

Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant

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Background: This study tested the hypothesis that there would be improved asthma control with increasing doses of beclomethasone dipropionate (BDP) formulated in hydrofluoroalkane-134a (HFA-BDP) and the standard chlorofluorocarbon propellants (CFC-BDP). Because HFA-BDP has improved lung deposition compared with CFC-BDP, this study also tested the hypothesis that HFA-BDP would provide more effective control of asthma than CFC-BDP.

Methods: In this multicenter, randomized, parallel-group blinded study, asthmatic subjects who had deterioration in asthma control after discontinuation of inhaled corticosteroids were randomized to receive one of 6 possible treatments: 100 µg/d, 400 µg/d, or 800 µg/d of HFA-BDP or 100 µg/d, 400 µg/d, or 800 µg/d of CFC-BDP for 6 weeks. Changes in spirometry, daytime asthma symptom and nighttime asthma-related sleep disturbance scores, morning and evening peak expiratory flows, and daily use of inhaled β-agonist for symptom control on diary cards were assessed over 6 weeks of treatment.

Results: Three hundred twenty-three patients were randomized to the 6 treatment groups, which had similar demographics and baseline lung function. There were significantly larger changes from baseline at week 6 in FEV₁ percent predicted with increasing doses of both HFA-BDP and CFC-BDP. The FEV₁ percent predicted dose-response curve for HFA-BDP was shifted to the left compared with the dose-response curve for CFC-BDP. By using the Finney bioassay method, it was calculated that 2.6 times as much CFC-BDP would be required to achieve the same improvement in FEV₁ percent predicted as HFA-BDP (95% confidence interval, 1.1-11.6). All treatment groups except the 100 µg/d CFC-BDP group tolerated study drug well. Ten (17%) of 59 patients in this group reported an acute asthma episode, increased asthma symptoms (6 of the 8 reports of increased asthma symptoms were classified as

severe), or both, and 8 patients withdrew from the study (3 for adverse events related to asthma).

Conclusions: Increasing doses of inhaled corticosteroids lead to improved lung function and asthma control. Moreover, the reformulation of BDP in HFA enables effective asthma control at much lower doses than CFC-BDP. (*J Allergy Clin Immunol* 1999;1215-22.)

Key words: Asthma, beclomethasone dipropionate, chlorofluorocarbons, hydrofluoroalkane-134a, propellants, metered-dose inhalers, inhaled corticosteroids

For patients with persistent asthma, anti-inflammatory therapy with inhaled corticosteroids is recommended. As asthma becomes more severe, larger doses of inhaled corticosteroids are advised. However, there is little convincing information in the literature regarding the dose effectiveness of inhaled corticosteroids, probably because of limitations in the study design.^{1,2} In this study we attempted to determine whether a rigorous design would show improvements in clinical parameters of asthma control with increasing doses of beclomethasone dipropionate (BDP) formulated in hydrofluoroalkane-134a (HFA-BDP) and chlorofluorocarbon propellants (CFC-BDP).

In evaluating options for which inhaled corticosteroid should be used in the treatment of persistent asthma, several factors have to be considered. These include the characteristics of the molecule, the formulation, and the effectiveness of the delivery system. Because of environmental concerns, CFCs will soon no longer be available for use in metered-dose inhalers (MDIs). Reformulation of BDP in the nonozone-depleting propellant HFA resulted in smaller particle sizes and improved lower airway deposition.³ In this study we also attempted to determine whether the more effective delivery system HFA-BDP provides improved asthma control compared with CFC-BDP.

METHODS

Patient recruitment

Patients were recruited from clinics of study investigators. Inclusion criteria were age of greater than 18 years, asthma history of at least 12 months, 12% or greater FEV₁ reversibility to inhaled β-agonist, inhaled β-agonist use for asthma symptom control, screening FEV₁ of 50% to 75% predicted of predicted value,⁴ and use of 400 to 1000 µg/d flunisolide, triamcinolone acetonide, or CFC-BDP

