The effect of inhaled corticosteroids in young children with asthma
Children with mild asthma: do they benefit from inhaled corticosteroids?

7.1

HGM Arets
AWA Kamps
HJL Brackel
PGH Mulder
NA Vermue
CK van der Ent

On behalf of a multi-centre study group.

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Abstract

In children with mild asthma, who show hardly any abnormalities in pulmonary function, objective measurement of the effect of inhaled corticosteroids (ICS) is difficult. We evaluated the short term effect of fluticasone propionate (FP) in these children, using both subjective and objective parameters. 68 children (5-10 years old) were randomly assigned to either FP 250 µg or placebo twice daily as pMDI via spacer during 12 weeks. Symptom scores, use of rescue medication, wheezing, parent global evaluation and pulmonary function tests (PFTs) including forced expiratory volume in 1 second (FEV₁), peak expiratory flow (PEF) and bronchial responsiveness were evaluated.

FP treated versus placebo treated children showed significant changes in % symptom free days (OR FP versus placebo =1.9, p=0.03), use of β2-mimetics (OR=3.08, p<0.01), morning (+16L/min, p<0.01) and evening PEF (+19 L/min, p<0.01), FEV₁ %pred (+4.6%, p=0.04) and wheezing (OR=0.38, p=0.04). No significant improvements were found for parent global evaluation, absolute values of FEV₁, nor for PD20.

These findings show that ICS are effective in children with mild asthma. This effect can be assessed by both objective and subjective parameters. Even when pulmonary function is normal early start of ICS should be considered.
Introduction

Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory drugs in the treatment of asthma in both children and adults. They reduce symptoms and number of hospitalisations, improve pulmonary function and bronchial hyperresponsiveness (BHR)\(^1\-\(^3\) and are more effective than \(\beta_2\)-agonist alone\(^4\). International guidelines consider ICS to be indicated in moderate to severe asthma, but more recent studies promote their use as well in less symptomatic and also in younger patients, because this approach might prevent permanent impairment of pulmonary function and irreversible structural airway remodelling\(^5\-\(^7\). However, until now international consensus reports do not recommend the use of ICS in subjects who have only mild and infrequent symptoms and who have normal airway calibre most of the time\(^8\).

In patients with severe and moderate asthma PFT parameters abnormal and can be used as effect parameters to evaluate ICS treatment. However, these parameters are often in the normal range in patients with mild asthma. In children these normal ranges are wide and PFT parameters could be decreased in a relative sense and show improvement after proper treatment. Especially in young children there is a lack of proper effect parameters. Symptom scores and the use of short-acting \(\beta_2\)-agonists are the most frequently used parameters, but these are sensitive to placebo effects (4). There are only few studies on the short\(^9\-\(^10\) or long term effect\(^11\) of ICS in children with mild asthma. Especially placebo controlled studies are rare\(^12\-\(^14\). The aim of this study was to evaluate the effect of short term treatment with ICS on both subjective and objective disease parameters in 5-10 year old children with mild asthma.

Patients and Methods

Patients

5-10 years old children with a doctor’s diagnosis of asthma\(^15\) were recruited. Patients were excluded if prior to the study they had used systemic cor-
ticosteroids in the last 2 months, ICS >100 µg budesonide (BUD) or beclomethasone dipropionate (BDP) daily in the last 4 weeks, salbutamol >1600 µg daily during more than 30% of days of the last year prior, if they had been hospitalised for asthma in the last 2 weeks or if they had other respiratory disorders, systemic disease or anatomical abnormalities. Written informed consent was obtained from parents of all participating patients.

Power analysis was performed with percentage of days without asthma symptoms as calculated from the diary cards as the primary outcome variable. For the power calculation the change from baseline of this variable was used. The standard deviation of this change was set at 30 percent points. The clinically relevant difference of change from baseline between the placebo group and the FP group was set at 20 percent points. To detect this difference with 80% power, 35 patients per treatment group were needed, given a test size of 5% (two sided).

Study Design and methods

This was a multi-centre, double blind, placebo controlled, randomised, parallel group study. Patients were recruited from one paediatric pulmonology outpatient clinic of a university hospital, one asthma centre and seven general hospitals. The study was approved by all local ethic committees. Subjects were randomly assigned to use either two puffs of FP 125 µg or two puffs of placebo bd from a pMDI via a plastic spacer device (Volumatic, Glaxo Wellcome, Zeist, The Netherlands) during 12 weeks. During the whole study salbutamol 200 µg via spacer was allowed as rescue medication. Exacerbation of asthma, defined as an increase in asthma symptoms not controlled with salbutamol up to 8 times 2 puffs daily, was treated at the discretion of the investigator with prednisolone 1-2 mg/kg daily during 3 days.

At visit 1, at the beginning of a 2 week run in period, the study was explained, medical history, concurrent medication and demography were recorded, together with the presence or absence of wheezing and PFTs were performed. Parents and children were instructed to use the PEF meter at home, to fill out the daily record card (DRC) and to use rescue medication if necessary. After comprehensive instructions they were able to inhale medication properly via a spacer device and perform PEF measurements. Only patients using BDP or BUD < 100 µg daily, prior to the study, were instructed to continue this medication throughout the study in addition to
the study medication.
At visit 2 after 14±3 days only patients with symptoms on at least 50% of
days during the run in period were randomised, excluding patients who
used rescue medication > 8 puffs/day on >4 days during the run in period.
Further visits were scheduled 3, 11 and 12 weeks later (visit 3, 4 and 5
respectively). At all visits baseline PFTs were performed. At visit 2 and 4
bronchoprovocation tests were performed after baseline PFT. At every visit
adverse events, concurrent medication, asthma exacerbations and compli-
ance with the study were checked.

Assessments

Throughout the study the parents filled out a DRC for presence of asth-
matic symptoms, use of rescue medication, both morning and evening PEF,
adverse events and concurrent medication.
PEF measurements were performed using the Personal Best PEF meter
(Healthscan, Cedar Grove, NJ, USA). The highest value of a minimum of
three acceptable measurements was recorded.
Maximal expiratory flow volume (MEFV) measurements were performed
conform the ECCS recommendations16 using a pneumotachometer system
(Masterscreen Pneumo, Erich Jaeger, Würzburg, Germany). The best of
three technically good measurements was recorded. The following param-
ters were recorded: FEV₁ and FEV₁ as percentage of predicted
(FEV₁,%pred)17. No bronchodilator had been used less than 8 hours before
PFT.
Bronchial responsiveness was measured using methacholine bromide
provocation according to a standardised protocol18.
At all visits wheezing, defined as the presence of a prolonged audible expi-
ratory phase during auscultation and/or use of accessory respiratory mus-
cles, was judged on physical examination by the same paediatrician. During
the last visit the parents were asked to rate the effect of study medication on
symptoms on a scale from 1 (strongly improved) to 4 (worsened).

