Beclomethasone dipropionate versus budesonide inhalation suspension in children with mild to moderate persistent asthma

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Abstract. – Inhaled steroids are the most effective long-term treatment of persistent asthma but many children are unable to use correctly the available inhalers. Administration of nebulized corticosteroids has some advantages over the administration with pressurised metered-dose inhalers (pMDIs). The objective of this multicenter randomised study was to compare the efficacy and tolerability of nebulized corticosteroids in paediatric patients with asthma. 127 patients aged ≥ 6 and ≤ 14 years with a diagnosis of mild to moderate persistent asthma (PEFR % predicted > 50% and < 85%) and positive response to the reversibility test were randomised. The patients were assigned by randomisation to one of the two treatment groups (4 weeks): beclomethasone dipropionate (BDP) 800 µg/daily b.i.d. (n = 66) or budesonide (BUD) 1000 µg/daily b.i.d (n = 61) both administered by nebulizer. The primary efficacy end point was the final mean of PEFR measured at clinical visit (clinic PEFR). In the BDP group clinic PEFR increased from 177.5 ± 80 L/min to 246.6 ± 84.2 L/min (p < 0.001 vs baseline), while in the BUD group the increase was from 180.4 ± 77.8 L/min to 260.9 ± 84.1 L/min (p < 0.001 vs baseline) (NS between treatments). FEV₁ (% predicted) increased from 77.8% to 92.7% (p < 0.001 vs baseline) and from 74.1% to 95.9% (p < 0.001 vs baseline) (NS between treatments). Patients reduced the use of salbutamol rescue medication by 76% and 81% in BDP and BUD group respectively (NS between treatments). Patients reduced the use of salbutamol rescue medication by 76% and 81% in BDP and BUD group respectively (p < 0.001 vs baseline, NS between treatments). 4 patients in the BDP group and 2 in the BUD group reported adverse events (AEs). AEs were mild to moderate and never there was the need to discontinue the treatments. In conclusion the results of this study demonstrate that both BDP (800 µg/daily) and BUD (1000 µg/daily) administered by nebulization are effective and with an acceptable safety and tolerability profile.

Key Words: Asthma, Beclomethasone dipropionate, Budesonide, Nebulized drugs.

Introduction

Asthma is one of the most frequent diseases, especially in children; it is estimated that it can affect 4-10% of the paediatric population in the world1. The prevalence of the disease has increased, together with its morbidity, as demonstrated by the increase of hospitalisations due to asthma2. Inhaled corticosteroids are the most effective medication for the long-term control of persistent asthma1. Their anti-inflammatory activity is responsible for the therapeutic effect and for the control of asthma symptoms, improvement of pulmonary function and reduction of exacerbation1.

There are a number of different aerosol delivery system such as pressurised metered-dose inhalers (pMDIs), with or without add on devices, dry powder inhalers (PDI) and nebulizers. The first class of drugs used in the nebulized form was the β₂-agonist bronchodilators, followed by the use of nebulized corticosteroids and anticholinergics. This mode of administration has an important role for some types of patients and especially children who cannot properly use pMDIs or DPI. In fact, the use of nebulized products can overcome coordination problems associated with the use of a pressurised aerosol3,4.
comparison between beclomethasone dipropionate (BDP) and budesonide (BUD) suspension for nebulization has never been reported. The purpose of the study was to compare the efficacy and the safety of BDP and BUD inhalation suspension in children with mild to moderate asthma.

**Material and Methods**

Male and female aged ≥ 6 and ≤ 14 years who had clinical diagnosis of persistent asthma as defined by the National Heart Lung and Blood Institute with PEFR value > 50% and < 85% of the theoretical value and positive response to the reversibility test, defined as an increase > 15% in the FEV₁ measured 30 minutes following 1 puffs (1 × 100 µg) of inhaled salbutamol, were eligible to participate in the study. Patients treated with oral steroids in the previous 12 weeks for more than 12 days, with history of clinically significant hepatic disease (transaminasis 2 times higher than the normal value) or renal impairment (creatinine ≥ 1.5 mg/dl), with heart failure, active peptic ulcer, active mycotic infection of the lung, tuberculosis, herpes simplex, insulin dependent diabetes mellitus, hypothyroidism, hypersensitivity to the study drugs were excluded from the randomisation.

