

Fluticasone Propionate via the Diskhaler or Hydrofluoroalkane-134a Metered-Dose Inhaler on Methacholine-Induced Airway Hyperresponsiveness*

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Study objectives: To compare the effect of 4 weeks of treatment with fluticasone propionate (FP), 100 µg bid, delivered either via the Diskhaler (GlaxoSmithKline; Middlesex, UK) or a hydrofluoroalkane (HFA)-134a pressurized metered-dose inhaler (pMDI) on airway responsiveness.

Design: A single-center, randomized, double-blind, double-dummy, placebo-controlled crossover study.

Setting: Outpatients.

Patients: Patients with mild asthma who had not received corticosteroids for 4 weeks prior to the study.

Interventions: FP, 100 µg bid, via the Diskhaler, HFA-134a pMDI, or placebo for periods of 4 weeks.

Measurements and results: The primary efficacy variable was the provocative dose of methacholine causing a 20% fall in FEV₁ (PD₂₀) at the end of each 4-week treatment period. The FP formulations were defined as equivalent if the treatment difference was within ± 1 doubling dose of methacholine. Forty-seven patients were included in the per-protocol population. The baseline PD₂₀ geometric mean was 0.21 mg, which increased to 0.55 mg with FP via the HFA-134a pMDI and to 0.68 mg with FP via the Diskhaler. The treatment difference between adjusted means was - 0.16 doubling doses (95% confidence interval, - 0.62 to 0.31 doubling doses; p = 0.503). Both significantly decreased airway responsiveness compared to placebo (p < 0.001), and also significantly increased lung function with no difference between the two active groups. FP was well tolerated with few adverse events and no effect on serum cortisol levels.

Conclusions: FP delivered via the HFA-134a pMDI is equivalent to FP via the Diskhaler in reducing airway responsiveness. (CHEST 2002; 122:806-811)

Key words: Diskhaler; fluticasone propionate; hydrofluoroalkane-134a; methacholine; placebo; provocative dose of methacholine causing a 20% fall in FEV₁

Abbreviations: CFC = chlorofluorocarbon; CI = confidence interval; FP = fluticasone propionate; HFA = hydrofluoroalkane; ITT = intent-to-treat; PD₂₀ = provocative dose of methacholine causing a 20% fall in FEV₁; PEF = peak expiratory flow; pMDI = pressurized metered-dose inhaler

Asthma is a chronic disease that manifests itself as episodic dyspnea, wheezing, and cough. Pathophysiologically, asthma is characterized by variable airway obstruction that is associated with an exaggerated response to various bronchoconstrictor stimuli.¹ This airway hyperresponsiveness leads to an increase

in both the sensitivity and the maximal response of the airways to stimuli such as inhaled histamine or methacholine.² Airway inflammation is associated with airway hyperresponsiveness,³ and several studies have shown that inhaled corticosteroids gradually reduce airway hyperresponsiveness,^{4,5} possibly by their anti-inflammatory action.⁶

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Fluticasone propionate (FP), an established inhaled corticosteroid in the treatment of asthma, has been shown to be very effective in decreasing airway hyperresponsiveness.^{5,7} FP is available in both pressurized metered-dose inhalers (pMDIs) and dry-powder devices including the Diskhaler (Glaxo-SmithKline; Middlesex, UK) and Diskus (Glaxo-SmithKline), and clinically has been shown to be microgram equivalent irrespective of inhalational device.⁸ FP has been successfully reformulated in hydrofluoroalkane (HFA)-134a (1,1,1,2, tetrafluoroethane), one of the replacement propellants in pMDIs for chlorofluorocarbons (CFCs).⁹ The pharmaceutical data show that the HFA- and CFC-containing formulations have a very similar particle-size distribution.⁹ Data from parallel group clinical studies have shown that FP formulated in HFA-134a at strengths of 50 µg per actuation, 125 µg per actuation, and 250 µg per actuation is equivalent to FP formulated in CFC-containing inhalers in increasing lung function in patients with asthma on a microgram-for-microgram basis.^{10–13} The safety of the HFA-134a propellant has also been demonstrated in these studies and also with other products, which have been reformulated, including salbutamol¹⁴ and beclomethasone dipropionate, although the beclomethasone dipropionate aerosol solution has not been reformulated at a microgram-equivalent dose.¹⁵

There is little evidence to show that the HFA pMDI is equivalent to a dry-powder inhaler such as the Diskhaler. Data have shown that the CFC pMDI is equivalent on a microgram basis to the Diskhaler,^{8,16} and as the Diskhaler is still an important device in some countries, the HFA pMDI and Diskhaler have been compared. The aim of this study was to therefore evaluate the 50 µg-per-actuation strength of FP delivered via the HFA-134a pMDI in reducing airway responsiveness in patients with mild asthma in comparison with FP delivered via the Diskhaler.

