Archives of Disease in Childhood 1993; **68**: 356–359

Treatment of severe steroid dependent preschool asthma with nebulised budesonide suspension

P Ilangovan, S Pedersen, S Godfrey, K Nikander, N Noviski, J O Warner

Abstract

The steroid sparing effect of nebulised budesonide suspension was assessed in a double blind placebo controlled parallel group study of 36 preschool children with severe asthma who were dependent on treatment with oral steroids. Nebulised budesonide suspension significantly reduced the requirement for treatment with oral steroids, and produced a marked improvement in overall health as scored on a visual analogue scale during the clinic visits. This study shows a significant step forward in the prophylactic treatment of asthma in children under the age of 3 years, in whom the efficacy of many other nebulised treatments has been questioned.

(*Arch Dis Child* 1993; **68**: 356–359)

Severe asthma in infancy poses many problems. Diagnosis is usually made on history alone, as lung function measurements require sophisticated equipment and expertise.[1] Although studies in children under 2 years of age have given predominantly negative results for most standard treatments for asthma,[2-5] clinical experience suggests that such treatments should be tested in these children.[6] Following this schedule a small number of infants with repeated hospital admissions for severe acute asthma attacks become dependent on treatment with oral steroids.

As inhaled corticosteroids of high topical potency and low systemic activity have been shown to be successful in controlling severe asthma in older children and adults, their application by nebuliser for infants has been an obvious development. The results with beclomethasone dipropionate suspension, until recently the only corticosteroid available for nebulisation, have been disappointing, however.[7-9] The poor response in these studies may have been related to the low drug concentrations used (50 μg/ ml), to a small fraction of 'respirable' particles of beclomethasone dipropionate suspension for nebulisation,[10] and the inclusion of infants with less severe asthma. Thus infants with severe asthma have continued to require oral steroids predominantly administered in a single dose on alternate days. The present study was performed to determine if nebulised budesonide suspension could be used as an alternative to this dose regimen in children with severe asthma who are dependent on steroids. In the first instance it was felt that only patients with severe disease should be studied to ascertain efficacy, thus it was necessary to set up a trial at three institutions with a special interest in childhood asthma.

Royal Brompton, National Heart and Lung Hospital, London
P Ilangovan
J O Warner

Kolding Hospital, Kolding, Denmark
S Pedersen

Hadassah University Hospital, Jerusalem, Israel
S Godfrey
N Noviski

Astra Draco AB, Sweden
K Nikander

Correspondence to:
Dr P B Ilangovan, Department of Child Health, Level G, Centre Block, Southampton General Hospital, Tremona Road, Southampton SO9 4XY.

Accepted 13 October 1992

Patients and methods

The study group consisted of children with severe asthma who were dependent on steroids, aged less than 5 years, and who had had recurrent, persistent symptoms of cough or wheeze, or both, which were not controlled by conventional non-steroidal prophylactic treatment despite correct use for at least two months before entry to the trial. The principle enrolment criterion was a dependency on a minimum of 0·75 mg/kg prednisolone on alternate days for at least four weeks before the trial. Children with cardiopulmonary disease other than asthma or families who could not comply with the protocol were excluded.

The design of the study was double blind placebo controlled with parallel groups. The children were enrolled from three centres: the Royal Brompton National Heart and Lung Hospital in London, the Hadassah University Hospital in Jerusalem, and Kolding Hospital in Kolding, Denmark.

After a run in period where the dose of oral prednisolone was adjusted to the minimum required to stabilise the disease, the children were randomly allocated to either the active budesonide or placebo group. During the eight weeks of treatment with the study drug, the dose of oral prednisolone was adjusted at weekly intervals according to the clinical state of the patient. This was evaluated by weekly telephone conversations based on information from diary cards and monthly visits to the clinic. The aim was to reduce the dose of prednisolone by 25% of the dose at the end of each week provided the child was symptom free during the previous week, or was less symptomatic than the previous week requiring nebulised bronchodilators no more than once a day.

