

REVIEW

Could treating asthma help rhinitis?

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Introduction

The incidence of asthma continues to rise. The National Asthma Campaign recently estimated that more than 9 million people in the UK will have wheezed over the past year, one-third of whom will suffer from asthma [1]. Rhinitis is also very common with approximately one person in six being affected [2]. The costs of asthma represent between 1 and 2% of medical expenditure in developed countries, whilst in less developed countries the cost is probably increasing faster than any other health cost [3]. Asthma costs were recently estimated at £500 million [1]. In the United States annual costs for rhinitis were estimated at \$1.8 billion in 1990.

Co-existence of asthma and rhinitis

Asthma and rhinitis are not often considered together although they frequently coexist and allergic rhinitis may be a risk factor for asthma [4,5]. Approximately 88% of patients with asthma have rhinitis and between 25 and 50% of patients with rhinitis have associated asthma [6]. In patients with both disorders rhinitis appears first in 45% and they are more likely to be atopic, suggesting that rhinitis may influence the development of asthma [7]. How rhinitis can contribute to the deterioration of lung function is only beginning to be understood [6]. For example, factors such as increased mouth breathing due to nasal blockage which increases airway exposure to allergens, the spread of inflammatory mediators to the lungs through postnasal drip, and bronchoconstriction induced by stimulation of sensory nerves and nasobronchial reflexes may all play a role [reviewed in reference 6].

Increased understanding of the pathology of asthma and rhinitis has indicated that they constitute a spectrum of related pathologies with varying severity and responsiveness to treatment [8]. The upper and lower airways have many cells and tissues that are similar, such as surface epithelium, glands, microvasculature and inflammatory cells. However, there are major differences such as the lack of smooth muscle in nasal passages, where the vasculature plays a

major role in nasal obstruction. The pathogenesis of both asthma and rhinitis is complex, involving many different cell types, inflammatory mediators, cytokines and adhesion molecules. Nevertheless, the underlying pathology of both rhinitis and asthma is inflammation in which eosinophilia is a characteristic feature [9,10]. Immunohistological and mediator studies suggest that the disease mechanisms may be similar in nasal and bronchial mucosa [11]. Hence, the key to successful therapy in both conditions is the prevention or suppression of inflammation [9,10]. Inflammatory changes such as activated eosinophils and degranulated mast cells are seen in both rhinitis and asthma, even in mild asthma treated only with bronchodilators. Moreover, bronchial hyperresponsiveness to histamine or methacholine is a common feature in subjects with either asthma or allergic rhinitis, although it occurs to a lesser degree in patients with rhinitis who have no symptoms of asthma [12]. Thus, there is increasing evidence that asthma and rhinitis should be considered together.

Current therapies for allergic rhinitis and asthma

Many of the inflammatory mediators involved in asthma and rhinitis are similar, and therefore both conditions are treated with similar anti-inflammatory medications, e.g. steroids and cromones. However, at present rhinitis and asthma are generally treated independently. One of the main reasons for this is that treatments tend to be applied topically, i.e. intranasal steroids or cromoglycate for rhinitis and inhaled drugs for asthma. The rationale for such topical treatment is to minimize the risk of systemic adverse events and to achieve high drug concentrations at the receptor level in the mucous membrane.

Histamine is one of the many mediators involved in the pathogenesis of allergic rhinitis, and so antihistamines are the mainstay of its treatment. Second generation antihistamines (e.g. terfenadine, cetirizine, loratadine, and astemizole) relieve itching and runny nose and sneezing, but have very little effect on nasal congestion [10]. Antihistamines are generally administered orally but intranasal antihistamines such as levocabastine are equally effective [13]. The use of antihistamines in asthma is unusual, especially in the USA where fears of sedation have restricted their use. Meltzer has suggested that their place in asthma is limited

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to mild to moderate disease where they can block the effects of histamine released spontaneously or in response to allergen or exercise, and may allow the dosage of other treatments to be decreased safely [14]. Although sedation is more unusual than with traditional antihistamines, the potential for cardiac adverse reactions with certain third generation antihistamines exists especially if combined with other medication such as erythromycin or ketoconazole [10,13].

