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Systemic Exposure to Fluticasone Delivered by Metered-Dose Inhaler; Influence of Age and Assist Device

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Summary

We performed this study to evaluate how age and device affect the systemic exposure of inhaled fluticasone propionate (FP) in children. The findings indicate an anti-static valved holding chamber significantly increases systemic exposure of FP.

Keywords

valved holding chamber; lung bioavailability; fluticasone propionate; asthma

INTRODUCTION

Previous studies in adults have shown that a valved holding chamber (VHC) increases drug delivery to the airways [1–3]. However, in children, guidelines state that less drug is delivered with a spacer [4]. As a consequence, we performed this study to evaluate how age and device affect the systemic exposure of inhaled fluticasone propionate (FP) in children.

METHODS

All subjects were studied in the Asthma Research Lab at the University of Florida. The study was approved by the University of Florida Institutional Review Board, and registered with clinicaltrials.gov (NCT00308932).

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Clinicaltrials.gov #NCT00308932

Conflicts of Interest: None

Study Design

This study was a single center, unblinded, cross-sectional, observational study of one hour steady-state FP plasma concentrations. 61 children with well controlled persistent asthma were enrolled in the study. Subjects 12–18 years used the actuator alone with optimal technique. Subjects 5–9 years of age were divided into 3 groups based on the device they could optimally use: actuator alone, a VHC with mouthpiece, or a VHC with mask. Children 1–4 years used a VHC with mask. Both VHCs were made from an anti-static polymer (AeroChamber MAX®, Monaghan Medical Corporation, Plattsburgh, NY).

All subjects were converted from their regular inhaled corticosteroid regimen (80.4% on ≥ 440μg/day) to hydrofluoroalkane fluticasone propionate MDI (Flovent® HFA), 110μg/actuation, 2 actuations BID for at least 3 days with the optimal delivery device as described above. This duration of treatment ensured that the fluticasone plasma concentrations would be at steady state in all subjects since the mean half life in children is about 6–8 hours[5].

Adherence to the twice daily regimen was documented by an electronic monitor (Doser®, Meditrack Products, Easton, MA). Four actuations of albuterol MDI (90μg/actuation) were administered 20 minutes before the FP test dose on each study day to minimize airway obstruction. Subsequently, the study coordinator observed the administration of the test dose and if it was optimal, a single 5mL blood sample was collected 1 hour later.

Measurements

FP plasma concentrations were measured by a liquid chromatography-mass spectrometry assay[6].

Statistical Analysis

An Analysis of Variance was used to assess the means of the one hour FP concentrations for each group. The differences between each group and the reference group were tested using the two-sided Dunnett Multiple Comparison Procedure[7].

RESULTS

In total, 88 subjects were screened. Of these subjects, 61 completed the study, with at least 12 in each group. The most common cause of withdrawal (11/27) was a documented adherence of less than 100% during the study. Additionally, nine subjects could not be taught proper inhalation technique and seven withdrew because of other reasons (e.g. child refused venipuncture). However, all subjects who completed the study had 100% adherence for at least three days before the test day.

Individual C_{max} values are depicted in Figure 3. The mean concentration in the 12–18 year MDI alone group was significantly lower ($p<0.003$) than all of the groups using a chamber but was not significantly different from the 5–9 year group who was able to use the actuator alone (Table).

There were no adverse events observed during this study.

DISCUSSION

The results of this study indicate that systemic exposure was significantly higher in all groups receiving FP through a VHC compared to the two groups who effectively used an MDI through the actuator alone. For the 5–9 age groups we can assume that the average volumes of distribution and clearances of the three groups were similar since there was no significant difference in mean body mass index (Table). The lack of a statistical difference

between the VHC with mask and the VHC with mouthpiece groups indicates that passive inhalation does not significantly decrease lung bioavailability. We recognize that this dose of FP is listed as high-dose in the NIH guidelines. However, this dose is routinely prescribed at our tertiary pediatric pulmonary center and that is why we chose to use it. The FP package insert states that the dose-related increase in systemic exposure occurred using a VHC in all age groups ≥4 years. Specifically, they stated that in patients ≥ 12 years receiving 220μg of FP twice a day with a chamber there was increased systemic exposure with a Cmax of 47.3pg/mL[8]. In our study systemic exposure using a VHC was much higher with averages ranging between 140–207pg/mL in all age groups when an anti-static VHC was used. These disparities may require clinical trials assessing the safety of using the FP HFA with antistatic VHCs.