The parents completed a daily diary card record of symptoms (table 1), number of doses of β agonists used and the oral steroids taken. Every four weeks parents gave a score between 0 and 10 (very symptomatic to totally symptom free) on the visual analogue scale based on their

Table 1 Daily diary card giving the symptom scores for day and night symptoms (0=asymptomatic; 3=very symptomatic)

Variables	*Score*
Night symptoms	
Completely peaceful	0
Restless with cough, not woken	1
Woken one or two times with cough or wheeze, or both	2
Woken one or two times with cough or wheeze, or both, needing extra nebulisers	3
Day symptoms	
Completely well	0
Occasional cough, no extra treatment	1
Needed no more than one extra nebuliser	2
Needed more than two nebulisers	3

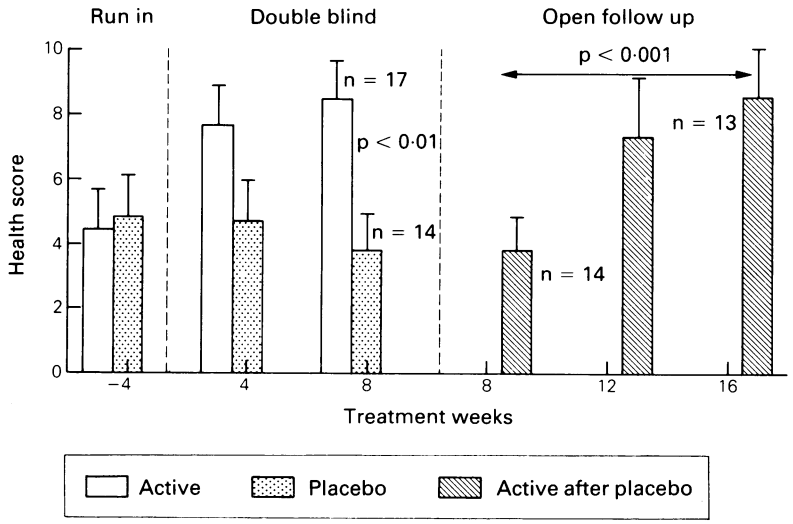

Figure 1 Child health score (0=very symptomatic to 10=totally symptom free) on visual analogue scale illustrating a significant improvement for the group treated with budesonide during the double blind period and a further improvement when the placebo group was treated with budesonide in the open follow up period. The bar indicates the SEM.

impression of the child's asthma symptoms and the need for extra bronchodilators during the week preceding the clinic visit (health score).

The double blind trial was followed by an open follow up period of a further eight weeks during which the children from the placebo group were treated with budesonide suspension. Children receiving active budesonide continued this treatment on a named patient basis.

The trial suspension was prescribed in 2 ml prepacked respules containing either budesonide suspension (0·5 mg/ml) or an identical preparation without budesonide. The trial materials were administered twice daily for five minutes through a Hudson Updraft 2 jet nebuliser via an open face mask, driven by a CR60 air compressor. The choice of this system was based on in vitro studies showing a combination of high drug output with a low mass median droplet diameter in a short nebulisation time,[11] in addition to availability in all three countries.

