



Characterization of respiratory deposition of fluticasone-salmeterol hydrofluoroalkane-134a and hydrofluoroalkane-134a beclomethasone in asthmatic patients

Chet L. Leach, PhD ^{*}; Philip J. Kuehl, PhD ^{*}; Ramesh Chand, MS ^{*}; Loren Ketai, MD [†]; Jeffrey P. Norenberg, PharmD [‡]; and Jacob D. McDonald, PhD ^{*}

^{*} Lovelace Respiratory Research Institute, Albuquerque, New Mexico

[†] Department of Radiology, School of Medicine, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

[‡] Radiopharmaceutical Sciences Program, College of Pharmacy, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

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ABSTRACT

Background: Fixed combination fluticasone-salmeterol is the most used anti-inflammatory asthma treatment in North America, yet no studies report the actual respiratory tract dose or the distribution of drug within the lungs. Inflammation due to asthma affects all airways of the lungs, both large and small. Inhaled steroid delivery to airways results from a range of drug particle sizes, with emphasis on smaller drug particles capable of reaching the peripheral airways. Previous studies suggested that smaller drug particles increase pulmonary deposition and decrease oropharyngeal deposition.

Objectives: To characterize the dose of fluticasone-salmeterol hydrofluoroalkane-134a (HFA) (particle size, 2.7 μm) delivered to asthmatic patients and examine the drug distribution within the lungs. The results were compared with the inhalation delivery of HFA beclomethasone (particle size, 0.7 μm).

Methods: A crossover study was conducted in asthmatic patients with commercial formulations of fluticasone-salmeterol and HFA beclomethasone radiolabeled with technetium Tc 99m. Deposition was measured using single-photon emission computed tomography/computed tomography gamma scintigraphy.

Results: Two-dimensional planar image analysis indicated that 58% of the HFA beclomethasone and 16% of the fluticasone-salmeterol HFA were deposited in the patient's lungs. The oropharyngeal cavity and gut analyses indicated that 77% of the fluticasone-salmeterol HFA was deposited in the oropharynx compared with 35% of the HFA beclomethasone.

Conclusions: The decreased peripheral airway deposition and increased oropharyngeal deposition of fluticasone-salmeterol HFA was a result of its larger particle size. The smaller particle size of HFA beclomethasone allowed a greater proportion of lung deposition with a concomitant decrease in oropharyngeal deposition.

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Introduction

The National Asthma Education and Prevention Program guidelines call for the use of monotherapy of an inhaled steroid along with a short-acting β -agonist as needed for the initial treatment of mild to moderate persistent asthma.¹ However, in the United States, contrary to the guidelines, nearly 70% of patients in this category are prescribed combination products as first-line therapy.² Recently, the US Food and Drug Administration provided further guidance regarding treatment of persistent asthma and placed emphasis on the use of single-agent inhaled corticosteroids

as first-line therapy. The Food and Drug Administration has further recommended limiting the long-term use of long-acting β -agonists with or without an inhaled corticosteroid.³ The question arises as to whether differences exist between particle sizes of combination products vs monotherapies that may affect safety and efficacy.

Fluticasone-salmeterol is the most prescribed fixed-combination anti-inflammatory inhaled product in North America, yet no published studies have characterized the actual dose of drug delivered to the respiratory tract of the patients or the distribution of drug within the lungs. Fluticasone-salmeterol hydrofluoroalkane-134a (HFA) is a metered-dose inhaler combination product that is classified as a drug suspension product. Such products rely on physical micronizing of the solid drug particle to as low a size as practical to reach the lungs and avoid oropharyngeal deposition. However, there is a physical limit to the particle size to which it can be micronized. Fluticasone-salmeterol HFA delivers a mean particle size of approximately 2.7- μm mass median aerodynamic diam-

Reprints: Chet Leach, PhD, Lovelace Respiratory Research Institute, 2425 Ridgecrest Drive, SE, Albuquerque, NM 87108; E-mail: cleach@lrri.org.