Data analysis

The symptoms and use of rescue medication were summarised daily as
symptom-free (yes/no) and rescue medication-free (yes/no). Within each
patient these daily scores constituted a series of repeated 0/1 data that were analysed using a generalised linear model for repeated measurements with model fitting based on Generalised Estimating Equations (GEE)\textsuperscript{19}. Because of the binary (0/1) outcome scores, the binomial distribution was assumed with the dependency of the probability parameter on the explanatory variables modelled through a logistic function. The day to day correlation structure of the outcome scores was assumed to be first order auto-regressive (“AR(1)”). In the logistic model the treatment effect was represented by an odds ratio (OR) (95\% confidence interval (CI)) of active relative to placebo treatment. Adjustment was made for the percentage of (%) symptom free (or rescue medication free) days during the baseline period as continuous covar and for time under treatment defined by four consecutive periods of three weeks as a within patient factor. The point of dividing the treatment period in four equal periods of 3 weeks was to find a general categorical treatment by time interaction without having to assume a priori a linear trend in this treatment by time interaction. The interaction between treatment and time was tested. If this interaction turned out to be significant with \( p < 0.10 \), then the treatment effect was presented per period. Else, one overall treatment effect (assumed to be constant in time) was presented.

Morning and evening PEF values, measured at home were used to calculate 3-week averages per patient for each of the four 3-week periods, for morning and evening separately. These averages constituted the four repeated measurements of the outcome variable, which were analysed using mixed model ANOVA. The independent variables in this analysis were treatment group (a 2-level between patient factor) and period (a 4-level within patients factor); the average PEF per patient over the baseline period was included in the model as a continuous covar. An AR(1) correlation structure between the repeated measures was assumed. The treatment by period interaction was tested and dealt with as described for DRC data.

Repeated PFTs were performed at baseline and three times during the 12 weeks treatment period. In a mixed model analysis of variance (ANOVA) the values of each PFT parameter during treatment were compared between the two treatment groups, adjusted for period (3 levels) and baseline measurement of the outcome variable at hand. Also the treatment by period interaction was tested and dealt with as described for DRC data. No structure was assumed for the (co)variance matrix of the residuals.

The dose of methacholine causing a 20\% decrease of FEV\(_1\) (PD\(20\)) was analysed as doubling doses after ln\(_2\)-transformation using non-parametric
tests, because values higher than 8 were coded as 8. The PD20 at visit 3 was compared between the two treatment groups, using the Mann-Whitney test. Within group changes from baseline were tested using the paired Wilcoxon test. PD20 was also analysed after dichotomization in hyperresponsive yes ($\ln_2 \text{PD20} < 8$) versus no. The measurement at visit 3 was compared between the two treatment groups using logistic regression analysis, with the baseline score as covariant. The treatment effect could then be expressed as an OR, adjusted for baseline.

There were four repeated physical examinations during the 12 weeks treatment period: visit 2 to 5. The absence or presence of wheezing was analysed using the same generalised linear model as described for DRC parameters. The between visit correlation structure of the responses was left unstructured. The treatment effect was represented by an OR (95% CI) of active versus placebo.

The parent global evaluation for both treatment arms was compared using the $\chi^2$ trend test.

Results

88 patients entered the run in period. 20 patients were withdrawn before randomisation, due to insufficient asthmatic symptoms (n=14), too frequent use of rescue medication (n=1), poor compliance (n=2), an asthma exacerbation (n=1), adverse effect of salbutamol (n=1) and withdrawal of parental informed consent on second thoughts (n=1) during the run in period. 68 patients were randomised and completed the study.

Patient baseline characteristics are shown in Table 1. There were no significant differences between withdrawn patients and included patients nor between patients in both treatment arms. During the run in period mean symptom scores and clinical scoring indices were low and mean pulmonary function parameters were within normal ranges.

Prior to the study 6 patients received maintenance treatment with budesonide (4) or beclomethasone < 100 $\mu$g daily (2). These ICS were continued by 1 (3%) and 5 (15%) of FP and placebo treated patients respectively. There were no significant differences between both treatment arms in number of asthma exacerbations, adverse events, concurrent medication, and compliance with the study.
The mean % symptom free days increased from 14% during the run in period to 25-49% in the placebo versus 42-66% in the FP treated group over the four consecutive periods (Figure 1). The estimated OR for FP versus placebo was 1.93 (95% CI 1.05-3.54; p=0.04). There was no suspicion that the OR changed in time (p=0.89).

The mean % rescue medication free days increased from 48% to 57-67% in the placebo versus 83-86% in the FP treated group over the four periods (Figure 2). The estimated OR of FP versus placebo was 3.08 (95% CI:1.49-6.36; p<0.01) without suspicion of changes of OR in time (p=0.76).
The mean difference in PEF between the FP and placebo treated group varied significantly over the periods (p<0.10) both for morning (p=0.01) and evening (p=0.09) values. Mean PEF was higher in the FP treated than in the placebo treated group (Figure 3). For morning PEF the mean differences between both groups was 16 L/min (p<0.01), varying from 11 to 24 L/min, for evening PEF this was 19 L/min (p<0.01), varying from 14 to 26 L/min. For all periods these effects were significant.

Figure 1. Changes in % symptom free days adjusted for baseline during 12 weeks of treatment with study medication.

Figure 2. Changes in % rescue medication free days adjusted for baseline during 12 weeks of treatment with study medication.
Pulmonary function tests

Compared to placebo treated children absolute values of FEV\(_1\) (FEV\(_1\)\(_{abs}\)) showed no significant change (+0.06 L, p=0.08), but there was a small but significant increase in FEV\(_1\)%pred in the FP treated children (+4.6%, p=0.04) (Figure 4).

Figure 3. Changes in morning and evening PEF values adjusted for baseline during 12 weeks of treatment with study medication.

Figure 4. Changes in FEV\(_1\)%pred (+ SE) during 12 weeks of treatment with study medication.
After 11 weeks of treatment ln$_2$ PD$_{20}$ was significantly higher in the FP treated group compared to placebo (7.14 versus 5.96, p=0.04) but there was no significant difference between the two groups in change of ln$_2$ PD$_{20}$ from baseline to week 11 (p=0.11).

