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Nebulised beclomethasone dipropionate in preschool asthma

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SUMMARY Twenty nine young children with severe recurrent asthma were given nebulised beclomethasone dipropionate or normal saline in a double blind manner over a six month period. Progress was monitored using diary score cards. Those receiving beclomethasone had lower symptom scores, had more symptom free days, and required less additional treatment with bronchodilator agents. The code needed to be broken more frequently if normal saline was used. Over the study period height and weight increases in the two groups were similar, and no serious side effects were noted.

Beclomethasone dipropionate, in both aerosol and powder capsule form, is now well established as a safe and effective prophylactic treatment in children with asthma.[1–4] It has recently become available as a suspension for use in nebulisers, and in this form it is particularly useful in young children who are unable to use other inhaled devices. Nebulised sodium cromoglycate and bronchodilator solutions are being increasingly used at home in preschool children with severe asthma. To date there is no documented evidence on the usefulness of nebulised beclomethasone dipropionate in young children, and the aim of this study was to compare the effects of nebulised beclomethasone dipropionate with nebulised placebo (normal saline) in this particularly difficult age group.

Patients and methods

Patients. Twenty nine children took part in the study, 18 boys and 11 girls. Their ages ranged from 20 months to 5·6 years (mean 3·6 years). In the six months before the study all had had severe recurrent wheezing episodes, which had responded well to treatment with nebulised bronchodilator agents on admission to hospital. The number of previous hospital admissions for asthma ranged from four to 14, with at least two in the previous six months. Twenty four children had received at least one oral prednisolone course, and 16 were already using a nebuliser at home. Eleven of these were receiving regular treatment with nebulised sodium cromoglycate and intermittent treatment with nebulised bronchodilator agents, while the other five were receiving treatment with nebulised bronchodilators only. The remaining 13 patients were receiving treatment with oral bronchodilator agents (salbutamol or terbutaline) with or without oral theophylline. None of the patients were satisfactorily controlled before the study. There was a past history of eczema in 12 of the patients and a family history of asthma, eczema, or hay fever in first degree relatives in 22 of the 29 patients.

Methods. Each patient's height (cm) and weight (kg) were measured at the beginning and end of the study. The study was carried out using a double blind parallel group design. Each patient was supplied with an identical Acorn nebuliser and Bard compression pump, and was randomly allocated to either beclomethasone dipropionate or placebo suspension in a double blind manner. The code was kept by the hospital pharmacist and Allen and Hanburys Ltd. The parents were instructed to nebulise 2 ml (100 mcg beclomethasone dipropionate or 2 ml normal saline) three times daily using a close fitting face mask, and if wheezing occurred they were instructed to give additional salbutamol nebules (2·5 mg) through the nebuliser as required. All other treatment for asthma was stopped. After a two week run in period each patient continued on this treatment for six months. Progress was monitored by diary score cards, and each patient was reviewed at two monthly intervals. The score cards recorded day and night time cough and wheeze, graded 0–3 (0=no symptoms, 1=mild, 2=moderate, and 3=severe), the daily presence of a runny nose (Yes/No), and all drugs given. Other drugs such as

oral bronchodilator agents, antibiotics, and prednisolone were allowed providing they were recorded on the score card.

As treatment with placebo (normal saline) was being used it was considered appropriate to adopt criteria for breaking the code. If the patient required two hospital admissions during the study period or if the parents thought the child was much worse than previously the code was broken. If placebo had been used the patient was begun on treatment with beclomethasone dipropionate suspension, but if beclomethasone dipropionate had been used the patient remained on this for the remainder of the study. All patients completed the full six months. Analysis of the results was made from day one of the treatment period until either the end of the study or the day the code was broken. Results after the code was broken were not included in the analysis. The study was fully explained to the parents before beginning and had previously been passed by the local ethical committee. The study took place over an 18 month period in an attempt to eliminate seasonal bias.[5]

Statistics. Assuming a response rate of 75% with beclomethasone dipropionate and 25% with saline, we attempted to recruit 18 patients to each group in order to have an 80% chance of showing a difference between the treatments.[6]

The results were analysed using a generalised Wilcoxon test, Student's *t* test, and Kendall's τ statistic. Kendall's τ statistic was found by dividing the trial into 13 two week periods from the starting date in the study of each patient. For each period an average (or total score for salbutamol) was calculated for each variable over the 14 days. If the number of days with complete data was less than seven then that period was not included. A negative value of Kendall's τ statistic implied that the variable was improving, and a positive value implied a deterioration over the trial.

