Improved delivery of inhaled steroids to the large and small airways

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The reformulation of asthma medications with non-ozone depleting propellants such as hydrofluoroalkane-134a (HFA) has provided the opportunity to apply new knowledge and inhaler technology to improve significantly the delivery of aerosol drugs to the respiratory tract. Beclomethasone dipropionate (BDP), the most commonly prescribed inhaled corticosteroid for asthma therapy, is effective therapy; however, currently available chlorofluorocarbon (CFC)-BDP metered dose inhalers typically deliver no more than 10% of the inhaled drug to the lungs with the remainder deposited in the oropharynx. Compared with an average particle size of 3.5 ± 4.0 μm for CFC-BDP, the new HFA-BDP formulation has an average particle size of 1.1 μm and a respirable fraction of approximately 60%. The lung deposition of 99mTc-radio-labelled HFA-BDP has been investigated in healthy volunteers and patients with asthma. Results showed that the HFA-BDP formulation reverses the pattern of distribution seen with CFC-BDP products, delivering most of the dose of inhaled steroid directly to the lungs rather than to the oropharynx and gut where it may lead to unwanted side-effects. As such, HFA-BDP is likely to achieve equivalent efficacy to existing CFC-BDP formulations with lower doses and with reduced potential for local adverse effects.

Introduction

The efficacy of inhaled corticosteroids for the treatment of asthma is well documented (1), with national and international treatment guidelines increasingly recommending their use as first-line therapy for all except very mild asthma (2, 3). Corticosteroids for the treatment of asthma are usually administered by inhalation of an aerosol. The most common device used to create an aerosol for drug delivery is the metered dose inhaler (MDI), which contains a suspension of drug in propellant. At present, the most commonly used propellants in MDIs are pressurized chlorofluorocarbons (CFCs) (4).

Successful clinical management of asthma depends on achieving adequate delivery of inhaled drugs to the lung, with anti-inflammatory agents such as corticosteroids appearing to be most effective when deposited throughout the airways (5). However, studies have shown that with CFC-MDIs the proportion of the released dose which actually reaches the airways is generally less than 20%, even with optimal inhaler technique (6). The remainder is deposited orally, where it may lead to unwanted local side-effects such as dysphonia and oropharyngeal candidiasis, as well as having the potential to contribute to systemic side-effects if swallowed (1).

The link between CFCs and depletion of the earth’s ozone layer, with the potential consequence of environmental damage, has led to a global phasing out of CFC products (7). This mandatory requirement to eliminate CFCs from MDIs has provided the opportunity to apply new knowledge and inhaler technology to improve significantly the delivery of aerosol drugs to the respiratory tract. Hydrofluoroalkane-134a (HFA) has been identified as a substitute for CFC propellants in pressurized MDIs (8, 9). Unlike CFC propellants, HFA does not contain chlorine and therefore has no ozone-depleting potential (10). Pre-clinical studies have shown it to be well tolerated and to present no safety concerns (11, 12).

HFA formulations of salbutamol, salmeterol and fluticasone propionate have been shown to be as effective and well tolerated as existing CFC formulations at...
equivalent dosages (13, 14). Beclomethasone dipropionate (BDP), the most commonly prescribed inhaled corticosteroid for asthma therapy, has also been reformulated using the new HFA propellant system (Qvar®M, 3M Pharmaceuticals, St. Paul, MN, U.S.A.). Unlike CFC MDIs, HFA BDP is a solution, rather than a suspension, of drug in propellant (15). This means that the solution forms an extrafine aerosol of small droplets as the propellant evaporates. Because of the smaller aerodynamic diameter of the spray particles, this new HFA–BDP extrafine aerosol is expected to deliver more drug to the patient’s lungs and less to the throat than existing CFC–BDP formulations (5, 14, 16).

The Importance of Particle Size

The importance of particle size for the therapeutic response to inhaled bronchodilators has been recognised for some time (5, 6, 17–19). Asthma is known to be a disease of both large and small airways (20). Inhaled particles of greater than 5 μm in aerodynamic diameter will tend to impact and be retained in the oropharynx, while those with an aerodynamic diameter of less than 5 μm (often approaching 1 μm) are more likely to deposit and distribute in the tracheobronchial and pulmonary regions of the lungs (17, 19). Correspondingly, studies in asthmatic patients have shown the greatest pulmonary response to bronchodilators to occur with particles of less than 5 μm diameter, presumably because of the increased amount of drug deposited in the airways when patients inhaled the smaller aerosol particles (18).

As shown in Fig. 1, existing CFC–BDP MDIs produce particles of approximately 3.5–4.0 μm in diameter and typically deliver no more than 10% of the inhaled dose to the lungs, with approximately 90% deposited in the oropharynx where it provides little therapeutic benefit and may lead to unwanted adverse effects. In contrast, the new HFA–BDP extrafine aerosol has an average particle size of 1.1 μm, with a respirable fraction of around 60% (16, 21). Animal and mechanical model studies suggest that this HFA–BDP formulation reverses the standard deposition pattern seen with CFC–BDP MDIs by delivering most of the drug to the airways and a much smaller proportion to the oropharynx and gut (21, 22).