MATERIALS AND METHODS

Study Subjects

Patients ≥ 18 years of age with a documented history of asthma, a resting FEV₁ $\geq 60\%$ of predicted, and a provocative dose of methacholine causing a 20% fall in FEV₁ (PD₂₀) ≤ 3.2 mg were recruited. Patients did not receive any corticosteroids (oral, parental, or inhaled), long-acting β_2 -agonists, oral β_2 -agonists, methylxanthine, or leukotriene antagonists in the 4 weeks prior to the study, and had no change in their regular asthma medications during this period. Patients were excluded from the study if they had an asthma exacerbation requiring hospitalization in the 3 months prior to the study or had a respiratory tract infection in the 4 weeks prior to entry. Patients

who were not eligible to perform the methacholine challenge test (including those who had had a recent myocardial infarction or cerebral vascular accident within the last 3 months, a recent aneurysm, uncontrolled hypertension, or epilepsy) were also excluded. All female patients of childbearing potential were required to be using appropriate contraception and have a negative pregnancy test result at screening. All patients were required to give written informed consent. The study was approved by the local ethics committee.

Study Design and Medication

This was a single-center, randomized, double-blind, double-dummy, three-way crossover, placebo-controlled study: (1) FP, 100 µg bid, via the Diskhaler and placebo via the HFA-134a pMDI; (2) placebo via the Diskhaler and FP, 100 µg bid, via the HFA-134a pMDI; and (3) placebo via the Diskhaler and placebo via the HFA-134a pMDI. Each patient was assessed at the end of all treatment arms to allow within-patient comparisons to be made, which helps reduce variability. No washout period was deemed necessary, as the first week of the active-treatment period would effectively act as a washout period for previous therapy.¹⁷ The treatment sequence was randomly allocated using the Patient Allocation for Clinical Trials software (GlaxoSmithKline).

Patients were given a Diskhaler device, 15 four-place Rotadisk (GlaxoSmithKline) disks, and an HFA-134a pMDI for each 4-week treatment period. Patients were instructed to take one dose from the Diskhaler and two actuations from the pMDI in the morning and evening within 2 min of each other. In addition, all inhaled short-acting bronchodilators were stopped at the screening visit and patients were provided with a salbutamol HFA-134a pMDI for symptomatic rescue relief as necessary. FP HFA-134a pMDI was administered with a large volume spacer (Volumatic; GlaxoSmithKline) if the investigator thought it was required for optimum drug delivery and compliance. There were five study visits: a screening visit to assess eligibility, a visit at the end of each treatment period, and a poststudy visit a week after the last treatment period or following withdrawal of the patient.

Patients were given electronic Micro Diary Cards (MicroMedical; Gillingham, UK) to record the values for morning peak expiratory flow (PEF) measurements and the number of occasions they used salbutamol for symptomatic relief. PEF measurements were made before receiving study medication or rescue salbutamol. Safety was monitored by recording adverse events at each clinic visit. In addition, fasting blood samples were collected at the screening visit and at the beginning of each 4-week treatment period, between 8 AM and 10 AM to measure serum cortisol levels and also routine biochemical and hematology parameters. An oropharyngeal examination was performed at all clinic visits, and swabs were obtained if candidiasis was suspected. Vital signs were also measured at each clinic visit.

Airway Responsiveness

Airway responsiveness was measured using methacholine inhalation tests quantified by the PD₂₀ using a modified method of Yan et al.¹⁸ DeVilbiss 646 nebulizers (Sunrise Medical; Wollaston, UK) and a Rosenthal dosimeter (PDS Research UK; Gravesend, UK) were used to deliver the methacholine. Doubling doses of methacholine chloride were administered given using three concentrations (1.5 mg/mL, 12 mg/mL, and 50 mg/mL) as illustrated in Table 1. The dosimeter was set to deliver a 1-s dose of methacholine during a 5-s inspiration. The best of three FEV₁ measurements (performed 1 min after administration of each solution) was recorded. The next dose of methacholine

Table 1—Methacholine Challenge Dosing Protocol

Dose Level	Methacholine Concentration, mg/mL	Inhalations, No.	Cumulative Dose, mg
1	Saline solution	4	0.0
2	1.5	1	0.015
3	1.5	1	0.03
4	1.5	2	0.06
5	1.5	4	0.12
6	12	1	0.24
7	12	2	0.48
8	12	4	0.96
9	50	2	1.96
10	50	4	3.96
11	50	4	5.96

line was administered immediately after the FEV₁ measurements. PD₂₀ was calculated by the spirometer (Super Spiro; MicroMedical; Rochester, UK). The methacholine challenges were performed at the screening visit and at the end of each study period.