**Study design**

Patients who met inclusion and exclusion criteria were assigned by randomisation to one of the two-treatment group: BDP 800 mg/daily b.i.d. (Clenil® A - Chiesi Farmaceutici S.p.A. - Parma, Italy) or BUD 1000 mg/daily b.i.d. (Pulmicort® Respules - Astra Pharmaceuticals Ltd. Kings Langly, Hertfordshire, England) commercially available. Both drugs were administered by a Pari Boy nebulizer (Pari Gmbh, Starnberg, Germany). Drugs that could interfere with the study treatment were excluded: anticholinergics, inhaled (including nasal) corticosteroids or oral corticosteroids, long acting inhaled bronchodilators, oral bronchodilators, cromoglicate-like drugs, antihistamines, leukotrienes antagonists, β-blockers. The use of short acting β₂ agonist was permitted when necessary. If inhaled therapy didn’t obtain a good control of the symptom during the study, oral prednisone 1 mg per kg body weight was allowed. After a one-week run-in period, in which each patient continued the use of previous treatment and β₂ agonist as needed, the patients who met inclusion and exclusion criteria were assigned to one of the two treatment groups for a treatment period of 4 weeks. During the treatment a visit every 2 weeks was planned.

Lung function was evaluated according to the American Thoracic Society Guidelines. A standard spirometer was used; the calibration had to be controlled each day of use. Clinic PEFR was evaluated from the flow/volume curve ratio or from the forced expiratory manoeuvre. Within three different measurements the best was reported. The use of the β₂ agonists had to be withdrawn at least 8 hours before the test. The time of lung tests was recorded in order to perform the tests at the same hour for all the study long, with a variation equal to ± 1 hour. Morning and evening PEFR were measured daily by patients using a Mini-Wright Low Range peak flow meter (Clement Clarke International - Harlow, Essex, England), always at the same hour of the day (8 ± 1 am, 7 ± 1 pm whenever possible). Three measurements were performed and the highest of the three values recorded in the diary card. The measurement was done before any use of bronchodilator inhaler. Global asthma symptoms, rated on 0 to 4 scale (0 = no present, 4 = so severe that the patient could not attend school or carry out normal activities) and bronchodilator use were assessed on a daily basis by the patients and recorded into the diary card. The institutional review board for each treatment centre approved the protocol, and the written informed consent was obtained from the parent or guardians of patients.

**Assessments**

The primary efficacy end point was defined as the final mean of clinic peak expiratory flow rate (PEFR) before bronchodilator use. Secondary efficacy end-points were the final mean values of forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), improvement of asthma symptoms, patients/parents opinion, consumption of β₂ agonists and morning peak expiratory flow rate (PEFR) measured by the patient. Adverse events were assessed throughout the study.
**Statistical analysis**

Sample size calculation was based on the criteria of equivalent efficacy between the two treatments. Considering as primary efficacy variable the final mean value of clinic PEFR, considering as clinically not relevant a difference between groups not superior of 10% of the BUD mean PEFR, considering the BUD mean PEFR value after 4 weeks equal to 270 L/min, considering the common standard deviation of PEFR equal to 55, with a sample of 61 patients per group a one side test with \( \alpha = 0.05 \) should have a 80% potency to refuse the null hypothesis that BDP and BUD are not equivalent in favour of alternative hypothesis that the two groups are equivalent.

Basal values comparison was done by a one way ANOVA for continuous variables, and by Wilcoxon 2-sample test or Chi-square test for categorical variables. Basal values of PEFR recorded on diary card were calculated as average of the values recorded during the run-in period. Within treatment analysis was performed on primary efficacy variable after 2 weeks and 4 weeks calculating 95% confidence interval of mean change from basal value.

Between treatment comparison was done using ANCOVA after 4 weeks considering basal value as covariate. Equivalence between the two treatments was tested calculating 95% unilateral confidence interval for the difference between groups of the basal-adjusted means of clinic PEFR at the end of treatment period. The two treatments were to be defined as equivalent if the confidence limits for the difference fall within the 10% of BUD mean.

Within treatment analysis for secondary variables was done calculating the 95% confidence interval of mean change at each visit from baseline. Between treatment comparison was done as for primary efficacy variable. Patient’s/parents’ opinion was evaluated using Chi-square test. A diverse events, as reported on the case report forms, were listed by treatment and by patient.

All randomized patients who received at least one dose of the study medications and with at least one visit after baseline were to be included in the ITT population analysis. Missing data were to be replaced with the “last observation carried forward” method. All patients included in ITT population who also meet all inclusion/exclusion criteria and who do not have any major protocol violation were to be included in the per protocol population (PP) and analysis. Intention-to-treat population was used as primary analysis for all variables. In the per-protocol population, clinic PEFR, FEV₁, and morning PEFR measured by the patients were also analysed.

