Significant variability in response to inhaled corticosteroids for persistent asthma

Stanley J. Szefler, MD, Richard J. Martin, MD, Tonya Sharp King, PhD, Homer A. Boushey, MD, Reuben M. Cherniack, MD, Vernon M. Chinchilli, PhD, Timothy J. Craig, DO, Myrna Dolovich, PEng, Jeffrey M. Drazen, MD, Joanne K. Fagan, PhD, John V. Fahy, MB, ChB, James E. Fish, MD, Jean G. Ford, MD, Elliot Israel, MD, James Kiley, PhD, Monica Kraft, MD, Stephen C. Lazarus, MD, Robert F. Lemanske, Jr, MD, Elizabeth Mauger, PhD, Stephen P. Peters, MD, PhD, and Christine A. Sorkness, PharmD, for the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute *Denver, Colo, Boston, Mass, New York, NY, Hershey, Pa, Madison, Wis, Philadelphia, Pa, San Francisco, Calif, Hamilton, Ontario, Canada, and Bethesda, Md*

Background: A clinical model is needed to compare inhaled corticosteroids (ICSs) with respect to efficacy.
Objective: The purpose of this investigation was to compare the relative beneficial and systemic effects in a dose-response relationship for 2 ICSs.
Methods: A 24-week, parallel, open-label, multicenter trial examined the benefit-risk ratio of 2 ICSs in persistent asthma. *Benefit* was assessed by improvements in FEV_1 and PC_{20}; *risk* was assessed by overnight plasma cortisol suppression. Thirty subjects were randomized to either beclomethasone dipropionate (BDP) 168, 672, and 1344 μg/day (n = 15) or fluticasone propionate (FP) 88, 352, and 704 μg/day (n = 15), both administered by means of a metered dose inhaler (MDI) with chlorofluorocarbon propellant via a spacer, in 3 consecutive 6-week intervals; this was followed by 3 weeks of FP dry powder inhaler (DPI) 2000 μg/day.

Results: Maximum FEV_1 response occurred with the low dose for FP-MDI and the medium dose for BDP-MDI and was not further increased by treatment with FP-DPI. Near-maximum methacholine PC_{20} improvement occurred with the low dose for FP-MDI and the medium dose for BDP-MDI. Both BDP-MDI and FP-MDI caused dose-dependent cortisol suppression. Responsiveness to ICS treatment was found to vary markedly among subjects. Good (>15%) FEV_1 response, in contrast to poor (<5%) response, was found to be associated with high exhaled nitric oxide (median, 17.6 vs 11.1 ppb), high bronchodilator reversibility (25.2% vs 8.8%), and a low FEV_1/forced vital capacity ratio (0.63 vs 0.73) before treatment. Excellent (>3 doubling dilutions) improvement in PC_{20}, in contrast to poor (<1 doubling dilution) improvement, was found to be associated with high sputum eosinophil levels (3.4% vs 0.1%) and older age at onset of asthma (age, 20-29 years vs <10 years).
Conclusions: Near-maximal FEV_1 and PC_{20} effects occurred with low-medium dose for both ICSs in the subjects studied. High-dose ICS therapy did not significantly increase the efficacy measures that were evaluated, but it did increase the systemic effect measure, overnight cortisol secretion. Significant intersubject variability in response occurred with both ICSs. It is possible that higher doses of ICSs are necessary to manage more severe patients or to achieve goals of therapy not evaluated in this study, such as prevention of asthma exacerbations. (J Allergy Clin Immunol 2002;109:410-8.)

Key words: *Asthma, beclomethasone dipropionate, exhaled nitric oxide, fluticasone propionate, inhaled corticosteroid, methacholine response, pulmonary response*

Many different inhaled corticosteroid (ICS) preparations and delivery devices are available for the treatment of asthma, but there is no standardized method by which to compare their beneficial and adverse effects. ICSs alleviate clinical symptoms, improve pulmonary function, and reduce airway inflammation.[1-5] However, higher doses and prolonged use of ICSs can have systemic effects.[6,7]

This study was designed to compare the relative beneficial and systemic effects in a dose-response relationship for 2 ICSs, beclomethasone dipropionate (BDP) and fluticasone propionate (FP), both administered by means of

From the National Jewish Medical and Research Center, Denver (R.M.C., M.K., R.J.M., S.J.S.); Brigham and Women's Hospital and Harvard Medical School, Boston (J.D., E.I.); Harlem Hospital Center and Columbia University, New York City (J.G.F., J.F.); Pennsylvania State University and Milton S. Hershey Medical Center, Hershey (V.M.C., T.J.C., T.S.K., E.M.); the University of Wisconsin, Madison (R.F.L., C.A.S.); Thomas Jefferson University, Philadelphia (J.E.F., S.P.P.); the University of California at San Francisco (S.C.L., H.A.B., J.V.F.); McMaster University, Hamilton (M.D.); and the National Heart, Lung and Blood Institute (J.K).

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Reprint requests: Stanley J. Szefler, MD, National Jewish Medical and Research Center, Department of Pediatrics, Room B104a, 1400 Jackson Street, Denver, CO 80206.

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Abbreviations used
ACRN: Asthma Clinical Research Network
BDP: Beclomethasone dipropionate
DPI: Dry powder inhaler
eNO: Exhaled nitric oxide
ED: Emitted dose
FPD: Fine particle dose
FP: Fluticasone propionate
ICS: Inhaled corticosteroid
MDI: Metered dose inhaler with chlorofluorocarbon (CFC) propellant

a pressurized metered dose inhaler (MDI) with the OptiChamber spacer (Respironics HealthScan, Cedar Grove, NJ). In this study, we combined the evaluation of systemic effect with multiple measures of beneficial effect to introduce a benefit-to-risk comparison model.

