Clinical efficacy of low-dose inhaled budesonide once or twice daily in children with mild asthma not previously treated with steroids

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ABSTRACT: The aim of the present study was to examine the efficacy of low-dose inhaled budesonide (BUD) administered *via* Turbuhaler® once or twice daily on symptoms, lung function and bronchial hyperreactivity in children with mild asthma.

One hundred and sixty-three children (mean age 9.9 yrs, 56 females/107 males) with mild asthma (forced expiratory volume in one second (FEV_1) 103% of predicted, morning peak expiratory flow (PEF) 87% pred, reversibility in FEV_1 3%, fall in FEV_1 after exercise 10.4% from pre-exercise value) and not previously treated with inhaled steroids, were included in a double-blind, randomized, parallel-group study. After a two-week run-in period, the children received inhaled BUD 100 μg or 200 μg once daily in the morning, 100 μg twice daily or placebo for 12 weeks. Exercise and methacholine challenges were performed before and at the end of treatment.

After 12 weeks of therapy, the fall in FEV_1 after an exercise test was significantly less in all three BUD groups (4.3–5.1%) than in the placebo group (8.6%). Bronchial hyperreactivity to methacholine with the provocative dose causing a 20% fall in FEV_1 decreased significantly in the BUD 100 μg twice-daily group compared with placebo (ratio at the end of treatment 156%). Changes in baseline lung function (FEV_1 and PEF) were less marked than changes in bronchial responsiveness.

In conclusion, low doses of inhaled budesonide, given once or twice daily, provided protection against exercise-induced bronchoconstriction in children with mild asthma and near normal lung function.
Eur Respir J 1998; 12: 1099–1104.

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The goal of asthma therapy in children is to allow them to be involved in normal everyday activities, including full participation in exercise and sports. There should not be excessive absence from school and children should be free from symptoms day and night. Lung function should be normalized, with low diurnal variation in peak expiratory flow (PEF) [1]. At present, glucocorticosteroids are the most effective anti-inflammatory drugs in the treatment of asthma and inhaled steroids are now recommended as first-line therapy in children with severe or moderate asthma. Treatment recommendations for children with mild, persistent asthma include either a low dose of the inhaled steroid cromolyn or nedocromil [2]. Long-term studies in children with asthma have shown that early intervention may prevent the development of irreversible airway obstruction [3, 4]. In the past few years, inhaled steroids have been introduced in the treatment of mild asthma with a recommended dose of 50–200 μg twice daily [5]. However, there is evidence to suggest that the lowest possible dose should be used to control asthma symptoms, since systemic effects of glucocorticosteroids are dose-dependent [6–8]. Previous studies have shown that low doses (100–200 μg) of inhaled steroids may be effective in controlling asthma symptoms in children, without causing apparent systemic side-effects [9–11].

In the present paper, a randomized, double-blind, placebo-controlled trial of low doses of inhaled budesonide (BUD) given once or twice daily in children with mild asthma is described.

Patients and methods

Study design

The study was a double-blind, single-centre trial. A two-week open run-in period, which served as a baseline and during which the children were introduced to the Turbuhaler® inhaler (Astra Draco, Lund Sweden), a peak flow meter and completing a diary, was followed by a 12-week double-blind treatment period with five visits to the clinic (at enrolment, at randomization and at four-week intervals). Patients were randomized into four parallel groups in balanced blocks. At randomization, each patient received two Turbuhaler inhalers, one to be used in the morning and the other in the evening. Group I patients were given BUD 100 μg once daily in the morning and placebo in the evening. Group II received BUD 200 μg once daily in the morning and placebo in the evening.

Group III received BUD 100 μg twice daily. The remaining group, group IV, received placebo twice daily.

The patients kept daily records of peak flow values, symptoms, use of β₂-agonists and intake of study medication. Clinical assessments and lung function tests (flow–volume curve and plethysmography) were performed at four-week intervals. Exercise tests were performed at enrolment and at the end of the 12-week treatment period. Measurement of the provocative dose of methacholine causing a 20% fall in the forced expiratory volume in one second (PD_{20}) was performed at randomization and after 12 weeks of treatment. After completing the baseline lung function tests and the exercise test at enrolment, a reversibility test to inhaled terbutaline was performed. Pulmonary function testing was performed at approximately the same time of the day for each patient. The exercise test and the methacholine provocation were performed on separate days.