Results

Fifteen patients were allocated active and 14 placebo treatment. There was no difference regarding age, height, weight, and severity of asthma between the two groups. Over the study period height and weight increases in the two groups were not statistically different (Student's *t* test for paired data). Table 1 shows the patient details in the two treatment groups. The code was broken in seven (50%) of the patients receiving placebo and in four (26·7%) receiving beclomethasone dipropionate. The mean number of days before the code was broken was 77 in the placebo group and 76 in the beclomethasone dipropionate group.

Table 1 *Patient details in the two treatment groups. Values are mean (SEM) or number*

	Treatment group	
	Beclomethasone dipropionate	*Placebo*
No of patients	15	14
No of boys	8	10
No of girls	7	4
Age (yrs)	3·6 (0·3)	3·4 (0·4)
Height (cm)	98 (2·6)	96 (2·7)
Weight (kg)	15·1 (1·2)	16·2 (0·8)
Previous No of admissions	6·1 (0·7)	6·5 (0·9)
Height increment in six months (cm)	4·23 (0·3)	4·42 (0·33)
Weight increment in six months (kg)	1·52 (0·22)	1·64 (0·36)

Table 2 shows the mean daily symptom scores and the percentage of symptom free days in each group. Symptom scores were consistently higher in the placebo group, and percentage symptom free days were consistently higher in the active group. Only wheeze symptoms, however, reached significance ($p<0·05$).

Almost twice the number of salbutamol nebules were needed in the placebo group—the mean daily number of salbutamol nebules required was 0·98 compared with 0·52 in the active group ($p<0·05$). The mean percentage of days when salbutamol nebules were required was 18% on active and 38% on placebo treatment.

Table 3 compares the trend in symptoms with the requirement for extra salbutamol between the treatment groups during the trial. There was a trend for less wheeze, less cough, and fewer nebules of salbutamol to be needed in the group given beclomethasone dipropionate. This difference was only significant in comparison of wheeze scores (Student's *t* test for independent samples; $p=0·06$).

Table 2 *Mean daily symptom scores and % symptom free days in the two treatment groups*

	Treatment group	
	Beclomethasone dipropionate	*Placebo*
Mean daily symptom scores:		
Cough (day)	0·39	0·43
(night)	0·36	0·51
Wheeze (day)	0·26	0·33
(night)	0·26	0·35
Mean % symptom free days:		
Cough (day)	70	66
(night)	73	63
Wheeze (day)	79	75
(night)	80	74

Table 3 *Comparison of trend in symptoms with the requirement for extra salbutamol between the treatment groups*

Treatment	*Case No*	*No of 14 day periods*	*Kendall's τ statistic*		
			Wheeze	*Cough*	*Symptomatic salbutamol*
Beclomethasone dipropionate					
	2	4	−0·33	−0·33	−0·67
	3	13	0·01	0·17	0·00
	7	13	−0·16	0·09	−0·17
	9	13	−0·33	−0·70	−0·33
	10	11	0·02	0·13	0·08
	11	13	−0·15	−0·24	−0·36
	12	13	−0·12	−0·18	0·03
	13	13	−0·01	0·04	−0·10
	15	5	−0·32	0·00	−0·40
	17	13	−0·49	−0·39	−0·39
	22	13	−0·60	−0·66	−0·44
	23	13	−0·39	−0·48	−0·37
	24	13	−0·12	−0·05	−0·02
	25	2	1·00	1·00	1·00
	27	8	−0·08	−0·40	−0·32
Mean			−0·22	−0·21	−0·25
(SEM)			(0·05)	(0·08)	(0·06)
Placebo					
	1	13	0·03	0·08	−0·27
	4	13	0·04	0·38	0·70
	5	7	0·52	0·52	0·72
	6	10	0·27	0·39	0·30
	8	4	0·00	0·67	0·33
	14				
	16	13	−0·13	−0·40	0·13
	18	8	−0·49	−0·42	−0·51
	19	3	0·33	−0·33	0·33
	20	3	−0·33	−1·00	−0·82
	21	13	−0·33	−0·43	−0·42
	26	12	−0·06	0·15	0·08
	28	13	−0·09	0·00	−0·22
	29	12	−0·37	−0·43	−0·29
Mean			−0·02	−0·06	0·01
(SEM)			(0·09)	(0·13)	(0·13)

