

Letter to the Editor

Systemic exposure to fluticasone MDI delivered through antistatic chambers

To the Editor:

In adults, studies have shown that a valved holding chamber (VHC) increases drug delivery to the airways.¹ However, guidelines state that in children less drug is delivered with a spacer.² We performed the present study to determine how age and device affect the systemic exposure of inhaled fluticasone propionate (FP) in children with persistent asthma.

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 parents or legal guardians gave written informed consent.

This was a single-center, unblinded, cross-sectional study of 1-hour steady-state FP plasma concentrations ($C_{\max}$). Sixty-one children with well-controlled persistent asthma were enrolled in the study (Table I). Subjects aged 12 to 18 years used the metered-dose inhaler (MDI) through the actuator alone with an optimal technique. Subjects 5 to 9 years of age were divided into 3 groups on the basis of the device that they could optimally use: actuator alone, a VHC with mouthpiece, or a VHC with mask. Children aged 1 to 4 years used a VHC with mask. Both VHCs were made from an antistatic polymer (AeroChamber MAX; Monaghan Medical Corporation, Plattsburgh, NY).

All subjects were converted from their regular inhaled corticosteroid regimen (see this article's Online Repository at www.jacionline.org for details) to hydrofluoroalkane FP MDI (Flovent HFA; GlaxoSmithKline, Research Triangle Park, NC), 110 μg per actuation, 2 actuations bid for at least 3 days with the device that they could use optimally. This duration of treatment ensured that FP plasma concentrations would be at steady state in all subjects since the mean half-life in children is about 6 hours.³

Adherence was documented by an electronic monitor (Doser; Meditrack Products, Easton, Mass). Four actuations of albuterol MDI (90 μg per 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 5-mL blood sample was collected 1 hour later.

FP plasma concentrations were measured by a liquid chromatography-mass spectrometry assay.⁴

An analysis of variance was used to compare the geometric mean $C_{\max}$ for each group. The differences between each group

and the reference group were tested using the 2-sided Dunnett Multiple Comparison Procedure.

In total, 88 subjects were screened. Of these, 61 subjects completed the study, with at least 12 in each group. The most common cause of withdrawal (11 of 27) was a documented adherence of less than 100% during the study. In addition, 9 subjects could not be taught proper inhalation technique and 7 withdrew because of other reasons (eg, child refused venipuncture). However, all subjects who completed the study had 100% adherence for at least 3 days before the test day.

Individual $C_{\max}$ values are depicted in Fig 1 and also listed in Table E1 in this article's Online Repository at www.jacionline.org. The geometric mean concentration in the MDI group of 12- to 18-year-olds was significantly lower ($P < .003$) than in all the groups using a chamber, but was not significantly different from the 5 to 9 year group members who were able to use the actuator alone (Table I).

There were no adverse events observed during this study.

The results of this study indicate that systemic exposure was significantly higher in all groups receiving FP through a VHC compared with the 2 groups who effectively used an MDI through the actuator alone. For the 5- to 9-year-old age group, we can assume that the average volumes of distribution and clearances of the 3 groups were similar, since there was no significant difference in mean body mass index (Table I). Therefore, the lack of a statistical difference between the VHC with mask and the VHC with mouthpiece group suggests that passive inhalation does not significantly decrease lung bioavailability.

We recognize that this dose of FP is listed as a "high dose" in the NIH guidelines.² However, this dose is routinely prescribed at our tertiary pediatric pulmonary center, and most subjects were on this dose or equivalent before the study (see Table E1). The FDA-approved labeling states that the use of a VHC increases systemic exposure in all age groups 4 years or older. In patients 12 years or older receiving 220 μg of FP twice a day through a static VHC, for example, $C_{\max}$ was 47.3 pg/mL.³ In our study, systemic exposure using an antistatic VHC was much higher, with geometric means ranging between 127 and 164 pg/mL in all age groups. The most likely explanation for the higher concentrations in our study, when compared with FP labeling, is the use of an antistatic chamber. In a previous crossover study, we found that FP concentrations were increased by an average of 65% when compared with static VHC.⁵

