

Comparison of the efficacy of beclometasone dipropionate and fluticasone propionate suspensions for nebulization in adult patients with persistent asthma

C. TERZANO¹, A. RICCI¹, V. BURINSCHI², K. NEKAM³ AND J. LAHOVSKY⁴

¹University La Sapienza, Rome, Italy; ²Institute of Physiopulmonology, Chisinau, Moldova; ³Department of Allergology and Clinical Immunology, Budapest, Hungary; ⁴Department of Allergology, Prague, Czech Republic

Abstract The use of nebulization for the administration of inhaled steroids plays an important role in asthma patients who are unable to use pressurized aerosol or dry-powder inhalers effectively. Moreover, the type of nebulizer used may affect how much drug is delivered to the lungs. The objective of this multinational, multicentre, randomized, active-controlled, parallel-group study was to compare the efficacy and safety of nebulized corticosteroids in adult patients with chronic asthma. Following a 1-week placebo run-in period, 205 patients, aged 18–65 years, with moderate persistent asthma were randomized to one of two treatment groups for 12 weeks: beclometasone dipropionate (BDP) suspension for nebulization 2400 µg day⁻¹ b.i.d. (*n*=103), or fluticasone propionate (FP) suspension for nebulization 2000 µg day⁻¹ b.i.d. (*n*=102), both administered by a jet nebulizer. Comparable efficacy in controlling asthma was demonstrated by the two treatments at study end, as evident when evaluating various efficacy parameters (pulmonary function tests, asthma exacerbations and symptoms, and the use of rescue salbutamol). The primary efficacy endpoint was the variation in the pulmonary expiratory flow (PEF) at treatment end over the baseline visit. For the intent-to-treat population, in the BDP group mean PEF values increased statistically significantly from 5.2 ± 1.3 l s⁻¹ to 5.7 ± 1.6 l s⁻¹, while in the FP group the increase was from 5.2 ± 1.2 l s⁻¹ to 5.8 ± 1.8 l s⁻¹. Mean PEF values as per cent of predicted also increased in a statistically significant way, from 71% to 77.1% in the BDP group, and from 70.1% to 76.9% in the FP group. The two treatments were equally well tolerated. A total of 23 and 32 patients in the BDP and FP groups, respectively, reported adverse events during the treatment period, and these were generally mild. In conclusion, the results of this study demonstrate that BDP 2400 µg day⁻¹ and FP 2000 µg day⁻¹, both suspensions for nebulization administered via a jet nebulizer, are equally effective, with an acceptable safety and tolerability profile, when used in adult patients with moderate persistent asthma.

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Keywords asthma; beclometasone dipropionate; fluticasone propionate; nebulized drugs.

INTRODUCTION

Nebulization of inhaled corticosteroids plays an important role in the management of asthma patients who cannot use other delivery systems effectively. Several clinical trials have shown that both beclometasone dipropionate (BDP) and fluticasone propionate (FP) are effective and well tolerated in the management of asthma. Moreover, studies comparing these corticosteroids when administered using a pressurized metered-dose inhaler (pMDI) have demonstrated equivalent clinical efficacy when used in children and adults with asthma of varying severity (2–7). However, to date direct comparison of BDP and FP suspensions for nebulization has not been reported. The purpose of this study was to compare the efficacy and safety of BDP and FP suspensions for nebulization

administered via a new jet nebulizer in adult patients with moderate persistent asthma. The jet nebulizer was used on the basis of a previous study in which both BDP and FP were delivered via nebulization with a mean MMAD (mass mean aerodynamic diameter) of 2.6 ± 0.2.

MATERIALS AND METHODS

Male and female outpatients, aged 18–65 years, with a clinical diagnosis of moderate persistent asthma (as defined by the National Heart, Lung and Blood Institute/World Health Organization), peak expiratory flow (PEF) between 60% and 80% of predicted normal value, a positive response to the reversibility test [defined as an increase of 15% in forced expiratory volume in 1 second (FEV₁) measured 30 minutes after a

bronchodilator dose of salbutamol spray given via an MDI at the screening and baseline visits], and study medication compliance of 85% during the placebo run-in period were eligible to participate in the study. Patients with chronic obstructive pulmonary disease, a history or current evidence of heart failure and ischaemic heart disease, myocardial infarction/percutaneous transluminal coronary angioplasty/coronary artery bypass grafts within the previous 6 months, haemodynamic relevant rhythm disturbances, clinically significant or unstable concurrent diseases, or intolerance to the study drugs and/or their constituents, or who received oral or parenteral steroids or investigational new drugs in the previous 12 weeks, were excluded from the randomization.

