

Budesonide: safety and efficacy aspects of its long-term use in children

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Fifty-two asthmatic children aged 4 to 13 years (mean 9.6) were enrolled in this open 12-month study of budesonide, 200 mcg bid, administered by tube-spacer inhaler (INHALET®, ASTRA DRACO). The aim of the study was to assess long-term safety, as well as efficacy, of budesonide in children whose asthma was not adequately controlled by their current therapy. Children attended the clinic every three months for assessment of lung function and height. In addition, an adrenal function test and routine clinical chemistry and haematology were performed. Parents completed diary cards once each week, recording the child's PEF, asthma symptoms, β_2 -agonist consumption and other medication (no prophylactic drugs or other inhaled steroids were allowed and oral steroids were used for emergency treatment only). There were significant increases in all clinic lung function tests (baseline to last visit) and in diary card PEF (first 3 months vs last 3 months). These were accompanied by decreases in asthma symptoms and use of β_2 -agonists or other medication. There was no indication that growth was affected by study treatment and basal adrenal function (basal cortisol) did not change significantly throughout the study. The adrenal response to Synacthen had actually increased significantly by the end of the study. No serious adverse events were associated with budesonide treatment. In conclusion, regular budesonide therapy was associated with a significant improvement in lung function and symptoms over one year. Budesonide was well-tolerated by the children and appeared to have no adverse influence on either growth or adrenal function.

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It is now widely believed that early introduction of inhaled corticosteroids in the management of asthma may slow down the inflammatory deterioration of the airways and improve the long-term prognosis of the disease (1). These drugs are highly effective inhibitors of the inflammatory process and effectively reduce bronchial hyperresponsiveness (2, 3), unlike bronchodilators which have little beneficial effect on this component of asthma and may even exacerbate it (4). Although inhaled corticosteroids are now commonly used to control asthma in children and do so very effectively in most cases, there is, inevitably, concern about the long-term effects of these drugs in children, particularly with regard to the hypothalamo-pituitary-adrenal axis and growth. The ultimate aim of any therapy must be to achieve a good therapeutic ratio, i.e., high efficacy with minimal side-effects.

The inhaled corticosteroid, budesonide, demonstrates a higher topical: systemic potency ratio than beclomethasone dipropionate (5) and should, therefore, provide safer control of childhood asthma in the long-term. This study was set up to evaluate the safety and efficacy of budesonide over a 12-month period in children whose asthma was not sufficiently controlled by their current anti-asthma therapy.

Methods

Patients

Children attending the outpatient clinic with asthma which was not controlled by their current therapy (including ketotifen, sodium cromoglycate, theophyllines, high dose β_2 -stimulants and/or inhaled beclomethasone dipropionate) were re-

cruited for study with the proviso that they were competent in the use of a tube-spacer inhaler. Poor asthma control was defined as persistent symptoms and abnormal lung function requiring regular use of bronchodilators. The physician was requested to select families who were likely to cooperate and all parents were required to give informed consent to the study of their children. Children with significant bronchopulmonary disease other than asthma or with significant disease of any other system were excluded from study. In addition, children with an acute exacerbation requiring intensive treatment, or with other disease requiring treatment which might interfere with evaluation of the study drug, were not to be included.

Study design

The study was performed as an open assessment over one year of budesonide 200 mcg (4×50 mcg puffs) bid, inhaled from a tube-spacer inhaler (INHALET®, ASTRA DRACO). During the entire study period, children were allowed to use bronchodilators as required for symptomatic relief, but prophylactic drugs such as inhaled beclomethasone dipropionate, disodium cromoglycate and ketotifen were not permitted. Oral steroids were to be used only in the case of an acute asthma attack, during which time their use was fully documented.

Clinical and laboratory assessments

Children attended the clinic on five occasions: at entry and then at 3-monthly intervals (consecutive 3 monthly intervals being referred to as Periods 1–4) for one year. At the start of the study (Visit 1), a complete medical history was taken for each child and a physical examination was performed. The child was asked to demonstrate use of the study inhaler several times (using placebo) until the doctor was satisfied that the correct inhaler technique had been adopted. The parent was then asked to supervise inhalation at home and technique was checked at all follow-up visits. Only children with adequate inhaler technique were included in the study. At all visits, height, weight, lung function tests (FEV₁, FVC and PEF) and asthma symptoms (none, mild, moderate or severe) were recorded. If there were signs of clinical candidiasis, a throat swab was taken for culture.