METHODS

Study population

Study subjects were asthmatic individuals who were 18 to 55 years of age and had a baseline FEV_1 of 55% to 85% of predicted, a β_2-adrenergic agonist response of ≥12%, an improvement of at least 200 mL in FEV_1, a methacholine PC_{20} value of ≤8 mg/mL, an exercise-induced fall in FEV_1 of ≥12%, a morning plasma cortisol value of ≥5 μg/dL, and a smoking history of <10 pack-years; none of the subjects had smoked within the previous year. Subjects were excluded if they had received corticosteroid treatment for any condition during the 6 months before enrollment with topical corticosteroids or ICSs or during the 12 months before enrollment with systemic corticosteroids. The protocol was reviewed by each center's Institutional Review Board and by a National Heart, Lung, and Blood Institute (NHLBI) Protocol Review Committee and an NHLBI Data Safety Monitoring Board. Each subject signed an approved consent form.

The investigation was designed as a feasibility study, not as a comparative trial. The sample size calculation was therefore based on an appropriate sample size for estimating the common variance with some level of precision, because this variance estimate would help determine the sample size of a larger, follow-up study. If σ^2 denotes the population variance and s^2 the sample variance, then the 95% CI for σ^2 is $(0.60s^2, 2.01s^2)$ for n = 24. Thus we decided to seek a sample size of n = 30 and allow for a few drop-outs.

Study design

Thirty subjects were randomized to receive one of 2 ICSs—either BDP-MDI (n = 15) or FP-MDI (n = 15)—in a 24-week, randomized, open-label, prospective, multicenter trial (Fig 1). Study doses were selected to result in comparable <5%, 20% to 30%, and 40% to 60% suppression of overnight plasma cortisol concentrations on the basis of a previous Asthma Clinical Research Network (ACRN) study of these 2 ICS–delivery device combinations.[8] For BDP-MDI, the serial study doses were 168, 672, and 1344 μg/day with Vanceril chlorofluorocarbon (CFC) 84 μg/actuation (Schering-Plough, Saddlebrook, NJ); for FP-MDI, the serial study doses were 88, 352, and 704 μg/day with Flovent CFC 44 μg/actuation (GlaxoSmith Kline, Research Triangle, NC). Both were administered with the OptiChamber spacer, and each study dose was administered daily for 6 weeks and monitored with a Doser CT device (MediTrack Products, Hudson, Mass) and canister weights. FP dry powder inhaler (DPI), 2000 μg/day, with Flovent Diskhaler 250 μg/actuation (GlaxoSmith Kline) was then administered in all subjects for 21 days to assess maximum response.[9] Airway function and markers of inflammation were measured before the initiation of treatment, after each of the 3 ICS-MDI study doses was administered for 6 weeks, and after a final 3-week FP-DPI dosing period. Overnight plasma cortisol measures were obtained before the initiation of treatment and after administration of each of the 6-week ICS-MDI study doses but not after the 3-week FP-DPI period.

Procedures

Spirometry, methacholine challenge, asthma control assessment, exhaled nitric oxide (eNO), and induced sputum values were measured as in previous ACRN studies.[10,11] Exercise testing was performed as previously described. Briefly, FEV_1 was measured at 15 to 20 minutes and 5 minutes before the exercise challenge. These 2 values were averaged and the result was determined to be the baseline FEV_1. The target heart rate was calculated as

$$(220 - a) \times 0.8,$$

where a is the subject's age in years. Electrocardiogram (ECG) electrodes were applied and a baseline ECG was obtained. A physician was notified to determine that the ECG result was within normal limits.[12]

Breathing through a mouthpiece, the subject began walking on a treadmill, and the rate and incline were increased to achieve the target heart rate and maintain it for at least 6 minutes. The test was stopped after this time or as soon as the patient experienced significant dyspnea, wheezing, chest pain, a decrease in oxygen saturation of ≥10% or to less than 85%, or significant ECG changes. Spirometry was conducted at 5, 15, 30, 45, and 60 minutes. Subjects received albuterol if significant dyspnea, chest pain, wheezing, shortness of breath, and/or a significant fall of ≥15% in the FEV_1 occurred or at the subject's or physician's request. The subject was discharged when his or her FEV_1 was greater than 90% of the preexercise baseline FEV_1. Overnight cortisol suppression was measured by collecting hourly blood samples via a heparinized catheter for 12 hours (from 7 PM to 7 AM) in a supervised clinical research unit.[8] Subjects at the University of Wisconsin, Columbia University, Brigham and Women's Hospital, and the University of California at San Francisco were admitted to National Institutes of Health General Clinical Research Units. Plasma cortisol was measured by high-pressure liquid chromatography.[13]

Particle size analysis

Drug delivery was evaluated by means of an Anderson Cascade impactor (Thermo Anderson, Inc, Smyrna, Ga) in the laboratory of one of us (M.D.) at McMaster University in Hamilton, Ontario, Canada, as described in our previous ACRN publication.[8] The emitted dose (ED) was measured as the amount of drug that leaves the OptiChamber. The fine particle dose (FPD) is the portion of the ED that is available for airway distribution (particle size, <4.7 μm in diameter).

