

Flunisolide hydrofluoroalkane with integrated spacer for treating asthma: An updated review

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ABSTRACT

Flunisolide hydrofluoroalkane (HFA) with integrated spacer is the most recent reformulated inhaled corticosteroid (ICS) for asthma available in the United States. It is the only product that combines a corticosteroid extrafine aerosol with a built-in spacer. The potential clinical benefit of the flunisolide HFA formulation and its integrated spacer for treating persistent asthma was assessed through a comprehensive review of the published literature and data from the past 10 years focusing on (1) flunisolide, the molecule, and the impact of the HFA reformulation; (2) updated information on the anti-inflammatory response to flunisolide HFA, particularly in the distal airways; and (3) the usefulness of an integrated spacer. Flunisolide HFA was found effective and safe in clinical studies and comparable with the chlorofluorocarbon (CFC) formulation, but at about one-third the dose of flunisolide CFC, likely reflecting both the device and the particle size of the reformulated product. Compared with the CFC formulation, the extrafine aerosol and smaller particle size of flunisolide HFA substantially increased pulmonary deposition and decreased oropharyngeal deposition. The integrated spacer further enhanced the pulmonary/oropharyngeal deposition ratio. Examination of lung biopsy specimens indicated a favorable anti-inflammatory response to flunisolide HFA in peripheral airways. Pediatric studies showed no significant effects on growth. The data indicate that flunisolide HFA is a safe and effective maintenance therapy for asthma patients. The integrated spacer may provide an added advantage for patients, especially those who may be more likely to experience adverse effects of ICSs, both local and systemic, including children susceptible to adverse effects on growth.

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Asthma affects 18.7 million adults and 6.8 million children in the United States or just >8% of the population.^{1,2} Annually, it accounts for ~16 million outpatient visits, 2 million emergency department visits, and 500,000 hospitalizations (average duration, 3.6 days).^{3–6} The mortality rate is estimated at 1.1 per 100,000 population or just over 3400 annually.⁷

The cost of the disease in terms of direct medical expenditures and lost school and work days, was estimated at \$56 billion in 2007, and according to the national databases the costs are continuing to trend upward.⁸

Good asthma control can be achieved for the majority of patients—those with mild-to-moderate persistent disease. The preferred maintenance therapy for these patients remains an inhaled corticosteroid (ICS).⁹ Although the general characteristics of the corticosteroid molecules have not changed significantly over the past

30 years, the 1987 Montreal Protocol on Substances that Deplete the Ozone Layer provided an opportunity to reformulate and repackage some of the available ICSs while eliminating the chlorofluorocarbon (CFC) propellant from metered-dose inhalers (MDIs).¹⁰ Reformulating the marketed products improved certain features—notably, the risk/benefit profile, depth of delivery into the lungs, and ease of delivery for the patient.¹⁰ Today's ICS formulations tend to have smaller particle sizes and greater respirable fractions, and the newer delivery devices may better meet the needs of some patients who have difficulty inhaling a drug.

A recent example is flunisolide, which was discovered in 1965 and was approved in the United States as a CFC-propelled MDI for the treatment of asthma (Aerobid; Forest Pharmaceuticals, Inc.) in 1981. Flunisolide was subsequently reformulated with a hydrofluoroalkane (HFA) propellant in response to the 1987 Montreal Protocol. (AerospanTM [flunisolide] Inhalation Aerosol, developed by Forest Pharmaceuticals, Inc., was approved in 2006. The product was acquired by Acton Pharmaceuticals, Inc. [Marlborough, MA] in 2009, and labeling was revised in August 2013. Meda Pharmaceuticals Inc. [Somerset, NJ] acquired Acton in October 2013 and began marketing Aerospan in March 2014.)

While the corticosteroid, flunisolide, is the same molecule, the reformulated HFA MDI (AerospanTM [fluni-

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Figure 1. The flunisolide hydrofluoroalkane metered-dose inhaler (HFA MDI) with integrated spacer. (Photograph courtesy of Meda Pharmaceuticals, Inc.)

solide] Inhalation Aerosol, Meda Pharmaceuticals Inc., Somerset, NJ) differs from the older CFC product with respect to three clinically important features.¹¹

1. It is a solution, not a suspension.
2. It delivers an extrafine aerosol from the device, with smaller and more uniform particles—mass median aerodynamic diameter (MMAD) of 1.2 μm versus 3.8 μm for the CFC formulation.^{12–15}
3. It is manufactured with a 50-mL integrated spacer.

The integrated spacer is shown in Fig. 1. After priming, each actuation delivers 139 μg of flunisolide from the actuator (canister valve) and 80 μg of flunisolide from the distal end of the spacer (the mouthpiece) at a flow rate of 30 L/min for 4 seconds.⁹

Several excellent reviews have described the pharmacologic and clinical properties of flunisolide HFA in relation to safety and efficacy.^{13,16,17} Building on those reviews and data made available in the past 10 years, this article provides an update of the potential clinical benefits of flunisolide HFA and its integrated spacer for treating patients with persistent asthma.

METHODS

Multiple MEDLINE searches from 1966 through June 2014, limited to English language and humans, were conducted.