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eter. Previous studies have shown that similarly sized fluticasone propionate chlorofluorocarbon (Flovent; GlaxoSmithKline, Research Triangle Park, North Carolina; particle size, 2.6 μm) delivered 13% of the drug to the lungs with comparatively little penetration to the peripheral lung regions.⁴ The remaining delivered dose was deposited in the oropharynx.

More recent technology has enabled some steroids to be formulated as a solution product wherein the steroid is dissolved in the propellant, and particles much smaller than those used in traditional suspension technology can be generated by adjusting the droplet size of the spray. Thus, particle sizes more suited for total lung penetration could be produced. This smaller particle has the added benefit of reducing oropharyngeal deposition.⁵ One such solution-based product is HFA beclomethasone (QVAR; Teva Specialty Pharmaceuticals LLC, Horsham, Pennsylvania). Previous studies have shown that HFA beclomethasone lung deposition ranged from 50% to 60% in adults, with penetration to all lung airways.^{6–9} A recent article described the importance of reaching all airways, including the small airways, to maximize treatment of inflammation sites due to asthma.¹⁰ The purpose of this open-label, crossover inhalation study in asthmatic patients was to characterize and compare the lung deposition of large particle fluticasone-salmeterol HFA with small particle HFA beclomethasone.

Methods

Radiolabeling

The radionuclide technetium T 99m ($^{99\text{m}}\text{Tc}$) was used to radiolabel formulations of HFA beclomethasone (QVAR) and fluticasone-salmeterol HFA (Advair HFA; GlaxoSmithKline) by the method for pressurized metered-dose inhalers (pMDIs) previously described.^{4–9} Briefly, the radiolabel was extracted out of the aqueous phase in 3-pentanone, which was then added to and evaporated from an empty canister. The contents of a filled canister containing the respective formulation were added at -80°C , and a valve was crimped in place. The vial was weighed, sonicated in water for 15 minutes, and weighed again. When it was determined that the vial was not leaking aerosol, prestudy quality control analysis was performed to ensure that the radiolabeled product matched the formulation and delivery characteristics of the original products.

Quality control analysis

To quantify the amount of radioactivity presented to each patient before dosing, the radiolabeled pMDI was actuated into a filter with a flow rate of 30 L/min drawn through the filter. Immediately after the actuation of one dose into the filter, the actuator, filter, and stem wipe were individually placed in a dose calibrator for quantification of radioactivity.

To confirm particle size distribution, each radiolabeled pMDI was actuated into a Next Generation Impactor. The actuator, US Pharmacopeia throat, each impactor stage, and backup filter were quantified for radioactivity in a dose calibrator before each day's dosing. Thus, the original drug dose and particle size from each canister were determined before patient use. The respective extracts were then held for at least 48 hours to decay before analysis via high-pressure liquid chromatography with UV detection for drug particle size analysis.

Study design

The primary objective of this open-label, nonrandomized study was to compare lung deposition of a single dose of HFA beclomethasone vs fluticasone-salmeterol HFA pMDI. Men 18 to 55 years of age classified as having mild asthma (per the National Asthma Education Program¹), with a forced expiratory volume in 1 second of more than 90% of predicted normal, were eligible for inclusion. Patients were required to have abstained from smoking for at least 1 year and had to be 155 to 180 cm in height with a normal body weight for their height and frame size. Exclusion criteria included receiving a radiation dose within the last 12 months for clinical or diagnostic tests; unstable or clinically significant endocrine, hematologic, hepatic, renal, gastrointestinal, neurologic, psychiatric, or immunologic disease; known or likely hypersensitivity to fluticasone-salmeterol HFA or HFA beclomethasone or their excipients; respiratory tract infection within the 2 weeks before screening; and/or a history of or current substance or alcohol abuse. There were no restrictions on asthma medications; however, no patient reported the use of β -agonists within 24 hours of steroid dosing or recent use of inhaled steroids. This study was reviewed and approved by the University of New Mexico Medical Center institutional review board. Each patient was given an oral and written consent form, and a signature was obtained from each patient.

