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Beclomethasone aerosol in childhood asthma

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Godfrey, S., and König, P. (1973). *Archives of Disease in Childhood*, **48**, 665. **Beclomethasone aerosol in childhood asthma.** Twenty children have been treated with the steroid aerosol beclomethasone, half of them in an open trial and the other half in a controlled cross-over trial. Children were assessed by means of clinical examination, diary records, and twice-daily peak flow rate measurements made at home.

After 1 to 2 months all but 1 of the 16 children who were initially taking systemic steroids or corticotrophin were weaned off these drugs. The cross-over trial showed a significant improvement on the active drug, in terms of diary score, bronchodilator use, steroid dose, and twice-daily peak expiratory flow measurements. Adrenal function was entirely normal after 1 and 3 months on the drug as measured by morning cortisol levels and the response to tetracosactrin. There were no side effects, apart from the reappearance of hay fever or eczema in some children previously on systemic steroids. Follow-up for a mean of $4 \cdot 5 \pm 2 \cdot 2$ (SD) months showed the continuing efficacy of beclomethasone, though an increase in dose has been needed in some children. The advantages of aerosol steroid therapy in children are noted.

Considerable interest has been aroused recently by a steroid aerosol (beclomethasone) for use in the treatment of bronchial asthma (Smith, Booth, and Davey, 1971; Choo-Kang *et al.*, 1972; Morrow Brown, Storey, and George, 1972; Clark, 1972; Lal *et al.*, 1972). Though most of these reports can be criticized on the basis of design or control, the study by Lal *et al.* (1972) gave conclusive evidence of the efficacy of this drug in adults using a double blind cross-over comparison with prednisone. The drug enabled patients to reduce or stop oral steroids while maintaining good clinical control, and yet without any evidence of systemic side effects or adrenal suppression. Adrenal function usually recovered if it was previously reduced.

Steroids present a great problem in childhood asthma because of their limiting effect on growth (Falliers *et al.*, 1963; Kerrebijn and De Kroon, 1968; Zachmann, 1970), as well as the other side effects seen in adults. A large proportion of severe perennial childhood asthmatics can now be adequately controlled by sodium cromoglycate without requiring steroids (Silverman *et al.*, 1972). There are, however, about 25% of such children in whom sodium cromoglycate has little or no effect and who consequently require steroids. Growth suppression and adrenal suppression can be avoided by giving a double dose of steroids on alternate mornings (Zachmann, 1970; Falliers *et al.*, 1972) but, in our experience, control of symptoms on the intermediate day is not very good. The only remaining course for the severe asthmatic is to give corticotrophin (Friedman and Strang, 1966), which means injections at intervals of 2 to 3 days. Children naturally do not like this.

For these reasons, beclomethasone has obvious attractions to the paediatrician treating severe asthma. Only a very few children were included in previous trials of this drug and it was therefore decided to carry out clinical and physiological studies in children.

Subjects and methods

All 20 patients were children attending the paediatric asthma clinic of the Brompton Hospital, and most had been known to one of us (S.G.) for several years. The children were put into the trial if they were already receiving regular corticosteroids or corticotrophin or, in 4 cases, because they needed to begin regular steroids as their asthma could not be controlled any other way. All children had been fully investigated clinically and physiologically and all had been given fully documented trials of disodium cromoglycate without being adequately

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controlled. Some relevant details of the patients are given in Table I. It can be seen that they were a severe group of asthmatics in that they had had asthma for 76% of their lives and had been on steroid therapy for 38% of the duration of their disease. The dose of prednisone shown in Table I refers to the mean weekly dose because most children were on an alternate-day regimen. Only Cases 7 and 14 were receiving daily steroids, and these children had been referred to the clinic recently. The parents were fully informed of the nature of the new drug and all were willing to co-operate with the trial because of their hope to avoid the problems of standard steroid therapy.

Two types of study were undertaken. When the early results in adults became available and suggested a good effect, 10 children were started on an open trial of the drug. They will be referred to as the 'open group'. In these children assessment was mainly by means of the opinion of the parents, coupled with the quantity of steroids and other drugs consumed. Some children also had diaries and peak flow meters to use at home. Adrenal function in this group was studied after 3 months on the drug.

In view of the apparently good response in this open group, it was decided that some type of controlled study was essential for a complete evaluation of the drug. A second group of 10 children was therefore studied by means of a single blind cross-over study. These children will be referred to as the 'cross-over group'. This study was single blind because it was felt to be unethical to give children requiring steroids a placebo drug without the physician and general practitioner being informed; and moreover, it was particularly undesirable to wean them off oral steroids on to the active preparation and then to switch (blindly) to the placebo. The children in this group received the placebo inhaler for the first month and the active inhaler for the second month, but the parents and child were not told which was which.

