

Fluticasone propionate plasma concentration and systemic effect: Effect of delivery device and duration of administration

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Background: Inhaled corticosteroids are the preferred therapy in persistent asthma. Dry powder inhalers (DPIs) generate a larger particle size compared with metered-dose inhalers (MDIs), which affects pulmonary deposition, bioavailability, and subsequent systemic effects of fluticasone propionate (fluticasone).

Objective: To examine the relationship of fluticasone pharmacokinetics and cortisol suppression for 2 fluticasone formulations (DPI and MDI) administered in adults over 1-week and 6-week treatment periods.

Methods: Two previous studies conducted in adults by the Asthma Clinical Research Network examined relative efficacy and systemic effect of fluticasone from MDI and DPI. Sample sets ($n = 33$) were analyzed for fluticasone after administration of 352 μg from the MDI, and 400 μg from the DPI formulation, twice daily, after a 1-week treatment period. The second study's sample sets ($n = 9$) were analyzed for fluticasone after 6 weeks therapy at 352 μg twice daily from the MDI formulation, allowing achievement of steady state.

Results: ANOVA revealed a significant trend of increasing fluticasone area under the curve from 0 to time t (AUC_{0-t}) when comparing DPI with MDI for 1 week with MDI for 6 weeks ($P < .0001$). Similarly, ANOVA revealed increasing cortisol suppression between these groups ($P = .007$). Linear regression demonstrated that increasing fluticasone AUC_{0-t} was significantly correlated with cortisol suppression ($P < .0001$; $r^2 = 0.41$). MDI for 6 weeks showed increasing fluticasone AUC ($P = .0008$, t test) compared with MDI for 1 week, suggesting accumulation.

Conclusion: Fluticasone plasma concentrations are significantly greater after MDI compared with DPI, and cortisol suppression is associated with fluticasone plasma concentrations. Accumulation of fluticasone concentrations suggests that time to steady state exceeds 1 week of treatment with MDI. (*J Allergy Clin Immunol* 2005;116:525-30.)

Key words: Pharmacokinetics, fluticasone propionate, metered dose inhaler, dry powder inhaler, cortisol suppression, drug accumulation, steady state

Inhaled corticosteroids (ICSs) are the cornerstone of treatment for persistent asthma, and were originally designed to limit the systemic effects usually associated with oral corticosteroid therapy by providing topical therapy directly to the airways. Although ICS therapy is associated with a low risk of systemic effect compared with oral corticosteroid administration, systemic absorption of corticosteroid still occurs with inhaled administration.¹⁻⁵ This may be observed as hypothalamic-pituitary-adrenal axis suppression in all age groups and reduced growth velocity in children.⁶⁻⁹ Systemic absorption is a result of gastrointestinal tract and pulmonary absorption, which differs for the various ICSs. The major fraction of an ICS is deposited in the mouth and oropharynx, and thus is subsequently swallowed; only a smaller fraction is deposited in the subglottic airways.

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Abbreviations used

AUC: Area under the curve
 AUC_{0→t}: Area under the curve from 0 to time t
 CFC: Chlorofluorocarbon
 DICE: Dose of Inhaled Corticosteroids with
 Equi-systemic Effects
 DPI: Dry powder inhaler
 ED: Emitted dose
 FPD: Fine particle dose
 FPF: Fine particle fraction
 ICS: Inhaled corticosteroid
 MDI: Metered-dose inhaler
 MDIs1: Metered-dose inhaler + spacer × 1 week
 MDIs6: Metered-dose inhaler + spacer × 6 weeks
 MICE: Measuring Inhaled Corticosteroid Efficacy
 MMAD: Mass median aerodynamic diameter

Along with the strategy of modifying the physical properties of the newer generations of ICS for improved efficacy, particle size is also a major factor.¹⁰⁻¹⁹ Optimal particle size distribution (or mass median aerodynamic diameter, MMAD) for pulmonary airway deposition is between 2 μ m and 4.7 μ m; particles greater than 4.7 μ m deposit in the mouth and oropharynx, whereas particles smaller than 2 μ m will deposit in the alveoli or may be exhaled (because of diffusion characteristics of the pulmonary acinus).^{18,19}

