Comparison of the efficacy and safety of beclometasone dipropionate suspension for nebulization and beclometasone dipropionate via a metered-dose inhaler in paediatric patients with moderate to severe exacerbation of asthma

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Abstract Nebulization simplifies the administration of effective inhaled medications to young asthmatics who experience hand-to-lung co-ordination problems and inspiratory difficulties associated with metered-dose and dry-powder inhalers, respectively. The objective of this double-blind, double-dummy, multicentre, randomized, parallel-group study was to compare the efficacy and safety of corticosteroids given by nebulization or metered-dose inhalation in paediatric patients with exacerbation of asthma. Following a 24-h run-in period, 151 patients, aged 6–16 years, with moderate to severe exacerbation of asthma were randomized to one of two treatment groups for 4 weeks: beclometasone dipropionate (BDP) suspension for nebulization 1600 µg day-1 b.i.d. given via a nebulizer (n=75), or BDP spray 800 µg day-1 b.i.d. given via a metered-dose inhaler (MDI) plus spacer (BDP MDI) (n=76). Superimposable and statistically significant improvements over baseline were noted at study end for the two treatment groups in the various efficacy parameters evaluated (pulmonary function tests, asthma symptoms scores, and the use of rescue salbutamol). The primary efficacy endpoint was the morning pulmonary expiratory flow rate (PEFR). In the BDP nebulization group, mean morning PEFR increased statistically significantly from 233.2 ± 86.3 l min-1 to 322.0 ± 101.8 l min-1, while in the BDP MDI group the increase was from 222.9 ± 87.3 l min-1 to 314.9 ± 96.6 l min-1. Moreover, an additional 4-week treatment period at half doses, completed by 26 patients, demonstrated that improvements were maintained or further enhanced. The two treatments were equally well tolerated. A total of 25 and 26 patients in the BDP nebulization and BDP MDI groups, respectively, reported adverse events during the treatment period, and these were generally mild. In conclusion, the results of this study demonstrate that BDP suspension for nebulization 1600 µg day-1 given via a nebulizer and BDP spray 800 µg day-1 given via an MDI plus spacer are equally effective, with an acceptable safety and tolerability profile, when used in paediatric patients with moderate to severe asthma exacerbation.

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INTRODUCTION

Inhaled corticosteroids are recommended for the long-term control of asthma in children (1). However, many children are unable to use the available pressurized metered-dose inhalers (MDIs) or dry-powder inhalers correctly or effectively, possibly resulting in undertreatment with anti-inflammatory drugs and overuse of oral steroids and inhaled β-agonists (1). Inhaled corticosteroids can be easily administered to paediatric asthmatics by nebulization, which can overcome the problems associated with other delivery systems (2,3). Indeed, nebulization of inhaled steroids now appears to be the most effective method for domiciliary treatment in young children with asthma.

The purpose of this study was to compare the efficacy and safety of a new formulation of beclometasone dipropionate (BDP) suspension for nebulization...
administered via a nebulizer with BDP spray administered via an MDI plus spacer (BDP MDI) in school-age children with moderate to severe exacerbation of asthma.

MATERIALS AND METHODS

Male and female children, aged ≥ 6 to ≤16 years, with a clinical diagnosis of exacerbation of asthma of moderate to severe degree [as defined by the National Heart, Lung and Blood Institute (4)], predicted normal forced expiratory volume in 1 second (FEV₁) at study entry of between ≥ 50% and ≤ 80% (5), and a positive response to the reversibility test (defined as an increase of at least 10% in FEV₁ measured 15 minutes following two puffs (2 × 100 μg) of inhaled salbutamol MDI) were eligible to participate in the study. Patients with evidence of symptomatic infection of the airways in the previous 4 weeks, with the likelihood of exposure during the study to allergens or occupational sensitizing agents of a seasonal or episodic nature proven or suspected to affect the patients, with a history of clinically significant cardiac, renal, neurological, hepatic, or endocrine disease, treated with steroids in the previous 4 weeks (8 weeks for depot steroids), hypersensitive to inhaled corticosteroids, involved in another trial in the previous 4 weeks, and with 2 ± 15% increase in FEV₁ from start to end of the study run-in period were excluded from the randomization.

