

Effect of intranasal corticosteroid treatment on asthma in children and adults

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Link between rhinitis and asthma

Rhinitis is common and prevalence rates are increasing in westernized countries (1). Rhinitis and asthma frequently coexist, recent estimates suggesting that up to 80% of patients with asthma may have coincident rhinitis symptoms. Rhinitis is a recognized "risk factor" for subsequent development of asthma (2). An important question is whether the frequent coexistence of rhinitis (B) and asthma (C) merely represents a common mucosal susceptibility to a variety of potential causal factors (A) (Fig. 1). Alternatively, the association between rhinitis and asthma may be causal in that various injurious agents (A) may provoke rhinitis (B) with subsequent development of asthma (C). A third possibility is that the association represents *both* a common mucosal susceptibility *and* various causal associations, the balance varying between different individuals. Finally, a less likely possibility is that asthma may be causally related to the development of rhinitis (i.e. C causes B).

A common mucosal susceptibility giving rise to rhinitis and asthma in the same individual is suggested by other common disease susceptibilities shared by the upper and lower airway. For example, sinusitis and bronchiectasis frequently coexist. Granulomatous diseases, such as sarcoidosis and Wegener's granuloma, frequently involve both the upper and lower airway. The viral "common cold" may often be associated with lower respiratory tract symptoms (3), although the temporal progression of symptoms from coryza to cough, with or without wheeze and mucus production, may argue in favour of either a common mucosal susceptibility or a causal association.

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Inflammatory mechanisms

Inhaled common allergens such as pollens and house dust mite represent important provoking factors in atopic individuals with rhinitis and asthma. The pathophysiology of allergic rhinitis involves the IgE-dependent activation of mast cells and/or basophils with the release of a plethora of inflammatory mediators (4) which include histamine, leucotrienes, prostaglandins, bradykinin, platelet-activating factor and various enzymes, particularly tryptase. These mediators are detectable in nasal lavage fluid at 30–60 min after local allergen provocation. Their biological properties include vasodilatation, increase in vascular permeability, mucus hypersecretion and initiation of neurogenic reflexes, features consistent with the induction of immediate rhinitis symptoms of itch, sneeze, watery discharge and nasal congestion following allergen provocation.

In addition allergen is processed via antigen-presenting cells to T cells. The predominant T cell associated with allergic rhinitis is of "TH₂"-type (5). TH₂ cells produce preferentially interleukin 4 (IL-4) and IL-13, important factors involved in the switching of B lymphocytes in favour of IgE production. Interleukin 4 and IL-13 also increase adhesion molecules on the vascular endothelium, including VCAM-1 which is specific for adhesion of eosinophils. TH₂ cells also produce interleukin 5 (specific for eosinophils), GM-CSF and interleukin 3. TH₁-type cells produce IL-2 and interferon-gamma (IFN- γ) but also produce GM-CSF and IL-3. These latter cytokines have eosinophil-modifying properties and induce the maturation and terminal differentiation of eosinophils within the bone marrow. These cytokines also prime eosinophils for exaggerated responses to other inflammatory mediators (C₅a, PAF). Interleukin 5 inhibits apoptosis of eosinophils thereby prolonging eosinophil survival in tissues. Allergen also gives rise to release of chemokines, including the C-C

chemokines RANTES (6) (released from activated normal T cells expressed and secreted) and eotaxin (7). IgE-dependent mechanisms (8) and eosinophil recruitment and activation are characteristic in both the upper and lower airways (9).

Late-phase responses develop in a proportion of subjects following allergen provocation, depending on the level of allergen exposure and the degree of allergen-sensitivity of the individual. Late-phase responses are more in keeping with "day-to-day" rhinitis symptoms since they are associated with development of nasal obstruction and nasal "hyperreactivity" with an increase in nasal susceptibility to other nonspecific triggers (tobacco smoke, domestic sprays, etc.) and a reduction in the threshold of responses to subsequent allergen exposure, possibly as a result of recruitment of inflammatory cells to the allergic nasal mucosa. Studies of early and late phase asthmatic responses in patients with allergic bronchial asthma show virtually identical mechanisms (reviewed in 10) (Fig. 2).

