

Systemic Exposure and Urinary Cortisol Effects of Fluticasone Propionate Formulated With Hydrofluoroalkane in 4- to 11-Year-Olds With Asthma

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The systemic exposure of fluticasone propionate with hydrofluoroalkane propellant compared with chlorofluorocarbon propellant and the effect of fluticasone propionate hydrofluoroalkane on 24-hour urinary cortisol in children aged 4 to 11 years with asthma were evaluated. Study 1 was an open-label, 2-way crossover study in which 16 subjects were randomized to 7.5 days each of fluticasone propionate hydrofluoroalkane 88 µg twice a day or fluticasone propionate chlorofluorocarbon 88 µg twice a day. In study 2, 63 subjects received 13.5 days of placebo followed by 27.5 days of fluticasone propionate hydrofluoroalkane 88 µg twice a day. The main outcome measure for study 1 was the difference between fluticasone propionate hydrofluoroalkane and fluticasone propionate chlorofluorocarbon in fluticasone propionate AUC_{last} (area under the plasma fluticasone propionate concentration-time curve from zero up to the last quantifiable plasma concentration), and for study 2, 24-hour

overnight urinary cortisol excretion. In study 1, fluticasone propionate systemic exposure was significantly lower (55%) with hydrofluoroalkane metered dose inhaler compared with chlorofluorocarbon metered dose inhaler. Study 2 showed no statistically significant changes in 24-hour overnight urinary cortisol excretion and no relationship to fluticasone propionate systemic exposure at this dose. The results of these 2 studies showed that in children aged 4 to 11 years with asthma, fluticasone propionate hydrofluoroalkane has lower systemic exposure compared with chlorofluorocarbon and no hypothalamic-pituitary-adrenal axis effects as measured by 24-hour urinary cortisol excretion.

Keywords: Children; asthma; fluticasone; systemic effects; urinary cortisol

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Asthma affects approximately 9 million (12%) children in the United States and is one of the most common chronic diseases of children.¹ The Centers for Disease Control National Health Survey found that in 2004, 4 million children (5.4%) had experienced an asthma attack in the past year.¹

According to current national and international asthma guidelines, inhaled corticosteroids (ICS) are the preferred treatment for all patients with persistent asthma.²⁻⁴ However, many children with asthma are not being managed in accordance with guideline recommendations. The cause may be persisting reluctance by physicians to prescribe and parents to administer inhaled corticosteroids. This reluctance

may be based in part on concern about risk for systemic side effects. To address this question, these studies evaluated systemic exposure of fluticasone propionate (FP) hydrofluoroalkane (HFA) compared with FP chlorofluorocarbon (CFC) and the effect of FP HFA on 24-hour urinary cortisol in children aged 4 to 11 years with asthma.

Fluticasone propionate HFA-propelled metered dose inhaler (MDI) has replaced the CFC-propelled MDI⁵ and is available in the United States as a metered-dose inhalation aerosol for patients ages 4 years and older. Efficacy of the FP HFA and that of the conventional CFC propelled formulation are comparable at the same microgram dose in pediatric patients and adults with asthma.⁶⁻¹⁰ Beclomethasone dipropionate is also available in an HFA formulation. The systemic exposure of this product has been reported to be 2- to 3-fold greater than the CFC formulation,¹¹ such that the administered dose must be halved.¹² In comparison, a prior study demonstrated lower systemic exposure of FP from the HFA formulation versus the CFC product in healthy adult volunteers.¹³

The 2 studies reported here were conducted to characterize systemic exposure and effects on urinary cortisol with FP HFA 88 µg twice daily in children with asthma 4 to 11 years of age.

MATERIALS AND METHODS

Patients

Both studies included male and premenarchal female outpatients aged 4 to 11 years with a diagnosis of asthma¹⁴ requiring pharmacotherapy (≥ 2 months [study 1, FAP10006]; ≥ 6 months [study 2, FAP19052]), a best clinic visit 1 peak expiratory flow (PEF) $\leq 85\%$ Polgar predicted¹⁵ (after not using all asthma medications for duration of action), and $\geq 12\%$ reversibility within 30 minutes following 2 puffs of albuterol 100 µg. Written informed consent was obtained from a parent/guardian.