Study design

This was a 13-week, randomized, active-controlled study undertaken in two parallel groups at 11 centres. Following a 1-week placebo run-in period, patients who met study entry criteria were assigned by randomization to one of the two treatment groups for a treatment period of 12 weeks: BDP suspension for nebulization 2400 $\mu\text{g day}^{-1}$ b.i.d. (Clenil-A®, Chiesi Farmaceutici SpA, Italy), or FP suspension for nebulization 2000 $\mu\text{g day}^{-1}$ b.i.d. (Flixotide Nebules®, Allen & Hanburys, U.K.). Both drugs were administered using the Clenny Aerosol Nebulizer (Chiesi Farmaceutici SpA, Italy), and all patients were instructed in its use. Long-acting β_2 -agonists, cromolyn sodium, nedocromil, methylxanthines, leukotriene modifiers, anticholinergics, antihistamines, and parenteral and oral corticosteroids were excluded. The use of short-acting β_2 -agonists, and of inhaled corticosteroids during the run-in phase, only at the same daily dosage used during the previous 4 weeks, was permitted. Patients were assessed at various clinic visits during the study: on screening, at the baseline/randomization visit, and at 4 and 12 weeks post-randomization.

Lung function measurements were conducted according to the ERS guidelines (8) at the same hour of the day, with a variation equal to ± 2 h compared with the baseline visit. Spirometric lung function parameters were measured at each clinic visit. The use of short-acting β_2 -agonists had to be withdrawn at least 8 hours before the tests. Three measurements were performed, and the best was reported. Asthma exacerbation was defined if one of the following criteria occurred: worsening of asthma symptoms, which required treatment with systemic steroids; a reduction in the morning PEF to $>30\%$ below the baseline value on 2 consecutive days; use of five inhalations of rescue medication on each of any 3 consecutive days since the previous visit. Morning and evening PEFs were measured daily by patients using the Mini-Wright peak flow meter (Clement Clarke International, U.K.) at the same hour each day (8 ± 1 a.m., and 7 ± 1 p.m. when possible) and the best of

three measurements recorded on a diary card. Diurnal and nocturnal asthma symptoms, rated on an eight-point scale (scores 1–8) ranging from 'poor' to 'excellent', evaluation of activity and sleep, and the use of short-acting β_2 -agonists were also assessed daily by patients and 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 efficacy endpoint was the variation in the PEF value assessed by the investigator at 12 weeks vs the baseline/randomization visit. Secondary efficacy variables were the number of exacerbations, FEV₁, forced vital capacity (FVC), morning and evening PEFs, improvements in asthma symptoms, and daily consumption of short-acting β_2 -agonists. Safety parameters included physical examination, vital signs (electrocardiograms (ECGs), blood pressure, and heart rate), routine blood and urine laboratory tests, and frequency, nature and severity of adverse events.

Statistical analysis

Sample size calculation was based on the criteria of equivalent efficacy between the two treatments (9), taking as clinically not relevant a difference between groups in PEF values of 10%. Considering that the mean expected value of final PEF (per cent of predicted) was 75, with a common standard deviation of 17 and with an α error of 0.05 (two-sided test), a total sample of 186 patients (93 per arm) will provide 85% power rejecting the null hypothesis in favour of the alternative one when a real difference between treatments will exist.

Within-treatment comparisons for the variation of PEF value assessed by the investigator at week 12 vs baseline visit were analysed by the *t* test for paired samples, and between-treatment comparisons by means of the non-parametric Kruskal-Wallis test.

When indicated, continuous secondary efficacy variables were analysed by the ANOVA (analysis of variance) model, and categorical variables were analysed comparing the two groups by the Chi-square test and, if necessary, by the Fisher's exact test.

A descriptive analysis was provided for all safety data, with absolute and relative frequencies demonstrated, together with the 95% confidence interval for each estimate. Changes from baseline of vital signs were analysed by the Student's *t* test, while between-treatment differences were analysed by the Chi-square statistic (Fisher's exact test) and within-treatment differences by the McNemar's test. Significance testing was two-tailed, with α error fixed at the 5% level.