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Abbreviations used

BDP:	Beclomethasone dipropionate
CFC:	Chlorofluorocarbon
FEF _{25-75%} :	Forced expiratory flow over 25-75% of the vital capacity
FVC:	Forced vital capacity
HFA:	Hydrofluoroalkane-134a
PEF:	Peak expiratory flow

for 4 weeks before the prestudy visit. Exclusion criteria were smoking within the previous 12 months, greater than 15 pack-years of smoking history, upper respiratory tract infection within previous 4 weeks, and lower respiratory tract infection within previous 6 weeks. Use of more than 2 short bursts of oral corticosteroids within the previous 6 months or oral or injectable corticosteroids within the previous 2 months was not allowed. Use of theophyllines, oral β -agonists, salmeterol, inhaled anticholinergics, greater than 400 μ g/d intranasal corticosteroids, nedocromil sodium, and sodium cromoglycate was not allowed for 48 hours before the prestudy visit and throughout the study. All patients gave informed consent to this institutional review board–approved study.

Study design (run-in)

Eligible patients signed an institutional review board–approved informed consent form and entered a 7- to 14-day run-in period. During the run-in period, patients continued to use their prescribed inhaled corticosteroid. They recorded the best of 3 peak expiratory flow (PEF) measures in the morning and evening on a diary card. They also recorded scores (based on a 6-point scale from none to so severe that they interfered with normal daily activities) each evening for 4 asthma symptoms (wheeze, chest tightness, cough, and shortness of breath) experienced during the day, scores (based on a 5-point scale from none to preventing sleep) each morning for asthma-related nighttime sleep disturbance, and daily inhaled β -agonist. They returned to the clinic 5 of the last 7 days of the run-in period to perform spirometry. Use of inhaled β -agonist was not allowed within 6 hours of clinic visits. Spirometry was performed at clinic visits, per American Thoracic Society criteria,⁵ in the morning $\pm$ 1 hour of the prestudy visit. The lowest FEV₁ value, the highest total asthma symptom and sleep disturbance scores, and the largest number of puffs of inhaled β -agonist recorded over the last 7 days of the run-in period were considered run-in values.

Study design (inhaled corticosteroid washout)

Patients adhering to run-in procedures and with a run-in FEV₁ of 45% to 75% of predicted value entered a 1- to 28-day, single-blind, inhaled corticosteroid washout phase. Their previously prescribed inhaled corticosteroid was discontinued, and they were given a blinded placebo MDI. Patients continued to complete their diary card and returned to the clinic 5 mornings per week to perform spirometry. Qualification for randomization occurred on the day that the FEV₁ decreased by at least 10% from run-in values, provided that on the day preceding the qualifying drop in FEV₁ there had been either a higher total asthma symptom and sleep disturbance score or an increase of at least 2 in the number of puffs of inhaled β -agonist compared with run-in values. Data collected on the day patients qualified for treatment were considered baseline data.

Randomized treatment

Patients were randomized to one of 6 treatments: 100 μ g/d, 400 μ g/d, or 800 μ g/d HFA-BDP (QVAR; 3M Pharmaceuticals, St Paul,

Minn) or 100 μ g/d, 400 μ g/d, or 800 μ g/d CFC-BDP (Vancril; Schering-Plough, Kenilworth, NJ). Both products were of the 50 μ g/puff ex-valve strength. A double-dummy, modified blind technique was used, requiring 9 puffs twice daily from 3 different MDIs. Spacers were not allowed.

During the 6-week treatment period, patients returned to the clinic 5 mornings per week to dose with study drug and to perform spirometry. They continued to complete the diary card daily. Reversibility of FEV₁ 30 $\pm$ 5 minutes after 2 puffs of an inhaled β -agonist was assessed weekly.

Safety features

Patients were to inform the clinic if their PEF fell below an alert PEF value, which was calculated as 80% of the PEF value recorded on the same day as the baseline FEV₁. Asthma exacerbations could be treated with nebulized β -agonists twice (either 2 times for the same exacerbation or 1 time for 2 separate exacerbations). Oral antibiotic use was allowed once during the trial. Further treatment necessitated study withdrawal. A physical examination and routine hematology and serum chemistry tests were performed before and after the study.

Adherence

Patients self-administered their morning dose of study drug under supervision at the clinic on visit days. MDI technique was reviewed and corrected by study staff at clinic visits, and patients were reminded to take their outpatient doses of study drug. All MDIs were returned at study end and weighed.

