

REVIEW

Is allergen avoidance effective?*

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Introduction

Exposure to common aeroallergens has been implicated in the exacerbation of asthma symptoms in individuals with established disease. Despite the methodological difficulties in assessing personal exposure, a consideration of the relationship between allergen exposure and asthma severity is fundamental to examining the arguments for aeroallergen avoidance in the treatment of disease.

Studies have attempted to assess the relationship between mite exposure and bronchial hyper-responsiveness by studying a population over a course of time when mite allergen levels can be shown to seasonally fluctuate. Rather small seasonal fluctuations in mite allergen exposure in one study [1] were related to parallel changes in bronchial non-specific hyper-responsiveness in nine asthmatics sensitized only to dust mite. However, using a similar approach, Kivity [2] found no temporal relationship between months of higher mite exposure and symptoms, spirometry or non-specific hyper-reactivity. The limitations of this type of study are small sample size and the great variation in serial measurements of reservoir allergen concentrations [3,4].

A few studies have directly identified a link between severity of symptomatology in mite-atopic adult populations [5–7]. We have previously shown that the presence of non-specific bronchial hyper-reactivity (BHR) was significantly higher in those with higher Der p 1 exposure. Furthermore, BHR correlated with mattress Der p 1 and Der p 2 levels in mite-sensitive people, as did peak flow variability and there was a negative correlation with FEV₁. Tunnicliffe [8] showed in a case control study of severe adult asthmatics matched with a mild group that a higher proportion of the severe group were sensitized and exposed to domestic mite, cat and dog allergens. In a recent case control study, Green [9] added to this work by demonstrating the synergistic effects of allergen exposure and virus infection on the risk of admission to hospital with acute asthma – an outcome known to be a risk factor for death from asthma [10]. However, demonstrating the link between exposure and asthma severity or risk of admission to hospital does not equate to demonstrating the benefits of allergen avoidance.

Occupational allergen avoidance as a model for aeroallergen avoidance

Occupational asthma lends us clues as to the relevance of allergen exposure to asthma symptoms and the effectiveness of allergen avoidance in the management of disease. The aetiological agent, the time course of exposure and the effect of exposure withdrawal can be more precisely studied in the occupational setting.

Firstly, occupational asthma can be broadly considered to be caused by either low molecular weight antigens such as the isocyanates and the plicatic acid of western red cedar (WRC), or high molecular weight antigens, such as the multiple antigens associated with bakers' asthma, the enzymes of soap powder detergent manufacture, and rat and mouse antigens to which laboratory workers are exposed [11]. The high molecular weight antigens can be considered true 'allergens' in that they commonly elicit a specific IgE response, and inhalational challenge where the agent often produces an immediate or biphasic response [12–15]. In addition, some low molecular weight agents may act in an IgE-dependent manner by acting as hapten-complexes with larger proteins [16]. It is also known that people who are atopic to common aeroallergens are more likely to become sensitized to high molecular weight industrial agents. The time between first exposure and onset of symptoms is heterogeneous, but broadly speaking is longer for people exposed to the high molecular weight agents [12]. By analogy, this helps to explain some of the difficulty in relating current exposure to domestic aeroallergens with asthmatic symptoms in sensitized individuals. A dose–response between exposure and prevalence of symptoms and lung function parameters has been established [17–19]. Finally, occupational asthma can respond to inhaled steroid medication [20].

So can we look to occupational allergen withdrawal as a model for studying aeroallergen withdrawal? Randomized controlled trials of allergen avoidance in the industrial setting are unethical and observational studies are confounded by the fact that more severely affected individuals tend to withdraw from the workplace more than less severely affected sufferers. However, in a cohort of people diagnosed with WRC-sensitive asthma who elected to stay working in this environment, no patients improved over a median follow up of 6.5 years, and a third significantly deteriorated [21]. In another, 40% of people who left the industry recovered completely [22]. While persistence of symptoms after cessation of exposure is widely reported for a number of different industrial agents [22–24], the proportions who do improve indicate a significant effect of allergen avoidance.

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Hayfever

Clues to the effectiveness of allergen removal come from hayfever. Pollen exposure is readily quantifiable, fluctuates with great seasonal variation, and results in a seasonal pattern of clinical symptoms [25]. A relationship between pollen exposure to hospital admission can be identified [26, 27].

What do altitude avoidance studies tell us?

At high altitude in Europe, mites do not grow. At centres in Misurina, Italy (alt. 1756 m) and in Davos, Switzerland, studies have examined the effects of a mite-free environment on the clinical activity of asthma in mite-sensitized children. Clinical improvements in high altitude conditions could conceivably be due to reductions in other environmental conditions such as particulate air pollution. However, mite exposure is considered to be the most important factor.

What is particularly striking about these studies is not only the consistency of the reported improvements in the parameters studied, but also the rapidity of deterioration measurable after a return to sea level.

