

The response of two different dosages of beclometasone dipropionate suspension for nebulization versus a standard dose of beclometasone dipropionate via a metered-dose inhaler on bronchoprovocation testing in adults with asthma

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Abstract The objective of this double-blind, randomized, placebo-controlled, parallel-group study was to compare the pharmacodynamic effects and safety of beclometasone dipropionate (BDP) given by nebulization or metered-dose inhalation in adult patients with asthma. Following a 1-week run-in period, 40 patients, aged 18–60 years, with intermittent bronchial asthma were randomized to one of four treatment groups for 3 weeks ($n=10$ in each group): beclometasone dipropionate (BDP) suspension for nebulization 1600 $\mu\text{g day}^{-1}$ b.i.d. via a nebulizer, BDP suspension for nebulization 3200 $\mu\text{g day}^{-1}$ b.i.d. via a nebulizer, BDP 800 $\mu\text{g day}^{-1}$ b.i.d. via a metered-dose inhaler (MDI) plus spacer, or placebo. At study end, comparable effects were reported for all active treatment groups on the primary pharmacodynamic endpoint of FEV_1 in response to methacholine bronchial provocation testing, with a statistically significant improvement shown in the BDP 3200 $\mu\text{g day}^{-1}$ suspension for nebulization group compared with pre-treatment for other parameters, including FEV_1 and peak expiratory flow rates. All treatments were comparable. All treatments were equally well tolerated. No significant effects on cortisol levels were reported in any of the treatment groups.

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INTRODUCTION

The aim of treatment with nebulizers is to deliver a therapeutic dose of the drug in the form of respirable particles within a short period of time, usually 5–10 minutes (1). Efficient nebulizer therapy requires a device that repeatedly and quickly delivers sufficient drug to the site of the action and with minimal wastage. Nebulizers used in aerosol drug delivery produce a polydisperse aerosol where most of the drug released is contained in particles 1–5 μm in diameter. Most nebulizers use compressed air for administration, but some use ultrasonic energy (2,3).

It has been reported that beclometasone dipropionate (BDP) suspension for nebulization 800 μg , delivered via a nebulizer, yields a respirable dose of 195 μg , which is approximately double the respirable dose obtained with BDP pressurized MDI 250 μg (95 μg), thus suggesting that in order to attain equivalent *in-vivo* performance the nebulizer product would be expected to be used in a dose ratio of 2:1 with respect to the pressurized inhaler (4).

The purpose of this clinical pharmacology study was to establish a dose–response relationship for a new

formulation of BDP suspension for nebulization by comparing the efficacy and safety of two different dosages administered via a nebulizer with those of a standard dose of BDP administered via an MDI plus spacer (BDP MDI) in adults with intermittent bronchial asthma, using the methacholine bronchoprovocation test as the primary pharmacodynamic variable and the measurement of FEV_1 and peak flow as secondary endpoints.

MATERIALS AND METHODS

Male and female patients, aged 18–60 years, with a clinical diagnosis of bronchial asthma of intermittent severity (as defined according to the GINA classification), predicted forced expiratory volume in 1 second (FEV_1) of $\geq 80\%$ at screening after at least an 8-h washout of inhaled β -agonist, positive response to the bronchial provocation test to methacholine (defined as a decrease of 20% in FEV_1 with inhalation of $\leq 8 \text{ mg ml}^{-1}$), and body mass index of 18–35 kg m^{-2} , and who were ambulatory, were eligible to participate in the study. Patients with a history of clinically significant major disorders or who received

an investigational drug in the previous 3 months were excluded from the randomization.