Statistical analysis

Change from baseline in FEV₁ percent predicted at week 6 was the primary efficacy variable. Daily FEV₁ percent predicted measurements were averaged for each weekly interval. A minimum of 3 nonmissing values were required to calculate a weekly average. For fewer than 3 values in a given week, the average was calculated by using data from previous weeks until 3 nonmissing data points were available. The change from baseline in FEV₁ percent predicted was analyzed for each week by using an ANOVA model with terms for dose, product, center, and their interaction terms. A linear trend test for unequally spaced doses with a contrast from the ANOVA assessed the changes from baseline in FEV₁ percent predicted with increasing doses for both HFA-BDP and CFC-BDP. Jonckheere's nonparametric trend test, adjusting for center, was also performed to evaluate dose response.⁶ The Finney parallel line bioassay method was used to quantify the dose-comparison relationship between HFA-BDP and CFC-BDP. The 95% confidence interval (CI) around the estimate of dose comparison was calculated by using Fieller's theorem.⁷

Confirmatory efficacy variables were the percentage change from baseline in forced expiratory flow over 25% to 75% of the vital capacity (FEF_{25-75%}), forced vital capacity (FVC), change from baseline in FEV₁ reversibility to inhaled β -agonist, morning and evening PEF values, asthma symptom and nighttime asthma-related sleep disturbance scores, and daily puffs of inhaled β -agonist used. The percentage of days and nights free of asthma symptoms was calculated. The confirmatory efficacy variables were tested by using the same ANOVA and linear trend methods as described for FEV₁ percent predicted.

Subgroup analyses were performed for sex, ethnicity, and protocol adherence. Protocol adherence was defined as use of $\pm$ 20% of calculated study drug on the basis of canister weights and no significant protocol departures on review of case report forms.

A sample size of 30 patients per treatment group ensured 80% power to detect a difference between the 400 μ g/d and 800 μ g/d HFA-BDP treatment groups of 7.5% in FEV₁ percent predicted at

TABLE I. Demographic characteristics and screening, run-in, and baseline lung function by treatment group

	HFA-BDP			CFC-BDP		
	100 µg/d (n = 50)	400 µg/d (n = 51)	800 µg/d (n = 56)	100 µg/d (n = 59)	400 µg/d (n = 55)	800 µg/d (n = 52)
Demographics						
Sex (F/M)	32/18	35/16	36/20	34/25	39/16	30/22
Race (W/B/A)	44/6/0	47/4/0	49/7/0	46/13/0	49/6/0	48/3/1
Smoking history (none/past)	34/16	38/13	45/11	39/20	40/15	42/10
Asthma duration (1-5 y/>5 y)	10/40	11/40	8/48	13/46	10/45	4/48
Allergy history (no/yes)	6/44	6/45	7/49	9/50	5/50	3/49
Screening lung function						
FEV ₁ (% predicted)*	64.8 ± 7.1	66.0 ± 7.6	64.9 ± 8.7	65.4 ± 7.6	64.4 ± 7.6	66.2 ± 7.6
FEV ₁ (% reversibility)*	25.8 ± 17.3	25.0 ± 14.1	26.6 ± 18.4	24.8 ± 13.7	28.6 ± 16.4	23.3 ± 12.1
Run-in lung function						
FEV ₁ (% predicted)*	67.8 ± 9.0	68.3 ± 9.5	68.6 ± 10.8	69.5 ± 10.2	66.8 ± 10.2	68.8 ± 8.0
Baseline lung function						
FEV ₁ (% predicted)*	52.3 ± 8.0	53.1 ± 8.5	52.1 ± 10.0	53.6 ± 9.0	51.6 ± 8.8	53.0 ± 8.0
FEV ₁ (% reversibility)*	42.2 ± 21.1	44.9 ± 20.2	47.5 ± 25.5	38.5 ± 21.1	45.7 ± 21.0	43.9 ± 23.1
FEF _{25-75%} (L/sec)	1.68 ± 0.61	1.68 ± 0.69	1.87 ± 0.74	1.83 ± 0.73	1.69 ± 0.69	1.91 ± 0.85
FVC (L)	3.54 ± 0.93	3.55 ± 0.96	3.53 ± 0.99	3.68 ± 1.07	3.59 ± 0.96	3.53 ± 1.02
Morning PEF (L/min)	316.0 ± 80.4	310.2 ± 86.9	327.4 ± 88.8	319.7 ± 101.3	307.4 ± 85.3	341.6 ± 107.6
Evening PEF (L/min)	350.0 ± 91.7	354.8 ± 106.8	369.4 ± 86.5	358.4 ± 113.7	341.1 ± 81.5	375.3 ± 108.8

W/B/A, White/black/Asian.