Most of the studies have followed the children for many months at high altitude. Boner conducted a study of 14 children with moderately severe asthma [28]. During an 8-month stay, a progressive improvement in exercise-induced bronchial reactivity was demonstrated, together with a reduction in medication, including oral corticosteroid dose. The same group also demonstrated improvements in serum markers of eosinophil activation [29] at high altitude. Others have reported improvements in non-specific bronchial hyper-responsiveness (adenosine monophosphate PC₂₀) after periods as short as 1 month [30]. Peroni [31] demonstrated improvements in non-specific and HDM-specific bronchial responsiveness and total and HDM-specific IgE after 3 and 9 months at high altitude with a deterioration in total IgE and measures of non-specific BHR 3 months after a return to sea level. Piacentini [32] outlined reductions in antigen-provoked basophil histamine release and specific IgE after 40 and 80 days at high altitude and found a rapid reversal of these improvements after only 15 days at sea level. He also demonstrated improvements in sputum eosinophilia [33] and epithelial shedding [34]. Reductions in T helper cell activation at high altitude have also been reported [35]. Exhaled nitric oxide (ENO) [36] decreased 2 weeks after arrival at high altitude and this reduction was maintained despite withdrawal of inhaled steroid therapy. A rapid return to higher exhaled NO levels 2 weeks after return home subsequently occurred. More recently, Grootendorst et al. conducted a parallel-group controlled trial of adolescent mite-atopic moderately severe asthmatics. Medication dosage was kept the same and after both 10 weeks of treatment and a further 6 weeks back home, there were maintained improvements in quality of life score, BHR to histamine and adenosine, and in urinary eosinophil protein X and leukotriene E₄ [37].

In the Manchester Asthma and Allergy Study [38], a low mite allergen environment was created in the homes of expectant parents and was maintained for the initial 18-month observation period. It remains to be seen whether such an environment can be maintained for the longer periods of time likely to be necessary for treating established disease. Even if mite exposure

in the home can be reduced to levels approaching those at high altitude, the removal of pet allergens from the environment is a more daunting task that may be unachievable without public health legislation. By just how much these allergen levels can be reduced, and need to be reduced, and which patients will benefit, and by how much is unclear at present.

Secondary mite avoidance trials

In 1998, the Cochrane group published a meta-analysis of secondary mite allergen avoidance [39, 40]. They concluded that 'current physical and chemical methods aimed at reducing exposure to allergens from house dust mites seem to be ineffective and cannot be recommended as prophylactic treatment for asthma patients sensitive to mites'. The paper proved controversial: Firstly, reduction in mite allergen exposure was only reported in six of the 23 studies included. Clearly, the effects of allergen abatement on symptoms cannot be evaluated in trials where such abatement is unsuccessful, or is not reported. Secondly, trials of acaricides, of barrier methods and also of air cleaners were combined in the meta-analysis. The use of air cleaners to abate domestic mite allergen exposure is illogical. Airborne mite allergen is only detectable in artificially disturbed circumstances. Thirdly, studies of both childhood and adult asthma were combined. Thus, it is unsurprising that the meta-analysis failed to inform us as to the benefit of secondary mite allergen avoidance. However, they do conclude 'If other types of studies are considered, we suggest that any further trials should be much larger and more rigorous, with careful monitoring of mite exposure and relevant clinical outcomes'.

There are indeed methodological concerns in many of the papers of domestic mite allergen avoidance. These difficulties are manifold: Firstly, there is the problem of measuring an effect of an intervention, where there is likely to be great heterogeneity of biological response, of severity of disease, of confounding treatments, sensitization to other allergens, and intercurrent infections. Sample sizes have been too small and studies often uncontrolled. Cross-over study designs fail to take account of the long and probably very variable 'wash-out' period which is likely to be required, and duration of treatments are highly variable. Inclusion criteria more often than not specify a population of individuals with >70% FEV₁ near-normal spirometry and peak flow [41–43], or in some cases 100% [44, 45]. In other studies, disease severity is not stated [46]. Thus, many studies of allergen avoidance have selected patients with mild disease in whom there is relatively little scope for symptom improvement. This is in contrast to the way in which clinical trials of therapies such as inhaled glucocorticoids (ICS) are now conducted. Patients are carefully selected, usually with moderate/severe disease with inclusion criteria of FEV₁ <70% and >15% reversibility to inhaled bronchodilators. It is doubtful that asthma drugs would perform well in trials with inclusion criteria such as those used to date in trials of allergen avoidance.

