Respiratory Medicine (2001) **95,** 565–570
doi:10.1053/rmed.2001.1104, available online at http://www.idealibrary.com on IDEAL®

Effect of inhaled budesonide therapy on lung function in schoolchildren born preterm

A. S. Pelkonen*, A. L. Hakulinen†, M. Hallman‡ and M. Turpeinen*

*Department of Allergic Diseases, Helsinki University Central Hospital, Helsinki, †Helsinki City Maternity Hospital, Helsinki and ‡University of Oulu, Oulu, Finland

We investigated the effect of inhaled glucocorticoid (GC) on bronchial obstruction and on bronchial lability in schoolchildren born preterm.

Twenty-one children with bronchial obstruction, increased responsiveness to a β_2-agonist, and/or increased diurnal variation in peak expiratory flow (PEF) were selected for an open longitudinal study of the value of inhaled GC. None of these children had an earlier diagnosis of asthma or current GC treatment. Eighteen children with median (range) birth weight 1025 (640–1600) g and gestational age 28 (24–35) weeks, age at study 10·1 (7·7–13) years, were treated with inhaled budesonide in initially high ($0{\cdot}8\,mg\,m^{-2}\,day^{-1}$ for 1 month) and subsequently lower dose ($0{\cdot}4\,mg\,m^{-2}\,day^{-1}$ for 3 months). Daily symptom scores were recorded. Spirometric values were measured in the clinic at the beginning and end of each treatment period. At home, children used a data storage spirometer.

After treatment with budesonide for 4 months, spirometric values in the clinic did not significantly change. The median forced expiratory volume in 1 sec (FEV_1) was 74% of predicted both at entry and after budesonide treatment. However, the median number of $\geq$20% diurnal change in PEF values at home decreased during treatment.

According to the present study, inhaled budesonide for 4 months had no significant effect on basic lung function but may decrease bronchial lability in schoolchildren born preterm.

Key words: inhaled budesonide; lung function; schoolchildren; preterm.

Respir. Med. (2001) **95,** 565–570

Introduction

Bronchial obstruction, bronchial lability (abnormal diurnal variation and/or increased responsiveness to β_2-agonist) and increased bronchial responsiveness, characteristic features of asthma (1), are common in schoolchildren born preterm (2–4). Asthma is associated with inflammatory changes in the bronchial mucosa and this inflammatory process has been suggested to be connected with abnormalities in lung function (5). Both changes may be affected by inhaled glucocorticoids (GC) (6,7). The causes of abnormal lung function in preterm born schoolchildren are complex. Impaired airway growth in infancy, smooth muscle hypertrophy, peribronchial and bronchial fibrosis, and pathological changes in the bronchial mucosa have been suggested (3,8). During the neonatal period neutrophilic inflammation plays a prominent role in the pathophysiology of early chronic lung disease (CLD) in preterm infants (9). The beneficial effect of GCs has been demonstrated in ventilator-dependent neonates (10) and in some wheezy preterm infants (11). Although these preterm born children may have bronchial obstruction, bronchial lability and respiratory symptoms in later childhood, most of them are content with their life (2). We do not know how to treat these schoolchildren with a clinical picture of asthma. It is not known whether chronic inflammation plays a role in the bronchial obstruction of these children as it does in asthma. To our knowledge, there has been only one previous report of short-term treatment with inhaled GC (12), in which treatment for 4 weeks with inhaled beclomethasone dipropionate in a dose of 0·4 mg daily did not affect the respiratory symptoms or bronchial responsiveness of schoolchildren born preterm.

With the aim of investigating the effect of inhaled anti-inflammatory therapy on bronchial obstruction and on bronchial lability in preterm born schoolchildren, we prescribed the prolonged use of inhaled budesonide for 21 children with bronchial dysfunction.

Received 30 June 2000 and accepted in revised form 9 March 2001.
Correspondence should be addressed to: Dr A. S. Pelkonen, Department of Allergic Diseases, Helsinki University Central Hospital, Meilahdentie 2, P.O. Box 160, 00029 Huch, Finland. Fax: +358 9 47186560.
Presented in part at the International Conference of the American Thoracic Society in May 1995 in Seattle.

0954-6111/01/070565+06 $35·00/0

Methods

STUDY DESIGN

In our two earlier cross-sectional studies (4,13), pulmonary function was investigated in a total of 63 schoolchildren born preterm at a median (range) age of 10·0 (7·4–13·9) years. For the lung function studies, all these 63 children made two visits to the Outpatient Department of Allergic Diseases, University of Helsinki Central Hospital. They all underwent lung function testing with an identical protocol and equipment.

