Particle size of inhaled corticosteroids: Does it matter?

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A question with respect to asthma therapy revolves around the issue of whether better efficacy occurs with an ultrafine-particle inhaled corticosteroid because of better lung deposition into the distal airways. This article reviews particle size and delivery devices of different steroids, clinical outcomes of small- versus large-particle steroids, and the issue of pharmacoeconomics. (J Allergy Clin Immunol 2009;124:S88-93.)

Key words: *Inhaled corticosteroids, particle size, delivery devices, clinical outcomes, pharmacoeconomics*

Abbreviations used
BDP: Beclomethasone dipropionate
CFC: Chlorofluorocarbons
DPI: Dry powder inhaler
HFA: Hydrofluoroalkane
HPA: Hypothalamic-pituitary-adrenal
ICS: Inhaled corticosteroid
MDI: Metered-dose inhaler

PARTICLE SIZE AND DELIVERY DEVICE DIFFERENCES OF INHALED CORTICOSTEROIDS

Asthma is known to be a disease of the entire respiratory tract, including the large, intermediate, and small airways. It has been clearly shown that inflammation, obstruction, and remodeling occur throughout the respiratory tract.[1] This is true for mild, moderate, and severe asthma, and although the severity can change with the classification of asthma, processes like inflammation occur in small airways, even in subjects with mild asthma.[2] It is of importance to note that natural allergens, such as cat allergen, fungal spores, and pollen, have particle sizes capable of reaching even the smallest airways.[3,4] Furthermore, the mediators of asthma, such as smooth muscle and immunocompetent cells, are also present in all airways. Thus it appears that all of the components considered fundamentally necessary for the pathogenesis of asthma are present in all sizes of airways. It is also known that steroid receptors are present in almost all of the cells in the respiratory tract, and the density of these receptors actually increases farther down the conducting airways.[5] Thus the relevant target tissue and inflammation caused by asthma is present throughout the airways, and the steroid receptors are also present in these same locations. Therefore it appears important that inhaled corticosteroids (ICSs) be able to reach all of the target sites for optimal treatment.

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Determining delivery characteristics

The Montreal Protocol of 1987 required the eventual banning of all chlorofluorocarbons (CFC), including those used in metered-dose inhalers (MDIs). This meant that all MDIs using CFC had to be reformulated with the new hydrofluoroalkane (HFA) propellants. This presented the opportunity to improve on 40-year-old CFC inhaler technology. As a result, the ability to produce a wide range of drug particles was developed. Some companies chose to reformulate the old CFC products to match the particle size of the existing CFC products (eg, the switch from CFC-fluticasone to HFA-fluticasone). This allowed for a much faster and less expensive switch to new HFA inhalers. However, other companies chose to produce MDI formulations with a smaller particle size distribution, which might be expected to deposit more widely in the large, intermediate, and small airways. Two examples of reformulated HFA small-particle products include HFA-beclomethasone and HFA-flunisolide. In addition, new inhaled products, such as ciclesonide, used the new HFA optimum particle size technology as a delivery platform.

Inhaled drug deposition studies

A suspension MDI is one in which the drug is physically ground down into solid particles and then the particles are suspended in the liquid propellant. That is why suspension inhalers need to be shaken. A solution MDI means that the drug is actually dissolved in the propellant/cosolvent formulation. By having the proper formulation concentration and the appropriate valve orifice size, the drug solution can produce aerosolized droplets in a size range that, when the propellant evaporates, would result in smaller, solid drug particles.

Table I shows particle size measurements for inhaled MDI and dry powder inhaler (DPI) steroids along with reported lung deposition values. It is clear that DPIs and suspension CFC and suspension HFA MDIs exhibit particle sizes of greater than 2.6 μm (median mass aerodynamic diameter). The lung deposition values appear to be no greater than 20%, with an oropharyngeal deposition of 80% to 90%. It was not until HFA solution technology was introduced that it was possible to engineer particles with an average size of 1.1 μm that optimal drug particles could be produced. For the first time for any type of DPI or MDI inhaler, lung deposition values were greater than 50%. Numerous human studies showed greater than 52% lung deposition for HFA-beclomethasone.[6-9] The solution formulation approach was further

TABLE I. Lung deposition and particle size comparison of steroid inhalers

Inhaled steroid	MMAD (μm)	Lung deposition value
Fluticasone DPI	~4.0	15%
Triamcinolone	4.5	14%
CFC-flunisolide	3.8	19%
CFC-beclomethasone	3.5	8%
CFC-fluticasone	2.6	13%
HFA-flunisolide solution	1.2	68%
HFA-beclomethasone solution	1.1	56%
HFA-ciclesonide solution	1.0	52%

MMAD, Median mass aerodynamic diameter.

exemplified by using human studies of HFA-ciclesonide[10] and HFA-flunisolide.[11] The average particle size of 1.1 μm for HFA-beclomethasone includes a range of particles (eg, represented by a geometric SD of 2.0) that allows for some larger particles to deposit in the large and intermediate airways.