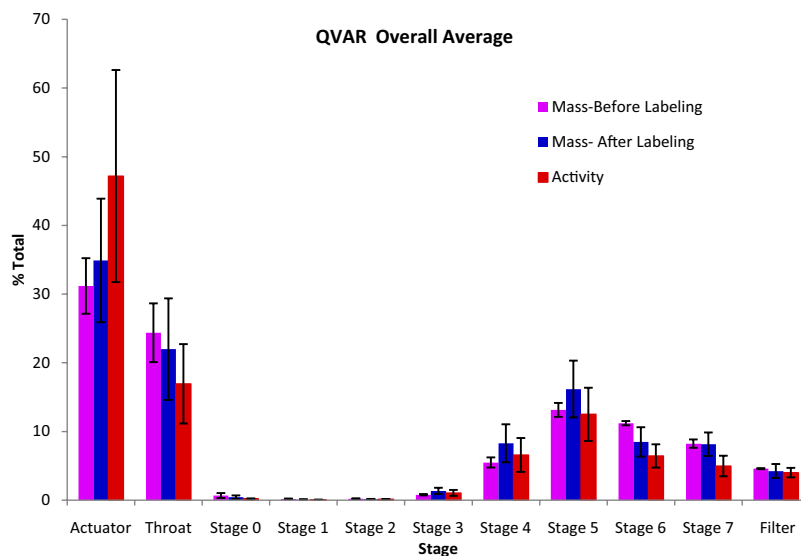


Figure 1. Overall mean predose and postdose particle size analysis for hydrofluoroalkane-134a (HFA) beclomethasone on all study days. The data represent the mean (SD) of 5 actuations of 40 μg of HFA beclomethasone (QVAR) into the cascade impactor particle sizing device.

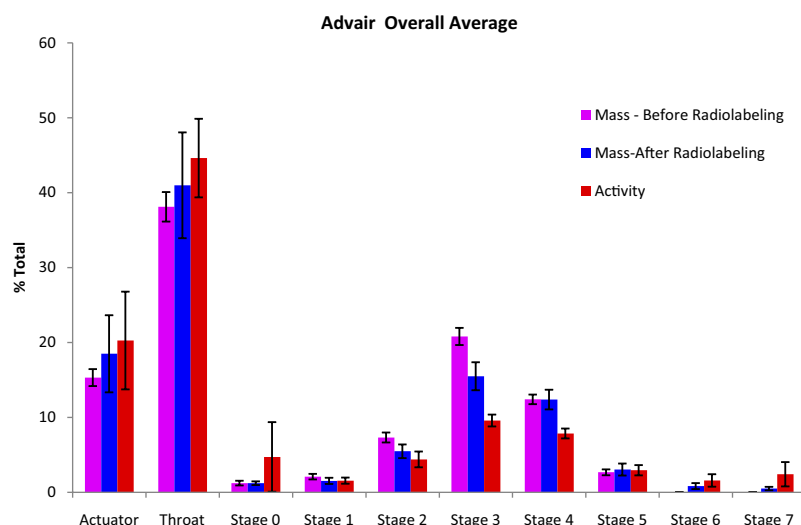


Figure 2. Overall mean predose and postdose particle size analysis for fluticasone-salmeterol hydrofluoroalkane-134a (HFA) on all study days. The data represent the mean (SD) of 5 actuations of 115/21 μg of fluticasone-salmeterol (Advair HFA) into the cascade impactor particle sizing device.

Patients were administered one dose of the respective radiolabeled formulations. The patients inhaled using standard inhalation techniques described in the package inserts of the respective products. Breath pattern parameters (eg, inspiration time and time to actuation) were collected each time a patient was dosed with the radiolabeled formulation to eliminate patient inhaler technique bias. These results showed that all patients conducted an approximate 3-second inhalation that initiated immediately before actuation of the radiolabeled pMDI. Breath holds were manually timed for each patient to achieve an approximate 10-second breath hold.