At the first hospital visit, clinical status was studied, body height and weight were measured, and questionnaires focusing on respiratory symptoms during the preceding year were completed. Flow-volume spirometry and a bronchodilation test were performed, and each child was trained to use a home spirometer. In addition, skin prick tests were made. Lung function was monitored twice daily at home. The effect of a β_2-agonist was measured by spirometry before and after terbutaline inhalation every morning and evening for the first 2 weeks of home monitoring, followed by treatment of a placebo for 2 weeks. Parents and children were blinded to these treatments. At the second visit, flow-volume spirometry was performed and the data of the home spirometer were downloaded.

Budesonide treatment was then given to those who met at least one of the following inclusion criteria i.e. bronchial obstruction, increased responsiveness to a β_2-agonist, and/or abnormal diurnal peak expiratory flow (PEF) variation (i.e. $\geq$20%). Bronchial obstruction was defined as at least two of the following spirometric parameters in the clinic: $FEV_1 < 80\%$, PEF $< 75\%$ or $FEF_{50} < 62\%$ of the predicted values (14). A positive response to terbutaline was defined as a FEV_1 or PEF increment of $\geq$15% after terbutaline in the clinic or at home (15).

The numbers of positive terbutaline responses and diurnal PEF variations of $\geq$20% during home monitoring were recorded. The numbers of abnormal diurnal PEF variations during the whole 4 weeks recording and separately during the 2 weeks terbutaline and 2 weeks placebo treatment were calculated as the differences between the morning and evening PEF values, and were expressed as percentages of the greater PEF value. Earlier studies have shown that a diurnal PEF variation $\geq$20% is a useful screening test for asthma and a good indicator of bronchial lability (16). Exclusion criteria was a previous asthma diagnosis and/or current GC treatment.

PATIENTS

Twenty-one children who met the inclusion criteria were selected for the budesonide trial, which was completed by 18 children. The median (range) birth weight and gestational age of these children were 1025 (640–1600) g and 28 (24–35) weeks respectively. The median (range) duration of mechanical ventilation and duration of supplementary oxygen treatment during the neonatal period were 7 (0–80) and 27 (1–131) days respectively. Six children were dependent on supplementary oxygen at the age of 36 postconceptional weeks, which was used as the criterion of CLD (17). Nine had been treated with exogenous surfactant. Two children had received either inhaled or systemic GC during treatment in the neonatal intensive care unit. Four children had used inhaled GC during the first 2 years of life but not thereafter.

The study was approved by our institutional ethics committee. Informed consent was obtained from the parents. The principal investigator did not know the neonatal history of the children at the time of testing.

METHODS

Flow-volume spirometry was done in the clinic with a pneumotachograph (Spirotrac III®, Vitalograph Ltd, Buckingham, U.K.). In accordance with the acceptability criteria of the American Thoracic Society, at least three technically correct forced expiratory curves were recorded during each measurement. The curve was considered to be reproducible if the largest forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1), and second largest FVC and FEV_1 from acceptable curves did not differ by more than 5% (expressed as a percentage of the largest observed FVC and FEV_1, regardless of the curve on which it occurred) (18). The curve with the highest sum of FEV_1 and FVC values was selected for the statistical analysis. The results of the lung function tests were expressed as percentages of the predicted values reported by Polgar and Promadhat (14). The following spirometric parameters were recorded: FVC, FEV_1, PEF and forced expiratory flow at 50% of FVC (FEF_{50}).

Spirometric parameters were measured in the clinic before and 15 min after 0·5 mg of terbutaline inhaled from a dry powder inhaler (terbutaline sulfate 0·25 mg, Bricanyl Turbuhaler® Astra Draco AB, Lund, Sweden). Peak inspiratory flow through a Turbuhaler® device was recorded during each terbutaline inhalation. Neither FEV_1 nor PEF changes were recorded when peak inspiratory flow was insufficient, i.e. $< 30\,l\,min^{-1}$ (19). The changes in FEV_1 and PEF values after terbutaline were expressed as percentage of the values recorded before terbutaline inhalation.