**Results**

**Patient population**

This was a multicenter study performed at 10 centres. One hundred and twenty eight patients were screened for the study. One patient withdrew before randomisation (refused to continue the study) and 127 were randomised, 66 to BDP group, and 61 to the BUD group. There were 9 major protocol violation and the PP population was 58 patients in BDP group and 60 patients in the BUD group. Patients demography, clinic PEFR, FEV₁ and morning PEFR measured by the patients were also analysed.

**Table I. Patient population.**

<table>
<thead>
<tr>
<th></th>
<th>BDP</th>
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<th>BUD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>Mean ± SD</td>
<td>No.</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td></td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>Males</td>
<td>48</td>
<td>73</td>
<td>9.6 ± 2.4</td>
<td>44</td>
</tr>
<tr>
<td>Females</td>
<td>18</td>
<td>27</td>
<td>37.2 ± 15.6</td>
<td>17</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td>141.9 ± 16.4</td>
<td></td>
</tr>
<tr>
<td>Clinic PEFR</td>
<td>67.1 ± 10.8</td>
<td></td>
<td>66.3 ± 10.4</td>
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</table>
frequent medication assumed by patients, during the 7 days run-in period, was salbutamol, assumed by 15.2% of the patients in the BDP group and by 11.5% of the patients in the other group. BUD was assumed by 9.1% of the patients in the BDP group and fluticasone by 1.6% of patients in the BUD group. 4.5% and 6.6% of the patients in the BDP and BUD group assumed theophylline respectively. All randomised patients concluded the 4 weeks treatment period.

**Evaluation of efficacy: clinic PEFR**

At the end of the study in both groups there was a constant increase over time of clinic PEFR values. After 4 weeks in the BDP group clinic PEFR increased from 177.5 L/min at baseline to 246.6 L/min, while in the BUD group the increase was from 180.4 to 260.9 L/min. The 95% unilateral confidence interval for the true difference between the two means of clinic PEFR at the end of treatment period, adjusted for basal value, was below the clinically accepted limit (95% CI -25.90; 2.25, 10% BUD = -25.96; p-value = 0.16). The same results were found in the per protocol analysis.

The mean % clinic PEFR changes from baseline were 50.4 and 55.7 in the BDP and BUD group respectively (Table II). In the BDP group the FEV1 mean values increased significantly ($p < 0.001$) from 1.5 L at the end of run-in period to 1.8 L after 4 weeks of treatment, while in the BUD group the increase was from 1.5 L to 1.9 L ($p < 0.001$). FEV1 % predicted increased significantly ($p < 0.001$) from 77.8% at baseline to 92.7% after 4 weeks and from 74.1% to 95.9% in BDP and BUD groups respectively (Figure 3). The same results were obtained in the per protocol analysis (Figure 4).

The mean increase from baseline in FVC was similar in both groups (Table III). Mean values for PEFR measured daily by the patients increased significantly ($p < 0.001$) from the baseline in both groups and the increase was higher in the morning than evening: at the endpoint, the increase in morning PEFR was from 274.0 L/min to 308.0 L/min in the BDP group and from 262.3 L/min to 313.7 L/min in the BUD group. An increase in morning PEFR was seen in 83.3% and 86.8% of the patients in the BDP and BUD groups respectively with no significant difference between treatments.

### Table II. Mean clinic PEFR % changes from baseline before and after bronchodilator in patients treated with BDP (800 µg/daily) or BUD (1000 µg/daily) – Intention to treat population.

<table>
<thead>
<tr>
<th></th>
<th>BDP (mean ± SD)</th>
<th>BUD (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEFR pre-bronchodilator (L/min)</td>
<td>50.4 ± 43.7'</td>
<td>55.7 ± 44.6'</td>
</tr>
<tr>
<td>PEFR pre-bronchodilator (% predicted)</td>
<td>49.6 ± 42.7'</td>
<td>55.2 ± 44.1'</td>
</tr>
<tr>
<td>PEFR post-bronchodilator (L/min)</td>
<td>15.2 ± 24.5'</td>
<td>12.4 ± 26.9'</td>
</tr>
<tr>
<td>PEFR post-bronchodilator (% predicted)</td>
<td>14.8 ± 24.4'</td>
<td>13.1 ± 25.3'</td>
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*p < 0.001 vs baseline.

### Evaluation of efficacy: other measures of pulmonary function

In the BDP group the FEV1 mean values increased significantly ($p < 0.001$) from 1.5 L at the end of run-in period to 1.8 L after 4 weeks of treatment, while in the BUD group the increase was from 1.5 L to 1.9 L ($p < 0.001$). FEV1 % predicted increased significantly ($p < 0.001$) from 77.8% at baseline to 92.7% after 4 weeks and from 74.1% to 95.9% in BDP and BUD groups respectively (Figure 3). The same results were obtained in the per protocol analysis (Figure 4).