Parents were requested to bring children to the clinic first thing in the morning (8 am) for each visit, having fasted them for 12 h. A blood sample was taken for routine laboratory assessments (electrolytes, glucose, creatinine, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), haematology (haemoglobin, total and

differential WBC count, eosinophils) and basal plasma cortisol. Children were then given an intramuscular injection of tetracosactrin (Synacthen Depot®, Ciba) to stimulate their adrenals and further blood samples were collected after 4 and 5 h to measure plasma cortisol and assess the adrenal response. The depot preparation of tetracosactrin is thought to provide a more sensitive test of adrenal function (6).

A compliance check on medication taken between clinic visits was made by weighing drug canisters returned at each visit and calculating actual versus predicted drug use for that study period.

Any adverse events mentioned spontaneously by either child or parent during the clinic visit were recorded in the case record book.

Families were supplied with mini-Wright peak flow meters and diary cards in which they were asked to record the following variables on four consecutive days as a pre-treatment run-in (baseline) and subsequently once each week: morning PEF (after rising but before using steroids or bronchodilators) and evening PEF, taking the best of three measurements on each occasion for entry into the diary card; subjective assessment of cough, wheeze and breathlessness (scored as 0 = none, 1 = mild, 2 = moderate or 3 = severe) and any other symptoms experienced during the night (recorded on the following morning) or during the day (recorded in the evening).

Statistical considerations

The aim was to recruit 30–50 children attending the outpatient clinic for this open, non-comparative study. Data were analysed using an “all patients treated” (APT) approach, with the last value obtained during active treatment being extended throughout the analysis (i.e., baseline values were *not* extended). Primary variables were also analysed using a per protocol approach.

The primary measure of efficacy amongst clinic variables was the change in FEV₁ from baseline to last visit. Morning and evening PEF measurements were considered to be the primary diary variables, with mean baseline PEF being compared with mean PEF during the last period of the study. Changes in lung function variables were assessed using paired t-tests, and analyses of trends in lung function with time were performed using the Wilcoxon Sign rank test. Changes in symptoms or in laboratory variables from first to last visit were also analysed using the Wilcoxon test, the significance level for all statistical tests being taken as 5%.

Actual growth throughout the study in relation to that predicted was assessed in individual chil-

Table 1. Demographic details and asthma history at entry

Total number of children enrolled	52
Number of boys/girls	37/15
Mean age (range)	9.6 years (4–13)
Mean weight $\pm$ SD	30.2 $\pm$ 7.3 kg
Mean height $\pm$ SD	132 $\pm$ 11 cm
Mean duration of asthma (range)	6.6 years (1–10)
Mean number of acute exacerbations in last year (range)	7.4 (2–18)
Mean lung function at entry (% predicted) $\pm$ SD	
FEV ₁	64.4 $\pm$ 17.4
FVC	76.3 $\pm$ 17.8
PEF	88.3 $\pm$ 22.4

dren using age-height relationships derived from British school children (7). Height scores were calculated for each child as follows:

$$\text{Height score} = \frac{\text{Observed-predicted height}}{\text{SD of predicted height}}$$

This score is thought to give an accurate indication of deviation from the normal growth curve. Scores obtained during active treatment (i.e. Visits 2, 3, 4 and 5) were compared with the baseline score (Visit 1) using a two-way analysis of variance. Page's test was also applied to the data to look for any significant trend in height score over time.

Results

Patients

Fifty-two children aged 4 to 13 years (mean 9.6 years) with a mean asthma duration of 6.6 years were enrolled in the study. There were 37 boys and 15 girls, all of whom were considered to have adequate inhaler technique. The youngest child was almost 5 years old and able to use the pressurised inhaler correctly. Thirty-four of the children had been taking inhaled beclomethasone dipropionate,

22 inhaled sodium cromoglycate and 26 oral ketotifen as prophylactic therapy. Forty-five of the children took more than one of these drugs. These therapies were discontinued in all patients when the study commenced. Demographic details and disease characteristics (including lung function at entry) for all children are included in Table 1. Data from all 52 children were considered for the APT analyses and data from 49 children for the PP analyses.