Similarities and differences

Rhinitis and asthma show a similar range of susceptibility to therapeutic agents although there are exceptions. Shared similarities of rhinitis/asthma are illustrated in Table 1. These similarities argue in favour of a common mucosal susceptibility to disease. However, there are important differences between rhinitis and asthma (Table 2). These differences may be explained at least in part by differences in macroscopic anatomy (11). Specifically, the nose represents a rigid box with no respiratory smooth muscle and a predominance of submucosal glands. In contrast, the lower airways in asthma are "suspended" in elastic lung parenchyma, have abundant peribronchial smooth muscle and far fewer submucosal glands. Furthermore, erectile venous sinusoids which are so prominent in the nose are virtually absent in the lower respiratory tract. Thus although the upper and lower airway share common pathogenetic mechanisms, differences between rhinitis and asthma may be explained largely by differences in the target organ "effector" tissues with prominent vasodilatation and watery mucus within the upper airway and bronchial smooth muscle constriction, bronchial wall thickening and inspissated mucus in the lower airways. A striking difference in pharmacology is the efficacy of antihistamines in rhinitis compared to asthma. Conversely beta-sympathomimetic agonists reverse bronchoconstriction in asthma but have virtually no effect on the upper airway in rhinitis.

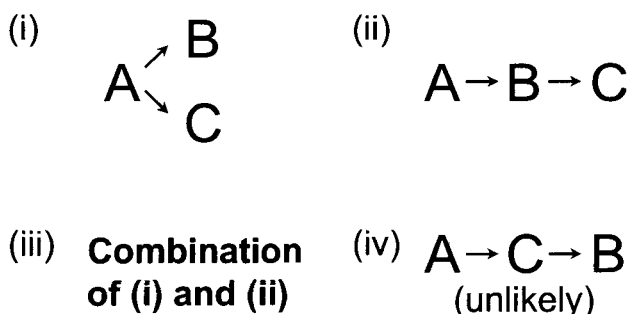


Figure 1. Possible explanation of the link between aetiological factors (A) rhinitis (B) and asthma (C).

Taken together, these observations provide strong evidence in support of a common mucosal susceptibility of the upper and lower airways to the effects of common inhaled allergens. The question of whether there may be in addition a causal association between rhinitis and asthma may be addressed by consideration of animal models and by studying the influence of topical therapy in patients.

Animal models

Animal models afford the opportunity of studying either the upper or lower airway in isolation with observation of the effect of treatment independently at both sites. In a rabbit model one study examined the influence of installation of an inflammatory mediator (C5a des Arg) in the maxillary sinus, compared with a "sham" challenge with saline. Changes in lower airway responsiveness were assessed by measuring changes in lower airway conductance following stepwise incremental histamine inhalation challenges (12). Application of C5a des Arg to the maxillary sinus provoked a shift to the left in the dose-response curve equivalent to a 10-fold reduction in histamine concentration, whereas no

Table 1. Rhinitis and asthma: similarities

- Asthma and rhinitis frequently coexist
- Respiratory pseudostratified columnar epithelium
- IgE-mast cell-dependent mechanisms
- T lymphocyte activation
- Eosinophil recruitment and activation
- Mast cell transepithelial migration
- Langerhans cells in epithelium
- "TH2-type" cytokines (particularly IL4, IL5)
- Corticosteroids are very effective
- Anticholinergics drugs are effective
- Leucotriene antagonists may be effective

changes were observed after saline. These changes in lower airway responsiveness following an isolated upper airway challenge were associated with a significant increase in recruitment of inflammatory cells to the lower airways measured in bronchoalveolar lavage fluid.

A further study examined anaesthetized, tracheostomized, ovalbumin-sensitized rats (13). Aerosolized ovalbumin challenge was performed separately to the upper and lower airway with simultaneous measurement of airways resistance concomitantly in the upper and lower airway.