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### Table III. Mean changes from baseline of FVC (% predicted), and FEV1/FVC ratio in patients treated with BDP (800 µg/daily) or BUD (1000 µg/daily) – Intention to treat population.

<table>
<thead>
<tr>
<th></th>
<th>BDP (mean ± SD)</th>
<th>BUD (mean ± SD)</th>
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<tbody>
<tr>
<td>FVC (% predicted)</td>
<td>10.5 ± 13.3'</td>
<td>14.9 ± 17.3'</td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td>5.2 ± 8.9'</td>
<td>7.5 ± 11.5'</td>
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</table>

*p < 0.001 vs baseline.
Evaluation of efficacy: signs and symptoms and rescue medication

Patients treated with BDP reduced the use of Salbutamol as rescue medication from an average of 0.42 puffs/day during the run-in period to an average of 0.15 puffs/day during the first two weeks of treatment until 0.08 puffs/day during the last 2 weeks \( (p < 0.001) \). Similarly patients treated with BUD reduced their need of Salbutamol from 0.44 puffs/day during the run-in period to 0.15 puffs/day during the first two weeks of treatment until 0.08 puffs/day during the last 2 weeks \( (p < 0.001) \).

In the BDP group the asthma symptom score decreased significantly \( (p < 0.001) \) from an average of 0.56 during the week of run-in to an average of 0.12 during the last two weeks of treatment. In the BUD group the score decrease was from 0.51 to 0.15 \( (p < 0.001) \).
The number of nocturnal awakenings due to asthma significantly decreased from an average of 0.29 per night to an average of 0.07 per night in the BDP group compared with a decrease from 0.39 to 0.11 in the BUD group.

The number of diurnal dispnea and asthma exacerbation episodes decreased significantly in both groups (*p* < 0.001).

Comparison between treatments was not statistically significant at any time (Figure 5).

At the end of the treatment, cough was completely absent in 78.5% of patients in the BDP group and 80.3% of patients in the BUD group, while ronchi and rales were absent or mild in all patients in both group.

Only one patient and one parent in each group expressed a negative opinion on drug. An opinion of “I feel better” or “I feel really better” was expressed by 78.5% of patients in the BDP group and by 85.2% of patients in BUD group; the difference was not significant.
Evaluation of safety
Safety data showed that both treatments were well tolerated. During the treatment period 4 patients reported adverse events (AEs) in the BDP group, and 2 in the BUD group. The number of AEs was 5 and 2 in BDP and in BUD groups respectively. The overall incidence of AEs was similar in the two treatment groups. The most common AEs were allergic rhinitis, otitis, hoarseness, respiratory tract related symptoms and sinusitis. AEs were mild to moderate and never there was the need to discontinue the treatment. No clinically relevant changes in vital signs and physical examination were observed in both treatment groups.

Discussion
The chronic inflammatory state of asthma requires that treatment with inhaled corticosteroids begin at an early stage of the disease in order to prevent long-term irreversible impairment of pulmonary function. Many children are not able to effectively inhale from pMDIs. A dm inistration of corticosteroids by nebulization has some advantages over pMDIs, inf act nebulized corticosteroids can be easily administered to patients who lack hand to lung co-ordination, allow an easy administration of high doses of drugs and give the possibility of reaching simultaneously the upper and the lower airways. The coexistence of rhinitis with asthma is a common finding and it has been reported that there is an improvement in the control of asthma following surgical or medical treatment of sinus disorders9. Using a facial mask, nebulization treatment with corticosteroids can reach simultaneously the upper and the lower respiratory tract.

This is the first study that compare two different nebulized corticosteroid in children with mild to moderate persistent asthma and the results showed that both BDP and BUD suspensions for nebulization significantly improve lung function and all spirometric parameters evaluated during the study period. The decrease in asthma score observed in this study was similar to the reductions reported by other authors in paedi atric patients treated with nebulized corticosteroids10-12.

The dose- efficacy relation between BDP and BUD showed in this study is similar to previous evidence in which the daily prescribed dose was higher in patients receiving BUD independent by of the age and type of inhalation device13.

In conclusion, this study demonstrate that the nebulization therapy is an effective method for the administration of inhaled drugs and can overcome the problems associates with the administration of inhaled corticosteroids with other devices in paedi atric pa-
tients. Moreover the results showed that both BDP (800 µg/daily) and BUD suspensions for nebulization (1000 µg/daily) are effective, therapeutically equivalent and with a good safety and tolerability profile.

References


Acknowledgements

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