Efficacy of nebulized budesonide in treatment of severe infantile asthma: A double-blind study

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Background and objective: *Treatments with inhaled corticosteroids yielded conflicting results in infants with severe asthma. The purpose of this study was to assess the efficacy of nebulized budesonide on the control of asthma in this age group.*
Methods: *In a double-blind, placebo-controlled study, 40 infants with severe asthma received either nebulized budesonide (1 mg) or placebo twice daily for 12 weeks, followed by a follow-up period of up to 12 weeks. A jet nebulizer driven by an air compressor was used to administer budesonide and placebo.*
Results: *Fewer patients in the budesonide group had an exacerbation during the treatment period (40%) compared with the placebo group (83%, $p < 0.01$). The duration of oral steroid therapy was shorter in the budesonide group than in the placebo group (median number of days of exacerbation as a proportion of the total treatment time, 0% vs 14.5%; $p < 0.05$). The incidence of daytime ($p < 0.05$) and nighttime wheezing ($p < 0.01$) was lower in the budesonide group than in the placebo group during the treatment period. The proportion of patients without an exacerbation of asthma during the entire 24 weeks was 28% for those patients who had received budesonide and 0% for those patients who had received placebo. Asthma improved in more patients in the budesonide group (17 of 19, 89%) than in the placebo group (7 of 16, 44%; $p < 0.005$). These results should improve and modify the treatment of infants with severe asthma.*
Conclusion: *Nebulized budesonide (1 mg twice daily) is a well-tolerated and efficient treatment for severe infantile asthma. (J Allergy Clin Immunol 1996;98:14-20.)*

Key words: *Infantile asthma, inhaled corticosteroids, nebulized budesonide*

Management of infantile asthma is difficult, in part because of the difficulty in defining the disease itself. Tabachnik and Levison[1] proposed in 1981 that "any infant with three or more episodes of wheezing should be considered as having asthma, regardless of the age of onset, evidence of atopy, apparent precipitating cause of wheeze or frequency of the wheeze." This definition does not permit distinction between those infants who wheeze only in response to viral infections and those who wheeze in response to additional precipitating factors.[2] However, the wheezing in this age group is important because early treatment might influence the long-term outcome.[3] Moreover, whatever the cause, it is likely that wheezing and dyspnea reflect inflammatory disorders in the airways.

Inhaled corticosteroids have been advocated to counteract the deleterious effects of bronchial inflammation in diseases in which inflammatory disorders are involved, such as bronchopulmonary dysplasia with or without asthma.[4, 5] In children, as well as in adults, inhaled steroids are an effective and recommended prophylactic treatment for

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moderate to severe asthma, and they are advocated in treatment of infants with severe symptoms.[6] However, in infants with asthma, therapeutic trials with inhaled corticosteroids have provided conflicting results.[7-11] Some of the discrepancy in results may be ascribed to differences in methodology, differences in treatment duration, severity of disease, age of patients studied, and the specific drug delivery problems associated with this age group.[12, 13]

We have therefore conducted a double-blind, placebo-controlled study with two parallel groups in infants younger than 30 months of age with severe asthma. The aim of this study was to assess the effectiveness of nebulized budesonide, 1 mg twice daily, during 12 weeks on the control of asthma during the treatment period and during a 3-month follow-up period.

METHODS

Infants were recruited for study from Hôpital des Enfants Malades, Paris, France between December 1991 and February 1992.

Diagnosis of asthma was defined by at least three exacerbations of dyspnea associated with wheezing during the 12 months before the study. Severe asthma was defined as either one exacerbation per month requiring oral steroid administration during the 3 months before inclusion in the study or persistent asthma with daily symptoms for at least 15 days before inclusion. Informed written consent was obtained from the parents, and the trial was approved by local ethical committees.

Infants with other recognized respiratory disease, including cystic fibrosis and bronchopulmonary dysplasia, and those with other major concomitant disease were excluded from the study.

The study had a double-blind, randomized, parallel-group design. Patients were randomly allocated to receive either nebulized budesonide 1 mg (2 ml) or placebo (2 ml) twice a day (i.e., one nebulization each morning and evening for 12 weeks), followed by a follow-up period of up to 12 weeks.