Study design

This was a 4–8-week, double-blind, double-dummy, randomized, controlled, open-labelled study undertaken in two parallel groups at six centres. Following a 24-h run-in period in which non-permitted medications were withdrawn, patients who met study entry criteria were assigned by randomization to one of the two treatment groups for a treatment period of 4 weeks: BDP suspension for nebulization 1600 μg day⁻¹ b.i.d. (Clenil-A®, Chiesi Farmaceutici SpA, Italy), plus four puffs twice-daily of placebo spray, or BDP spray 800 μg day⁻¹ b.i.d. (four puffs twice-daily) (Becotide®, Allen & Hanburys, UK), plus placebo suspension for nebulization twice-daily. The suspension for nebulization was administered using a Pari Boy® compressor and an LC Plus® nebulizer (Pari Turbo Boy®) (Pari, Germany), and the spray was given via an MDI plus spacer (Volumatic®, Allen & Hanburys, U.K.). If required by the investigator, patients were allowed to continue treatment for an additional nonmandatory 4 weeks at half doses. Theophylline, anticholinergics, inhaled (other than the test BDP) or oral corticosteroids, long-acting inhaled bronchodilators, oral bronchodilators, oral antihistamines, and leukotriene antagonists were excluded. The use of inhaled salbutamol (Ventolin®, Glaxo-Wellcome, U.K.) given via an MDI, inhaled or oral sodium cromoglycate or nedocromil sodium in patients already receiving this, and appropriate treatment for concomitant disease if it did not interfere with study evaluation parameters was permitted. Patients were assessed at various clinic visits during the study: at the start of the run-in period, at the start of active treatment, and at 1, 2, and 4 weeks post-randomization. An additional visit was made after 8 weeks if the patients continued non-mandatory test treatment for a further 4 weeks.

Lung function measurements were conducted according to the Official Statement of the European Respiratory Society (6) in the morning at approximately the same hour of the day. Spirometric lung function parameters were measured at each clinic visit. Morning and evening peak expiratory flow rates (PEFRs) were measured daily, before the administration of the test treatment, by patients using the Mini-Wright® peak flow meter (Markos, Italy/Clement Clarke International, U.K.) and the highest of three measurements recorded on a diary card. Asthma symptoms scores, rated on a five-point scale (from 0= no symptoms to 5= symptoms so severe that patient did not sleep/could not perform normal daily activities), and salbutamol consumption, were also assessed, twice-daily, by patients and recorded on a diary card. Patient and investigator opinions of efficacy, and investigator opinion of tolerability, were rated on a four-point scale ranging from ‘poor’ to ‘excellent’ and recorded at study end. Morning serum cortisol levels were measured at the start and end of randomization, and vital signs at each clinic visit. The institutional review board for each treatment centre approved the protocol, and written informed consent was obtained from the parents or guardians of the patients.

Assessments

The primary efficacy endpoint was morning PEFR. Secondary efficacy variables were evening PEFR, FEV₁, forced vital capacity (FVC), day- and night-time consumption of salbutamol, morning and evening asthma symptoms scores, and patient and investigator opinions of efficacy. The primary safety parameter was the morning serum cortisol level. Secondary safety variables included adverse events and adverse drug reactions, vital signs (heart rate and blood pressure), and investigator opinion of tolerability.