The National Heart, Lung, and Blood Institute Asthma Clinical Research Network previously published the results of 2 studies designed to examine the comparable local and systemic effects of various ICSs. One study, Dose of Inhaled Corticosteroids with Equi-systemic Effects (DICE),¹⁸ identified the marked difference in particle size distributions between the metered-dose inhaler (MDI) and dry powder inhaler (DPI) formulations of fluticasone. The fine particle fraction (FPF) was defined as the percentage of drug particles <4.7 μ m. From this, the fine particle dose (FPD) was determined by emitted dose (ED) and FPF (ie, FPD = FPF × ED). From the DICE study, the fluticasone propionate MDI + spacer (OptiChamber; Respironics, Murrysville, Pa) ED and FPD were 27.0 μ g ± 5.6 μ g and 85.2%, respectively, calculating a FPD of 23.0 μ g ± 4.8 μ g. This compares with the fluticasone DPI (Rotadisk Diskhaler; GlaxoSmithKline, Research Triangle Park, NC) with an ED and FPF of 49.4 μ g ± 2.8 μ g and 10.9%, calculating a FPD of 5.4 μ g ± 0.7 μ g. Similar findings have been previously reported.^{20,21} The MDI + spacer has 4.3 times the pulmonary delivery of the DPI, which was supported by the cortisol suppression data.¹⁸ Bioavailability of fluticasone via gastrointestinal absorption is negligible (<1%); therefore, systemic bioavailability is primarily a result of pulmonary bioavailability.^{16,22}

By using selected plasma sample sets from the DICE and Measuring Inhaled Corticosteroid Efficacy (MICE)²³ studies, we sought to determine differences in systemic effect by different delivery devices and length of therapy.

TABLE I. Study participant demographics (means ± SDs)*

Study group	DPI	MDIs1	MDIs6
Age (y)	28.2 ± 5.5	34.2 ± 13.3	28.8 ± 8.9
Dose (given as twice daily)	400	352	352
Weight (kg)	74.5 ± 16.5	77.7 ± 15.2	76.2 ± 10.8
Height (cm)	172.5 ± 9.8	173.5 ± 10.4	176.1 ± 7.7
μ g/kg (per dose)	5.6 ± 1.2	4.7 ± 0.9	4.7 ± 0.8
Baseline FEV ₁ % predicted (%)	75.0 ± 12.8	69.4 ± 13.8	75.1 ± 7.6

*There were no significant differences between each group.

This was analyzed by comparing pharmacokinetic parameters with cortisol suppression.¹⁸ In DICE, study participants received fluticasone from the MDI + spacer and the DPI formulations for 1 week at 352 μ g and 400 μ g twice daily, respectively (MDI + spacer × 1 week; MDIs1). A similar procedure was performed in MICE,²³ in which fluticasone MDI + spacer was administered as 352 μ g twice daily over a period of 6 weeks (MDI + spacer × 6 weeks; MDIs6).

METHODS

Sample selection

Plasma sample sets from selected study participants in DICE and MICE (originally for plasma cortisol concentrations) were used to measure plasma fluticasone concentration.^{18,23} Inclusion and exclusion criteria are detailed in these studies (DICE and MICE).^{18,23} Demographics of the selected study participants are shown in Table I.

At the end of the study interval, plasma samples were collected overnight at 1-hour intervals in both studies (DICE, 8 PM through 8 AM; MICE, 9 PM through 9 AM). Drug was administered 2 hours after sampling had begun. The fluticasone MDI formulation (GlaxoSmithKline) was administered with an OptiChamber spacer in both studies. The DPI formulation (GlaxoSmithKline) used for the DICE study was the Flovent Rotadisk Diskhaler. For participants in the DICE study, a total of 33 sample sets were analyzed (17 in DPI arm, and 16 in MDI arm), and 9 sample sets were analyzed from the MICE study. Selected sample sets for this study were based on complete sample collection for plasma cortisol analysis.