Patients with more persistent or severe rhinitis or asthma are usually treated with topical corticosteroids or sodium cromoglycate, the efficacy of topical steroids being greater [10,15,16]. Nasal steroids are effective and generally well tolerated. They treat all the symptoms of rhinitis including nasal congestion but have only moderate effects on eye symptoms, which are better controlled with antihistamines or cromoglycate eye drops [10]. Corticosteroids exert their effects at multiple points in the inflammatory cascade and have recently been shown to be associated with abrogation of Langerhans cells, which are probably the route of antigen presentation in the nose [17]. Their onset of action is slow and it may take several days or weeks to achieve full therapeutic efficacy. Thus, treatment should be started prior to allergen exposure in seasonal rhinitis. Topical steroid use should be regular and, as with asthma, maintained even in the absence of symptoms. However, these ideals are rarely achieved in reality and poor compliance with medication is the most common reason for treatment failure with topical corticosteroids both in asthma and rhinitis.

The most common reported adverse effects of nasal steroids are local stinging, dryness, pharyngeal irritation, and minor epistaxis; there have also been very rare reports of nasal septal perforation. Inhaled corticosteroids are undoubtedly effective in the treatment of asthma but concerns remain about side-effects at higher doses on, for example, growth and adrenal function [18], the larynx [19], and bone mineral density [20,21]. Since topical steroids are widely used in the management of both asthma and rhinitis, it is not unlikely that individuals who have both conditions may be taking inhaled and intranasal steroids simultaneously. Consequently, the potential for systemic side-effects is increased and should be considered, especially in children.

Sodium cromoglycate is commonly used in the management of asthma and rhinitis, particularly in children and in those with a short history of disease. It is well tolerated and moderately effective against all symptoms of rhinitis, but is generally less effective than nasal corticosteroids except on ocular symptoms where it can be used directly as eye drops. Corticosteroid drops should not be used in the eye except under the supervision of an ophthalmologist because of the risks of herpetic keratitis, glaucoma, and cataracts [13].

Older patients respond less well to sodium cromoglycate [22]. It also has the disadvantage of slow onset of action and needs to be taken at least four times daily which may lead to poor compliance [10], with the added complication of requiring two types of 'puffers' (nasal and inhaled).

Costs of asthma and rhinitis

The economic impact of diseases such as asthma and rhinitis are generally divided into direct, indirect, and intangible costs. Direct costs of asthma include costs of medications, primary care consultations, and hospital in- and out-patient care [23]. In general practice prescriptions account for 85% of the direct costs of asthma [24]. However, the cost of hospital care — much of which may be preventable [23] — dominates the overall costs of asthma and this has nearly doubled in the last 10 years [1]. Indirect costs include those associated with loss of time at school and work, and early mortality among others. Studies have found that patients with both asthma and rhinitis have more lost productivity than those with either asthma or rhinitis alone [25]. In 1988, Meltzer reported that the direct costs of allergic rhinitis in the USA included annual drug expenditures of \$2 billion and estimated indirect costs to include 28 million days of restricted activity and two million lost school days annually [26]. In the UK, the majority of treatments for rhinitis are purchased 'over-the-counter' (OTC). Thus, in contrast to asthma, most expenditure in rhinitis is borne by the patients themselves. The cost of medications may be one reason for poor compliance with therapy and the resulting poor control of symptoms. It can therefore be speculated that, for patients with asthma and concomitant rhinitis, careful prescribing of drugs that treat both nasal and lung symptoms could lead to cost savings for both the healthcare system and the patient, in terms of direct and indirect costs.

Intangible costs are also of great importance in asthma and rhinitis, and are associated with the impact of the disease and its treatment on daily life with a consequent reduction in quality of life; thus, it is hard to put a monetary value on such costs. Quality of life measures provide standardized estimates of the effects of asthma on the patient's daily life and well-being [27]. The influence of therapy upon quality of life is probably one of the most important considerations from the patient's perspective, as patients with allergic rhinitis often find their symptoms annoying, distressing, and incapacitating [13]. Indeed, quality of life measures in rhinitis give worse results for severe rhinitis than for asthma [28,29].