The primary topic was “flunisolide” (searched as keyword, using “fluocinolone acetonide” as subject heading), which was combined with the terms, “HFA” and “anti-asthmatic agents.” The results (67 citations) were separately combined with the terms, “clinical efficacy,” “safety,” and “anti-inflammatory activity”;

and the results of these individual searches provided the basis for the review of flunisolide HFA.

Each search was subsequently limited using the term, “clinical trial,” as publication type, to also identify appropriate clinical studies. This resulted in 24 citations, the abstracts of which were reviewed as to the following criteria: clinical study of efficacy and/or safety of flunisolide HFA as approved in the United States. Four papers met these criteria and are summarized in Table 1.^{12,18–20} Studies that reported nonclinical outcomes (*e.g.*, patient preferences, pharmacoeconomics, and device comparisons) or that reported on unapproved uses (*e.g.*, acute asthma and children < 6 years old) were excluded. The medical report for an additional study was acquired through communication with the sponsor.^{12,18–21}

The review of spacers in this article is based on a separate simple MEDLINE search using the terms, “spacer device,” “spacer,” or “add-on spacer,” and applying the limits, English language and humans. This yielded 275 articles, the abstracts of which were reviewed for relevance.

Additionally, relevant references were used from author recommendations and from the bibliographies of the specific articles reviewed.

CLINICAL EFFICACY AND SAFETY

Flunisolide CFC was safely and effectively used in children and adults with asthma for >20 years before reformulation was mandated. The clinical studies evaluating the efficacy and/or safety of flunisolide HFA are summarized in Table 1 and include one 12-week study¹² and one 52-week study¹⁸ in adults and adolescents, ≥ 12 years old (450 subjects exposed to flunisolide HFA, 162 for 1 year) and three trials in pediatric subjects (4–11 years old): one for 12 weeks²¹ and two for 52 weeks^{19,20} (505 subjects exposed to flunisolide HFA, 274 for 1 year). Three studies (one adult and two pediatric) were placebo-controlled.^{12,20,21} The other two studies used an open-label parallel-group design that compared flunisolide HFA with beclomethasone dipropionate CFC,^{18,19} and, in children, also to cromolyn sodium.¹⁹ The 12-week, placebo-controlled trials directly compared treatment with flunisolide HFA with its flunisolide CFC predecessor.^{12,21}

At the time these studies were performed, it was thought that the delivered doses of flunisolide were 85, 170, and 340 μg , and the articles report those doses. However, subsequent evaluations determined the actual delivered doses to be 80, 160, and 320 μg , respectively.¹¹ As such, we note both the cited dose as reported in the study publication and the actual dose based on the subsequent evaluation.

In these studies, treatment with flunisolide HFA was effective and safe at about one-third the CFC

Table 1. A summary of some of the key the outcomes of clinical studies with flunisolide HFA

Parameter	Adult Studies		Pediatric Studies		
	Casale <i>et al.</i> ¹⁸	Corren <i>et al.</i> ¹²	Meadow ¹⁹	Gillman <i>et al.</i> ²⁰	Bensch <i>et al.</i> ²¹
Placebo-controlled	No	Yes	Yes	No	Yes
Duration	52 wk	12 wk	12 wk	52 wk	52 wk
No. of subjects	215	669	653	235	249
Mean age, yr (range)	33.1 (12–60)	36	(4–11)	8.3 (4–11)	6.4 (4–9.5)
Asthma severity	Mild to moderate	Mild to moderate	Mild to moderate	Mild to moderate	Mild, persistent
Flunisolide HFA, dose (n)	1–4 puffs b.i.d., 85 µg/puff as reported; actual dose: 80 µg/puff (162)	1, 2, and 4 puffs b.i.d., 85 µg/puff as reported; actual dose: 80 µg/puff (75, 100, and 113, respectively)	1 and 2 puffs b.i.d., 85 µg/puff as reported; actual dose: 80 µg/puff (114 and 117, respectively)	2 puffs b.i.d., 85 µg/puff as reported; actual dose: 80 µg/puff (152)	2 puffs b.i.d., 85 µg/puff as reported; actual dose: 80 µg/puff (122)
Comparators, doses (n)	BDP-CFC: 3–4 puffs b.i.d., 84 µg/puff (53)	Placebo b.i.d. (104); FLU-CFC: 1.2, 4 puffs b.i.d., 250 µg/puff (76, 103, and 98, respectively)	Placebo b.i.d. (116); FLU-CFC: 1 and 2 puffs b.i.d., 250 µg/puff (123 and 113, respectively)	BDP-CFC: 2 puffs b.i.d., 84 µg/puff (39); CROM: 4 puffs q.i.d., 400 µg/puff (44)	Placebo b.i.d. (127)
Primary variables	Safety (1)	FEV ₁ , change from baseline	FEV ₁ , change from baseline	Safety (1); growth (2)	Growth (2)
Primary outcomes	All Tx safe, well tolerated; no HPA axis effects; <i>Candida albicans</i> : FLU-HFA, 1.2%; BDP-CFC, 9.4% (<i>p</i> = 0.0004)	Comparable dose response for HFA and CFC vs placebo	Comparable improvements for HFA and CFC vs placebo with no clear dose response for either	Increase in height: FLU-HFA = CROM (6.2 cm) > BDP-CFC (5.1 cm); growth velocity (cm/yr): FLU-HFA, 6.2; BDP, 5.3; CROM, 6.9; all Tx safe, well tolerated; no HPA axis effects; <i>C. albicans</i> : FLU-HFA, 13.7%; BDP-CFC, 21.4%; CROM, 3.6%	Increase in height: FLU-HFA, 6.14 cm; P, 6.31 cm; growth velocity (cm/yr): FLU-HFA, 6.01; P, 6.19
Secondary variables	Efficacy (3)	Efficacy (3); asthma Sx; safety (1)	Efficacy (3); safety (1)	Efficacy (3)	Radiographic bone age; <i>C. albicans</i> cultures
Secondary outcomes	Comparable improvements in efficacy	Comparable improvements in efficacy and Sx: trending FLU-HFA > FLU-CFC but did not reach significance; all Tx safe, well tolerated; no HPA axis effects; <i>C. albicans</i> : FLU-HFA, 1.2%; P, 0.9%	Comparable improvements in efficacy for HFA and CFC vs placebo with no clear dose response for either; all Tx safe, well tolerated; no HPA axis effects; <i>C. albicans</i> : FLU-HFA, 1 puff, 1.8%; FLU-HFA, 2 puffs, 0%; FLU-CFC, 1 puff, 0.8%; FLU-CFC, 2 puffs, 0.9%; P, 0%	Comparable improvements in efficacy	Comparable: mean radiographic bone age, 6.7 yr for both; <i>C. albicans</i> , 0.8% for both

