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REVIEW ARTICLE

Optimizing Drug Delivery to the Lung: Design of a CFC-Free Corticosteroid Metered-Dose Aerosol System

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ABSTRACT

The mandatory replacement of chlorofluorocarbons (CFCs) with ozone–friendly propellants, such as hydrofluoroalkanes (HFAs), has provided an opportunity to optimize aerosol design and improve drug delivery to pulmonary tissue. Asthma is an inflammatory disorder of the lungs that appears to affect both small and large airways, so ideally, inhaled corticosteroid should reach both central and peripheral sites. This review considers the development of an aerosol system containing beclomethasone dipropionate in hydrofluoroalkane–134a (HFA) propellant (Qvar™, 3M Health Care, Loughborough, UK) designed to target medication delivery throughout the bronchopulmonary tree and to improve the therapeutic ratio (topical efficacy: systemic safety), thereby offering potential clinical benefits to asthma patients.

INTRODUCTION

Pressurized metered-dose inhalers (pMDIs) are the most widely prescribed devices used to treat respiratory disease. Successful medication delivery from pMDIs is achieved by the use of propellants to aerosolize the drug formulation into respirable particles that can be inhaled into the lung. Until recently, chlorofluorocarbons (CFCs) were used as propellants in pMDIs, but recognition that they deplete the ozone layer has led to an international phase-out of their commercial production and use under the Montreal Protocol 1987 (1,2). Consequently, the continued availability of pMDIs has relied on finding alternative propellants to CFCs that are both nontoxic and have zero ozone-depleting potential. Extensive investigation has identified hydrofluoroalkane-134a (HFA) as a replacement but, because of different physical and chemical properties, direct substitution into existing inhaler devices has not been possible (3–5). Manufacturers have been challenged to reformulate and modify inhaler components

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to accommodate the new HFA propellant and also, where possible, to improve product performance and drug delivery characteristics (6).

TARGETING DRUG DELIVERY IN THE ASTHMATIC LUNG

Asthma is one of the most common chronic conditions in the developed world and, with rising morbidity and mortality rates, it is recognized as a major global health concern (7,8). It is now known that asthma is a chronic inflammatory disorder of the lungs and usually requires prophylactic treatment with antiinflammatory agents, such as inhaled corticosteroids, to control symptoms and improve lung function. Indeed, this is reflected in national and international guidelines that increasingly recommend the use of inhaled corticosteroids as first-line therapy in all but the mildest cases (9,10).

Advancing knowledge about the pathophysiology of asthma, including evidence from tissue biopsies and immunohistochemical studies, has shown that the inflammatory process occurs in both large and small airways, including alveolar tissue (11–14). The realization that small airways may contribute a significant component of the disease process in asthma, coupled with the presence of glucocorticoid receptors within the alveolar wall, airway smooth muscle, and epithelium (15), necessitates reappraisal of the therapeutic targets in its clinical management.

It is generally understood that inhaled corticosteroids exert their therapeutic effects topically on lung tissue rather than from systemic absorption of the inhaled dose (16,17). Consequently, to reach the foci of inflammation found in asthma, drug delivery should be targeted throughout the bronchopulmonary tree. Existing CFC-containing aerosols do not specifically target small airways and therefore are unable to treat effectively the entire pathologic region of involvement in asthma. The mandatory requirement to replace CFCs in pMDI devices has provided an opportunity to embrace current understanding of asthma pathology and target drug delivery to both small and large airways with the intention of treating inflammation more effectively.

