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Nebulised beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis

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SUMMARY Forty four children with recurrent obstructive episodes after acute bronchiolitis in infancy were treated with nebulised beclomethasone dipropionate or placebo for eight weeks in a randomised double-blind study. They were seen monthly for a year afterwards, and also if they had acute respiratory illnesses with or without bronchopulmonary obstruction. The two treatment groups were well matched. The children receiving active treatment had significantly fewer symptomatic respiratory illnesses and fewer episodes of bronchopulmonary obstruction during the follow up period. The children given placebo had significantly higher obstructive scores during the study period, and they were treated with inhaled β_2 agonists and theophylline for longer periods of time during the follow up period.

The results suggest that nebulised beclomethasone dipropionate may have prolonged effects on subsequent asthmatic symptoms after termination of treatment in children with recurrent obstructive episodes after acute bronchiolitis.

Acute bronchiolitis in infancy is most often associated with respiratory syncytial virus infection, and is associated with later episodes of bronchopulmonary obstruction and the development of bronchial asthma in children.[1 2] Inhalation of beclomethasone dipropionate, as an aerosol or as powder, is effective and safe prophylaxis of childhood asthma,[3 4] possibly because it reduces the non-specific bronchial hyperreactivity in asthma.[5] As the use of both aerosols and powder inhalation is difficult in infants and small children, we have investigated whether nebulised beclomethasone dipropionate could be used in infants and small children with recurrent episodes of bronchopulmonary obstruction after acute bronchiolitis, and whether treatment with beclomethasone dipropionate for eight weeks could possibly influence the outcome. We have therefore conducted a placebo controlled double blind study in children under 2 years of age to study the effect of inhaled nebulised beclomethasone dipropionate for eight weeks with a follow up period of one year. The aim of the study was to examine whether inhalation of nebulised beclomethasone dipropionate influenced the frequency of recurrent attacks of bronchopulmonary obstruction during treatment, as well as the subsequent development of episodes after the treatment.

Patients and methods

A total of 44 children aged between six and 24 months were randomly allocated to be treated by placebo (n=22) or beclomethasone dipropionate (n=22) in a double blind manner. To be included in the study the patients had to fulfil the following criteria: they had to be previously admitted to the paediatric department of Ullevål hospital (the municipal hospital of Oslo) with acute bronchiolitis, and they had to have had a history of at least one attack of bronchopulmonary obstruction after the initial attack of bronchiolitis. The diagnosis of bronchiolitis was made according to the criteria of Court.[6] Table 1 shows that the groups were comparable. To diagnose an episode of bronchopulmonary obstruction three of the following signs were required: wheezing, expiratory dyspnoea, paradoxical chest movements on inspiration, rapid respiratory rate (>40 a minute) and audible râles and sibilant rhonchi.[2] Children were not included in the study if they had other serious disabling diseases or had received prolonged courses of systemic treatment with steroids. Children who had received steroid treatment for only a few days during previous severe attacks of bronchopulmonary obstruction were included.

Double blind parallel groups received either

Table 1 *Clinical details of children treated wtih nebulised beclomethasone dipropionate (n=22) and placebo (n=22). Figures given are mean (SEM)*

	Placebo	*Nebulised beclomethasone dipropionate*	*p Value (two tailed)*
Age at inclusion (months)	17·3 (0·9)	14·1 (1·2)	0·09
Birth weight (g)	3300·0 (200)	3300·0 (200)	0·99
Duration of breast feeding (months)	6·1 (1·3)	5·6 (0·9)	0·66
Weight at inclusion (kg)	11·2 (0·3)	10·1 (0·4)	0·05
Height at inclusion (cm)	80·5 (1·0)	77·6 (1·4)	0·21
No of respiratory illnesses at inclusion	7·9 (0·7)	6·1 (0·6)	0·09
No of lower respiratory infections at inclusion	3·5 (0·4)	4·3 (0·6)	0·52
No of episodes of bronchopulmonary obstruction at inclusion	4·8 (0·6)	4·4 (0·6)	0·55
No of courses of antibiotic treatment at inclusion	3·9 (0·7)	3·9 (0·6)	0·86
Boys:girls	15:7	18:4	0·29

placebo or beclomethasone dipropionate, and the children were stratified in six blocks according to the number of previous attacks of bronchopulmonary obstruction (one or two attacks, three or four attacks, and more than four attacks) they had had as well as according to whether or not respiratory syncytial virus was detected in their sputum during the first episode of bronchiolitis. Each of these six blocks were randomised separately in such a way that half the patients within each block was given beclomethasone dipropionate and the other half was given placebo, in order to obtain a balanced design.