All randomized patients with baseline evaluation of each symptom and who received at least one dose of the

Table 1. Baseline demographic and lung function data for the randomized population of adults with moderate persistent asthma treated with beclometasone dipropionate or fluticasone propionate suspensions for nebulization

Demographic characteristics/ lung function parameters	Beclometasone dipropionate	Fluticasone propionate
Gender:		
Male	39	38
Female	63	62
Total	102	100
Mean \pm SD age (years)	43.7 \pm 14.8	43.3 \pm 14.4
Mean \pm SD weight (kg)	74.2 \pm 15.3	75.7 \pm 14.7
Mean \pm SD height (cm)	168.8 \pm 9.1	168.8 \pm 9.2
Mean \pm SD PEF ($l\ s^{-1}$)	5.2 \pm 1.3	5.2 \pm 1.2
Mean \pm SD FEV ₁ (l)	2.4 \pm 0.8	2.4 \pm 0.7
Mean \pm SD FVC (l)	3.0 \pm 1.0	3.0 \pm 1.0

PEF, peak expiratory flow; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

study medication were to be included in the ITT population analysis. Missing data were replaced with the LOCF (last observation carried forward) method, except in the analysis of the number of exacerbations, days and nights without asthma symptoms, physical examination, and ECGs.

RESULTS

Patient population

Of the 222 patients screened for the study, 205 were randomized: 103 to the BDP group, and 102 to the FP group. Three patients (one in the BDP group and two in the FP group) were excluded from the efficacy analysis sample due to protocol violations at selection, and 20 patients (7 in the BDP group and 13 in the FP group) were excluded from the PP analysis due to various reasons. The ITT population was therefore made up of 202 patients (102 treated with BDP and 100 with FP),

and the PP population of 182 patients (95 treated with BDP and 87 with FP). Assessment of safety of the two treatments was based on 202 patients. Patient demography and values for lung function parameters at baseline were comparable for the two groups in the randomized population (Table 1).

Evaluation of efficacy: PEF

Statistically significant increases in PEF measured by the investigator were reported over baseline in the ITT population for both treatment arms at study end, with mean values rising from 5.2 $l\ s^{-1}$ to 5.71 $l\ s^{-1}$ in the BDP group ($P=0.0002$), and from 5.2 $l\ s^{-1}$ to 5.81 $l\ s^{-1}$ in the FP group ($P=0.0002$), and with no significant difference found between the two groups (Figure 1). Mean PEF values as per cent of predicted also increased in a statistically significant way from 71% to 77.1% in the BDP group ($P=0.0001$), and from 70.1% to 76.9% in the FP

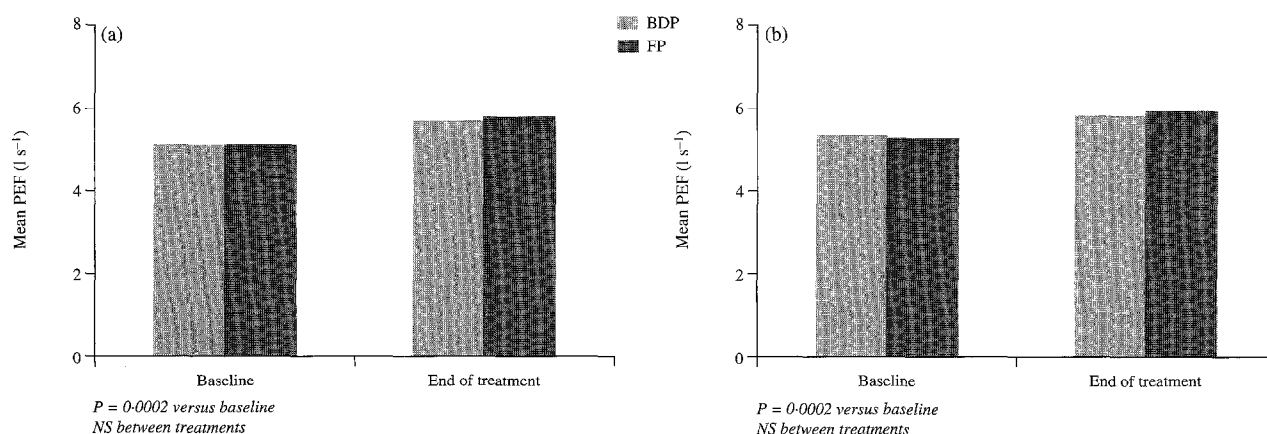


FIGURE 1. Mean values for peak expiratory flow in the (a) intent-to-treat and (b) per protocol populations of adults with moderate persistent asthma at baseline and after 12 weeks of treatment with beclometasone dipropionate or fluticasone propionate suspensions for nebulization.

