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Effect of nasal inflammation and of intranasal anti-inflammatory treatment on bronchial asthma

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It is logical to look upon the nose and the bronchi as integrated parts of one 'united airway' and we would like to advance the hypothesis that optimal management of airway disease, caused by inhaled allergens, may necessitate control of inflammation in all parts of the airways. Nasal inflammation can aggravate asthma symptoms, and there is a rationale for giving intranasal anti-inflammatory treatment to patients with asthma. (i) Inhaled allergens are predominantly deposited in the nose, whether a patient suffers from rhinitis, asthma or both. (ii) Antigen presentation consequently takes place in the nose, and the response of the airway immune system is thus initiated in the nasal mucous membrane. (iii) Antigen presentation in the nose may possibly induce cell recruitment and activation not only in the nasal mucosa but also in the lower airways. (iv) Suppression of nasal inflammation may therefore be necessary for optimal management of asthma.

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Introduction

It is common clinical practice to treat rhinitis and asthma as two separate diseases, using intranasal corticosteroids (and antihistamines) for nasal symptoms, and orally inhaled corticosteroids (and bronchodilators) for asthma. It seems logical, however, to look upon the airways as a single entity from the tip of the nose to the alveoli, and evidence is accumulating that nasal inflammation can influence the lower airways and that intranasal anti-inflammatory treatment may have a beneficial effect on asthma (1).

Below, we will discuss an issue which, with a popular term, can be called the 'united airways' concept. It presents the rationale for treating the nose in asthma patients.

We will emphasize that this concept is based largely on speculations, and at present there is no strong case for changing the therapeutic practice. However, we hope that the hypothesis presented may be an inspiration for the performance of controlled studies, which may or may not confirm the hypothesis.

Rhinitis and Asthma are Inflammatory Diseases

It is our starting point that both allergic rhinitis and asthma are inflammatory consequences of allergic sensitization and reaction to inhaled allergens, at least when the diseases begin in childhood and adolescense (2).

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The Nose is a Filter

It is normal to breathe through the nose, which acts as a filter for the inhaled air, thereby protecting the delicate structures in the lower airways (3). Due to its specialized anatomy, the nose is an efficient filter, retaining the majority of particles, larger than 10 μm, and this includes pollen grains and mite faeces pellets (4). A part of small particles in the inhaled air will also be deposited in the nose due to turbulence of the inhaled airstream behind the narrow entrance, the internal ostium localized 1·5 cm from the nostril (5). At least 50% of the entire resistance to the inhalation is localized to the internal ostium (6), which indicates that this area plays an important role in normal airway physiology.

Antigen Deposition and Presentation in the Nose

Fokkens and coworkers have shown that the nasal mucosa contains potent antigen-presenting cells which have the characteristics of dendritic Langerhans cells (7). As a major part of inhaled allergens, as mentioned, are deposited in the nose, it follows that antigen presentation takes place mainly in the nasal mucosa, whether a patient suffers from rhinitis, asthma or both. The number of nasal antigen-presenting Langerhans cells is increased by experimental allergen challenge and in symptomatic allergic rhinitis (7).

Immunological Homing

As T lymphocytes cannot directly recognize antigen in solution, their stimulation requires antigen processing and

presentation by antigen-presenting cells. This probably takes place in the nasal mucosa and in the regional lymph nodes.

The activated T cells 'home' in the mucous membrane, initially stimulated by the antigen. It is known from studies of the gastrointestinal tract that homing is not confined exclusively to the antigen-stimulated mucous membrane, but occurs also in adjacent mucosal areas (8). If the same applies to the airways, it means that antigen deposition and presentation in the nose may result in T-cell-induced inflammation in the bronchi. This issue, significant for our hypothesis, needs further investigation in the airways.

Release of Cytokines and Mediators Leads to Cell Recruitment and Activation

When the allergen reacts with mediator cells in the nasal mucosa, they generate and release cytokines, chemokines and mediator substances (9). These molecules recruit the inflammatory cells by upregulation of adhesion molecules in the nasal vasculature (9). However, cytokines/chemokines and mediators are also released to the circulation, and it is possible that these molecules can recruit and activate circulating inflammatory cells, which may reach not only the nasal mucosa but also other parts of the airways.

These speculations on an effect of nasal antigen stimulation and allergic inflammation on the lower airways have gained support from observations that an allergen challenge in the nose increased bronchial reactivity in asthma patients (10–12).

Effect of Intranasal Corticosteroid Treatment on Lower Airways

A number of studies have shown that intranasal corticosteroid treatment for allergic rhinitis has a beneficial effect on non-specific bronchial responsiveness and on asthma symptoms (13–20). There are at least two possible explanations of this phenomenon.

1. Intranasal corticosteroid treatment results in a dramatic reduction in the number of nasal antigen-presenting Langerhans cells (7). This inhibition of the initial step in the allergic sensitization and reaction may have the potential of inhibiting not only allergic inflammation in the nose but also in the bronchi, as described above.
2. We have recently shown that intranasal corticosteroid therapy not only abolishes the allergen-induced increase in the number of eosinophils and of eosinophil markers in nasal lavage fluid but also in the circulation (21). It seems likely that the treatment inhibits the release of cytokines/chemokines and the subsequent upregulation of adhesion molecules in the allergen-challenged nose, which may be the cause of the reduced eosinophil recruitment and activation, locally and systemically. Thus, it is possible that intranasal treatment may reduce the cytotoxic effect of eosinophil proteins in the entire airway mucosa.

Therapeutic Implications

The above theoretical speculations and experimental observations indicate that treatment of nasal inflammation may be required in order to obtain full control of bronchial inflammation and asthma symptoms. There is now a series of placebo-controlled therapeutic trials which support this hypothesis.

Some rhinosurgeons claim, on the basis of uncontrolled observations, that radical surgical removal of the pathologically changed mucous membrane in the paranasal sinuses can improve the asthma condition in patients with nasal polyposis, hyperplastic sinusitis and non-allergic asthma (22).

There is anecdotal evidence, and a few clinical studies, which suggest that treatment of upper airway infection and inflammation may be necessary for the full control of exacerbations of asthma in childhood (23,24). Before these observations can result in a changed therapeutic practice, they must be confirmed in controlled prospective trials. Also, studies of the effect of intranasal corticosteroids on recalcitrant asthma in children and in adults are warranted.

Nasal Inhalation of Corticosteroid for the Simultaneous Treatment of Rhinitis and Asthma

Rhinitis and asthma can be treated simultaneously by a single nasal inhalation of corticosteroid through a spacer device. We have found a pronounced clinical effect of this treatment on both rhinitis and asthma symptoms in pollen-allergic adults (25), and there is a similar effect in children with perennial rhinitis and asthma (26).

In principle, a nasal inhalation of an anti-inflammatory drug is more logical than an oral inhalation in patients with allergy to inhalants, because allergens are deposited in the nose and not in the mouth. In addition, local adverse effects in the mouth can be avoided completely.

However, there are also arguments against nasal inhalation. First, more corticosteroid is absorbed from the nasal mucosa than from the mouth. Second, a 50% larger dose is needed in order to obtain a similar bronchial deposition with nasal as compared with oral inhalation (27,28). Therefore, it is too early to say whether a nasal inhalation will have a better therapeutic index than an oral inhalation. However, we find it logical to deposit corticosteroid in a way similar to that of the inhaled allergen. If the nose is not treated, potentially harmful inflammatory reactions will continue in asthmatic patients.

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