The patients were randomly allocated to receive either placebo or active treatment with nebulised beclomethasone dipropionate. Identical bottles contained either an aqueous suspension of beclomethasone dipropionate 50 μg/ml or placebo solution containing the preservatives and buffers of the active suspension. The patients were supplied with the PaRi Inhaler Boy nebuliser (Paul Ritzau Pari-Werk GmbH) for home treatment and received a dose of 2 ml four times daily for the first two weeks, and then 2 ml twice daily for the remaining six weeks. The patients also received additional treatment for bronchopulmonary obstruction according to the standard clinical practice of the hospital. During the follow up period the patients were seen regularly each month, and on additional occasions if they had an acute respiratory illness with or without bronchopulmonary obstruction. Whenever they were seen a questionnaire was filled in by the examining doctor, and a score of the degree of bronchopulmonary obstruction was obtained during acute attacks (table 2). The maximum possible score at any one visit was 15.

At the end of the study period allergic reactions were sought by skin test, radioallergosorbent test (Phadebas, RAST), and measurement of total IgE (Phadebas, PRIST). The skin test and the RAST tests were carried out as reported in a previous study.[7]

When respiratory tract illnesses occurred, nasopharyngeal aspirates were obtained and examined for respiratory viruses by rapid immunofluorescence and cell culture as previously described.[7] This was also done during hospital admissions before the study.

The results are given as medians with 95% confidence intervals calculated by the Bernoulli-Wilcoxon method.[8]

Table 2 *Score used in the evaluation of the patients during episodes of bronchopulmonary obstruction*

Variable	*Score*
Respiratory rate:	
<40/minute	0
40–60/minute	1
>60/minute	2
Rib retraction, use of accessory respiratory muscles, wheeze, rales:	
None	0
Moderately affected	1
Definitely obstructive	2
Chest radiograph:	
Not performed or normal	0
Hyperinflation or increased translucency	1
Consolidation or atelectasis	2
Capillary blood gases:	
Not performed or normal	0
PCO_2 between 6–7 kPa	1
PCO_2 >7 kPa, pH <7·3	2
General condition:	
Not affected, playing normally	0
Pallid, moderately affected	1
Severely affected, cyanotic	2
Treatment score:	
No bronchodilator	0
Epinephrine aerosol or inhaled salbutamol	1
Intravenous theophylline or steroids	2
Artificial ventilation	3

Both one and two tailed tests were used. Differences were considered significant when the p values were less than or equal to 0·05. The significance of differences between groups was tested by the Wilcoxon midrank sum test.[8] Time until the first symptomatic respiratory illness and the time until the first episode of bronchopulmonary obstruction were both calculated by the Kaplan-Meier estimate[9] and Gehan's statistic.[10]

The parents of the participating children received oral as well as written information about the aims and the means of the study and gave informed written consent before the children were included in the study which was conducted according to the Declaration of Helsinki as revised in Tokyo, 1975. Approval for the study was obtained from the national committee on drugs of Norway and by the local ethical committee of Ullevål hospital.

Results

Twenty two children were randomised to receive placebo and 22 to receive beclomethasone dipropionate. There were no significant differences between the two treatment groups in the incidence of neonatal respiratory disease (p=0·31), or allergic disease among the mothers (p=0·52), the fathers (p=0·40), the siblings (p=0·31), or the grandparents of the patients (p=0·52). This was true also for other pre-existing diseases among parents, siblings, and grandparents. In addition no significant differences were found for family relationship (p=0·47), number of siblings (p=0·40), hygienic state of the home (p=0·20), floor covering in the homes (carpets or not) (p=0·55), pets in the home (p=0·12), place of stay during the day (for example, kindergarten, nursery, at home) (p=0·66), and tobacco smoking in the home (p=0·95). Other background variables are given in table 1. The children in the placebo group were generally older and heavier than the treated children at the time of inclusion in the study. They also had more acute respiratory tract illnesses before their entry in the study, though the difference was not significant. There were no differences in the number of lower respiratory tract infections, the number of episodes of bronchopulmonary obstruction or the number of courses of antibiotics (table 1). Previous history of respiratory virus infections before the inclusion in the study did not differ between the two groups. Fifteen children in the placebo group and 18 in the treated group had no history of previous virus infections. Of those with a history of previous virus infection, respiratory syncytial virus had been found in three children in the placebo group and in two in the treated group, adenovirus in two in the placebo group and one in the treated group, rhinovirus in three in the placebo group, and parainfluenza virus infection in one in the treated group.

No child was withdrawn during the eight weeks of treatment with beclomethasone dipropionate or placebo, and no side effects were observed in either group. During the follow up period one child was withdrawn from the study, and two children dropped out. One child who received beclomethasone dipropionate was withdrawn because severe symptoms occurred a few weeks after stopping the inhalation treatment, and because of this the randomisation code was broken. This child was included in the statistical evaluation of the results with the least favourable results in the beclomethasone dipropionate group. One child who was also receiving beclomethasone dipropionate dropped out of the study because the family moved to another part of Norway during the follow up period. Another child who was receiving placebo dropped out shortly after inclusion in the study because the wrong inclusion criteria had been applied. These two subjects were not included in the statistical evaluation of the results, and were replaced by other children.