Statistical Analysis

Equivalence between FP via the HFA-134a pMDI and FP via the Diskhaler was demonstrated if the two-sided, 95% confidence interval (CI) for the treatment difference (MDI – Diskhaler) lay within ± 1 doubling doses of methacholine in the per-protocol population, defined as all randomized patients who did not have any protocol violations that could affect their efficacy assessment. This population was used for analysis of the primary end point only. Data from previous studies provided an estimate of the within-subject variation of 1.5 doubling doses.¹⁹ A sample size of 36 evaluable subjects was sufficient to ensure that, if there was no difference between the treatments, the study would have at least 85% power to declare treatments being equivalent using a two-sided 5% test.¹⁷ Due to the fact that methacholine was administered using the doubling cumulative dose protocol, PD₂₀ values were transformed using log base 2, and the transformed values analyzed using analysis of variance, with factors for subject, period, and treatment, with subject considered as a fixed effect. Tests for first-order treatment carryover were also performed by adding this term to the main effect model and evaluated at the 10% significance level. PD₂₀ was also analyzed in the intent-to-treat (ITT) population, defined as all randomized patients who received treatment. Serum cortisol was transformed using a natural log scale and analyzed using analysis of variance as described above. The untransformed values for FEV₁ and mean morning PEF over weeks 3 to 4 were also analyzed as described above. Daily salbutamol use over weeks 3 to 4 was analyzed nonparametrically using Wilcoxon rank-sum tests (Koch's method) appropriate for a crossover design.

RESULTS

Patient Characteristics

A total of 59 patients were enrolled, of whom 48 patients were randomized to receive study medication and constituted the ITT population. One subject was

excluded from the per-protocol population for analysis of the primary variable, due to not having a PD₂₀ ≤ 3.2 mg at screening. Eleven patients were withdrawn before randomization because of failure to meet the entry criteria. The baseline characteristics of the ITT population are outlined in Table 2. All patients, except one, were receiving inhaled short-acting β_2 -agonists at screening. Four subjects were withdrawn after randomization; two subjects were withdrawn due to an adverse event unrelated to lack of efficacy during treatment with FP via the Diskhaler, and two subjects were withdrawn for other reasons, one at the end of placebo treatment, due to inability to attend the follow-up visit, and one during treatment with FP via the MDI, due to realization that the screening criteria had not been met.

PD₂₀

In the per-protocol population, the geometric mean PD₂₀ at baseline was 0.21 mg. The adjusted geometric mean (adjusted for subject, period, and treatment) at the end of the study periods was 0.56 mg for FP via the pMDI and 0.63 mg for FP via the Diskhaler. There was no statistically significant difference in PD₂₀ between FP devices ($p = 0.503$). The 95% CI for the difference in PD₂₀, on the doubling scale, between FP via the pMDI and FP via the Diskhaler was -0.62 to 0.31 doubling doses, which lies within the ± 1 doubling-dose limit required to show equivalence. The geometric mean PD₂₀ for placebo was 0.25 mg, and the difference between placebo and each FP device was statistically significant ($p < 0.001$; Table 3). The results in the ITT population were identical to the per-protocol analyses, as the subject excluded from the per-protocol population had no postbaseline data. Tests for treatment carryover effect were not significant.

Prechallenge FEV₁

The baseline FEV₁ at screening measured prior to the methacholine challenge was 3.21 L in the ITT

Table 2—Baseline Demographics*

ITT Population	Data
Patients, No.	48
Sex	
Male	18 (38)
Female	30 (63)
Mean age, yr	32.6 \pm 9.2
Patients using a spacer	4 (9)
Duration of reversible obstruction > 15 yr	32 (67)
FEV ₁ , L	3.2 \pm 0.7
% predicted FEV ₁	93.5 \pm 11.8
Never smoked	28 (58)
Current smoker	3 (6)

*Data are presented as No. (%) or mean \pm SD.