For at least the 15 days before the first visit and throughout the study, patients received oral salbutamol solution 100 μg/kg three times daily. The placebo and budesonide suspensions were administered in identical brown bottles to make the study double-blind. It was randomized by Astra Draco AB (Lund, Sweden) and was administered to each patient by means of a De Vilbiss 646 jet nebulizer (De Vilbiss, Arcueil, France) with an open face mask (Europe Médical, Bourgen Bresse, France), driven by a CR60 air compressor (Medic Aid, Pagham, U.K.). The choice of air compressor and jet nebulizer was based on results of a previous study,[14] which showed an adequate mass median droplet diameter and drug output. Parents were instructed to hold the mask close to their child's face. The duration of a nebulization was not to exceed 5 minutes.

On referral, parents were instructed to keep a symptom diary during the study. Every day they recorded asthma symptoms (yes or no): wheezing, cough, and bronchial secretions; nighttime and daytime symptoms; and treatment other than study medication. In case of exacerbation, the parents were instructed to administer nebulized 0.5% salbutamol (0.03 ml/kg, minimum 0.3 ml). Oral corticosteroids were administered if the infant failed to respond to two salbutamol nebulizations.[15]

The children were seen as outpatients during weeks 4, 8, and 12 of treatment and also every 4 weeks during the follow-up period until the first exacerbation occurred or 12 weeks had passed. Budesonide suspension was dispensed at visits 1, 2, and 3 in bottles of 140 ml (70 doses) from which budesonide was dispensed into nebulizers with syringes. All bottles were returned at the next visit.

At each visit, the daily diary cards were collected; and weight, height, results of a chest examination, and any oral thrush or facial skin irritation were recorded. Nebulization technique and compliance with use of the nebulizer were checked. At the end of the treatment period, asthma status was assessed by the parents as "improved" or "unchanged."

Statistical analysis

An "all patients treated" approach to the analysis is reported. Of the 40 patients treated, 38 (including three of the patients who dropped out) recorded some data after the initial visit and were included in this analysis. A "per protocol" approach was also used, and it provided similar results and the same conclusions.

Comparisons between the two treatment groups were made by using information from diary cards. Intake of oral corticosteroids on 2 or more consecutive days was used as an indicator of asthma exacerbation. The number of exacerbations for each patient was compared by means of the Wilcoxon rank sum test. The number of patients with at least one exacerbation in each group during the treatment period was compared by using the chi square test. The proportion of the total days of exacerbation out of the total treatment time for each patient was compared between the treatment groups by using the Wilcoxon rank sum test. The proportion of patients who were free of exacerbation of asthma at 12 and 24 weeks (using time between randomization and the first exacerbation of asthma) was calculated by the Kaplan-Meier product limit technique. The log-rank test was used to compare the treatment groups.

An analysis of the possible influence of type of asthma (i.e., persistent or recurrent) and atopy of parent (i.e., atopic or nonatopic) was performed by using a Cox regression analysis. This analysis examined the treatment effects adjusted for any significant prognostic influence of these factors.

TABLE I. Demographic data for the 38 patients analyzed

	Budesonide group ($n = 20$)	Placebo group ($n = 18$)
Mean age (mo)	16.4	18.1
Range (mo)	6-30	8-28
Sex (male/female)	16/4	17/1
Passive tobacco smoking	12	9
Atopic father or mother	7	11
Persistent asthma	6	5
Recurrent asthma	14	13
Mean weight (kg)	11.2	11.6
Mean height (cm)	78.8	81.6

Other efficacy variables were proportion of days with each symptom and proportion of days when nebulized salbutamol was administered during the treatment period for each patient; treatment groups were compared by using the Wilcoxon rank sum test.

RESULTS

Forty patients, 35 boys and 5 girls, with a mean age of 17 months (range, 6 to 30 months) were recruited for study. Thirty-five patients completed the 12-week treatment period; three patients were withdrawn prematurely: one was withdrawn because of lack of efficacy (placebo group), one was lost to follow-up (placebo group), and one could not tolerate the device (budesonide group). Two patients in the placebo group were excluded from the analysis because they had no data apart from the data recorded at the initial visit.

Demographic data for the 38 infants analyzed are reported in Table I. Twenty-seven infants were considered as having recurrent asthma (13 in the placebo group and 14 in the budesonide group), and 11 as having persistent asthma (five and six, respectively).