Statistical analysis

Sample size calculation (7) was based on the criteria of equivalent efficacy between the two treatments. Considering as the primary efficacy variable the final mean value of morning PEFR, the following was taken into account: the baseline-adjusted final mean value obtained in the BDP MDI group was estimated to equal
300 l min⁻¹; the equivalence of efficacy between groups was defined as a difference between mean values not more than 10% of the BDP MDI mean; the standard deviation of the difference between mean values was estimated as equal to 70 l min⁻¹; the expected difference between the mean value in the two groups was estimated as equal to 0; the power of the trial was defined as equal to 80% and the level of significance equal to 5%.

With the exception of the main efficacy analysis, where statistical analysis was performed using a unilateral confidence interval, all P values and confidence intervals for percentages of change from baseline were calculated on a bilateral basis. Missing data were replaced with the LOCF (last observation carried forward) method.

Statistical significance in the study was declared if P<0.05. Baseline values were compared using a two-sided Mann-Whitney test for continuous variables, and by the Chi-square test or Fisher's exact test for categorical variables. Values for parameters recorded on diary cards in the 24-hour run-in period, and values recorded at the end of the run-in period at the clinic, were considered as baseline.

Within-treatment comparisons for morning PEFR were analysed by calculating the 95% confidence interval for the mean change from baseline, and between-treatment comparisons by using the analysis of covariance (ANCOVA) model at each 1-week period. This model included terms for investigator and treatment effects and baseline value as a covariate. A preliminary test for the investigator-by-treatment interaction was undertaken at 0.10 significance level. The non-inferiority of BDP nebulization to BDP MDI was evaluated by calculating the lower limit of the unilateral 95% confidence interval for the difference between the least square means (LSM), from ANCOVA, in the two groups, with BDP nebulization being defined as non-inferior to BDP MDI if this lower limit did not exceed 10% of the LSM of the BDP MDI.

Secondary efficacy parameters were analysed by calculating the 95% confidence interval for the mean change from baseline at each visit, and between-treatment comparisons were undertaken using ANCOVA. Patient and investigator opinions of efficacy were compared using the Chi-square test.

Morning cortisol serum levels and cardiovascular parameters were analysed by calculating the 95% confidence intervals for the changes from baseline. Between-treatment comparisons for cortisol levels were made using the unpaired t test, for the incidence of adverse events, and adverse drug reactions, using the Chi-square test or the two-tailed Fisher's exact test, and for investigator opinion of tolerability using the Chi-square test.

RESULTS
Patient population
Of the 163 patients screened for the study, 151 were randomized: 75 to the BDP nebulization group, and 76 to the BDP MDI group. Seven patients (all in the BDP nebulization group) were withdrawn during the active treatment period due to various reasons: the intent-to-treat (ITT) population was therefore made up of 144 patients, the same as for the per protocol population since there were no major protocol deviations. Assessment of safety of the two treatments was based on the randomized population. For the additional 4-week study, 26 patients participated: 14 in the BDP nebulization group, and 12 in the BDP MDI group. Patient demography and values for lung function parameters at baseline were comparable for the two groups in the randomized population (Table I).
Evaluation of efficacy: Morning PEFR

Comparable and statistically significant improvements in morning PEFR were reported over baseline in both the BDP nebulization and BDP MDI groups at the end of the initial 4-week treatment period. In the BDP nebulization group, mean values increased from 233·2 l min$^{-1}$ to 322·0 l min$^{-1}$, while in the BDP MDI group the increase was from 222·9 l min$^{-1}$ to 314·9 l min$^{-1}$ (Figure 1). The lower limit of the unilateral 95% confidence interval was -21·7 and did not exceed -10% (~32·0 of the LSM of the BDP MDI group, thus demonstrating that BDP nebulization was not inferior to BDP MDI. In addition, the 95% bilateral confidence intervals for the difference between the LSM in the ANCOVA model was -20·6; 25·4 and fell within 10% of the LSM of the BDP MDI group (±32·0 l min$^{-1}$) to confirm that the two treatments were equivalent following 4 weeks of treatment. Moreover, in the additional 4-week treatment period mean morning PEFR values increased further for both groups in the completer population: from 342·6 l min$^{-1}$ at week 4 to 360·7 l min$^{-1}$ at week 8 ($P=0·012$) in the BDP nebulization group, and from 296·5 l min$^{-1}$ to 317·1 l min$^{-1}$ ($P=0·191$) in the BDP MDI group (Figure 1).