At the time these studies were performed, it was thought that the delivered doses were 85, 170, and 340 µg; and the articles and clinical study reports cite those doses. However, subsequent evaluations determined the actual delivered doses to be 80, 160, and 320 µg, respectively.¹¹ Both, the dose as reported in the study publication and the actual dose based on the subsequent evaluation are shown.

(1) Safety variables included: AEs: clinical lab values; HPA axis function; *C. albicans* throat cultures. (2) Growth variables included: absolute change in height and growth velocity. (3) Efficacy variables included: FEV₁, p_{rn} albuterol, morning and evening PEFR, nocturnal awakenings.

AE = adverse event; BDP = beclomethasone dipropionate; b.i.d. = twice daily; CFC = chlorofluorocarbon; CROM = cromolyn sodium; FEV₁ = forced expiratory volume in 1 second; FLU = flunisolide; HFA = hydrofluoroalkane; HPA = hypothalamic–pituitary–adrenal axis; P = placebo; PEFR = peak expiratory flow rate; p.r.n. = as needed; q.i.d. = 4 times a day; Sx = symptoms; Tx = treatment.

dose.^{12,18–21} No suppression of the hypothalamic–pituitary–adrenal (HPA) axis was evident in children and adults studied for up to 1 year.^{18,19} Oral candidiasis was low, ~1–2% in four studies,^{12,18,20,21} and comparable with placebo in the studies that included a placebo arm.^{12,20,21}

Flunisolide HFA is approved for the treatment of asthma in children as young as 6 years of age, making growth an important safety consideration. Controlled clinical studies have shown that ICSs may cause a reduction in growth velocity in pediatric patients.^{22–26} In these studies, the mean reduction in growth velocity was ~1 cm/yr (range, 0.3–1.8 cm/yr) for the first several years of treatment in relation to the dose and duration of exposure. The reduction in growth was observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity may be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than other commonly used measures of HPA axis function. Although the full significance of the ICS-related decrease in growth for final adult height remains unclear, the U.S. Food and Drug Administration requires disclosure of potential growth effects.

Growth velocity was the primary outcome variable in 2 year-long pediatric studies of flunisolide HFA.^{19,20} In the study by Bensch *et al.*, 163 prepubescent children (4–10 years old) with mild persistent asthma completed 1 full year of twice-daily (b.i.d.) treatment with either placebo or flunisolide HFA at a reported dose of 170 µg (actual dose, 160 µg), which is the maximum dose for children 6–11 years old.¹⁹ The growth curves of the two groups overlapped, with no significant differences in growth observed at any time point. The respective growth velocities for flunisolide HFA and placebo were 6.43 ± 1.77 (SD) and 6.75 ± 1.12 cm/yr for 4- to 5-year-old children and 5.68 ± 1.84 cm/yr (SD) and 5.70 ± 1.24 cm/yr for the 6- to 9-year-old children. Additionally, bone maturation, measured by wrist radiography, was also comparable between groups.¹⁹ The data support similar findings of a previous open-label study in children (4–11 years old) with mild-to-moderate asthma that found no differences in linear growth or growth velocity between flunisolide HFA and the active control, cromolyn sodium (known to not affect growth), over the course of 1-year treatment.¹⁹

PHARMACOKINETICS AND PHARMACODYNAMICS

The clinical profile of an inhaled glucocorticoid reflects its pharmacokinetic and pharmacodynamic properties.²⁷ When the HFA formulation is compared with the older CFC formulation (Table 2), the pharmacologic profile of flunisolide has not changed with