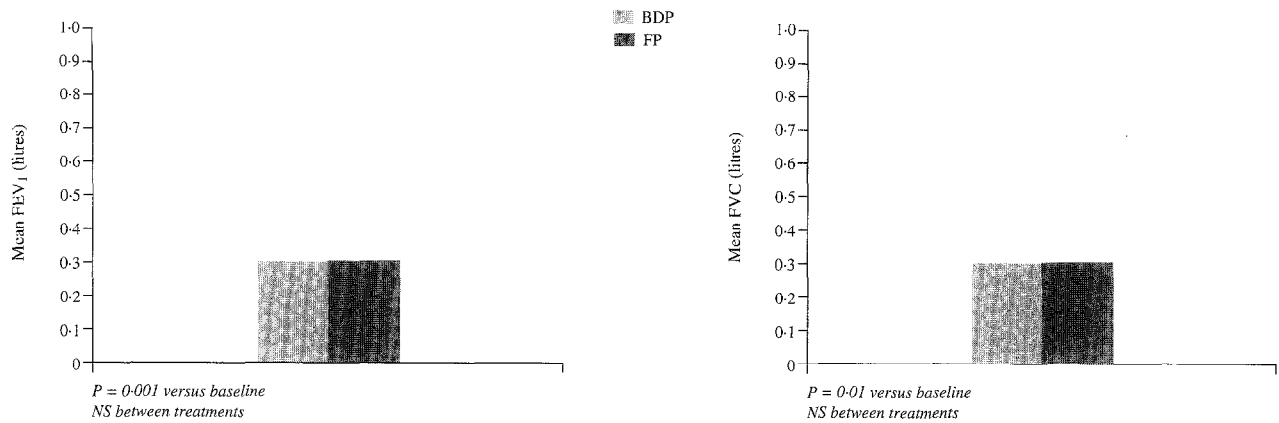


FIGURE 2. Mean changes over baseline in forced expiratory volume in 1 second and forced vital capacity in the intent-to-treat population of adults with moderate persistent asthma after 12 weeks of treatment with beclometasone dipropionate or fluticasone propionate suspensions for nebulization.

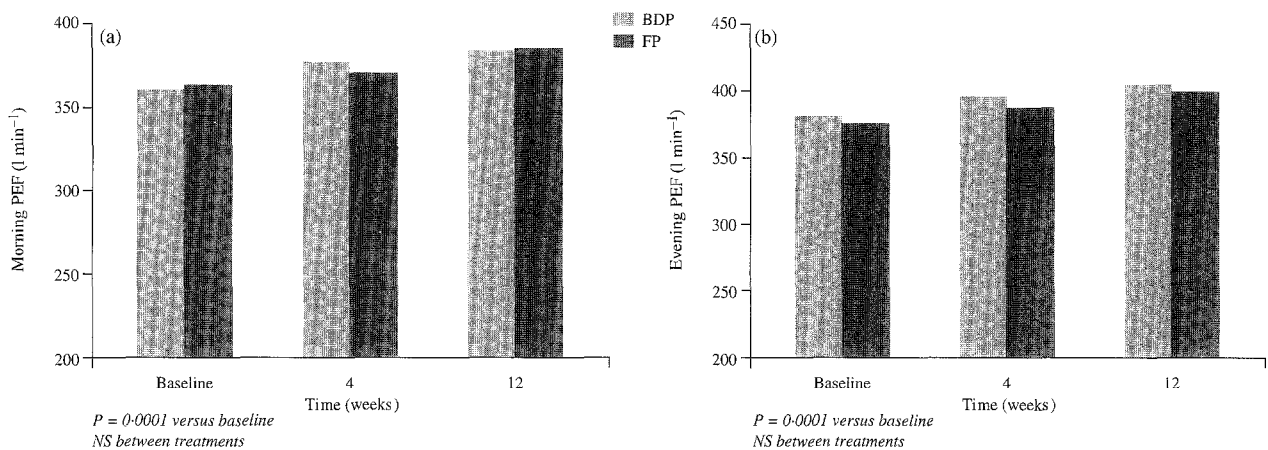


FIGURE 3. Mean values for (a) morning and (b) evening peak expiratory flow in the intent-to-treat population of adults with moderate persistent asthma at baseline, and after 4 and 12 weeks of treatment with beclometasone dipropionate or fluticasone propionate suspensions for nebulization.