Since patients with inadequately controlled asthma have high expenditures in health care costs, especially hospitalization, a significant cost reduction appears possible by improving asthma control [3]. This has been shown in a study where inhaled corticosteroids were

added to beta-agonists in the maintenance treatment of patients with asthma. More than half of the extra costs of adding the inhaled steroid were compensated for by a reduction in costs of other health care services [30].

Similarly, a recent study in general practice achieved a 43% reduction in hospital admissions, a 65% fall in out-patient appointments and a 23% reduction in exacerbations by increasing prescribing costs from £39 000 to £89 000 [31]. The savings are likely to be greatest among the 10–20% of severely affected asthma patients who normally account for about 50% of the total costs, largely due to repeated hospitalization [3]. The effects of intervention in severe asthma have been studied in New Zealand where strict application of management guidelines has reduced asthma-related mortality and hospitalization [32]. Introduction of inhaled steroids elsewhere has decreased the need for oral steroid courses and hospitalization [33], and patient education has decreased costs [3]. The costs associated with the long-term side-effects of high-dose inhaled corticosteroids are minimal compared with hospitalization costs. Thus, by increasing prophylaxis of asthma and rhinitis, hospitalization costs can be kept to a minimum.

Allergen avoidance

A large proportion of patients suffering from asthma and rhinitis, especially in childhood, have symptoms caused by an allergic response. Identification of their major allergens followed by allergen avoidance measures, where possible, is obviously sensible [16,34]. Allergen avoidance has been shown to lead to a reduction in bronchial hyperresponsiveness in children with allergic asthma [35]. Furthermore, evidence is accumulating that avoidance of allergens during early life may prevent or delay the development of atopic sensitization and subsequent allergic disease in susceptible children [36]. Thus, allergen avoidance may be particularly important for children.

Recent advances in house dust mite avoidance have been made, notably with breathable, allergen-proof bedding which can decrease the symptoms of rhinitis by 40% and those of asthma by 50% [37,38]. Superheated steam at 135°C is becoming available for home use, and destroys both the mites and the remaining faecal allergens [39]. Families with sufferers from atopic asthma should avoid furry or feathered pets [40]; however, where this is not feasible, washing the family cat or dog once a week can achieve a reduction in allergen levels in the home. Allergen avoidance measures therefore impose certain restrictions and necessitate lifestyle changes. These may have different effects on the quality of life of different members of the household. For example, a reduction in troublesome symptoms may improve the quality of life of the sufferer, whereas the additional housework or emotional upset caused by

removal of a family pet may adversely affect the parents and siblings of an asthmatic child. The extent to which individual patients or their families include allergen avoidance measures in their normal lifestyle will depend largely on the severity of their symptoms. Allergen avoidance will ideally reduce the need for medications and medical services, and will provide a cost-effective method for improving quality of life of patients. However, the purchase of special equipment such as bedding imposes an extra financial burden on the household [23]. Another simple strategy to reduce costs associated with asthma is to encourage pregnant women and those with small children to give up smoking and not to permit any smoking in the house where there are young children [40].

Management

If allergen avoidance fails to control symptoms completely, therapeutic intervention is warranted. Antihistamines are the mainstay of treatment for allergic rhinitis, providing relief from symptoms such as sneezing, pruritis and rhinorrhoea. In those patients whose rhinitis symptoms are not adequately controlled by antihistamines, intranasal steroids or cromoglycate should be used.