Table 2. Pharmacokinetic characteristics (value ± SD) of flunisolide HFA (dose as reported, 340 µg b.i.d.; actual, 320 µg b.i.d.) compared with flunisolide CFC (1000 µg b.i.d.) on day 1 of treatment in healthy subjects

pK Characteristic	Flunisolide CFC (1000 µg b.i.d.)	Flunisolide HFA (340 µg b.i.d.)
Flunisolide		
C _{max} (ng/mL)	2.62 ± 1.19	2.51 ± 1.19
AUC _{0–tlast} (ng/hr/mL)	4.65 ± 1.61	2.78 ± 1.19*
t _{max} (hr)	0.12 ± 0.09	0.10 ± 0.03
t _{1/2} (hr)	1.46 ± 0.19	1.37 ± 0.26
Cl/F (L/hour)	210 ± 89	137 ± 51*
Vd/F (L)	445 ± 192	260 ± 80*
6β-OH-flunisolide		
C _{max} (ng/mL)	0.86 ± 0.20	0.23 ± 0.08**
AUC _{0–tlast} (ng/hr/mL)	3.14 ± 0.72	0.66 ± 0.39**
t _{max} (hr)	1.00 ± 0.46	1.18 ± 0.49

Similar trends were observed after 14 days of treatment.¹⁵

p* < 0.05; *p* = 0.0001.

AUC_{0–tlast} = area under the drug concentration–time curve from time 0 to the last time measured; b.i.d. = twice daily; CFC = chlorofluorocarbon; Cl/F = oral clearance; C_{max} = maximum observed drug concentration; HFA = hydrofluoroalkane; pK, pharmacokinetics; t_{1/2} = terminal half-life; t_{max} = time of the maximum plasma drug concentration; Vd/F = apparent volume of distribution.

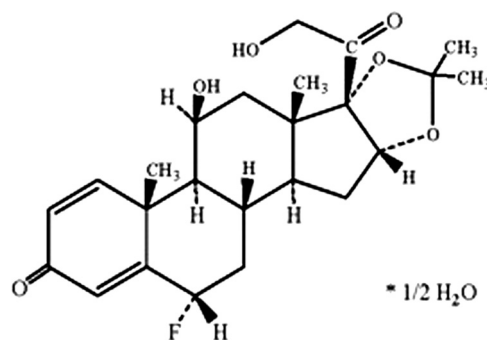
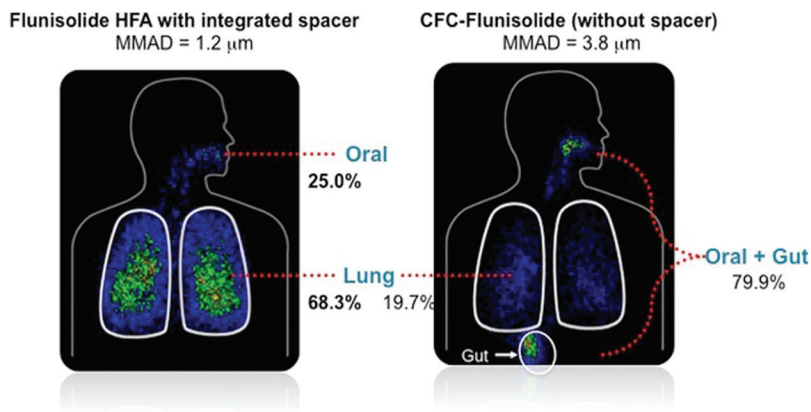


Figure 2. The chemical structure of flunisolide.

regard to the underlying molecular characteristics, specifically,

- The molecule has a hydroxyl on carbon position 21 (Fig. 2), which is available for esterification with fatty acids in the lungs, a property suggested to enhance the volume of distribution and possibly increase pulmonary retention time.^{16,17}
- Flunisolide has a very short plasma elimination half-life.^{28–30}

Figure 3. Lung scintigraphy deposition patterns of ^{99m}Tc -radiolabeled flunisolide hydrofluoroalkane (HFA) and flunisolide chlorofluorocarbon (CFC) within the respiratory tract from a single-dose scintigraphy trial in 12 healthy subjects. The results represent average oral and lung deposition as shown in a representative subject.^{14,31} (Photograph courtesy of Meda Pharmaceuticals, Inc.)



- Hepatic first-pass metabolism is rapid and extensive with ~93% of the molecule undergoing conversion to the mostly inactive metabolite, 6β-OH-flunisolide (activity, 10 times less than cortisol).^{28–30}
- Protein binding is ~80%.¹⁷
- Clearance occurs quickly, regardless of the administered dose and despite the relatively low level of protein binding. Within 12 hours of dosing, the molecule is not detectable in plasma.¹⁷
- Flunisolide has a relatively low affinity for the glucocorticoid receptor, a property that may be offset by greater lung deposition of flunisolide HFA, related to its extrafine particle size, and possibly to lipid conjugation in the lung.^{16,17}

The pharmacologic properties of flunisolide are well described in the published reviews.^{13,16,17}

What has changed in the pharmacologic profile of flunisolide with regard to the HFA formulation is its oral bioavailability as related to altered distribution patterns between the lung and the oropharynx. The change reflects the size of the particles emitted from the device and their subsequent deposition in the airways compared with the CFC MDI.^{13–17,29}