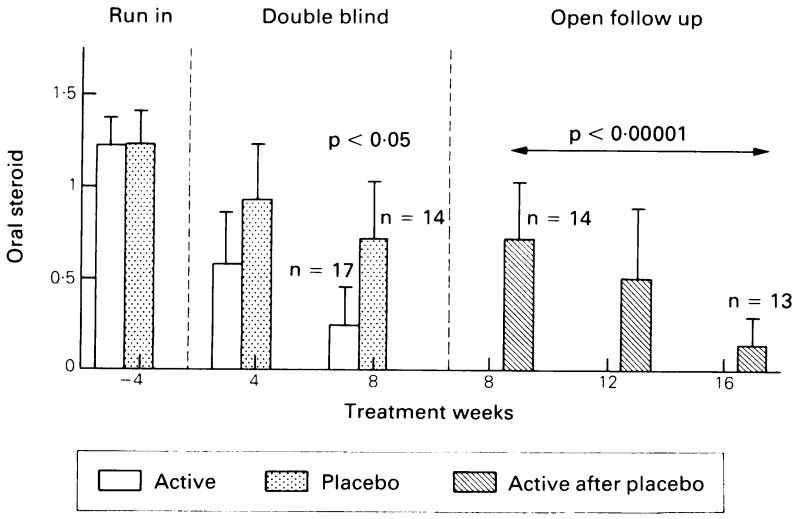

Figure 2 Dose of prednisolone by mouth (mg/kg/alternate day) showing a significant reduction for the group treated with budesonide during the double blind period and the open follow up period. The bar indicates the SEM.

Parents were advised to wash the infant's face after each dose. The nebuliser was soaked in hot water with household detergent for five minutes and rinsed thoroughly in running water after use to remove any residual drug particles. Throat swabs were checked for candida colonisation at the end of the run in period and during the study and open follow up periods.

The trial was approved by the hospital ethics committees of all three institutions and informed written consent was obtained from the parents.

STATISTICS

Comparisons between the two treatment groups were made using an unpaired *t* test of the change from entry to the trial to the end of the active study period. Paired *t* tests were used when comparing the end of the placebo period with the open active budesonide treatment period that followed. Differences were regarded as significant if $p<0·05$. For diary data mean values were obtained for each patient for each diary variable over the last week of the run in period and weekly during the study and the open follow up period. The data were also analysed for possible centre effects.

Results

Thirty six children (boys:girls, 2:1) aged between 10 months and 5 years (mean age 26·7 months) were enroled. Fifteen children were from London, 11 from Denmark, and 10 from Israel. There was no significant centre effect noted on our analysis. Thirty two children were under 3 years of age, 17 of these were under 2 years, and 12 under 18 months of age. The mean age of onset of asthma was 9·4 months (minimum age 2 months) and the mean duration of asthma before entering the study was 17·5 months. More than half the children in the study had a history of atopy and three children had IgA, IgG_2, and IgG_4 subclass deficiencies. The mean dose of prednisolone given on alternate days was 1·32 mg/kg (0·78–3·57 mg/kg) at entry into the study.

One child did not complete the run in period and of the remaining 35 who were enroled in the trial, three children had their code broken early due to a worsening of their symptoms. All three were receiving placebo, but thereafter were given the active drug for a further eight weeks during the open follow up period. One child from the group receiving active treatment was not included in the analysis due to non-compliance associated with the break up of the parents' marriage.

Fourteen children from the placebo group and 17 children from the group receiving active treatment completed the double blind trial. Of the 14 children from the placebo group, 13 completed the open follow up as the family of one child from the placebo group emigrated during the study and hence did not complete the open follow up period.

VISIT AT THE CLINIC

During the double blind period there was a highly significant difference in the child's health

Table 2 Weekly mean (SEM) (n) scores from diary cards for day and night symptoms and number of β agonists consumed for the double blind period and the open follow up period, showing a significant improvement in the reduction of symptoms during the day for the group treated with budesonide

	Run in	Double blind		Open follow up		
	Week −4	Week 4	Week 8	Week 12	Week 16	p Value
Day symptoms (0–3)						
Placebo	1·5 (0·07) (18)	1·5 (0·06) (17)	2·0 (0·09) (13)	0·9 (0·08) (11)	0·3 (0·06) (7)	p<0·05*
Budesonide	1·3 (0·06) (17)	0·8 (0·04) (18)	0·4 (0·04) (16)			p<0·05†
Night symptoms (0–3)						
Placebo	1·0 (0·05) (18)	0·8 (0·05) (17)	0·7 (0·06) (13)	0·5 (0·06) (11)	0·0 (0·0) (6)	p≤0·16*
Budesonide	1·2 (0·06) (17)	0·6 (0·03) (18)	0·4 (0·02) (16)			p=0·07†
No of β agonists						
Placebo	2·3 (0·11) (18)	2·0 (0·11) (17)	2·3 (0·12) (13)	0·9 (0·1) (11)	0·3 (0·11) (7)	p=0·04*
Budesonide	2·1 (0·1) (17)	1·5 (0·08) (18)	1·0 (0·08) (16)			p=0·56†