Table 3—Statistical Analysis of PD₂₀ for the Per-Protocol Population Following Treatment With FP, 100 µg bid, via a HFA-134a MDI, Diskhaler, or Placebo*

Visit	Placebo, mg/mL	FP via HFA-134a pMDI, mg/mL	FP via Diskhaler, mg/mL	Statistical Analysis			
				Comparisons	Treatment Difference (SE) Doubling Doses	95% CI	p Value
2	0.21 (15)	0.93 (15)	0.67 (16)	FP pMDI vs Diskhaler	- 0.16 (0.23)	(- 0.62, 0.31)	0.503
3	0.24 (16)	0.29 (16)	1.11 (13)	FP pMDI vs placebo	1.18 (0.23)	(0.71, 1.65)	< 0.001
4	0.36 (14)	0.64 (15)	0.48 (16)	FP Diskhaler vs placebo	1.34 (0.24)	(0.87, 1.80)	< 0.001
Overall	0.25	0.56	0.63				

*Data are presented as geometric mean (No. of patients) unless otherwise indicated.

population. The adjusted mean prechallenge FEV₁ at the end of the study periods for FP via the pMDI was 3.23 L, compared to 3.21 L for FP via the Diskhaler. The 95% CI for the difference between the adjusted mean for FP via the pMDI and for FP via the Diskhaler was - 0.043 to 0.075 L, which was not statistically significant (p = 0.591). The adjusted mean for placebo was 3.14 L. The differences between FP via the pMDI and placebo, and FP via the Diskhaler and placebo were statistically significant (Table 4). Tests for treatment carryover effect were not significant.

Morning PEF for Weeks 3 to 4

The adjusted mean morning PEF over weeks 3 to 4 for FP in the ITT population were 447.8 L/min (pMDI) and 444.1 L/min (Diskhaler) and 429.5 L/min for placebo. The differences between FP via the pMDI and FP via the Diskhaler were not statistically significant, whereas the differences between FP via the pMDI and placebo, and FP via the Diskhaler and placebo were statistically significant (Table 5). Tests for treatment carryover effect were not significant.

Median Daily Salbutamol Usage

The median daily salbutamol use for weeks 3 to 4 was zero for each treatment and, as expected, the median treatment difference was also zero for all pairwise comparisons. However, a statistically signifi-

cant difference was found in the distribution of median salbutamol use between the HFA pMDI and placebo (p = 0.015). There was no statistically significant difference between the pMDI and the Diskhaler (p = 0.083) or the Diskhaler and placebo (p = 0.073).

Safety

The most commonly reported events during treatment by ≥ 5% of patients were upper respiratory tract infection in 10 patients receiving placebo, in 11 patients receiving FP via the pMDI, and in 8 patients receiving FP via the Diskhaler; and lower respiratory tract infections in 1 patient receiving placebo, in 2 patients receiving FP via the pMDI, and in 4 patients receiving FP via the Diskhaler. The incidence of pharmacologically predictable adverse events expected for inhaled corticosteroids, hoarseness/dysphonia, candidiasis, throat irritation, and skin reactions was similarly low across all treatment groups. The only event reported by ≥ 5% of patients was throat irritation in three patients receiving placebo, in four patients receiving FP via the pMDI, and in one patient receiving FP via the Diskhaler. No serious adverse events were reported in the study. A slight reduction in eosinophil counts was observed after treatment with FP either via the pMDI or the Diskhaler. Mean ± SD eosinophil count at baseline was 0.304 × 10⁹/L, which decreased to 0.292 × 10⁹/L after FP via the pMDI and 0.275 × 10⁹/L after FP via

Table 4—Prechallenge Mean FEV₁ Data in the ITT Population for Patients Treated With FP, 100 µg bid, via a HFA-134a MDI, Diskhaler, or Placebo*

Visit	FEV ₁ , L			Statistical Analysis			
	Placebo, L	FP via HFA-134a pMDI, L	FP via Diskhaler, L	Comparisons	Difference	95% CI	p Value
2	3.12 (16)	3.30 (15)	3.17 (16)	FP pMDI vs Diskhaler	0.016	- 0.043, 0.075	0.591
3	3.12 (16)	3.18 (16)	3.26 (13)	FP pMDI vs placebo	0.081	0.022, 0.140	0.008
4	3.22 (14)	3.15 (15)	3.18 (16)	FP Diskhaler vs placebo	0.065	0.006, 0.124	0.031
Overall	3.14	3.22	3.21				

*Data are presented as mean (No. of patients) unless otherwise indicated.