Treatment period

The number of exacerbations of asthma for each patient was lower in the budesonide group but did not reach significance ($p = 0.13$) (Table II). However, significantly fewer patients in the budesonide group had at least one exacerbation (40%) compared with the placebo group (83%) (difference, 43%; confidence interval, 16% to 71%; $p < 0.01$). Duration of exacerbations was also significantly shorter in the budesonide group, as shown by the significantly lower median duration of oral corticosteroid therapy compared with the placebo group (median duration, expressed as the percentage of the total treatment time, 0% vs 14.5%; $p < 0.05$). The median duration of nebulized salbutamol was slightly lower in the budesonide group than in the placebo group, but the difference did not reach significance (5.2% vs 8.8%, $p = 0.27$). At 12 weeks, the proportion of patients who were free of exacerbation of asthma was significantly higher in the budesonide group (55%) than in the placebo group (8%) (difference, 47%; confidence interval, 21% to 73%) (Fig. 1). For asthma symptoms (Fig. 2), a significantly lower incidence of daytime wheezing ($p < 0.05$) and nighttime wheezing ($p < 0.01$) was observed in the budesonide group compared with the placebo group. Asthma, assessed by the parents, was improved in significantly more patients in the budesonide group (17 of 19, 89%) than in the placebo group (7 of 16, 44%; $p < 0.005$).

Entire study

At 24 weeks, 28% of patients in the budesonide group and 0% of patients in the placebo group were still free of exacerbation of asthma (difference, 28%; confidence interval, 7% to 48%) (Fig. 1).

There was no significant prognostic influence of atopy of a parent on the time that the patients were free of exacerbations (Cox regression analysis). There was a significant influence of the type of asthma ($p = 0.0005$). Patients with persistent asthma were more likely (hazard ratio, 4.47) to have an exacerbation sooner than patients with recurrent asthma. After adjusting for this influence, there was still a significant effect of budesonide ($p = 0.01$) compared with placebo.

For 11 patients in the budesonide group and for 15 in the placebo group at least one adverse event was reported during the treatment period. Eight patients in the placebo group and three in the budesonide group had upper airway infection. No facial skin reaction was observed. One patient in the budesonide group had oral candidiasis, and another had transient hyperexcitability. Mean increases in height and weight for each age range were similar between the treatment groups. Neither bronchoconstriction nor coughing were reported after nebulized budesonide was administered.

DISCUSSION

Our results provide evidence that the administration of 1 mg of nebulized budesonide twice daily for 12 weeks was an effective treatment for severe asthma in children younger than 30 months of age. Significantly fewer patients in the budesonide group had exacerbations requiring administration