*Values are means ± SD.

week 6, assuming a standard deviation of 10% ($\alpha = .05$). Because it was anticipated that 40% of randomized patients might not adhere to the protocol, minimum study enrollment was set at 50 patients per treatment group or 300 total patients.

RESULTS

Patient disposition and characteristics

Between February and December 1996, 496 patients were screened for study entry, and 323 were randomized. The most common reason for screening ineligibility was an FEV₁ value outside the 50% to 75% predicted range. After randomization, 18 patients withdrew from the study (6 for personal reasons, 5 for adverse events, 3 for an inadequate response, and 4 for miscellaneous reasons). The 100 µg/d CFC-BDP group had 8 withdrawals; no other treatment group had more than 3.

No significant differences in demographic characteristics and screening, run-in, and baseline lung function were found among treatment groups (Table I). Across all treatment groups at baseline, the FEV₁ percent predicted had fallen about 16% from the run-in value to a mean of 52.4% ± 8.7% (SD), which corresponded to an absolute mean FEV₁ of 1.85 ± 0.50 L (SD). Run-in daytime asthma symptom and nighttime asthma-related sleep disturbance scores ranged from 0.3 to 1.6 (minimal to mild) and had not significantly changed at baseline. β -Agonist use across all treatment groups increased from 4.8 ± 2.5 puffs (SD) per day at run-in to 6.8 ± 2.8 puffs (SD) per day at baseline.

Primary efficacy variable

For each treatment group, FEV₁ percent predicted increased over the first 4 weeks of treatment and tended to reach a plateau by week 6 (Fig 1). Change from base-

line at week 6 in FEV₁ percent predicted was greater ($P = .049$) with 800 µg/d HFA-BDP than 400 µg/d and marginally, but not significantly, greater ($P = .09$) with 800 µg/d CFC-BDP than 400 µg/d. The ANOVA showed a significant dose effect across both products ($P < .001$). Both the linear trend and Jonckheere's trend test confirmed a significantly larger change from baseline in FEV₁ percent predicted at week 6 with increasing doses of both HFA-BDP ($P = .009$) and CFC-BDP ($P = .003$).

The dose-response curve for change in FEV₁ percent predicted at week 6 was shifted to the left for HFA-BDP compared with CFC-BDP (Fig 2). Comparing the dose effect of HFA-BDP with CFC-BDP, it was calculated, by using the Finney bioassay method, that it would take 2.6 (95% CI, 1.1-11.6) times the dose of CFC-BDP to obtain the same improvement in FEV₁ percent predicted obtained by using HFA-BDP.

Confirmatory efficacy variables

The ANOVA showed significant dose effects across both products for FEF_{25-75%}, FVC, FEV₁ reversibility to inhaled β -agonist, and morning, but not evening, PEF (Table II). Significant dose effects were not found for absolute asthma symptom and nighttime sleep disturbance scores (data not shown) but were found across both products for percentage of days free from wheeze, percentage of days free from chest tightness, and daily inhaled β -agonist puffs used (Table III). The dose-response curve for percent change from baseline in FEF_{25-75%} at week 6 for HFA-BDP was shifted to the left compared with that for CFC-BDP (Fig 3). Comparison between the dose effects of HFA-BDP and CFC-BDP on the basis of the Finney bioassay method showed that it would take 3.2 (95% CI, 1.3-15.8) times the dose of