Study 1. Subjects must have been taking ICS >1 month prior to screening. Patients were excluded if prior to screening they had used oral or parenteral corticosteroids within 4 weeks, daily oral corticosteroids ≥ 2 months in the past 6 months, or intranasal corticosteroids (INS) in the past week.

Study 2. Patients were excluded if prior to screening they had used oral or parenteral corticosteroids within 10 weeks, medium- to high-dose ICS within 6 weeks (or low-dose ICS [eg, 176 µg/d FP] within 2 weeks), or INS in the past 2 weeks. Topical corticosteroids equivalent to $>1\%$ hydrocortisone cream were excluded after screening.

Study Design

Two multiple-dose studies with FP (Flovent®, GlaxoSmithKline) 88 µg MDI twice a day without spacer were conducted. Study 1 evaluated the pharmacokinetics (PK) of FP HFA, specifically FP systemic exposure compared with FP CFC. Study 2 evaluated the pharmacodynamics (PD) of FP HFA, specifically the effect on 24-hour urinary cortisol excretion. Albuterol was permitted as needed to relieve acute symptoms of asthma in both studies.

Patients and/or parents or guardians were required to demonstrate the ability to effectively use the MDI using the demonstration kit provided. Protocols were approved by institutional review boards for all sites (Quorum Review, Inc, Seattle, Wash, and National Jewish Medical and Research Center, Denver, Colo, for study 1 and IntegReview Ethical Review Board, Austin, Tex, for study 2). Subjects were assigned to treatment sequences according to a randomization schedule prepared in advance by the sponsor. Per request from the Food and Drug Administration, randomization was stratified for subjects 4 to 7 years and 8 to 11 years, so that approximately one third of subjects would be ≤ 7 years old.

Study 1. On the morning of day 1, prior ICS use was discontinued and patients were randomized to 1 of 2 crossover sequences: 7.5 days of 2 puffs twice daily with open-label FP 44 µg HFA MDI or FP 44 µg CFC MDI. The second period immediately followed with no washout period.

Study 2. Patients received 13.5 days of placebo (HFA propellant only) (period 1) immediately followed by 27.5 days of treatment with FP HFA MDI 88 µg twice a day (period 2). On day 13 of period 1 and day 27 of period 2, overnight inpatient stays were conducted for 24-hour urine and blood PK sample collections. Nonsteroid asthma medications were allowed during the study.

Measurements

PD and PK measures. Plasma FP analysis for both studies was done at York Bioanalytical Solutions using a solid phase extraction and liquid chromatography using tandem mass spectrometric detection method.¹⁶ The lower limit of quantification of the assay was 5 pg/mL.

Study 1 PK measures. Predose and serial postdose (20 and 40 minutes, 1, 2, 4, 8, and 12 hours) blood samples (4 mL) for analyses of FP were taken on day 8 of each study period. The primary end point was area under the plasma FP concentration-time curve

from zero up to the last quantifiable plasma concentration (AUC_{last}). Other end points included maximum observed plasma FP concentration (C_{max}), time to maximum observed plasma FP concentration (t_{max}), minimum observed plasma FP concentration (C_{min}), and terminal elimination half-life ($t_{1/2}$, calculated if adequate and sufficient data available).

Study 2 PD and PK measures. The primary end point was 24-hour urinary cortisol excretion. Excretion of the primary metabolite, 6- β -hydroxycortisol, was also assessed. The PK/PD relationship in terms of 1-hour plasma FP concentration data and 24-hour urine pharmacodynamic parameters was examined.