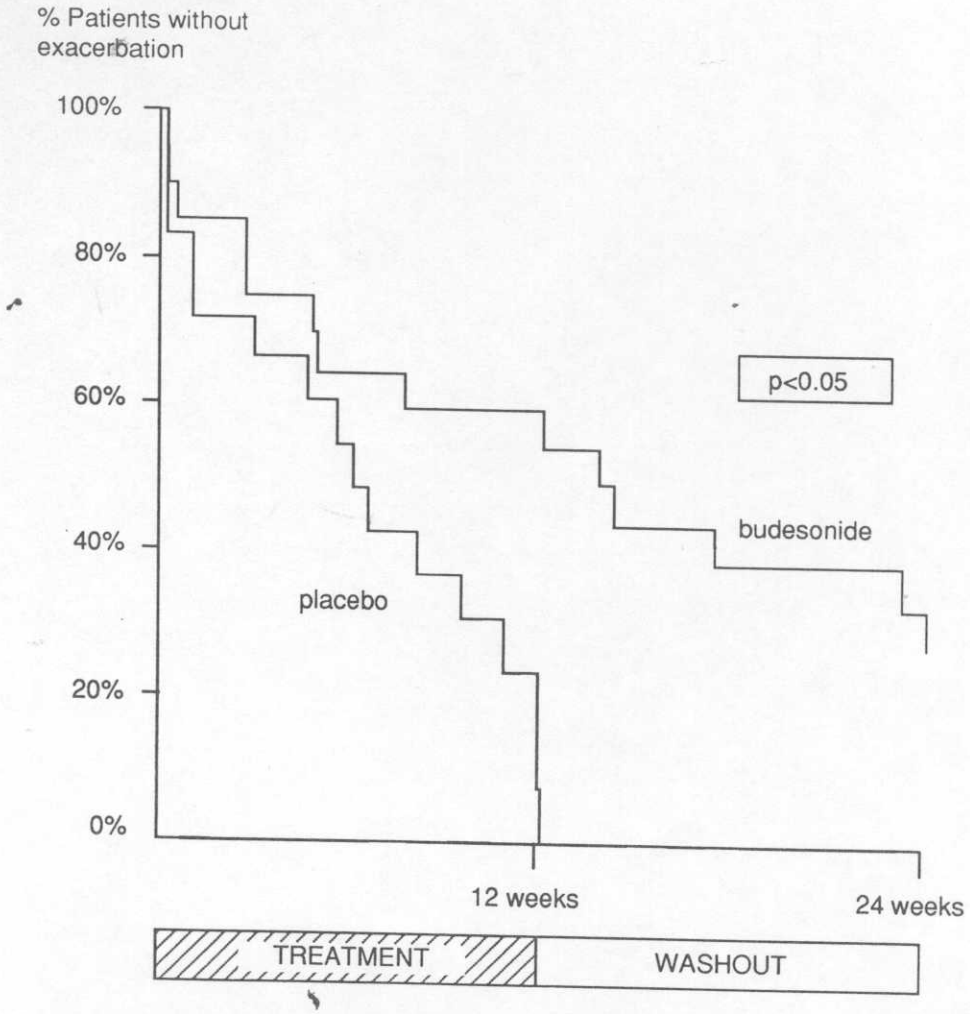

FIG. 1. Percentage of patients without exacerbation of asthma in budesonide and placebo groups during treatment and follow-up periods.

TABLE II. Efficacy of nebulized budesonide (1 mg twice daily) and placebo on control of asthma

	Placebo group	Budesonide group	*p* Value
No. of exacerbations per patient*	1 (0-3)	0 (0-4)	=0.13
Patients with at least 1 exacerbation (%)	83	40	<0.01
Duration of oral corticosteroid therapy (%)	14.5	0	<0.05
Patients without exacerbation of asthma at 12 wk (%)	8	55	<0.05
Improvement of asthma, parent's assessment (%)	44	89	<0.005
Incidence of daytime wheezing (%)*	11.6 (0-91)	2.2 (0-56)	<0.05
Incidence of nighttime wheezing (%)*	6.5 (0-24)	0.6 (0-30)	<0.01

*Median values are given with ranges in parentheses.

of oral corticosteroids, and for those who had such exacerbations, the duration of oral corticosteroid therapy decreased. The incidence of daytime and nighttime wheezing was lower in the budesonide group than in the placebo group. Furthermore, significantly more parents in the budesonide group than in the placebo group believed that their children experienced improvement as a result of the treatment.

It should be noted that nebulized budesonide was more effective in infants with recurrent asthma than in infants with persistent daily symptoms, mainly persistent wheezing. However, even in this latter group, nebulized budesonide was more ef-

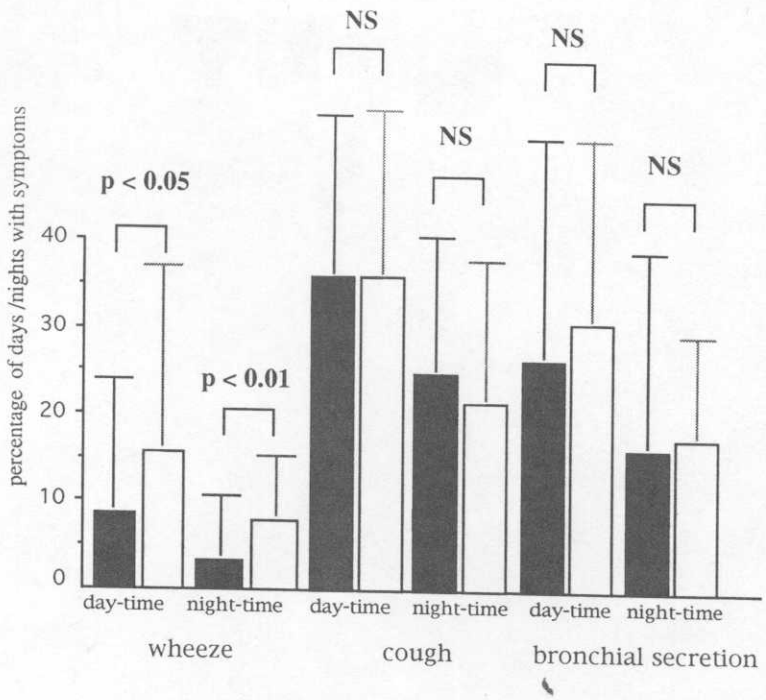

FIG. 2. Proportion of days and nights with symptoms during the treatment period in the budesonide group (■) and in the placebo group (□). (Values are expressed as means ± SD.) *NS,* Not significant.

