Safety and efficacy of HFA-134a beclomethasone dipropionate extra-fine aerosol over six months

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ORIGINAL ARTICLE

Inhaled corticosteroids (ICSs) have been used effectively for many years in the long-term treatment of asthma and are considered by recent therapeutic guidelines to be the mainstay of asthma therapy (1,2). Hydrofluoroalkane-134a beclomethasone dipropionate (HFA-BDP) extra-fine aerosol (QVAR, 3M Pharmaceuticals, Canada) is a new formulation of BDP. Unlike the conventional chlorofluorocarbon (CFC) formulations of BDP, which are suspensions, HFA-BDP is a solution of BDP in an HFA propellant. This reformulation, combined with improvements in inhaler technology, delivers an extra-fine aerosol of BDP with a smaller mean particle size (1.1 µm) than that produced by CFC-BDP inhalers (3.5 µm) (3) in a warmer, gentler spray (4).

OBJECTIVE: To compare the systemic safety and efficacy of hydrofluoroalkane beclomethasone dipropionate (HFA-BDP) extra-fine aerosol over six months. Can Respir J 2004;11(2):123-130.

CONCLUSIONS: HFA-BDP 800 µg/day has a systemic adverse event profile comparable to that of CFC-BDP 1500 µg/day, and further control of asthma symptoms may be achieved after a switch from CFC-BDP 1500 µg/day to HFA-BDP 800 µg/day.

Key Words: Asthma; Hydrofluoroalkane beclomethasone dipropionate; Inhaled corticosteroids; Systemic safety
active drug to the lungs (3,5). Additionally, while drug deposition with CFC-BDP is mostly confined to the central airways, inhalation of HFA-BDP results in drug deposition in the large, intermediate and peripheral airways (3,5). The improved lung deposition of HFA-BDP compared with CFC-BDP provides equivalent asthma control at approximately one-half the daily dose and demonstrates a similar safety profile (6-10). However, few patients receiving high doses of HFA-BDP for more than 12 weeks have been studied.

The improved delivery characteristics of HFA-BDP would translate into a clinically relevant advantage if a higher ratio of therapeutic efficacy to adverse events were obtained. The lower daily doses and reduced oropharyngeal deposition of HFA-BDP may result in lower incidences of local adverse events such as dysphonia and candidiasis. Furthermore, the potential for systemic adverse events, such as hypothalamic-pituitary-adrenal (HPA) axis suppression, changes in the markers of bone metabolism and ocular effects, may also be reduced as a result of the lower daily doses and reduced absorption of swallowed BDP from the gastrointestinal tract. However, pharmacokinetic studies have shown that the systemic bioavailability of HFA-BDP is increased relative to CFC-BDP, presumably due to the enhanced delivery of HFA-BDP to the lower respiratory tract (11). This may imply that there is a potential for equivalent or even increased systemic adverse events from HFA-BDP at one-half the daily dose of CFC-BDP.

A previous 12-week study concluded that the maximum recommended dose of HFA-BDP, 800 µg/day, provides equivalent asthma control to CFC-BDP 1500 µg/day in patients with moderate to severe asthma (8). The present study was undertaken to compare the systemic safety profile of HFA-BDP in patients with moderate to severe asthma adequately controlled by CFC-BDP 1000 µg/day to 2000 µg/day over six months of treatment. Systemic safety was assessed by evaluating HPA axis function, intraocular pressure and skin bruising. A secondary objective of the study was to evaluate the efficacy of the reduced daily dose of HFA-BDP.

**PATIENTS AND METHODS**

**Study design and patients**

This was a six-month, randomized, parallel-group, double-blind, double-dummy study, conducted at five sites in Canada. The study was conducted in accordance with the Food and Drug Administration Code of Federal Regulations and the revised Declaration of Helsinki (South Africa 1996) (12). The ethics committee at each investigation site approved the study, and all patients gave their written, informed consent.