Analysis

The primary outcome variable for assessing comparative efficacy was FEV_1, secondary outcomes being methacholine PC_{20}, exercise-induced fall in FEV_1, eNO, and sputum eosinophils. Arithmetic means and SDs were calculated for FEV_1, FEV_1 percent of predicted, postbronchodilator FEV_1, postbronchodilator FEV_1 percent of predicted, maximum absolute fall in FEV_1 after exercise, maximum relative fall in FEV_1 after exercise, and eNO. Each of these measures was compared between the treatment groups at baseline through use of a 2-sample t test. For measures with a log-normal distribution (methacholine PC_{20}, area under the curve [AUC] of FEV_1 drop after exercise, and cortisol AUC), geometric means and coefficients of variation were computed to describe the distribution

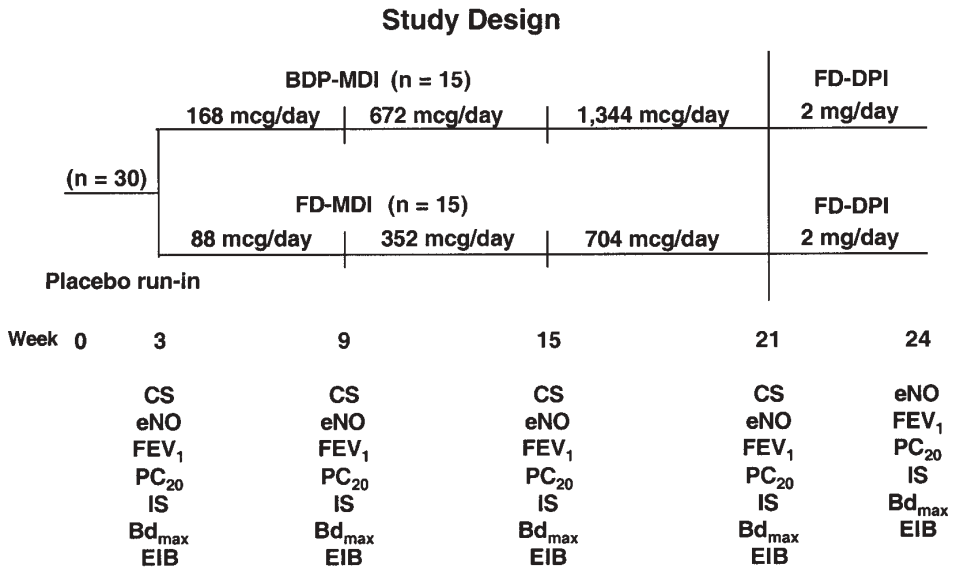

FIG 1. Study design for comparison of inhaled steroid efficacy and systemic effect. BDP, 84 μg per inhalation of Vanceril Double Strength, was administered with an OptiChamber to 15 subjects. FP, 44 μg per inhalation of Flovent-44, was also administered with an OptiChamber to 15 subjects. Inhaled FP (Flovent Diskhaler 250), 4 inhalations twice daily, was administered in the last 3 weeks to all 30 subjects. Study procedure key: cortisol suppression *(CS)*, measured by hourly plasma cortisol concentrations (7 PM to 7 AM) beginning 12 hours before pulmonary function testing; eNO, measured before spirometry; FEV_1, spirometry; PC_{20}, methacholine challenge; *IS,* induced sputum; BD_{max}, spirometry before and after treatment with 6 to 8 inhalations of albuterol (90 μg/inhalation); *EIB,* exercise challenge.

of the values. These outcomes were compared between the 2 treatment groups through use of a 2-sample *t* test on the log scale. Finally, maximum reversibility and the outcomes measured from induced sputum, which are not distributed according to a normal or log-normal distribution, were all summarized through use of medians and quartiles, and the test between the treatment groups at baseline was based on a 2-sample nonparametric Wilcoxon test.

To describe the relationship between study dose during the treatment period and the efficacy/suppression measures, only complete cohort data was used. For the efficacy and suppression outcomes that have an underlying normal or log-normal distribution, the values at the end of each of the 3 escalating doses and the high-dose DPI fluticasone were compared in a repeated-measures analysis of covariance model with adjustment for body mass index and sex. To adjust the outcomes for baseline levels in each model, the responses were defined in terms of the natural log of the values for each study dose relative to baseline. However, efficacy in terms of methacholine PC_{20} was modeled as doubling dilutions; therefore, the difference between each study dose and baseline on the log base 2 scale was compared among the study doses. For the outcomes measured from induced sputum, which are not normally distributed, we produced an overall test among the study doses by evaluating nonparametric tests for each pairwise comparison and applying a Bonferroni-corrected *P* value for the overall comparison.

To identify potential predictors of response defined by percent improvement in FEV_1 and change in PC_{20} during the treatment period, baseline demographic information and measures of efficacy were evaluated. Spearman correlation coefficients were calculated and χ^2 tests performed to determine whether any of the baseline factors were significantly associated with the categoric response measures (poor/marginal/good response). Continuous baseline measures were summarized by their median and first and third quartile values for each level of the response variable. Categoric baseline measures were summarized by median values and percentages.

RESULTS

Study population

A total of 30 subjects were enrolled (15 in each group); there were no significant differences between the 2 groups at baseline (Table I). Table II presents the results of cohort data with a complete sample set for each parameter. Of the 30 subjects enrolled, 26 completed the study. Of the 4 subjects who stopped participating, 3 withdrew their consent (2 were unwilling to follow the protocol and 1 did not feel the treatment was effective); 1 subject was lost to follow-up.

Cortisol suppression

Overnight plasma cortisol was suppressed in a dose-dependent manner, as summarized in Table II for all study patients with complete data and in Fig 2 for subjects completing all measurements for the FEV_1 and PC_{20} response measures as well as the cortisol suppression data.