fective than placebo. In contrast, analysis of the possible influence of parent status (atopic or nonatopic) did not reveal any significant prognostic influence. This is in agreement with several epidemiologic studies, which failed to show a link between early wheezing in infancy (almost always caused by a viral infection) and familial atopy.[16-18] Familial predisposition to allergy seems unlikely to be of major importance.

In our study nighttime and daytime wheezing were significantly reduced in the budesonide group, whereas cough and bronchial secretions did not differ in the budesonide and placebo groups. Although cough is an important symptom of respiratory disease, particularly of asthma, assessment of cough may be difficult; and assessment of bronchial secretions may be even more difficult. Falconer et al.[19] showed that in 15 children with asthma, there was poor agreement between reported and recorded nocturnal cough. Moreover, in infants upper respiratory tract infections and colds are common and may contribute to cough and bronchial secretions.

Only few therapeutic trials have been carried out in infants with asthma. Some uncontrolled studies have shown beneficial effects of inhaled corticosteroids.[20-24] The few controlled studies have yielded conflicting results.[5-9] In their controlled study, Carlsen et al.[7] administered nebulized beclomethasone dipropionate during 8 weeks to 22 of 44 children with recurrent wheezing after an episode of acute bronchiolitis. Beclomethasone dipropionate was effective in reducing the number of episodes of wheezing, but there was no change in the severity of individual exacerbation. In contrast, the study of Van Bever et al.[8] was unable to demonstrate a significant improvement when nebulized budesonide was used. In this crossover study, 23 infants received nebulized budesonide suspension, 0.5 mg, twice daily for 1 month or placebo. Daily wheezing, rhinitis score, and lung auscultation demonstrated improvement after 1 month of budesonide nebulization, but the difference with placebo was not statistically significant. There might be several explanations for the lack of efficacy of budesonide in that study: the low dose of nebulized budesonide (0.5 mg twice daily), the short treatment duration (1 month), the crossover design without a washout period, and the selection of children with mild asthma as evidenced by the low asthma symptom scores at inclusion.

In our study the methodology, the dose of budesonide, and the material used are likely to contribute to the observed favorable results. Our study is the first double-blind, randomized, parallel-group study to include such a large number of

infants with severe asthma. All of them were recruited during autumn and winter and treated for a long period (3 months) with budesonide administered through an adapted nebulizer driven by an appropriate compressor.

The analysis of Fig. 2 shows that the difference between the two groups occurred after 1 month and was maintained for the budesonide group during several weeks of the follow-up period, suggesting a prolonged protective effect. This demonstrates that both short-term treatment and crossover study design are not suitable for a comparison of inhaled corticosteroids. This prolonged effect is similar to that observed in older children and adults with asthma. Juniper et al.[25] and Haahtela et al.[26] showed that when inhaled steroid is withdrawn after regular use, improvement may persist for at least 3 months and that clinical deterioration precedes an increase in bronchial hyperreactivity.

Our results are in agreement with those of Ilangovan et al.[11] who enrolled 1- to 5-year-old children. There were 17 infants younger than 2 years. All had severe asthma requiring oral corticosteroids for treatment of acute dyspneic episodes. Duration of oral corticosteroid use was significantly reduced in the budesonide group.

Our results are also in agreement with those of studies in which corticosteroids were delivered by spacers with face masks attached to them. The study by Bisgaard et al.[9] included infants who were treated successfully with budesonide, 400 μg administered twice daily by pressurized metered-dose inhaler (Nebuhaler; ASTRA Pharmaceuticals, Lund, Sweden) for 12 weeks. Noble et al.[10] showed that the administration of budesonide 150 μg twice daily by pressurized metered-dose inhaler with Nebuhaler attached to a Laerdal face mask (Staranger, Norway) significantly improved both daytime cough and wheezing and daytime and nighttime breathlessness. In contrast, only daytime and nighttime cough significantly decreased during a 6-month study with budesonide, 400 to 800 μg/day, performed by Connet et al.[27] In this study budesonide was also administered through Nebuhaler and Laerdal face mask. Wheezing and use of bronchodilator and oral corticosteroids were less important during budesonide treatment, but differences did not reach significance.