The results of treatment with nebulised beclomethasone dipropionate compared with placebo are shown in table 3. The time from the start of treatment until the first acute symptomatic respiratory illness and until the first episode of bronchopulmonary obstruction were significantly longer in the beclomethasone dipropionate group. The probability of not contracting an acute symptomatic respiratory illness from the start of the treatment for the two groups of patients is shown in fig 1, and the probability of not contracting an episode of bronchopulmonary obstruction is shown in fig 2; the probabilities for both variables were significantly higher in the beclomethasone dipropionate group. The placebo group also had significantly more symptomatic acute respiratory illnesses and more episodes of bronchopulmonary obstruction during the study period (table 3). They also had a significantly higher total mean obstructive score during the study period, whereas the mean obstructive score for an episode did not differ between the two groups (table 3). The placebo group did not, however, have more respiratory virus infections diagnosed than the beclomethasone dipropionate group (p=0·24). In the placebo group three respiratory syncytial virus, four rhinovirus, one adenovirus type 2, and one parainfluenza virus type 3 infections were diagnosed, whereas in the beclomethasone dipropionate group six respiratory syncytial virus, one rhinovirus, one adenovirus type 2 and one parainfluenza virus type 3 infections were diagnosed.

Apart from the double blind treatment with

Table 3 *Observations during active treatment period and during follow up period. Figures given are median (95% confidence interval)*

	Placebo	*Nebulised beclomethasone dipropionate*	*p Value (one tailed)*
Time until first symptomatic respiratory illness (weeks)	4·0 (2 to 8)	7·5 (2 to 23)	0·035
Time until first episode of bronchopulmonary obstruction (weeks)	4·0 (2 to 7)	7·0 (2 to 23)	0·025
No of symptomatic respiratory illnesses during study	10·0 (6 to 12)	6·5 (4 to 8)	0·005
No of episodes of bronchopulmonary obstruction during study	9·0 (6 to 12)	4·5 (3 to 6)	<0·005
Total obstructive score	19·5 (12 to 23)	12·0 (7 to 22)	0·025
Mean obstructive score an episode	5·5 (5 to 6·6)	5·3 (4 to 7)	0·36
Duration of treatment with β-2 agonists (weeks)	20·0 (12 to 30)	7·0 (3 to 12)	<0·005
Duration of treatment with theophylline (weeks)	8·5 (6 to 14)	2·0 (1 to 8)	<0·005
Total IgE (kU/l) at end of study	11 (4 to 94)	15·5 (5 to 41)	0·49

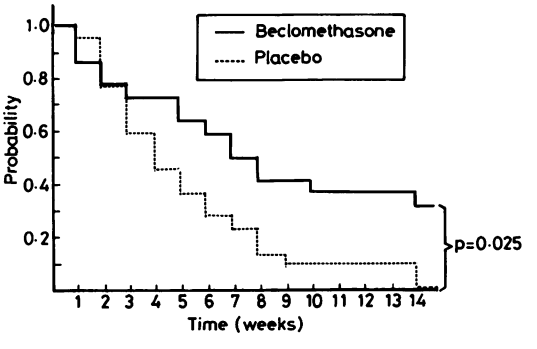

Fig 1 *The probability of not contracting an acute symptomatic respiratory tract illness as a function of time in weeks after start of treatment with placebo and with nebulised beclomethasone dipropionate calculated by the Kaplan-Meier estimate and Gehan's statistic.*

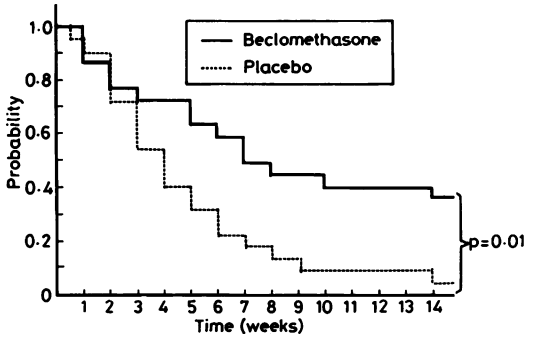

Fig 2 *The probability of not contracting an episode of bronchopulmonary obstruction as a function of time in weeks after start of treatment with placebo and with nebulised beclomethasone dipropionate. Calculated by the Kaplan-Meier estimate and Gehan's statistic.*

nebulised beclomethasone dipropionate and placebo during the first eight weeks of the study period, other symptomatic treatment was given as necessary according to the clinical condition, and recorded. The placebo group were treated with β_2 agonists (usually by inhalation) for significantly longer periods of time than the beclomethasone dipropionate group (table 3). The same was found for theophylline (usually given rectally or orally) (table 3).

