A new HFA-134a propellant in the administration of inhaled BDP via the Jet \textsuperscript{R} spacer: controlled clinical trial vs the conventional CFC

V. Vondra *, K. Sladek †, J. Kotasova †, M. Teřl $, A. Rossetti $ and L. Cantini $

*Pneumology Department, Prague, Czech Republic, †Department of Medicine, Jagiellonian University, Krakow, Poland, ‡Prague’s University Student’s Policlinic, Prague, Czech Republic, §Pneumology Clinic, Plzen, Czech Republic, and * Medical Department, Chiesi Group, Parma, Italy

Abstract This study was carried out with the aim of demonstrating the efficacy and tolerability of beclomethasone dipropionate (BDP) aerosol spray 500\(\mu\)g b.i.d. via a spacer device (Jet \textsuperscript{R}, Chiesi Farmaceutici S.p.A.) using a new HFA-134a formulation or chlorofluorocarbon (CFC) propellant. After having completed a 2-week run-in period, 154 adult patients (77 in each group) with mild-to-moderate persistent asthma were randomised into two groups to receive the study treatment for a duration of 12 weeks in a double-blind, multinational, multicentre, parallel-group design. Morning and evening peak expiratory flow rate (PEFR), use of rescue salbutamol, number of day- and night-time asthma attacks, number of night-time awakenings due to asthma and clinical symptoms were recorded daily by patients on diary cards. Pulmonary function tests (FEV\(_1\), FVC, PEFR, FEF\(_{25-75}\%\), MEF\(_{50}\) and FEF\(_{25}\)) and vital signs were measured at the clinic at study entry, at the start of treatment and every 2 weeks thereafter. Morning serum cortisol (8.00–10.00 a.m.) was measured at the start and at the end of the treatment period. Adverse events were recorded throughout the total study period. Significant improvements over baseline were reported in both groups in terms of lung function, symptoms and use of rescue inhaled salbutamol. Equivalence between groups was demonstrated for the primary end-point morning PEFR, as well as for evening PEFR and FEV\(_1\). No statistically significant differences in the comparisons between groups, except for FEF\(_{25}\) \((P=0.044)\), were observed in any of the other efficacy variables. Adverse events were reported in 31% of patients in the BDP–HFA group and in 32% in the CFC group. Adverse drug reactions were 4 and 2 in the two groups, respectively. No drug-related serious adverse events were reported in either of the groups.

No signs of relevant adrenal suppression were observed in both groups; 2 patients in each group had final values below the normal range. In conclusion, the BDP–HFA-134a formulation proved to be equivalent in efficacy and comparable in safety to the standard BDP–CFC product over 12 weeks in adult patients with mild-to-moderate persistent asthma.

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INTRODUCTION

Chlorofluorocarbons (CFCs) have been used as propellants in pressurized metered dose inhalers (pMDIs) in the last four decades, and their delivery of a number of treatments for asthma and chronic obstructive pulmonary disease (COPD) has been proved as inexpensive, reliable and effective. However, due to their deleterious effects on the ozone layer (I), the Montreal protocol (2) called for a phasing-out of the production of most ozone-damaging substances, including CFCs, and a great challenge has been posed to pharmaceutical companies in the reformulation of MDIs-products into CFC-free forms. A number of drug substances, including inhaled corticosteroids, \(\beta_2\)-receptor agonists and anticholinergics, has been developed with the use of the hydrofluorocarbons (HFA) I34a, a propellant defined as adequate for the use in pMDI-delivered products (3). Beclomethasone dipropionate (BDP) was the first available inhaled corticosteroid delivered with the HFA-I34a. Based on the evidence that the reformulation process may modify the particle size distribution, and hence the lung-deposition, the earliest extrafine HFA-I34a-containing BDP is marketed at a reduced recommended...
posology, compared with that of CFC-product (4). A new HFA-134a formulation has been recently developed by Chiesi Farmaceutici S.p.A. (Parma, Italy) with the inclusion of glycerol as non-volatile co-solvent, in order to render the particle size of the inhaled drug as close as possible to that of the conventional CFC (5). It has also been noted that the selection of an appropriate actuator orifice diameter contributes to modulate an aerosol cloud which can allow the maintenance of the 1:1 ratio between the doses of HFA and CFC-formulated drugs (5).