Two consecutive and approximately 12-hour collections for urinary cortisol began immediately after evening dosing on day 13 (session 1) and day 27 (session 2) Urinary cortisol and 6- β -hydroxycortisol levels were determined using reverse phase liquid chromatography with tandem mass spectrometry detection with a limit of detection of 1 ng/mL for cortisol and 5 ng/mL for 6- β -hydroxycortisol. Two mobile phases were used: (A) water containing 0.1% (vol/vol) formic acid and (B) acetonitrile/water/formic acid (95:4.9:0.1 vol/vol) using a gradient mode at a flow rate of 1.0 mL/min. A Luna C18, 250-mm lg \times 4.6-mm ID 5- μ particle size column (Phenomenex) was used in a Perkin Elmer Sciex API III Plus. Prior to injection, a 300- μ L sample was applied to an Oasis HLB extraction plate preconditioned with 100 μ L of methanol and 100 μ L of water. The plate was then washed with 400 μ L of water followed by 400 μ L of 40% methanol in water before eluting the samples with 400 μ L of methanol. Following evaporation under nitrogen, the sample was reconstituted with 9:1 vol/vol 0.1% formic acid/acetonitrile for injection. All samples were measured at Simbec Research Limited (South Wales, UK).

Plasma samples. A single 6-mL blood sample for analysis of plasma FP concentration was collected 1 hour postdose following the morning dose on day 14 (period 1) and on day 28 (period 2).

Adverse events. Adverse events were collected in both studies. Subjects/guardians were queried about medical problems at clinic visits, during phone call assessments, and, in study 2, via diary cards on which subjects/guardians recorded any medical problems. For each adverse event, investigators recorded whether they considered it to be related to study medication.

PEF. In study 2, PEF was performed to monitor asthma symptoms and severity. Subjects or parents were advised to contact the study site should PEF fall below 20% from the screening visit PEF.

Data Analysis and Statistics

Study 1. The primary outcome measure was the difference between treatments in FP AUC_{last} . AUC data from another study¹⁷ indicated that a sample size of 12 subjects would ensure that the width of the 90% confidence interval (CI) for the ratio of geometric means was 33% of the ratio.

Pharmacokinetic analysis was carried out by Quintiles Limited. Noncompartmental pharmacokinetic analysis was performed by the Clinical Pharmacokinetics/Modelling & Simulation Department (Glaxo Smith Kline, UK) using actual sampling times. For each of the derived parameters, descriptive statistics were calculated for each treatment. Geometric means and related 95% CIs were also calculated. All data, except t_{max} , were analyzed after \log_e -transformation. An analysis of variance, adjusted for the effects of period and treatment group with random effect of subject, was performed using a linear mixed model to compare the two treatments. Treatment ratios (ratios of geometric least square means) and 90% CIs were constructed for each pharmacokinetic end point. Values of t_{max} were analyzed nonparametrically using Wilcoxon's matched pairs methods to construct point estimates and 90% CIs for the median difference between the formulations. Because the analysis was descriptive in nature, adjustments for multiple comparisons or multiple end points were not made.

Study 2. The outcome measure was the difference between placebo and active treatment on 24-hour urinary cortisol excretion. The study was a descriptive comparison, and traditional power calculations were not performed. A prior study¹⁸ indicated that the \log_e standard deviation of 24-hour total urine cortisol was approximately 0.65. Therefore, 30 subjects would allow 90% power to detect a 35% difference between groups as measured by the ratio of geometric means assuming a correlation between treatment and placebo measurements of 0.70.

The data were natural-log-transformed prior to analysis to improve compliance with the normality assumption underlying the analysis. Absolute values (and change from the placebo treatment assessment value) for urinary cortisol, 6- β -hydroxycortisol, and the sum of the 2 analytes were summarized by treatment including 95% CIs. Linear regression was used in a post hoc analysis to examine the relationship between FP exposure and change in urinary cortisol excretion; a *t* test was used to determine whether the slope was significantly different from zero.