Lung function was recorded at home every morning and evening for 4 weeks, using a Vitalograph Data Storage Spirometer (Vitalograph Ltd) particularly designed for long-term recordings and storage of lung function parameters. The device consists of a pneumotachograph and a computer capable of recording FVC, FEV_1, PEF and peak inspiratory flow values. Before use, the device was calibrated with a standard volume (variation within $\pm$1%). After home recordings, the calibration was checked. The difference between these two calibration values (before and after home monitoring) was $\leq$5%. Each time, the test was repeated a maximum of five times, until the results of the two best curves met the criteria (18). When this was not achieved with five attempts, the failure was recorded. These recordings were not used in the analyses. The data storage

spirometer stored the curve with the largest sum of FEV_1 and FVC in the built-in electronic diary.

During the first 2 weeks, lung function was monitored before and 15 min after inhalation of terbutaline 0·25 mg twice daily, followed by inhalation of placebo for 2 weeks from a Turbuhaler®. Lactose was used as placebo; otherwise, the device was identical to the budesonide (Pulmicort) Turbuhaler®. The results were analysed after home monitoring for 4 weeks. The compliance in inhalation therapy was recorded by measuring peak inspiratory flow with a pneumotachograph (Spirotrac III®) through the dry powder inhaler, Turbuhaler® Children recorded their respiratory symptoms (cough or wheezing) twice daily assigning a single score ranging from 0 to 10 to the memory of the home spirometer before medication and lung function measurement.

Skin tests were made by the skin-prick technique, using eight common allergen extracts. A negative vehicle solution and a positive histamine hydrochloride ($10\,mg\,ml^{-1}$) solution were used as controls. Atopy was defined as at least one wheal reaction $\geq$3 mm diameter in the absence of a response to the negative control solution.

BUDESONIDE TREATMENT

During the first month, the daily dosage of budesonide (Pulmicort Turbuhaler®, $0{\cdot}2\,mg\,dose^{-1}$; AstraZeneca R&D, Lund, Sweden) was $0{\cdot}8\,mg\,m^{-2}\,day^{-1}$ divided into morning and evening doses. Monitoring of spirometric values at home continued twice daily during the first month of budesonide treatment. After that (at the third visit to the clinic), flow–volume spirometry was performed and the home spirometer was downloaded. Budesonide treatment was continued for 3 months with a dose of $0{\cdot}4\,mg\,m^{-2}\,day^{-1}$ divided into two doses. During the last month of the GC treatment period, home monitoring of spirometric values was performed twice daily. At the fourth visit to the clinic, body height and weight were measured, flow volume spirometry and downloading of the home spirometer were performed. The numbers of abnormal diurnal PEF variations and the sum of the symptom scores were recorded and compared between the following periods: 2 weeks of terbutaline treatment, 2 weeks of placebo treatment and the 2 last weeks of the 2 periods of inhaled GC treatment, respectively.

STATISTICAL METHODS

Results of lung function tests were analysed as percentages of the predicted values. Statistical analyses were performed using the Statgraphics computer programme. The normality of the data distribution was tested using a Kolmogorov–Smirnov one-sample test. Spearman's rank correlation (r_s) was used to analyse the correlation between the neonatal variables and the subsequent lung function parameters and between the different lung function parameters and the symptoms. Statistical comparisons of longitudinal lung function measurements during terbutaline, placebo and budesonide treatment were performed with Friedman's non-parametric analysis of variance.

Results

PATIENT SELECTION FOR BUDESONIDE TREATMENT

Twenty-one children met our criteria for a budesonide treatment trial, and 18 completed the study. Three children were not motivated to continue the program after 1 month of budesonide treatment. In 16 of the children in the budesonide trial, bronchial obstruction had been found in baseline spirometry in the clinic; 13 of them also had a positive response to terbutaline at least three times during the first 2 weeks of home monitoring and/or abnormal diurnal PEF variation. In addition, two children had only a positive response to terbutaline at least three times during home monitoring and/or abnormal diurnal PEF variation without bronchial obstruction.

The median (range) age and height of 18 study children was 10·1 (7·7–13) years and −0·7 (−2·5–2·8) SD. Eight (44%) children had had dyspnoeic symptoms at least once during the year preceding the study, or had suffered from continuous troublesome coughing for more than 3 weeks. Atopy was diagnosed in three (17%) children. Thirty-three per cent of the children had a first-degree relative with physician-diagnosed allergy. Fifty per cent of the families reported smoking at home.

At entry, the median spirometric values (range) were FVC 87 (67–121)%, FEV_1 74 (51–95)%, PEF 65 (44–77)% and FEF_{50} 59 (35–103)% of the values of predicted for these 18 children. In the bronchodilator test in the clinic the median (range) ΔFEV_1 2·6% (−5·1–15%).