The study was approved by the Regional Medical Ethics Committee in Oslo.

Patients

A total of 163 children with mild asthma were included in the study (107 male and 56 female, aged 7–16 yrs). A total of 166 patients were enrolled in the run-in period of the study and three discontinued prior to randomization. Two of these were excluded because their asthma deteriorated and one patient because of noncompliance. Patients were selected from the outpatient clinic at the Section of Allergy and Pulmonology, Dept of Paediatrics, Ullevål University Hospital in Oslo.

Inclusion criteria were the diagnosis of asthma, based on the definition in the International Consensus report [12] and in the Nordic Consensus report [13], with three previous obstructive episodes or one previous obstructive episode with atopy. At least one of these episodes had to have occurred within the year prior to the first visit. The patients did not use inhaled steroids within 2 months, or cromoglycate and/or nedocromil within 4 weeks of entry. No patient had any lower respiratory tract infection or exacerbation of asthma requiring an emergency room visit and/or hospitalization in the 4 weeks prior to entry.

Methods

BUD (daily dose 100 μg or 200 μg) or placebo was inhaled from Turbuhaler in the morning and evening during the 12-week treatment period. The patients were instructed to rinse their mouths out with water after each use. All patients were supplied with terbutaline (Bricanyl Turbuhaler® 250 μg), to be used as needed during the study. Children were required to demonstrate that they were competent in using Turbuhaler before enrolment, after the run-in period, and thereafter at four-week intervals during the study. A Vitalograph® peak flow meter (Vitalograph, Ennis, Ireland) was dispensed at enrolment. Patients measured their PEF every morning and evening throughout the entire study period. The highest PEF value from three exhalations was recorded on each occasion. At each clinic visit, staff checked that the children could use the PEF meter correctly. Patients were instructed to fill in a diary

twice daily, recording intake of study medication as well as rescue medication, PEF values, and symptom score. Asthma symptoms were scored on a four-point scale, which ranged from 0 (no symptoms) to 3 (severe symptoms). The diary sheet was collected at every visit.

Exercise-induced bronchoconstriction. This was determined at enrolment and at the end of the 12-week treatment period by the use of a motor-driven treadmill, where the children were instructed to run for 6 min with a submaximal exercise load [14]. The inclination of the treadmill was 5.5% and the speed was adjusted to a submaximal load to achieve a steady-state cardiac frequency of 170–180 beats·min⁻¹. The cardiac frequency was recorded electronically (Sport-Tester® PE 3000 with memory function: Polar Electro KY, Kempele, Finland). The submaximal run on the treadmill was performed at the same speed (exercise load) on both test occasions (at randomization and after 12 weeks of treatment) for each individual child. Forced expiratory volume in one second (FEV_1) was measured before running, immediately after, and 3, 6, 10 and 15 min after running. The maximum percentage fall in FEV_1 after the exercise test was calculated by:

$$\frac{(\text{Pre-exercise } FEV_1 - \text{Minimum post-exercise } FEV_1) \times 100}{\text{Pre-exercise } FEV_1}$$

Bronchial hyperreactivity. This was measured at randomization and at the end of the 12-week treatment period by a methacholine chloride inhalation test for the determination of PD_{20}, [15]. Methacholine was inhaled in doubling doses from 0.128 μmol up to a maximum dose of 16.32 μmol or until FEV_1 had fallen Š20% compared with FEV_1 after an initial saline (0.9%) inhalation. The bronchial aerosol provocation system (APS) (Jaeger, Würzburg, Germany) with the Sandoz nebulizer (Jaeger) were used for this procedure. The Sandoz nebulizer was calibrated to nebulize 5 μL per nebulization and was triggered by inspiration on tidal ventilation. Each nebulization lasted for 0.5s. Lung function was measured 1 min after each inhaled dose. PD_{20} was determined by linear interpolation on a semilogarithmic scale [15, 16].