Measuring Lung Deposition

Comparing two formulations of the same inhaled glucocorticoid by conventional clinical parameters requires large study populations. However, alternative methods, such as lung deposition studies, can provide a valid comparison of different formulations using much smaller numbers of patients (23). At present, there are two main ways of assessing lung deposition of inhaled drugs in vivo (24). Pharmacokinetic studies, which measure drug levels in plasma or urine, give information on the percentage of the dose absorbed (as opposed to exhaled, or remaining in the spacer or the mouthpiece), but provide little direct information on the site of absorption (pulmonary or systemic). Alternatively, radiolabelling studies use γ cameras to obtain images of the distribution of drug labelled with 99mTc within the respiratory tract and lungs.

Radiolabelling studies can be further subdivided into indirect and direct studies. Indirect radiolabelling studies use inert particles of known size such as Teflon microspheres, and so provide information about drug deposition only by inference. Direct radiolabelling studies use radiolabelled drug aerosols and therefore provide an exact model of the behaviour of drug particles in the lung. However, direct radiolabelling studies require verification before the results can be considered valid. In particular, in vitro validation must show that representative particles of all sizes are radiolabelled and confirm that the size distribution of the radiolabelled particles exactly parallels that of non-radiolabelled drug for each clinical dosing session. This ensures that the radiolabel does not distribute preferentially to particles of a certain size and thereby produce misleading results. Furthermore, the radiolabel must be shown to be stable over the period of time used.

![Fig. 1. Comparison of CFC–BDP (■) and HFA–BDP (□) particle sizes.](image-url)
A further consideration is the need for a control group. Comparisons between products can be performed by using parallel-group designs (where the control and experimental groups comprise different individuals), or cross-over designs (where each patient acts as his or her own control). The latter avoids problems due to interindividual variability but requires reproducibility of inhaler technique to permit valid comparisons between the different study periods. The cross-over design also reduces the need to determine tissue attenuation due to γ ray absorption and scattering. This is important because no well-validated methods of determination of tissue attenuation exist for technetium-labelled lung deposition studies.

Lung Deposition of Hydrofluoroalkane-134a-Beclomethasone Dipropionate Extrafine Aerosol

STANDARDIZATION OF INHALATION PATTERN AND DRUG VALIDATION

The lung deposition of 99mTc-radiolabelled HFA–BDP extrafine aerosol has been investigated in healthy volunteers and patients with asthma (21, 22). A critical aspect of these studies was to ensure standardization of the inhalation pattern of each patient. This was achieved using a novel visual biofeedback system developed by 3M Pharmaceuticals. This respiratory device allowed subjects to observe a real-time visual display of their breath pattern (including time of inhalation, time to actuation and breath hold time) on a computer screen. Subjects could then reproduce the desired breath pattern for a specific comparison, ensuring standardization of inhaled doses. In addition, a digitised breath pattern of the actual breath when the radiolabelled drug was inhaled could be collected and stored. The respiratory device in no way interfered with the drug delivery characteristics or patient ergonomics.

An extensive validation process was followed to ensure the desirable association of radiolabel with drug. It was necessary to ensure that the mass distribution of the formulation did not change during the labelling process and that the mass and radiolabel size distributions agreed. Radiolabelled BDP canisters were prepared each morning of a clinical study day. Andersen 1 ACFM Particle Sizing Samplers (Mark II) and the Quartz Crystal Microbalance Cascade Impactor System were used to determine these distributions. If the distributions agreed, the formulation was considered to be properly labelled for the clinical study.

LUNG DEPOSITION IN HEALTHY VOLUNTEERS

Differences in lung deposition and distribution between HFA–BDP and CFC–BDP were investigated in an open-label pilot study involving 12 healthy male subjects (22). Subjects of similar physique and pulmonary function were selected to facilitate comparability of dosing. To be included in the study, subjects were also required to demonstrate excellent MDI technique and reproducible inspiratory technique using the respiratory biofeedback device. The same biofeedback system was used to record the inhalation of the radiolabelled drug. Radiolabelling was validated using the method described previously.

Products of similar ex-valve delivery (HFA–BDP 50 μg and CFC–11/12 BDP 50 μg) and of similar expected efficacy (HFA–BDP 100 μg and CFC–11/12 BDP 250 μg) were compared. Following inhalation of study medication, the amount of drug deposited in the lungs, abdomen, oropharynx and inhaler adapter, as well as the amount the subject expired through a filter trap, were measured by γ scintigraphy.