Assessment in this cross-over group was made by means of a daily diary of symptoms and drug usage (Connolly and Godfrey, 1970) and twice-daily measurements of peak expiratory flow rate (PEF) recorded at home with a Wright Peak Flow Meter (Airmed Limited). Adrenal function studies were performed before starting the trial and after each month, and blood was taken for haematological and biochemical analysis at the same time. For the adrenal studies, plasma cortisol was measured by a modification of the method described by Mattingly (1962) between 9.00 and 10.00 hours and then 1 mg of depot tetracosactrin was given intramuscularly. Plasma cortisol was again measured two hours later. Spirometry was performed at each monthly clinic visit but was not used to assess the results of the trial because of the uselessness of such random measurements (Chai *et al.*, 1968; Silverman *et al.*, 1972).

The dose of beclomethasone (or placebo) was 2 puffs (100 μg) three times daily in both groups.

The parents were instructed to continue all other medication and to add the new inhaler. If they felt that the child was well after a week, they were told to reduce other medications, including steroids, in a stepwise

TABLE I

Mean weekly prednisone dose of 20 children

Case no.	Age (yr)	Sex	Duration of asthma (yr)	Duration of steroid treatment (yr)	Time on steroids / Duration of asthma (%)	Weekly equivalent of prednisone (P) and tetracosactrin (T) over previous 2 mth (mg)	Skin tests
Open trial							
1	8	M	5	1·5	30	P 26·6	+
2	9	F	3	0	0		+
3	5	F	3	2·0	66	P 52·5	+
4	11	M	11	7·0	63	P 35·0	+
5	4	M	4	1·5	37	P 35·0	+
6	9	M	7	0	0		+
7	15	F	15	6·0	40	P 52·5	Not done
8	9	M	7	2·9	41	T 0·6	+
9	11	M	10	0·5	5	P 43·8	+
10	8	F	5	0·8	16	P 17·5	+
Cross-over trial							
11	9	F	8	5·1	63	P 35·0	+
12	6	M	3	0·8	26	P 8·8	Not done
13	7	M	4	4·0	100	P 35·0	+
14	13	M	10	8·0	80	P 21·0	+
15	13	M	12	7·6	63	T 0·8	+
16	13	M	8	8·0	100	T 0·5	+
17	11	M	7	0	0		Negative
18	8	M	7	0	0	P 35·0	Not done
19	7	F	6	2·1	35	P 26·3	+
20	7	M	4	0	0		+
Mean	9·2		7·0	2·9	38·5	P 32·6	
SD	2·9		3·3	3·0	33·4	P 12·8	

fashion and to continue this procedure as long as the child remained well. In the cross-over study (and in some of the later open studies) they were also told not to reduce other medication unless the PEF had been greater than 60% of expected normal for at least 10 out of the 14 measurements in the previous week.

Standard statistical analysis of the data was carried out. Differences were considered significant when the probability of a difference being due to chance was less than 1 in 20 ($P < 0 \cdot 05$).

Results

Open study. 10 children took part in this study and their clinical details are given in Table I. 8 were receiving regular steroid therapy at the start of the trial, and by the end of 3 months all of them had been completely weaned off steroids, whether oral prednisone or corticotrophin injections (Table II). Moreover, the consumption of bronchodilators and/or cromoglycate was also significantly reduced (Table II). Coupled with this, all the children felt better than when they were on their previous medication, and in those children who had been given flow meters in the open study, this symptomatic improvement was amply confirmed by objective data.

The improvement has been maintained in all children studied to date, and the follow-up for 6 months in 9 of the 10 children is given in Table II. The longest open assessment at the time of writing has been for 8 months without any sign of relapse.

At the end of 3 months on beclomethasone, resting plasma cortisol was within the normal range (Falliers *et al.*, 1972) in all the children and the response to tetracosactrin was also normal (Table III). No abnormality was detected in haematology, liver function, urea, electrolytes, urine analysis, or blood pressure in any child.

Cross-over study. There were 10 children in this study whose clinical details are given in Table I. As in the open study there was a clear-cut response to beclomethasone. Before entering the trial 7 children were on regular steroids (5 on prednisone and 2 on corticotrophin), and 1 child started prednisone treatment at the same time as beclomethasone placebo because his asthma was so severe. At the end of the first month on placebo, there had been no significant change in this pattern. By the end of the next month on the active drug, 3

TABLE II

Results of open trial

	Before trial	After 3 mth on beclomethasone	After 6 mth on beclomethasone
No. of children on regular prednisone	7	0	0
Mean daily prednisone dosage (mg)	3·75	0	0
No. of children on corticotrophin (Synacthen)	1	0	0
Mean weekly corticotrophin (mg)	0·6	0	0
No. of children on regular sodium cromoglycate	5	1	1
No. of children on regular bronchodilators	8	0	0
No. of children feeling better	—	10	9
Total no. of children	10	10	9*

*Only 9 children had completed 6 months' treatment at time of writing.