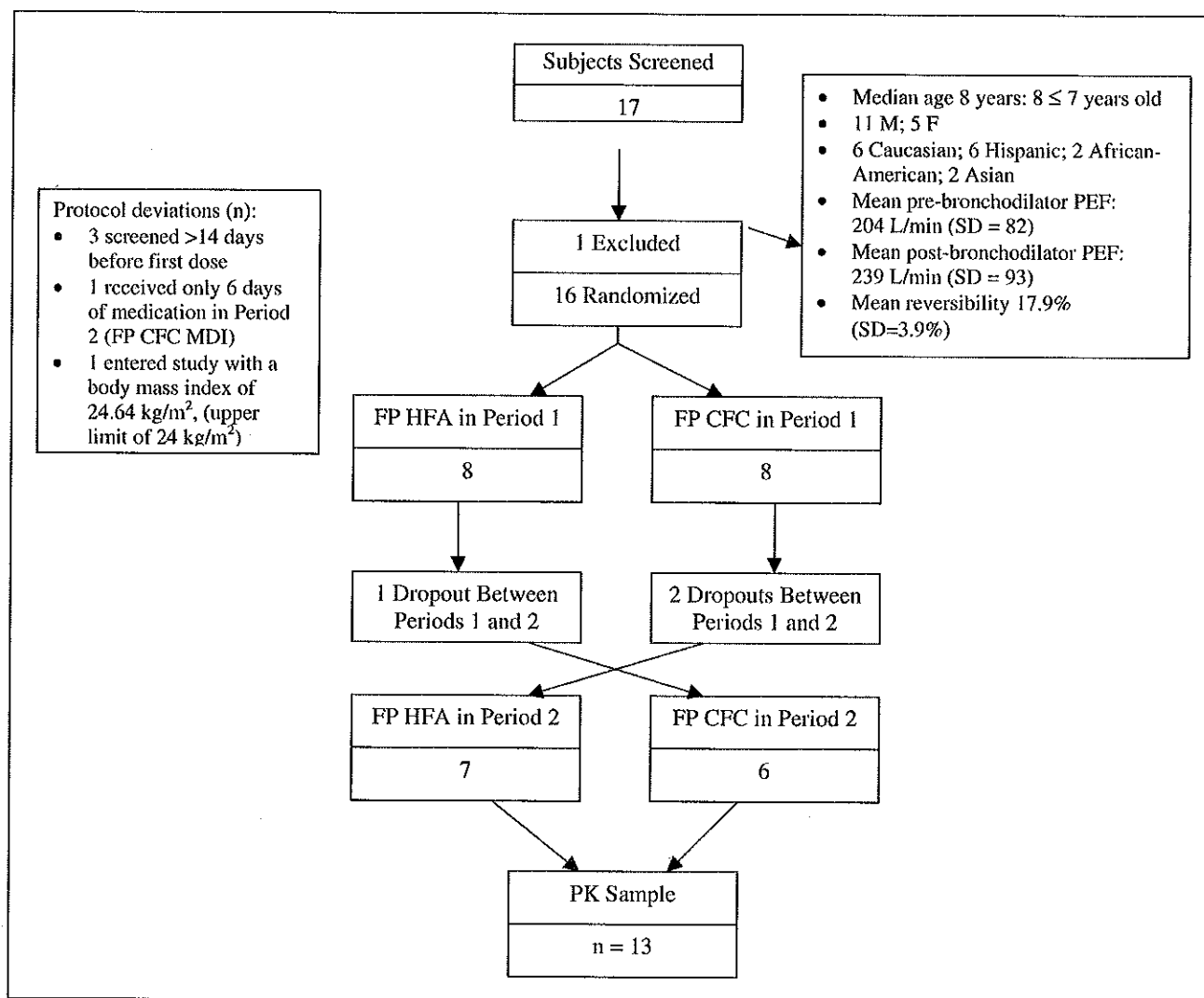


Figure 1. Patient flow diagram for study 1. FP, fluticasone propionate; CFC, chlorofluorocarbon; MDI, metered dose inhaler; HFA, hydrofluoroalkane; PK, pharmacokinetics; PEF, peak expiratory flow.

RESULTS

Study 1—Effect of HFA on FP Systemic Exposure

Patients. Figure 1 shows the patient flow and patient demographic data for this study, conducted October through December 2003. The mean age of the children randomized to treatment was 7.5 years (SD 2.8 years).