The aim of the present study was to assess if BDP administered with this newly developed HFA product is equivalent, in terms of both efficacy and safety, with the conventional BDP-CFC, both drugs being given with the addition of the Jet® (Chiesi Farmaceutici S.p.A., Parma, Italy) spacer.

PATIENTS AND METHODS

Study population

Adult asthmatic patients were selected in eight centres, located in Czech Republic and Poland, in an ambulatory setting from patients attending the out-patients hospital clinics.

Eligible patients had to satisfy the following criteria: age between 18 and 70 years, mild-to-moderate persistent asthma as defined in standard guidelines (6), forced expiratory volume in one second (FEV1) between 60 and 90% of the predicted normal value, reversibility to \( \beta_2 \)-agonists in the recent history and a satisfactory degree of co-operation. Subjects with evidence of asthma exacerbation or respiratory tract infections in the previous 4 weeks, clinically significant diseases whose treatment and sequelae could have interfered with the result of the study, intake of oral corticosteroids (when taken at study entry) were also excluded from the treatment phase.

Among the antiasthma treatments, inhaled corticosteroids were excluded from participating in the study. Subjects whose FEV1 increased \( \geq 10 \% \) at the end of the run-in with respect to the value measured at study entry were also excluded from the treatment phase.

Among the antiasthma treatments, inhaled corticosteroids (when taken at study entry) were permitted during the run-in, sodium cromoglycate or nedocromil sodium (when taken at study entry) were permitted at a constant dose throughout recorded in a diary card. Patients were withdrawn from the study when any of the following treatment was taken: theophyllines, anticholinergics, antihistamines, leukotriene receptor antagonists, oral corticosteroids, inhaled long-acting \( \beta_2 \)-agonist and oral bronchodilators.

Study design and protocol

This was a multicentre, randomised, double-blind, parallel-group trial. Eligible patients entered a 2-week run-in period and were then randomised to receive inhaled BDP delivered with the HFA or the CFC (Clenil Forte® Jet®; Chiesi farmaceutici S.p.A., Italy) propellant, both drugs given at a dose of 2 puffs (250 \( \mu \)g \( \times \)2) twice daily, morning and evening. The two treatment tests were administered with a spacer device (Jet® Chiesi Farmaceutici S.p.A., Italy) at a constant dose (1 mg/day) over a 12-week treatment duration.

Visits at the clinics took place every 2 weeks. On each visit, the following pulmonary function tests were measured: FEV1 (L), forced vital capacity (FVC, L), peak expiratory flow rate (PEFR, L/s), mid-expiratory flow at 50% vital capacity (MEF50, L/s) and forced expiratory flow at 25 and 75% FVC (FEF25–75%, L/s). Three tests were performed on each session and the best (that with the highest FEV1) was recorded. If inhaled salbutamol was used, a minimum of 6 h had to elapse between inhalation and pulmonary function measurements. Measuring conditions, equipment and daily calibration of the instrument were standardised as recommended by the Guidelines of the European Respiratory Society (7). A daily self-measurement of PEFR (L/min) was also performed twice daily (morning and evening) using a portable peak flow meter (Mini-Wright®, Airmed, Clement Clarke, U.K.); the best of three consecutive flows had to be recorded. In addition, the intake of rescue salbutamol (number of puffs/day) was recorded daily by patients in a diary card, as well as the number of day- and nighttime asthma attacks and the number of nighttime awakenings caused by asthma. Clinical symptoms (dyspnoea, tachypnoea, wheezing, cough and catarrh) were also measured daily using a 4-point rating scale (where 0 = none; 1 = slight and transient; 2 = moderate; and 3 = severe) to obtain a global sum of scores.

A blood sample was taken from an antecubital vein between 08.00 and 10.00 a.m. at the start and at the end of treatment for the measurement of morning serum cortisol; assessment was done in a centralised laboratory using a solid-phase, chemiluminescent enzyme immunoassay.