Subjects were aged 14 years or older and had a six-month or longer history of asthma that had been adequately controlled over the previous two weeks with CFC-BDP 1000 µg/day to 2000 µg/day, budesonide 800 µg/day to 1600 µg/day or fluticasone propionate 500 µg/day to 1000 µg/day, and short-acting beta-agonists. Patients were required to have a forced expiratory volume in 1 s (FEV1) of 55% predicted or greater and to demonstrate an increase in FEV1 of 12% or greater or an increase in peak expiratory flow (PEF) of 20% or greater in response to an inhaled beta-agonist, or to have a provocative concentration of methacholine of 8 mg/mL or less (13).

Eligible patients entered a two-week run-in period, during which they received CFC-BDP 1500 µg/day. Patients recorded PEF, asthma symptom scores and beta-agonist use each day in a diary throughout the run-in period. PEF was measured three times using a Mini-Wright peak flow meter before the morning and evening doses of asthma medication. Daytime symptoms of wheezing, coughing, shortness of breath and chest tightness were rated on a scale of 0 to 5 (0 = no symptoms present; 5 = symptoms so severe that the patient could not attend school or work, or carry out normal daily duties). Sleep disturbance scores were recorded each morning and were rated on a scale of 0 to 4 (0 = no asthma symptoms during the night; 4 = asthma symptoms so severe that the patient did not fall asleep at all).

Patients who remained free from asthma exacerbations were randomly assigned to remain on CFC-BDP (Becloforte, GlaxoSmithKline, Canada) or to receive HFA-BDP 800 µg/day. To maintain blinding, placebo inhalers identical to the active inhalers were made for each treatment. Subjects were instructed to take both four puffs twice daily from the HFA-BDP 100 µg inhaler (active or placebo) and three puffs twice daily from the CFC-BDP 250 µg inhaler (active or placebo). In this way, patients were unaware of which active treatment they were receiving. Patients were randomly assigned in blocks of four using the Ranpro software program (Applied Logistics Associates Corporation, USA). Drug supplies for each patient were packaged and labelled by Simirex (Mount Laurel, USA), and patients were randomly assigned in sequential order at each study site. Study personnel were not aware of the treatment assignment.

The use of spacers was not allowed during the study. Patients were allowed to use short- and/or long-acting beta-agonists or theophylline, anticholinergics, cromolyn and nedocromil, and one course of oral corticosteroids (seven days or less) for an asthma exacerbation during the study. Clinic visits were made on day 1 and at the end of months 2, 4 and 6. Before each clinic visit, patients were asked to withhold their morning dose of study drug and to observe the allowed medication withholding restrictions of 6 h for short-acting beta-agonists, anticholinergics, cromolyn and nedocromil; 12 h for long-acting beta-agonists and short-acting theophylline; and 24 h for long-acting theophylline.

**Safety evaluations**

Systemic safety was assessed at the day 1 and month 6 clinic visits or at study withdrawal by evaluating adrenal function (24 h urine free cortisol [UFC], morning plasma cortisol and response to standard adrenocorticotropic hormone [ACTH] stimulation) and intraocular pressures. All adverse events reported by patients in response to nonspecific questioning by the investigator were recorded, and their severity (mild, moderate or severe) and relationship to study medication (probably, possibly or probably not) were assessed at all clinic visits. Serious adverse events were defined as those that were fatal, life threatening, permanently or temporarily disabling or incapacitating, or resulted in hospitalization or prolonged hospital stay. Oropharyngeal candidiasis and skin bruising were also monitored at each clinic visit.

**Efficacy evaluations**

FEV1, forced vital capacity and forced expiratory flow over 25% to 75% of the vital capacity (PEF25%-75%) were measured at each clinic visit in accordance with American Thoracic Society criteria.
Patients continued to record PEF, asthma symptom scores and beta-agonist use in their diaries each day for two weeks after random assignment, and then for two weeks before the month 6 clinic visit. Asthma exacerbations were monitored throughout the study. Asthma exacerbations were defined as asthma symptoms severe enough to necessitate hospitalization or urgent medical care in the clinic or emergency room.