The study design for DICE and MICE differed in the following ways. ICS in the DICE study was administered in a dose escalation design as 100, 200, 400, and 800 μ g daily for the DPI, and 88, 176, 352, and 704 μ g daily for the MDI (given as divided doses, twice daily). Each total daily dose was administered in 1-week serial increments. ICS in the MICE study was also conducted as a dose escalation design protocol, with the participants receiving 88, 176, 352, and 704 μ g daily (divided doses, twice daily), each for 6 weeks. Sample sets were selected from the highest dosing regimens from each study (800 μ g/d and 704 μ g/d from DPI and MDI, respectively; Fig 1).

Sample analysis

Plasma fluticasone concentrations were measured by liquid chromatography–mass spectrometry, as previously described (Shimadzu LCMS QP-8000 Liquid Chromatographer Mass Spectrometer; Shimadzu, Kyoto, Japan).²⁴ Assay sensitivity was 20 pg/mL (with

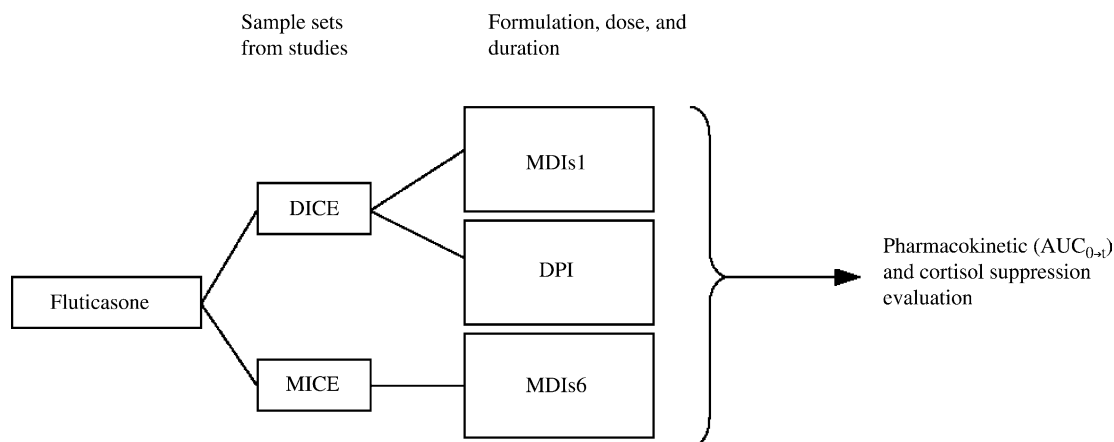


FIG 1. Study design. Selected study participants from the DICE and MICE studies were analyzed for $AUC_{0 \rightarrow t}$ and cortisol suppression. Measured after 1 week of 800 μg daily of fluticasone administered via *DPI* (Rotadisk Diskhaler); *MDIs1*, fluticasone by MDI with OptiChamber for 1 week at 704 μg daily; *MDIs6*, fluticasone by MDI with OptiChamber for 6 weeks at 704 μg daily.

a range of 20-500 pg/mL and a coefficient of variation of 15% to 20%). Because of the limits of assay sensitivity, the higher treatment doses from both studies were used. Plasma cortisol samples were analyzed by HPLC, as previously described.²⁵

Data analysis

For fluticasone pharmacokinetic analysis, area under the concentration time curve ($AUC_{0 \rightarrow t}$; $t = 12$ hours) for fluticasone was calculated by the trapezoidal rule (WinNonlin version 4.1; Pharsight Corp, Mountainview, Calif; Microsoft Excel 2000; Microsoft, Redmond, Wash). Percent cortisol suppression was calculated as:

$$\left(1 - \left(\frac{\text{Plasma cortisol AUC at the end of the treatment regimen}}{\text{Plasma cortisol AUC at baseline}} \right) \right) \times 100$$

Statistical analysis

Fluticasone $AUC_{0 \rightarrow t}$ and percent cortisol suppression were compared in each treatment group (DPI, MDIs1, and MDIs6) by using 1-way ANOVA. Post hoc Tukey tests were performed to compare the differences between treatment groups. Fluticasone $AUC_{0 \rightarrow t}$ was also compared between MDIs1 and MDIs6 by using the Student t test. Linear regression analysis was used to compare the relationship between fluticasone $AUC_{0 \rightarrow t}$ and percent cortisol suppression across all 3 groups (JMP 5.1; SAS Institute, Cary, NC; Microsoft Excel 2000).