group ($P=0.0002$) (NS between treatments). Similarly, in the PP population mean PEF values rose statistically significant from 5.31 s^{-1} to 5.71 s^{-1} in the BDP group ($P<0.0001$), and from 5.21 s^{-1} to 5.81 s^{-1} in the FP group ($P=0.0002$), with the between-group difference again being non-significant (Figure 1). Mean values as per cent of predicted also increased statistically significantly from 70.9% to 77.6% in the BDP group ($P<0.0001$), and from 70.5% to 77.6% in the FP group ($P=0.0003$) (NS between treatments).

Evaluation of efficacy: Number of exacerbations

The number of patients who experienced asthma exacerbation was small in both treatment groups in the ITT analysis: two (2%) in the BDP group and five (5.1%) in the FP group, with no significant difference reported between the two treatment arms.

Evaluation of efficacy: Other measures of pulmonary function

At study end, significant mean changes of 0.3 litres were reported over baseline for both treatment groups in the ITT population for both FEV₁ and FVC, with no significant between-treatment difference being found for either parameter (Figure 2).

Mean morning PEF values increased from 359.2 l min^{-1} at baseline to 383.7 l min^{-1} at treatment end in the BDP group, and from 357.8 to 384.2 l min^{-1} in the FP group, with no significant difference found between the two groups (Figure 3). Similar results were seen for mean evening PEF values, which rose from 379.3 l min^{-1} at baseline to 405.2 l min^{-1} at the end of treatment for BDP-treated patients, and from 377.8 to 399.3 l min^{-1} in FP-treated patients, again with no significant between-treatment difference noted (Figure 3).

Table 2. Adverse events reported in adults with moderate persistent asthma during 12 weeks of treatment with beclometasone dipropionate or fluticasone propionate suspensions for nebulization

Parameter	Beclometasone dipropionate (n=102)	Fluticasone propionate (n=100)
Number of patients with adverse events	23 (22.5%)	32 (32%)
Number of adverse events	30 (39.5%)	46 (60.5%)
Number of patients with treatment-related adverse events	2 (2%)	4 (4%)
Number of treatment-related adverse events	2 (25%)	6 (75%)
Number of dropouts due to treatment-related adverse events	1 (0.9%)	0 (0%)

Evaluation of efficacy: Signs and symptoms and rescue medication

In the ITT population, significant improvements in asthma symptoms over baseline were noted for both treatment groups at the end of the study. The number of patients reporting symptoms scores defined as 'excellent' rose from 16 (15.7%) at baseline to 54 (52.9%) at treatment end in the BDP group, and from 12 (12%) to 46 (46%) in the FP group, with the difference between the two groups being non-significant. When examining the means of the symptoms scores sum, values increased statistically significantly from 4.7 at baseline to 6.3 at treatment end in the BDP group ($P<0.001$), and from 4.6 to 6.3 in the FP group ($P<0.001$), with no significant difference found between the two treatments.

The number of symptom-free patients during the day (symptom score 0) increased significantly for the two groups at study end vs before treatment: from 13 patients to 43 in the BDP group, and from 10 to 35 in the FP group. No significant between-group difference was found. Similarly, notable increases were also reported for the two groups in the number of symptom-free patients during the night, rising from 22 to 51 in the BDP group, and from 21 to 48 in the FP group. Again, no significant difference was noted between the two treatment arms.

In the BDP group, the use of salbutamol as rescue medication was reduced from an average of 2.8 puffs day⁻¹ during the run-in period to 2.2 puffs day⁻¹ during the first 4 weeks of treatment, and then again to 2.0 puffs day⁻¹ during the last 8 weeks. Similarly, patients treated with FP reduced their need for salbutamol from an average of 2.6 puffs day⁻¹ during the run-in phase to 2.2 puffs day⁻¹ during the initial 4 weeks of treatment, and again to 2.1 puffs day⁻¹ during the final 8 weeks. No significant difference was found between the two treatment groups.