The clinical relevance of our finding of increased systemic exposure with the use of an antistatic VHC is unclear. In adults,

TABLE I. Demographics and results of subjects who completed the study

	Age (y)	Gender, male:female	Race, Caucasian: African American: Hispanic	Body mass index (kg/m ²)	Duration of FP treatment (d)	1-h FP plasma concentration (pg/mL), geometric mean (95% CI)
1-4 y VHC/mask (n = 12)	2.8 $\pm$ 0.8	10:2	9:3:0	16.76	5.2 $\pm$ 1.7	156 (124-196)
5-9 y VHC/mask (n = 13)	6.2 $\pm$ 0.8	8:5	8:5:0	18.73	6.2 $\pm$ 3.2	127 (95-170)
5-9 y VHC/mouthpiece (n = 12)	6.5 $\pm$ 1.0	8:4	5:7:0	19.49	6.4 $\pm$ 2.6	164 (104-260)
5-9 y Actuator alone (n = 12)	8.1 $\pm$ 1.1	7:5	7:5:0	18.67	6.8 $\pm$ 6.4	67 (43-106)
12-18 y Actuator alone (n = 12)	15.1 $\pm$ 1.6	8:4	7:4:1	27.20	6.5 $\pm$ 3.8	57 (34-96)*

*Significantly lower than all groups using a VHC.

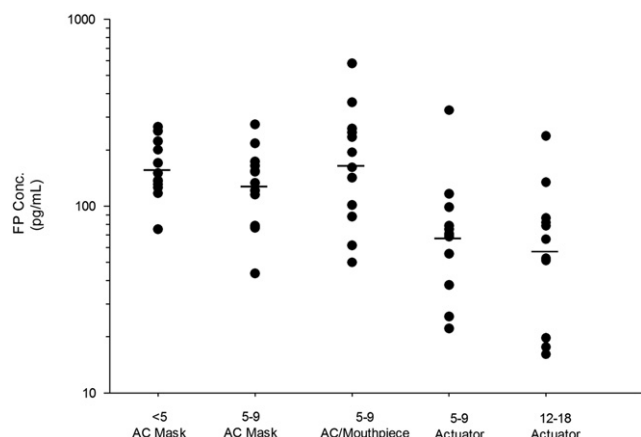


FIG 1. Peak steady-state fluticasone concentrations. The geometric means (95% CI) in pg/mL were as follows: 12-18 year, 57 (34-96); 5-9 year actuation alone, 67 (43-106) ($P = .75$); 5-9 year VHC/mouthpiece, 164 (104-260) ($P = .0006$); 5-9 year VHC/mask, 127 (95-170) ($P = .07$); and 1-4 year VHC/mask, 156 (124-196) ($P = .016$). The 12 to 18 year group values were significantly lower than those of all groups receiving drug through a chamber ($P = .003$).

the plasma concentration of FP producing a 50% decrease in maximal cortisol secretion was 100 pg/mL.⁶ The corresponding value for children is unknown. However, Eid et al⁷ reported a dose-dependent decrease in 8 AM cortisol concentrations in children receiving long-term therapy with FP through a conventional (static) VHC. In those receiving 440 μ g/day, the dose administered in our study, 35% had an abnormal cortisol concentration that subsequently normalized after dose reduction. In contrast, Lipworth et al⁸ did not find a difference in overnight urinary cortisol/creatinine excretion between 200 and 400 μ g/day 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.⁹ We, therefore, recommend initiating therapy with a lower dose of FP (176 μ g/day) or reducing the dose as soon as asthma control is achieved if therapy is initiated with 440 μ g/day.

In addition, the differences between our results and previous GlaxoSmithKline studies suggest the need for a longer-term clinical trial assessing the safety of delivering FP HFA through an antistatic VHC.