*Within group. †Between groups.

score based on the visual analogue scale completed by the parents during the clinic visits (p<0·01) (fig 1) in favour of the group receiving active treatment. Similarly, there was a significant difference (p<0·05) in the reduction in the dose of oral prednisolone in the group receiving active treatment (fig 2) at the end of study period (80% reduction) compared with the placebo group (41% reduction). Furthermore, the reduction in prednisolone dosage was statistically significant (p<0·00001) during treatment with budesonide in the open follow up of the placebo group.

DIARY CARDS

There was a significant reduction in day symptoms (p<0·05) from the diary card in the group receiving active treatment compared with the placebo group at the end of the double blind study period (table 2). Similarly, there was an almost significant difference for the requirement for nebulised bronchodilator (p=0·057) and reduction in night symptoms (p=0·07). During the open follow up period considerable improvements were noted for the placebo group once children were treated with active budesonide for day symptoms (p<0·05) and the requirement for nebulised bronchodilator (p<0·05).

Five of eight children who were under the age of 2 years from the group receiving active treatment were weaned off oral prednisolone at the end of the eight week study period, compared with one child of eight from the placebo group. Furthermore, there was a significant improvement (p<0·005) in the health score of the group receiving active treatment compared with the placebo group for this age range (fig 3). The reduction in the dose of oral prednisolone was statistically significant (p<0·005) as was the improvement in health score (p<0·0005) for the placebo group during the open follow up period.

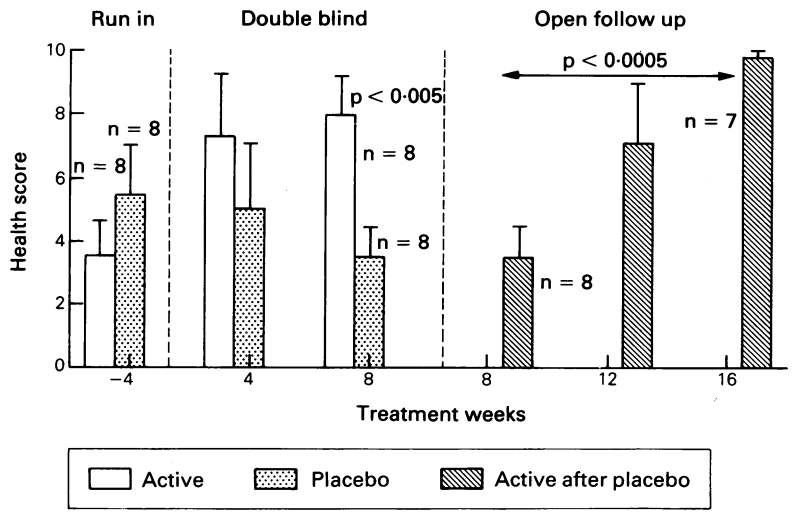

Figure 3 Child health score for the patients aged under 2 years showing a similar significant improvement for the group treated with budesonide. The bar indicates the SEM.

SIDE EFFECTS

Two children developed an eczematous rash in the area circumscribed by the face mask while receiving active budesonide. This was controlled by applying barrier cream before nebulisation and washing the face thoroughly afterwards. It was not necessary to stop treatment for this problem. No candida was grown from throat swabs taken throughout the study. No other side effect was noted.