Evaluation of efficacy: Other measures of pulmonary function

In the BDP nebulization group, evening PEFR improved statistically significantly from a mean of 241·7 l min$^{-1}$ at baseline to 330·8 l min$^{-1}$ after 4 weeks' treatment, and in the BDP MDI group from 237·1 l min$^{-1}$ to 323·0 l min$^{-1}$, with no significant difference noted between the two treatments (Figure 2). For the additional 4 week period of treatment, mean values increased progressively in the two groups from week 4 to week 8: from 354·9 l min$^{-1}$ to 371·0 l min$^{-1}$ in the BDP nebulization group, and from 303·3 l min$^{-1}$ to 318·4 l min$^{-1}$ in the BDP MDI group (Figure 2).

Mean FEV$_1$ rose statistically significantly in the BDP nebulization group from 1·4 litres at day 1 to 2·0 litres at treatment end, and in the BDP MDI group from 1·5 to 2·1 litres, with no significant between-group difference.
noted (Figure 2). Mean values increased again for both groups in the additional 4-week period of treatment: from 2.2 litres at week 4 to 2.3 litres at week 8 in the BDP nebulization group, and from 2.1 to 2.3 litres in the BDP MDI group (Figure 2).

In the BDP nebulization group, mean FVC increased statistically significantly from 1.8 litres at day 1 to 2.3 litres after 4 weeks' treatment, and in the BDP MDI group from 1.8 to 2.4 litres, with no significant difference found between the two treatments (Figure 2). In the additional 4-week treatment period, further increases in mean values were reported: from 2.6 litres at week 4 to 2.7 litres at week 8 and from 2.6 to 2.8 litres in the BDP nebulization and BDP MDI groups, respectively (Figure 2).

**Evaluation of efficacy: Signs and symptoms and rescue medication**

Following treatment for 4 weeks, superimposable and statistically significant improvements in morning and evening asthma symptoms scores were reported for the two treatment arms. Mean values fell in both groups from 1.8 at baseline to 0.4 at treatment end for morning scores, and from 1.9 to 0.5 in the BDP nebulization group and 1.9 to 0.5 in the BDP MDI group in evening scores. Moreover, in the additional 4-week treatment period improvements were maintained or further enhanced in both groups, with mean morning scores falling from 0.6 at week 4 to 0.4 at week 8 in the BDP nebulization group, and from 1.0 to 0.7 in the BDP MDI group, and mean evening scores from 0.6 to 0.4 in the BDP nebulization group, and from 1.0 to 0.7 in the BDP MDI group.

Equivalent statistically significant reductions were also reported in morning and evening salbutamol consumption in both groups at the end of the 4-week treatment period when compared with baseline. For morning consumption, the mean number of puffs fell from 0.8 puffs day\(^{-1}\) to 0.2 puffs day\(^{-1}\) in the BDP nebulization group, and from 0.9 puffs day\(^{-1}\) to 0.2 puffs day\(^{-1}\) in the BDP MDI group, and for evening consumption from 2.1 puffs day\(^{-1}\) to 0.5 puffs day\(^{-1}\) in the BDP nebulization group, and from 1.9 puffs day\(^{-1}\) to 0.6 puffs day\(^{-1}\) in the BDP MDI group. Values remained stable or further declined for the additional 4-week treatment period: changes from 0.5 puffs day\(^{-1}\) at week 4 to 0.3 puffs day\(^{-1}\) at week 8 were noted for the BDP nebulization group, and from 0.3 puffs day\(^{-1}\) to 0.2 puffs day\(^{-1}\) in the BDP MDI group, for morning use; and from 1.1 puffs day\(^{-1}\) to 0.7 puffs day\(^{-1}\) in the BDP nebulization group, and from 1.0 puffs day\(^{-1}\) to 1.1 puffs day\(^{-1}\) in the BDP MDI group, for evening use.