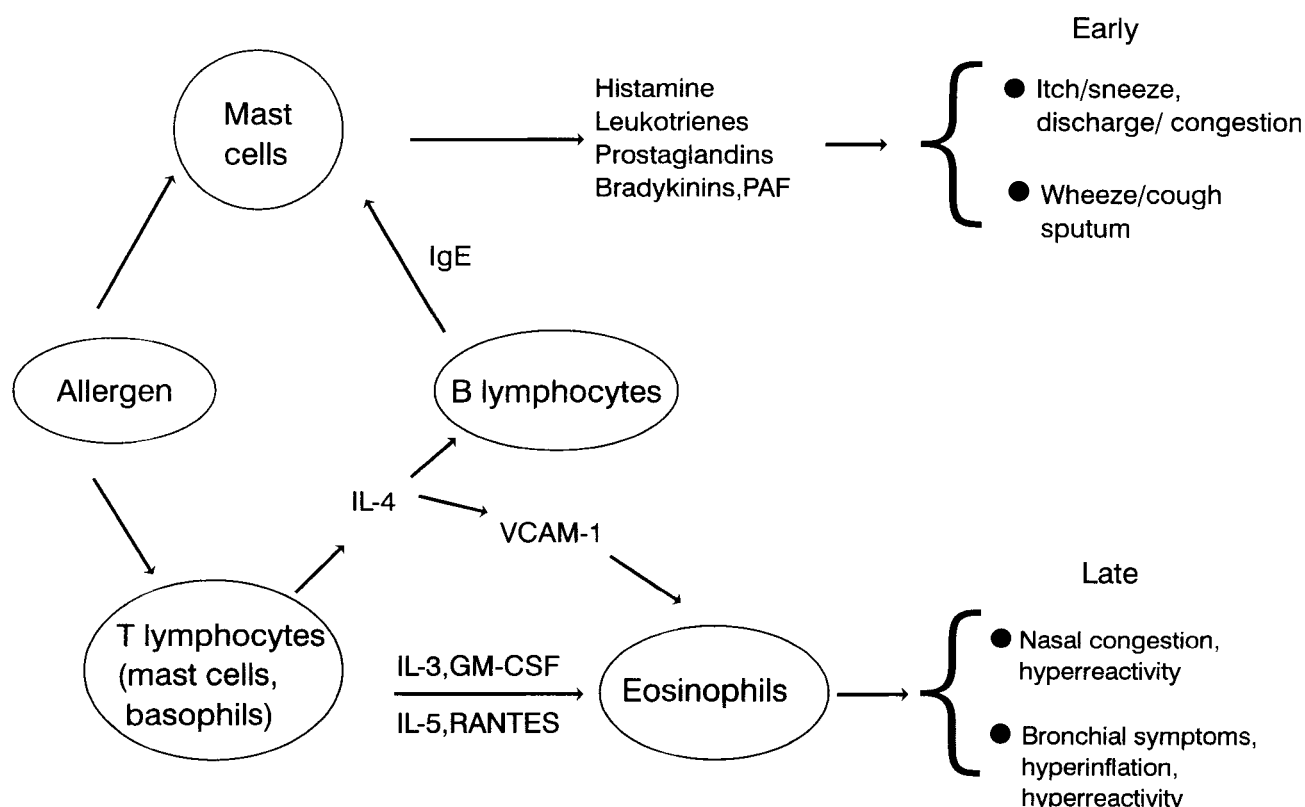


Figure 2. Hypothesis on mechanisms of allergic rhinitis and asthma. Immediate responses result from the IgE-dependent activation of mast cells. Late responses are accompanied by release of "TH2-type" cytokines and chemokines and eosinophil recruitment, activation and prolonged survival in tissues.

Table 2. Rhinitis and asthma: differences

Rhinitis	Asthma
• Epithelium intact	• Epithelium disrupted
• Basement membrane zone normal	• Basement membrane zone abnormal
• No airway smooth muscle	• Airway smooth muscle prominent
• Venous sinusoids	• None
• Submucosal glands	• Submucosal glands much less prominent
• Antihistamines effective	• Antihistamines ineffective
• Beta ₂ -sympathomimetic agonists have no effect	• Beta ₂ -sympathomimetic agonists very effective

Whereas ovalbumin challenge to the nose induced changes in lower airway responsiveness, endotracheal ovalbumin challenge had virtually no influence on upper airway resistance. Changes in lower airway resistance after ovalbumin challenge to the nose were inhibited by pretreatment with atropine which provided evidence for a mechanism involving cholinergic nerve. The findings in this animal model argue against allergic asthma "causing" rhinitis. They also argue that the induced changes in lower airway physiology are likely to be related to a nasobronchial reflex rather than systemic effects via the blood stream of mediators produced locally in the nasal mucosa.