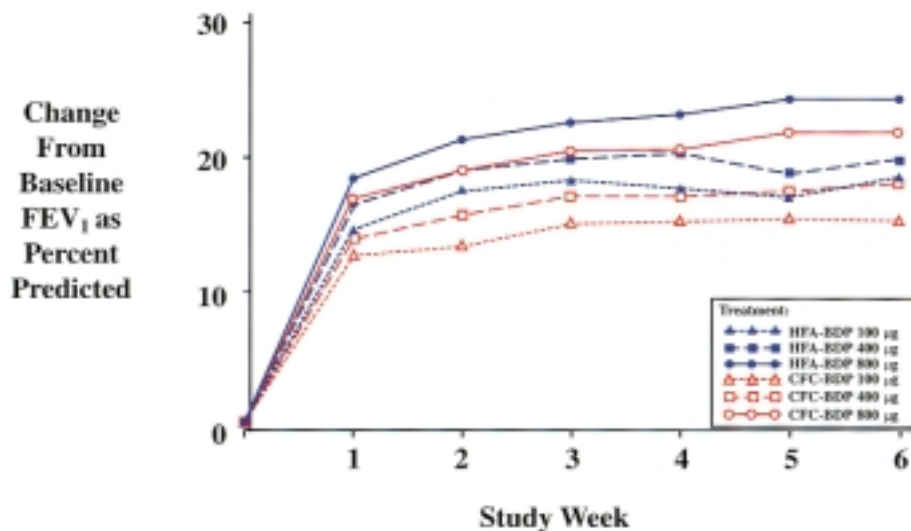


FIG 1. The change from baseline in FEV₁ percent predicted is shown over the 6 weeks of active treatment for each of the 6 active treatment groups. At each time point, regardless of study drug, the results with treatment of 400 µg/d were better than those for treatment with 100 µg/d, and results with treatment of 800 µg/d were better than those with 400 µg/d. Also, at each time point, the results for HFA-BDP-treated patients were better than those for CFC-BDP-treated patients at equivalent doses. The values are means of the weekly averages.

TABLE II. Change from baseline in confirmatory physiologic efficacy variables at week 6 by treatment group

	HFA-BDP			CFC-BDP		
	100 µg/d	400 µg/d	800 µg/d	100 µg/d	400 µg/d	800 µg/d
FEF _{25-75%} (%)*	60.4 ± 8.9	69.5 ± 8.7	98.9 ± 8.4	45.6 ± 8.5	52.9 ± 8.7	76.7 ± 8.7
FVC (%)*	21.4 ± 2.6	21.0 ± 2.5	36.8 ± 2.4	19.3 ± 2.4	24.5 ± 2.5	27.8 ± 2.5
FEV ₁ , reversibility to β-agonist (%)*	-24.3 ± 3.2	-25.1 ± 3.2	-32.7 ± 3.1	-22.5 ± 3.1	-22.6 ± 3.1	-31.3 ± 3.2
Morning PEF (L/min)*	39.1 ± 7.1	49.9 ± 7.0	61.9 ± 6.7	32.5 ± 6.7	53.2 ± 6.9	51.2 ± 7.0
Evening PEF (L/min)	35.9 ± 6.2	26.2 ± 6.1	37.2 ± 5.8	20.4 ± 5.8	34.9 ± 6.0	36.3 ± 6.1

Values are means ± SEM.

**P* < .05 dose effect as assessed by ANOVA with terms for dose, product, center, and interaction terms

TABLE III. Percentage of days free from asthma symptoms, percentage of nights free from asthma-related sleep disturbance, and number of puffs of inhaled β-agonist used on a daily basis at week 6 by treatment group

	HFA-BDP			CFC-BDP		
	100 µg/d	400 µg/d	800 µg/d	100 µg/d	400 µg/d	800 µg/d
Days free from wheeze (%)*	37.4 ± 6.8	41.0 ± 6.6	55.4 ± 6.4	34.3 ± 6.3	50.8 ± 6.6	48.8 ± 6.6
Days free from shortness of breath (%)	23.0 ± 6.2	28.6 ± 6.0	39.7 ± 5.8	27.0 ± 5.7	34.7 ± 6.0	34.6 ± 6.0
Days free from cough (%)	59.5 ± 6.5	74.3 ± 6.3	69.3 ± 6.1	64.2 ± 6.0	69.0 ± 6.3	66.9 ± 6.3
Days free from chest tightness (%)*	26.0 ± 6.2	31.1 ± 6.0	41.3 ± 5.8	22.3 ± 5.7	44.4 ± 6.0	38.2 ± 6.0
Nights free from asthma-related sleep disturbance (%)	77.1 ± 5.3	74.0 ± 5.2	84.0 ± 5.0	76.8 ± 4.9	76.1 ± 5.2	79.8 ± 5.2
Puffs of β-agonist used per day*	4.8 ± 0.4	4.5 ± 0.4	3.7 ± 0.4	5.5 ± 0.4	4.7 ± 0.4	4.0 ± 0.4

Values are means ± SEM.