Pulse and blood pressure were measured at each visit. Patients reported adverse events at each visit and their severity, outcome and correlation with the study treatments were assessed.

Compliance was evaluated by recording the daily doses of the administered drug into a diary card and by inspecting the used and unused returned canisters at each visit. The proportion of the administered drug was...
then calculated: the limit for a satisfactory compliance was set at 75%.

**Ethics**

The study protocol, patient information leaflet and informed consent form were reviewed and approved by the Independent Ethics Committees of each participating centre prior to the start of the study.

**Statistics**

The primary outcome variable was the morning peak flow. Based on the following assumptions: mean morning PEFR final value (last 2-week period) of 460 L/min and standard deviation (SD) of 90 L/min in the CFC group; power equal to 80% and level of significance equal to 5%; the sample size was determined to be 50 patients per group. Equivalence was proven if the 95% confidence interval (CI) for the difference between treatment means fell within the range of ±10% of the adjusted mean of the BDP CFC group (8).

Adjusted least-squares means (LSMs) of the two treatments were derived from an ANCOVA model using baseline values as covariate. The 95% CI for the difference between LSMS was used to assess equivalence between the two treatments for morning and evening PEFR, and FEV1, whereas the other PF tests, salbutamol daily use, asthma attacks, clinical symptoms, morning serum cortisol and vital signs were analysed by calculating the 95% CI for the mean change from baseline: data were compared between groups using ANCOVA.

The baseline data was that derived from the mean values of the 2-week run-in period recorded on the dairy cards and the data measured at the 2nd clinic visit. Two weekly means were also calculated for the variables recorded in the dairy cards.

All randomised patients with post-baseline data were included in the intent-to-treat (ITT) analysis and patients with major protocol violations were to be excluded from the per-protocol (PP) population. The last observation carried forward (LOCF) method was used to deal with the missing data.

**RESULTS**

A total of 154 patients were randomised to receive study medication, 77 in either of the group. Four patients, all in the BDP-CFC group, were withdrawn from the study: two of them did not satisfy the inclusion criteria (noted throughout the study), one withdrew the consent and another had adverse events (upper respiratory tract infection). Only one of them did not have post-baseline data and was excluded from the ITT population. Since no major protocol violation occurred, the same patients’ population entered the PP and the ITT analysis.

Most of patients were taking inhaled corticosteroids at study entry and during run-in at a daily dose equal or less than 1 mg: 43 (78.2%) patients in the HFA-134a group and 38 (77.6%) in the CFC group were taking BDP, whereas the remaining took budesonide, 11 (20.0%) in the HFA-134a group and 10 (20.4%) in the CFC group, or flunisolide, 1 (1.8%) in the HFA-134a group, and 1 (2.0%) in the CFC group.

The individual patient demographic details are presented in Table I. The two groups were well matched in respect of demographics and other baseline characteristics, including the duration and severity (FEV1% predicted) of asthma.

The results of the primary outcome variable mean morning PEFR and of evening PEFR, recorded daily by patients, are presented in Fig. 1. Both variables significantly increased over baseline at any 2-week period.

Morning PEFR (mean ± SD) increased from 416.7 ± 95.2 L/min (baseline) to 438.6 ± 95.0 L/min (final) in the BDP–HFA group, and from 413.7 ± 84.2 to 431.0 ± 88.1 L/min in the BDP–CFC group. Evening PEFR increased from 427.2 ± 91.5 to 447.4 ± 93.7 L/min in the BDP–HFA group and from 428.5 ± 86.2 to 442.3 ± 91.2 L/min in the BDP–CFC group.

The LSMS for morning PEFR were 437.7 L/min for BDP–HFA–134a and 431.7 L/min for BDP–CFC, with a difference of −6.05 L/min. Statistical analysis demonstrated that BDP–HFA–134a was equivalent to BDP–CFC: bilateral 95% CI for the treatment difference was −19.7–7.6 L/min, well within the equivalence limit of ±43.17 L/min.