Compliance
Compliance with the study medication was evaluated during months 4 to 6 by weighing inhalers and converting the weights to the number of doses administered. If the number of doses administered was within 40% of the number predicted for 100% compliance, then patients were designated as compliant.

Statistical methods
The primary variable of this study was 24 h UFC. Fifty-seven patients were required in each treatment group to provide at least 80% power to detect a clinically significant difference between the treatments. This assumed that 40% of the CFC-BDP 1500 µg/day group would have a 24 h UFC value below the reference range at the end of the study, compared with 15% in the HFA-BDP 800 µg/day group. It was estimated that there would be a 10% dropout rate and a 10% noncompliance rate; therefore, the sample size was adjusted to 140 patients (70 patients in each treatment group).

Safety and efficacy variables were analyzed in the intent-to-treat (ITT) population (ie, all patients who received one dose of study medication). Only patients with data obtained on day 1 and month 6 were included in the analysis of systemic safety. The last observations were carried forward for missing efficacy data, with the exception of diary data. Diary data were not carried forward if the patient withdrew before completing the first of the second two weeks of diary data (ie, week 25). The dropout rate was low in this study and did not have a large influence on the data. As the primary objective of the study was to evaluate systemic safety, 24 h UFC, morning plasma cortisol and response to ACTH stimulation were also analyzed in the per-protocol population, which excluded data from some patients. Criteria for exclusion of data from the per-protocol analysis included: taking a medication that could affect either safety or efficacy outcomes (for oral or injectable corticosteroids, all data for eight weeks from the start of corticosteroid treatment were excluded); taking 30 min or 60 min ACTH blood draws at more than 5 min outside the time; not starting the end-of-study ACTH test within 30 min of the time set by the prestudy test; and not conducting the end-of-study intraocular pressure examination within 60 min of the time set by the prestudy examination. For those patients in the per-protocol population who had 24 h urine creatinine within the reference range of 7 nmol to 18 nmol for men and 5 nmol to 16 nmol for women, 24 h UFC was analyzed.

Fisher’s exact test was used to make between-group comparisons for all safety variables. An analysis of covariance (ANCOVA) model, with treatment, centre and appropriate baseline value as covariates, was used to test the percentage change from baseline in 24 h UFC and morning plasma cortisol. These data were normally distributed; therefore, log transformation was not performed before analysis. All other assumptions of ANCOVA were examined, including tests for nonparallelism and significance of the covariate. An analysis of variance model, including terms for treatment and centre, was used to make between-group comparisons for transitions within the reference range (from to or from low, normal or high). The Mann-Whitney Test was used to analyze the change in the number of skin bruises from baseline.

For the efficacy variables, either the actual change or the percentage change from baseline was analyzed using an ANCOVA model with treatment, centre and appropriate baseline value as covariates. The baseline FEV₁ and FEV₁/FEV₅ values were those obtained on study day 1; all other baseline efficacy values were obtained over the last seven days of the run-in period. Ninety-five per cent CIs for the difference between groups were calculated. The time to first asthma exacerbation or increased asthma symptoms was compared between treatments using the Wilcoxon Test, and Kaplan-Meier estimates were calculated.

Potential differences in response across centres were explored graphically, and further exploration was planned if marked differences were observed. No evidence of any difference in treatment effects across centres was found. All statistical tests were two-tailed, and P<0.05 was considered statistically significant. Statistical analyses were performed using Statistical Analysis System Version 6.08 (SAS Inc, USA).

RESULTS
Patients
Of the 141 eligible patients, 70 were randomly assigned to receive HFA-BDP 800 µg/day, and 71 were randomly assigned to receive CFC-BDP 1500 µg/day. Significantly more male patients were randomized to receive HFA-BDP (60.0%) than CFC-BDP (36.6%) (P=0.005) (Table 1). The two treatment groups were similar in terms of lung function, asthma symptoms and daily beta-agonist use, with the exception of morning PEF, which was significantly higher in the HFA-BDP group (P=0.006). This was probably a result of the higher proportion of male patients in this group; when PEF was expressed as per cent predicted, which corrects for sex, there was no difference between the groups.