Study design

This was a 4-week, double-blind, randomized, placebo-controlled study undertaken in four parallel groups at two centres. Following a 1-week run-in period, patients who met study entry criteria were assigned to one of the four treatment groups for an active treatment period of 3 weeks: BDP suspension for nebulization 1600 $\mu\text{g day}^{-1}$ b.i.d. (Clenil-A®, Chiesi Farmaceutici SpA, Italy), plus placebo suspension for nebulization twice-daily, plus two puffs twice-daily of placebo spray; BDP suspension for nebulization 3200 $\mu\text{g day}^{-1}$ b.i.d., plus two puffs twice-daily of placebo spray; BDP spray 800 $\mu\text{g day}^{-1}$ b.i.d. (Becotide®, Allen & Hanburys, U.K.) (two puffs twice-daily), plus placebo suspension for nebulization twice-daily; or placebo suspension for nebulization twice-daily, plus two puffs twice-daily of placebo spray. The suspension for nebulization was administered using the air compression Pari LC Plus® nebulizer (Pari Turbo Boy®) (Pari, Germany), and the spray was given via an MDI plus spacer (Volumatic®, Allen & Hanburys, U.K.). Theophyllines, inhaled (other than the test BDP) or oral corticosteroids, and long-acting inhaled β -agonists were excluded. The use of short-acting inhaled β_2 -agonists at the same dosage used previously, inhaled or oral sodium cromoglycate or nedocromil sodium at a constant dosage during the study period, oral β -agonists, anticholinergics, antihistamines, and leukotriene antagonists was permitted. Patients were assessed at clinic visits before and postrandomization.

Bronchoprevention testing was performed at baseline and after 3 weeks of study medication. Increasing concentrations of methacholine from 0.0625 mg ml^{-1} to 128 mg ml^{-1} were administered via an air compressor-driven nebulizer (Pari LC Plus®), doubling the concentration at each step. FEV₁ was measured following each increase in methacholine dose. FEV₁, measured using the Vitalograph-compact spirometer, physical examination, vital signs, temperature, laboratory safety tests, and random morning serum cortisol levels were assessed at baseline and at the end of the treatment. Morning peak expiratory flow rate (PEFR) was measured daily by patients using a Mini-Wright® peak flow meter (Clement Clarke International, Essex, U.K.) and the best of three measurements recorded on a diary card. The institutional review board for each treatment centre approved the protocol, and written informed consent was obtained from the patients.

Assessments

The primary pharmacodynamic endpoint was the change in FEV₁ in response to methacholine bronchial provocation testing, by determining the change in concentration of methacholine that resulted in 20% reduction in FEV₁

from baseline (PC₂₀). Secondary pharmacodynamic variables were FEV₁, morning PEFR, and PEFR variability. Safety parameters were random morning cortisol levels, physical examination, vital signs, temperature, various laboratory safety tests, and adverse events.

Statistical analysis

No formal power calculations were undertaken for this study since it is an efficacy study and hence there should be adequate data for power. The sample size was based on previous data from similar studies involving comparisons of inhaled steroids in mild asthmatics using methacholine bronchial provocation as a method to determine efficacy.

Statistical analysis of the bronchial provocation test was carried out by calculating the mean ratio of PC₂₀ values at study end/PC₂₀ values pretreatment, of predicted FEV₁ by calculating the difference in mean values between baseline and study end, of morning PEFR and PEFR variability by calculating the difference between mean values at the start of run-in – pretreatment and poststudy, and of random cortisol concentrations by calculating the difference between mean values at baseline and study end. Within- and between-treatment comparisons were undertaken using one- or two-sample *t* tests.

RESULTS

Patient population

In total, 40 patients were randomized: 10 to the BDP 1600 $\mu\text{g day}^{-1}$ nebulization group, 10 to the BDP 3200 $\mu\text{g day}^{-1}$ nebulization group, 10 to the BDP MDI group, and 10 to the placebo group. All enrolled patients completed the trial. Assessment of safety was based on all randomized patients. Patient demography at baseline was comparable for the four groups in the randomized population (Table 1).

Evaluation of efficacy: bronchial provocation test

Increases in PC₂₀ were seen with all active treatment groups at the end of the 3-week treatment period compared with pretreatment, with the improvement reported in the BDP 3200 $\mu\text{g day}^{-1}$ nebulization group being statistically significant. However, there were no statistically significant differences in PC₂₀ between any of the active treatment groups at the end of the study. The mean study end/pretreatment bronchoprovocation test ratio for each treatment group is shown in Figure 1.

Evaluation of efficacy: Other measures of pulmonary function

Similar changes in mean predicted FEV₁ values were observed in all active treatment groups at treatment end when compared with baseline.