Regression analysis showed that there was no correlation between wheeze, treatment, and use of salbutamol (least square mean). This implied that the declining trend in wheeze scores was related to treatment with beclomethasone dipropionate rather than to increased use of salbutamol.

Discussion

The objective assessment of treatment for asthma in preschool children is difficult to evaluate because of the unpredictable and episodic nature of the illness. In this age group peak flow values and other lung function tests are unreliable, so that diary score cards remain the most useful way of monitoring treatment with drugs. Half of the children receiving treatment with placebo in this study completed the six months, and in most of these the parents thought they required less additional treatment with bronchodilator agents and were less symptomatic than before the study. The severity of the asthma had no effect on the response to treatment with beclomethasone dipropionate or placebo. The placebo effect makes it difficult to show a clear difference between various medications, especially when the treatment is prophylactic rather than symptomatic. We have shown, however, that those children who received beclomethasone dipropionate needed the code to be broken less frequently, had lower symptom scores, had more symptom free days, and required less additional treatment with bronchodilator agents than those receiving placebo.

Statistical differences have been shown between the two groups in wheeze scores but not in cough scores. It may be that normal saline has a greater placebo effect for cough, but, in general, parents admitted they found cough scores more difficult to evaluate than wheeze. Runny nose symptoms were recorded to assess the degree of allergic rhinitis and the presence of viral upper respiratory tract infections. As we used face mask nebulisations we were interested to see if beclomethasone dipropionate had any effect on nasal symptoms but were not surprised to find the scores to be identical in both groups, as many children inhale the mist through their mouths.

Hospital admissions were scattered throughout the year with the largest number occurring in October. There was no significant difference in the rate of hospital admissions between the two groups. More children completed the study on active treatment and were therefore on beclomethasone dipropionate for longer than those on placebo (a total of 2503 days compared with 1915 days on placebo).

Clinical results in older children using powder capsules or aerosol beclomethasone dipropionate are often dramatically encouraging. At the beginning of this study we were sceptical that we would show any difference between the two treatment groups because of the low dose of beclomethasone dipropionate. Although there are 100 μg beclomethasone dipropionate in 2 ml, much of this is lost in expiration, on the facial skin, in the nebuliser and tubing, or swallowed. It is theoretically possible to reduce the loss on the facial skin by using a wide bore tube instead of a face mask, but this does not eliminate the other losses and, in our experience, tubes are poorly tolerated by very young children. Greater differences may have been shown between the treatment groups if the study had continued for one year or if more patients had been included. We considered, however, that the parents would have been less willing to continue for a further six months, and this may have led to inaccuracies in completing the score cards. We only included the most severe young children with asthma in the

study, and this was the determining factor in patient numbers.

The face mask nebulisation was well tolerated by all children, and no serious side effects were noted in either treatment group. No child experienced cough or airway irritation during treatment with beclomethasone dipropionate or saline. Four patients receiving beclomethasone dipropionate and two receiving saline complained of transient irritation of the perioral skin, but no atrophy of facial skin was observed. There was no clinical evidence of oral thrush in either treatment group. During the study, parents were unable to identify which treatment their children were receiving.

Conclusion

We have shown that nebulised beclomethasone dipropionate is safe and more effective than saline in the management of asthma in preschool children. The clinical response, however, is less than that seen in older children receiving powder capsules or aerosol beclomethasone dipropionate. Further studies are needed to determine the optimum therapeutic dose as higher concentrations of beclomethasone dipropionate may well be necessary to deliver a sufficiently large amount of the drug to the part of the respiratory tract where it is required.

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Annual meetings

1986	15–19 April	York University
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