**Wheezeing score.**

At the end of treatment 32 of 35 FP treated (91%) and 26 of 33 (79%) placebo treated patients showed normal wheezing scores. This difference was not statistically significant (p=0.11), but significant improvement in wheezing score were seen in the FP versus placebo group at visit 4 (p=0.008 respectively), not at other visits. The OR for FP versus placebo for wheezing was 0.38 (95% CI 0.15-0.96, p=0.04) for the whole study period.

**Parent global evaluation**

71% of parents of FP treated versus 52% of placebo treated children reported an improvement of symptoms. Increasing symptoms were experienced by 15% of parents of placebo versus 0% of FP treated children. This difference was not significant (p=0.062).

**Discussion**

In this study the effects of ICS in 5-10 year old children with mild asthma was compared to placebo, using both subjective and objective parameters. Treatment with FP significantly improved % symptom free days, % rescue medication free days, both morning and evening PEF values, FEV$_1$ %pred and wheezing score. No significant improvements were found for parent global evaluation, absolute values of FEV$_1$ and PD$_{20}$. In mildly symptomatic adult patients there is evidence of airway inflammation, improving after treatment with ICS$^{20}$. In adults improvement of night time symptoms, rescue medication use and morning PEF were recorded as well$^{21}$. 
Until now only few studies evaluated the effect of ICS in children with mild asthma\textsuperscript{9-13}. Most of these studies were performed in older children and using different effect parameters. Partially contradictory results were found. Effects were found on symptom scores. Some found improvement of PEF values\textsuperscript{9,10}, others did not or found only improvements in evening, not in morning PEF\textsuperscript{12,13}. Hockx et al. found a significant improvement of PEF values in older children after 8 weeks of treatment with both FP 400 µg and budesonide 400 µg, despite the fact that at the beginning of the study the lung function was near normal. However, the latter study was not placebo controlled and patients were not steroid naive\textsuperscript{10}. An improvement of bronchial responsiveness in children with mild asthma was described in two papers\textsuperscript{12,13}. In contrast to the present study, no significant effect on FEV\textsubscript{1} was found in most studies\textsuperscript{9-13}.

The present study provides further evidence for a positive effect of ICS in children with only mild asthma. The conjecture that asthma in the patients studied was mild is supported by the fact that at an age > 5 years most of the patients were not treated with anti-inflammatory agents, on average had mild symptoms, pulmonary function and bronchial responsiveness were rather normal and salbutamol use was low. Still improvements in both subjective and objective effect parameters were found. Most prominent were changes in symptom scores and use of rescue medication, but significant changes were found in PFT results as well. No significant changes in BHR were recorded.

The use of symptom scores and use of rescue medication is easy and can be used even in young children who cannot perform lung function tests. The participating patients were selected on basis of symptoms and the use of B2 agonists, so that bias because of regression to the mean may have caused part of the improvements in both the treatment and placebo groups. Although baseline FEV\textsubscript{1} %pred values were high (>100% pred) and reversibility was poor in contrast to other studies\textsuperscript{12,13} a small, though significant improvement in FEV\textsubscript{1} %pred was recorded after only 12 weeks of treatment. The only comparable study was performed by Jonasson et al\textsuperscript{12}.

In a later study, they also found a significant dose response effect on FEV\textsubscript{1} in a 24 months follow up study with ICS in 122 mildly asthmatic children\textsuperscript{14}. Recently, in a large, placebo controlled, long term study, the Childhood Asthma Management Program Research Group found significant improvements of pre bronchodilator FEV\textsubscript{1} %pred and FEV\textsubscript{1}/FVC (%) in mildly to moderately symptomatic 5-12 year old children after 4-6 years treatment with BUD. However, the improvement of FEV\textsubscript{1} %pred was
attributed to a smaller stature in the BUD treated group. Also airway responsiveness and symptom control improved\textsuperscript{14}.

The present study shows that in children with mild asthma pulmonary function can improve after only short term treatment. Improvements are only small but significant, especially when normal baseline parameters are considered. Normal lung function in children with symptoms of asthma does not rule out airway obstruction, improving after proper treatment.

As in earlier reports this study demonstrated that after the start of ICS treatment the improvement of PEF and symptoms often precede the improvement of other lung function parameters\textsuperscript{4}. In the present relatively short study it could be expected that these parameters would change most prominently. The improvement of PFT parameters gradually increased during the study (Fig 3 and 4). Earlier studies in children with normal lung function may have been too short or the ICS dose too low to observe these effects.

In the present study no changes in BHR were found in both treatment arms. The finding of BHR in this study population indicates that airway inflammation is present even in mild asthma. Although this finding supports treatment with ICS, no significant benefit of treatment on BHR could be established in the present study. As mentioned before this may be due to the relatively short treatment period and is in agreement with the existing concept that improvement of BHR is a relatively late response after institution of ICS and that improvement can continue over years. Van Essen Zandvliet et al showed that reduction in BHR increases gradually and only stabilises after 20 months of treatment with ICS\textsuperscript{4}. The value of long term treatment and the possible preventive effects on remodelling still need to be established.

Normally lower doses of ICS are used for treatment of children with moderate (or mild) asthma. However larger doses are sometimes used by paediatricians and paediatric pulmonologists especially in a step down therapy. With the present dose we did not expect serious adverse reactions in this relatively short study, while optimal treatment effects could be expected, compared to placebo.

In conclusion, in 5-10 year old children with mild asthma treatment with FP results in improvement of symptoms, salbutamol use, PEF and FEV\textsubscript{1},%pred. These findings suggest that normal lung function does not rule out airway obstruction and even in young patients with mild asthma early start of ICS maintenance might be considered. In view of these results and the emerging knowledge of long term airway remodelling in patients with chronic asthma treatment of mildly asthmatic patients with ICS is recommended.
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References


Inhaled corticosteroids and long acting $\beta_2$-agonists in preschool children with recurrent asthmatic symptoms: are they effective and can the effect be predicted?

7.2

HGM Arets
HJL Brackel
PGH Mulder
NA Vermue
CK van der Ent

On behalf of a multi-centre study group.

