Introduction

The relative importance of small airways in asthma

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Why are the small airways important in the pathology and treatment of asthma? Asthma is an inflammatory disorder of the airways often associated with structural abnormalities and progressive decline in lung function. Successful therapy therefore requires efficacious drug delivery to these airways. Traditionally, inhaled asthma therapies have mainly targeted the large airways of the lung. There is increasing evidence, however, of inflammation and chronic structural changes within the small airways in patients with asthma, and thus it is pertinent that the therapeutic targets for inhaled corticosteroids are reconsidered to take into account all of the pulmonary tissues that may respond to inhaled anti-inflammatory treatment.

The challenge now lies in evaluating the value of the small airways as therapeutic targets in asthma. The articles in this supplement critically assess the evidence for inflammatory and structural changes in the airways of patients with asthma, recent technical advances in the monitoring of inflammation, and the clinical efficacy of topical corticosteroids and how this may relate to their ability to target the small airways.

As the small airways normally contribute only about 10% of airway resistance (the 'quiet zone'), the difficulty of in vivo sampling and physiological measurements that are specific for this site has led to their considerable under-evaluation (1). However, techniques such as transbronchial biopsy, along with the analysis of resected lung tissue and post-mortem tissue, have demonstrated that extensive disease exists in the small airways. Airway remodelling, potentially leading to a component of fixed airflow obstruction, has also been shown to occur in the small airways (2). Fibroblast proliferation and collagen deposition may also contribute to this permanent tissue damage (3,4).

In contrast to conventional pulmonary function tests, which lack specificity for small airways, recent advances in high-resolution computed tomography imaging have allowed non-invasive reproducible measurements of structure-function relationships in the small airways and in vivo assessment of drug deposition (5,6). This method, although providing indirect data of air trapping and hyperinflation as an indication of small airways obstruction, is a step forward from the standard approach of planar imaging (7).

Inefficient drug delivery systems have long been accepted, providing they produce a clinical response. Recent evidence, however, indicates that inflammation of the lung persists in those patients treated with corticosteroids that are deposited only in the central large airways (8), highlighting the need for the optimization of drug delivery to the small airways. Chronic poorly controlled inflammation in the peripheral airways may contribute to the observed accelerated decline in lung function with age (9) and, notably, in patients with newly diagnosed asthma (10). Furthermore, delayed or inadequate anti-inflammatory treatment may allow deleterious airway remodelling to take place, resulting in permanent loss of lung function (11-14).

Recently published data from a 15-year follow-up of the Copenhagen Heart Study has highlighted the extent of FEV₁ decline over time in adults with asthma (15). This decrease in FEV₁ was significantly greater among subjects with asthma than among those without the disease (P < 0.001), regardless of smoking history, although smoking, as anticipated, significantly accelerated the decline in FEV₁. Such findings support the perception of ongoing tissue injury and repair associated with asthma which may reduce distensibility of the lungs and adversely affect lung function (14).

From the evidence that inflammatory and structural changes occur throughout the airways, it is clear that anti-inflammatory treatment needs to be directed at both the large and small airways to achieve suppression of inflammation throughout the entire bronchial tree. Enhanced drug deposition can be achieved with the aid of improved technology. However, not all metered-dose inhalers (MDIs) and dry powder inhalers are necessarily efficient at specifically depositing medication in the peripheral airways of the lung.

Even with optimal inhalation technique only 10% of the steroid dose generated by chlorofluorocarbon (CFC)-based MDIs reaches the lower respiratory tract, with most of the medication deposited in the oropharynx (16). However, new propellants have been researched and developed following the decision to discontinue the use of CFCs. For example, beclomethasone dipropionate (BDP) has been reformulated in hydrofluoroalkane-134a (HFA) propellant (QVAR™, 3M Pharmaceuticals, St Paul, MN, U.S.A.).
Due to improved inhaler technology, this MDI produces an extrafine aerosol of medication. As the particle size of HFA-BDP (1.1 μm) is three times smaller than that with the conventional CFC-BDP formulation, approximately 60% of the inhaled dose is deposited in the lungs (17). Furthermore, improved drug delivery to the small airways is achieved as the drug enters the lungs with uniform distribution (18). As a greater proportion of drug is distributed in the lungs, lower doses can be used to achieve an equivalent clinical response to conventional CFC-based corticosteroid inhalers.

Clearly, the small airways are an important therapeutic target for inhaled corticosteroids which cannot be overlooked. If we are going to make a positive long-term impact on the function and structure of the airways in asthma, we need to be committed to providing inhaled therapies that are distributed throughout the airways, both centrally and peripherally, to maximize both the efficacy and safety of these treatments.

References