If the patient had inhaled a β₂-agonist within 8 h prior to the lung function tests, the challenge was postponed until the next day.

Lung function. This was measured at every visit using maximal forced expiratory flow–volume curves and whole-body plethysmography (Masterlab Body; Jaeger) under body temperature, barometric pressure, saturated with water vapour (BTPS) conditions. Predicted lung function values were calculated using reference values from ZAPLETAL *et al.* [17]. At least three independent flow–volume curves were obtained on each visit and the curve with the highest FEV_1 was chosen. Values for the forced expiratory flow at 25% of the forced vital capacity ($FEF_{25\%}$), $FEF_{50\%}$ and $FEF_{75\%}$ were also obtained from selected flow–volume curves. Calibrations were carried out daily on all lung function measuring equipment used in the study. Reversibility was tested at the entry visit, 15 min after administration of 500 μg of inhaled terbutaline from Turbuhaler.

Adverse events. Information was obtained at each visit by asking the patients or guardian "Have you/your child had any health problems or symptoms not usually associated with your/his/her asthma since the last visit?" The onset, severity and outcome of each adverse event were recorded.

Sample size

It was assumed that the standard deviation of a change in morning PEF was 30 L·min⁻¹ and with 40 patients per treatment group there would have been an 80% chance of detecting a difference of 20 L·min⁻¹ between two treatment effects when using a two-sided t-test with a significance level of $p<0.05$.

Statistical evaluation

The change from baseline to the end of treatment was subjected to analysis of variance (ANOVA) with treatment as a factor and baseline value as a covariate. The ANOVA was used to obtain estimates of the pairwise differences between treatment effects and the standard deviation of each pairwise difference between treatment effects. An additive model was used when analysing diary variables, lung function variables and the maximum fall in FEV1 after the exercise test, whereas a multiplicative model was used when analysing plethysmography variables and PD20. The efficacy of BUD 100 µg once daily and placebo was compared using a two-sided t-test at a $p<0.05$ significance level. The effect of BUD 200 µg once daily and BUD 100 µg once daily was compared in the same manner. The statistical analysis was based on the All Patients Treated approach; thus, all patients who had received at least one dose of study medication were included. Missing values were handled by applying the Last Value Extended principle. For diary variables, this was accomplished by extending the period means.

Results

The 163 randomized patients had a mean age of 9.9 yrs, a mean weight of 37.7 kg and a mean height of 143.4 cm

Table 1. – Patient characteristics at baseline for each treatment group

Characteristics	BUD 100 *b.i.d.*	BUD 200 *o.d.*	BUD 100 *o.d.*	Placebo
Number of patients	40	42	41	40
Males/Females	26/14	23/19	31/10	27/13
Age yrs	10.2	10.0	9.8	9.6
Height cm	145.4	144.9	142.1	141.2
Atopics n	26	25	31	28
FEV1 L	2.34	2.21	2.15	2.08
FEV1% pred	105 (14)	101 (11)	103 (12)	102 (14)
Reversibility in FEV1%	2.6 (5.1)	1.9 (7.2)	4.2 (4.7)	3.3 (5.4)
PEF morning L·min⁻¹	260 (86)	272 (81)	245 (71)	237 (63)
PEF morning % pred	86 (17)	91 (16)	86 (14)	85 (14)
Methacholine PD20 µmol	3.67	4.14	3.74	3.02
Maximum fall in FEV1 after exercise test %	8.4	11	12.3	9.6

Results are given as mean values with SD in parentheses. BUD: budesonide; FEV1: forced expiratory value in one second; PEF: peak expiratory flow; PD20: provocative dose causing a 20% fall in FEV1.