There are other differences with HFA MDI solution formulations beside the smaller particle size distribution. For example, the normal force of the drug plume on the back of the throat is approximately 100 mN for typical CFC ICS suspension inhalers; the force is approximately 30 mN for HFA-beclomethasone. The temperature at the back of the throat of a typical ICS suspension MDI is approximately −17°C compared with +3°C for HFA-beclomethasone.[12] It is possible that patients would tolerate a warmer softer spray with less cough, cold Freon reaction, or both.

Another consideration with a small-particle ICS formulation is that particles stay suspended in airways, oropharyngeal areas, and even add-on spacers longer than seen with the high-inertial-impact, large-particle, ICS suspension MDIs. Theoretically, a small-particle aerosol that remains suspended in the air for longer should provide an advantage for discoordinated patients, possibly even improving lung deposition of the drug. This hypothesis was evaluated in a study in which patients were trained to use a discoordinated approach to the small particle HFA-beclomethasone. They were specifically instructed to initiate their inhalation either before MDI actuation or well after MDI actuation. These techniques represented extreme examples of patient discoordination (ie, early or late breath-cycle inhalation compared with device actuation). Results showed that coordinated actuation resulted in the usual 50% to 60% lung deposition. Results also showed that discoordinated actuation either before breathing or very late in inspiration resulted in greater than 30% lung deposition.[13] Additional studies showed that lung deposition values averaged approximately 55% over large inspiratory flow rates, ranging from approximately 30 L/min to more than 200 L/min. Thus patients having periods of relative obstruction or mistakes in inhalation effort had approximately the same inhaled dose. It is considered that more consistent doses to the lungs will allow for downward steroid dose titration.[14] Other benefits of the suspended small-particle HFA-beclomethasone were shown in a study in children using a spacer that allowed 5- to 17-year-olds to breathe freely through the spacer. The resultant lung deposition was 35% to 55%. This study also showed that the optimized use of HFA-beclomethasone through a spacer was obtained with a breath hold whereby lung deposition values were approximately 57% in children 5 to 17 years old.[15,16]

Conclusions

It is clear that the treatment of asthma can be improved by education, compliance, and optimized products. The advent of HFA solution technology in MDIs has enabled developers to produce virtually any size particle desired. It was determined that for ICSs such as beclomethasone, ciclesonide, and flunisolide, a particle size average of approximately 1.1 μm improved lung deposition from very low values to approximately 50% to 60% while minimizing oropharyngeal deposition to 30% or less. This smaller particle size also resulted in ameliorating discoordination effects and improving add-on spacer performance.

ICS THERAPY: SMALL VERSUS LARGE PARTICLES

Although ICSs are effective for the treatment of asthma, unfortunately, regular use of ICSs will not ensure total control of the disease in all patients.[17] Furthermore, ICS use has been associated with a variety of systemic and upper airway side effects that limit regular use.[18] Improving the clinical efficacy and decreasing the safety concerns of ICSs would be an extremely useful step in enabling more effective asthma control. There are 2 possible ways to improve the risk/benefit profile of ICSs. Newer ICSs could be developed with greater intrinsic potency and a pharmacokinetic profile that would limit systemic effects. Unfortunately, the pharmaceutical industry has not been able to design potent but safer ICSs. Alternatively, ICSs could be formulated in devices that preferentially target lung delivery for enhanced effect and simultaneously decrease delivery to sites vulnerable to safety concerns. Examples of how reformulation of ICSs could lead to an improved risk/benefit profile occurred as a consequence of the public health concerns recognized with CFC propellants. MDIs had historically relied on CFCs as propellants, but their ban led to reformulation of products in MDIs with environmentally safer HFA propellants. The reformulation process of 2 ICSs (beclomethasone dipropionate [BDP] and flunisolide) resulted in solution aerosols with smaller particle sizes. The change in particle size of BDP and flunisolide had practical (see above), biologic, and clinical consequences.

Biologic significance

Corticosteroids are effective anti-inflammatory agents, but it had been unclear whether administering corticosteroids by means of inhalation resulted in an anti-inflammatory effect directly in the lung or indirectly through systemic absorption. This question was addressed in a study in which asthmatic patients were randomized to one of 4 treatment arms: a placebo control arm, an arm receiving a large dose of oral fluticasone, and 2 arms receiving fluticasone, either low or high dose, by means of inhalation.[19] At the end of 6 weeks' treatment, asthma control was assessed, and serum fluticasone levels were measured. Asthma control was effectively obtained with low-dose inhaled fluticasone, but no serum levels of drug were detected. Conversely, high serum fluticasone levels were measured in the group receiving a large dose orally, but asthma control was not achieved. This study confirmed that ICSs control asthma inflammation and related symptoms through a topical anti-inflammatory effect occurring at their site of deposition in the lung and not through systemic absorption.

Recognizing that ICSs provide a topical anti-inflammatory effect at their site of deposition in the lung has important biologic implications. Because the airway epithelial layer is the first site of