Table 5—Statistical Analysis of Morning PEF for Weeks 3 to 4 in the ITT Population

Comparisons	Treatment Difference, L/min (SE)	95% CI	p Value
pMDI-Diskhaler	3.72 (4.05)	− 4.34, 11.77	0.361
pMDI-placebo	18.28 (4.08)	10.17, 26.40	< 0.001
Diskhaler-placebo	14.57 (4.09)	6.44, 22.69	0.001

the Diskhaler, and increased to 0.348×10^9 /L after placebo treatment. There was no evidence to suggest any treatment effect on any other laboratory or vital-sign parameter.

The geometric mean baseline serum cortisol level was 406.7 nmol/L. The adjusted geometric mean after FP via pMDI treatment was 422.2 nmol/L, after FP via the Diskhaler was 395.0 nmol/L, and after placebo was 414.1 nmol/L. There was no statistical difference between any of the treatment groups.

DISCUSSION

This study was a short-term crossover comparison to assess whether FP delivered from an HFA-134a pMDI or a Diskhaler showed equivalent efficacy in the reduction of bronchial responsiveness in adult patients with mild asthma. FP at a dose of 100 µg bid (the minimum approved for the treatment of adults with asthma) has been shown to be effective,²⁰ and this dose was therefore chosen for this study, as the subjects had mild asthma and were not being treated with inhaled corticosteroids. Inclusion of patients with mild asthma, demonstrated by baseline lung function and methacholine responsiveness, allowed for inclusion of a placebo arm, which is important in a pharmacodynamic challenge study such as this to confirm that both treatments are effective. The study was crossover in design, which is the optimal design for bronchial challenge studies.²¹ Each patient was assessed at the end of all treatment arms to allow within-patient comparisons to be made. Each patient is used as his own control, which eliminates between-patient variation. By using a crossover design, fewer patients have to be recruited to obtain the same number of observations. In this study, the challenge test was performed at the end of the respective treatment periods, and therefore no wash-out period was deemed necessary, as the first week of the active-treatment period would effectively act as a washout period for previous therapy.¹⁷ Any effects of previous therapy would have been eliminated by the time of the challenge test, and therefore the data at that point reflected the effects of the

latest treatment rather than any carryover effect from the previous treatment. There was no evidence of any carryover effect for any measured variable in this study.

It is recognized that this study only used one dose of inhaled corticosteroid. It is possible to evaluate dose-response relationships for inhaled corticosteroids in methacholine challenge studies.^{3,22} Since this has already been performed for FP,^{4,23} and this study was primarily about device interchangeability, it was not deemed necessary.

Short-term comparisons of inhaled corticosteroids using bronchial responsiveness have previously shown small but significant effects on airway responsiveness following 4 to 6 weeks of treatment.^{5,22} FP at a dose of 100 µg bid has been shown to significantly reduce bronchial hyperresponsiveness when compared to both placebo and FP, 50 µg bid, after 4 weeks treatment in a parallel group study,³ and also in a crossover study when compared to the leukotriene antagonist, zafirlukast.⁷ A 4-week treatment period (rather than the more common 6 to 8 weeks) was used, as this has been shown to be adequate in a previous study.¹⁷ In this study, both formulations of FP significantly reduced the bronchial responsiveness when compared to placebo with comparable efficacy demonstrated between the HFA-134a pMDI and the Diskhaler. The CIs for the treatment difference between treatment with the pMDI and the Diskhaler were < 1 doubling dose and fell completely within the required CIs for equivalence. This adds to the existing evidence of the comparable efficacy on a microgram-equivalent dose of the pMDI and the Diskhaler obtained in previous studies.^{8,16} Although published data have compared dry-powder devices with pMDIs propelled by CFCs, there is now a wealth of data showing that the CFC and HFA-134a pMDIs are equivalent in both efficacy and safety for a number of drugs including FP at all marketed strengths.^{10–13}

In this study, the therapeutic equivalence indicated by the effects on bronchial responsiveness between the two inhalers was supported by both the change in diary card PEF and by clinic spirometry measurements of lung function. Both formulations of FP significantly improved mean morning PEF over weeks 3 to 4 of treatment when compared to placebo, and clinic visit FEV₁ was also significantly improved, with no statistical difference being observed between the inhalers.

There was also no difference between the FP formulations in terms of safety. The adverse-event profile was similar, and there was no difference between the treatments on the morning serum cortisol values, although we accept that this study was not designed to examine the long-term safety of FP,

which has been confirmed for the Diskhaler²⁴ and the HFA-134a pMDI in other studies.¹²

In conclusion, FP administered via the HFA-134a pMDI and via the Diskhaler at microgram-equivalent doses resulted in an equivalent decrease in bronchial hyperresponsiveness and improvement in lung function. Both formulations were well tolerated.

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