Five patients did not complete the study. Three children withdrew in Period 1 – one was involved in an accident which resulted in hospitalisation for bone fractures (see adverse event section), one had uncontrolled asthma and requested withdrawal from the study and one dropped out from the study after run-in. Data from these three children were excluded from all PP analyses and from the APT analyses of clinic data, as only pre-treatment values were available. Diary data were included in the APT analyses up to the point of withdrawal. A further two children withdrew during Period 2 of the study, one who complained of headache and requested withdrawal and one who reported tachycardia and requested withdrawal. Data from these patients were included in all APT analyses.

Lung function and symptoms

Mean values for FEV₁, FVC, PEF and symptoms recorded at each clinic visit are summarised in Table 2. Mean change in FEV₁ from baseline to last visit was highly significant ($p < 0.0001$) for both APT (+13%) and PP (+12%) analyses. Changes in FVC and PEF were calculated for APT and highly significant increases ($p < 0.0001$) were also noted for these variables (11% and 19%, respectively). The largest increase in lung function occurred between Visits 1 and 2, i.e. during the first three months, after which it stabilised. How-

Table 2. Mean ($\pm$ SD) lung function visit variables and symptoms for all patients treated and change from baseline to last visit

Variable	Visit 1 Baseline	Visit 2 3 months	Visit 3 6 months	Visit 4 9 months	Visit 5 12 months	Change Visit 1–Visit 5
<i>At the clinic</i>						
% pred. FEV ₁	64.4 (17.4)	75.9 (14.5)	74.4 (13.4)	76.9 (13.1)	77.6 (12.5)	12.6 (16.5)***
% pred. FVC	76.3 (17.8)	86.8 (14.2)	85.7 (13.1)	87.9 (13.7)	88.5 (13.5)	11.4 (16.2)***
% pred. PEF	88.3 (22.4)	105.7 (20.9)	105.3 (22.0)	107.6 (20.6)	108.9 (21.1)	19.2 (25.5)***
Breathlessness	0.25 (0.52)	0.08 (0.4)	0.14 (0.46)	0.16 (0.55)	0.10 (0.37)	–0.12 (0.67) NS
Cough	0.69 (0.83)	0.18 (0.53)	0.24 (0.60)	0.24 (0.60)	0.33 (0.72)	–0.35 (0.99)**
Wheeze	0.48 (0.70)	0.18 (0.49)	0.29 (0.65)	0.20 (0.58)	0.14 (0.41)	–0.29 (0.79)*
<i>Weekly diary card</i>						
PEF morning (% pred.)	78.6 (23.1)	88.9 (22.0)	93.4 (23.8)	94.6 (24.5)	94.2 (23.2)	14.5 (16.8)***
PEF evening (% pred.)	84.0 (23.0)	90.0 (22.4)	94.4 (25.0)	95.9 (24.9)	95.2 (24.5)	10.1 (17.8)***

*** p -value = 0.0001, ** p -value = 0.01, * p -value = 0.02, NS, Not significant

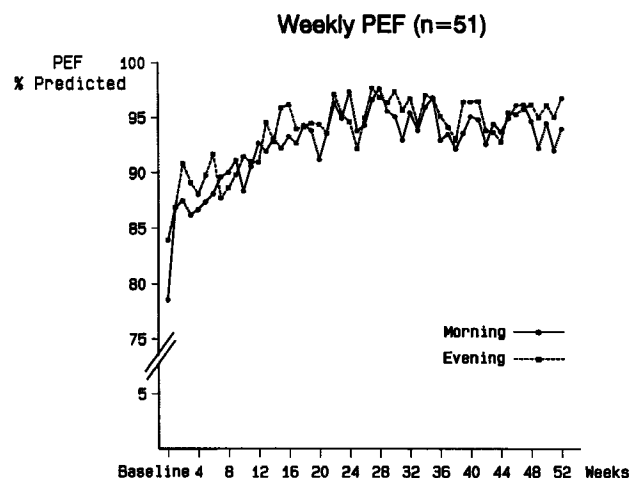


Fig. 1. Mean weekly PEF for all patients treated ($n=51$), recorded over 1 year.

ever, when these data were subjected to a trend analysis, no significant trends were detected over the year. There were significant decreases in cough and wheezing scores at the last visit when compared with those recorded at entry, but breathlessness was not statistically significant (Table 2).

Mean diary card PEF (morning and evening) and symptoms at baseline and during each treatment period were calculated for APT. Statistically significant increases ($p < 0.0001$) in both morning and evening PEF were observed from baseline to the end of the study (Table 2, PEF is presented as % predicted to take growth into account). The increases occurred mainly during the first six months of the study and were sustained during the second six months.