Anti-inflammatory effects of topical corticosteroids in allergic rhinitis

Topical nasal corticosteroids have broad anti-inflammatory effects which include decreases in effector cell numbers within the nasal mucosa, including mast cells, eosinophils (14) and basophils (15). Decreased numbers of CD4⁺ T lymphocytes and a decrease in seasonal increases in the number of Langerhans (antigen-presenting) cells are also observed (16). Recent work suggests that IgE which may be produced locally in the nasal mucosa is also inhibited (8, 17). It seems likely that many of these effects may occur indirectly as a consequence of inhibition of the production of cytokines, particularly IL-4 and IL-5 from T lymphocytes (and possibly mast cells, eosinophils and basophils) (17, 18, 19) and chemokines including RANTES by corticosteroids (20).

Effect of nasal corticosteroids on asthma in patients with seasonal allergic rhinitis

The influence of topical nasal corticosteroids on upper and lower airway symptoms has been assessed in patients with

seasonal ragweed hay fever (Fig. 3). A double-blind placebo-controlled parallel-group study of two topical nasal corticosteroids (aqueous beclomethasone and flunisolide) were compared with the effects of topical sodium cromoglycate and placebo treatment (21). There was an increase in nasal symptoms in all four groups which showed dose- and time-dependency in relation to parallel changes in the ragweed pollen count. All treatments were effective compared with placebo and both topical corticosteroids were more effective when compared with sodium cromoglycate nasal spray. The time course of asthma symptoms was different from that observed for nasal symptoms. There was a progressive increase in asthma symptoms which peaked long after the falls in pollen counts. Sodium cromoglycate was effective compared with placebo only during the early pollen season, whereas both topical corticosteroids completely inhibited the increase in mean weekly asthma scores at all timepoints examined during and for several weeks after the rise in pollen counts.

Owing to their large size pollen grains tend to lodge in the nose and have poor penetration of the lower airways. This fact, together with the effects of nasal steroids on the sequential time course of nasal and asthma symptoms during and after the pollen season, support a causal association with an effect on the lower airways following nasal administration of the drugs. Possibly, it could be argued that the effects of topical steroids on the lower airway are due to systemic absorption. However, systemic absorption is low and administration of equivalent doses of nasal corticosteroid orally compared to the intranasal route produces no clinical benefit.

Several studies have examined the effects of topical nasal corticosteroids on seasonal pollen-induced changes in lower airway responsiveness.

The effects of nasal beclomethasone 326 µg/daily was compared with placebo in adult patients with seasonal ragweed-induced rhinitis (22). Patients recorded daily nasal and chest symptoms. Bronchial responsiveness to metha-

choline was measured before and 6 weeks into the ragweed pollen season. Beclomethasone improved nasal but not asthma symptoms, although there was a significant inhibition of seasonal increases in methacholine responsiveness, as reflected by a decrease in the concentration of methacholine to cause a 20% fall in FEV₁ (Fig. 4).

The effect of once-daily aqueous fluticasone propionate nasal spray 200 µg was examined in 50 patients with grass pollen- and *Parietaria*-induced seasonal allergic rhinitis in 50 adult patients (23). Fluticasone significantly reduced nasal obstruction, itching and rhinorrhoea. There was also a reduction in eosinophil numbers in blood and bronchoalveolar lavage fluid following nasal fluticasone administration. In agreement with the study of Corren (22), fluticasone significantly attenuated seasonal pollen-induced decreases in mean airway methacholine responsiveness compared to placebo treatment.

On the other hand, Pelucchi (24) failed to demonstrate a decrease in seasonal methacholine responsiveness in grass pollen seasonal allergic rhinitis in 45 adult patients following intranasal corticosteroid treatment. However, the dose of beclomethasone employed was low (200 µg daily) and in contrast to the above studies patients gave no clinical history of previous seasonal or perennial asthma.