**Evaluation of efficacy: Patient and investigator opinions**

According to patient opinion, almost all patients in both treatment groups considered efficacy as 'excellent' or 'good' (98.5% and 100% of patients in the BDP nebulization and BDP MDI groups, respectively), with no significant difference noted between the two treatment arms. Similarly, according to investigator opinion nearly all patients in the two groups reported efficacy as 'excellent' or 'good' (91.3% and 97.4% in the BDP nebulization and BDP MDI groups, respectively), with the between-treatment difference again being non-significant.

**Evaluation of safety**

Safety data showed that both treatments were well tolerated. During the treatment period, 25 (33.3%) patients in the BDP nebulization group and 26 (34.2%) in the BDP MDI group reported adverse events (NS between treatments) (Table 2). The respective number of adverse events was 43 and 48, and these were generally mild.

The two treatments had a comparable effect with respect to morning serum cortisol levels, and no clinically relevant changes were reported for vital signs in either group (NS between treatments). Furthermore, investigator opinion of tolerability was 'excellent' or 'good' for all patients in both groups, with no significant difference noted between the two treatments.

**DISCUSSION**

This study was designed to evaluate the efficacy and safety of a new formulation of BDP suspension for nebulization given via a nebulizer and BDP spray given using an MDI plus spacer as a 4-week treatment for moderate–severe asthma exacerbation in paediatric patients. An additional 4-week treatment period was undertaken in order to verify if patients could benefit from longer maintenance therapy at half doses.
Although no previous studies have compared the effects of BDP delivered by nebulizer and MDI, two studies in asthmatic children assessed the effects of terbutaline via either nebulizer or MDI plus spacer. One study of 12 asthmatic children found no statistical difference in FEV\textsubscript{1} increase between 500 \( \mu \)g terbutaline via MDI and 4 mg by nebulizer, although the direction of effect did favour the latter. At 1 mg MDI there was again no statistical difference but the direction of effect favoured the MDI (8). A second study involving 22 asthmatic children found no statistical difference in any measures of lung function or patient-reported symptom scores following administration of terbutaline by MDI or nebulizer with an MDI:nebulizer dose ratio of 1:4 (9).

The results of this study demonstrated that nebulized and MDI forms of BDP significantly, and to a similar degree, improved pulmonary function and asthma symptoms scores, and reduced the need for rescue medication. Almost all patients in both groups also considered efficacy to be ‘good’ or ‘excellent’. Moreover, statistical analysis of the results for the primary efficacy variable of morning PEFR confirmed that BDP nebulization was not inferior to BDP MDI and that the two treatments were equivalent. Furthermore, improvements were maintained or further enhanced when both treatments were used for an additional 4 weeks at half doses. The improvements in pulmonary function tests and symptoms, and the equivalence between the two delivery systems, are noteworthy if it is taken into account that the children were suffering from asthma exacerbation and had FEV\textsubscript{1} values of around 60% of the predicted normal (moderately to severe exacerbation) at study entry. Consequently, there was wide scope for improvement, and the results show that normal pulmonary function was restored following treatment and by a similar extent with the two delivery systems. In addition, the safety profile was comparable for the two groups with respect to the incidence of adverse events, potential adrenal suppression (as indicated by morning serum cortisol levels), and vital signs.

In conclusion, this study demonstrates that BDP suspension for nebulization 1600 \( \mu \)g day\textsuperscript{-1} given via a nebulizer and BDP spray 800 \( \mu \)g day\textsuperscript{-1} given via an MDI plus spacer are effective and therapeutically equivalent, with a good safety and tolerability profile, when used as a treatment for asthma exacerbation in school-age children.

REFERENCES