RESULTS

Fluticasone pharmacokinetics

$AUC_{0 \rightarrow t}$ was 265.24 ± 232.90 pg/mL/h (mean $\pm$ SD) after 1 week of treatment with the DPI, 918.69 ± 567.32 pg/mL/h for MDIs1, and 1814.11 ± 543.7 pg/mL/h for MDIs6. One-way ANOVA revealed significant differences in fluticasone area under the curve (AUC) across all 3 groups ($P < .0001$, Fig 2), and post hoc Tukey tests revealed significant differences between groups ($P < .05$).

The Student t test showed that MDIs6 had significantly greater $AUC_{0 \rightarrow t}$ than MDIs1 ($P = .0008$), suggesting accumulation of fluticasone during the extended dosing period.

Fluticasone systemic absorption and cortisol suppression

Cortisol suppression was observed in all 3 groups, with $6.0\% \pm 55.5\%$ after 1 week of treatment with the DPI, $40.9\% \pm 37.1\%$ for MDIs1, and $62.0\% \pm 22.4\%$ for MDIs6. One-way ANOVA revealed significant differences in cortisol suppression across all 3 groups ($P = .0071$, Fig 3), and post hoc Tukey tests revealed a significant difference between the DPI and MDIs6 ($P < .05$).

Linear regression showed a significant positive association with increasing fluticasone AUC (fluticasone AUC was logarithmically transformed for normalization) and percent cortisol suppression ($P < .0001$; $r^2 = 0.41$; Fig 4) across all 3 data sets. There were no significant differences in lung function changes (FEV₁, peak expiratory flow rate; FEV₁ versus fluticasone $AUC_{0 \rightarrow t}$) for any of the groups (data not shown).

DISCUSSION

Our findings show that plasma fluticasone concentrations are significantly greater when the drug is inhaled from an MDI than from a DPI delivery device. These results are consistent with analyses showing that DPI delivery devices generate particles with a larger MMAD than that generated from the MDI devices, and they complement the original reports from the 2 Asthma Clinical Research Network studies. The DPI delivery devices had a FPF (fraction below 4.7 μm) of 10.9%, whereas MDI delivery devices (with OptiChamber) had

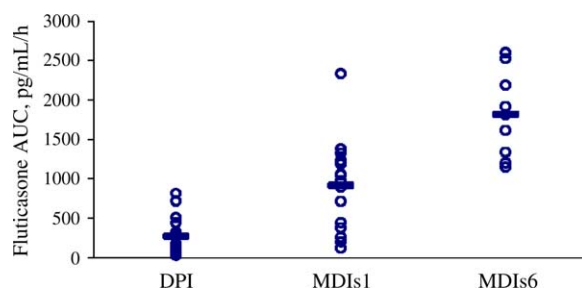


FIG 2. Comparison of fluticasone $AUC_{0 \rightarrow t}$ for between delivery devices and duration of therapy. ANOVA revealed significant differences across all 3 groups ($P < .0001$), and Tukey test revealed significance between each group ($P < .05$). The Student t test revealed a significant difference in duration of therapy (MDIs1 vs MDIs6; $P = .0008$). Open circles, individual data; bar, mean.