TABLE III

Resting cortisol levels and response to tetracosactrin

	Before trial	After 1 mth on placebo	After 1 mth on beclomethasone	After 3 mth on beclomethasone
Resting cortisol (μg/100 ml)				
Mean	11·8	13·4	12·7	11·9
SE	1·8	1·5	1·6	1·1
No.	10	9	10	11
Cortisol after tetracosactrin (μg/100 ml)				
Mean	39·2	41·1	41·0	44·3
SE	3·3	4·1	1·4	1·2
No.	10	9	10	11

Note: One child did not have the test after placebo. Results at 3 months include children from both open and cross-over trials.

children had been weaned off steroids and most of them had considerably reduced all other drugs (Fig. 1, Table IV). Of the 5 children who were still having oral steroids or tetracosactrin injection at the end of 1 month on the active drug, 4 had stopped them by the end of 2 months on beclomethasone (Fig. 1). One child (Case 4) had been weaned off prednisone but still required a smaller dose of tetracosactrin than he had taken before. The reduction in steroids and bronchodilator consumption for the whole group between the placebo month and the first month on the active drug was highly significant (steroids $P<0\cdot001$; bronchodilators $0\cdot025>P>0\cdot020$).

The changes in symptoms and in airway resistance as reflected by the mean diary score and PEF are shown in Fig. 1 and 2. Little change occurred in either during the placebo month, but the diary score fell and PEF rose rapidly with the switch to the active drug. There was a clear relation between

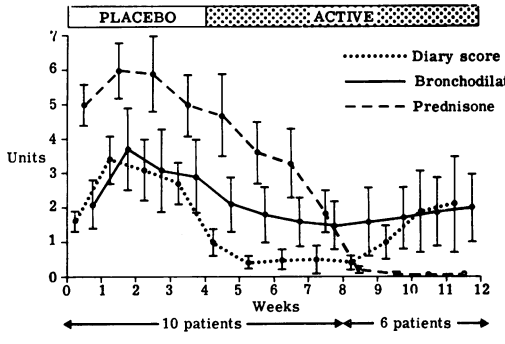

FIG. 1.—*Mean weekly values for diary score, bronchodilator usage, and prednisone dosage in the cross-over trial. Bars indicate ±1 SE. 6 children continued records for a further 4 weeks and these results are included.*

TABLE IV

Significance of differences between placebo and active months in cross-over trial for each child

Case no.	Diary score	Bronchodilator	Mean daily PEF
11	xxx	x	xxx
12	xx	NS	x
13	xxx	xxx	xxx
14	xxx	xx	x
15	x	NS	NS
16	xxx	xx	xxx
17	xxx	xxx	xxx
18	xx	xx	xxx
19	xxx	xxx	xxx
20	x	NS	xxx

x, $0\cdot05>P>0\cdot01$; xx, $0\cdot01>P>0\cdot001$; xxx, $P<0\cdot001$; NS, not significant. PEF, peak expiratory flow rate.

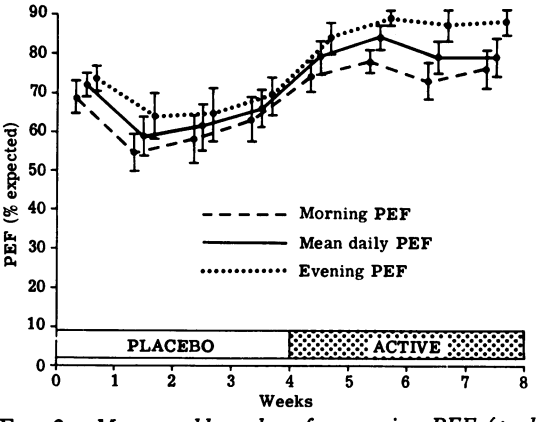

FIG. 2.—*Mean weekly values for morning PEF (peak expiratory flow rate), evening PEF, and mean daily PEF in the cross-over trial.*

the improvement in the diary score and the decrease in prednisone dosage. Comparing the total scores of the whole group for the placebo and active month, there was a highly significant fall in mean daily diary score ($P<0\cdot001$) and rise in mean daily PEF ($0\cdot01>P>0\cdot005$), morning PEF ($0\cdot05>P>0\cdot025$), and evening PEF ($0\cdot005>P>0\cdot001$). When individual children were considered by comparing the data for the whole of the placebo month with the whole of the beclomethasone month, these group results were confirmed (Table IV). In all 10 children the diary score was significantly lower on beclomethasone, in 7 bronchodilator usage was significantly lower, and in 9 mean daily PEF was higher. The position with respect to conventional steroid usage was more complicated because a deliberate policy of slow weaning was used, which meant that no reduction in dose occurred for at least 1 week on the active drug. The monthly conventional steroid consumption is better judged from the results shown in Fig. 1 and by the fact that all but one of the children on these drugs during the placebo month had been totally weaned off them after 2 months on beclomethasone. The swing in PEF during the day was assessed by noting the standard deviation of the twice-daily measurements in each child over the month. The mean of this value for the whole group during the placebo month was greater than that for the active month, but did not quite reach statistical significance ($0\cdot1>P>0\cdot05$). Thus, the PEF was better on the drug than on the placebo, and the daily variability was similar.