The aerosol droplets emitted from the MDI with spacer have an MMAD of 1.2 μm, in contrast to the 3.8-μm MMAD of the suspension particles from the CFC MDI.^{12–15} Aerosol particles with MMAD < 4.7 μm are in the respirable range.³¹ Approximately 70% of the aerosol particles in a dose of flunisolide HFA are within the respirable range compared with ~30% of flunisolide CFC.¹⁸

Deposition studies using γ-technetium lung scintigraphy in 12 healthy subjects have shown that after inhalation of a single dose of labeled flunisolide HFA, ~68% of the labeled dose is deposited in the airways, 25% is deposited in the oropharynx, and the remainder is either exhaled or swallowed.¹⁴ For the CFC the numbers were reversed, with ~20% of the inhaled dose deposited in the airways and 79% found in the oropharynx and gastrointestinal (GI) tract (Fig. 3).

In agreement with increased pulmonary deposition for flunisolide HFA compared with flunisolide CFC, pharmacokinetic studies in healthy subjects have shown dose proportionality for the HFA product at about one-third of the CFC dose (when administered without a spacer) along with reduced systemic bioavailability (reflected in the lower Area under the drug concentration-time curve from time 0 to the last time measured which was 8 hours) related to lower oropharyngeal deposition and subsequent absorption into the GI tract.^{15,28} Flunisolide HFA satisfies a number of the properties considered “ideal” for an ICS (Table 3).²⁷

TARGETING THE SMALLER AIRWAYS

It is well documented that the underlying airway inflammation of asthma affects both the central and the peripheral airways and that ICSs reduce inflammation in the larger airways.^{31–33} As depth of reach increases with the newer extrafine HFA formulations, the question arises as to whether an effect on peripheral inflammation can be shown.

This question was first addressed in a small study involving 12 adult patients with mild-to-moderate asthma who were treated with flunisolide HFA (as reported, 340 μg b.i.d.; actual dose, 320 μg b.i.d.) for 6 weeks.³⁴ Before and after treatment endobronchial and transbronchial biopsy specimens were taken (reflecting large and distal airway pathology, respectively), and spirometry was performed.

The endobronchial and transbronchial biopsy specimens showed significant decreases in eosinophils and the eosinophil-associated cytokines, IL-5 and eotaxin, in both the central and the distal airways after treatment with flunisolide HFA. The investigators proposed that flunisolide HFA decreased eosinophilic inflammation by inhibiting mRNA transcription of IL-5 and eotaxin throughout the lungs, a hypothesis that requires further testing.³⁴ Significant increases in both forced expiratory volume at 1 second, as a measure of central airway function, and forced expiratory flow at

Table 3. Some ideal pharmacologic characteristics of an ICS²⁷ evaluated with regard to flunisolide HFA

Characteristic ²⁷	Why Considered Ideal	Does FLU-HFA Fulfill?	Comments
High RRA	Increased potential for topical anti-inflammatory activity at the site of deposition	No	Anti-inflammatory activity is a complex interplay between RRA, deposition (<i>e.g.</i> , particle size), and pulmonary retention time (<i>e.g.</i> , esterification) ^{16,17}
Small particle size	Increased depth of reach into the airways, even into smaller, peripheral airways	Yes	Solution aerosol
Minimal oral deposition	Decreased potential for local side effects in mouth and throat, and subsequent GI absorption and systemic AEs	Yes	Decreased oropharyngeal deposition with extrafine ICS aerosol, further decreased by integrated spacer ^{14,18,28}
High lung deposition, including peripheral airways	Increased potential for targeting of pulmonary inflammation	Yes	Increased pulmonary targeting likely related to smaller particle size and integrated spacer ^{14,18,28}
Esterification and lipid conjugation	Increased pulmonary retention time and potential for interaction with the glucocorticoid receptor in the airway; possible once-daily dosing	Yes	OH group at C21; Earlier data with flunisolide CFC suggested that once daily dosing might be possible, but data are needed for the HFA formulation ^{16,28}
Low oral bioavailability	Reduced potential for systemic AEs	Yes	
High systemic clearance	Reduced potential for systemic AEs	Yes	
High protein binding	Less free drug available to interact with systemic receptors reducing the potential for systemic AEs	No	Moderate protein binding may be tempered by high systemic clearance and low oral bioavailability ¹⁷

AEs = adverse events; C = carbon; CFC = chlorofluorocarbon; HFA = hydrofluoroalkane; GI = gastrointestinal; ICS = inhaled corticosteroid; OH = hydroxyl; RRA = relative receptor binding.

25–75%, as a measure of small airway function,^{13,34} occurred concomitant with the reduction in airway inflammation. Although this study did not compare the effects of flunisolide HFA on central and peripheral airways with those of a larger-particle suspension aerosol, it did show that the extrafine aerosol of flunisolide HFA was capable of suppressing allergic inflammation in the distal airways.