Evaluation of safety

Safety data showed that both treatments were well tolerated. During the treatment period, 23 (22.5%) patients in the BDP group and 32 (32%) in the FP group

reported one or more adverse events (Table 2). The number of adverse events reported was 30 (39.5%) and 46 (60.5%) in the BDP and FP groups, respectively, and these were generally mild (NS between treatments for both variables). In total, six patients reported adverse drug reactions: two (2%) in the BDP group, and four (4%) in the FP group, with two (25%) and six (75%) adverse drug reactions seen in the respective groups (NS between treatments for both parameters). Furthermore, only one patient (0.9%) in the BDP group discontinued treatment due to treatment-related adverse events. Moreover, no significant difference was found between the two treatments with regard to laboratory tests, and no clinically relevant changes in vital signs or physical examination were observed in either treatment group.

DISCUSSION

Inhaled corticosteroids are very effective in controlling symptoms in asthmatic patients of all ages and disease severity (10). A number of previous clinical studies have compared the effects of specific corticosteroids, efficacy having been assessed for a wide range of doses in terms of reduction of symptoms and exacerbations, improvement of lung function, and a decreased need for bronchodilator rescue therapy (11).

A very important study involving BDP and FP compared multiple doses of FP (100–800 µg day⁻¹ by pMDI) with a single dose of BDP (400 µg day⁻¹ by pMDI) in 672 patients (2). A flat dose-response curve of lung function was seen, with no statistically significant differences in clinical efficacy between any dose of FP compared with the single dose of BDP, nor between the various doses of FP. The authors concluded that 400 µg BDP pMDI was equivalent to 200 µg FP pMDI. An important study comparing BDP (1600 µg day⁻¹) and FP (2000 µg day⁻¹), both delivered by pMDI, showed that the two were similar in improving the efficacy of asthma control when prescribed to 134 patients who had previously received a lower dose of inhaled corticosteroid (3). Another study in 274 adults found that treatment with 1500 µg day⁻¹ FP pMDI resulted in significantly higher morning and evening PEF values and

fewer exacerbations than the same dose of BDP pMDI (4). Three studies have compared BDP with half the dose of FP; no difference in clinical effect was found between the two treatments in any of them. One compared BDP (400 $\mu\text{g day}^{-1}$) and FP (200 $\mu\text{g day}^{-1}$), both given by pMDI with plastic spacer to 398 children with asthma (5). Another compared BDP (2000 $\mu\text{g day}^{-1}$) and FP (1000 $\mu\text{g day}^{-1}$) in 154 adults with severe asthma (6). The third compared BDP (400 $\mu\text{g day}^{-1}$) and FP (200 $\mu\text{g day}^{-1}$), both given by pMDI to 261 adult patients with mild to moderate asthma (7).

Based on these studies comparing BDP and FP delivered via pMDI, it is not possible to draw any firm conclusion about the comparative potencies of BDP and FP. Furthermore, comparisons between the effects of BDP and FP delivered via nebulizer have not previously been available. Therefore, ours is the first study that compares, in asthmatic patients, the clinical effects of BDP and FP delivered via a jet nebulizer, adding to our two recently published studies: flunisolide 500 μg vs budesonide 500 μg , both administered twice-daily by jet nebulizer for 4 weeks in 133 children (12), and BDP 800 $\mu\text{g day}^{-1}$ b.i.d. or budesonide 1000 $\mu\text{g day}^{-1}$ b.i.d. both administered by jet nebulizer in 127 children with mild to moderate persistent asthma (13). Both studies highlight the equivalent clinical responses and good safety profiles of nebulized corticosteroids in children.

This study demonstrates that suspension for nebulization forms of BDP 2400 $\mu\text{g day}^{-1}$ and FP 2000 $\mu\text{g day}^{-1}$, given via a jet nebulizer, are effective and therapeutically equivalent and have a good safety and tolerability profile when used to control moderate persistent asthma in adult patients. Corticosteroids delivered via nebulizer may be an effective and attractive alternative to pMDIs, especially when it is necessary to administer high doses of drug (>500 μg), and to avoid problems related to poor hand-respiration coordination that are seen in some patients that use pMDIs.

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