Discussion

The efficacy parameters recorded in this study did not include any 'objective' lung function measurements as they are difficult, if not impossible, to perform in this age group. Therefore all parameters were based on 'subjective' recordings of symptoms and health status by the parents. For all these parameters we were able to show marked effects of the treatment, probably because all children had severe disease with numerous hospital admissions and required regular use of high doses of oral prednisolone.

The children receiving the active drug were able to reduce treatment with oral steroids and simultaneously showed an improvement in their overall child health score, whereas the placebo group deteriorated in this. The improvement in the double blind trial for the group receiving active treatment was further confirmed by the identical results from the open cross over follow up period for the placebo group.

Our observation of a small reduction in the dose of oral prednisolone required during the placebo period is similar to the findings of Shapiro *et al* in their placebo controlled study of a pressurised metered dose inhaler for the administration of flunisolide.[12] Despite having a run in period where the dose of oral steroid

was reduced to a minimum they still managed to achieve a further 53% dose reduction in the placebo group and a 100% dose reduction in the group receiving active treatment. Hence the reduction in the requirements for oral prednisolone by the placebo group in our study was not unexpected. The dose reduction interval was short (one week) during our study with a substantial risk of carry over effect. It would be expected to take longer than this for the child to become symptomatic, especially when we were dependent on 'subjective' assessment by the parents to determine the progress. This may also have contributed to the continuous reduction of prednisolone by 25% during the placebo period. A degree of deterioration in lung function is probably required before this is reflected in the parents' 'subjective' assessment. In fact the reduction in the dose of oral prednisolone was achieved at the expense of a simultaneous increase in the symptoms (table 2). This is reflected in the dose of oral prednisolone required by the placebo group being temporarily reversed during the first week of the open follow up period.

There have been two anecdotal reports on the effectiveness of nebulised budesonide at similar concentrations to those used here.[13,14] In contrast, Van Bever *et al* did not detect any significant differences between patients treated with placebo and active nebulised budesonide.[15] Even though they define their group of patients as having severe asthma, none of the children was dependent on oral steroids. Furthermore, the dose of budesonide was 50% less than that used here, the treatment period was only one month, and the design was a cross over study without any washout period so the risk of carry over effects was more pronounced. In contrast with our study, no in vitro measurements were performed with the nebuliser equipment used so the drug output characteristics were not known. Finally, their statistical analysis did not include any comparison between baseline and the treatment periods, thus the possibility of a regression towards the mean was not excluded.

A daily dose of 2 mg was chosen empirically on the basis of the results from single cases treated by the investigators. This dose, though it seems high, was found to be effective in controlling the symptoms in those children, but we do not know whether this was the optimum dose. Some data,[16] however, suggest that only 10% of the budesonide dose from a nebuliser is actually delivered to patients in this age group. Furthermore, only an unknown fraction of this 10% will be expected to be delivered to the intrapulmonary airways. Therefore it is unlikely that the dose chosen could have been much lower than this in our children who had severe disease.

O'Callaghan[10] has evaluated the drug output of beclomethasone dipropionate suspension and has shown that of the 150 μg nebulised via the Pari Inhalierboy only 16% of the output contains particles of less than 5 μm. This may be one of the main reasons why the results of the trials with beclomethasone dipropionate suspension have been disappointing.[7-9] Beclomethasone dipropionate suspension is only available at a concentration of 50 μg/ml, which makes it impractical for a sufficient effective dose to be delivered.

The only side effect noted was facial irritation due to the active drug and this did not necessitate withdrawal of patients from the study. Caution is required to protect the facial skin from the concentrated corticosteroid suspension. We also suggest that measures should be taken to avoid the side stream aerosol impinging on the eyes.[17] Thus the holes in the face mask pointing towards the child's eyes should be covered and new holes made such that the exhaust spray is directed away from the child. We did not perform any studies of adrenal function. It is expected that large doses of inhaled corticosteroids will have some systemic effect[18-21] and before this compound is used in children with less severe asthma more detailed studies of risk benefit ratios must be conducted. Furthermore, as soon as the asthma is adequately stabilised, even in patients with severe disease, the dose of inhaled corticosteroids should be progressively reduced.

