Targets for inhaled treatment

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Introduction

The role of small airway inflammation in asthma has received much attention in recent years (1-3). This review discusses the targets of inhaled corticosteroid asthma medication, highlighting the aerosol characteristics required to achieve deposition of drug throughout the airways of the lung, including the small airways.

Airway inflammation in asthma

Airway inflammation is the basic underlying abnormality in asthma and is apparent in all asthma severities (4). Inflammation is present throughout the lung, affecting both the large and small (internal diameter <2 mm) airways (5). However, the inflammation that occurs in the small peripheral airways may be more severe than that seen in the large central airways (6). In addition, inflammation in the alveolar compartment, as indicated by increased numbers of CD4+ T-lymphocytes, appears to be particularly associated with nocturnal asthma (7,8).

The aim of any asthma therapy is to prevent and reverse airway inflammation. At present, inhaled corticosteroids such as beclomethasone dipropionate (BDP), are the most effective anti-inflammatory agents available for the treatment of asthma (4). Inhalation, for example via a pressurized metered dose inhaler (pMDI), is the most common method of administering these agents. Delivery via the inhaled route often uses a nominal dose, achieves a high local airway concentration, results in a quicker response, and produces fewer systemic side effects than oral administration (9).

Glucocorticoid receptors

Corticosteroids act by binding to glucocorticoid receptors (GRs) that are found in the cellular cytoplasm (10). The mechanism of genomic action is complex and has been reviewed previously (10-12). In brief, the effect of corticosteroids starts with the activation of the GR to increase or decrease transcription of various target genes linked with chronic inflammatory processes.

GRs are ubiquitously distributed throughout the lung, with a higher density found in the alveolar walls and endothelium and the smooth muscle of the bronchial and pulmonary vessels (13). Smaller numbers of GRs are found in the upper airway epithelium and smooth muscle. Since there is evidence of a high density of GRs in the alveoli, it seems reasonable to include this site as a likely target for inhaled corticosteroids. In order to reach all GRs it is clearly important to deliver medication to small, medium and large airways.

Deposition mechanisms

There are three deposition mechanisms that act concurrently on aerosol particles; inertial impaction, gravitational sedimentation and Brownian diffusion. For a given breathing pattern and lung morphology, the different fraction of the aerosol, based on particle size and density, will be acted upon by the three lung deposition mechanisms to different degrees.

The logarithms of the particle sizes in an aerosol from an MDI are normally distributed (14). They can be defined by the following equation (15):

\[ \ln \text{MMAD} = \ln \text{CMD} + 3(\ln \text{GSD})^2 \]

where the mass median aerodynamic diameter (MMAD) is the aerodynamic diameter above and below which 50% of the mass of particles within the aerosol are contained, the count median diameter (CMD) is the diameter above and below which 50% of the total number of particles within the aerosol are contained, and the geometric standard deviation (GSD) is the range of distribution of aerosol particle size around the median.

For MDIs, cascade impactors give a direct measure of the MMAD and GSD. The aerodynamic parameter is most commonly used to describe pharmaceutical aerosols, however, it should be remembered that the CMD distribution is markedly skewed towards much smaller particle sizes. This may well be important therapeutically. For aerosols with an MMAD of between 0.5 and 5 μm, deposition in the tracheobronchial airways will be due to impaction and sedimentation, whereas deposition in the lower airways will be due to sedimentation and Brownian diffusion. Which deposition mechanism (and, therefore, site of deposition) predominates depends primarily on particle size. For larger particles, movement by gravitational sedimentation is most important. For particles smaller than 0.5 μm, Brownian diffusion becomes a more
appropriate explanation for deposition mechanism than sedimentation, and as particle size decreases, the particles are able to travel further by this mechanism of diffusion:

When considering the design of an aerosol plume, both the MMAD and GSD should be taken into consideration. If two MDIs have the same MMAD but a different GSD, or vice versa, modeling shows that they will have a different lung deposition profile (16). Changes in both measures of particle size are likely to affect the dose to the target tissues and the site of drug deposition in the airways (16).

The overall cross-sectional surface area of the airways increases towards the periphery of the lung (17). As the surface area increases, the flow of air decreases. At the terminal bronchioles there is no airflow and small particles of drug may move into the alveoli by the process of Brownian diffusion (Fig. 1).