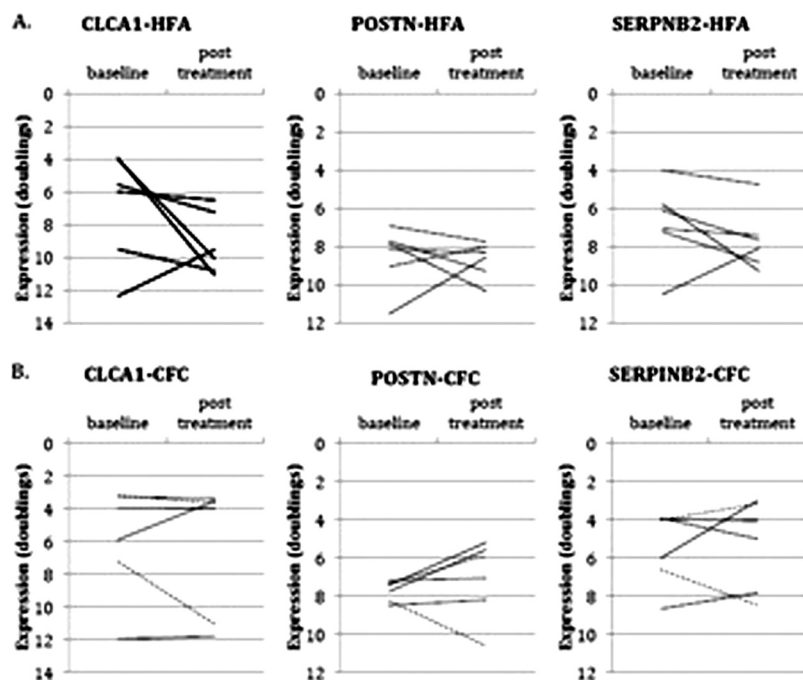
The biopsy specimens were also used by Bergeron *et al.*³⁵ to evaluate airway remodeling, using immunocytochemistry for collagen III, α -smooth muscle actin, and transforming growth factor β , a growth factor involved in airway remodeling and fibrosis.³¹

Remodeling, including collagen deposition and increased smooth muscle mass, is an important feature in the pathology of asthma, contributing to both airflow obstruction and bronchial reactivity.^{36,37} Studies with ICSs have shown little or no effect on remodeling in the

central airways, except at relatively high doses and relatively long treatment times.³⁸ With the reported 340- μ g dose of flunisolide HFA (actual dose, 320 μ g) given b.i.d. over 6 weeks of treatment, Bergeron *et al.*³⁵ showed a significant decrease in smooth muscle actin in peripheral but not central airways. Furthermore, the reduction in smooth muscle content correlated with functional improvement in small airway physiology, as reflected by a 20% improvement in forced expiratory flow at 25–75% ($p = 0.034$). No changes were determined for the other parameters of remodeling, in contrast to an *in vitro* study that reported significant inhibition of transforming growth factor β release when induced sputum cells from 12 patients with mild-to-moderate asthma were incubated with flunisolide (10 μ M).³⁹

A 6-week pilot study reported that treatment with flunisolide HFA, but not flunisolide CFC, substantially reduced expression of the asthma-related

Figure 4. Chloride channel accessory 1 (CLCA1), periostin (POSTN), and serpin peptidase inhibitor (SERPB2) in distal lung brushings from 12 patients with steroid-naïve mild-to-moderate asthma before and after treatment with flunisolide chlorofluorocarbon (CFC) or flunisolide hydrofluoroalkane (HFA). Subjects underwent bronchoscopy before and after 6 weeks of flunisolide CFC or flunisolide HFA; and distal samples were obtained via peripheral lung brushings. RNA was extracted from the brushings and genomic microarray was performed.⁴⁰ (Data provided courtesy of Michelle Zeidler, M.D., UCLA School of Medicine, Los Angeles, CA.)



genes—chloride channel accessory 1, periostin, and serpin peptidase inhibitor—in distal lung brushings (Fig. 4).⁴⁰

The available data suggest a favorable response in peripheral airways to flunisolide HFA, likely reflecting the extrafine particle size, greater peripheral lung deposition, and better accessibility in the thinner distal airways to its action on inflammatory and smooth muscle processes.^{27,39}

AN INTEGRATED SPACER

Although the change from CFC to HFA propellants led to the development of ICS formulations with more particles in the respirable range, it is important to note that all components of the MDI affect drug delivery.^{41–43} This includes the canister, the metering valve, and the actuator; and in the case of flunisolide HFA, it also includes the integrated spacer. The integrated spacer is a 50-mL tube extension of the MDI mouthpiece. To use the spacer, the patient pulls the actuator out and snaps it into an “L” shape (Fig. 1).¹¹

The spacer and the formulation contribute to less oropharyngeal and more pulmonary deposition as shown in a single-dose study comparing the HFA MDI with integrated spacer to the HFA MDI alone in 12 healthy subjects.¹⁴ γ -Scintigraphy indicated that ex-valve lung deposition of flunisolide nearly doubled with the integrated spacer (HFA MDI alone, 22.6%; HFA MDI with integrated spacer, 40.4%; $p < 0.01$) and oropharyngeal deposition decreased approximately fourfold (HFA MDI alone, 59.8%; HFA MDI with integrated spacer, 14.9%; $p < 0.01$).). This results in a deposition of 68.3% of the emitted ex-device dose (*i.e.*,

the percentage of emitted dose deposited within the lungs).¹⁴ Consistent with the changes in deposition, significantly lower levels of the metabolite, 6 β -OH-flunisolide, were observed in healthy volunteers after a single dose of the MDI with integrated spacer compared with the MDI alone, reflecting lower oropharyngeal deposition and GI absorption of the active drug.²⁸ Similar data are lacking in patients with asthma, and further studies are warranted.