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METHODS

Subjects

Subjects were excluded from the study if they were not fully cooperative, if they could not be taught optimal inhalation technique with one of the test methods, if they were unable to discontinue intranasal or dermal fluticasone for the duration of the study, if they experienced an increase in asthma symptoms during the study, or if a urine pregnancy test was positive in females 12 to 18 years of age.

Subjects older than 5 years provided verbal assent. Also, the study was approved by the US Food and Drug Administration as an investigator-sponsored Investigational New Drug Application (#64,917) since the use of an MDI is not approved in children younger than 4 years.

Based on previous studies, the correlation between $C_{\max}$ and area under the curve was 0.94.^{E1,E2}

Study design

Subjects 12 to 18 years of age were the reference group. These subjects used the actuator alone with an optimal technique. Using the closed-mouth MDI method, the technique involved shaking the canister, simultaneously depressing the canister and breathing in slowly and deeply, and holding their breath for 10 seconds. This process was repeated for the second puff. Subjects 5 to 9 years of age were divided into 3 groups on the basis of the device they could optimally use: actuator alone, a VHC with mouthpiece, or a VHC with mask. Initially, these subjects attempted the actuator alone using the above technique. However, if they were unable to do this optimally, they were tested with a VHC with mouthpiece using the following technique: shake canister, place mouthpiece in mouth, depress canister and simultaneously breath in slowly and deeply so that the whistle does not sound, hold breath for 10 seconds, remove chamber/mouthpiece, and repeat the process with a second puff. However, if the children were unable to use the VHC with mouthpiece effectively, they were tested with the VHC with mask by using the following technique: shake canister, fit optimal-sized mask around nose and mouth without leaks, depress the canister, watch inhalation valve flip 6 times, remove chamber/mask, and repeat the process with a second puff. Similarly, children 1 to 4 years of age used a VHC with mask with the same technique.

Measurements

The lower limitation of quantification for the FP plasma concentrations measured by a liquid chromatography-mass spectrometry assay^{E3} was 5 pg/mL, and the coefficient of variation for within-assay precision was 13% at 5 pg/mL, 9.2% at 20 pg/mL, and 4.4% at 50 pg/mL.

RESULTS

The majority of subjects who completed this study were males (Table E1). Caucasians comprised the majority of subjects (36 of

61, 59%), with African Americans (24 of 61, 39%) and 1 Hispanic subject accounting for the rest of the group (Table E1). The mean duration of therapy was 5 to 7 days (Table E1).

DISCUSSION

In adults, studies have shown that the VHC increases drug delivery to the lungs.^{E4,E5} However, in children, previous studies have indicated that lung bioavailability of albuterol^{E6} and budesonide^{E7} when delivered by a VHC/mask with an antistatic treatment was reduced in preschool children compared with older children receiving the drugs through a VHC/mouthpiece. So why, then, would systemic exposure between the 1 to 4 year and 5 to 9 year groups in our study receiving the drug through a VHC/mask not be significantly different? The most likely explanation is that the reduced volume of distribution and hepatic blood flow because of a smaller body weight^{E8} (ie, lower clearance) in the 1- to 4-year-old age group compensates for reduced lung bioavailability, thus achieving similar plasma concentrations as in the older age group using a VHC. Anhøj et al^{E7} made a similar observation by using 8-hour budesonide plasma concentrations.