At present anti-inflammatory therapy for the nose and chest is applied topically, either in the form of corticosteroids or as sodium cromoglycate. This route allows a low dose of medication to be applied directly to the site of action, with minimal side-effects. Despite such considerations, non-compliance with treatment is a common problem. The consequences of poor compliance are an increase in morbidity and increased costs as a result of poorly controlled disease. Therefore, asthma/rhinitis costs could probably be reduced if patient compliance with therapy was improved. Precise monitoring techniques to assess compliance with asthma treatment have only recently been available but suggest great under-usage of prophylactic therapy with surprisingly little over-use of bronchodilator rescue medication [40]. Twice- or once-daily regimens of any form of treatment are associated with compliance rates of 50–80%; however, an increase in dose frequency to three or four times daily reduces compliance to around 40% [41]. Anxiety and depression are also associated with poor compliance [42]. Strategies to improve the regular taking of medication include a simple regime, handwritten instructions, a good patient/doctor rapport, the decreased possibility of side-effects, and patient education with self management schemes [41,43]. Opinions are divided about relative compliance with oral and inhaled medications: one study suggests that there is no difference, i.e. that compliance is patient-dependent rather than drug-dependent [44], whilst another suggests that compliance with oral theophylline is better

than with inhaled corticosteroids. However, in this study the number of patients taking inhaled corticosteroids was very small [45].

Novel therapeutic agents

A single medication with a good tolerability profile and which could effectively treat both asthma and rhinitis could be an advantage in terms of reduced cost and improved compliance. In particular, compliance with preventative treatments that need to be used on a regular basis may be enhanced if the medication can be taken orally once- or twice-daily. Several oral medications are currently available, e.g. corticosteroids, theophylline and antihistamines, and some novel therapeutic agents should be available in the near future, e.g. leukotriene receptor antagonists. Oral corticosteroids are undoubtedly effective in the treatment of asthma and rhinitis but, their use is limited to short spells during exacerbations of asthma or in severely obstructed rhinitis because of systemic side-effects.

Theophylline has long been used in the treatment of asthma and rhinitis, but its anti-inflammatory properties have only recently been recognized [46]. The major place of theophylline in the present treatment of asthma is as a nocturnal adjunct to inhaled corticosteroid therapy in patients with poorly controlled night-time symptoms. Theophylline has also been shown to block symptoms of allergic rhinitis and to decrease mediators such as histamine in nasal lavage [47]. However, the benefits of theophylline may be outweighed by the high risk of adverse effects. Theophylline has a variable clearance rate and a narrow therapeutic window making side-effects such as nausea, gastrointestinal disturbances, tremor and insomnia common, especially in children [48]. These can have a serious effect upon compliance with therapy.

The place of antihistamines is also under review. Recent studies with cetirizine suggests that it has a minor effect on relieving lower airways obstruction but that this, added with salbutamol, a β_2 -agonist, provides prolonged relief over 7–8 h [49]. Cetirizine used in patients with allergic rhinitis showed a protective effect on bronchial hyperreactivity to methacholine at 6 h [50]. Moreover, in patients with allergic rhinitis and concomitant asthma, cetirizine reduces symptoms of both diseases [51,52].

Leukotrienes are potent inflammatory mediators that appear to play a role both in asthma and in allergic rhinitis [53,54]. The novel leukotriene synthesis inhibitors and receptor antagonists have proved to be good bronchodilating drugs with some additional anti-inflammatory properties, and thus may be useful alternative treatments in both asthma and rhinitis.

The investigation of leukotrienes as mediators of immediate type hypersensitivity reactions began with their isolation

in 1940 as a slow reacting substance associated with antigen challenge of sensitized lung preparations [55], and was greatly stimulated by the elucidation of their chemical structure in 1979 [56]. Increased amounts of leukotrienes are found in antigen-challenged lungs of patients with asthma [57,58], in tears [59], and nasal fluid [60–62] after allergen challenge, and in other allergic and inflammatory conditions [63]. Intradermal injection of very low concentrations of sulphidopeptide leukotrienes produces a weal-and-flare reaction [64], they also cause bronchospasm [65], mucus production in the respiratory tract [66], and increased nasal blood flow [67]. Leukotriene B₄ also has chemotactic effects [68] and alters endothelial permeability [69]. Recently, there has been a great effort to develop inhibitors of 5-lipoxygenase, the enzyme responsible for leukotriene synthesis, and leukotriene receptor antagonists [70]. These novel drugs appear to be effective in the treatment of asthma and can also alleviate some of the symptoms of allergic rhinitis [54].