(table 1). The mean FEV1 was 103% predicted and the mean reversibility in FEV1 was 3%. Atopy was diagnosed in 67.5% of the children. Three patients were withdrawn from the study after randomization (all from the BUD 100 µg once-daily group), two of these because their asthma deteriorated and one due to noncompliance. At entry, the treatment groups were comparable regarding the number of patients, mean age, mean height and number of atopic patients. The proportion of females and males varied between the groups, as did baseline mean values for PEF and FEV1, with the placebo group having the lowest mean values (table 1).

Exercise-induced bronchoconstriction

The mean maximum fall in FEV1 (% fall from pre-exercise value) after the exercise test at baseline is presented in table 1. After 12 weeks of treatment, the corresponding values were: 4.3% for the BUD 100 µg twice-daily group, 5.1% for the BUD 200 µg once-daily group, 5.0% for the BUD 100 µg once daily group and 8.6% for the placebo group (fig. 1). All pairwise comparisons of active treatment *versus* placebo revealed statistically significant differences, with no differences between the active treatments (table 2).

Methacholine hyperreactivity

The mean percentage increase in PD20 (µmol) from baseline to end of treatment was 110% in the BUD 100 µg twice-daily group, 40% in the BUD 200 µg once-daily group, 60% in the BUD 100 µg once-daily group, and 40% in the placebo group.

Pairwise comparison of active treatments *versus* placebo revealed a statistically significant difference between BUD 100 µg twice daily and placebo, with an estimated treatment effect ratio of 156% in favour of the BUD group (table 3).

Lung function

Baseline morning PEF values varied considerably among the four treatment groups (table 1). However, changes
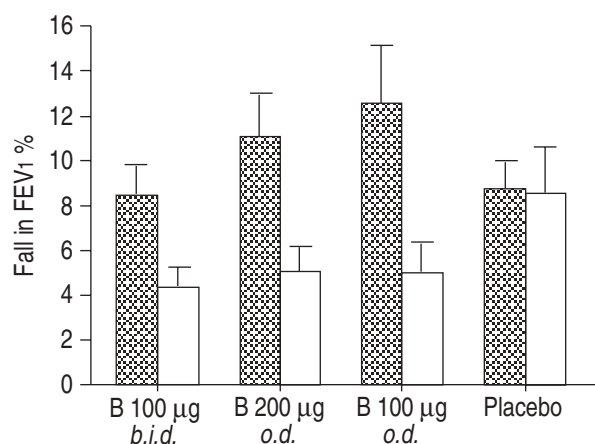

Fig. 1. – Comparison between different treatment effects on maximum fall in the forced expiratory volume in one second (FEV1). B: budesonide after exercise test (% fall from pre-exercise value) from baseline to week 12. ▨ : Baseline; ☐ : week 12.

Table 2. – Comparison between different treatment effects, on maximum fall in forced expiratory volume in one second (FEV1) after exercise test (% fall from pre exercise value) after 12 weeks of therapy

Treatment group	Estimated difference in fall FEV1%	CI	p-value
BUD 100 *b.i.d.*/Placebo	-4.19	-7.6–-0.8	0.01
BUD 100 *o.d.*/Placebo	-4.69	-8.1–-1.3	<0.01
BUD 200 *o.d.*/Placebo	-4.15	-7.5–-0.8	0.015
BUD 200 *o.d.*/BUD 100 *b.i.d.*	-0.05	-3.3–3	NS
BUD 200 *o.d.*/BUD 100 *o.d.*	0.54	-2.8–3.9	NS

CI: 95% confidence interval; BUD: budesonide; NS: nonsignificant.

from baseline did not differ between the groups throughout the treatment period. A pairwise comparison between the different treatment groups showed no significant differences (table 4). An analysis of change in PEF (% pred) gave consistent results as compared with the change in actual PEF values.

A statistically significant difference in FEV1 was only found between BUD 100 μg twice daily and placebo (0.1 L, p=0.015). At the end of the treatment period, no statistically significant difference was found between the treatment groups in FEF25%, whereas there was a significant difference in both FEF50% (0.3 L, p=0.001) and FEF75% (0.1 L, p=0.039) between BUD 100 μg twice daily and placebo, and also between BUD 100 μg twice daily and BUD 200 μg once daily (FEF50%: 0.3 L, p=0.002; FEF75%: 0.1 L, p=0.04) in favour of the BUD 100 μg twice-daily group. Moreover, FEV1 (% pred) showed a difference between BUD 100 μg twice daily and placebo (5.2%, p= 0.008) and between BUD 100 μg twice daily and BUD 200 μg once daily (4.1%, p=0.035) in favour of the BUD 100 μg twice-daily group.