The clinical relevance of our finding of increased systemic exposure with the use of an anti-static VHC is unclear. In adults, the plasma concentration of FP producing a 50 % decrease in maximal cortisol secretion (EC_{50}) was 100 pg/mL in one study[9] and 130 pg/ML in another[10]. The corresponding value for children is unknown. However, Eid et al[11] reported a dose-dependent decrease in 8 am cortisol concentrations in children receiving long term therapy with FP through a conventional VHC. In those receiving 440 μg/d, the medium dose employed in our study, 35 % had an abnormal cortisol concentration that subsequently normalized after dose reduction. In contrast, Lipworth et al [12] did not find a difference in overnight urinary cortisol/creatinine excretion between 200 and 400 μg/d of FP delivered by large volume spacer to children, but the duration of treatment was only 4 days with each dose and urinary cortisol excretion is less sensitive than plasma cortisol concentrations[13]. We, therefore, recommend initiating therapy with a lower dose of FP (176 μg/d) or reducing the dose as soon as asthma control is achieved if therapy is initiated with 440 μg/d.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS

C_{max}	the peak plasma concentration
EC_{50}	the concentration of FP suppressing the maximum cortisol excretion by 50%
FEV_1	forced expiratory volume in the first second
FP	fluticasone propionate
HFA	hydrofluoroalkane
MDI	metered-dose inhaler
Vd	volume of distribution
VHC	valved holding chamber

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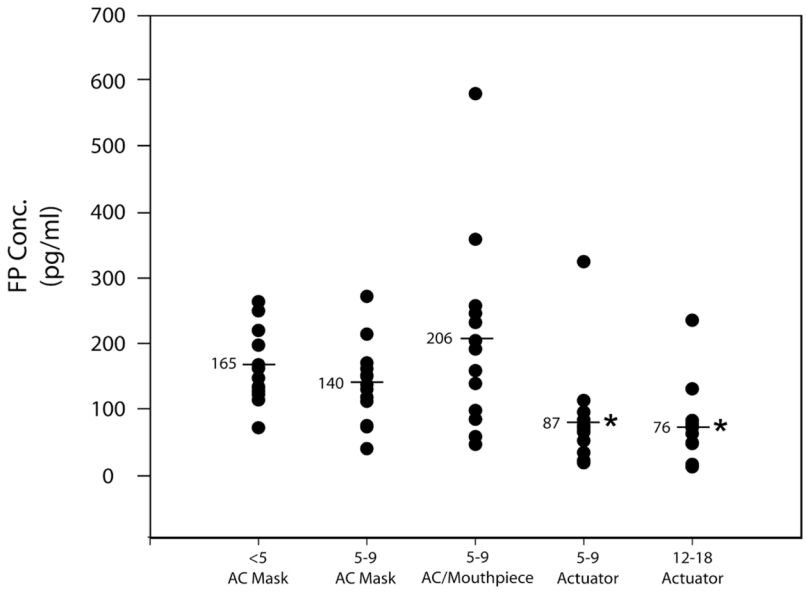

Figure 1.

Individual one-hour post-dose steady state fluticasone propionate plasma concentrations. The mean±SD in pg/mL were as follows: 12–18 yr reference group, 76±61; 5–9 yr actuation alone, 87±80 (p=0.75); 5–9 yr VHC/mouthpiece, 207±149 (p=0.0006); 5–9 yr VHC/mask, 140±61 (p=0.07); and 1–4 yr VHC/mask, 165±58 (p=0.016). *Significantly lower than groups receiving FP through VHC (p=0.003).

TABLE 1

Demographics and Results of Subjects who Completed the Study

	Age (years)	Gender Male: Female	Race Caucasian: African American: Hispanic	BMI (kg/m^2)	Duration of FP treatment (days)	1-hr FP plasma conc pg/mL Geometric mean (95% CI)
1 to 4 yrs VHC/mask (n=12)	2.8 ± 0.8	10:2	9:3:0	16.76	5.2 ± 1.7	155 (124:196)
5–9 yrs VHC/mask (n=13)	6.2 ± 0.8	8:5	8:5:0	18.73	6.2 ± 3.2	127 (95:170)
5–9 yrs VHC/mouthpiece (n=12)	6.5 ± 1.0	8:4	5:7:0	19.49	6.4 ± 2.6	164 (103:259)
5–9 yrs Actuator alone (n=12)	8.1 ± 1.1	7:5	7:5:0	18.67	6.8 ± 6.4	67 * (43:105)
12–18 yrs Actuator alone (n=12)	15.1 ± 1.6	8:4	7:4:1	27.20	6.5 ± 3.8	57 (33:95) *

* Significantly lower than all groups using a VHC.