After the breath hold, patients immediately underwent planar gamma camera scanning, followed by single-photon emission computed tomography (SPECT) and then second planar scanning. During one of the treatment days, patients underwent computed tomography (CT) to locate the tissues in the oropharynx and thorax for future drug deposition overlays.

Analysis of planar distribution and deposition

Immediately after the dose administration, the patient was returned to the previously established position and a 45-second dynamic planar image was collected with SPECT/CT (Siemens Symbia;

Siemens Medical Solutions USA Inc, Malvern, Pennsylvania). Acquisition was conducted with Syngo MI Applications software (version 8.1.15.7; Siemens Medical Solutions). For analysis, the CT data were resampled and resized to match the voxel size and dimensions of the SPECT data. The dynamic planar data were loaded and a region mask was applied to a 2-dimensional (2D) plane. The lung regions were identified and split into left and right lobes. The lung locations were used to establish geometrical oropharyngeal and gut overlay masks. Therefore, the final mask consisted of 4 distinct regions: left lung, right lung, oropharyngeal region, and gut.

3D SPECT analysis

Analysis of the 3-dimensional (3D) data was conducted using an in-house Lung Onion Model analyzing topographic thinning. In this model, a seeded, automatic, 3D segmentation routine was used to extract the lung and airway regions from the CT. The seed point of the onion, identified from the coregistered CT image overlay, was the primary bronchus for each right and left lung section. From this seed point, a topographic thinning model was applied to look at the deposition of radioactivity as a function of the distance from the seed point. Imaging data were then normalized for the inhaled dose

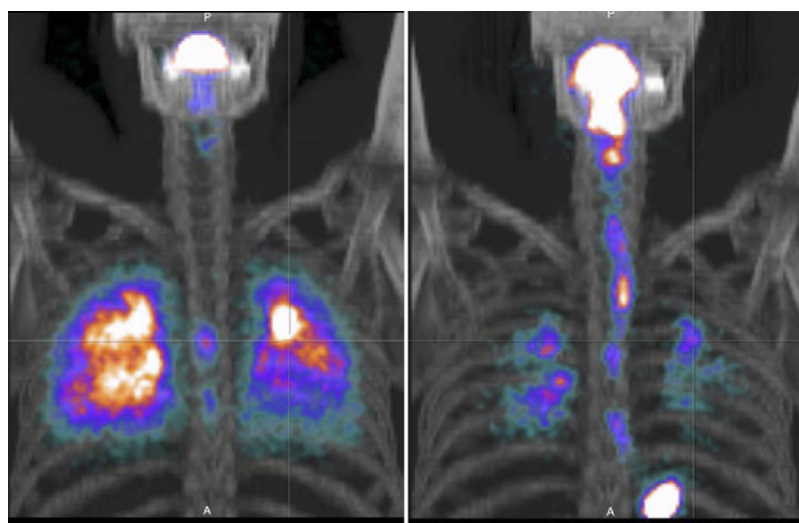


Figure 3. Example deposition patterns of hydrofluoroalkane-134a (HFA) beclomethasone (single inhalation of 40 μg of QVAR) (left) and fluticasone-salmeterol HFA (single inhalation of 115/21 μg Advair HFA) (right) for the same patient. Lighter colors represent higher quantities of drug present (ie, white color is the highest quantity of drug).