Carefully conducted clinical trials of inhaled steroid medication were not always the norm [47] and clinical questions regarding the use of ICS remained unanswered. The dose-response relationship with clinical effectiveness [48, 49] and with side-effects [50, 51] are only now being addressed by adequately designed studies. Despite this history of methodological inadequacies, the medical profession has been ready to

accept the benefits of ICS while dismissing those of allergen avoidance out of hand. In essence then, studies of both inhaled glucocorticosteroid therapy and allergen avoidance studies may have had similar methodological difficulties, yet the former is a treatment that is often unquestioningly accepted, and the latter is often dismissed out of hand. Adequately designed allergen avoidance trials are now needed. One such study on the effect of mite allergen avoidance by the use of allergen impermeable bedding on asthma control in adults is currently being carried out in the UK, and the results are expected by the end of 2002. This is a randomized, double-blind, placebo controlled trial, with 1500 adults being randomized. During the first six months of the trial (phase A) patients will take their usual inhaled steroid therapy, and during the following six months (Phase B, months 6–12) patients will make a controlled reduction of inhaled steroids. The results of this study should conclusively show whether a simple intervention designed to reduce domestic mite allergen exposure can improve the clinical control of asthma, which subgroups of patients benefit, and whether a reduction in regular inhaled steroid use can be achieved in primary care patients.

Can we measure personal allergen exposure?

The nature and distribution of the common aeroallergens themselves compounds the difficulty of studying the relationship between exposure and symptoms and the effects of allergen avoidance. Mite allergens are borne on larger particles [52, 53], with only a smaller proportion considered directly respirable. Furthermore, air-borne mite-bearing particles are only detectable with disturbance, implying that most mite exposure occurs in bed, at night. Such exposure then, is likely to be low-grade and chronic. Despite the fact that mite allergen levels in the UK are lower than in other climates such as Australia, mite-sensitization remains the commonest risk factor for atopic asthma. How then, given its large particle size, might exposure cause symptoms? It is considered that the impaction of a mite-bearing particle on the nasal epithelium may elicit a hypersensitivity reaction of magnitude sufficient to drive inflammatory processes further down in the lung [54]. A major problem with studying avoidance of mite allergens is that methods of exposure measurement are on the whole only surrogate. Dust mite allergen concentrations in reservoir dust cannot directly reflect personal exposure. Few studies have managed to measure personal exposure to mite in undisturbed conditions [55], although the development of the intra Nasal Air Sampler [56] may address this issue by providing a measure of directly inspired allergen-bearing particles.

The point is that we do not know how much directly inspired mite allergen is required to cause asthmatic symptoms, where in the respiratory tract the allergen may exert its influence and how quickly asthmatic symptoms are produced. This results in great difficulties in planning the ultimate mite allergen secondary avoidance trial.

Cat and dog allergens have the advantage that they are borne on a spectrum of particle sizes smaller than mite [52, 54, 57, 58], and are therefore considered to penetrate deeper into the respiratory tract. This means that asthmatic symptoms are more readily identifiable in a temporal relationship to the exposure to the pet or allergen, and so avoidance studies could perhaps be

designed with a clear idea as to necessary duration of avoidance. However cat and dog allergens are ubiquitous [59–61], and carried from place-to place on clothing [59–62] and so may be difficult to avoid even outside the home setting. Not only are they widely detectable in public places [63], they are present in quantities often sufficient to cause symptoms in non-pet owning sensitized children in school who share classrooms with other pet owners [64]. However, the largest difficulties in studying pet removal must be the general reluctance of pet owners to part with their pets, and the need for concomitant carpet and furnishing removal to abate cat allergen. Cat [65] and dog [66] washing may cause an immediate reduction in detectable allergen, but this is not sustained, necessitating frequent washing if abatement is to continue. Again, this would rarely seem practical.

Conclusion

In summary, there is good evidence for the link between mite and pet allergen exposure and sensitization to these allergens, and between sensitization and asthma. A threshold of exposure has been suggested in a number of studies of $2 \mu\text{g/g}$ for mite sensitization for those with prior sensitization to another allergen and $8 \mu\text{g/g}$ for cat [67]. These thresholds give some indication of the levels of exposure we must aim for when avoidance studies are planned. Corollaries with occupational asthma strengthen the argument for allergen avoidance as a therapeutic option and hence allergen avoidance continues to be recommended by professional bodies [68, 69]. However, limitations in the design of previous trials have meant that we do not yet have an answer as to whether secondary domestic aeroallergen avoidance is effective. Creation of a low-allergen environment has been proved possible and studies are in progress to assess the effect of primary allergen avoidance on the incidence of aeroallergen sensitization [38]. The next challenge will be to establish whether a package of allergen avoidance measures in the home can make a difference to the severity of established asthma, and whether such measures will prove universally acceptable. Other important questions which need addressing are whether substantial reduction in allergen levels can be achieved by measures which are flexible to suite the individual needs and are at the same time practical and not prohibitively expensive and how to identify suitable patients who may benefit from such an intervention.

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