Total IgE did not differ between the two groups at the end of the study (table 3). Six children in the placebo group and one child in the beclomethasone dipropionate group had positive RASTs at the end of the study, whereas four children in the placebo group and one child in the beclomethasone dipropionate group had positive skin tests at the end of the study. These differences were not significant.

Discussion

The association between bronchiolitis in infancy and subsequent obstructive airways disease[1 2] may be a result of increased bronchial hyper-reactivity as Henry *et al*[11] found two years after acute broncholitis. The prophylactic effect of inhaled beclomethasone dipropionate as powder or aerosol for childhood asthma[3 4] may possibly work through inhibition of the enzyme phospholipase A_2, preventing the release of prostaglandins and leukotrienes.[12]

In the present study the positive effect of nebulised beclomethasone dipropionate was already apparent after the first week of treatment. This effect increased gradually throughout the period, and also after the eight week treatment. Several observations confirm the beneficial effect of nebulised beclomethasone dipropionate: time until the first symptomatic respiratory illness and obstructive episode after starting treatment, number of symptomatic respir-

atory illnesses and episodes of bronchopulmonary obstruction during the entire year of follow up, total obstructive score during the study period, and a reduction in the use of other treatments in the beclomethasone dipropionate group. The confidence intervals of the time until the first episode of bronchopulmonary obstruction (table 3) confirm the prolonged effect after stopping treatment. It is of interest that the number of diagnosed respiratory virus infections did not differ between the two groups, whereas the number of symptomatic respiratory illnesses and episodes of bronchopulmonary obstruction were less in the beclomethasone dipropionate group. This suggests that nebulised beclomethasone dipropionate may indirectly reduce bronchial hyper-reactivity.

The two treatment groups had been carefully matched and were comparable. The placebo group was slightly though not significantly older than the beclomethasone dipropionate group at the time of entry in the study, which probably accounts for the difference in weight. No other significant differences in background variables were found.

Other authors have reported similar results, though in different groups of patients. Maayan *et al*[13] showed improvement of lung function and symptomatic score after two weeks treatment with nebulised beclomethasone dipropionate in nine infants aged 15 to 36 weeks old who had persistent wheezing after acute bronchiolitis. Their study was double blind with few patients, had no follow-up, and also had the possibility of a carry over effect because of the crossover design.[13] Both their study and the present study raise the possibility that inhalation with nebulised beclomethasone dipropionate at the time of recurrent respiratory infections with bronchopulmonary obstruction may have a prolonged subsequent effect after treatment has finished. This may be caused by the anti-inflammatory effect of the inhaled steroid.

Pedersen and Prahl[14] treated 18 children with bronchial asthma aged two to 26 months with nebulised beclomethasone dipropionate in an open study without placebo. They found that 15 of the 18 children improved during the treatment period of two to six months.

Storr *et al*[15] evaluated the use of nebulised beclomethasone dipropionate over a six month period in 29 children with bronchial asthma aged 20 months to 5·6 years old in a placebo controlled double blind study. They found that nebulised beclomethasone dipropionate was significantly better than placebo, whereas Webb *et al*[16] in a placebo controlled double blind crossover study of 16 children with moderate to severe asthma, age range 18 months to six years, only found a favourable trend with nebulised beclomethasone dipropionate which was not significant. In the study of Webb *et al*, however, only 13 of 16 children completed the study. The two treatment periods, each consisting of two months of active or placebo treatment, did not have any washout period in between.[16] Although the patients in the present study were younger and in a different category from those of Storr *et al*[15] and Webb *et al*,[16] our results may partly explain the differences between these two studies. We found that nebulised beclomethasone dipropionate was effective even after stopping treatment, thereby increasing the likelihood of a carry over effect in a crossover study. This makes the interpretation of data generated in crossover studies difficult.[16]

The evidence at present supports the prophylactic effect of nebulised beclomethasone dipropionate in obstructive airways disease in infants and small children. We have shown in a previous study[2] that infants at particular risk of recurrent obstructive episodes after acute bronchiolitis may be identified by a discriminant function analysis at the time of the acute attack. Infants identified in this way may benefit from nebulised beclomethasone dipropionate. The present study suggests that inhalation of nebulised beclomethasone dipropionate at a critical time period for infants and children at risk may have a prolonged effect (after treatment has been stopped) on the subsequent development of recurrent episodes of bronchopulmonary obstruction and hence upon the possible development of asthma in these children. These suggestions must be confirmed by further studies. Treatment of this kind may be of great value, especially as inhalation of topical steroids in moderate doses is devoid of serious side effects during prolonged periods of treatment.[3]

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