Change in pulmonary function, methacholine response, and symptoms

For BDP-MDI, FEV_1 (n = 13) increased to a maximum with the medium dose (Table II and Fig 2). For FP-MDI,

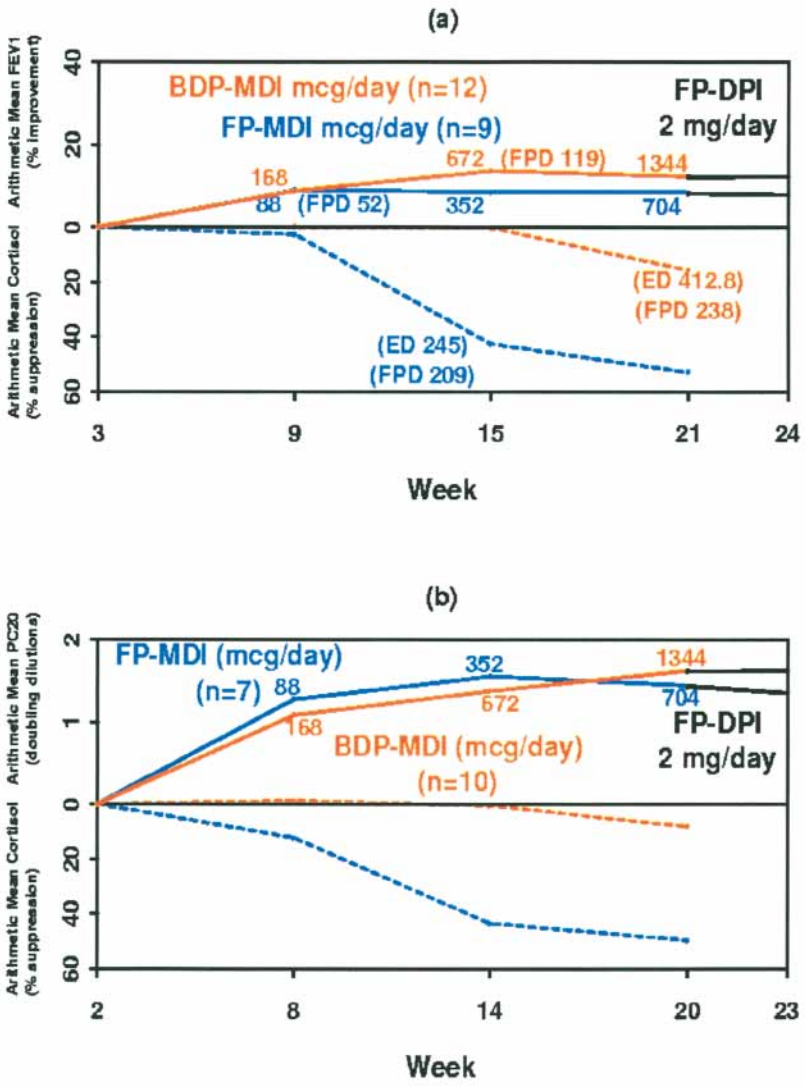

FIG 2. a, Comparative effect of inhaled BDP (n = 12) and inhaled FP (n = 9) on increase in FEV_1 versus overnight plasma cortisol suppression. Both measures are presented in relation to the baseline value. Study doses are indicated at each dose level. For selected doses, numbers in parentheses indicate ED and FPD. **b,** Comparative effect of inhaled BDP (n = 10) and inhaled FP (n = 7) on increase in methacholine PC_{20} doubling doses versus overnight plasma cortisol suppression.

FEV_1 increased to a maximum at low dose (n = 12). In neither treatment group did FEV_1 increase further on treatment with 2000 µg/day FP-DPI. The near-maximum change in methacholine PC_{20} occurred with the low dose for FP-MDI (n = 7) and the medium dose for BDP-MDI (n = 10). The maximum PC_{20} achieved with either ICS was not increased with FP-DPI. For both ICSs, symptom reduction and rescue bronchodilator use also achieved maximal reduction with low to medium doses.

Exercise challenge response

For BDP-MDI (n = 9), maximum inhibition of the absolute fall in FEV_1 and of the AUC from baseline occurred with medium-dose BDP-MDI (Table II). The effect of FP-MDI was difficult to assess because of the small number of subjects who completed this test and because of the low values for exercise-induced fall in FEV_1, whether measured by absolute fall or by AUC. The data obtained showed that maximum inhibition of the absolute fall in FEV_1 (n = 6) and of AUC decline (n = 5) occurred at the high dose and only slightly exceeded the effect that occurred with medium-dose FP-MDI.

eNO and induced sputum analysis

For each ICS, eNO was reduced to near maximum with the low dose (Table II). For BDP-MDI, maximum reduction in sputum eosinophils (n = 5) occurred with the high dose. For FP-MDI, sputum eosinophils (n = 6) were reduced maximally with the medium dose. Comparison of these effects was made difficult by baseline differ-