Table 1. Baseline demographic data for the randomized population of adults with intermittent bronchial asthma treated with beclomethasone dipropionate given by nebulization or metered-dose inhalation, or placebo

Demographic characteristics	Beclomethasone dipropionate via a nebulizer 1600 µg day ⁻¹	Beclomethasone dipropionate via a nebulizer 3200 µg day ⁻¹	Beclomethasone dipropionate via a metered-dose inhaler 800 µg day ⁻¹	Placebo
Mean ± SD age (years)	29 ± 3.7	24 ± 5.1	26 ± 8.3	26 ± 7.2
Mean ± SD weight (kg)	66.7 ± 9.5	71.9 ± 15.0	70.6 ± 8.5	72.7 ± 10.7
Mean ± SD height (m)	1.7 ± 0.1	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.1
Mean ± SD body mass index (kg m ⁻²)	23.2 ± 2.0	22.3 ± 2.9	22.8 ± 3.2	23.1 ± 3.6

Table 2. Mean values for morning peak expiratory flow rates (l min⁻¹ ± SD)

	Day (-7)–day 1	Day 14–21
Beclomethasone dipropionate via a nebulizer 1600 µg day ⁻¹	489.68 ± 17.98	476.13 ± 3.34
Beclomethasone dipropionate via a nebulizer 3200 µg day ⁻¹	545.36 ± 6.88	546.16 ± 8.94
Beclomethasone dipropionate via a metered-dose inhaler 800 µg day ⁻¹	542.75 ± 20.45	539.19 ± 8.08
Placebo	569.75 ± 11.7	568.38 ± 9.46

P < 0.05: placebo vs active treatment groups at baseline

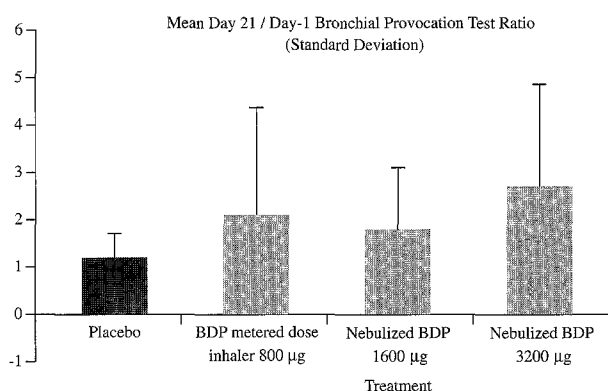
Changes in morning PEFR were of limited clinical significance because patients were mild asthmatics with high baseline PEFR values and statistically significant differences were found between the groups prior to treatment (Table 2).

Both of the BDP nebulization groups produced similar changes in mean PEFR variability at study end vs pretreatment, and an increase was shown in the BDP MDI group that was statistically significant. This unexpected latter finding may be explained by the fact that the group size was not powered.

Evaluation of safety

Safety data showed that all active treatments were well tolerated. During the treatment period, 23 patients (five patients each in the BDP 1600 µg day⁻¹ nebulization, BDP MDI, and placebo groups, and seven in the BDP 3200 µg day⁻¹ nebulization group) reported adverse events. The number of adverse events reported was 82: 13, 34, 19, and 15 in the BDP 1600 µg day⁻¹ nebulization, BDP 3200 µg day⁻¹ nebulization, BDP MDI, and placebo groups, respectively, and these tended to be mild to moderate in severity and were most commonly headache and sore throat. Of these adverse events, 16 were considered to be related to treatment, with seven of these occurring in placebo-treated patients. No patients were withdrawn from the study due to the adverse events reported.

In addition, no notable changes in mean random morning cortisol levels were seen in any of the groups at the end of the treatment period vs baseline, and no significant between-treatment differences were found (Figure 2). Moreover, no clinically significant changes

**FIGURE 1.** Mean values for study end/pretreatment broncho-provocation test ratio (standard deviation) in the randomized population of adults with intermittent bronchial asthma after 3 weeks of treatment with beclomethasone dipropionate given by nebulization or metered-dose inhalation, or placebo.

were reported in any of the groups during the treatment period for vital signs or temperature, and none of the abnormal findings noted for physical examination or laboratory safety tests was considered to be of relevance with respect to the study or study treatments.

DISCUSSION

This study was designed to evaluate the efficacy and safety of two different dosages of a new formulation of BDP given via a nebulizer and a standard dose of BDP given using an MDI plus spacer as a 3-week treatment for intermittent bronchial asthma in adult patients.