Submitted
Abstract

We evaluated the short term effects of inhaled corticosteroids in pre-school children with recurrent or chronic asthma-like symptoms, using both subjective and objective parameters. The predictive power of several baseline characteristics for this effect was studied too. 99 children (1-4 years old) were randomly assigned to receive either fluticasone propionate (FP) 250 µg or placebo twice daily during 6 weeks. Changes in symptom scores, use of rescue medication and pulmonary function test (PFT) parameters were assessed. Interrupter resistance (Rint), oscillation resistance and reactance (R5 and X5) and time and volume to peak tidal expiratory flow divided by total expiratory time (or volume) (tPTEF/tE and VPTEF/VE respectively) were measured. FP treated children showed significant improvements of Rint (p = 0.024), tPTEF/tE (p = 0.009) and VPTEF/VE (p = 0.003), compared to placebo. Almost significant changes were found for R5 (p = 0.13) and X5 (p = 0.07). No significant changes in % symptom free days or % rescue medication free days were found. PFT improvement could not be predicted from baseline characteristics, but children with decreased baseline pulmonary function showed the best improvement of subjective markers. We conclude that the effect of 6 weeks treatment with ICS in pre-school children with asthma-like symptoms is best demonstrated by PFT markers, not by subjective markers. Decreased pulmonary function appears to predispose to a beneficial effect.
Introduction

During early childhood as many as 40% of children experience recurrent asthmatic symptoms such as wheezing, cough or breathlessness. In more than half of these children symptoms disappear around the age of 6 years. These symptoms are thought to reflect congenitally narrow airways, which predispose to wheezing during viral infections. In other children symptoms persist and the latter group is eventually labelled as asthma. Pulmonary function testing (PFT) in asthmatic children shows bronchial hyperresponsiveness and bronchodilator responsiveness. Many of these patients have a positive family history for atopy and personal skin prick test positivity and increased levels of total and specific IgE.

The treatment of asthma with inhaled corticosteroids (ICS) has shown to be effective and safe in adults and older children. There is a tendency to treat young children with recurrent asthmatic symptoms in a similar way. However, in most of these patients the diagnosis of asthma is uncertain and the effect of ICS is less well established.

Few studies concentrate on the effect of ICS in pre-school children. Some small clinical trials showed variable effects of continuous, prophylactic treatment with ICS in pre-school children. Recently some bigger studies showed improvement in “subjective” effect parameters during treatment with ICS.

One of the major problems in evaluating the effect of ICS in pre school children is the lack of proper objective effect parameters. In most studies only subjective parameters as symptom scores, use of rescue medication and number of exacerbations were used. Objective effect parameters of ICS have been used scarcely in pre-school children.

Although there are certain “predictors” of asthma in pre school children, there is no readily available instrument to identify pre-school children with recurrent asthmatic symptoms who will benefit from ICS treatment.

The purpose of this study was to evaluate both the subjective and objective effects of ICS treatment in symptomatic 1-4 year old children with recurrent or chronic respiratory symptoms and to determine specific patient characteristics and risk factors that might predict these effects.
Methods

The primary efficacy endpoint of this study was the effect of treatment on percentage (%) of symptom free days and the secondary endpoints the effect on % rescue free days and change in lung function parameters.

This was a prospective double blind, placebo controlled, randomised, parallel group study, conducted at the outpatient departments of 8 centres in the Netherlands (one paediatric pulmonology department of a university hospital and seven general hospitals) conform the Declaration of Helsinki and Good Clinical Practice. The study was approved by all local ethic committees and written informed consent was obtained from parents of all participating patients.

For the power calculation the change from baseline of % symptom free days was used. The standard deviation of this change was set at 29 percent points (calculated from the study by Bisgaard et al.). The clinically relevant difference of change from baseline between the placebo group and the FP group was set at 15 percent points. To detect this difference with 75% power, 50 patients per treatment group were needed, given a test size of 5% (two-sided). Study drugs were randomly assigned numbers in blocks and arbitrarily distributed among sites and each patient was assigned a medication number on entry. Treatment assignments were not known to patient nor investigator during or after the trial.

Study population.

Children aged 12-48 months with a documented history of recurrent (≥ 5 periods of ≥ 10 days during the last year) or persistent (≥ 1 month) asthmatic symptoms (coughing, wheezing and/or breathlessness) were recruited for this study. Patients were excluded if they had used systemic corticosteroids or inhaled corticosteroids in the 2 months and 1 month before the run in period, respectively. Patients were excluded if they had used salbutamol ≥ 800 µg daily during more than 30% of days of the year prior to the study, had been hospitalised for their asthma in the 2 weeks prior to the study or had other respiratory disorders, systemic disease or anatomical abnormalities.
Study design.

At visit 0, at the beginning of a 2 week run in period, the study was explained and medical history, concurrent medication and demography were recorded. Parents were instructed to fill out a daily record card. Children proved to be able to inhale study medication and rescue medication using a plastic spacer (Babyhaler (BH), Glaxo Wellcome, Zeist, The Netherlands) with support of their parents. During the run in period all patients used placebo 2 puffs twice daily to minimise placebo effects due to changes of therapy routine. Throughout the study patients used inhaled salbutamol 200 µg, 1 puff delivered via the pMDI and spacer, each time as needed for relief of asthmatic symptoms. Parents were instructed to wash the spacer once monthly, or more often if necessary and let it dry on air.

At visit 1, after 14±3 days, all patients who had shown any respiratory symptoms (coughing, wheezing and/or dyspnoea) on at least 50% of days during the run in period were definitively included. Patients who experienced an exacerbation of symptoms that had to be treated with extra inhaled or systemic steroids during the run in period or patients who needed >4 puffs of salbutamol 200 µg during >7 days during the run in period were excluded.

During the following week patients received salmeterol xinaphoate 25 µg per puff twice daily. After 7 days the effect of salmeterol was checked via a telephone call and the parents were instructed to restart placebo 2 puffs twice daily during the following week (wash out period).

At visit 2, 14 (±3) days after visit 1, pulmonar function tests were performed and blood samples taken for allergy markers.

For the next 6 weeks subjects were randomly assigned to use either two puffs of fluticasone propionate (FP) 125 µg or placebo twice daily.

Three weeks after visit 2 a telephone call was made for control and reassurance of treatment.

At visit 3, 6 weeks (± 3 days) after visit 2, pulmonar function tests were performed, study medication was stopped and parents were instructed to use rescue medication on demand (wash out period).

At the final visit 4, 4 weeks(±3 days) later study medication was stopped and further treatment was started at the discretion of the investigator. The study was completed with follow-up telephone contact after 2 weeks.
Assessments

Patient history, daily record card check, parent global evaluation, subjective effect of rescue medication and physical examination were performed at all visits. Pulmonary function tests were performed before (visit 2) and after (visit 3) treatment.