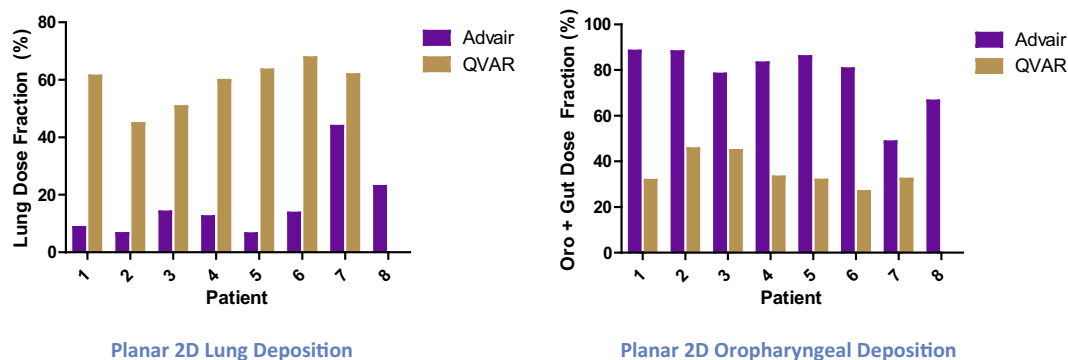


Figure 4. Direct comparison of dose fraction for the lung, oropharynx, and gut for all patients with the 2-dimensional data. Note that patient 8 received only fluticasone-salmeterol hydrofluoroalkane-134a (HFA) and not HFA beclomethasone.

so that all presented data represent dose fractions for direct correlation to dose.

C to P ratio analysis

An analysis of the central (C) to peripheral (P) deposition (C to P ratio) was conducted on the 3D data as previously described.¹¹ In this, the lung was segmented into 2 regions (C and P), with the C region making up 33% of the lung area and the P region comprising 67% of the lung area. The fraction of the lung dose in each region was then determined and used in the following equation to calculate the C to P ratio: C to P Ratio = [(Fraction in Central Region)/(Fraction in Peripheral Region)].

Statistical analysis

To compare the region of interest analysis, a Wilcoxon matched-pairs signed rank test (paired, 2-tailed *t* test with 95% confidence interval) was used to compare the mean dose fraction for each product. Differences were determined to be significant at $P < .05$.

Results

A 7-patient crossover study was conducted with commercial formulations of HFA beclomethasone (40 μ g of beclomethasone dipropionate per actuation; QVAR) and fluticasone-salmeterol HFA (115 μ g of fluticasone propionate and 21 μ g of salmeterol per actuation; Advair HFA), each radiolabeled with ^{99m}Tc. Before patient dosing, a validation of the radiolabeling procedure was conducted to ensure the fidelity of the radiolabel to the respective drug. The results of these procedures showed that the particle size distribution of the original product was not altered for either HFA beclomethasone or fluticasone-salmeterol HFA after labeling with ^{99m}Tc (Figs 1 and 2).

Planar analysis and deposition

Quantitative image analysis of HFA beclomethasone and fluticasone-salmeterol HFA was conducted to determine the percentage of the dose in the lungs (right lung added with the left lung), oropharynx, and gut and the amount exhaled. Qualitative inspection of the images initially revealed different deposition patterns. Examples of the HFA beclomethasone and fluticasone-salmeterol HFA planar deposition patterns for a representative patient are shown in Figure 3. These images showed a more complete central and peripheral coverage of the lungs with HFA beclomethasone when directly compared with fluticasone-salmeterol HFA.

The individual patient lung dose and oropharynx and gut dose fraction data are shown in Figure 4. Analysis of the 2D images showed that an overall mean of 58% of the HFA beclomethasone dose was deposited in the lungs of the patients compared with 16% for fluticasone-salmeterol HFA ($P < .05$). Similarly, analysis of the oropharyngeal cavity and the gut indicated that 77% of the fluticasone-salmeterol HFA dose was deposited in the oropharynx, whereas only 35% of the HFA beclomethasone dose was initially deposited in the oropharynx ($P < .05$).

The individual patient data were averaged and analyzed via a paired *t* test (Wilcoxon matched-pairs signed rank test) (Fig 5). These analyses indicated that there was a significantly greater ($P = .02$) amount of lung deposition from the HFA beclomethasone formulation when compared with the fluticasone-salmeterol HFA formulation. Furthermore, the oropharynx plus gut deposition was significantly greater ($P = .008$) for fluticasone-salmeterol HFA when compared with HFA beclomethasone.