Eight patients were withdrawn prematurely from the study: three (4.3%) from the HFA-BDP group and five (7.0%) from the CFC-BDP group. The most common reasons for study withdrawal were noncompliance, protocol violation or an adverse event (two patients each).

Data for 58 patients were partially excluded from the per-protocol assessment of systemic safety, either for a specific time period or from analyses. Twenty-three patients (seven patients from the HFA-BDP group and 16 patients from the CFC-BDP group) used concomitant medication (either oral or intravenous corticosteroids) during the study, which could have affected the outcome of the safety assessment. Of these patients, 20 received oral corticosteroids for an asthma exacerbation. Forty-two patients had blood samples taken outside of the prespecified times (either the scheduled ACTH blood draws at 30 min and 60 min were more than 5 min outside the time, or the end-of-study ACTH stimulation test was not started within 30 min of the time set by the prestudy test). One patient who had an end-of-study intraocular eye examination outside the prespecified time (ie, within 60 min of the prestudy examination), and two patients who violated the inclusion or exclusion criteria (one with a diagnosis of oropharyngeal candidiasis on day 1 and one who did not use a short-acting beta-agonist before or during the study) were also partially...
excluded. Patients may have had more than one partial exclusion, so the number of patients with partial exclusions was less than the total number of partial exclusions. Of the 84 patients in the per-protocol population for analysis of 24 h UFC, 70 had adrenalin function.

At baseline, 13% (six of 46) of patients in the HFA-BDP group had a 24 h UFC value below the reference range of 37 nmol/24 h to 225 nmol/24 h in the per-protocol population. After six months of treatment, 15% (seven of 46) of patients in the HFA-BDP group had a 24 h UFC value below the reference range, compared with 25% (six of 24) of patients in the CFC-BDP group (P=0.346). Similar results were observed in the ITT population: 13% (eight of 60) and 15% (nine of 60) of patients in the HFA-BDP group, and 18% (10 of 56) and 25% (14 of 56) of patients in the CFC-BDP group had a 24 h UFC value below the reference range at baseline and month 6, respectively (P=0.244 at month 6).

In the per-protocol population, the mean 24 h UFC values at baseline were 86.1 nmol for the HFA-BDP group (n=67) and 76.3 nmol for the CFC-BDP group (n=59). The mean 24 h UFC values increased in both groups after six months of treatment (+14.1% in the HFA-BDP group [n=46] and +24.7% in the CFC-BDP group [n=24], P=0.617). In the ITT population, the mean 24 h UFC values at baseline were 86.4 nmol for HFA-BDP patients (n=68) and 79.1 nmol for CFC-BDP patients (n=66), and the mean per cent changes from baseline at month 6 were +24.1% (n=60) and +162.4% (n=56) for these groups, respectively (P=0.344). There was no significant difference between treatment groups with regard to transitions from or to low, normal or high, relative to the reference range in 24 h UFC from baseline to month 6 (per-protocol or ITT populations).

The percentage of patients in the per-protocol population with a morning plasma cortisol level below the reference range of 166 nmol to 828 nmol at baseline was 8% (four of 43) in the HFA-BDP group and 17% (five of 30) in the CFC-BDP group. A higher percentage of patients in the CFC-BDP group (seven of 30, 23%) had a morning plasma cortisol level below the reference range at the end of the study than in the HFA-BDP group (six of 43, 14%) (P=0.360). In the ITT population, 9% (six of 65) and 14% (nine of 65) of patients in the HFA-BDP group, and 15% (10 of 68) and 22% (15 of 68) of patients in the CFC-BDP group had a morning plasma cortisol level below the reference range at baseline and month 6, respectively (P=0.263 at month 6).