Daily record cards
Throughout the study the parents filled out a daily record card, rating their child’s asthmatic symptoms (coughing, wheezing and/or shortness of breath) on a scale from 0 to 4 for both daytime (0 = no symptoms, 1 = once short symptoms, 2 = more than once symptoms, 3 = frequent symptoms and 4 = almost continuous symptoms) and night-time (with 0 = no symptoms, 1 = waking up through symptoms once, 2 = waking up through symptoms more frequently and 4 = hardly or not sleeping at all). Also the number of salbutamol puffs (rescue medication), adverse events and concurrent medication were recorded.

Clinical scoring index and physical examination
The clinical scoring index provided a description of the general impression of the paediatrician about the patient’s asthma related physical condition. Both pulmonary auscultation and inspection were rated, ranging from 0 (=normal breathing, no wheezing), 1 (= expiratory wheezing without use of accessory respiratory muscles), 2 (=in and expiratory wheezing without use of accessory respiratory muscles), 3 (=in and expiratory wheezing with mild use of accessory respiratory muscles) to 4 (=wheezing audible without stethoscope and marked use of accessory respiratory muscles).

Pulmonary function tests
In 7 centres tidal breathing analysis (TBA) was performed, in 3 centres interrupter resistance (Rint) measurement and in the academic centre also impedance measurements with the impulse oscillation system (IOS) were performed. When applicable the order of performance was TBA, followed by IOS and finally Rint.

TBA was performed by a fully computerised TBA system (Master Screen Paediatric, Erich Jaeger, Würzburg, Germany) with use of a mouthpiece\(^{15,16}\). We used \(t_{\text{PTEF}}/t_{\text{E}}\) (time to peak tidal expiratory flow divided by total expiratory time) and \(v_{\text{PTEF}}/v_{\text{E}}\) (expiratory volume to peak tidal...
expiratory flow divided by total expiratory volume) as measures of airway obstruction.

Airway resistance was measured by the interrupter technique (Rint), using a commercial device (MicroRint, MicroMedical Ltd, Rochester, UK) as described previously\textsuperscript{17}. Rint was calculated using the back extrapolation technique to $t = 0$ ms after shutter closure during 100ms\textsuperscript{18}.

Subjects were, if necessary, supported by parent or guardian. After explanation of the technique at least one practice attempts was made before really starting the procedure. They were instructed to breath quietly, sitting upright with slightly extended neck and the chin and cheeks supported by the investigator. A nose clip was used. After a period of quiet breathing in response to a trigger during expiration at the peak tidal expiratory flow a single shutter closed automatically within 10 ms and stayed closed for 100 ms. After 10 interruptions a minimal number of 5 correct tracings was obtained. From these the median value was recorded. The logarithm of this median value was used in the statistical analyses. Tracings were rejected in case of tachypnoea, usage of vocal cords, irregular or forced breathing or leakage.

The impedance of the total respiratory system was measured using a commercially available oscillometry system (Masterlab-IOS, Erich Jaeger, Germany), which has been described elsewhere\textsuperscript{19}. In this study mean R and X values were calculated over a measurement period of 60 sec in the frequency range 5 - 35 Hz. We used only values measured at 5 Hz (R5 and X5). During IOS measurement the children were sitting upright, their head resting against the back of the chair. They were instructed to breath quietly through the face mask. To reduce loss of energy in the upper airways their cheeks and chin were supported by the hands of the investigator who was standing behind the patient.

All lung function tests of a patient were performed on the same time of the day and, if possible in these young children, all PFTs were repeated 15 minutes after administration of salbutamol 800 µg through pMDI and spacer.

**Efficacy of salbutamol rescue medication**

After the run-in period the parents were asked to judge the efficacy of the salbutamol medication to treat the symptoms of their child, by using the following questionnaire: “After the inhalation of the salbutamol rescue medication the symptoms of my child have: 1 = strongly improved, 2 = improved, 3 = unchanged, 4 = increased, 5 = strongly increased. Salbutamol efficacy was also measured as bronchodilator response (BDR)
using all three PFTs: \( BDR = \frac{R_{\text{int pre}}}{R_{\text{int post}}} \), \( \frac{tPTEF}{tE_{\text{pre}}} - \frac{tPTEF}{tE_{\text{post}}} \)
and \( R_{5\text{pre}} - R_{5\text{post}} \).

**Efficacy of salmeterol**
During the run-in period and the salmeterol test period the parents recorded the symptoms and salbutamol use in the daily record card. The data were averaged over the week before and the week during the salmeterol test. The differences of the scores were investigated for their modifying strength on the efficacy of fluticasone versus placebo. The efficacy of salmeterol was also checked by parent global evaluation, asking the parents to judge the clinical course at the end of the salmeterol test week, using the same questionnaire as stated under Parent Global Evaluation.

**Predictors of effect**
Data for the following determinants were analysed for possible modification of ICS effect:

1. Medical history: age category (1 to 2, 2 to 3, 3 to 4 yrs), sex (male/female), height (cms), number of atopic subjects in first degree relatives (0, 1, > 2), smoking history of the parents (0, 1 or 2 parents), number of exacerbations in the past 12 months, living conditions (pets, floor covers, humidity) (yes/no), reported other allergic manifestations (yes/no), eczema (yes/no) frequent rhinitis (yes/no) and frequency of symptoms (frequent = \( \geq 75\% \) of days, infrequent = \(< 75\% \) of days during run in).
2. Wheezing at physical examination at one or more visits (yes/no)
3. Laboratory tests: total IgE and RAST (positive versus negative).
4. Pulmonary function parameters (\( \frac{tPTEF}{tE} \) above median versus under median, \( R_{\text{int}} \) above versus under median) and BDR at visit 2. We did use neither \( R_{5} \) nor \( X_{5} \) under versus above median because of the small numbers of children performing IOS.
5. Subjective evaluation of the effect of salbutamol rescue medication at visit 1.
6. Parent global evaluation: perceived efficacy of rescue medication and of 1 week treatment with salmeterol 50 \( \mu \)g bd via pMDI with Babyhaler.
7. Change of symptoms (described in the daily record card) during treatment with salmeterol, compared to the run in period.
Data analysis

The symptoms and use of rescue medication were summarised daily as symptom-free (yes/no) and rescue medication-free (yes/no). Within each patient these daily scores constituted a series of repeated 0/1 data that were analysed using a generalised linear model for repeated measurements with model fitting based on Generalised Estimating Equations (GEE)\(^2\). Because of the binary (0/1) outcome scores, the binomial distribution was assumed with the dependency of the probability parameter on the explanatory variables modelled through a logistic function. The day to day correlation structure of the outcome scores was assumed to be first order auto-regressive (“AR(1)”). In the logistic model the treatment effect was represented by an odds ratio (OR) (95% confidence interval (CI)) of active relative to placebo treatment.