1 Connolly N, Godfrey S. Assessment of the child with asthma. *J Asthma Res* 1970; **8**: 31–6.
2 Lenney W, Milner AD. At what age do bronchodilator drugs work? *Arch Dis Child* 1978; **53**: 532–5.
3 O'Callaghan C, Milner AD, Swarbrick A. Paradoxical deterioration in lung function after nebulised salbutamol in wheezy infants. *Lancet* 1986; ii: 1424–5.
4 Prendiville A, Green S, Silverman M. Paradoxical response to salbutamol in wheezy infants, assessed by partial expiratory flow-volume curves. *Thorax* 1987; **42**: 86–91.
5 Henry RL, Hiller EJ, Milner AD, Hodges IGC, Stokes GM. Nebulised ipratropium bromide and sodium cromoglycate in the first two years of life. *Arch Dis Child* 1984; **59**: 54–7.
6 Warner JO. Asthma – a follow up statement from an international paediatric asthma consensus group. *Arch Dis Child* 1992; **67**: 240–8.
7 Storr J, Lenney CA, Lenney W. Nebulised beclomethasone dipropionate in pre-school asthma. *Arch Dis Child* 1985; **61**: 270–3.
8 Pederson W, Prahl P. Jet nebulised beclomethasone dipropionate in the management of bronchial asthma. *Allergy* 1987; **42**: 272–5.
9 Carlsen KH, Leegard J, Larsen S, Orstavik I. Nebulised beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis. *Arch Dis Child* 1988; **63**: 1428–33.
10 O'Callaghan C. Particle size of beclomethasone dipropionate produced by two nebulisers and two spacing devices. *Thorax* 1990; **45**: 109–11.
11 Newman SP, Talaee N, Nikander K, Berg E, Clarke SW. Evaluation of nebulisers and compressors for use with budesonide nebuliser suspension. *Eur Respir J Suppl* 1988; **2**: 211.
12 Shapiro GG, Izu AE, Furukawa CT, Pierson WE, Bierman CW. Short-term double-blind evaluation of flunisolide aerosol for steroid dependent asthmatic children and adolescents. *Chest* 1981; **80**: 671–5.
13 Godfrey S, Avital A, Rosler A, Mandelberg A, Uwyyed K. Nebulised budesonide in severe infantile asthma. *Lancet* 1987; ii: 851–2.
14 De Jongste JC, Duiverman EJ. Nebulised budesonide in severe childhood asthma. *Lancet* 1989; i: 1388.
15 Van Bever HP, Schuddinck L, Wojciechwski M, Stevens WJ. Aerosolized budesonide in asthmatic infants: a double blind study. *Pediatr Pulmonol* 1990; **9**: 177–80.
16 Lødrup Carlsen KC, Nikander K, Carlsen K-H. How much nebulised budesonide reaches infants and toddlers? *Arch Dis Child* 1992; **67**: 1077–9.
17 Kewly GD. Possible association between BDP aerosol and cataracts. *Australian Paediatric Journal* 1980; **16**: 117–8.
18 Balfour-Lynn L. Growth and childhood asthma. *Arch Dis Child* 1986; **61**: 1049–55.
19 Kerrebijin K, Dekroon J. Effect of height of corticosteroid therapy in asthmatic children. *Arch Dis Child* 1968; **43**: 556–61.
20 Falliers C, Tan L, Szentivanyi J. Childhood asthma and steroid therapy as influence on growth. *Am J Dis Child* 1963; **105**: 127–37.
21 Law CM, Marchant JL, Honour JW, Preece MA, Warner JO. Nocturnal adrenal suppression in asthmatic children taking inhaled beclomethasone dipropionate. *Lancet* 1986; **i**: 942–4.