For the per-protocol population, mean morning plasma cortisol levels were similar for the two treatment groups at baseline (360 nmol/L for HFA-BDP patients [n=64] and 334 nmol/L for CFC-BDP patients [n=69]). A significant difference between treatments in mean percentage change from baseline in morning plasma cortisol levels was seen at month 6: +15.4% for HFA-BDP patients (n=43) and –12.8% for CFC-BDP patients (n=30) (P=0.018). For the ITT population, the mean morning plasma cortisol levels at baseline were 370 nmol/L for HFA-BDP patients (n=68) and 339 nmol/L for CFC-BDP patients (n=71), and the mean percentage changes from baseline at month 6 were +20.0% (n=65) and +11.4% (n=68) for these groups, respectively (P=0.693) (Figure 1). There was no significant difference between treatment groups with regard to transitions from or to low, normal or high, relative to the reference range in 24 h UFC from baseline to month 6.
erence range) in morning plasma cortisol levels from baseline to month 6 (per-protocol or ITT populations).

Table 2 shows the percentage of patients in the per-protocol and ITT populations with an abnormal response to the ACTH stimulation test at baseline and at month 6. Although the percentage of patients with an abnormal response was higher in the CFC-BDP group than in the HFA-BDP group at baseline and at month 6 in both populations, the differences were not significant at either time point.

Other safety variables

The frequencies of skin bruising and abnormal intraocular pressures (greater than 20 mmHg) were low during the study, and no significant differences were observed between treatment groups at any time point. There was no difference between treatment groups in the percentage of patients who reported an oropharyngeal adverse event: 27% (19 of 70) of patients in the HFA-BDP group and 24% (17 of 71) of patients in the CFC-BDP group (ITT population). Only one of these patients (in the HFA-BDP group) had a confirmed case of candidiasis on oral swab, which resolved on treatment.

Table 3 shows the percentage of patients in the per-protocol and ITT populations reporting at least one adverse event associated with inhalation or a respiratory system disorder. These resolved with benzodiazepine treatment. Two patients, both receiving HFA-BDP, experienced serious adverse events. One patient experienced several episodes of tachycardia, which were related to anxiety, requiring hospitalization. These resolved with benzodiazepine treatment (lorazepam; Ativan, Wyeth Laboratories Inc, USA). A second patient experienced palpitations, anterior chest pain, diarrhea and nausea during the study, and required hospitalization. Extensive testing revealed malabsorption related to lactose intolerance and gluten enteropathy. No serious adverse events were attributed to HFA-BDP treatment.

Adverse events

The overall pattern of reporting of adverse events was similar for both treatment groups (Table 3). There was no significant difference between treatment groups in the percentage of patients who reported at least one adverse event: 90% in the HFA-BDP group and 94% in the CFC-BDP group (P=0.366) (Table 3). Similarly, there was no significant difference between treatment groups in the percentage of patients who reported an adverse event associated with inhalation or a respiratory system disorder (Table 3). Increased asthma symptoms were reported by 27% of patients in the CFC-BDP group, compared with 14% in the HFA-BDP group (P=0.095) (Table 3). The increased asthma symptoms were classified as severe (ie, the patient was unable to perform their usual activities) for 7% (five patients) in CFC-BDP group and for 3% (two patients) in the HFA-BDP group. The percentage of patients reporting sinusitis was higher in the HFA-BDP group than in the CFC-BDP group (11% and 3%, respectively; P=0.055), as was the percentage of patients reporting abdominal pain (9% and 1%, respectively; P=0.063) (Table 3). However, the difference between treatments was not considered clinically or statistically significant, and no incidence of either adverse event was considered to be related to study medication by the investigator.

Treatment-related adverse events occurred in 16 patients (23%) receiving HFA-BDP and 15 patients (21%) receiving CFC-BDP. In the CFC-BDP group, 12 patients (17%) reported an adverse event on inhalation (cough [two patients], dysphonia [four patients], increased asthma symptoms [one patient] and inhalation site sensation [five patients]), compared with 10 patients (14%) in the HFA-BDP group (cough [one patient], dysphonia [five patients], inhalation site sensation [four patients] and inhalation taste sensation [two patients]). One CFC-BDP-treated patient reported an episode of hemoptysis, which the investigator considered to be treatment related.