AEROSOL CHARACTERISTICS AND TOPICAL DRUG DELIVERY IN THE LUNG

Although topical drug delivery in the lung is influenced by respiratory tract morphology and ventilatory parameters (tidal volume, airflow rate, and respiratory rate), the only factors open to modification by the pharmaceutical technologist relate to aerosol design. There are a number of aerosol variables that can affect drug deposition in the respiratory tract, but the single most important is particle size. The importance of generating the most appropriate particle size for therapeutic response has been studied with inhaled bronchodilators, wherein response to particles <5 μm was found to be greater than that for larger particles (18). Quite often, the in vitro mass fraction <5 μm is regarded as comprising the respirable mass of an aerosol, but this cut-off value gives no account of the actual deposition pattern or relevance to therapeutic efficacy in vivo. It has been suggested that a more useful in vitro measure of the mass fraction of drug available for topical delivery in the lower respiratory tract is represented by the particle mass fraction <2 μm (19). Mathematical models designed to correlate particle size to the site of deposition predict that particles with a mass median aerodynamic diameter (MMAD) of approximately 1 μm would deposit to a greater extent in the lung periphery than particles with an MMAD of 4 μm, which would have a tendency to deposit more centrally and in the oropharynx (20). Although theoretical modeling and in vitro testing are useful development tools, they are unable to account totally for factors that affect particle deposition in vivo, such as inhalation technique and airway pathophysiology in asthma (bronchospasm, excess mucous, and inflammatory oedema), and in vivo studies are required to determine actual sites of drug distribution and clinical response.

Because aerosol drug delivery is influenced by ventilatory parameters, any feature of the aerosol cloud that disturbs the breathing pattern and prevents deep inhalation or breath-holding after inhaler actuation may profoundly affect drug delivery. Aerosols generated by CFC propellants can induce the "cold freon" effect, which describes the cessation of inhalation in reaction to the high-velocity impact and evaporative cooling of the propellant plume as it impacts on the back of the throat (21,22). It would be advantageous if new CFC-free aerosols were designed to have a softer, warmer plume that was more comfortable and acceptable to patients.

SHORTFALLS OF CFC-CONTAINING BECLOMETHASONE DIPROPIONATE (CFC-BDP) AEROSOL SYSTEMS

The primary goal of inhaled administration of corticosteroids in the treatment of asthma is to deliver drugs

directly to the lungs thereby treating inflammation locally, while minimizing systemic side effects. Beclomethasone dipropionate (BDP) is the most commonly prescribed inhaled corticosteroid for asthma treatment and, as with all aerosol medications, its therapeutic efficacy depends on sufficient drug being deposited on target pulmonary tissue (23). However, distribution patterns from CFC-containing pMDIs and dry powder inhalers have shown that typically only 4–30% of the actuated dose is deposited in the lung and the remainder in the oropharynx (24,25). Oropharyngeal deposition is associated with local side effects such as candidiasis and hoarseness (26,27). Of additional concern is the proportion of drug that is swallowed and absorbed through the gastrointestinal tract, thereby contributing to the risk of systemic complications (28).

Given the mandatory replacement of CFC propellants in drug aerosols and the shortfalls of existing CFC-BDP formulations, it is desirable to develop a new BDP aerosol system that diminishes oropharyngeal deposition and produces a more diffuse distribution of drug throughout asthmatic airways.

DEVELOPMENT OF AN HFA-BDP AEROSOL SYSTEM

Development Strategy

At the outset, the research program to replace CFC propellants with HFA propellant in BDP aerosol systems had the option of taking one of two possible routes: to develop a CFC-free "generic equivalent" or to capitalize on advancing medical knowledge and pharmaceutical technology to improve asthma therapy. Although the generic equivalent option offered the potential advantages of a transparent changeover for patients and a comparatively direct development plan, it overlooked the opportunity to enhance drug delivery characteristics and to improve product performance. After the decision to accept the challenge and optimize drug delivery, it was necessary to devise an appropriate development strategy.

Optimization of Particle Size

Unlike the formulations of conventional CFC-BDP aerosols, comprising drug and surfactant suspended in a mixture of two CFC propellants, formulation of BDP in HFA-134a propellant resulted in a solution without the need of surfactant (Qvar, 3M Health Care, Loughborough, UK) (6). Integration of new valve and actuator technology with the solution formulation produced a new generation of finer aerosols. Comparative in vitro particle size analysis of the emitted aerosol, as measured by the Andersen cascade impactor, revealed differences in mean particle size and distribution between the HFA-BDP and CFC-BDP formulations (Fig. 1) (29). First, a smaller fraction of the emitted dose from the HFA-BDP aerosol impacted in the throat of the apparatus, which simulates the human oropharynx. Second, the HFA-BDP solution generated an aerosol with a smaller MMAD (1.1 vs. 3.5 μm from the CFC-BDP suspension). Third, taking the respirable mass fraction to be particles <4.7 μm (which is usual for the Andersen impactor), approximately 60% of the HFA-BDP dose was <4.7 μm. This compares with approximately 30% of the CFC-BDP dose of <4.7 μm, a value consistent with that reported previously (30). Although these in vitro data suggested that compared