PK end points. Median plasma concentrations of FP were measurable up to 4 hours after a dose of FP HFA 88 µg and up to 8 hours after FP CFC 88 µg

(Figure 2). Summary statistics are presented in Table 1. FP systemic exposure (AUC_{last}) was significantly lower (55%) following HFA MDI administration compared with the CFC MDI. The C_{max} for FP was 26% lower following administration of the HFA MDI compared with the CFC MDI, but the difference did not reach significance. The median difference in t_{max} for FP was not significant between the 2 formulations. Estimates of terminal half-life were not possible in most subjects because FP was not detected in the terminal portion of the curve. Because FP was only measurable over the first 4 to 8 hours, C_{min} and

Table I Pharmacokinetic Parameters of Fluticasone Propionate (FP)

	FP HFA MDI 88 µg BID	FP CFC MDI 88 µg BID	HFA/CFC ^a
AUC _{last} , pg·h/mL, n = 13			
Geometric mean	28.3	64.7	0.45
95% CI	9.99, 80.3	27.4, 152.8	0.23, 0.88
C _{max} , pg/mL, n = 13			
Geometric mean	15.1	20.4	0.74
95% CI	8.50, 26.6	13.0, 32.0	0.46, 1.20
t _{nmax} ^b , n = 11			
Median	0.67	0.92	-0.003 ^c
Range	0.33-4.00	0.37-4.00	-0.740 to 0.655

HFA, hydrofluoroalkane; MDI, metered dose inhaler; BID, twice daily; CFC, chlorofluorocarbon; AUC_{last}, area under the plasma FP concentration–time curve from zero up to the last quantifiable plasma concentration; CI, confidence interval; C_{max}, maximum observed plasma FP concentration; t_{nmax}, time to maximum observed plasma FP concentration.

a. Ratio of geometric least square means and 90% CI.

b. Median difference.

c. Median difference for t_{nmax}.

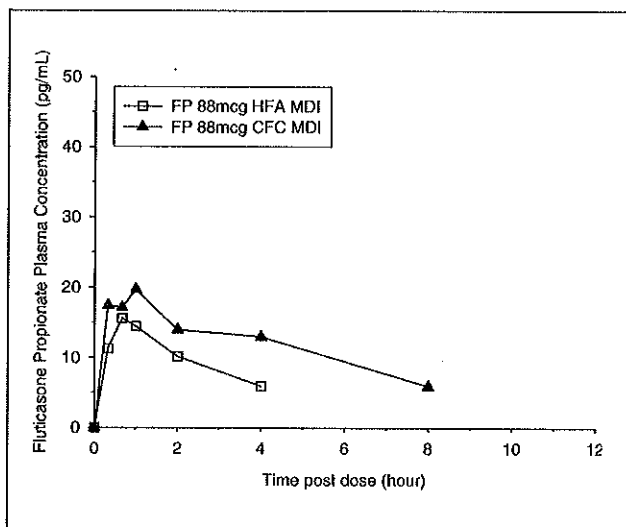


Figure 2. Patient flow diagram for study 2. FP, fluticasone propionate; CFC, chlorofluorocarbon; MDI, metered dose inhaler; HFA, hydrofluoroalkane.

terminal plasma elimination rate constant (λ_z) were not calculated.

Adverse events. More adverse events were reported with FP CFC compared with FP HFA (18 vs 4 events, 8 vs 3 subjects). Adverse events reported more than once included nasal congestion (2 HFA, 4 CFC), pyrexia (3 CFC), pharyngitis (2 CFC), and asthma (1 each). No adverse events were considered related to study medication, and no subject was withdrawn

because of an adverse event. All events resolved by the end of the study.

Study 2—Effect of FP HFA on 24-Hour Urinary Cortisol

Patients. Figure 3 shows the patient flow and patient demographic data for this study, conducted August through November 2004. The mean age of the children randomized to treatment was 7.5 years (SD 2.3 years).