The increase in morning PEF was greater than that for the evening, indicating a reduced diurnal variation. This is illustrated in Fig. 1. A trend analysis for both morning and evening PEF throughout the study (% predicted/week, omitting baseline values) showed a positive and significant increase throughout the study for morning PEF (slope from linear regression 0.12, $p = 0.02$) and evening PEF (slope from linear regression 0.12, $p = 0.002$). Per protocol analyses of PEF data confirmed all of the above significant changes in PEF throughout the study.

Changes in diary asthma symptom scores, other symptoms, β_2 -agonist medication and other asthma medication from baseline to last period (9–12 months) were calculated for all patients treated. There was a decrease in each of these mean variables from baseline to the end of the study, but no changes were statistically significant.

Compliance and concomitant medication

Patient compliance was assessed by calculating the amount of study drug actually taken as a percentage of that intended to be taken. Mean percentage drug taken for Periods 1–4 respectively was 100%, 93.5%, 93.2% and 90.6%. During each of these periods, the actual numbers of patients with less than 90% compliance were 6, 17, 17 and 19, respectively.

Nine children required a 3-day course of oral steroid therapy, eight of them on one occasion and one on two occasions during the study. As the courses were short and in so few patients, the influence of this medication on the overall results is considered to be minimal.

Adrenal function

Adrenal function was assessed by comparing plasma cortisol levels before and after intramuscular depot injection of tetracosactrin. Basal cortisol was expected to lie within a normal range of 70–250 ng/ml and to rise to between 270 and 750 ng/ml post-tetracosactrin. There was no significant change in mean basal cortisol from the first to the last visit. The mean response to tetracosactrin at the last clinic visit was significantly higher at both 4 h ($p = 0.02$) and 5 h ($p = 0.02$) than that observed pre-treatment (Fig. 2).

Clinical chemistry and haematology

For all laboratory variables, pre-entry values were compared with last visit values. There was a significant increase in plasma glucose ($p = 0.0001$) and in the blood neutrophil count ($p = 0.002$). In addition, there were significant decreases in blood lym-

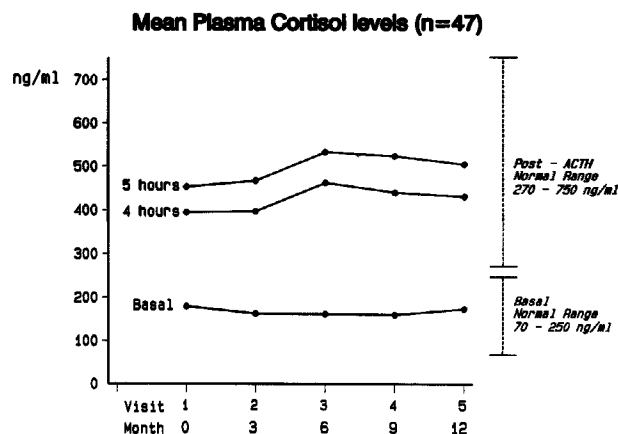


Fig. 2. Mean plasma cortisol levels (ng/ml) measured at each clinic visit, pre-Synacthen (basal) and 4 and 5 h post-Synacthen.

phocytes ($p = 0.01$) and monocytes ($p = 0.007$). None of these changes was considered to be of clinical significance.

Growth

Complete data for height measurements (at each clinic visit) were obtained for 47 children. Mean height increased from $132.9(\pm 10.6)$ cm at the first visit to $138.5(\pm 10.9)$ cm at the last visit. When height scores calculated for each patient at visits 2 to 5 (i.e. active budesonide treatment) were compared with baseline, there was no significant change in score ($p = 0.696$).

Similarly, there was no significant within-treatment variation in score ($p = 0.439$), indicating that the relationship between actual growth and predicted growth had not changed over the year.

Candidiasis

Only two children presented with positive results in the assessment of throat candida and only during one period of treatment.

Adverse events

A total of 6 adverse events were reported, five of them at clinic visits and one child was involved in a traffic accident. Three children were withdrawn from study as a result; the child who was involved in a traffic accident suffered bone fracture which necessitated hospitalisation. This was considered to be the only serious adverse event, but was thought to be unrelated to study treatment. Another child was withdrawn because of headache and one because of tachycardia. Respiratory infection was reported in two children and mild hoarseness in a third, but these children were not withdrawn from study.