Resistance of the respiratory system (R_{rs}) and airway conductance (G_{aw}) differed significantly between BUD 100 μg twice daily and placebo (estimated ratio R_{rs} 89.3%, p=0.03; estimated ratio G_{aw} 115.2%, p=0.006). In a pairwise comparison between the groups, no other significant differences for G_{aw} and R_{rs} were found.

Symptom scores

Mean values for asthma symptoms were low throughout the study for all treatment groups. The mean symptom scores were already low at baseline, with a daytime mean symptom score of 0.39 and a night-time mean symptom score of 0.16.

Table 3. – Provocative dose of methacholine (μmol) causing a 20% fall in the forced expiratory volume in one second: estimated ratio between treatment effects after 12 weeks of therapy

Treatment group	Estimated ratio %	CI	p-value
BUD 100 *b.i.d.*/Placebo	156	101.5–239.1	0.04
BUD 100 *o.d.*/Placebo	121	78.3–186.7	NS
BUD 200 *o.d.*/Placebo	107	70.0–163.5	NS
BUD 100 *b.i.d.*/BUD 200 *o.d.*	146	95.4–222.2	NS
BUD 200 *o.d.*/BUD 100 *o.d.*	89	57.7–135.9	NS

CI: 95% confidence interval; BUD: budesonide; NS: nonsignificant.

Table 4. – Comparison between different treatment effects on change in peak expiratory flow after 12 weeks of therapy

Treatment group	Estimated difference L·min⁻¹	95% CI	p-value
BUD 100 *b.i.d.*/Placebo	5.8	-8.1–19.7	NS
BUD 100 *o.d.*/Placebo	3.0	-10.8–16.8	NS
BUD 200 *o.d.*/Placebo	2.9	-11.0–16.7	NS
BUD 200 *o.d.*/BUD 100 *b.i.d.*	2.9	-10.8–16.6	NS
BUD 200 *o.d.*/BUD 100 *o.d.*	-0.1	-13.9–13.6	NS

Adjusted means from the analysis of variance and 95% confidence interval (CI). BUD: budesonide; NS: nonsignificant.

Statistically significant differences in symptoms during the night were found between BUD 200 μg once daily and placebo (-0.11, p=0.047), as well as between BUD 200 μg once daily and BUD 100 μg once daily (-0.11, p=0.040). This applied to both the mean symptom score and the frequency of symptom-free nights.

At baseline, the children used a mean number of 0.49 β2-agonist inhalations during the day and 0.11 inhalations during the night. There were no significant differences in mean change from baseline between the treatment groups.

Adverse events

The adverse event profile observed in the three active treatment groups was similar to that reported for the placebo group. The most common adverse events were respiratory infection, coughing, and headache. One adverse event was regarded as serious: one patient receiving placebo experienced pharyngitis and high fever and was admitted to hospital for 3 days. A causal relationship to the study drug was judged unlikely. None of the patients discontinued the study because of adverse events.

Discussion

The present study in children with asthma shows that a low dose of BUD, administered once or twice daily for 12 weeks, protects against an exercise-induced reduction in lung function.

The once-daily morning regimens were shown to be as effective as the twice-daily dosing regimen with regard to the protective effect against exercise-induced asthma.

The majority of the patients selected for the present study had mild asthma, mild being defined as low-grade symptoms that did not interfere with sleep and lifestyle, or episodes of cough and wheeze occurring less than a month [1]. Patients were selected on the basis of known asthma symptoms in the past year and not because of previously documented bronchial hyperresponsiveness. The fact, that mean reversibility was only 3% after inhalation of a bronchodilator and that FEV1 at baseline showed a mean value of >100% pred indicate that the patients had near-normal lung function at baseline with little room for improvement. The mean bronchodilator use at baseline was 0.6 inhalations·24 h⁻¹. This relatively high use in this group of patients with mild disease can partly be explained by the fact that many of the children were using a bronchodilator routinely before exercise.