**P* < .05 dose effect as assessed by ANOVA with terms for dose, product, center, and interaction terms.

CFC-BDP to result in the same improvement in FEF_{25-75%} as that obtained with HFA-BDP.

Adherence

Overall mean adherence with the study drug use was 93%. Adherence with scheduled clinic visits was also high: 84% of patients visited the clinic an average of 5

times per week, and 99% visited an average of 4 times per week.

Subgroup analyses

The results of the analyses were consistent in subgroups on the basis of sex, ethnicity, and adherence with the protocol.

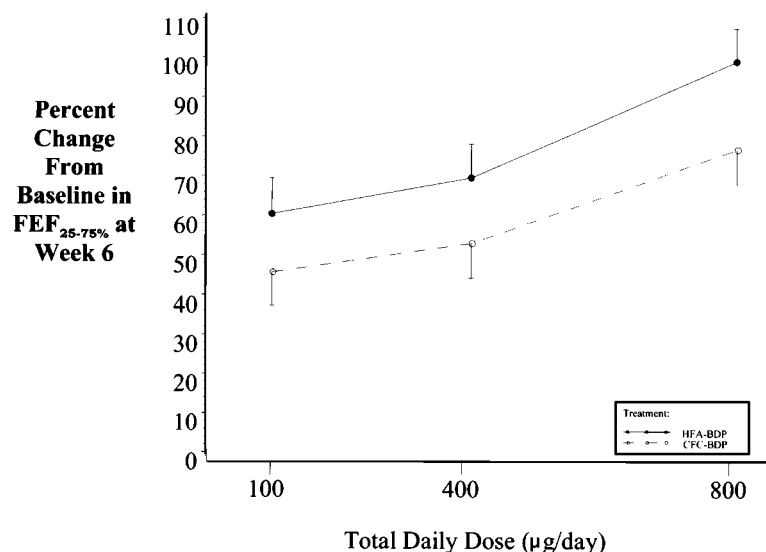


FIG 2. The results of the regression analysis for change from baseline in FEV₁ percent predicted at week 6 is shown by treatment group. There is a beneficial shift in the dose-response curve for HFA-BDP compared with that for CFC-BDP. This shift is quantified by the relative dose ratio of 2.6, which indicates that it would require 2.6 times the dose of CFC-BDP to achieve the same change from baseline in FEV₁ percent predicted as HFA-BDP; that is, it would require 400 µg/d CFC-BDP to achieve the same effect as 150 µg/d HFA-BDP.

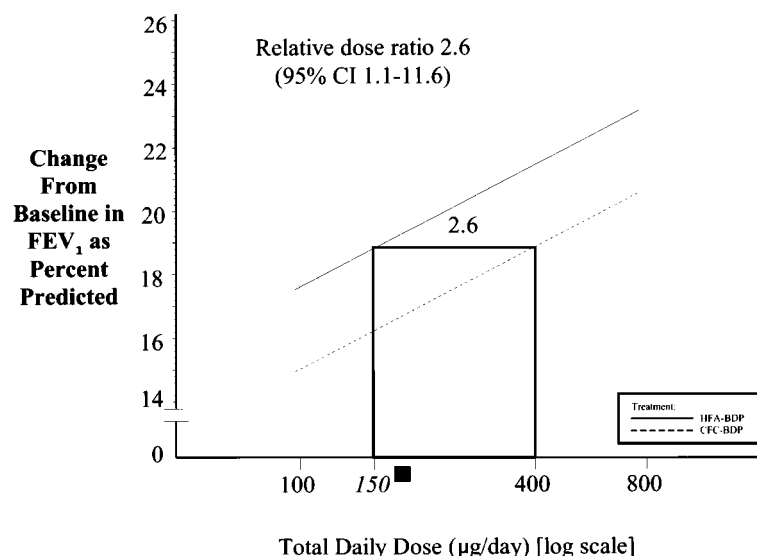


FIG 3. The percent change from baseline in FEF_{25-75%} at week 6 is shown by treatment group. There is a clear trend for improvement in FEF_{25-75%} with increasing doses of HFA-BDP and CFC-BDP, along with a beneficial shift in the dose-response curve for HFA-BDP compared with that for CFC-BDP. The values are the means (SE) of the week 6 average.