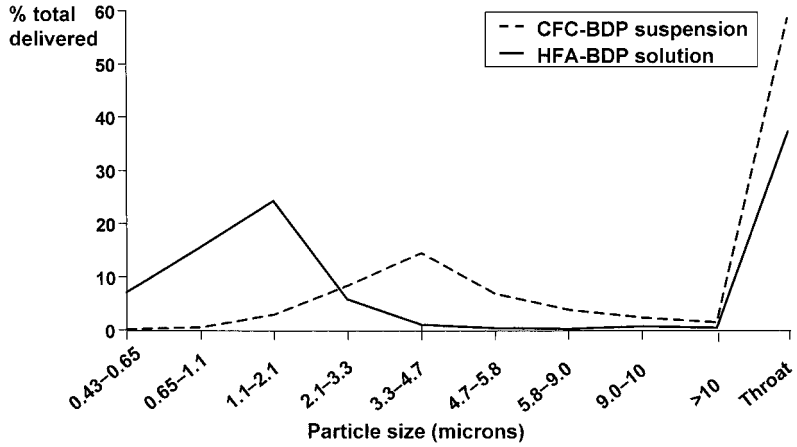

Figure 1. Particle size distribution of BDP in CFC suspension and HFA solution (29).

with CFC-BDP, a greater proportion of the exactuator dose from the HFA-BDP aerosol would be targeted in the lung and less deposited in the oropharynx, additional studies were required to ascertain actual drug distribution in vivo.

In Vivo Drug Deposition Profile

To evaluate the deposition of the drug particles in the lung, direct radiolabeling studies were performed. After validation of the radiolabeling technique to ensure that representative particles of all sizes were labeled and that the radiolabeling method had not altered aerosol characteristics (MMAD, total mass of drug released from the actuator, respirable fraction), lung deposition of ^{99m}Tc-radiolabeled HFA-BDP and CFC-BDP (Beclovent, Glaxo Wellcome, Research Triangle, NC) was studied in healthy subjects and patients with mild asthma (29). Each participant had to demonstrate excellent pMDI technique and a reproducible inhalation pattern. After inhalation, the amount of drug deposited in the lungs and oropharynx and exhaled through a filter trap was measured by gamma scintigraphy. Figure 2 shows typical gamma camera images of the deposition patterns of both radiolabeled aerosol systems. The aerosol generated from the HFA-based solution not only delivered most of the drug to the lungs (>50% of the exactuator dose) and less in the oropharynx (<35% of the exactuator dose), but also distributed drug throughout the lungs. A diffuse distribution pattern was seen from HFA-BDP, with drug deposition evident in central, intermediate, and peripheral airways. Also, because of the particle size characteristics, approximately 10% of the dose was exhaled. In comparison, the majority of the drug from CFC-BDP was deposited in the oropharynx, and <10% of the exactuator dose reached the lungs, mostly in the central airways.

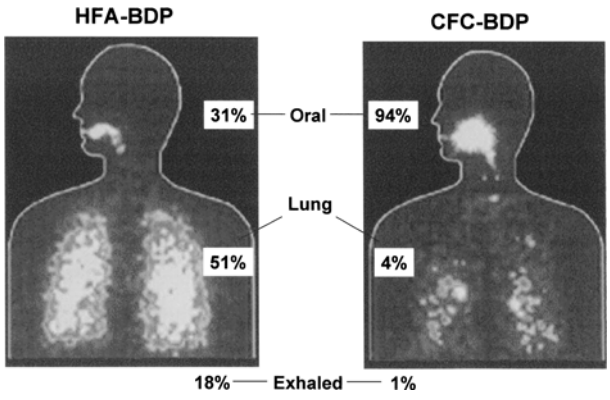

Figure 2. Comparative deposition patterns of radiolabeled BDP from HFA- and CFC-based aerosol systems (29).