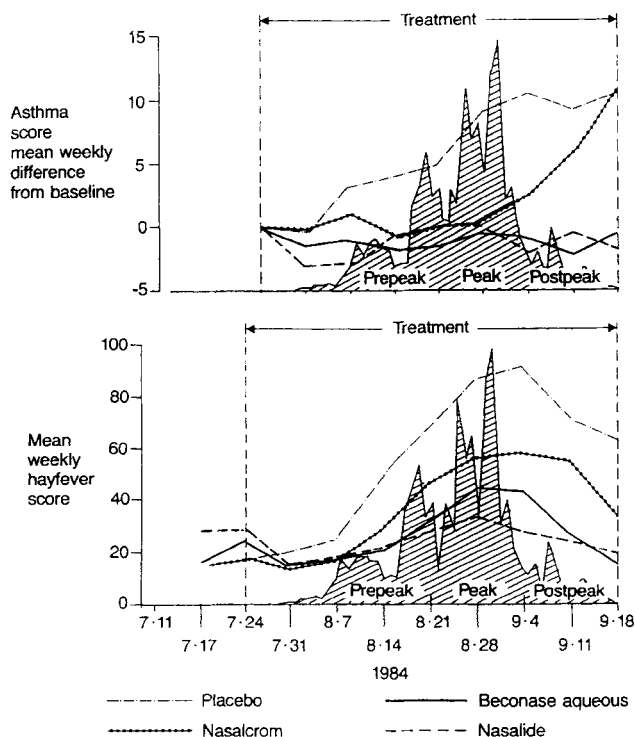


Figure 3. Effect of beclomethasone, flunisolide and sodium cromoglycate in relieving asthma (top) and rhinitis (bottom) symptoms during the ragweed pollen season (reprinted from Ref. 21).

Furthermore, the patients' baseline airway responsiveness to methacholine outside the pollen season was normal (PC₂₀ methacholine > 10 mg/ml). These limitations may possibly explain a failure to detect inhibition of seasonal increases in airway responsiveness in this study.

Effect of nasal corticosteroids in patients with perennial rhinitis and asthma

The effect of nasal corticosteroids on lower airway responsiveness has been studied in patients with perennial allergic disease. A careful study was performed in 21 children with perennial allergic rhinitis and asthma and with documented lower airway hyperresponsiveness (PC₂₀ methacholine < 8 mg/ml). Patients received intranasal aqueous beclomethasone nasal spray 200 µg twice daily (25). Results were compared with a matched-placebo nasal spray with a double-blind placebo-controlled cross-over design. Aqueous beclomethasone significantly improved nasal symptoms. There was a trend for a reduction in asthma symptom scores and a significant reduction in lower airway methacholine responsiveness. There was no washout period between treatment arms in this study, although this would tend to have underestimated any corticosteroid-induced reductions in symptoms and lower airway responsiveness.

Studies of intranasal corticosteroids may be criticized on the basis that the effect on lower airway responsiveness may possibly be due to the effects of corticosteroid that has been absorbed from the nasal mucosa into the systemic circula-

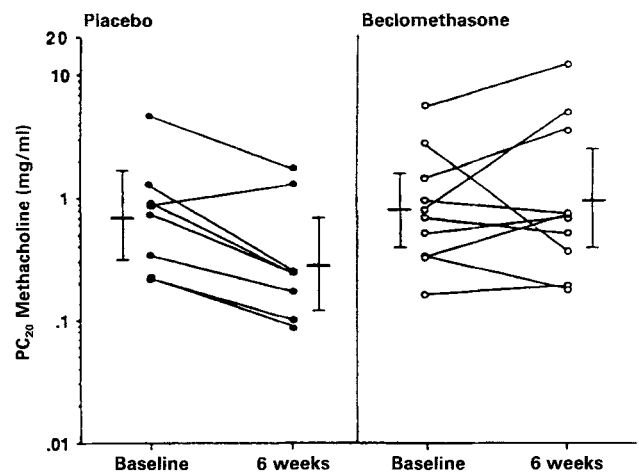


Figure 4. Airway methacholine responsiveness (PC₂₀ methacholine, mg/ml) before and after 6 weeks' treatment with aqueous beclomethasone nasal spray or matched placebo nasal spray in adult patients with seasonal rhinitis during the ragweed season. $P=0.02$.