The percentage of symptom-free and rescue free days were calculated in each child, during the last week before randomisation and during the 6-weeks treatment period. Adjustment was made for the % symptom free (or rescue medication free) days during the baseline period as continuous covariate and for time under treatment defined by three consecutive periods of two weeks as a within patient factor; also the interaction between treatment and time was tested. If this interaction turned out to be significant with \( p < 0.10 \), then the treatment effect was presented per period. Else, one overall treatment effect (assumed to be constant in time) was presented.

The change in the percentages of symptom free and rescue free days and nights during the salmeterol test week were tested using the paired Wilcoxon test.

PFTs were performed before (visit 2) and after the 6 weeks treatment period (visit 3). In an analysis of co-variance (ANCOVA) the values of each PFT parameter after treatment was compared between the two treatment groups, adjusted for baseline measurement of the outcome variable at hand. Partial correlation analysis, adjusted for treatment group, was used to correlate changes in symptoms and salbutamol use with changes in PFT parameters.

Initial patient characteristics were investigated for their possible modifying role of therapy effect on the % symptom-free and rescue free days and on the PFT variables. This was done by including and testing the interaction
between the initial patient characteristics and treatment in the above-men-
tioned logistic regression and ANCOVA models. As there were many of
these patient characteristics available and the study was not specifically
powered to detect their interactions with treatment, these analyses were of
a more exploratory nature. In order not to rule out a priori the detection of
a potential effect modifying role, a p-value < 0.10 was considered signifi-
cant.

Results

131 subjects started the run in period, 32 subjects were excluded after this
run in period because of too little symptoms (n=29), parental unwillingness
to proceed the study (2), and salbutamol use >4 puffs per day during 10 of
14 days during run in (1). Patient characteristics are presented in Table 1.
There is a preponderance of males, but this inequality is equally distribut-
ed in both treatment arms.

The effect of ICS

Improvements of subjective effect parameters were seen in both treatment
arms. In the total group of treated patients there were no significant differ-
ences between placebo and FP treated children for percentage of symptom
free days or nights and percentage of rescue free days or night (Figure 1).
Also changes in symptom scores did not show significant differences
between FP and placebo (Figure 2).
TBA measurements were performed in all 99 children and were possible in
43 of placebo and 42 of FP treated patients at visit 2. At visit 3 these figures
were 43 and 38 respectively. In 86 children Rint measurements were per-
formed. These were possible in 25 of placebo, 20 of FP at visit 2 and 24 and
25 respectively at visit 3. IOS was performed in 40 children and possible in
12 and 8, and 11 and 7 children respectively.
TBA parameters improved significantly in the FP treated children, com-
pared to placebo treated children (tPTEF/tE +4.61% versus -1.0%, p =
0.009 and VPTEF/VE +3.61% versus -0.17%, p = 0.003) (Figure 3).
Significant improvement was also seen for Rint (-0.18 kPa/L/s versus
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>fluticasone propionate</th>
<th>placebo</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sex M/F</td>
<td>36/12</td>
<td>38/13</td>
<td>98/33</td>
</tr>
<tr>
<td>height cm</td>
<td>91.4 (8.9)</td>
<td>90.6 (10.2)</td>
<td>90.7 (9.1)</td>
</tr>
<tr>
<td>weight kg</td>
<td>14.1 (2.2)</td>
<td>13.6 (2.9)</td>
<td>13.8 (2.6)</td>
</tr>
<tr>
<td>age yrs</td>
<td>1.9 (0.9)</td>
<td>1.8 (0.9)</td>
<td>1.9 (0.9)</td>
</tr>
<tr>
<td>birthweight kg</td>
<td>3.3 (0.7)</td>
<td>3.3 (0.8)</td>
<td>3.3 (0.7)</td>
</tr>
<tr>
<td>no of exacerbations</td>
<td>7.8 (4.1)</td>
<td>6.6 (4.7)</td>
<td>6.6 (4.4)</td>
</tr>
<tr>
<td>during last year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATOPY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no of atopic 1st line relatives</td>
<td>0</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>&gt;2</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>IgE U/ml</td>
<td>71.8 (140.0)</td>
<td>72.5 (109.8)</td>
<td>70.6 (124.1)</td>
</tr>
<tr>
<td>positive RAST Y/N</td>
<td>17/30</td>
<td></td>
<td>17/33</td>
</tr>
<tr>
<td>not measured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>history of allergic disease Y/N</td>
<td>5/43</td>
<td>11/40</td>
<td>18/113</td>
</tr>
<tr>
<td>allergic rhinitis Y/N</td>
<td>15/33</td>
<td>19/32</td>
<td>48/83</td>
</tr>
<tr>
<td>eczema Y/N</td>
<td>11/37</td>
<td>10/41</td>
<td>26/105</td>
</tr>
<tr>
<td>ENVIRONMENTAL EXPOSURE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>smoking mother Y/N</td>
<td>8/40</td>
<td>8/43</td>
<td>24/106</td>
</tr>
<tr>
<td>smoking father Y/N</td>
<td>18/30</td>
<td>14/37</td>
<td>42/88</td>
</tr>
<tr>
<td>smoking pregnancy Y/N</td>
<td>5/43</td>
<td>7/44</td>
<td>18/112</td>
</tr>
<tr>
<td>floor covers living room Y/N</td>
<td>3/44</td>
<td>8/43</td>
<td>25/106</td>
</tr>
<tr>
<td>floor covers sleeping room Y/N</td>
<td>14/34</td>
<td>15/36</td>
<td>37/94</td>
</tr>
<tr>
<td>humidity high living room Y/N</td>
<td>9/39</td>
<td>7/44</td>
<td>19/112</td>
</tr>
<tr>
<td>humidity high sleeping room Y/N</td>
<td>9/39</td>
<td>8/43</td>
<td>20/111</td>
</tr>
<tr>
<td>PETS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>birds Y/N</td>
<td>4/44</td>
<td>1/50</td>
<td>8/123</td>
</tr>
<tr>
<td>dogs Y/N</td>
<td>10/38</td>
<td>10/41</td>
<td>25/106</td>
</tr>
<tr>
<td>cat Y/N</td>
<td>12/36</td>
<td>12/39</td>
<td>29/102</td>
</tr>
<tr>
<td>other Y/N</td>
<td>7/41</td>
<td>5/46</td>
<td>15/116</td>
</tr>
<tr>
<td>no pets Y/N</td>
<td>24/24</td>
<td>31/20</td>
<td>75/56</td>
</tr>
<tr>
<td>PHYSICAL EXAMINATION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wheezing at physical examination Y/N</td>
<td>8/40</td>
<td>10/41</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as means (SD) unless stated otherwise.
+0.16 kPa/L/s, p = 0.024) (Figure 4). Although there was improvement of R$_5$ and X$_5$ this did not reach significance in this small group (p = 0.13 and 0.07 respectively).