PD end points. Median 24-hour urinary cortisol excretion was 8,870 µg after 13.5 days of HFA propellant only (baseline) and 10,309 µg after 27.5 days of FP HFA 88 µg twice a day. Mean (\pm SD) 24-hour urinary cortisol excretions for FP HFA and placebo were 9.54 µg (\pm 4.19) and 9.66 µg (\pm 4.58); ratio of the means (FP/placebo) was 0.987 (95% CI 0.796, 1.223). The relationship of urinary cortisol + 6- β -hydroxycortisol excretion ratio as a function of FP plasma concentration is shown in Figure 4 and further demonstrates no effect on the hypothalamic–pituitary–adrenal axis with this low level of FP HFA exposure ($r^2 = 0.0012$; $P = .84$).

Adverse events. Adverse events (AEs) were reported by 21 subjects (34%). Headache was the most common AE (5 placebo, 8 FP). Most AEs were mild or moderate in intensity. Severe AEs were reported by 3 subjects: severe headache with pyrexia (requiring exclusion of meningitis), asthma, and upper respiratory tract infection; severe headache and vomiting; and severe asthma (1 subject each). None

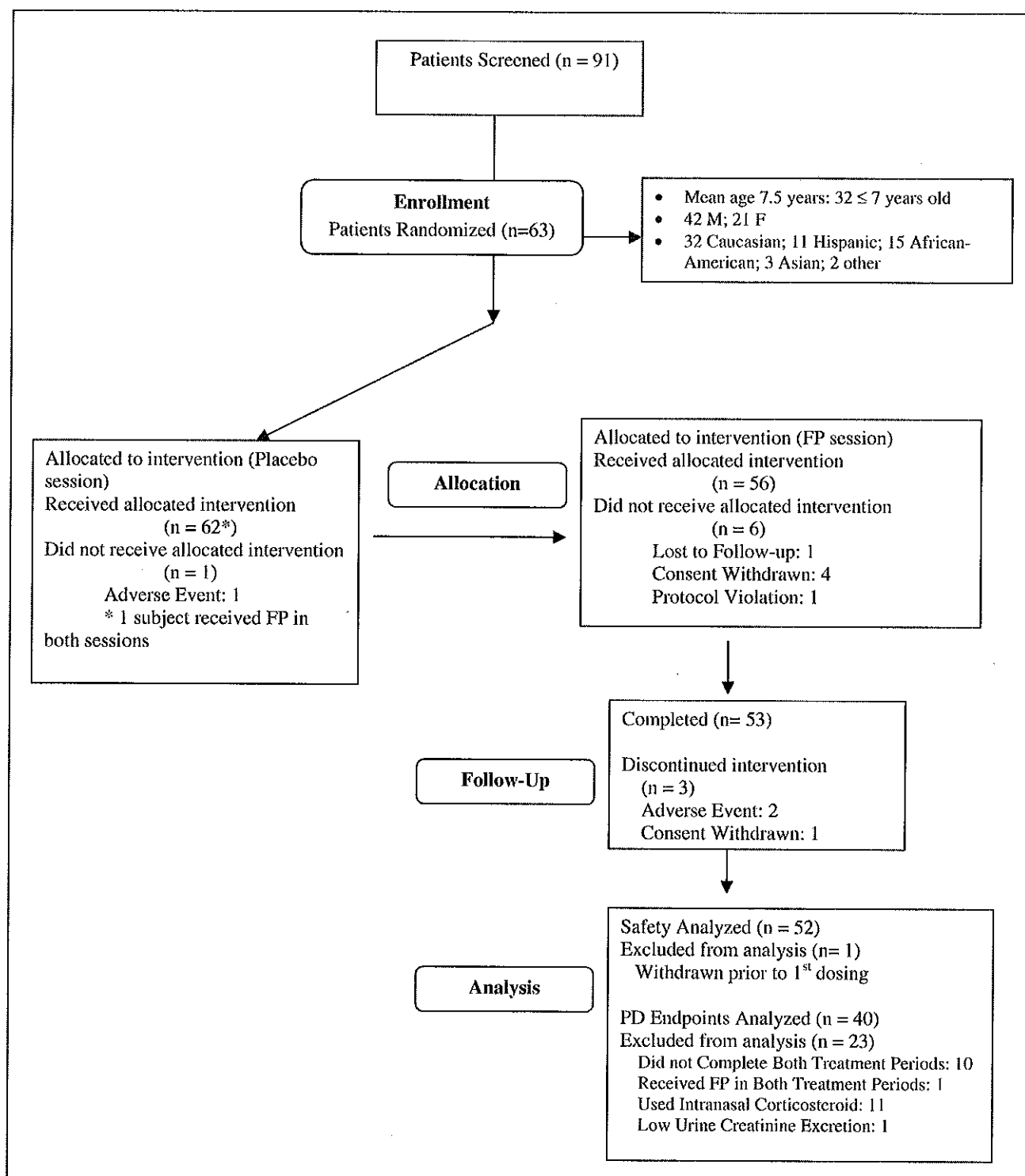


Figure 3. Study 1. Median fluticasone propionate (FP) concentration (pg/mL) time profiles. FP hydrofluoroalkane (HFA) 88 = FP HFA 88 mg twice a day; FP chlorofluorocarbon (CFC) 88 = FP CFC 88 mg twice a day. FP HFA was not detectable after 4 hours postdose. PD, pharmacodynamics.

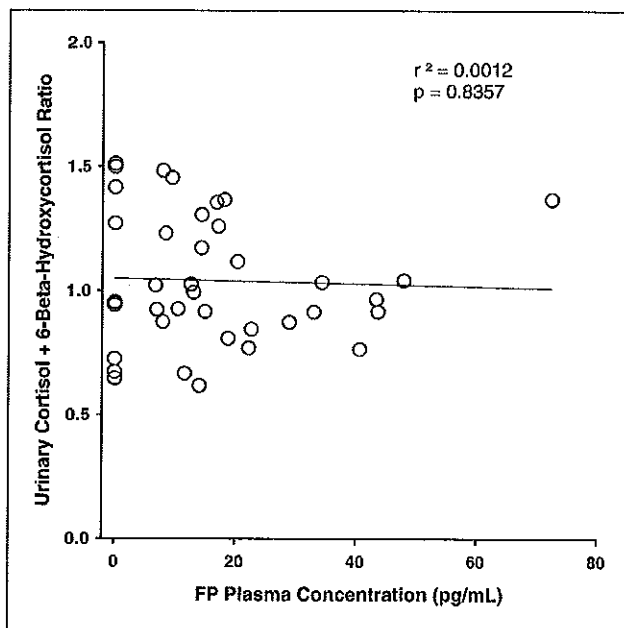