The inhalation system in which the spacer and face mask are used might seem more convenient by allowing easier, cheaper, less time-consuming, and more reliable administration than nebulizers. However, comparison of these two techniques is difficult. Comparison has been performed in children with acute asthma[28] but has not been done in infants with acute asthma or infants receiving long-term treatment. Using this inhalation system may prove difficult: in the study by Noble et al.[10] three of 20 infants were able to tolerate the face mask only while asleep, and four others did not accept the device, even when asleep, and had to be withdrawn from the study. In contrast, only two of 40 infants in our study did not accept the nebulizer. This may be because the face mask must be applied tighter to the child's face when spacers are used in order to provide an airtight seal.

It should be noted that studies with spacer devices with face masks enrolled infants with less severe asthma than infants of our study.[9, 10] In the study by Bisgaard et al.[9] infants who had received oral corticosteroids during the month before the study were excluded, and requirement of oral prednisolone during the trial in the placebo group was only 7% of the days. Another advantage of nebulization, as compared with the use of a pressurized metered-dose inhaler, is the avoidance of chlorofluorocarbon propellants, which is a growing necessity.[29]

Performances of compressors and nebulizers are highly variable.[30, 31] However, nebulization is a very suitable inhalation technique in infants, provided that several conditions are fulfilled: delivery of particules smaller than 5 μm, short nebulizing time (<10 minutes), and sufficient drug output.[14, 32]

The adequate dose of nebulized corticosteroids has yet to be determined. We did not observe any adverse clinical effects of nebulized budesonide, but our study did not address possible systemic effects. Our daily dose of 2 mg of budesonide was clinically efficient, as in the study by Ilangovan et al.[11] In contrast the study by Van Bever et al.[8] showed no benefits with 1 mg of budesonide per day. A 2 mg daily dose of nebulized budesonide may seem high, but the delivered dose of budesonide is only 10% of the nominal dose.[26] Moreover, the fraction of active drug reaching the lungs is unknown.[12] However, because of the potential side effects, the lowest dose required to maintain control is necessary.[33]

In conclusion, this study demonstrates the efficacy of nebulized budesonide as a treatment for severe infantile asthma. These results should improve and modify the treatment of infants with severe asthma. Recent studies suggest that in older children, early introduction of inhaled steroid improves long-term control of asthma and reduces

the risk of irreversible airway obstruction.[34] Further studies are necessary to assess the implications of early inhaled steroid use in infants, in terms of both control of asthma and safety. The delivery system must also be improved to permit more accurate determination of safe and effective doses of the drug.

