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Nebulised beclomethasone dipropionate suspension

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SUMMARY We compared nebulised beclomethasone dipropionate suspension against placebo in 16 children with moderately severe asthma in double blind crossover fashion. Three children withdrew due to deterioration while on placebo. Of the remaining 13, eight were better on beclomethasone and five on placebo. These trends in favour of nebulised beclomethasone were not significant and do not suggest that the suspension is as effective as inhaled powder or aerosol topical steroid formulation.

The role of beclomethasone dipropionate in childhood asthma is well established, with proven clinical efficacy when administered by either metered dose inhaler[1] or powder capsule[2 3] form. Neither of these two delivery systems is suitable, however, for treatment of very young children, due to the degree of cooperation and coordination required in their use.

It is only fairly recently that a suspension form of beclomethasone, for delivery by nebuliser, has become available, but to date there is only one published clinical trial of its effectiveness in a suitable population of young children.[4] We have therefore conducted a randomised double blind crossover study, comparing beclomethasone dipropionate suspension against placebo in a group of children with moderately severe asthma aged between 18 months and 6 years.

Patients and methods

The age limits of 18 months and 6 years were chosen to include those children old enough to be responsive to treatment with bronchodilator[4] but too young to be able to manage treatment with rotahaler or metered dose aerosol effectively. All the children had an established clinical diagnosis of asthma and all had been considered to be inadequately controlled on regular nebulised sodium cromoglycate with nebulised bronchodilator as required.

After an initial two week run in period, during which regular prophylactic treatment was stopped, the patients entered two consecutive two month treatment periods. In each of these they received, through a Pari Inhalierboy nebuliser and face mask, either beclomethasone respirator suspension 150 μg (3 ml) or placebo 3 ml (the commercially available preparation minus the active ingredient) on a double blind, randomised crossover basis, and as the sole form of prophylactic treatment.

Throughout the trial the parents were asked to maintain a daily diary record of: (i) symptom score, allocating a score of 0–3 for each of cough, wheeze, and breathlessness for both day and night, giving a worst possible score of 18 for each 24 hours; (ii) morning and evening peak expiratory flow rate if the child was capable, using a Wright's Mini Peak Expiratory Flowmeter; (iii) the number of bronchodilator doses; (iv) any other medication required—for example, corticosteroids.

The children were seen as outpatients at monthly intervals during the trial, at which time they were examined and possible side effects of treatment sought.

Statistical methods employed were Wilcoxon's signed rank test, Fisher's exact test, and the Sign test.

Fully informed parental consent was obtained before entry into the trial, and the study was approved by the local ethical committee.

Results

Twenty children were entered into the study, but four were withdrawn and their results not analysed—one because of severe deterioration while off prophylactic treatment during the run in period, one due to non-compliance in diary recording, and two after the parents changed their mind after the run in period. Details of the 16 patients who entered the treatment periods are shown in Table 1.

Three children failed to complete the full double blind treatment period of four months. All three failures were due to appreciable deterioration in

Table 1 *Details of the 16 patients entering the treatment period*

	Mean (SD)	*Range*
Age (months)	40·9 (11·6)	23·6–59·8
Age at onset of asthma (months)	8·9 (8·9)	0–36
Duration of asthma (months)	32·1 (13·3)	12–58
Sex (male:female)		14:2
Personal history of:		
Eczema		7
Rhinitis		11
Allergies (skin)		6
Current treatment:		
Nebulised bronchodilator		16
Nebulised sodium cromoglycate		13
Inhaled steroid:		
Budesonide spacer		2
Nebulised beclomethasone		1
Oral corticosteroids (daily)		1
Previous treatment:		
Oral corticosteroids (courses)		13

control of asthma to the extent that the parents were understandably unwilling to continue treatment on a blind basis. Each child was on placebo at the time of deterioration, one in the first two months of treatment and the other two in the second.

Of the 13 patients who completed the trial, eight were considered by their parents to be better controlled while on nebulised beclomethasone (analysis of diary records supported their views), but five were considered to be better controlled on placebo. This difference was not significant using the relatively insensitive Sign test, but even if the three placebo treatment failures were included in the 'beclomethasone beneficial' group, the difference of 11 *v* 5 was only significant at the 25% level.

Analysis of the diary records had to be restricted to the 13 children who completed the trial. As can be seen from Table 2, there are no significant differences between the two treatment periods in terms of individual symptom and total symptom scores (similarly, there was no difference between treatments on daytime scores or night time scores). The number of extra bronchodilator doses required was similar in the two groups, and the number of children requiring a course of oral corticosteroid was identical. The one child on daily maintenance oral corticosteroid therapy consumed a total of 228 mg of prednisolone in the six weeks of treatment with placebo, but only marginally less (180 mg) while on nebulised beclomethasone.

Although the order of treatments was randomly determined, the distribution was uneven. Of all 16 patients, five were given beclomethasone first and 11 placebo first, with no significant order effect on the result (p=0·28, Fisher's exact test). In the 13 completed trials, however, three were given beclomethasone first and 10 placebo first, with an order effect that is almost significant at the 5% level in favour of beclomethasone (p=0·07, Fisher's exact test).

There was no discernable seasonal influence, there being an even distribution of treatment periods throughout the calendar months.

No side effects of treatment were detected clinically.