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TABLE E1. Individual demographic data, results, and ICS history

Patient no.	Sex	Age (y)	Race	Weight (kg)	Height (cm)	Body mass index (kg/m ²)	FEV ₁ (L) (%)	Duration (d)	FP Conc. (μg/mL)	Previous inhaled corticosteroids (μg/d)
<i>Aerochamber with mask, 1-4 y</i>										
1	M	2.8	AA	14.5	97.0	15.4		7	136	Flovent MDI 440
2	M	2.1	AA	10.5	74.0	19.2		6	137	Flovent MDI 440
3	M	2.1	AA	10.9	76.0	18.9		6	170	Flovent MDI 440
4	M	2.1	C	13.6	84.5	19.0		5	150	Flovent MDI 440
5	M	2.8	C	13.0	88.5	16.6		8	222	Flovent MDI 440
6	M	3.9	C	16.0	101.0	15.7		4	200	Flovent MDI 220
7	M	3.9	C	16.1	101.4	15.7		4	130	Flovent MDI 220
8	F	2.6	C	12.5	86.2	16.8		8	266	Flovent MDI 440
9	M	3.0	C	12.6	91.4	15.1		4	252	Flovent MDI 440
10	M	3.8	C	17.7	102.0	17.0		4	126	Flovent MDI 440
11	M	1.9	C	4.6	78.0	7.6		4	117	Flovent MDI 440
12	F	2.5	C	18.1	92.7	21.1		3	75	Flovent MDI 440
Mean		2.8		13.3	89.4	16.5		5		403
SD		0.7		3.7	10.0	3.4		2		86
GM									156	
95% CI									124-196	
<i>Aerochamber with mask, 5-9 y</i>										
13	M	7.0	AA	32.5	124.0	21.1	1.26 (79)	7	121	Flovent MDI 440
14	F	6.8	C	22.7	119.0	16.0	1.00 (74)	4	164	Flovent MDI 440
15	M	5.9	C	17.3	106.7	15.2	Unable	8	77	Flovent MDI 440
16	M	5.1	AA	33.6	121.9	22.6	Unable	4	154	Flovent MDI 440
17	F	6.5	AA	21.3	110.5	17.4	Unable	5	121	Flovent MDI 440
18	M	5.6	C	19.9	110.0	16.4	Unable	5	133	Flovent MDI 440
19	F	5.3	AA	18.0	113.0	14.1	Unable	4	216	Flovent MDI 110
20	M	5.8	C	22.4	119.0	15.8	1.32 (96)	7	173	Flovent MDI 440
21	M	6.6	C	27.6	126.4	17.3	1.89 (120)	3	78	Flovent MDI 440
22	M	6.5	C	32.2	125.7	20.4	1.61 (104)	3	274	Flovent MDI 440
23	M	7.5	C	42.0	123.0	27.8	1.14 (83)	15	44	Flovent MDI 440
24	F	5.0	C	19.3	95.3	21.3		7	115	Flovent MDI 440
25	F	7.0	AA	22.7	120.0	15.8	1.06 (76)	8	153	Flovent MDI 440
Mean		6.2		25.5	116.5	18.6		6		415
SD		0.8		7.5	9.0	3.9		3		92
GM									127	
95% CI									95-170	
<i>Aerochamber with mouthpiece, 5-9 y</i>										
26	M	7.4	AA	32.2	131.0	18.8	1.60 (90)	5	142	Flovent MDI 440
27	M	7.5	AA	26.8	123.0	17.7	Unable	4	88	Advair Diskus 250
28	F	7.2	C	38.6	129.5	23.0	1.69 (98)	10	194	Flovent MDI 440
29	M	6.5	AA	25.3	116.8	18.5	1.05 (99.9)	4	248	Flovent MDI 440
30	F	5.6	AA	20.0	109.0	16.8	Unable	5	259	Flovent MDI 440
31	M	5.8	AA	18.6	112.0	14.8	Unable	7	62	Flovent MDI 440
32	M	5.2	C	39.5	150.0	17.6	Unable	9	234	Flovent MDI 440
33	M	5.2	AA	36.8	122.0	24.7	Unable	10	101	Flovent MDI 440
34	F	5.6	C	26.5	120.5	18.3	Unable	3	580	Flovent MDI 440
35	M	6.5	C	25.0	NR	NA	Unable	4	50	Flovent MDI 440
36	M	7.4	AA	38.9	128.0	23.7	Unable	9	161	Flovent MDI 440
37	F	7.7	C	30.9	125.7	19.6	Unable	7	360	Flovent MDI 440
Mean		6.5		29.9	124.3	19.4		6		424
SD		1.0		7.4	11.0	3.1		3		55
GM									164	
95% CI									104-260	
<i>Actuator alone, 5-9 y</i>										
38	M	7.2	AA	29.5	127.0	18.3	1.10 (67)	3	22	Flovent MDI 440
39	M	9.4	AA	24.5	133.5	13.7	1.34 (72)	4	38	Flovent MDI 440
40	F	8.9	AA	37.3	132.0	21.4	1.44 (79)	3	71	Flovent MDI 220
41	F	9.6	C	39.5	142.5	19.5	1.51 (66)	26	116	Flovent MDI 440