TABLE I. Baseline data for 2 inhaled steroid study groups

	Inhaled fluticasone propionate			Inhaled beclomethasone dipropionate			
No. of subjects	15			15			*P* value
Male: n (%)	12 (80.0)			11 (73.3)			1.000[F]
Minority: n (%)	4 (26.7)			4 (26.7)			1.000[F]
Characteristic	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	
Age at entry (y)	15	29.58	7.21	15	30.27	7.64	.801[T]
Height (cm)	15	175.62	7.86	15	177.17	10.17	.642[T]
Weight (kg)	15	77.74	16.22	15	82.99	15.12	.367[T]
BMI (kg/m^2)	15	25.01	3.91	15	26.43	4.33	.354[T]
FEV_1 (L)	15	3.04	0.75	15	3.01	0.63	.918[T]
FEV_1 percent of predicted	15	75.07	11.16	15	73.33	11.08	.673[T]
Maximum reversibility (FEV_1 percent change)*	14	17.07	9.54,22.07	14	9.11	7.30,25.22	.323[W]
Postbronchodilator FEV_1 (liters)	14	3.64	0.72	14	3.52	0.90	.701[T]
Postbronchodilator FEV_1 percent of predicted	14	90.14	5.64	14	85.57	15.58	.317[T]
Methacholine PC_{20} (mg/mL)†	14	0.60	1.32	13	0.44	1.44	.559[TL]
Maximum absolute fall in FEV_1 (L) after exercise	8	0.57	0.34	11	1.01	0.77	.113[T]
Maximum relative fall in FEV_1 (percent of baseline) after exercise	8	17.68	9.81	11	31.52	21.74	.082[T]
AUC fall after exercise†	8	6.28	1.49	10	17.01	1.27	.145[TL]
Cortisol AUC†	15	48.06	0.33	15	47.42	0.41	.921[TL]
Exhaled nitric oxide (ppb)	15	18.57	10.88	14	20.04	11.29	.724[T]
Sputum eosinophils + 0.2 (%)*	11	0.70	0.20,3.40	10	3.10	0.60,8.10	.097[W]
Sputum neutrophils (%)*	11	38.80	21.10,45.70	10	48.85	39.80,54.20	.113[W]
Sputum eosinophilic cationic protein*	11	88.00	25.00,397.00	10	153.00	40.00,443.00	.647[W]
Sputum tryptase*	8	8.50	5.50,32.55	5	8.00	5.30,9.00	.509[W]
Weekly average of daily symptoms*	15	0.26	0.04,0.51	15	0.35	0.01,0.61	.819[W]
Weekly average of daily rescue*	15	1.83	0.00,5.17	15	1.63	0.00,4.22	.801[W]

BMI, Body mass index; *AUC,* area under the curve.
*Median and 1st and 3rd quartiles are reported. The 0.2 for eosinophil percent is added to avoid division-by-zero errors when values relative to baseline are being determined (on the basis of 500 cells being read from each slide, adding 0.2 is equivalent to adding 1 count of an eosinophil cell to each slide).
†Geometric mean and coefficient of variation are reported.
[F]Fisher exact test (2-tailed) for differences in proportions between treatment groups.
[T]Two-sample *t* test for differences between treatment groups.
[TL]Two-sample *t* test for differences between treatment groups on the log scale.
[W]Two-sample nonparametric Wilcoxon test for differences between treatment groups.

ences in sputum eosinophils, which tended to be higher in the BDP-MDI group at baseline (3.1% for n = 11 from Table I) than in the FP-MDI group (0.7% for n = 10; P = .097). There appeared to be no effect of either ICS on sputum neutrophils and eosinophilic cationic protein.

Particle size measurement

For BDP-MDI 84 μg/actuation, the ED from the outlet of the Optichamber delivery device was 25.8 μg (31% of the labeled dose; Fig 2, *a*); the FPD was 14.9 μg (18% of the labeled dose). For FP-MDI 44 μg/actuation, the ED was 30.6 μg (70% of the labeled dose) and the FPD was 26.2 μg (59% of the labeled dose). Therefore, FP-MDI delivered a higher proportion of drug in the desired respirable range.

FP-MDI reached maximum efficacy by the FEV_1 parameter at an FPD of 52 μg/day, approximately one half that of BDP-MDI at 119 μg/day, suggesting a higher potency for efficacy with FP-MDI. When ED was evaluated for systemic effect, the FP-MDI of 245 μg/day ED at the medium dose was found to result in approximately 50% cortisol suppression, whereas an ED of 413 μg/day at a high dose of BDP-MDI resulted in 20% cortisol suppression, suggesting a higher potency of FP-MDI for this measure of systemic effect. The FPD values at these 2 dose levels—medium dose for FP-MDI and high dose for BDP-MDI—were comparable.

Variability in FEV_1 response

Five of 12 subjects had a good (>15% increase) response to the 3 doses of BDP-MDI, whereas 5 subjects had a poor (<5% increase) and 2 subjects had a marginal (5 to 15%) increase in FEV_1 (Fig 3, *a*). Three of the 9 subjects treated with FP-MDI had a good FEV_1 response, and 3 of the patients had a poor response to all 3 doses of FP-MDI as well as to FP-DPI (Fig 3, *b*). The remaining 3 of 9 subjects had a marginal increase in FEV_1 with the 3 FP-MDI doses. This poor response cannot be attributed to poor adherence to study medication, inasmuch as documentation of the systemic effect is evident from the overnight plasma cortisol suppression during the treatment with FP-MDI.