PEF, which is often used when evaluating the effect of inhaled steroid treatment, was shown to be a less sensitive measure than an exercise test in detecting treatment effects in the present study in children with near normal lung function and mild symptoms. The results of the peak flow measurements failed to demonstrate any statistically significant difference between the active treatments and placebo.

In a study on children with moderate to severe asthma (PEF 55% pred), PEDERSEN and HANSEN [11] found that an exercise test is a more sensitive parameter than PEF and FEV1 in detecting differences between various doses of BUD. Even low doses of BUD, approximately 100 µg·day-1 showed marked effects. This also proved to be true in this study in patients with mild asthma, where all active treatments provided better protection against exercise-induced bronchoconstriction than did placebo.

The results are important and useful for future studies, since protection against exercise-induced asthma may be used as a sensitive measure of the efficacy of inhaled steroids, which may reveal differences between different treatments that are not apparent when standard lung function tests are used. The result of the PEF data obtained in this study is supported by a study by UWYYED et al.[18], where it was concluded that PEF monitoring is not sensitive enough to register meaningful changes in children and young adults with mild asthma (FEV1 82% pred and PEF 87% pred).

WAALKENS et al.[19] compared the effects of treatment with budesonide 200 µg twice daily and terbutaline with the effects of terbutaline alone in a placebo-controlled, double-blind study in 27 children with mild asthma (FEV1 93% pred) over 8 weeks. They found that mean FEV1 did not change in either group and that there was no significant change in morning PEF, although they found a significant difference in favour of BUD for evening and nocturnal PEF. Airway hyperresponsiveness (provocative concentration of histamine causing a 20% fall in FEV1 (PD20)) decreased in the BUD/terbutaline-treated patients compared with the placebo/terbutaline group.

In the present study, the methacholine PD20 was significantly larger in the children receiving BUD 100 µg twice daily than in those receiving placebo. The differences in PD20 in the two other treatment groups were not statistically significant, compared with placebo, although there were numerical increases in all treatment groups. VAN ESSEN-ZANDVLIET et al. [20] showed that a reduction in the direct nonspecific bronchial responsiveness (PD20 for histamine) increases gradually and first stabilizes after 20 months of treatment with inhaled budesonide in children with asthma. These findings can partly explain the weak response in the methacholine challenge test in the present study, with a treatment period of only 3 months.

With respect to spirometry, the high baseline FEV1 values (>100% pred) and poor reversibility gave little room for improvement. Although statistically significant, the increase in FEV1 in the twice-daily group was small. As pointed out by FERGUSON [21], FEF25–75 is a more sensitive indicator of airflow than PEF or FEV1. He suggest- ed that frequent assessment of FEF25–75 is required for optimal assessment of the effectiveness of therapy. In the present study this is demonstrated by the finding of a significant difference between BUD 100 µg twice daily and placebo as well as between BUD 100 µg twice daily and

BUD 200 µg once daily for FEF50% and FEF75%, otherwise the results were consistent when compared to FEV1 or PEF.

The effect of switching from twice-daily to once-daily treatment with budesonide in well-controlled asthmatic children was studied by MCCARTHY [22] and MÖLLER et al.[23]. They found that PEF, FEV1, symptom scores and bronchodilator use during once-daily treatment were not different from those during twice-daily treatment.

In summary, the present study showed that low doses of inhaled budesonide administered at a dose of 100 µg or 200 µg once daily or 100 µg twice daily via Turbuhaler® provided protection against exercise-induced bronchoconstriction in children with mild asthma and that all three treatment regimens were well tolerated. An exercise test is suggested to be more sensitive than peak expiratory flow and forced expiratory volume in one second, in evaluating the efficacy of treatment with inhaled steroids in asthmatic children with mild disease and near-normal lung function.

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