treatment.

In conclusion, beclomethasone dipropionate is an efficient drug for the relatively long-term treatment of childhood asthma and appears to have no systemic side effects in doses which are varied up to 800 $\mu\text{g}/\text{day}$. Over half the children will need some additional oral steroid cover for severe exacerbations from time to time during the year, but this plan of treatment does not result in any adverse effect on growth or adrenal function. Patients, parents, and doctors should be aware of the need for oral or parenteral steroids if a simple increased dose of aerosol does not rapidly bring an attack under control.

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