tion, with subsequent effects on the lower airways. A reduction in peripheral blood eosinophils, in addition to decreases in eosinophils in nasal lavage following beclomethasone treatment, might also argue in favour of a systemic effect of intranasal corticosteroid. A further possibility is that intranasal corticosteroids may possibly be inhaled directly into the lower airways. However, in one study restriction of intranasally deposited beclomethasone to the nose was confirmed by use of radio-labelled aqueous beclomethasone (25). In this study 20–50% of beclomethasone remaining in the nose, 48–78% was swallowed and less than 2% of total radioactivity was identified in the chest area (lungs, trachea and oesophagus).

Comparison of intranasal with inhaled corticosteroid on bronchial hyperresponsiveness

Eleven adult atopic adults with perennial allergic rhinitis of greater than 2 years' duration were studied (26). Patients gave no history of asthma symptoms although all patients had documented abnormal lower airway responsiveness as judged by carbachol inhalation challenge. Airway responsiveness was defined as the concentration of carbachol that decreased specific airway conductance by 35% from base line. Control measurements were repeated at 1-week intervals, in order to assess reproducibility of the measurement. Patients then received 2 weeks' treatment with either intranasal beclomethasone dipropionate 100 µg four times daily by oral inhalation or by topical intranasal application. The study was double-blind, double-dummy placebo-controlled with a cross-over design and a 2-week washout period before drug administration. After 2 weeks' intranasal beclomethasone there was a marked increase in carbachol PD₃₅ ($P < 0.001$), whereas no significant change in PD₃₅ was noted after 2 weeks of intra-bronchial beclomethasone (Fig. 5). These data show that intranasal beclomethasone but not intrabronchial beclomethasone in the same dose had a protective effect on lower airway carbachol responsiveness. If confirmed, this study may prove to be a classic in studies of the relation between the upper and lower airway.

Finally, the effects of intranasal steroids in patients with perennial allergic rhinitis were examined in patients with perennial allergic rhinitis and sensitivity to cats (27). Triamcinolone acetonide nasal spray 110 µg twice daily was compared with matched placebo nasal spray in a double-blind cross-over trial in 12 cat-allergic patients. Endpoints included the effects of treatment on nasal and chest

symptoms and alterations in FEV₁ following 1 h natural exposure to cats in a specially designed "cat room". The results showed that nasal symptoms were moderately reduced ($P = 0.06$), as were lower respiratory symptoms and reductions in FEV₁. However, the changes observed were modest and measurements of nonspecific airway responsiveness before/after cat exposure before/after steroids were not performed.

Mechanism of action of intranasal corticosteroids on lower airway function

The mechanism by which treatment of the nose with intranasal corticosteroids improves lower airway responsiveness is unknown. The radionuclide studies performed by Watson and colleagues (25) would suggest that a direct anti-inflammatory effect of intranasal corticosteroids on the lower airway would seem to be unlikely. Similarly, a systemic effect of nasal corticosteroids following the local absorption would seem improbable. Certainly, comparable oral doses have no clinical effect compared to intranasal corticosteroids. Alternative hypotheses include local inhibition of mediator release in the nose, prevention of systemic mediator absorption with distant effects on the lung, or inhibition of a nasobronchial neurogenic reflex. A nasopulmonary reflex is well described in animals and it is possible that intranasal corticosteroids may influence a similar reflex in patients with allergic rhinitis. A simple explanation may be that corticosteroids reverse nasal obstruction with restoration of the normal air conditioning function of the upper airway which warms and humidifies inhaled air. Mouth breathing, frequently associated with "dry throat" may result in inhalation of cold dry air comparable to that observed during exercise-induced asthma. Further studies are required to evaluate these various possible effects of topical corticosteroids.