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REFERENCES

1. Tabachnik E, Levison H. Infantile bronchial asthma. J Allergy Clin Immunol 1981;67:339-47.
2. Wilson NM. Wheezy bronchitis revisited. Arch Dis Child 1989;64:1194-9.
3. Milner AD. Inhaled topical corticosteroid in the first two years of life. Eur Respir Rev 1993;3:329-32.
4. König P, Shatley M, Levine C, Mawhinney TP. Clinical observations of nebulized flunisolide in infants and young children with asthma and bronchopulmonary dysplasia. Pediatr Pulmonol 1992;13:209-14.
5. Cloutier MM. Nebulized steroid therapy in bronchopulmonary dysplasia. Pediatr Pulmonol 1993;15:111-6.
6. Warner JO. Asthma—a follow-up statement from an international paediatric asthma consensus group. Arch Dis Child 1992;67:240-8.
7. Carlsen KH, Leegaard J, Larsen S, Ørstavil I. Nebulised beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis. Arch Dis Child 1988;64: 1428-33.
8. Van Bever HP, Schuddinck L, Wojciechowski M, Stevens WJ. Aerolized budesonide in asthmatic infants: a double blind study. Pediatr Pulmonol 1990;9:177-80.
9. Bisgaard H, Munck SL, Nielsen JP, Petersen W, Ohlsson SV. Inhaled budesonide for treatment of recurrent wheezing in early childhood. Lancet 1990;336:649-51.
10. Noble V, Ruggins V, Everard ML, Milner AD. Inhaled budesonide for chronic wheezing under 18 months of age. Arch Dis Child 1992;67:285-8.
11. Ilangovan P, Pedersen S, Godfrey S, Nikander K, Noviski N, Warner JO. Treatment of severe steroid dependent preschool asthma with nebulised budesonide suspension. Arch Dis Child 1993;68:356-9.
12. Everard ML, Clark AR, Milner AD. Drug delivery from jet nebulisers. Arch Dis Child 1992;67:586-91.
13. Everard ML, Clark AR, Milner AD. Drug delivery from holding chambers with attached facemask. Arch Dis Child 1992;67:580-5.
14. Newman SP, Talace N, Nikander K, Berg E, Clarke SW. Evaluation of nebulisers and compressors for use with budesonide nebuliser suspension [abstract]. Eur Respir J 1988; 1(suppl 2):211.
15. National Heart, Lung and Blood Institute. National Asthma Education Program Expert Panel Report. Guidelines for the diagnosis and management of asthma. J Allergy Clin Immunol 1991;88:425-534.
16. Wilson NM, Phagoo SB, Silverman M. Atopy, bronchial responsiveness, and symptoms in wheezy 3 year olds. Arch Dis Child 1992;67:491-5.
17. Mertsola J, Ziegler T, Ruuskanen O, Vanto T, Koivikko A, Halonen P. Recurrent wheezy bronchitis and viral respiratory infections. Arch Dis Child 1991;66:124-9.
18. Burr ML, Limb ES, Maguire MJ, et al. Infant feeding, wheezing, and allergy: a prospective study. Arch Dis Child 1993;68:724-8.
19. Falconer A, Oldman C, Helms P. Poor agreement between reported and recorded nocturnal cough in asthma. Pediatr Pulmonol 1993;15:209-11.
20. Godfrey S, Avital A, Rosler A, Mandelberg A, Uwyyed K. Nebulised budesonide in severe infantile asthma. Lancet 1987;2:851-2.
21. Maayan C, Itzhaki T, Bar-Yishay E, Gross S, Tal A, Godfrey S. The functional response of infants with persistent wheezing to nebulized beclomethasone dipropionate. Pediatr Pulmonol 1986;2:9-14.
22. Pedersen W, Prahl P. Jet nebulised beclomethasone dipropionate in the management of bronchial asthma. Allergy 1987;42:272-5.
23. Hultquist C. Nebulised budesonide in severe childhood asthma [letter]. Lancet 1989;1:380.
24. Yuksel B, Greenough. Randomised trial of inhaled steroids in preterm infants with respiratory symptoms at follow up. Thorax 1992;47:910-3.
25. Juniper EF, Kline P, Vanzieleghem MA, Hargreave FE. Reduction of budesonide after a year of increased use: a randomized controlled trial to evaluate whether improvements in airway responsiveness and clinical asthma are maintained. J Allergy Clin Immunol 1991;87:483-9.
26. Haahtela T, Järvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. N Engl J Med 1994;331:700-5.
27. Connett GJ, Warde C, Wooler E, Lenney W. Use of budesonide in severe asthmatics aged 1-3 years. Arch Dis Child 1993;69:351-5.
28. Kerem E, Levison H, Schuh S, et al. Efficacy of albuterol administered by nebulizer versus spacer device in children with acute asthma. J Pediatr 1993;123:313-7.
29. Epstein SW. Is the MDI doomed to extinction? [editorial]. Chest 1993;103:1313.
30. O'Callaghan C. Particle size of beclomethasone dipropionate produced by two nebulizers and two spacing devices. Thorax 1990;45:109-11.
31. Alvine G, Rodgers P, Fitzsimmons KM, Ahrens RC. Disposable jet nebulizers. How reliable are they? Chest 1992; 101:316-9.
32. Lødrup Carlsen KC, Nikander K, Carlsen K-H. How much nebulised budesonide reaches infants and toddlers? Arch Dis Child 1992;67:1077-9.
33. Warner JO. Use of corticosteroids in children with asthma. Eur Respir Rev 1993;3:326-8.
34. Agertoft L, Pedersen S. Effects of long term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir Med 1994;88:373-81.