It is apparent from radiolabeled drug deposition studies that the fine aerosol of HFA-BDP reverses the pattern of distribution typically observed with existing CFC-BDP inhalers. In particular, HFA-BDP has improved drug delivery to the peripheral airways and significantly reduced oropharyngeal deposition. Additional investigation was warranted to determine whether the improved delivery characteristics of the HFA-BDP aerosol translated into therapeutic benefits, such as a reduction in BDP dose while maintaining control of asthma symptoms.

Modification of Spray Force and Temperature

The "cold freon" effect experienced by some patients using pMDIs is regarded as a function of aerosol spray force and plume temperature. A test apparatus was constructed to measure spray force and plume temperature at a distance, simulating the aerosol spray striking the back of the throat. A quantitative difference was found among various pMDIs, but modification to components in the HFA-BDP inhaler allowed emission of a softer and warmer plume than in other devices, which is less likely to induce a cold freon response (Figs. 3 and 4) (31).

Assessment of Clinical Benefits from Improved Drug Delivery

The improved pattern of drug distribution found with the HFA-BDP aerosol has provided an opportunity to assess the potential clinical benefits of delivering antiinflammatory medication topically to both small and large airways. Presently, several different methods of assessment have been used:

- Dose-response measures of asthma control, such as lung function (forced expiratory volume in 1 [FEV_1])
- Bronchoalveolar lavage to determine the effect on markers of bronchial and alveolar inflammation
- Helical thin-section high-resolution computed tomography (HRCT) to assess small airway function

Dose–Response Study

The design of clinical studies to compare the efficacy of inhaled corticosteroids is confounded by numerous factors other than drug and device differences, such as inhalation technique. However, the most conclusive

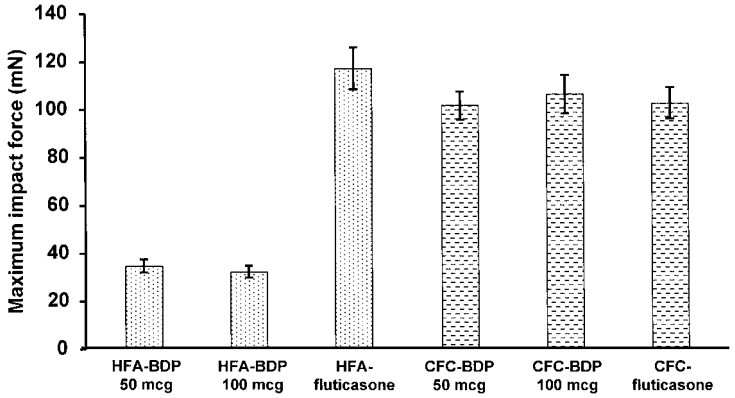

Figure 3. Mean maximum impact force of spray (m*N*) for pMDI corticosteroids ($n = 15$) (31).

data for evaluating two inhaled corticosteroids are derived from dose–response studies (24). A rigorous dose–response study was designed to evaluate the comparative dose ratio of HFA-BDP and CFC-BDP while taking account of the factors that have previously contributed to inconclusive dose–response outcomes (32,33). For example, patient noncompliance with treatment and variability of efficacy measures were reduced by ensuring correct pMDI and pulmonary function test technique at frequent clinic visits (5 days/week) under direct supervision. A total of 323 steroid-responsive patients with moderately severe asthma were randomized to receive HFA-BDP or CFC-BDP (Vanceril, Schering-Plough, Kenilworth, NJ) at daily dosages of 100, 400, or 800 μg for 6 weeks. A plot of the mean change in the baseline for FEV_1 as percentage predicted showed a notable improvement in the first week that tended to plateau by week 6 (Fig. 5). Regression analysis of change from baseline in FEV_1 as a percent of predicted normal at week 6 showed a significant linear trend for dose–response for both HFA-BDP ($p = 0.009$) and CFC-BDP ($p = 0.003$), with Finney's bioassay method estimating the comparative dose ratio of HFA-BDP compared with CFC-BDP to be 2.6 [95% confidence interval (CI):1.1–11.6] (Fig. 6).