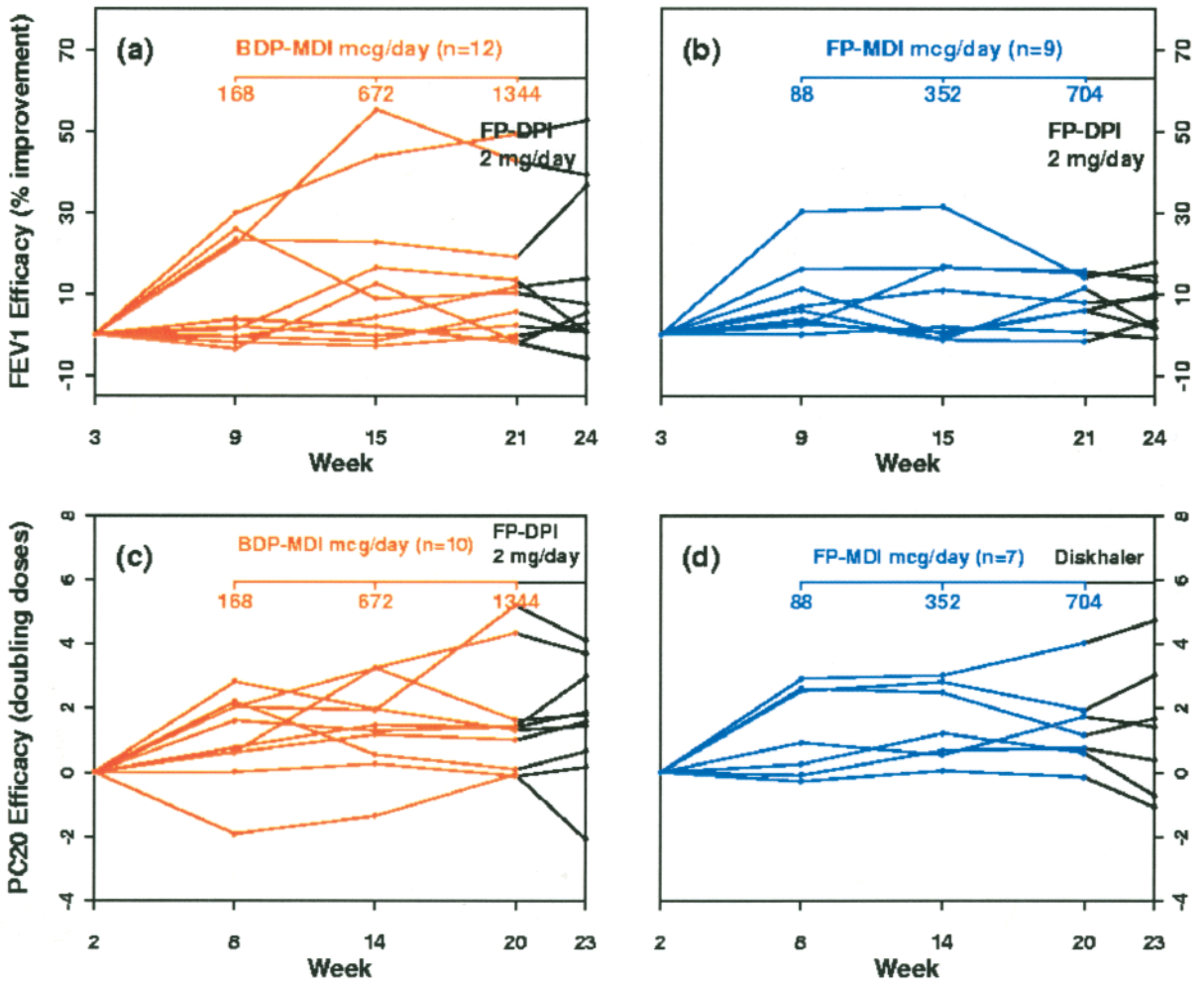

FIG 3. Variability in FEV_1 response (**a** and **b**) and methacholine PC_{20} response (**c** and **d**) for BDP-MDI (**a** and **c**) and FP-MDI (**b** and **d**) for the 3 study doses and the 2-mg/day dose of FP via Diskhaler. Only subjects with complete data sets are included.

The 2 groups were combined to examine baseline patient characteristics associated with a level of response (Table III). Good responders had a significantly higher median eNO, greater median maximum bronchodilator reversibility, and a lower median FEV_1/forced vital capacity ratio before treatment than poor responders. Good responders also tended to have a higher median postbronchodilator FEV_1 percent of predicted before treatment.

Variability in methacholine PC_{20} response

For the 2 ICS groups, 7 of 26 subjects with complete data for the 3 doses had an excellent response, as defined by increase in methacholine PC_{20} by >3 doubling dilutions, whereas 5 subjects had a poor (<1 doubling dilution) response (Table III). The remaining 14 subjects had a good (1 to 3 doubling dilutions) response (Fig 3, *c* and *d*). Subjects with an excellent response had higher sputum eosinophil levels before treatment and were older at the onset of asthma. Excellent responders also tended to have a lower methacholine PC_{20} and higher eNO before treatment than poor responders.

DISCUSSION

This study compared the dose-response effects of 2 ICSs on markers of benefit (FEV_1, PC_{20}) and of systemic effect (overnight plasma cortisol) in corticosteroid-naive subjects with persistent asthma. In lieu of more-difficult-to-obtain indicators for significant clinical effects, such as growth, bone density, and cataracts, attention has turned to measures of cortisol suppression as a surrogate marker of systemic effect.[14]

The 2 ICSs differed in their dose-response profile for both efficacy and systemic effect. For BDP-MDI, the maximum increases in FEV_1 and attenuation of exercise-induced bronchospasm were achieved at the medium dose, with minimal effect on cortisol suppression. Further reductions in bronchial reactivity, eNO, and sputum eosinophils were achieved with high-dose BDP-MDI.