The mean percentage of total radioactivity in the lungs was found to be greater with the HFA–BDP products than with the CFC–11/12 BDP products, with ex-actuator lung deposition of 51% and 4%, respectively. In contrast, deposition of BDP in the oropharynx was much less with both strengths of HFA–BDP (30%) than with CFC–11/12 BDP (94%). No attenuation correction was performed because each subject served as his own control. γ camera imaging confirmed that lung deposition of BDP was greatest with the HFA formulation (Fig. 2). Drug deposition of HFA–BDP was evident throughout the central, intermediate and peripheral airways, while with CFC–BDP deposition was most evident in the oropharynx and large central airways. The mean mass of drug delivered to the lungs ex-actuator was found to be 20.9 and 48.9 μg for HFA–BDP 50 μg and HFA–BDP 100 μg, respectively. This approximately linear relationship between lung deposition and administered dose is consistent with observations in pharmacokinetic studies (25).

LUNG DEPOSITION IN ASTHMATIC PATIENTS

The lung deposition of radiolabelled HFA–BDP 50 μg delivered from a standard press and breathe (P&B) MDI has also been evaluated in a open-label study involving 16 patients with mild asthma (21, 22). All patients demonstrated excellent technique in the use of the P&B MDI and reproducibility of their inspiratory flow pattern using the respiratory biofeedback device.
FIG. 2. Comparative deposition patterns of (a) CFC–BDP and (b) HFA–BDP in healthy volunteers. The same biofeedback system was used to record the inhalation of radiolabelled drug. Radiolabelling was validated using the method previously described. Following inhalation of study medication, the amount of drug deposited in the lungs, upper abdomen, oropharynx, inhaler adapter and spacer as well as the amount the subject expired through a filter trap were measured by γ scintigraphy. As in the study in healthy volunteers, most of the drug was delivered to the lungs (56%), with only a comparatively small quantity deposited in the oropharynx (28%). γ scintigraphy confirmed that BDP was distributed throughout the central, intermediate and peripheral airways with the HFA–BDP MDI, with minimal drug deposition in the oropharynx even without the use of a spacer attachment (Fig. 3). The mean drug mass delivered exactuator to the lungs was calculated to be approximately 23.1 μg assuming a delivery of 41 μg per actuation.

**Discussion**

The lung deposition studies in healthy volunteers and asthmatic patients reviewed in this paper confirm that the unique formulation of the HFA–BDP extrafine aerosol provides greater lung deposition and less oropharyngeal deposition than CFC–BDP. γ camera

FIG. 3. Deposition of HFA–BDP delivered from a standard P&B MDI in asthmatic patients.
imaging demonstrated that BDP was deposited throughout the central, intermediate and peripheral airways with the HFA formulation, while deposition of BDP was largely restricted to the oropharynx and central airways with the CFC product. Since the HFA–BDP extrafine aerosol delivers most of the dose of inhaled glucocorticoid directly to the lungs rather than to the oropharynx and gut, it should result in greater therapeutic benefit with a reduced incidence of oropharyngeal adverse events.

The extensive validation methodology employed by these studies allows great confidence to be placed in the results. Validation procedures demonstrated that product performance remained unchanged during the radiolabelling process and confirmed that representative samples of these studies allows great confidence to be placed in the results. Validation procedures demonstrated that product performance remained unchanged during the radiolabelling process and confirmed that representative particles of all sizes were radiolabelled, while the use of the visual biofeedback respiratory device ensured consistent breathing patterns for comparison. These procedures ensured that the inhaled dose of radiolabelled drug was standardized, allowing comparison of γ scintigraphy results between subjects and study days.

Throughout the studies, these validation methods confirmed that the mass distributions of both the HFA–BDP extrafine aerosol and the CFC–11/12 BDP formulations remained unchanged by the radiolabelling process. Similarly, the mass distributions of the unlabelled HFA–BDP products were the same as the radiolabel size distributions of the labelled HFA–BDP. However, because it is a suspension formulation, the mass distributions of the unlabelled CFC–11/12 BDP products did not always precisely match the radiolabel size distributions of the labelled CFC–11/12 BDP. Thus, the values obtained from CFC–BDP were considered less precise and were estimated to be 3–8%.

In conclusion, the results of lung deposition studies confirm that HFA–BDP extrafine aerosol reverses the pattern of distribution seen with other steroid inhalers, delivering most of the drug to the airways. In particular, these deposition studies with HFA–BDP extrafine aerosol have shown improved delivery of inhaled steroid to the small airways. Even without the use of a spacer, oropharyngeal deposition was reduced from 90% to 30%. These improved delivery characteristics are likely to provide a number of important clinical benefits. They suggest that HFA–BDP extrafine aerosol will achieve equivalent efficacy to existing CFC–BDP formulations at a significantly lower total daily dose, with a reduced potential for local adverse effects. It also reduces the need to use a spacer attachment.

References

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