The results of adrenal function studies are summarized in Table III. The children were either receiving alternate-day steroids or corticotrophin

before the study rather than daily steroids, and hence adrenal function was relatively normal at the beginning. There was no significant change after the placebo or beclomethasone month. As in the open study, no abnormality was detected in blood pressure, haematology, liver function, urea, electrolytes, or urine analysis.

Side effects. The only side effects seen in either study have been the reappearance of hay fever or the exacerbation of eczema in some children who had these symptoms earlier in their disease but in whom they had been suppressed by systemic steroid therapy. These symptoms were never severe enough to require the reintroduction of systemic steroids and the eczema seemed to respond to beclomethasone cream (Propaderm) in one particularly bad case. Parents and general practitioners were warned about the theoretical dangers of severe asthma or systemic stress, which would require oral or parenteral steroids, but these have not so far been required. Occasionally a child was wheezy at the time a dose of beclomethasone or placebo was due, and this was dealt with simply by inhaling a puff of salbutamol, waiting 10 minutes, and then taking the beclomethasone. These inhalations of bronchodilator were charted on the diaries and have been included in the assessment of bronchodilator usage given above. After completion of the cross-over trial, the dose of beclomethasone was varied up or down to keep symptoms to a minimum. It was found that requirements varied from two puffs (100 μg) to 12 puffs (600 μg) per day with no obvious difference between subjects requiring different doses.

During the period of the trials, and subsequently for a maximum of 8 months' follow-up, there was no evidence whatsoever of growth suppression in any child, but neither was accelerated growth seen.

Discussion

We believe that these studies have shown that beclomethasone aerosol is highly effective and without systemic effects in severe asthmatic children for up to 8 months. If this initial response is maintained, then this type of drug may well become the treatment of choice for asthmatic children requiring steroids.

Our findings in children reflect the recent findings in adults (Smith *et al.*, 1971; Morrow Brown *et al.*, 1972; Clark, 1972), and our single blind cross-over study confirms the finding of the controlled adult study of Lal *et al.* (1972). It is true that a single blind study is not as ideal as a double-blind randomized cross-over study, but we felt this to be unethical in the severely asthmatic children. Since the diary score, drug dose, and PEF were all recorded at home by the mother or child who had no idea of the nature of the treatment, we feel that the results were unlikely to be subject to systematic bias.

There has been one earlier report of failure of beclomethasone in adults (Choo-Kang *et al.*, 1972), but it is difficult to analyse their data because so little clinical information was given. The problem of coincident irreversible lung disease is always present in adults. Our study suggests that the results in children appear to be, if anything, better than those in adults. Whereas Lal *et al.* (1972) found no improvement in PEF, the children did improve significantly. Possibly they had been maintained beforehand on suboptimal doses of steroids for asthma in order to avoid growth suppression.

Although the mean resting cortisol level and mean response to corticotrophin for the children were not changed much by treatment with beclomethasone, this was hardly surprising since the prestudy levels were normal in most cases. In the 3 children who showed evidence of adrenal suppression before the study, recovery occurred during treatment with beclomethasone (Table V).

TABLE V

Resting cortisol and response to tetracosactrin in 3 children

	Cortisol (μg/100 ml)	
	Before trial	After beclomethasone trial
Case 4		
Resting	1·0	10·0
After tetracosactrin	6·0	38·0
Case 7		
Resting	1·0	10·0
After tetracosactrin	0·6	43·0
Case 14		
Resting	6·0	17·0
After tetracosactrin	30·0	45·0

Paediatricians and others concerned with treating childhood asthma are naturally apprehensive about giving steroids to children. At the present time, sodium cromoglycate must be the treatment of choice for some 75% of severe, perennial, asthmatic children in whom it works very well (Silverman *et al.*, 1972). Until a full trial of this drug has been used in the child, normally 4 to 5 capsules daily for a

month, one would be unwise to proceed to steroids. In those children who do not respond to sodium cromoglycate or who already receive oral or parenteral steroids, then beclomethasone appears to be ideal for long-term therapy. It must be stressed, however, that we still require longer-term studies to be certain that its effect is maintained, and an increase in dose has been needed in some of our children.

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