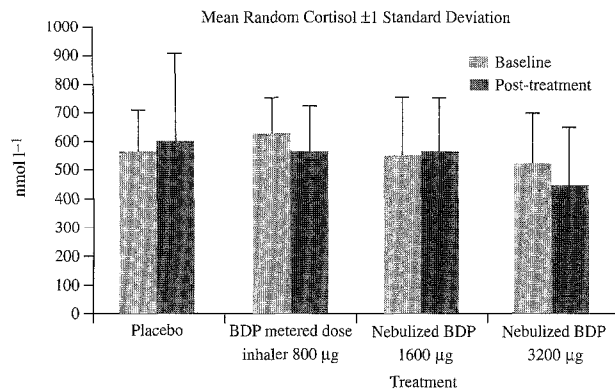


FIGURE 2. Mean values for random morning cortisol levels \pm standard deviation in the randomized population of adults with intermittent bronchial asthma at baseline and after 3 weeks of treatment with beclomethasone dipropionate given by nebulization or metered-dose inhalation, or placebo.

Several studies have compared the efficacy of budesonide given via nebulizer and MDI. In a study of 21 adult patients with asthma, budesonide suspension delivered from a nebulizer activated during inspiration exhibited a dose-dependent effect, apparently equipotent to the MDI administration as evaluated from daily peak expiratory flow (PEF) measurements and symptom scoring (5). Continuous nebulization of budesonide in 18 schoolchildren with bronchial asthma similarly showed a dose-dependent improvement of lung function and symptom score, though in a 1:2 potency ratio compared with MDI administration (6). More recently, a study involving 26 adult asthmatics compared budesonide 0.8 mg twice-daily administered by pMDI with spacer and budesonide 1 mg and 4 mg twice-daily administered by a Pari Inhaler Boy jet nebulizer, activated only during inspiration. The total mass output was similar from the two devices, but their fraction of small particles differed by a factor of 2 in favour of pMDI. Effect was evaluated from daily home measurements of PEF, need of β_2 -agonist, and symptom scores. A consistent trend showed the nebulizer treatment to be at least as efficient as the pMDI plus spacer treatment. In actual fact, the apparent order of effect was 4 mg nebulized suspension treatment \geq 1 mg nebulized suspension treatment \geq 0.8 mg pMDI with spacer treatment (7).

The primary objective of this study was to determine the effect of the treatments on FEV₁ in response to methacholine challenge, with the bronchial provocation test ratio being the main efficacy variable. The results of the methacholine test expressed as a ratio of PC₂₀ after 3 weeks' treatment compared with the PC₂₀ value before treatment, although not statistically significant (probably due to the small sample size in each treatment

group), demonstrated a protection of bronchial hyper-reactivity with the different types of active treatment, a significant dose effect at the highest dosage level of nebulized BDP, and equivalent effects with BDP 1600 $\mu\text{g day}^{-1}$ nebulization and BDP MDI 800 $\mu\text{g day}^{-1}$. The data showed that only nebulized BDP 3200 $\mu\text{g day}^{-1}$ produced a significant change in PC₂₀ between pretreatment and study end, but a between-treatment analysis indicated that there was no treatment-related difference when compared with placebo.

The study was intended as a comparison of efficacy on bronchial reactivity to confirm a dose response and that the 2:1 ratio of nebulized BDP to BDP MDI was appropriate. The within-treatment difference observed with BDP nebulization 3200 $\mu\text{g day}^{-1}$ compared with baseline is supportive of a trend towards a dose response. The absence of between-treatment differences indicates that the proposed 2:1 ratio is appropriate, and that BDP nebulization 1600 $\mu\text{g day}^{-1}$ is indistinguishable from BDP MDI 800 $\mu\text{g day}^{-1}$. The increased systemic exposure would justify use of BDP 3200 $\mu\text{g day}^{-1}$ nebulization in subjects with more severe asthma.

All three active treatments were equally well tolerated, as demonstrated by examining a number of safety parameters. Furthermore, morning serum cortisol levels remained within normal ranges and, although not statistically significant (probably on account of the small number of patients in each group), the results indicated a dose effect with nebulized BDP and an absence of any detrimental effect with the lower dose (1600 $\mu\text{g day}^{-1}$).

In conclusion, this study demonstrates that BDP suspension for nebulization 1600- and 3200 $\mu\text{g day}^{-1}$ given by a nebulizer and BDP spray 800 $\mu\text{g day}^{-1}$ given via an MDI plus spacer have equivalent effects with respect to the bronchoprovocation test, with a good safety and tolerability profile.

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