Inhaled drug deposition into the airways

Since GRs are found throughout the airways it is important to distribute the drug throughout the lung, including the peripheral airways. The design of any inhaler device/corticosteroid combination should strive to achieve this distribution. Therefore, the delivery profile of an inhaled corticosteroid into the tracheobronchial tree is an important characteristic with likely therapeutic consequences.

Particles of less than 5 µm have been termed ‘respirable’ (9) as they are more likely to distribute further than the upper airways, resulting in tracheobronchial and pulmonary distribution (18). Less deposition of inhaled drug occurs in the upper respiratory tract and more in the airways of the lower respiratory tract as MMAD decreases (19). Therefore, the probability of a particle penetrating the tracheobronchial tree is correlated with MMAD. The smaller the MMAD, the further down the tracheobronchial tree the drug particle is likely to deposit (Fig. 2). Furthermore, for a given respirable mass, the number of particles in the dose increases exponentially as the MMAD decreases. The greater number of small particles facilitates more even distribution as the aerosol cloud is inhaled and transported through the many bifurcations from the central to the peripheral airways.

Hydrofluoroalkane-134a (HFA)-BDP extrafine aerosol (QVAR™, 3M Pharmaceuticals, St Paul, MN, U.S.A.) has a smaller average MMAD (1.1 µm) than conventional chlorofluorocarbon (CFC)-BDP (3.5 µm) (20). Due to the smaller mass and, therefore, momentum of the HFA-BDP particles, HFA-BDP is delivered with a considerably lower impact force compared with CFC-BDP (21). This softer spray results in less undesirable throat deposition with HFA-BDP than with CFC-BDP. The plume from the HFA-BDP MDI is also warmer (approximately 3°C) than CFC-containing MDIs (as low as -30°C), thus minimizing the likelihood of the patient experiencing the ‘cold-freon’ effect, which can prevent the patient inhaling the product sufficiently (21). These factors may explain the increased total lung deposition (with consequent decreased oropharyngeal deposition) seen with HFA-BDP compared with CFC-BDP. In healthy subjects, the mean percentage lung...
deposition of radiolabelled HFA-BDP was 55% compared with 4% with CFC-BDP (20). This study also demonstrated that, in patients with asthma, 56% of a dose of radiolabelled HFA-BDP was deposited in the lungs. Further, the distribution of xenon-133 gas (used as an indicator of maximum lung dispersion) was similar to that of HFA-BDP, indicating that the distribution of HFA-BDP throughout the lung is virtually optimal (Fig. 3). Clinical studies have confirmed the therapeutic benefits of improved lung deposition. A dose-response study comparing HFA-BDP with CFC-BDP (both at 100, 400 and 800 μg day⁻¹) demonstrated that HFA-BDP provided equivalent asthma control at less than half the daily dose of CFC-BDP (22). HFA-BDP had equivalent efficacy at a 2.6-fold lower dose than CFC-BDP with regard to FEV₁ percentage predicted and at a 3.2-fold lower dose than CFC-BDP with regard to FEF₂₅₋₇₅%.

Computed tomographic scanning

Airway resistance in the small airways is very low and is estimated to be about 10% of the total (23). This means that inflammation in the small airways is not easily detected by conventional measures of assessing lung function and, particularly during the early stages of asthma development, may not manifest itself as measurable symptoms (23). From a study of patients with newly diagnosed asthma, Laitinen et al. (24) concluded that airway inflammation exists even at the early presentation of asthma.

Computed tomographic (CT) scanning captures fine details of the airways of the lung (25,26) and may be able to show subtle differences, particularly in the small airways, that are not readily identified by conventional measures of pulmonary function. For example, a recent double-blind randomized study showed HFA-BDP to have greater efficacy in the peripheral airways than CFC-BDP as assessed by functional high resolution CT imaging techniques (27).

Conclusion

GRs are key targets for inhaled therapy as they are involved in modulation of the inflammatory process that occurs in asthma. They are located throughout the airways of the lung, including the alveoli. A small aerosol particle size of an inhaled corticosteroid, for example 1 μm as seen with HFA-BDP extrafine aerosol, appears to have the optimum characteristics for reaching the entire tracheobronchial tree including the small airways. This, in turn, should lead to a favourable efficacy profile, since the active drug is presented as an aerosol designed to reach all of the desired inflammatory targets in the airways.

References

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