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 ($AUC_{0\rightarrow t}$) 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 $AUC_{0\rightarrow t}$ 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
$AUC_{0\rightarrow t}$: 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 μm and 4.7 μm; particles greater than 4.7 μm deposit in the mouth and oropharynx, whereas particles smaller than 2 μm 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 μm. 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 FPF were 27.0 μg ± 5.6 μg and 85.2%, respectively, calculating a FPD of 23.0 μg ± 4.8 μg. This compares with the fluticasone DPI (Rotadisk Diskhaler; GlaxoSmithKline, Research Triangle Park, NC) with an ED and FPF of 49.4 μg ± 2.8 μg and 10.9%, calculating a FPD of 5.4 μg ± 0.7 μg. 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
μg/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 μg and 400 μg 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 μg 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 μg daily for the DPI, and 88, 176, 352, and 704 μg 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 μg daily (divided doses, twice daily), each for 6 weeks. Sample sets were selected from the highest dosing regimens from each study (800 μg/d and 704 μg/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