TABLE II. Cohort analysis for effect of inhaled fluticasone propionate and beclomethasone propionate for study measures

		Baseline		Low dose BDP: 168 FP: 88		Medium dose BDP: 672 FP: 352		High dose BDP: 1344 FP: 704		2000 μm/day Flovent Diskhaler	
Parameter	**N***	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Cortisol†‡											
BDP	13	48.76	0.44	46.51	0.31	42.45	0.34	35.82	0.42	—	—
FP	9	46.14	0.40	41.67	0.57	24.86	0.57	17.77	0.77	—	—
FEV_1 (L)§											
BDP	13	3.02	0.66	3.28	0.68	3.38	0.65	3.35	0.57	3.34	0.72
FP	12	3.03	0.77	3.40	0.61	3.39	0.71	3.40	0.72	3.41	0.61
Methacholine PC_{20} (mg/mL)†											
BDP	10	0.50	1.33	1.06	1.50	1.30	1.24	1.55	1.56	1.56	1.48
FP	7	0.62	1.22	1.51	0.48	1.83	0.54	1.70	0.63	1.60	0.48
Exhaled nitric oxide (ppb)§											
BDP	13	19.50	11.56	11.49	6.81	13.08	6.43	9.46	4.53	11.18	5.50
FP	11	17.14	7.91	8.65	3.49	10.66	7.98	11.95	8.11	8.13	2.08
Exercise maximum absolute fall in FEV_1 (L)§											
BDP	9	1.18	0.74	0.71	0.51	0.49	0.36	0.51	0.44	0.62	0.52
FP	6	0.57	0.37	0.49	0.35	0.51	0.39	0.39	0.17	0.32	0.26
Exercise AUC decline†											
BDP	9	23.66	0.78	6.92	1.82	5.94	1.30	8.91	0.90	8.90	1.45
FP	5	5.43	1.89	9.42	1.03	14.80	1.12	6.70	0.69	4.08	2.62
Sputum eosinophils + 0.2 (%)‖											
BDP	5	8.10	1.60,13.70	0.90	0.60,2.50	0.20	0.20,2.30	0.30	0.20,0.40	0.20	0.20,0.80
FP	6	0.80	0.50,3.60	0.65	0.40,0.90	0.20	0.20,0.30	0.20	0.20,0.40	0.20	0.20,0.20
Sputum neutrophils (%)‖											
BDP	5	44.60	40.40,53.30	59.60	55.10,60.50	69.20	47.90,77.60	49.90	35.40,91.70	71.50	40.20,79.10
FP	6	39.70	21.10,41.00	31.45	17.00,55.20	49.35	32.70,66.00	37.95	15.70,68.80	52.10	25.00,70.50
Sputum eosinophilic cationic protein‖											
BDP	5	214.00	212.00,443.00	98.00	81.00,228.00	128.00	52.00,160.00	53.00	52.00,108.00	99.00	79.00,156.00
FP	6	70.00	19.00,89.00	132.00	50.00,274.00	97.00	48.00,246.00	51.00	25.00,54.00	78.50	40.00,133.00
Weekly average of daily symptoms‖											
BDP	13	0.34	0.01,0.56	0.06	0.00,0.10	0.04	0.00,0.16	0.03	0.00,0.18	0.02	0.00,0.39
FP	12	0.25	0.06,0.44	0.03	0.00,0.20	0.02	0.00,0.12	0.03	0.00,0.19	0.02	0.00,0.40
Weekly average of daily rescue‖											
BDP	14	1.48	0.00,3.08	0.33	0.00,1.00	0.58	0.00,1.33	0.14	0.00,1.00	0.00	0.00,0.40
FP	12	0.74	0.00,2.98	0.00	0.00,0.34	0.00	0.00,0.00	0.00	0.00,0.20	0.00	0.00,0.08

FP, Fluticasone propionate; *BDP,* beclomethasone dipropionate; *AUC,* area under the curve.
*Number of subjects with complete data for each measure.
†Geometric mean and coefficient of variation are reported.
‡Cortisol area under the curve changed significantly over time for each treatment arm on the basis of a repeated-measures model ($P < .10$).
§Arithmetic mean and SD are reported.
‖Median and 1st and 3rd quartiles are reported.

TABLE III. Median values (1st quartile, 3rd quartile) of baseline predictors of response and Spearman correlation *P* values for the test of association

	Percent improvement in FEV_1				
Predictor	**≤5% (n = 8)**	**5% to 15% (n = 5)**	**≥15% (n = 8)**	**3-group *P* value**	**<5% vs ≥15% *P* value**
Exhaled nitric oxide (ppb)	11.1 (7.9,14.2)	21.6 (15.1,31.5)	17.6 (16.1,23.0)	.002	.002
Maximum reversibility (FEV_1 percent change)	8.8 (7.1,10.7)	9.1 (6.4,9.5)	25.2 (15.8,54.5)	.007	.002
FEV_1/FVC ratio	0.73 (0.68,0.78)	0.68 (0.67,0.73)	0.63 (0.53,0.70)	.025	.041
	Change in PC_{20}				
	<1 DD (n = 5)	**1-3 DD (n = 14)**	**>3 DD (n = 7)**	**3-group *P* value**	**<1 vs >3 P value**
Sputum eosinophils + 0.2 (%)	0.30 (0.20,0.55)	1.3 (0.6,4.7)	3.6 (3.4,7.8)	.011	.013
Age of onset of asthma* (y)	<10 (80)	<10 (62)	20-29 (71)	.002†	.034†

FVC, Forced vital capacity; *DD,* doubling dose.
*Median and percentage are reported.
†Fisher exact *P* value.

However, cortisol suppression increased to more than 20%. For FP-MDI, near-maximal efficacy for FEV_1 and methacholine PC_{20} response and reduction in eNO were achieved with the low dose. Increasing to the medium dose of FP-MDI led to further reduction in airway hyperresponsiveness, as evident with methacholine and exercise, and also in sputum eosinophils, but it also led to a significant increase in overnight plasma cortisol suppression. However, the effect on exercise challenge must be interpreted conservatively because of the small number of patients with complete data sets.