Efficacy of salmeterol

During one week salmeterol treatment there were improvements in % symptom free days (p = 0.004), % symptom free night (p = 0.06), rescue
free days (p <0.001) and rescue free nights (p =0.03), compared to the week preceding salmeterol treatment.

Predictors of effect of ICS

The numbers of subjects with a positive family history, positive history of allergy, eczema, allergic rhinitis, IgE levels, RAST positivity, and wheezing
at physical examination are presented in Table 1. Neither these markers nor bronchodilator response were significantly related to ICS effect. Also frequency of symptoms during run in period and number of exacerbations during the preceding 12 months were not related to ICS effect. Improvements in % symptom free days during salmeterol therapy were unrelated to improvements of both subjective and objective effect parameters during ICS treatment. Baseline pulmonary function was not significantly related to pulmonary function improvement, but significant improvements of some subjective

Figure 2. Changes in mean symptom scores, before, during and after treatment with study medication (SD).
disease markers were seen in children with decreased airway patency (high Rint and low \( \frac{t_{PTEF}}{t_{E}} \)), with OR varying from 2.12 to 4.01 for Rint and 1.17 to 7.39 for \( \frac{t_{PTEF}}{t_{E}} \) (Table 2).

There were significant correlations between some markers of indoor environment and ICS effect on some subjective markers. Especially patients living in houses with carpets and biparental smoking showed significant improvements in symptoms and use of rescue medication during ICS treatment (Table 3). However, the presence of pets was correlated with less improvement in % symptom free days and nights.

Figure 3. Changes in \( \frac{t_{PTEF}}{t_{E}} \) and \( \frac{VPTEF}{VE} \) during treatment with study medication (SD).
### Table 2

<table>
<thead>
<tr>
<th></th>
<th>% symptom free days</th>
<th>% symptom free nights</th>
<th>% rescue free days</th>
<th>% rescue free nights</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>p</td>
<td>OR</td>
<td>p</td>
</tr>
<tr>
<td>FP vs placebo effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rint &gt; mean (^a) (n=20)</td>
<td>1.36</td>
<td>0.61</td>
<td><strong>3.01</strong></td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Rint &lt; mean (^b) (n=21)</td>
<td>0.64</td>
<td>0.39</td>
<td>1.11</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>difference</strong></td>
<td>2.12</td>
<td>0.36</td>
<td>2.72</td>
<td>0.18</td>
</tr>
<tr>
<td>FP vs placebo effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tPTEF/tE &lt; mean (^b) (n=43)</td>
<td>1.09</td>
<td>0.83</td>
<td><strong>1.92</strong></td>
<td><strong>0.05</strong></td>
</tr>
<tr>
<td>tPTEF/tE &gt; mean (^b) (n= 42)</td>
<td>0.98</td>
<td>0.94</td>
<td>1.12</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>difference</strong></td>
<td>1.17</td>
<td>0.84</td>
<td>1.65</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*Fluticasone versus placebo effect (measured by daily record card parameters) for groups with better\(^a\) versus worse\(^b\) pulmonary function. The FP versus placebo effect is expressed as Odds ratio (OR) for both groups. Then the OR is given for the “worse” versus “better” group. Significant OR is presented in bold.*
### Table 3

<table>
<thead>
<tr>
<th></th>
<th>% symptom free days</th>
<th>% symptom free nights</th>
<th>% rescue free days</th>
<th>% rescue free nights</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>p</td>
<td>OR</td>
<td>p</td>
</tr>
<tr>
<td><strong>carpets living room (n=11)</strong></td>
<td>1.3</td>
<td>0.87</td>
<td>7.97</td>
<td>0.0008</td>
</tr>
<tr>
<td><strong>hard floor living room (n=87)</strong></td>
<td>1.19</td>
<td>0.52</td>
<td>1.3</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>difference</strong></td>
<td>1.09</td>
<td>0.96</td>
<td><strong>6.13</strong></td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td><strong>carpets sleeping room (n=29)</strong></td>
<td>2.2</td>
<td>0.14</td>
<td>3.75</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td><strong>hard floor living room (n=69)</strong></td>
<td>0.85</td>
<td>0.55</td>
<td>1.05</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>difference</strong></td>
<td>2.59</td>
<td>0.12</td>
<td><strong>3.57</strong></td>
<td><strong>0.018</strong></td>
</tr>
<tr>
<td><strong>current smoking 2 parents (n=11)</strong></td>
<td>1.69</td>
<td>0.13</td>
<td><strong>1.92</strong></td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td><strong>current smoking 1 parent (n=26)</strong></td>
<td>0.94</td>
<td>0.89</td>
<td>1.98</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>current smoking no (n=62)</strong></td>
<td><strong>0.15</strong></td>
<td><strong>0.0001</strong></td>
<td><strong>0.4</strong></td>
<td><strong>0.09</strong></td>
</tr>
<tr>
<td><strong>difference between 2 vs no smoking parents</strong></td>
<td>11.3</td>
<td><strong>0.0001</strong></td>
<td>4.8</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td><strong>pets yes (n=44)</strong></td>
<td>0.68</td>
<td>0.31</td>
<td>0.82</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>pets no (n=55)</strong></td>
<td>1.71</td>
<td>0.11</td>
<td><strong>2.6</strong></td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td><strong>difference</strong></td>
<td><strong>0.40</strong></td>
<td><strong>0.07</strong></td>
<td><strong>0.32</strong></td>
<td><strong>0.02</strong></td>
</tr>
</tbody>
</table>

*Fluticasone versus placebo effect (measured by daily record card parameters) for groups with several indoor environment characteristics (as reported by parents). The FP versus placebo effect is expressed as Odds ratio (OR) for specific groups. Then the OR is given for first versus last mentioned group. Significant OR are presented in bold.*
In the present study, evaluating the effects of ICS in pre-school children with recurrent or chronic asthmatic symptoms we found beneficial effects on pulmonary function parameters, not on subjective parameters. There were no single predictors for pulmonary function improvement but subjective improvement was seen in patients with signs of airway obstruction on pulmonary function measurement. Especially generally recognised indicators of asthma such as bronchodilator response, atopy, positive family history and wheezing were found to be unrelated to ICS effectiveness in this study.