As regards to evening PEFR, the LSMS were 448.1 L/min for BDP–HFA–134a and 441.2 L/min for BDP–CFC, with a difference of −6.95 L/min. The bilateral 95% CI for the treatment difference was −20.8–6.9 L/min, within the equivalence limit of ±44.12 L/min.

| Table I. Baseline characteristics of the patients’ population |
|------------------|------------------|------------------|
|                  | BDP–HFA (n=77)   | BDP–CFC (n=77)   |
| Sex:             |                  |                  |
| Males (n)        | 39 (51%)         | 43 (56%)         |
| Females (n)      | 38 (49%)         | 34 (44%)         |
| Age, years (mean ± SD) | 38.0 ± 12.1 | 37.4 ± 13.3 |
| Height, cm (mean ± SD) | 171.4 ± 93  | 172.6 ± 95  |
| Weight, kg (mean ± SD) | 73.5 ± 14.7 | 75.8 ± 12.6 |
| Duration of asthma, years (mean ± SD) | 91.7 ± 93   | 93 ± 8.0    |
| Morning PEFR, L/min (mean ± SD) | 416.7 ± 95.2 | 413.7 ± 84.2 |
| Evening PEFR, L/min (mean ± SD) | 427.2 ± 91.5 | 428.5 ± 86.2 |
| FEV1, predicted, % (mean ± SD) | 77.2 ± 79    | 76.8 ± 90    |
Results of the other pulmonary function tests, measured at clinic visits, are shown in Table 2: FEV₁, FVC, PEFR, FEF₂₅₋₇₅% and MEF₅₀ markedly increased throughout the study period in both groups. No statistically significant differences between groups were reported except for FEF₂₅ (P=0.044), due to a more marked increase in the CFC group.

An additional equivalence analysis was also performed for FEV₁: the bilateral 95% CI was −0.05 to 0.22 l, which lies entirely within the equivalence limit of ± 0.30 l; this confirms that BDP–HFA-1₃₄₄ is equivalent to BDP–CFC.

Results of rescue daily salbutamol consumption and clinical parameters are shown in Table 3. The asthma control tended to improve during the study in both groups with statistically significant changes over baseline for the majority of the parameters. There were no differences between groups for the salbutamol use or in clinical symptoms.

No relevant changes in the mean values of morning serum cortisol were reported in both groups: a negligible decrease occurred in the BDP–HFA group (baseline: 15.74 μg/100 ml, final: 15.43 μg/100 ml), whereas a more pronounced reduction was observed in the BDP–CFC group (baseline: 17.57 μg/100 ml, final: 15.76 μg/100 ml). However, the analysis within treatment and between groups did not show any significant change.

The individual patients’ data of morning serum cortisol in the two groups (patients with both baseline and final data) are shown in Fig. 2. Two patients went from normal to low levels in both groups; one patient in the BDP–CFC group also had a low value at baseline. The remaining patients had values within the normal range at both baseline and end of treatment.

A total number of 64 adverse events (AEs) were reported during the study, 32 in both groups, and they occurred in 31% of patients in the BDP–HFA-1₃₄₄ and in 32% of patients in the CFC group. These included 6 ADRs (adverse events with a definite, probable, possible or doubtful relationship with the test treatment), with 4 in the BDP–HFA-1₃₄₄ group and 2 in the BDP–CFC group. The majority of adverse events was due to seasonal dis-