Safety assessments

Reporting rates for total and most individual adverse events were similar for the 6 treatment groups. However, 10 (17%) of the 59 patients receiving 100 µg/d CFC-BDP reported an acute asthma episode, increased asthma symptoms, or both; 6 of the 8 reports of increased asthma symptoms in the CFC-BDP 100 µg/d treatment group were classified as severe. Only 2 (4%) of the 50 HFA-BDP-treated patients receiving 100 µg/d reported an

acute asthma episode, increased asthma symptoms, or both, none of which were severe. Eight patients receiving 100 µg/d CFC-BDP withdrew from the study (3 for adverse events related to asthma), whereas only 2 patients receiving 100 µg/d HFA-BDP withdrew (1 for an asthma related adverse event). The one serious adverse event in this study (hospitalization for an upper gastrointestinal hemorrhage) occurred in a patient taking 100 µg/d CFC-BDP and was not attributed to study drug use. More reports of pharyngitis occurred in the HFA-

BDP 800 µg/d group than in the CFC-BDP 800 µg/d group (27% vs 17%, respectively). Clinically meaningful abnormalities on either physical examinations or laboratory testing were not found.

DISCUSSION

This study shows that increasing doses of inhaled corticosteroids in patients with severe asthma result in improved lung function and asthma control. Also, HFA-BDP provided larger increases in lung function than CFC-BDP, presumably because of improved pulmonary deposition.³

The effects of increasing doses of BDP in this study, expressed in terms of absolute FEV₁, are clinically meaningful.⁸ Patients treated with 800 µg/d HFA-BDP had on average a 170-mL larger increase in FEV₁ from baseline at week 6 than patients treated with 400 µg/d and a 230-mL larger increase in FEV₁ than patients treated with 100 µg/d. Similar differences were found among the CFC-BDP treatment groups. FEV₁, a clinically relevant marker of asthma control,⁹ had adequate sensitivity to distinguish dose effects in this study because of the requirement for FEV₁ percent predicted to decrease during the inhaled corticosteroid washout. The fall in FEV₁ during the inhaled corticosteroid washout period provided assurance that FEV₁ percent predicted would increase with study drug treatment. FEV₁ had not distinguished dose effects in previous inhaled corticosteroid dose-response studies,^{1,2} leading to the use of antigen challenge^{10,11} and exercise challenge¹² to demonstrate dose effects. These methods may be difficult for clinicians to relate to clinical asthma control. Significant dose effects found in this study for physiologic-based (FEF_{25-75%}, FVC, FEV₁ reversibility to inhaled β-agonist, and morning PEF) and symptom-based (percentage of days free from wheeze, percentage of days free from chest tightness, and daily inhaled β-agonist use) efficacy variables confirmed that asthma control had improved with increasing doses of HFA-BDP and CFC-BDP.

The effects of HFA-BDP were distinguished from those of CFC-BDP by the Finney bioassay method, which calculated the dose of each product required to obtain the same benefit in lung function. This novel approach to characterizing effectiveness demonstrated a highly relevant difference in dosing characteristics between HFA-BDP and CFC-BDP. It would require 2.6 times the dose of CFC-BDP to obtain the same change in FEV₁ percent predicted as that obtained with HFA-BDP; 1000 µg of CFC-BDP would be approximately dose equivalent with 400 µg of HFA-BDP. Because BDP has not been altered in the reformulation with HFA, improved asthma control in HFA-BDP-treated patients must be due to increased amounts of BDP reaching the airways. HFA-BDP has a smaller mean particle size than CFC-BDP, and radiolabeled deposition work indicates that HFA-BDP has much greater pulmonary, especially small airway, deposition than CFC-BDP.³ This difference in delivery appears to produce clinically relevant differ-

ences in efficacy. Asthma is an inflammatory disease of large and small airways,^{13,14} and inhaled corticosteroids improve asthma control through their topical anti-inflammatory effect.^{15,16,17} Topically acting anti-inflammatory inhaled corticosteroids should be more effective if deposition occurs at the site of inflammation in both the large and small airways.