Two patients, both receiving HFA-BDP, experienced serious adverse events. One patient experienced several episodes of tachycardia, which were related to anxiety, requiring hospitalization. These resolved with benzodiazepine treatment (lorazepam; Ativan, Wyeth Laboratories Inc, USA). A second patient experienced palpitations, anterior chest pain, diarrhea and nausea during the study, and required hospitalization. Extensive testing revealed malabsorption related to lactose intolerance and gluten enteropathy. No serious adverse events were attributed to HFA-BDP treatment.

Efficacy

There were no statistically significant differences between treatments in mean change from baseline in FEV1 per cent predicted at months 2, 4 or 6, in mean percent change from baseline in FEF25-75% at months 2, 4 or 6, or in mean percent change from baseline in morning or evening PEF during weeks 1, 2, 25 or 26.

The changes from baseline in percentage of days without wheeze, cough, shortness of breath or chest tightness were
significantly greater in the HFA-BDP group than in the CFC-BDP group at some time points during weeks 1, 2, 25 and 26 (Figure 2). Similar results were seen for the percentage of nights without sleep disturbance.

Daily beta-agonist use remained relatively constant and low during the course of the study, with no significant differences between the two treatment groups in the mean change from baseline at any time point.

There was a trend toward earlier onset of the first asthma exacerbation or increased asthma symptoms in the CFC-BDP group than in the HFA-BDP group (P=0.076) (Figure 3). Seven patients (10%) in the HFA-BDP group and 13 patients (18%) in the CFC-BDP group experienced an asthma exacerbation.

**DISCUSSION**

ICSs are considered the mainstay of anti-inflammatory therapy for asthma. Although most asthmatic patients require low to medium doses of ICSs, some may require high doses, either for periods of exacerbation or for prolonged periods of time (1,2,15). ICSs may be associated with dose-related systemic adverse events, such as HPA axis suppression, ocular events and ecchymosis (16). Therefore, it is essential to ensure that the increased systemic exposure of HFA-BDP resulting from improved lung deposition does not increase the incidence of systemic adverse events, particularly when used at the maximum recommended dose.

While HPA axis suppression can be considered to be without significant clinical relevance and may not result in adverse clinical events, measuring HPA axis suppression is one of the best ways to assess the systemic effects of ICSs (16). Measurement of 24 h UFC excretion is one of the most sensi-
systemic safety, only patients who were well controlled on CFC-BDP have been investigated for HFA-BDP. This may result in fewer systemic adverse events, though this has not been investigated for HFA-BDP.

The use of a spacer further reduces oropharyngeal deposition and lower daily doses of HFA-BDP are expected to be approximately fourfold lower for HFA-BDP than for CFC-BDP, assuming an oropharyngeal deposition of approximately 30% for HFA-BDP and 60% for CFC-BDP (3,5). The overall delivery of BDP to the lungs; assuming lung deposition of approximately 60% for HFA-BDP and 15% for CFC-BDP (3,5), and using a dose ratio of two to one (CFC-BDP to HFA-BDP), the dose of BDP to the lung would be expected to be nearly twofold higher for HFA-BDP than for CFC-BDP. Additionally, there is increased delivery of BDP to the peripheral airways, a major site of inflammation in asthma (18-21) that is poorly penetrated by conventional CFC formulations of BDP (3,5).

**CONCLUSIONS**

The results from the present safety study show that HFA-BDP 800 µg/day has a comparable systemic adverse event profile to CFC-BDP 1500 µg/day over six months. Supplemental efficacy measures suggest that there may be further control of asthma symptoms after a switch from CFC-BDP 1500 µg/day to HFA-BDP 800 µg/day, supporting the hypothesis that there is an improved therapeutic ratio for HFA-BDP over CFC-BDP.

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