Both symptom scores and use of rescue medication are sensitive to placebo effect. In younger children this effect is expected to exist too, also when symptoms are interpreted and presented by parents or caregivers. Therefore, a placebo controlled study design is necessary. We treated all patients during the run in period with placebo via Babyhaler to minimise placebo effects during the study period and to be sure that good inhalation technique was practised.

Among others, the Dutch consensus on treatment of young children with asthmatic symptoms suggest to test patients on their response to a short
acting bronchodilator as an indicator for asthma before starting ICS therapy. However subjective evaluation of the effect of a short acting bronchodilator is difficult, both for parents and doctors. That’s why we evaluated also the response to a long acting bronchodilator as a test for bronchodilator response. However no correlation with ICS efficacy was found. The dose of ICS used in the present study was higher than the recommended dose in daily practice to reach an all or not effect. The short period of intervention decreased the chance for important side effects. However, this relatively short period might also be a reason for not fully established effects on individual effect parameters.

Bisgaard et al have shown that in pre-school children with asthmatic symptoms treatment with fluticasone propionate 100 and 200 µg daily via Babyhaler is effective and safe. They found significant effects on symptoms, use of rescue medication and exacerbation frequency. There was no dose dependent effect11. In a retrospective analysis they pointed to the cost-effectiveness of FP treatment in these children24. In children with recurrent viral wheeze some authors found a beneficial effect of inhaled corticosteroids but in 1995 Wilson could not proof any prophylactic effect of ICS in this patient group10.

The present study is a support to the use of objective effect parameters and especially pulmonary function measurements to evaluate the effect of ICS and other interventions. There are no earlier studies on the effect of ICS on TBA parameters in younger children nor on the usability of TBA parameters or Rint to predict the ICS effect. The only study that also used objective disease markers to evaluate the ICS effect in pre-school children was performed by Nielsen and Bisgaard13. They found a significant improvement of Rint, R₅ and X₅ after 8 weeks of 800 µg budesonide daily in 2-5 year old moderately asthmatic children, most of whom had been on ICS treatment before the run in period13. Although in this study the symptom severity was probably greater compared to the present study, results were rather comparable and they also found effects on pulmonary function tests to be more significant than effects on subjective parameters.

It seems reasonable that many pre-school children with recurrent asthmatic symptoms are incorrectly treated when given inhaled steroids, because the diagnosis can not adequately be made. Especially children who present with recurrent or persistent cough, but without a history of wheeze are rarely asthmatic25. This was recently confirmed in a study by McKenzie et al. who showed that recurrent coughers without wheeze are rarely atopic although they may show bronchodilator response26.
Roorda et al. found that especially children with chronic persistent symptoms and a positive family history for asthma are the ones responding best to treatment with fluticasone propionate. Their findings were not confirmed in the present study. Few primary patient factors could predict a positive ICS effect. The present study is the first that uses pulmonary function parameters to predict ICS efficacy. Only a subgroup with high Rint or low \( \text{IPTEF}/\text{tE} \) showed significant correlation with a positive FP versus placebo effect on subjective disease markers. Although this finding has to be confirmed in future studies, it shows that pulmonary function tests using recently developed pulmonary function techniques might offer a possibility to determine a subgroup of pre school children with asthmatic symptoms with optimal benefits from ICS treatment.

A remarkable finding was the beneficial effect in a subgroup of children growing up in an unfavourable indoor environment (smoking, carpets). This finding is difficult to interpret but might indicate that children living under non-optimal environmental conditions have more pronounced inflammation and therefore may be expected to show more beneficial effects from ICS treatment. On the contrary, it could also mean that after optimisation of the home situation an additive effect of ICS can not be expected.

In general, this study shows that the effect of ICS in pre-school children with asthmatic symptoms can not be derived from experiences in asthmatic school children and adults. The international consensus to treat pre-school children in a similar way as adults, i.e. based on the presence of atopy, wheezing and a positive family history and effect of bronchodilators is not supported by this study. Different “asthma phenotypes” with probably different inflammatory patterns might show different reactions to ICS therapy. Predictors of asthma appear to be different from predictors of ICS effect (e.g. worse pulmonary function, indoor environment) in young children. It remains unclear if the improvement in pulmonary function in young children is related to the presence of “real” asthma in this group. It could also be that different asthma “phenotypes” show similar responses to ICS treatment.

On the other hand, the present study indicates that objective parameters such as pulmonary function results are more sensitive to ICS effects and might be more useful parameters to use in population studies. Recently performed studies in adults show that pulmonary function tests and especially bronchial hyperresponsiveness can be an additional guide of long term asthma treatment. These PFT results might also support the concept
to treat mild and uncertain asthma, as suggested in recent studies, indicating that early start of ICS treatment for asthma can prevent the development of irreversible, structural airway remodelling\cite{31,32}. Further studies should evaluate efficacy in different subgroups that only differ in asthma “phenotype”.

In conclusion, 6-weeks treatment with ICS in pre-school children with recurrent asthmatic symptoms was effective in improvement in objective effect parameters, but not of subjective markers. ICS effect on pulmonary function could not be predicted from baseline pulmonary function testing, but baseline pulmonary function predicted a beneficial subjective effect of ICS. This study suggests that pulmonary function testing can and probably should be implemented in efficacy studies in this age group.

The multi-centre study group consisted of the following physicians: Dr JAAM van Diemen-Steenvoorde and Dr FB Plötz (St Antonius Hospital Nieuwegein), EHG van Leer and FGA Versteegh (Groene Hart Hospital Gouda), Dr PLP Brand and A Kamps (Isala Klinieken Zwolle), Dr GPJM Gerrits (Canisius Wilhelmina Hospital Nijmegen), NJ van de Berg and KL Tjia (Flevo Hospital Almere), WA Verwijs (Hofpoort Hospital Woerden) and Dr AAPH Vaessen-Verberne (De Baronie Hospital Breda), JH van der Laag and Dr EEM van Essen-Zandvliet (University Medical Centre Utrecht).
References

THE EFFECT OF ICS