In general, measures of pulmonary function such as peak expiratory flow and FEV_1 improve quite rapidly with low doses of ICS.[15-18] These pulmonary function measures often fail to demonstrate a dose-response relationship in clinical studies.[16,18] We have demonstrated that maximum FEV_1 response is achieved with low-dose FP-MDI and medium-dose BDP-MDI in this population of patients who primarily had mild to moderate persistent asthma.

eNO, an easily obtained and safe measure even in children, has shown a response to ICS therapy, but the relevance of this marker as an indicator of chronic inflammation is still controversial.[19] Our study shows that the near-maximum effect on eNO occurred with the low dose for each of the 2 ICSs studied. However, eNO has not been validated as a biomarker of relevant airway inflammation.

For sputum eosinophils, the levels at baseline were high enough only for the BDP-MDI group to permit detection of a dose-dependent effect. If reduction in sputum eosinophils is selected as an indicator for comparative effects of ICS, it will necessitate the enrollment of subjects with a number of sputum eosinophils at some defined threshold at baseline to measure a response.

The results indicate that our study design can be used as a model for comparison of ICS delivery systems. The clinical implication of our observations is that low to medium doses of the 2 ICSs are adequate to achieve a near-maximum effect for improvement in FEV_1 and methacholine PC_{20} within the period studied. Increasing the dose beyond this point of maximum efficacy provided only marginal improvement for these 2 parameters but resulted in increasing systemic effect, especially with FP-MDI with its CFC propellant. The particle size measurements suggest that the higher efficacy and systemic effect of FP-MDI in comparison with BDP-MDI might be related to a combination of higher intrinsic potency and higher proportion of the dose within the fine particle size range. It is likely that these smaller particles are available for systemic absorption from the lung. The maximum effect for the 2 efficacy measures can be achieved before significant cortisol suppression occurs.

We describe significant variability in response to ICSs for 2 important measures of efficacy—FEV_1 and methacholine PC_{20}—a poor response to each measure being identified in approximately one third of the study subjects. This variability in response is consistent with observations reported in several other studies. Malmstrom et al[20] evaluated the comparative effects of montelukast 10 mg daily and inhaled beclomethasone 200 μg twice daily in patients with persistent asthma. Although the average percent change from baseline in FEV_1 was 13.1% with beclomethasone, considerable variability in FEV_1 change was observed for both medications, approximately 25% of subjects showing no improvement with BDP.

Following the observations of variable FEV_1 response to ICSs, we reviewed a data base from an ACRN dose-response evaluation of 6 ICS–delivery device combinations.[8] In this study, 102 of 144 asthma subjects began the study with an FEV_1 between 55% and 85% predicted; this is comparable to the entry criteria of the current study. Although the focus of the previous study was cortisol suppression and the study design differed by involving the administration of 4 increasing doses over 1-week intervals, similar variability in FEV_1 response was observed. Approximately 40% of the study population had a poor FEV_1 response, and it occurred with all 6 ICS–delivery device combinations, including FP by MDI and DPI administration. Although we have not studied individuals with severe asthma, failure to increase FEV_1 after administration of high-dose systemic corticosteroids has been reported to occur in approximately 25% of adolescent patients with severe asthma.[21]

In a study by Kerrebijn et al,[22] significant variability in methacholine PC_{20} after inhaled budesonide therapy in children was reported, 4 of 12 patients failing to show a significant improvement. These investigators were unable to identify patient characteristics associated with the level of improvement in methacholine PC_{20} response. This interesting observation of variability in response to ICSs has received insufficient attention in evaluating individual patient responses to ICS therapy.

In our study population, subjects with elevated eNO, higher bronchodilator reversibility, and a lower FEV_1/forced vital capacity ratio before ICS treatment had a good FEV_1 response to ICS, and subjects with higher sputum eosinophil levels and a greater age at onset of asthma had an excellent methacholine PC_{20} response to ICS. Although certain patient characteristics identified in this study were associated with the varying levels of response, a larger study is needed to verify them as predictors. Little et al[23] reported that elevated levels of eNO and sputum eosinophils before treatment were useful in predicting an improvement in FEV_1 with a course of treatment with an oral corticosteroid. Pavord et al[24] reported a significant positive correlation between sputum eosinophil count and the doubling-dose change in methacholine PC_{20} after treatment of 23 asthmatic patients with budesonide 400 μg twice daily administered via a Turbuhaler (AstraZeneca AB, Sonertalje, Sweden).

In summary, our findings show that in this study population of individuals with mild to moderate persistent asthma, low-to-medium–dose FP-MDI and BDP-MDI was sufficient to attain a maximal increase in FEV_1 and methacholine PC_{20} response. Although FP-MDI was considered a higher-potency ICS, its therapeutic index diminished as the dose was increased above that needed to obtain the maximal effect—namely, a low-to-medium dose. Maximum effect was achieved with the medium

dose of BDP-MDI. Similarly, the therapeutic index for BDP-MDI decreased as the dose was increased beyond the medium dose. This study design can serve as a model for comparing other ICS–delivery device combinations. However, the significant variability in response necessitates the inclusion of a large number of subjects to define a clear dose-response relationship in efficacy measures. At present, with regard to clinical decisions, if a patient does not respond to low- to medium-dose ICSs, then higher doses might be necessary to provide some level of improvement—eg, in relation to symptom reduction or prevention of exacerbations. This observation of variable response to ICSs indicates that further studies are needed to characterize patient responses to ICS therapy so that alternative treatment strategies can be instituted if needed. Additional studies are also needed to verify these predictors of response and to define the dose-response relationship of ICSs for protection against asthma exacerbations.

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