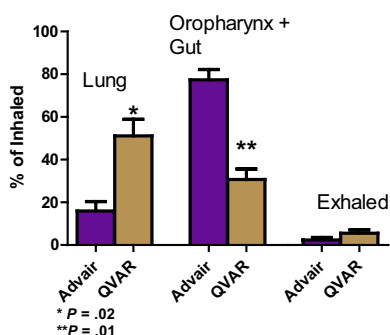


Figure 5. Summary data of all patients imaged after hydrofluoroalkane-134a (HFA) beclomethasone and fluticasone-salmeterol HFA dose administration for the 2-dimensional data.

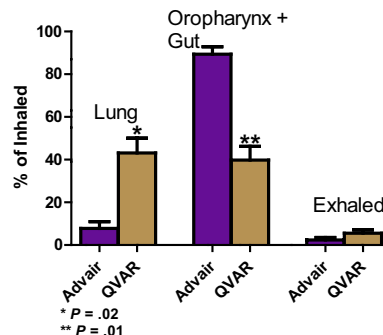


Figure 6. Summary data of all patients imaged after hydrofluoroalkane-134a (HFA) beclomethasone and fluticasone-salmeterol HFA dose administration for the single-photon emission computed tomography data.

Table 1
Patient central (C) to peripheral (P) lung fractions ($\times 100$) and C to P ratios

Patient No.	HFA beclomethasone ^a			Fluticasone-salmeterol HFA ^b		
	C fraction	P fraction	C to P ratio	C fraction	P fraction	C to P ratio
1	55	45	1.2	64	36	1.8
2	41	59	0.7	59	41	1.5
3	64	36	1.8	61	39	1.5
4	72	28	2.6	93	7	12.4
5	72	28	2.5	84	16	5.1
6	35	65	0.5	94	6	16.5
7	67	33	2.0	21	79	0.3
8	NP	NP	NP	21	79	0.3

Abbreviations: HFA, hydrofluoroalkane-134a; NP, not performed.

^aMean (SD) = 1.6 (0.8).

^bMean (SD) = 4.9 (6.2).

3D SPECT analysis

The 2D data were used to evaluate initial deposition for both the head and thorax regions, and the 3D data were used to determine within-lung deposition comparisons, such as the C and P analyses. Quantitative image analysis of the 3D images was conducted to determine the percentage of the drug in the lungs (right lung added with the left lung), oropharynx, and gut and the amount exhaled. The individual patient lung and oropharynx plus gut dose fraction data consistently showed for all patients that the dose fraction deposited in the lung was greater for HFA beclomethasone, with a higher dose fraction of fluticasone-salmeterol HFA being deposited in the oropharynx and gut.

The individual 3D SPECT patient data were averaged and analyzed via a paired *t* test (Wilcoxon matched-pairs signed rank test) (Fig 6). These analyses indicated that there was a significantly greater amount of lung deposition from the HFA beclomethasone formulation when compared with the fluticasone-salmeterol HFA formulations ($P = .02$). Furthermore, the oropharynx plus gut deposition was significantly greater ($P = .008$) for fluticasone-salmeterol HFA when compared with HFA beclomethasone.

The fraction of the lung dose in each of the C and P regions for HFA beclomethasone and fluticasone-salmeterol HFA is given in Table 1. These data demonstrated an increase in the C to P ratio for fluticasone-salmeterol HFA, which is the result of decreased deposition in the P region of the lung. Also of note is the increased variability of fluticasone-salmeterol HFA (SD, 6.2) when compared with HFA beclomethasone (SD, 0.8). Although the removal of any data is not appropriate because there is no biological justification for removal, the variability of fluticasone-salmeterol HFA triggered a sensitivity analysis where the top 2 (patients 4 and 6) and bottom 2 (patients 7 and 8) were removed. This analysis reproduced the initial conclusions in that HFA beclomethasone again showed a lower C to P ratio and fluticasone-salmeterol HFA again showed higher variability (SD, 1.8, with patients 4, 6, 7, and 8 removed).