Leukotriene biosynthesis inhibitors include the 5-lipoxygenase inhibitor zileuton [54]. In patients with mild to moderate asthma, zileuton was shown to improve lung function and symptoms, and to reduce bronchodilator usage [71]. The improvement in FEV₁ over baseline was 13.4% at the higher dose (10.6% at the lower dose) equivalent to that achieved with inhaled corticosteroids. Zileuton reduced nasal congestion and LTB₄ levels, but did not alter histamine secretion or sneezing in patients with allergic rhinitis [72]. Although zileuton is orally active it must be administered four times daily, and concerns exist regarding potential hepatotoxicity. The more potent A78773 protected patients with allergic rhinitis from congestion and rhinorrhoea in response to allergen challenge but had no effect on nasal itch or sneezing [72].

Several potent, specific, orally active leukotriene receptor antagonists have been developed and have been shown to be effective and well tolerated in patients with mild to moderate asthma [73–78]. They exert an antibronchoconstrictor effect, reduce asthma symptoms, improve lung function, and reduce the need for bronchodilator use. One of these, zafirlukast (Accolate, ICI 204 219), has an efficacy in patients with mild to moderate asthma [79,80]. As yet, the use of leukotriene receptor antagonists in rhinitis has not been studied fully although zafirlukast, given orally once-daily, did alleviate the main acute symptoms of seasonal allergic rhinitis in a rapid dose-related fashion [81]. Drugs of this class should become available in the UK in tablet form during 1997 and have already been launched in Ireland, Finland, and the USA.

In some patients, aspirin and related nonsteroidal anti-inflammatory drugs (NSAIDs) can provoke profound nasal symptoms such as profuse rhinorrhoea and congestion and/or life-threatening bronchoconstriction. In most patients, the

first symptoms are intense rhinitis followed by chronic nasal congestion which appears over a period of months. Nasal polyps are usually present and asthma and intolerance to aspirin develops subsequently [82]. This aspirin intolerance appears to be due to an overproduction of and increased sensitivity to leukotrienes [73,83]. The 5-lipoxygenase inhibitors and leukotriene receptor antagonists have been shown to decrease the bronchoconstrictor response to aspirin and to prevent all of the nasal responses induced by aspirin in aspirin-sensitive individuals [83]. Thus, anti-leukotriene drugs may be particularly suitable for the treatment of patients with aspirin sensitivity.

Rhinitis treatment benefits asthma

Recently, evidence has emerged that anti-inflammatory treatment of rhinitis with topical corticosteroids [84,85] or sodium cromoglycate [86] can improve lower airways function. There are several possible mechanisms for this [6], other than the obvious one of nasal breathing being superior to mouth breathing in terms of filtration, warming, and humidification of inspired air. Conversely, patients with uncontrolled rhinosinusitis may have difficulty in controlling their asthma, despite good compliance with asthma medication. It is not yet known whether early effective treatment of rhinitis can delay or prevent the progression to asthma.

Conclusions

Questions still remain relating to the benefit of treating asthma and the effects new therapeutic agents have on concomitant diseases: is it necessary to treat both the nose and chest with topical anti-inflammatory agents or will treatment of one site (the nose) help both?; what are the long-term implications of high-dose corticosteroid therapy?; how can compliance be improved, both with environmental and therapeutic measures?; and, most importantly, will oral therapy which treats both asthma and rhinitis prove popular with patients and improve compliance, thus conferring economic benefit?

It is important to bear in mind that underdiagnosis of asthma or late institution of anti-inflammatory medication can result in irreversible loss of respiratory function. It also increases the need for emergency care and in-patient treatment, and leads to underachievement both in the sufferer, who may miss school and work, and in his or her immediate relatives.

The treatment of rhinitis and asthma, and the economic implications when patients' symptoms are not controlled pose interesting problems in the treatment of asthma and concomitant diseases. Further research is required into whether the early treatment of rhinitis can prevent or

delay asthma, and if an oral therapy, which treats both asthma and rhinitis, proves popular with patients. An improvement in compliance will thus confer economic benefits.

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