Figure 4. Study 2. Relationship between urine cortisol + 6- β -hydroxy urinary cortisol excretion ratio and fluticasone propionate (FP) C_{max} (pg/mL) ($r^2 = 0.0012$; $P = .84$).

of these AEs were considered related to study medication. The AEs considered related to study medication were cough (3 subjects), headache (1 subject), and nausea (1 subject).

DISCUSSION

Lower FP exposure from the HFA formulation compared with the CFC formulation observed in study 1 has also been observed in 2 single-dose, crossover studies in healthy adults. FP systemic exposure following 1760 μ g ($8 \times 220 \mu$ g) of FP HFA was 30% lower compared with FP CFC, with less effect on 24-hour serum cortisol AUC.¹⁹ Similar observations were noted in healthy adults administered 880 μ g ($8 \times 110 \mu$ g) of FP.¹³ Results described in the current report confirm the lower FP exposure with the HFA MDI after therapeutic doses given to children with asthma. Despite this lower systemic exposure, the 2 formulations have been shown to be of nearly identical particle size and have similar fine particle mass (FPM) distribution.^{20,21} The 44- μ g formulation of FP HFA has a mass median aerodynamic diameter (MMAD) of 2.3 μ m; the corresponding CFC formulation has an MMAD of 2.3 to 2.4 μ m. The FPMs for the HFA and CFC products are 24 μ g and 22 μ g, respectively. Thus, the lower FP systemic exposure

with the HFA formulation cannot be explained by differences in particle size or FPM.