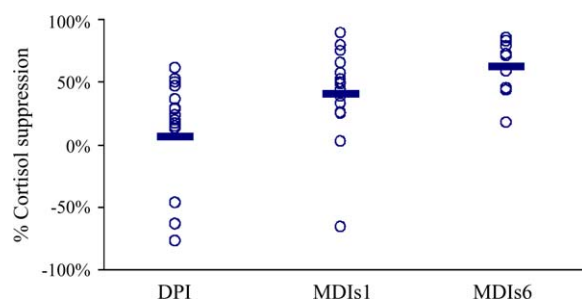


FIG 3. Percent cortisol suppression between delivery devices and duration of therapy. ANOVA revealed significant differences across all 3 groups ($P = .0071$), and Tukey test revealed significant differences between the DPI (Rotadisk Diskhaler) and MDIs6 groups ($P < .05$). Open circles, individual data; bar, mean.

a PPF of 85.2%.¹⁸ The MMAD of the DPI is reported as 4.3 μm ,²⁰ whereas the MDI is reported as 2.0 μm .¹² The higher plasma concentrations and AUCs after administration from the MDI delivery device compared with the DPI device are consistent with the concept that the systemic effect (ie, percent cortisol suppression) of fluticasone is indeed primarily a result of pulmonary absorption from the inhaled route.

It is important to note that as of September 2004, Flovent Rotadisk Diskhaler (GlaxoSmithKline) was removed from the US market. The combination product of fluticasone and salmeterol Diskus (Advair; GlaxoSmithKline) is the only fluticasone DPI currently available. The Rotadisk Diskhaler's systemic bioavailability for fluticasone is 11.6%, whereas the Diskus's is 16.6%.²⁶ These differences are not suspected to affect our findings.

We observed that fluticasone AUC after treatment with the MDI formulation for 6 weeks was significantly greater than fluticasone AUC after 1 week with MDI treatment ($P < .05$, Tukey test; $P = .0008$, Student t test; Fig 2). This finding suggests that drug accumulation continues to accrue beyond 1 week of administration, before achieving steady state. Overall, study participants treated with fluticasone for 6 weeks with the MDI had, on average, plasma concentrations approximately twice as

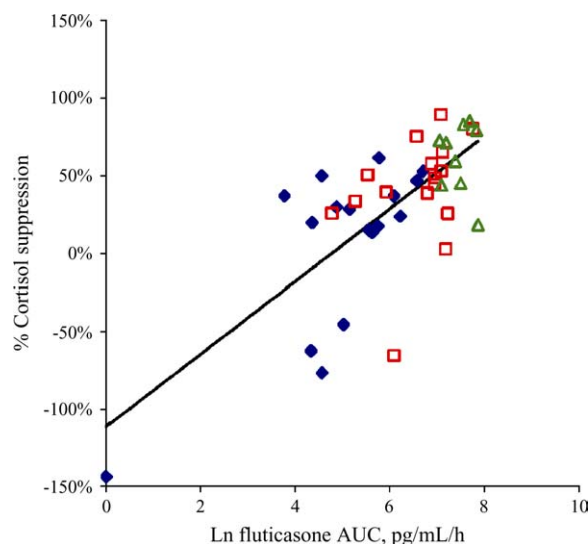


FIG 4. Fluticasone $AUC_{0 \rightarrow t}$ versus percent cortisol suppression. With natural log (Ln) transformation of the fluticasone AUC data, regression analysis for all 3 treatment groups demonstrates a significant and positive correlation between increasing fluticasone AUC and percent cortisol suppression (linear regression; $P < .0001$; $r^2 = 0.41$). Blue closed circles, DPI; red open squares, MDIs1; green open triangles, MDIs6.

high as those of participants treated for 1 week with the MDI formulation.

Previous fluticasone pharmacokinetic studies determined that steady state was achieved after a week of therapy. This is based on the consistency of pharmacokinetic parameters of peak concentration (C_{max}), AUC, and half-life demonstrating steady-state qualities.^{2-4,27,28} However, our analysis of fluticasone after 6 weeks of therapy suggests that subtle differences may exist, and the terminal half-life may be longer than previously reported.