From the shape of the dose–response curves usually found with inhaled corticosteroids, it was anticipated that the approximate 10-fold increase in pulmonary delivery of HFA-BDP compared with CFC-BDP would not lead to a 10-fold improvement in lung function. However, the leftward shift of the dose–response plot for change from baseline in FEV_1 as percent of predicted indicated that a greater dose of CFC-BDP than of HFA-BDP was required to produce the same improvement in lung function. Indeed, HFA-BDP gave equivalent improvement in lung

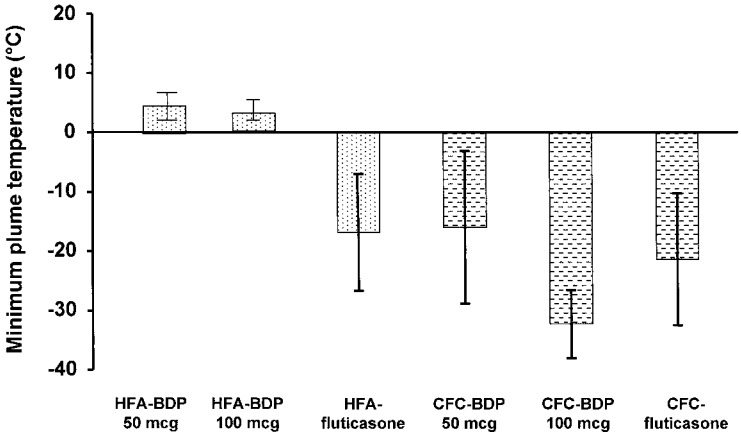

Figure 4. Mean minimum temperature of spray (°C) for pMDI corticosteroids ($n = 10$) (31).

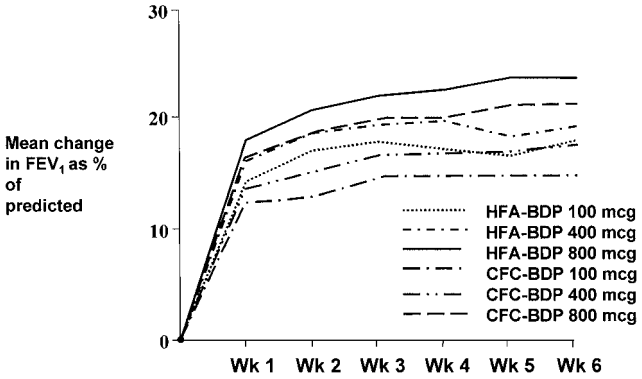

Figure 5. Mean change from baseline in FEV_1 as percent predicted by week (32).

function to CFC-BDP at approximately half the total daily dose, suggesting that it may be possible to reduce the nominal BDP dose without compromising asthma control.

Evaluation of Bronchial and Alveolar Inflammation

Bronchoalveolar lavage (BAL) is an in vivo technique that involves flushing an area of the lung with saline and retrieving the fluid containing cells and secretions for analysis. BAL was performed on two groups of 10 healthy, nonsmoking subjects before and 2 weeks after a course of either inhaled CFC-BDP (Filair, 3M Health Care, Loughborough, UK) or HFA-BDP (400 μg), or placebo, twice daily (34). Alveolar macrophages, a type of inflammatory cells, were harvested from BAL fluid and incubated with inflammatory stimulants to induce the release of the proinflammatory mediator tumor necrosis factor alpha (TNF-alpha). Analysis showed that in vitro production of TNF-alpha by alveolar macrophages was significantly modulated after in vivo administration of HFA-BDP ($p < 0.01$), but was unaltered by CFC-BDP compared with placebo. This infers that unlike the larger particles from CFC-BDP, the drug particles released from HFA-BDP are able to penetrate and modify the inflammatory response within the terminal airways and alveolar space.

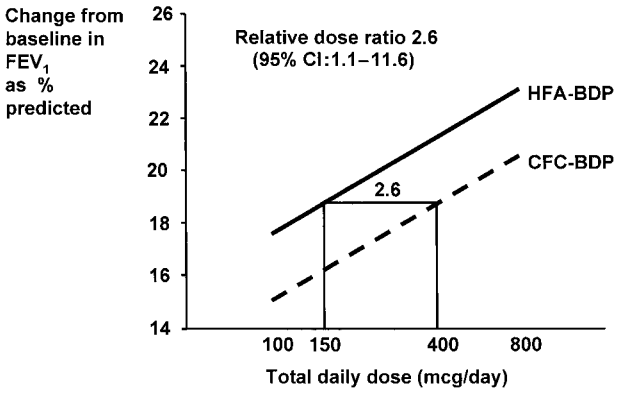

Figure 6. Regression analysis of change from baseline in FEV_1 as percent predicted at week 6 (32).