Critical issues in designing an ideal inhaled corticosteroid dose-response study are ensuring adherence with study drug use and identifying a study population with well-defined responsiveness to inhaled corticosteroids.^{1,2} Adherence with study drug use in this study was addressed by having patients return to the clinic 5 times per week and self-dose with study drug at these clinic visits. Frequent clinic visits were also an important safety feature, allowing careful monitoring of asthma control during the inhaled corticosteroid washout and treatment phases of the study. A study population with well-defined dependence on inhaled corticosteroids was identified by evaluating asthma control and daily variability in FEV₁ during a run-in period while patients were still receiving their usual dose of inhaled corticosteroids. Inhaled corticosteroids were then withdrawn to induce a clinically meaningful deterioration in asthma control.^{18,19} Deterioration was defined by a 10% decrease in FEV₁ from the lowest FEV₁ during the run-in period, along with increases in either asthma symptoms or short-acting β-agonist use to control asthma symptoms. Choosing the lowest FEV₁ from the run-in period as the comparison ensured that daily fluctuations in lung function were not misinterpreted as asthma deterioration.

This study design avoided issues limiting the value of previous inhaled corticosteroid dose-response studies. Doses of HFA-BDP and CFC-BDP were within label recommendations, unlike other studies, which used doses above recommended levels to demonstrate dose effects. The parallel-group design avoided the issue of washout duration, which may confound the interpretation of sequential dosing^{10,21,22} and crossover design^{23,24} studies. Unlike earlier dose-response studies,^{10,11} the study duration of 6 weeks was long enough to demonstrate a plateau of effect with each dose level. Concomitant use of oral prednisone complicates interpretation of previous dose-response studies with inhaled corticosteroids.^{22,24} Oral prednisone and long-acting β-agonists were not allowed in this study. The same delivery devices were used for each study drug, and spacers were not allowed, ensuring product comparisons would not be confounded by differences in inhalation techniques. A study limitation was that optimal asthma control was not achieved at treatment end. Further improvements in FEV₁ may have occurred with higher doses of HFA-BDP. Dosing was limited to 800 µg/d HFA-BDP because this daily dose has been shown to have a favorable systemic safety profile compared with the same dose of CFC-BDP.²⁵

This study is the first, to our knowledge, to successfully show a clinical distinction between 2 different inhaled corticosteroids over multiple doses (3 different doses of each study drug). The dose effects of HFA-BDP

therefore could be clearly distinguished from those of CFC-BDP by the shift in the dose-response curve for FEV₁ percent predicted. This should be the standard method for comparing different inhaled corticosteroids in future studies because it provides precise estimates of product comparability.¹ Significant and parallel dose-response curves were required for the different products for this statistical analysis; both of these conditions were met in this study. Only one previous study has compared multiple doses of 2 different inhaled corticosteroids.²⁶ Because dose-response effects were not found in that study, dose comparisons could not be performed. A dose reduction method²⁷ was used in a pediatric study to compare minimally effective doses of inhaled corticosteroids, but this approach did not provide information across an entire dose range. Chervinsky et al²⁸ reported a trend for dose response using asthma control as an efficacy variable. Because only a single inhaled corticosteroid product was used in this study, it is unclear whether this design would have been adequately sensitive to detect differences between treatments.

The lowest total daily dose of HFA-BDP, 100 µg/d, improved lung function and was well tolerated. The lowest total daily dose of CFC-BDP, 100 µg/d, was not well tolerated. Patients in this dosing group reported unacceptably frequent episodes of increased asthma symptoms. There were very few adverse event reports of oropharyngeal candidiasis, dysphonia, and cough with HFA-BDP treatment in this study. The only remarkable safety observation, a larger number of reports of pharyngitis for the 800 µg/d HFA-BDP treatment groups, probably occurred by chance. Few of these reports were attributed to study drug use, and a previous study with a larger sample size found that only a small percentage of patients treated with 800 µg/d HFA-BDP reported pharyngitis.²⁹ Although this study design precluded assessment of systemic effects, previous work has shown that treatment with 800 µg/d HFA-BDP for 2 weeks has similar effects on 24-hour urinary-free cortisol levels, a sensitive marker of the hypothalamic-pituitary-adrenal axis, as treatment with 800 µg/d CFC-BDP.³⁰

In conclusion, this study shows that increasing doses of inhaled corticosteroids lead to improved lung function and asthma control. Moreover, the reformulation of BDP in HFA enables effective asthma control at much lower doses than CFC-BDP. These data support the concept that inhaled corticosteroid effectiveness increases with larger doses and indicate that the inhaled formulation is also a factor in determining therapeutic effectiveness.

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