The time required for the initial 2D scan was less than 60 seconds. However, the time required for the 3D scans was approximately 12 minutes. These 12 minutes were enough time for oropharyngeal clearance through oral and gut membranes to begin to affect the total mass balance of drug to be calculated. Thus, the 2D analyses were considered most appropriate for initial deposition numbers when comparing lung with oropharyngeal dose deposition. The 3D analyses were considered most appropriate for within-lung deposition determinations, such as the C and P analyses.

Discussion

The results illustrated by Figure 3 show that the small particle HFA beclomethasone formulation covered all airways in the lungs as opposed to the large particle fluticasone-salmeterol HFA formulation, which covered primarily the central airways, similar to the

coverage obtained from chlorofluorocarbon-radiolabeled studies previously reported.⁴ This central deposition of large particle inhaled steroids is reflected by the results illustrated in Table 1 in which the C to P ratio was much higher and more variable for fluticasone-salmeterol HFA compared with HFA beclomethasone.

Asthma is a disease of the entire respiratory tract. Inflammation occurs in all airways, both large and small, even in the case of mild and moderate asthmatic patients. It is generally known that steroids work best when they are targeted directly to the sites of inflammation. Figure 7 represents a lung scan from a typical man. Because of the resolution, the small airways are not displayed, but the large and intermediate airways are grossly visible. It is clear that on a gross level that anywhere there is lung tissue there are airways. Given the fact that inflammation from asthma is present in all airways, it is to be expected that inhaled steroids would be most effective if the entire lung was covered by the radiolabeled steroid.

Beclomethasone chlorofluorocarbon is the same drug (ie, beclomethasone dipropionate) contained in QVAR. These drugs differ primarily in particle size, with HFA beclomethasone being approx-



Figure 7. Lung scan of a man depicting large and intermediate size airways.

imately 1 μm and beclomethasone chlorofluorocarbon being approximately 3.5 μm . Several studies^{12–14} conducted in moderate to severe asthmatic patients showed that asthma control was effectively maintained at half the dose of the small particle HFA beclomethasone compared with beclomethasone chlorofluorocarbon, despite using forced expiratory volume in 1 second as the primary variable. When using forced expiratory flow (presumed to be a better measure of small airways function) in one study,¹⁴ it was calculated that for a given dose of HFA beclomethasone a 3.2-fold greater dose of beclomethasone chlorofluorocarbon would be required to provide the same improvement. This hypothesis of requiring less dose of a small particle inhaled steroid was recently confirmed in a large retrospective study of asthmatics in the United Kingdom.¹⁵ The data showed that 82% of the patients were well controlled with a prescribed and assumed HFA beclomethasone dose of 339 $\mu\text{g}/\text{d}$ without long-acting β -agonists or combination products compared with 79% of patients using a prescribed and assumed beclomethasone chlorofluorocarbon dose of 574 $\mu\text{g}/\text{d}$. Thus, on the basis of the prescribed doses, equivalent control required approximately twice the dose of beclomethasone chlorofluorocarbon compared with HFA beclomethasone, a result most likely due to the improved lung deposition with HFA beclomethasone. Additional supportive studies have also shown that markers of inflammation, such as exhaled nitric oxide, were improved in patients treated with HFA beclomethasone, who exhibited significantly less exhaled alveolar nitric oxide than patients using large particle beclomethasone.¹⁶ For example, HFA beclomethasone showed a significant reduction in baseline alveolar nitric oxide (ie, 3.7 ppb) vs large particle beclomethasone reduction from baseline of 2.1 ppb. Both large and small particle beclomethasone reduced bronchial exhaled nitric oxide, but no significant difference was found between the two drugs.¹⁶ Finally, a recent, large, retrospective clinical study comparing HFA beclomethasone with large particle beclomethasone chlorofluorocarbon showed that patients were more likely to achieve asthma control with HFA beclomethasone and HFA beclomethasone was effective at controlling asthma at half of the dose of beclomethasone chlorofluorocarbon.¹⁷

This study shows that smaller, more optimized inhaled steroid particles can deposit more drug to the lungs with better distribution within the airways and less deposition in the oropharynx than larger particle inhaled steroids.

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