SPIROMETRY IN THE CLINIC AND RESPIRATORY SYMPTOMS

There were no statistical significant differences between spirometric values at entry and after placebo treatment. During 4 months treatment with budesonide, spirometric values before and after each treatment periods did not change. Changes are as follow: median (range) FEV_1 74 (51–95)%–74 (59–92)%, FVC 87 (67–121)%–90 (66–120)%, PEF 65 (44–77)%–66 (51–91)% and FEF_{50} 59 (35–103)%–55 (29–104)% (Table 1). The sum of symptom scores significantly decreased only during treatment with budesonide for 1 month ($P = 0{\cdot}02$) (Table 2). The median compliance of budesonide treatment during the first two weeks was 89% (range (71–100%) and during the last two weeks 79% (54–100%).

SPIROMETRY AT HOME

An abnormal diurnal PEF variation of $\geq$20% was found at least four times during the 4 weeks home monitoring in ten of the study children (56%), the median (range) frequencies of diurnal PEF variation $\geq$20% were 5 (0–9), 2 (0–6) during

TABLE 1. Spirometry in the clinic

Parameter	Baseline	After placebo	After 1 month budesonide	After 4 months budesonide	*P*-value
FVC	87 (67–121)	86 (64–131)	88 (66–131)	90 (66–120)	0·3
FEV_1	74 (51–95)	73 (55–96)	75 (55–99)	74 (59–92)	0·5
PEF	65 (44–77)	61 (48–86)	68 (52–92)	66 (51–91)	0·07
FEF_{50}	59 (35–103)	53 (35–94)	58 (42–89)	55 (29–104)	0·7

Values are expressed as medians and ranges.
Lung function tests are expressed as percentages of the predictive values.

TABLE 2. PEF variation and symptoms at home

Parameter	After terbutaline (1)	After placebo (2)	After 1 month budesonide (3)	After 4 month budesonide (4)	*P*-value
Symptom score	26 (0–106)	18 (0–119)	3 (0–86)	4 (0–104)	2 *vs.* 3 $P=0·02$
PEF variation*	2 (0–6)	1·5 (0–5)	0·5 (0–3)	0 (0–4)	2 *vs.* 3 $P=0·05$
					2 *vs.* 4 $P=0·02$

Values are expressed as medians and ranges.
P = Not significant for the comparison with 1 and 2.
*The number of diurnal PEF variations $\geq$ 20% during home monitoring.

the 2 weeks terbutaline treatment and 1·5 (0–5) during the placebo treatment. There were no significant differences in PEF variation recorded at home during the 2 weeks terbutaline or placebo treatments (Table 2). The median (range) frequencies of diurnal PEF variation $\geq$20% during the whole 4 months study period decreased significantly, from 1·5 (0–5) during the 2 weeks placebo treatment period to 0(0–4) during last 2 weeks of budesonide treatment ($P=0·02$).

CORRELATIONS

Gestational age at birth correlated positively with the PEF increment after budesonide treatment in the clinic ($r_s=0·54$, $P<0·05$). Other neonatal variables, parental smoking, respiratory symptoms or atopy at school age had no correlation with the different lung function parameters. Diurnal variation in PEF recorded during the treatment period with placebo and short-term reversibility in response to terbutaline correlated significantly with the decrease in diurnal PEF variation during budesonide treatment ($r_s=0·90$ and 0·53, respectively, $P<0·05$ for both).

Discussion

We wanted to investigate the effect of inhaled anti-inflammatory therapy on lung function of schoolchildren born preterm. In our study budesonide treatment for 4 months had no significant effect on basic lung function in our selected group of schoolchildren born preterm, although diurnal PEF variation decreased during the treatment.

In the clinic, flow volume spirometry combined with a bronchodilator test and challenge tests are the conventional methods used for measuring bronchial obstruction and bronchial lability. Serial recordings at home make it possible to detect changes in lung function within a day and for weeks and months. In our two cross-sectional studies (4,13) lung function of preterm born schoolchildren have been recorded in the clinic and at home. Monitoring pulmonary function throughout successive days in preterm born schoolchildren, as in asthma diagnosis and treatment, it might provide information about bronchial lability that would probably be missed with a single measurement obtained in the clinic.