Summary and conclusions

The relationship between rhinitis and asthma may simply represent a parallel susceptibility to various injurious agents rather than a causal association. Animal studies suggest that nasal inflammation may directly induce lower airway inflammatory changes and associated increases in lower airway responsiveness, whereas the reverse may not be the case. Studies in humans have shown that rhinitis is a risk factor for development of asthma later in life. The

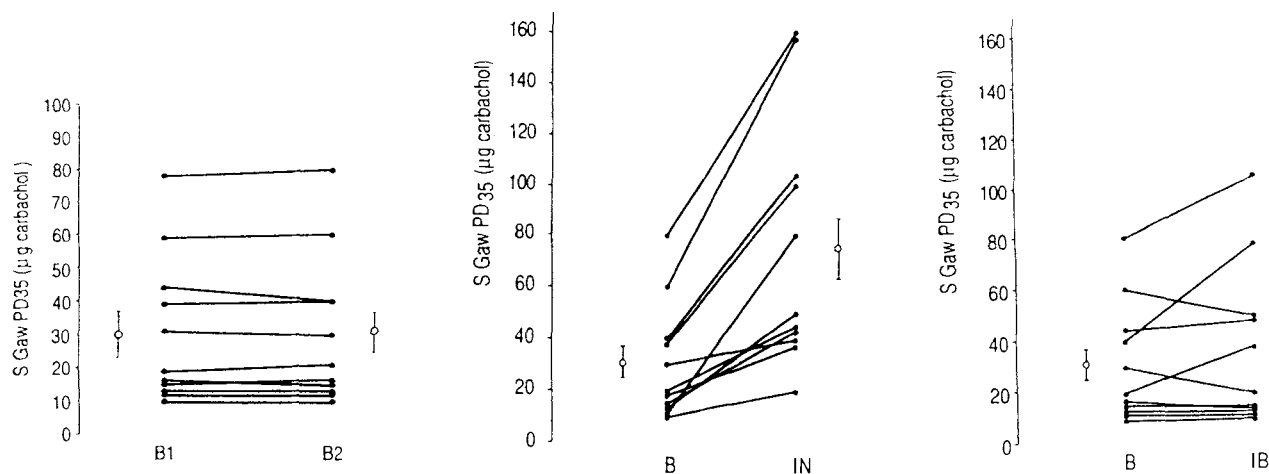


Figure 5. Carbachol SGaw PD₃₅ (provocation dose of carbachol that caused a 35 % decrease in SGaw) after two baseline challenges (B1, B2) and after intrabronchial beclomethasone (iB) compared with baseline and following intranasal beclomethasone (iN) compared with baseline (from Ref. 22).

distinct time course and seasonal allergen dose-dependency of nasal symptoms in ragweed-sensitive patients which precede the development of asthma symptoms and persist for weeks after the decline in pollen counts also provide circumstantial evidence for a causal association between upper and lower airway symptoms following natural allergen exposure. Furthermore, the above studies performed in both seasonal and perennial allergic rhinitis provide compelling evidence that therapeutic intervention in the upper airway may improve lower airway symptoms, increase lung function parameters and reduce the level of lower airway responsiveness. These studies, which have been performed in different centres internationally, using a wide range of intranasal corticosteroids in both children and adults with either seasonal or perennial disease and a wide range of allergen-sensitivities, are remarkably consistent in showing a therapeutic effect of intranasal corticosteroids on lower airway function. However, there are also limitations to the findings. In general, patient numbers studied were small. Similarly, treatment effects, as judged by the magnitude of changes in either asthma symptoms or airway responsiveness, were relatively modest.

Important studies remain to be carried out. These include a large double-blind placebo-controlled trial of intranasal corticosteroids in patients "selected" for bronchial asthma and concurrent rhinitis. Intranasal corticosteroids or placebo nasal spray could be added to patients' usual inhaled corticosteroid treatment. An alternative approach would be to take a group of patients with perennial allergic asthma on inhaled corticosteroids and randomize them to receive either their whole dose of corticosteroid by inhalation or half the dose delivered to the nose and half the dose delivered by inhalation using a double-dummy design. Outcome variables should include requirement for asthma medication (both preventer and reliever medication) as well as nasal and asthma symptoms and changes in airway responsiveness. Clearly, further studies of the mechanism of the effect of intranasal corticosteroids on lower airway function are required. There is an urgent need for a further study comparing comparable doses of topical corticosteroid via the intranasal or intrabronchial route. On balance, however, current evidence suggests that the link between upper and lower allergic airway disease is heterogeneous, involving both a common mucosal susceptibility as well as a causal association [option (iii) in Fig. 1].

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