These findings are not unexpected because other studies have shown that using any spacer, regardless of type or brand, increases pulmonary targeting concomitant with less deposition in the oropharynx.^{41,44–48} Understandably, with optimal inhalation technique most inhalers perform well and spacers add little benefit.^{49,50} However, optimal technique is an inconsistent reality⁵¹ and, as such, the question is whether most patients, if not all patients, should use a spacer—one with which they are comfortable.

A spacer—whether add-on or integrated—provides additional volume to capture the aerosol generated from an MDI. By increasing the distance between the MDI and the patient’s mouth, a spacer slows down the aerosol spray permitting both evaporation of the propellant and trapping, by inertial impaction within the spacer, of larger aerosol particles. The end result is lower oropharyngeal deposition and greater lung deposition.^{41–43,48} Commercially available add-on spacers range in volume from 20 to 750 mL (Table 4).⁴² The volume of the integrated flunisolide spacer is 50 mL.¹¹ Spacers are sufficiently important that in regions where commercially available spacers are not available or not affordable, devices have been devised from sim-

Table 4. Some commercially available add-on spacers in the United States, by category

Spacer	Volume (mL)	Inhaler Adapter
Valved holding chamber		
ACE MDI Holding Chamber (Smiths Medical, Dublin, OH)	170	None*
Aerochamber Plus FlowVu Anti-Static Valved Holding Chamber (Activis plc, aka Forest Laboratories, Parsippany, NJ)	145	Universal
Easivent Valved Holding Chamber (Mylan Specialty, Basking Ridge, NJ)	140	Universal
LiteAire (Thayer Medical Corp., Tucson, AZ)	158	Universal
Optichamber (Philips Healthcare, Andover, MA)	218	Universal
Tube Spacer		
RiteFlo (Destal Industries, Inc., Columbus, IN)	140	Universal
Reverse flow reservoir		
E-Z Spacer (FSC Pediatrics, Inc., Charlotte, NC)	700	None*

*MDI canister fits directly into the spacer.

MDI = metered-dose inhaler.

ple household items such as toilet paper rolls or plastic soda bottles.^{9,43,46}

Spacers are grouped into three categories by design: tubes, which are basically extensions to the inhaler mouthpiece; holding chambers, which usually have a one-way valve in the mouthpiece; and reverse-flow devices in which the spray is directed away from the patient into a bag or chamber from which the patient then inhales.^{9,41,42,52,53} Substantial differences exist between these three categories, so that the most appropriate design for the patient's age and ability should be carefully considered. This is particularly true for patients who have difficulty coordinating actuation of the inhaler with inspiration—notably, children, the elderly, the frail, and persons with arthritis or other conditions that reduce finger dexterity or strength. Hand-lung discoordination in these groups is well documented, and for these patients, valved holding chambers and reverse-flow devices, which permit separation of the actuation and inhalation steps, can help.^{41–43,45,50–54} As a tube design with no reservoir or holding chamber, the flunisolide integrated spacer would not be expected to affect issues relating to discoordination.

As drug delivery devices, MDIs are lightweight, easy to carry, and target the medication to the lung. Patient instructions appear relatively simple, but inconsistent dosing related to inefficient inhalation is a potentially serious problem.^{43,50} It is estimated that up to 90% of patients (average, 50%) struggle at some time with proper MDI technique, despite following the product instructions or being trained by a health care professional. In fact, many health care professionals do not know how to properly use an MDI.^{48,49,53,55} The optimal inhalation technique has four steps: after first exhaling, the patient (1) wraps his/her lips around the

mouthpiece; (2) begins to inhale through the mouth while at the same time pressing down on the canister to activate the device and release the drug; (3) continues to inhale the aerosol deeply, slowly, and steadily through the mouth, thereby minimizing excess deposition by inertial impaction in the oropharynx and central airways; and then (4) breath holds for 10 seconds to allow time for the smaller particles to deposit by gravitational sedimentation.^{43,48,49,55–58}

Inhaling before or after activating the MDI and inhaling with excessive force or too quickly, as well as nose breathing and forgetting to breath hold all contribute to inconsistent dosing.^{43,45,49,53,54} That these errors have clinical consequences was shown in an early study of bronchodilators: decreased bronchodilation was directly correlated with poor MDI inhalation technique.⁵⁹ An inverse correlation has been reported between asthma control and the number of inhaler technique errors observed in patients using ICSs delivered by MDIs.⁶⁰

These issues may be less significant for the newer HFA formulations, particularly those generating a relatively high proportion of extrafine aerosol particles. Nonetheless, regardless of formulation, particle size, and adequate technique, between 50 and 80% of the drug may be deposited in the oropharynx,^{48,49,54} thereby increasing the risk of oral candidiasis and dysphonia and increasing the drug's oral bioavailability and systemic exposure. These findings support the need for an auxiliary device (*i.e.*, spacer) even for the HFA reformulations to limit oropharyngeal deposition and enhance drug access to the airways.