Discussion

The purpose of this study was to evaluate the efficacy of long-term budesonide inhalation in children whose asthma was not being kept under control by their existing medication. For ethical reasons, therefore, the study was not placebo-controlled, but took the form of an open longitudinal study of budesonide treatment. In consequence, any changes observed during the study cannot be attributed conclusively to study treatment. However, as the improvements in lung function were sustained throughout the whole study period of one year, it seems likely that they were largely the result of regular intake of active medication rather than the result of a sustained

placebo effect. This hypothesis is supported by the significant increase in lung function tests measured at the clinic over one year, the positive trends in weekly morning and evening PEF measurements (from diary cards), the tendency to have less asthmatic symptoms and the accompanying reduction in bronchodilator usage, all of which indicate good control of the childrens' asthma. There was a slight tendency towards worsening of asthma symptoms (particularly during daytime) during the last month of the study. This may have been due to a slight deterioration in compliance towards the end of the study. It is also possible that external factors such as house dust mites played some role as they have their reproductive cycle between February and April, and thus posed a higher allergenic challenge at the time when most of the patients were completing the study.

From the safety point of view, there was no evidence in this study that budesonide compromised adrenal function in these children. There was no deleterious effect of treatment on either basal cortisol (which gives an indication of hypothalamo-pituitary integrity) or on tetracosactrin-stimulated cortisol (which gives an indication of adrenal integrity). In fact, the adrenal response to stimulation was significantly improved during the study. Bisgaard et al. (8) compared the effects of budesonide and beclomethasone dipropionate in doses ranging from 200 mcg–800 mcg/day over a period of 4 weeks on the adrenal response to tetracosactrin and showed no significant dose-related differences in either group. They also examined 24-h urinary free cortisol and demonstrated a highly significant dose-related decrease in cortisol production in the beclomethasone group but no significant changes in the budesonide group. As the number of patients in the budesonide group was only 10 compared with 20 on beclomethasone, however, these authors went on to study budesonide in a larger group of children (9). They randomised 33 children aged 7–15 years to treatment with 3 different consecutive doses of budesonide, 200, 400 or 800 mcg/day each given via conventional inhaler for a period of 8 weeks. No significant dose-related suppression of unstimulated 24-h urinary free cortisol was found. The authors concluded that budesonide had a favourable ratio between its topical and systemic effects in asthmatic children and this has now been borne out in our long-term study of budesonide, where there was little effect of budesonide on basal cortisol (pre-treatment versus last visit) and a significant increase in the response to ACTH by the end of the year.

Varsano et al. (10) studied the effect of 200 mcg/day budesonide via Nebuhaler in young children

(aged 3½–7 years) over 1 year. These authors concluded that long-term administration of inhaled budesonide to pre-school children was safe, in that no adverse influences of budesonide on basal or ACTH-stimulated cortisol were observed and weight and height did not deviate from expected growth patterns.

This study was not set up to monitor growth and has not, therefore, used measures of growth such as knemometry (11). However, height measurements recorded at each clinic visit were converted into height scores using predicted normal heights obtained from a population of British schoolchildren (7). (No predicted tables are published for Portuguese children.) These scores did not change significantly from baseline to budesonide treatment and there was no significant trend in the height scores over the year, suggesting that any deviation in height from that predicted in these children at entry, remained constant throughout the study. Hence growth seemed to be unaffected by treatment with inhaled budesonide. Varsano et al. (10) performed serial assessments of bone age in their study of budesonide and also found that bone age advanced normally throughout one year of treatment in younger children (aged 3½–7 years). Wolthers & Pedersen (12) studied the effects of budesonide on growth using knemometry and found dose-related suppression of short-term linear growth in children aged 6–13 years with mild asthma. These results have encouraged pediatricians to view inhaled steroid use in children with caution.

Although the majority of long-term studies including our present one have shown that conventional doses of inhaled corticosteroids do not adversely affect growth (13), there is considerable inter-individual variability in sensitivity to steroids (14). Hence, the risks and benefits of a long-term course of treatment should be tailored to the individual child.

In conclusion, this study suggests that control of childhood asthma can be improved by the addition of inhaled budesonide to existing therapy (with simultaneous withdrawal of any other inhaled steroid therapy). In addition to an improvement in objective lung function measurements, there was an improvement in the risk/benefit ratio, i.e., improvement in lung function was associated with a reduction in systemic side-effects such as compro-

mised adrenal function and there was no indication of growth inhibition.

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