Assessment of Small Airway Obstruction

Airway obstruction, a hallmark of asthma, causes air trapping and regional hyperinflation even in mild disease. Although small airways are not directly visible by current radiographic techniques, indirect assessment is possible by helical thin-section HRCT (35). A double-blinded, parallel group study was performed in 31 patients with mild to moderate asthma who were randomly assigned treatment with HFA-BDP or CFC-BDP (Beclovent), 200 μg daily, for 4 weeks (36). Each patient responded to methacholine challenge, and the lowest concentration of methacholine that induced a 20% drop in baseline FEV_1 was determined. Helical thin-section HRCT was performed before and immediately after methacholine challenge at study entry and at the end of treatment. Regional hyperinflation was assessed by lung attentuation curves (LAC), which showed the distribution of attenuation in the pulmonary region under examination. A shift in the methacholine-induced LAC showed significantly reduced air trapping in the HFA-BDP group compared to the CFC-BDP group. This observation was attributed to the enhanced penetration of HFA-BDP into peripheral airways alleviating small airway obstruction.

Translation of Enhanced Drug Delivery in Clinical Practice

Reduced drug deposition in the oropharynx and more efficient drug delivery throughout the lungs suggest that the HFA-BDP aerosol may have an improved therapeutic ratio (topical efficacy:systemic safety). Clinical data show that HFA-BDP provides asthma control equivalent to that for CFC-BDP, at approximately half the total daily dose and, in addition, did not reveal any unexpected adverse effects (37,38). Furthermore, despite the potential of greater systemic availability through topical absorption in the lung, HFA-BDP caused no more adrenal suppression than did CFC-BDP at the same exactuator dose (39). Overall, equivalent efficacy at a lower dose and equivalent safety at the same dose imply that HFA-BDP may have an improved therapeutic ratio compared to CFC-BDP.

OTHER CFC-FREE CORTICOSTERIOD METERED-DOSE AEROSOL SYSTEMS

As yet there is limited data in the literature referring to the in vitro aerosol characteristics, in vivo deposition, and clinical efficacy of other corticosteroids formulated in HFA propellant. Some manufacturers may have chosen to develop HFA-aerosol systems with the same particle size distribution and characteristics as CFC-aerosol systems to allow a simple transition from CFC-based to HFA-based products. Indeed, solution formulations of BDP and budesonide in HFA with the addition of nonvolatile components (glycerol or polyethylene glycol) and modification of the actuator have produced similar patterns of in vitro deposition as CFC aerosols (40). Considering that these formulations show pharmaceutical equivalence, they may also be expected to have clinical equivalence and similar high oropharyngeal and low lung deposition profiles. Also, a formulation of flunisolide in HFA has shown fractionation of the drug in the oropharynx and lung comparable with that of the CFC formulation in normal subjects and similar ratios of distribution in the peripheral and central regions of the lung (41).

CONCLUSIONS

It is possible to develop HFA-containing aerosols with in vitro and in vivo characteristics similar to those of CFC-containing aerosols, allowing a seamless transition from CFC- to HFA-based products. Alternatively, in view of the fact that asthma is an inflammatory disorder that involves both small and large airways, the mandatory necessity to reformulate BDP in a CFC-free aerosol system has presented an opportunity to improve drug delivery characteristics and target both central and peripheral airways. Advances in formulation design and inhaler technology have led to the development of a finer HFA-BDP aerosol that delivers most of the inhaled dose to the lung rather than to the oropharynx, unlike existing CFC-BDP systems. As a consequence, extrafine HFA-BDP achieves equivalent asthma control to conventional CFC formulations at a significantly reduced dose. In consideration of the equivalent efficacy at a lower dose and the apparent equivalent safety at the same dose, HFA-BDP appears to have a more favorable therapeutic ratio than does CFC-BDP and represents an advancement in the clinical management of asthma.

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