**Table 2.** Pulmonary function tests (95% CI of changes from baseline in brackets)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline (mean ± SD)</th>
<th>After 6 weeks (mean ± SD)</th>
<th>After 12 weeks (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (L)</td>
<td>BDP–HFA 2.73 ± 0.66</td>
<td>2.90 ± 0.68 (0.10 – 0.27)</td>
<td>2.92 ± 0.69 (0.10 – 0.27)</td>
</tr>
<tr>
<td></td>
<td>BDP–CFC 2.75 ± 0.71</td>
<td>2.94 ± 0.78 (0.10 – 0.26)</td>
<td>3.00 ± 0.82 (0.16 – 0.37)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>BDP–HFA 3.62 ± 0.93</td>
<td>3.83 ± 0.94 (0.11 – 0.30)</td>
<td>3.85 ± 0.95 (0.14 – 0.32)</td>
</tr>
<tr>
<td></td>
<td>BDP–CFC 3.82 ± 1.11</td>
<td>3.96 ± 1.13 (0.02 – 0.21)</td>
<td>4.03 ± 1.13 (0.09 – 0.32)</td>
</tr>
<tr>
<td>PEFR (L/s)</td>
<td>BDP–HFA 6.37 ± 1.83</td>
<td>7.15 ± 2.01 (0.42 – 1.03)</td>
<td>7.05 ± 1.74 (0.34 – 1.02)</td>
</tr>
<tr>
<td></td>
<td>BDP–CFC 6.25 ± 1.79</td>
<td>6.96 ± 1.79 (0.33 – 0.91)</td>
<td>7.13 ± 1.87 (0.54 – 1.16)</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅%</td>
<td>BDP–HFA 2.54 ± 1.05</td>
<td>2.69 ± 1.08 (0.01 – 0.33)</td>
<td>2.72 ± 1.06 (0.00 – 0.35)</td>
</tr>
<tr>
<td></td>
<td>BDP–CFC 2.34 ± 0.75</td>
<td>2.63 ± 0.95 (0.17 – 0.49)</td>
<td>2.64 ± 0.97 (0.15 – 0.51)</td>
</tr>
<tr>
<td>MEF₅₀ (L/s)</td>
<td>BDP–HFA 2.90 ± 1.09</td>
<td>3.02 ± 1.15 (0.07 – 0.31)</td>
<td>3.06 ± 1.09 (0.03 – 0.34)</td>
</tr>
<tr>
<td></td>
<td>BDP–CFC 2.74 ± 0.92</td>
<td>2.98 ± 1.10 (0.12 – 0.48)</td>
<td>3.01 ± 1.18 (0.11 – 0.51)</td>
</tr>
<tr>
<td>FEF₂₅ (L/s)</td>
<td>BDP–HFA 1.32 ± 0.69</td>
<td>1.35 ± 0.69 (0.04 – 0.16)</td>
<td>1.35 ± 0.66 (0.07 – 0.14)</td>
</tr>
<tr>
<td></td>
<td>BDP–CFC 1.20 ± 0.52</td>
<td>1.39 ± 0.61 (0.09 – 0.28)</td>
<td>1.33 ± 0.56 (0.10 – 0.31)</td>
</tr>
</tbody>
</table>

FIG. 1. PEFR (l/min) measured daily expressed as two Weekly means (SD in bars).
The results of the present study have provided evidence that BDP given via a new HFA-134a formulation and the conventional CFCs are equivalent in efficiency and have a comparable safety profile in adult patients with mild-to-moderate asthma. The two groups were equivalent in terms of the primary efficacy variable, morning PEFR, as well as for evening PEFR and FEV1. In fact, the LSMs in the two groups were similar and the calculated 95% CIs for the difference between treatments were well within the 10% of the CFC group, being also contained in the ±5% for morning and evening PEFR. The other efficacy parameters, consisting of pulmonary function tests measured at clinics, clinical symptoms (including asthma attacks and nocturnal awakenings) and use of rescue salbutamol daily measured by patients, showed comparable results in the two groups, without statistically significant differences between them (apart from FEF25, P=0.044 in favour of the HFA group).

The selection criteria of the patients’ population (FEV1 between 60 and 90% of predicted normal) was planned in order to treat subjects who had room for improvement, despite a similar subset of patients in the two groups were receiving inhaled steroids at study entry and during run-in. In fact, according to recent reports (9,10), treatments should be compared in the step part of the dose–response curve, thus allowing a real difference, if present, to be detected. The results of this study have shown marked and significant improvements over baseline in the two groups in terms of lung function (i.e. at least 20 L/min in a.m. and p.m. PEFR or 0.2 l in FEV1), symptoms and use of rescue salbutamol, thereby showing that the two selected groups were adequate to achieve better asthma control.