Most of the earlier studies extending to school age had shown that schoolchildren born preterm have bronchial obstruction and bronchial hyperreactivity regardless of CLD (2–4). There was also a reactive component of bronchial obstruction in many subjects, as indicated by the bronchodilator response. In a recent study, 57% of all children, not only those with a history of CLD but also preterm children without a history of CLD in the control group, showed a significant response to bronchodilation (20). In our 63 study children about half had bronchial lability as judged from abnormal diurnal PEF variation and/or significant changes in bronchodilator test. In

addition, continuous or frequently intermittent respiratory symptoms were common in agreement with earlier studies (2,4,13). The physiological hallmark of asthma is variable bronchial obstruction with respiratory symptoms. According to this, about half of the preterm born schoolchildren had a clinical picture of asthma. Is there an inflammatory process in lungs of the CLD children as in asthma? Very little is known about possible inflammatory basis of these lung function abnormalities in schoolchildren born preterm. We also do not know, if we should treat these children with anti-inflammatory medication.

In the present study, spirometric values in the clinic did not change neither during placebo, terbutaline nor during 4 months inhaled budesonide. This finding suggest that lung function abnormalities in schoolchildren born preterm might be due to mechanical factors, remodelling of the airways resulting from a neonatal lung disease and abnormal pattern of lung growth. Increased bronchial responsiveness observed in these children might be pronounced by a structural airway narrowing (2,3,8). Persistent airway obstruction in CLD might be related to submucosal fibrosis, hypertrophy or hyperplasia of bronchial smooth muscle, as suggested also by Chan and Silverman (12). They selected 15 schoolchildren born preterm with respiratory symptoms and bronchial hyperreactivity for treatment with inhaled beclomethasone dipropionate in a dose of 0·4 mg daily or placebo in a cross-over design for 4 weeks. No significant differences in respiratory symptoms, basic lung function or in the response to histamine were observed between the treatments.

The common finding of bronchial lability in preterm born schoolchildren is difficult to explain solely by structural changes in the lung. Supporting this theory preliminary data suggested that mechanical ventilation in healthy lungs led to bronchial hyper-reactivity long term after treatment (21). Another explanation of lung function abnormalities in children born preterm could be the different pattern of inflammation as in asthma. In addition, the long duration of disease, the dose and duration of treatment with GC may influence the therapeutic response in schoolchildren born preterm as in the case of asthma. In most asthma studies investigating the effects of inhaled GC on lung function, diurnal variation disappeared and obstruction parameters were normalized in the early stages of treatment (7,22). Later during prolonged treatment, an effect on bronchial hyper-responsiveness was usually detectable (23,24). In children with asthma, a significant dose-response effect of inhaled budesonide was found on basic lung function parameters and on bronchial responsiveness (25). In addition, in both adults and children the effect of inhaled GC on lung function seems to depend on the duration of asthma symptoms before the intervention of GCs (23,24,26).

Our aim was to investigate the effect of prolonged use of inhaled budesonide on bronchial obstruction and on bronchial lability in preterm born schoolchildren. In agreement with the previous report (12), budesonide treatment had no significant effect on basic lung function of preterm born schoolchildren. Our earlier results showed that lung function abnormalities in schoolchildren born preterm are related to an imbalance in the CD4 : CD8 ratio in the peripheral blood (27). These both findings differ from those reported in asthma. In our study before treatment with budesonide, the level of diurnal variation of PEF was abnormal in study children. During the treatment with budesonide, diurnal PEF variation were decreased significantly in keeping with asthma studies (6). This change correlated significantly with the diurnal variation in PEF recorded during the treatment period with placebo and with the bronchodilatory response during the treatment period with a β_2-agonist supporting our finding. However, it is well known that the effects of placebo are very significant among asthmatic children (28,29). In open studies, like in the present report the evaluation of improvement in home recordings and especially the improvement of symptom scores during treatment may be difficult. The present changes might depend on the pharmacological effect of GC although the placebo effect can not be ruled out. In previous asthma studies improvements have been observed during placebo treatment in spirometry performed in the clinic, e.g. in FEV_1 values and also in PEF values at home (28,29).

In conclusion, inhaled budesonide treatment for 4 months had no significant effect on basic lung function but may decrease bronchial lability in schoolchildren born preterm.

Acknowledgements

This study was supported by Astrazeneca R&D Lund, Sweden.