Pharmacokinetic studies report the terminal half-life of fluticasone from 5 to 14 hours. These discrepancies might be a result of assay sensitivity and/or length of sampling time after a dose (usually ranging from 12-48 hours after a dose).^{2-4,27,28} Fluticasone demonstrates variable absorption and elimination as modeled by multicompartment pharmacokinetics.^{3,22} Different delivery devices may affect fluticasone's absorption profile—for example, prolonged absorption from the pulmonary site into systemic circulation associated with the MDI formulation. This could therefore result in accumulation of plasma fluticasone concentration over time. Implementation of an extended treatment interval along with longer washout sampling times could elucidate the true pharmacokinetic disposition of fluticasone after inhaled administration. Assay sensitivity limited our study to analysis of the higher dosing intervals; newer assays using gas chromatography-mass spectrophotometry can detect fluticasone as low as 0.5 pg/mL but were not feasible for this analysis.²⁹

Differences in fluticasone pharmacokinetics are observed when comparing patients with asthma with healthy

participants. Brutsche et al²⁷ demonstrated that subjects with asthma absorb less fluticasone (MDI + Volumatic spacer; Glaxo Wellcome, Middlesex, United Kingdom) systemically than do normal healthy controls.²⁶ Significant reductions in fluticasone AUC ($P < .001$) and systemic availability ($P = .001$) were reported in those with asthma compared with healthy controls, but no differences were observed in half-life (samples were collected over a period of 12 hours).²⁷ Daley-Yates et al³⁰ examined data from 13 pharmacokinetic studies (both single and multiple dosing) to compare systemic exposure between healthy individuals and patients with asthma. They determined that overall, patients with asthma had 2 to 3 times less systemic availability (as determined by AUC and percent cortisol suppression) than healthy individuals.

Differences in percent cortisol suppression were noted among the 3 treatment groups, with reductions of 6%, 41%, and 62% suppression for participants treated with the high-dose fluticasone via DPI, MDIs1, and MDIs6, respectively (Fig 3). ANOVA revealed a significant trend across all 3 groups ($P = .0071$). Post hoc Tukey tests showed significance between the DPI and MDIs6 groups. With linear regression, a significant relationship between increasing fluticasone AUC₀₋₁ and percent cortisol suppression was observed ($P < .0001$; $r^2 = 0.41$; Fig 4). These findings indicate that cortisol suppression (pharmacodynamics) is dose-dependent and related to plasma fluticasone concentration (pharmacokinetics).

The absence of changes in pulmonary function with increasing fluticasone AUC and plasma concentrations was likely caused by the plateau effect of the high-dose therapy. The participants in these 2 studies had mild to moderate asthma, with an average baseline FEV₁ of 75%, 69%, and 75% predicted for DPI, MDIs1, and MDIs6, respectively. The greatest improvements in lung function occurred in the lowest dosing regimens (100 µg/d for DPI, and 88 µg/d for MDIs1 and MDIs6).^{18,23} Derom et al³¹ investigated the effects of 200 µg and 1000 µg of the fluticasone Rotadisk Diskhaler given twice daily on cortisol suppression and lung function in corticosteroid-naïve subjects with asthma. Although lung function (FEV₁) improved compared with placebo, no significant improvements were found in the participants who were given 1000 µg twice daily compared with participants who received 200 µg twice daily.

Hydrofluoroalkane delivery devices of inhaled steroids are now available, replacing the chlorofluorocarbon (CFC) formulations of the MDI. The hydrofluoroalkane formulation allows the drug to form a solution, generating a smaller MMAD, resulting in greater lung deposition and systemic absorption.¹² In a single-dose study, Mackie et al³² observed the pharmacokinetics between the CFC and hydrofluoroalkane formulations for fluticasone. Although the pharmacokinetics of these 2 formulations were comparable (C_{max} of 560 versus 540 pg/mL, for CFC and hydrofluoroalkane, respectively), the investigators observed that the fluticasone terminal slope (half-life) of the hydrofluoroalkane formulation was slightly longer

compared with the CFC formulation (11.5 h vs 10.0 h), with a greater bioavailability for the hydrofluoroalkane (28.6%) compared with the CFC formulation (26.4%).³²

Future pharmacokinetic studies with fluticasone should evaluate currently available delivery devices, an extended treatment period, longer washout sampling times, and more sensitive assay methods. Applying this design strategy will define the true pharmacokinetic disposition of inhaled fluticasone and other ICSs, with an accurate analysis of the systemic effects associated with long-term ICS therapy.

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