The safety results have shown that the two treatments were equally well tolerated. Only two patients in

| Table 3. Clinical parameters recorded on dairy cards (95% CI of changes from baseline in brackets) |
|---------------------------------------------|-----------------|-----------------|-----------------|
| Treatment                                | Baseline (mean ± sd) | Weeks 5-6 (mean ± sd) | Weeks 11-12 (mean ± sd) |
| Salbutamol consumption (No. of puffs)    | BDP–HFA 1.64 ± 0.197 | 1.01 ± 0.136 (−0.98–−0.29) | 0.88 ± 0.132 (−1.11–−0.42) |
|                                          | BDP–CFC 1.25 ± 0.180 | 1.00 ± 0.159 (−0.58–−0.07) | 0.94 ± 0.152 (−0.68–−0.03) |
| Daytime asthma attacks (number)          | BDP–HFA 0.52 ± 0.104 | 0.37 ± 0.076 (−0.36–−0.06) | 0.30 ± 0.072 (−0.42–−0.02) |
|                                          | BDP–CFC 0.44 ± 0.079 | 0.29 ± 0.057 (−0.29–−0.01) | 0.28 ± 0.056 (−0.29–−0.03) |
| Nighttime asthma attacks (number)        | BDP–HFA 0.15 ± 0.044 | 0.09 ± 0.026 (−0.15–−0.03) | 0.07 ± 0.022 (−0.17–−0.02) |
|                                          | BDP–CFC 0.17 ± 0.035 | 0.09 ± 0.027 (−0.14–−0.00) | 0.05 ± 0.018 (−0.19–−0.03) |
| Nighttime awakenings (number)            | BDP–HFA 0.12 ± 0.035 | 0.04 ± 0.011 (−0.16–−0.01) | 0.03 ± 0.012 (−0.17–−0.03) |
|                                          | BDP–CFC 0.11 ± 0.024 | 0.07 ± 0.024 (−0.09–−0.02) | 0.03 ± 0.011 (−0.11–−0.03) |
| Clinical symptoms (sum of scores)        | BDP–HFA 2.28 ± 0.190 | 1.36 ± 0.152 (−1.31–−0.53) | 1.07 ± 0.128 (−1.61–−0.81) |
|                                          | BDP–CFC 2.14 ± 0.220 | 1.42 ± 0.150 (−1.09–−0.21) | 1.22 ± 0.163 (−1.34–−0.37) |
each group had final serum cortisol values below the lower limit of the normal range (one of them also had a low baseline value).

The amount of patients with adverse events and adverse drug reactions was also similar in the two groups. Most of the adverse events were seasonal diseases affecting the upper respiratory tract and only a small proportion of patients in the two groups had local effects due to the intake of inhaled corticosteroids.

The Jet® (Chiesi Farmaceutici S.p.A., Parma, Italy) is a small-size spacer device aimed to retain the largest particles of the active substance and propellant within its internal walls; the effects of the Jet® spacer on the pattern of the deposition profile (11) and the advantages in terms of systemic absorption when inhaled steroids are given at high dose (12) have been previously demonstrated. It is therefore likely that the addition of the spacer and the use of the 1 mg/day dose might have reduced the possibility to detect any difference, if it exists, in terms of systemic tolerability. However, this study was designed to provide equivalence on the absolute efficacy in an adequate sample of patients using robust outcome measures; the results have shown that the new HFA formulation can be used to replace the same dose given with the conventional CFC without any loss of efficacy.

The earliest HFA-134a formulations have been developed with the aim to enhance the efficiency of BDP delivery to the respiratory tract (14); as a consequence, the recommended dose was reduced at approximately half of that of conventional CFCs without altering efficacy and safety in the switching phase. In order to facilitate a smooth transition from CFCs to alternative chlorine-free propellants, the BDP–HFA-134a formulation used in the present study has been developed to obtain a particle size distribution similar as much as possible to that of CFCs, and thus maintain the 1:1 ratio.

The results of the present study have shown that this new formulation is therapeutically equivalent to the BDP–CFC product and may represent a valid alternative in the administration inhaled BDP in adult patients with mild-to-moderate persistent asthma.

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