Obviously, the type of spacer and how it is accepted and used by the patient will markedly affect the use and delivery of asthma medications and clinical outcomes. For add-on spacers, differences in performance

Table 5. Some advantages and disadvantages of using an add-on spacer with a MDI vs using an integrated spacer such as is available on the flunisolide HFA MDI

Characteristic	Add-On Spacer			Integrated Flunisolide Spacer
	Tube	Holding Chamber	Reverse Flow Reservoir	
Potential advantages				
Decreased oropharyngeal deposition with increased or maintained pulmonary deposition ^{41–43,48}	Yes	Yes	Yes	Yes
Improved coordination of actuation and inhalation ^{41–42,44,49,52,53}	No	Yes	Yes	No
Potential disadvantages				
Need for an additional prescription ⁴⁸	Yes	Yes	Yes	No
Added expense beyond the MDI ⁴⁸	Yes	Yes	Yes	No
May not be covered by insurer ⁴⁸	Yes	Yes	Yes	No (1)
May not be available through pharmacy/formulary (2) ⁴⁸	Yes	Yes	Yes	Yes
Variability in drug delivery possible (3) ⁵³	Yes	Yes	Yes	Yes
Reduced drug delivery from some plastic devices because of electrostatic charge, with requirement to wash carefully to dissipate ^{41–43,53}	Yes	Yes	No	No
Inconvenience of carrying an additional device, bulkiness ^{41,43,45}	Yes	Yes	Yes	No
Training required for how to put on and use the spacer in addition to training for using the pMDI ⁴¹	Yes	Yes	Yes	No
Possible loss of drug due to ill-fitting face masks or poor adaptor connections ^{41,42}	Yes	Yes	No	No
One-way valves may not operate efficiently at all likely inhalation pressures ⁴²	No	Yes	Yes	No
Need for maintenance/hygiene vs excessive washing, which may lead to a build-up of electrostatic charge on some plastic devices, reducing drug delivery ⁶²	Yes	Yes	Yes	No (2)
Increased potential for patient technique errors (e.g., multiple actuations into the spacer before inhalation; too long a delay between actuation and inhalation) ⁴¹	No	Yes	Yes	No

(1) Spacer is integrated and, thus, would not require separate coverage by insurer. (2) All delivery devices and accessory devices are subject to changes in availability at the level of the pharmacy and formulary. (3) Proper inhalation technique and maintenance are necessary for consistency in dosing from any device.

HFA = hydrofluoroalkane; MDI = metered-dose inhaler.

have been reported between different MDIs. This has led to the recommendation that spacers be used only with the MDIs for which they have been evaluated.^{41,61,62} Some potential disadvantages for spacers, both add-on and integrated, are shown in Table 5. Although no direct comparison exists, the flunisolide HFA MDI integrated spacer appears to negate many of the disadvantages associated with the accessory devices.

AUTHORS' COMMENTS

The main advantages of flunisolide HFA are its extrafine aerosol formulation and delivery with the integrated spacer, resulting in increased lung deposition throughout the airways and lower oropharyngeal ex-

posure. Patients who experience local side effects (e.g., throat irritation, thrush, and dysphonia) from spacerless devices should benefit the most. The reduced oral bioavailability may also provide an advantage for patients in terms of a decreased likelihood of systemic adverse effects, including, for children, negative effects on growth. Pediatric studies showing no adverse effects on growth and growth velocity are reassuring. There may also be advantages for patients who need a spacer but prefer a single integrated device rather than carrying an MDI and an add-on spacer.

Nonetheless, although increasing the user-friendliness of the delivery system may help some patients with asthma by making the daily treatment more simple, even an integrated spacer cannot replace proper

technique. No medication will work if it is not taken properly and consistently as directed. Although the flunisolide system seems almost intuitive compared with using an add-on spacer, the literature suggests that errors in technique are common even with the easiest of devices. All patients need formal training on how to properly use their MDIs (with or without spacers), and they need to have their technique reviewed regularly by health care professionals who themselves know how to properly use an inhaler. The lack of patient training and follow-up are both well documented.^{45,49,51} Likewise, the fact that many health professionals do not know how to properly use an inhaler—again, with or without a spacer—is well documented.^{45,49,51}

More data are needed to confirm the assumed clinical benefits and to determine whether ease of use enhances acceptability and compliance. At this stage of product development the best and most practical measure may simply be direct observation in the office or clinic of the reduction of critical errors in inhaler technique by a patient and its relation to subsequent improvement in clinical outcomes.

CONCLUSION

The reformulated flunisolide HFA with integrated spacer is the most recent ICS product for asthma on the market in the United States and the only product that combines a corticosteroid extrafine aerosol and built-in spacer. It is a safe and effective maintenance therapy for asthma patients, comparable with the established safety and efficacy of the CFC formulation without spacer, but at one-third the dose. Compared with flunisolide CFC, the HFA formulation also shows increased pulmonary and decreased oropharyngeal deposition. Although more studies are needed, the available data suggest that flunisolide HFA with integrated spacer may provide added advantage for patients with persistent asthma, especially those who may be more likely to experience adverse effects of ICSs, both local and systemic, and including children, who are susceptible to negative effects on growth.

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