References

1. Ryan G, Latimer KM, Dolovich J, Hargreave FE. Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway calibre. *Thorax* 1982; **37:** 423–429.
2. Northway WH Jr, Moss RB, Carlisle KB, *et al*. Late pulmonary sequelae of bronchopulmonary dysplasia. *N Engl J Med* 1990; **323:** 1793–1799.
3. Chan KN, Elliman A, Bryan E, Silverman M. Clinical significance of airway responsiveness in children of low birthweight. *Pediatr Pulmonol* 1989; **7:** 251–258.
4. Pelkonen AS, Hakulinen AL, Turpeinen M. Bronchial lability and responsiveness in schoolchildren born very preterm. *Am J Respir Crit Care Med* 1997; **156:** 1178–1184.
5. Bousquet J, Chanez P, Lacoste JY, *et al*. Eosinophilic inflammation in asthma. *N Engl J Med* 1990; **323:** 1033–1039.
6. Haahtela T, Järvinen M, Kava T, *et al*. Comparison of aβ_2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991; **325:** 388–392.

7. Van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF. Effects of 22 months treatment with inhaled corticosteroid and/or β_2-agonist on lung function, airway responsiveness, and symptoms in children with asthma. *Am Rev Respir Dis* 1992; **146:** 547–554.
8. Marcgraft LR, Tomashefski JR, Bruce MC, Dahms BB. Morphometric analysis of the lung in BPD. *Am Rev Respir Dis* 1991; **143:** 391–400.
9. Pierce MR, Bancalari E. The role of inflammation in the pathogenesis of bronchopulmonary dysplasia. *Pediatr Pulmonol* 1995; **19:** 371–378.
10. Greenough A. Bronchopulmonary dysplasia: early diagnosis, prophylaxis, and treatment. *Arch Dis Child* 1990; **65:** 1082–1088.
11. Yuksel B, Greenough A. Randomised trial of inhaled steroids in preterm infants with respiratory symptoms at follow up. *Thorax* 1992; **47:** 910–913.
12. Chan KN, Silverman M. Increased airway responsiveness in children of low birth weight at school age: effect of topical corticosteroids. *Arch Dis Child* 1993; **63:** 120–124.
13. Pelkonen AS, Hakulinen AL, Hallman M, Turpeinen M. Effect of neonatal surfactant therapy on lung function at school age in children born very preterm. *Pediatr Pulmonol* 1998; **25:** 182–190.
14. Polgar G, Promadhat. Philadelphia: *Pulmonary Function Testing in Children: Technics and Standards*. W.B. Saunders, 1971.
15. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. Official statement of the American Thoracic Society. *Am Rev Respir Dis* 1991; **144:** 1202–1218.
16. Hetzel MR, Clark TJH. Comparison of normal and asthmatic circadian rhythms in peak expiratory flow rate. *Thorax* 1980; **35:** 732–738.
17. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: Prediction from oxygen requirement in the neonatal period. *Pediatrics* 1988; **82:** 527–532.
18. American Thoracic Society. Standardization of spirometry: 1994 update. *Am Rev Respir Dis* 1995; **152:** 1107–1136.
19. Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. *Arch Dis Child* 1990; **65:** 308–319.
20. Jacob SV, Coates AL, Lands LC, *et al*. Long-term pulmonary sequelae of severe bronchopulmonary dysplasia. *J Pediatr* 1998; **133:** 193–200.
21. Sulc J, Dlask Y, Hruda J, *et al*. Bronchial hyperreactivity in healthy lung long term after conventional mechanical ventilation (CMV). *Eur Respir J* 1999; **14**(Suppl. 30): A2086.
22. Kerrebijn KF, van Essen-Zandvliet EE, Neijens HJ. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. *J Allergy Clin Immunol* 1987; **79:** 653–659.
23. 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:** 700–705.
24. 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:** 373–381.
25. Pedersen S, Hansen OR. Budesonide treatment of moderate and severe asthma in children: a dose-response study. *J Allergy Clin Immunol* 1995; **95:** 29–33.
26. Zeiger RS, Dawson C, Weiss S. The Childhood Asthma Management Program (CAMP) Research Group. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP). *J Allergy Clin lmmunolgy* 1999; **103:** 376–387.
27. Pelkonen AS, Suomalainen K, Hallman M, Turpeinen M. Peripheral blood lymphocyte subpopulations in schoolchildren born very preterm. *Arch Dis Child Fetal Neonatal Ed* 1999; **81:** F188–F193.
28. Simons FER. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *N Engl J Med* 1997; **337:** 1659–1665.
29. Knorr B, Matz J, Bernstein J, *et al*. Montelukast for chronic asthma in 6- to 14-year old children: a randomized, double-blind trial. *JAMA* 1998; **279:** 1181–1186.