Discussion

This study has failed to show clear benefit from the use of nebulised beclomethasone dipropionate suspension in young chidren with moderately severe asthma. These results are quite at variance with similarly small studies using the metered dose inhaler[1]and powder capsule[2] delivery systems, which showed unequivocally improved asthma control, albeit in slightly older children who were able to use these devices. We do not therefore doubt the efficacy of the drug itself. Thus, if our results reflect a true picture, there must be three areas for further

Table 2 *Dairy records of 13 completed courses (analysis restricted to last six weeks of each treatment period)*

	Maximum	*Placebo*		*Beclomethasone*		*Wilcoxon*
		Median	*Range*	*Median*	*Range*	
Cough	252	73	1–142	90	2–149	NS
Wheeze	252	37	6–112	49	2–108	NS
Breathlessness	252	89	0–112	42	0–179	NS
Total score	756	182	8–312	182	4–395	NS
Symptom free days	42	2	39–0	5	40–0	NS
Bronchodilator doses		89	0–159	59	1–346	NS
Prednisolone:						
Short courses (No of children)		4		4		—
One child on daily treatment (mg total)		228		180		—
Admissions (No of children)		2 (× 3 admissions)		0		—

enquiry. Firstly, could it be some property of the physical suspension that makes it less effective (all other anti-asthma nebuliser preparations are in the form of a solution); secondly, could the physical characteristics of the suspension have affected nebuliser function, reducing its efficiency; and, thirdly, could the recommended dose simply be too low (most other nebuliser dosages are considerably higher than inhaler dosages, though the proportion of either that reaches the lungs is said to be similar at about 9–12%[5 6])? It is impractical to expect toddlers and young children to be able to tolerate a higher dose at each sitting as even the nebuliser time for 3 ml of suspension (50 mcg/ml) represented an appreciable burden to many of our parents and children.

Although no side effects were noted in our study, there is a theoretical risk of secondary steroid effects upon the facial skin if beclomethasone is delivered by face mask, and the manufacturers do recommend that a mouth piece be used. In our experience, however, young children tolerate face masks much more readily than mouthpieces, and this might therefore constitute a greater risk in long term treatment.

Clearly, if beclomethasone dipropionate suspension is to continue to be recommended on the basis of the undoubted efficacy of the drug itself then further clinical trials of its usefulness in the currently available dosage and in the appropriate age group are urgently required.

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References

1 Godfrey S, Konig P. Beclomethasone aerosol in childhood asthma. *Arch Dis Child* 1973;**48**:665–70.

2 Edmunds AT, McKenzie S, Tooley M, Godfrey S. A clinical comparison of beclomethasone dipropionate delivered by pressurised aerosol and as a powder from a rotahaler. *Arch Dis Child* 1979;**54**:233–5.

3 Hiller EJ, Groggins RC, Lenney W, Milner AD, Stokes M. Beclomethasone dipropionate powder inhalation treatment in chronic childhood asthma. *Progress in Respiratory Research* 1981;**17**:285–9.

4 Storr J, Lenney CA, Lenney W. Nebulised beclomethasone dipropionate in preschool children. *Arch Dis Child* 1986;**61**: 270–3.

5 Lenney W, Milner AD. At what age do bronchodilator drugs work? *Arch Dis Child* 1978;**53**:532–5.

6 Newman SP, Pavia D, Moren F, Sheahan NF, Clarke SW. Deposition of pressurised aerosols in the human respiratory tract. *Thorax* 1981;**36**:52–5.

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Commentary

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The discrepancy between the similar studies of Storr *et al*[1] who obtained a positive result and Webb *et al* a negative one with the same drug, inhaled beclomethasone diproprionate, is puzzling and raises several questions.

The studies were similar but not identical insofar as Storr *et al's* was a double blind parallel study and Webb *et al's* a double blind crossover one, though this should not necessarily matter. Even so, there was a (non-significant) trend in favour of beclomethasone in that of Webb *et al* and the discrepancy may be in the study designs.

The most obvious difference is the dose inhaled, 2 ml (100 μg) versus 3 ml (150 μg), respectively. But the lower dose worked and the higher dose failed to do so, ruling out a dose related effect.

Nebulisation details were incomplete for both studies and in neither was the optimal liquid volume (usually drug+saline) of 4 ml used—this to reduce the proportion of dead volume left in the nebuliser after conclusion and to optimise the output.[2] It seems likely, however, that both systems produce similar respirable (about 2–5 μm) particles.[3] Nevertheless, the inescapable conclusion must be not that the drug does not work but that in the study of Webb *et al* it somehow failed to reach the lungs—such doses of beclomethasone have virtually no systemic effect.

In both studies the children inhaled the nebulised drug through a face mask, close fitting in the study of Storr *et al* and loose fitting in the study of Webb *et al*. With loose fitting masks much of the drug may impact on the face and lips, leaving little to be inhaled.[4]

Although it is difficult to pinpoint the error precisely, nevertheless, when using nebulised drugs, strict attention should be paid to the details of nebulisation and inhalation, otherwise anomalous results may arise.

References

1 Storr J, Lenney CA, Lenney W. Nebulised beclomethasone dipropionate in preschool asthma. *Arch Dis Child* 1986;**61**: 270–3.

2 Clay MM, Pavia D, Newman SP, Lennard-Jones T, Clarke SW. Assessment of jet nebulisers for lung aerosol therapy. *Lancet* 1983;ii:592–4.

3 Sterk PJ, Plomp A, Van der Vate JF, Qaunter PH. Physical properties of aerosols produced by several jet and ultrasonic nebulisers. *Bull Eur Physiopathol Respir* 1984;**20**:65–72.

4 Clarke SW, Newman SP. Therapeutic aerosols. 2 Drugs available by the inhaled route. *Thorax* 1984;**39**:1–7.