(Continued)

TABLE E1. (Continued)

Patient no.	Sex	Age (y)	Race	Weight (kg)	Height (cm)	Body mass index (kg/m ²)	FEV ₁ (L) (%)	Duration (d)	FP Conc. (μg/mL)	Previous inhaled corticosteroids (μg/d)
42	M	7.5	C	23.3	127.0	14.4	1.65 (103)	5	56	Flovent MDI 440
43	M	9.0	AA	25.6	122.5	17.1	1.21 (100)	9	79	Advair Diskus 500
44	M	9.0	C	25.0	128.0	15.3	1.35 (83)	4	99	Flovent MDI 440
45	F	6.5	C	29.1	123.0	19.2	1.55 (106)	7	75	Flovent MDI 440
46	F	8.3	C	28.2	125.0	18.0	1.42 (91)	3	69	Flovent MDI 440
47	F	8.6	AA	41.8	127.4	25.8	1.41 (86)	8	70	Advair Diskus 500
48	M	8.1	C	41.8	136.0	22.6	1.66 (82)	6	26	Advair Diskus 500
49	M	6.1	C	30.2	127.0	18.7	1.61 (88)	3	326	Advair Diskus 250
Mean		8.2		31.3	129.2	18.7		6.8		421
SD		1.1		6.9	5.8	3.4		6.4		91
GM									67	
95% CI									43-106	
<i>Actuator alone, 12-18 y</i>										
50	F	12.9	C	84.1	160.0	32.9	2.51 (80)	9	17.6	Flovent MDI 220
51	M	16.2	AA	87.3	167.5	31.1	3.02 (85)	7	237.5	Flovent MDI 110
52	M	15.9	C	80.9	170.2	27.9	3.77 (102)	3	16.1	Flovent MDI 440
53	M	17.9	H	70.0	172.7	23.5	3.30 (85)	3	133.9	Flovent MDI 440
54	F	15.7	AA	103.6	173.0	34.6	2.48 (100)	14	66.4	Advair Diskus 500
55	M	14.2	C	62.7	172.5	21.1	3.47 (90)	6	51.1	Pulmicort DPI 200
56	F	15.9	AA	99.4	173.0	33.2	2.47 (77)	6	78.4	Advair Diskus 500
57	F	14.4	C	65.5	159.0	25.9	3.33 (109)	13	52.5	Advair Diskus 500
58	M	12.9	C	30.3	147.3	14.0	2.22 (91)	7	81.7	Advair Diskus 500
59	M	15.1	AA	101.8	172.0	34.4	3.29 (86)	4	19.7	Pulmicort DPI 400
60	M	13.6	C	38.6	142.0	19.1	2.08 (93)	9	66.4	Flovent MDI 440
61	M	16.8	C	76.8	175.9	24.8	4.35 (107)	4	86.2	Flovent MDI 440
Mean		15.1		75.1	165.4	26.9		7		391
SD		1.6		23.3	11.1	6.7		4		135
GM									56.9	
95% CI									34-96	

AA, African American; C, Caucasian; DPI, dry powder inhaler; H, Hispanic; MDI, metered-dose inhaler; NR, not recorded.