The similarities of the particle size properties between FP HFA and FP CFC, yet differences in pharmacokinetic and pharmacodynamic properties, are in contrast to those of the 2 aerosol formulations of beclomethasone dipropionate. Leach et al²² reported a smaller MMAD for the HFA BDP formulation (1.1 μ m) compared with the CFC product (3.5 μ m). Because the smaller particles of the HFA BDP are associated with a 2- to 3-fold increase in systemic exposure,¹¹ the administered dose needs to be decreased to one half that of the CFC formulation for comparable safety and efficacy.¹² In comparison, at equivalent doses as noted above, a significant reduction in systemic exposure is observed with FP HFA versus FP CFC.^{13, 19} In addition, previous studies showed that the HFA and CFC formulations of inhaled FP are therapeutically comparable at equal-microgram doses in both pediatric patients and adults with asthma.⁶⁻¹⁰ For example, Lyttle et al⁶ evaluated the efficacy of 200 μ g of FP HFA versus 200 μ g of FP CFC in 315 pediatric patients less than 16 years of age (mean age 9.3 years) in a randomized, double-blind, 4-week study. Equivalence was demonstrated between the 2 treatment groups (90% CI -6 to 3 L/min; $P = .589$) in improvements in mean morning peak flow. Why these differences between FP HFA/CFC and HFA/CFC BDP exist is unclear. HFA BDP is a solution that contains ethanol as a co-solvent. FP HFA is a suspension without any co-solvents. Whether the differences in formulation explain in part the lower MMAD with HFA BDP is uncertain. Nevertheless, these data suggest that particle size and fine particle mass are not the sole determinants of systemic exposure. In adolescents and adults, FP HFA systemic exposure is 30% less than the CFC formulation, resulting in significantly less effect on cortisol suppression.¹⁹ Because, as shown in the study reported here, the systemic exposure using the HFA formulation in children is 45% of the CFC product, similarly a lesser effect on the hypothalamic-pituitary-adrenal axis may be predicted in children as well. Thus, based on the results of the current study and those of prior studies,⁷⁻¹⁰ and of importance to clinicians, FP HFA can be administered at the same dosage as used with the CFC formulation with comparable efficacy but improved safety on the hypothalamic-pituitary-adrenal axis.

FP HFA 88 μ g twice daily was well tolerated in these children aged 4 to 11 with asthma, and headache was the most frequently reported AE, although this was believed to be related to study medication in

only 1 subject. Furthermore, the AEs that were serious or led to premature study discontinuation were also not believed to be related to study drug. No episodes of candidiasis occurred in this study. This is most likely related to the short study duration, because a recent double-blind placebo-controlled study in a similar population reported oral candidiasis in 2 of 160 FP HFA-treated children compared with none of 81 children who received placebo.²³

No evidence of hypothalamic-pituitary-adrenal axis suppression was observed following 4 weeks of treatment with FP HFA 88 µg twice daily, as assessed by 24-hour urinary cortisol excretion and by the sum of urinary cortisol and 6-β-hydroxycortisol. These findings are consistent with a previous 12-week placebo-controlled study in children who received FP 100 µg twice daily via a dry powder inhaler.²⁴ Unsurprisingly, with this low dose of FP, the current study found no correlation between plasma FP levels and cortisol excretion.

CONCLUSION

Fluticasone propionate HFA is approved in the United States for the treatment of asthma in children 4 years of age and older. A recent trial in children aged 4 to 11 years also demonstrated efficacy of FP HFA 88 µg twice a day over placebo in terms of lung function, albuterol use, and nighttime awakenings.²³ The 2 studies reported here show that FP systemic exposure from FP HFA was significantly lower compared with the FP CFC formulation and that there was no effect from FP HFA on the hypothalamic-pituitary-adrenal axis as measured by 24-hour urinary cortisol excretion. Therefore, as used in this pediatric population, the potential for systemic adverse events in susceptible individuals would be reduced with FP HFA and may provide an opportunity for an improved therapeutic index.

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