House dust mite avoidance measures improve peak flow and symptoms in patients with allergy but without asthma: A possible delay in the manifestation of clinical asthma?

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Background: Asthma caused by allergy to house dust mite is a growing problem. Patients with allergy who do not have asthma (yet) might develop asthma depending on exposure to precipitating factors.

Objective: We sought to determine whether house dust mite avoidance measures have an effect on the development of asthma.

Methods: Patients with allergy (n = 29) who had no diagnosis of asthma (FEV1 of 99.1% ± 10.6% of predicted, peak flow variability of 5.21% ± 3.41%, reversibility of FEV1 after 400 µg salbutamol of 3.92% ± 3.75% according to the reference values) were randomly allocated (subjects blinded) to a treatment group and a placebo group (n = 313). House dust mite avoidance treatment consisted of applying Acarosan (Alergopharma, J. Ganzer KG, Hamburg, Germany) (the placebo group used water) to the floors (living room, bedroom), and the use of covers for mattresses and bedding that were impermeable to house dust mite (the placebo group used cotton covers for mattresses only). We tested whether the intervention had an effect on peak flow parameters and asthma symptom scores during 6 weeks of treatment.

Results: Significant improvements were seen in the treatment group in symptom scores (morn. evening, and variability) were seen in the treatment group also. No significant changes were seen in the placebo group.

Conclusions: Although this study is not long enough to study the development of asthma, the results indicates that house dust mite avoidance measures had an effect on peak flow parameters and asthma symptom scores in patients with allergy but without asthma. These findings might implicate that a shift in developing clinically manifest asthma could be achieved with house dust mite avoidance measures. To give a better answer to whether preventing the development of asthma is possible, larger studies with a longer follow-up period are necessary. (J Allergy Clin Immunol 1997;100:313-9.)

Key words: House dust mite, allergen avoidance, peak flow, asthma symptoms, prevention

Asthma caused by allergy to house dust mite seems to be a growing problem in the western world. In the Netherlands, about 21.8% of subjects 20 to 44 years old are allergic to the house dust mite and about 7% of these have asthma. Considerable epidemiological evidence indicates a (causal) relationship between the level of exposure to house dust mite allergens and the risk of asthma. These findings implicate that in some subjects, being allergic may be an expression of a possible genetic disposition for the development of asthma. Hence, subclinical asthma might become clinically manifest asthma after exposure to allergens or other precipitating factors. Obviously, this presumption emphasizes the need for allergen avoidance protocols as a tool for prevention. The treatment of asthma in adults should be focused on treating the disease as well as on preventing further development of the disease by avoiding allergens in patients with subclinical asthma. Allergens of house dust mites are some of the most important triggers for the manifestation from allergy to asthma. Therefore, we investigated the effect of reducing house dust mite allergen exposure on the manifestation of asthma in subjects who have an allergy to the house dust mite, but who do not (yet) have asthma.

Several studies investigated the effect of avoidance measures to reduce exposure to dust mite allergens in patients with already established asthma. Avoidance measures included tannic acid, acaricides, and covers for bedding. Most of these products have been shown to be capable of reducing the level of exposure to house dust mite allergen to a certain degree. Data also indicate that a combination of measures gives a more pronounced result in reducing exposure to these allergens. Furthermore, several studies found a favorable influence on clinical parameters as a result of these measures. So far, all of these measures have
been aimed at patients who have already developed asthma,\textsuperscript{16,24} and no attention has been paid to the preventive effect of these products on the development from allergy to asthma in patients with allergy. Because investigation of the manifestation from subclinical to clinical asthma would need very long-term, large studies, we first performed a trial to assess what kind of effects house dust mite avoidance measures have in a group of adult patients with allergy during a relatively short follow-up period of 6 weeks. In none of the selected patients had asthma been diagnosed. Patients were specifically excluded if they had been diagnosed as having asthma or if they used inhaled corticosteroids or Cromones. The house dust mite reducing measures used in this study were the combination of allergen avoidance measures (treatment group) and peak flow parameters.

\section*{Methods}

\subsection*{Patients}

Patient characteristics are given in Table I. Patients were recruited after their general practitioners referred them to the hospital for intradermal skin testing. All patients had an allergy test because they had some very mild signs of asthma (mostly early morning dyspnea or wheeze), but none had a diagnosis of asthma. After this test, patients remained under the medical care of the general practitioner and not of a specialist. Patients were excluded if they had a confirmed diagnosis of asthma, if they had received anti-inflammatory medication at any time, or if they had an increased peak flow variability (>15%) or a reversibility of the obstruction (>15% of predicted FEV1 after 400 \textmu g salbutamol). According to the recent World Health Organization/National Institutes of Health consensus, these patients are not defined as having asthma (even mild asthma).\textsuperscript{25}

This study focused only on asthmatic and not on nasal symptoms; rhinitic complaints were not an exclusion criterion and no data about nasal symptoms were collected.

Patients were selected from intradermal skin test records during 1991 and 1992. All patients were tested for 16 common aeroallergens (pollen, pets, molds, and house dust mite; ALK, Assen, The Netherlands). Histamine served as a positive control and a solution without a specific allergen served as a negative control. A reaction was defined as positive when the reaction (wheal size) to an allergen was \textasciitilde0.7 times the reaction (wheal size) of the positive control. Wheel size was calculated by multiplying the longest length with the perpendicular width and this total was divided by two. All patients had a positive intradermal allergy test for house dust mite. The reaction to cats, dogs, and \textit{Aspergillus fumigatus} had to be less than the reaction to house dust mite to avoid interference with these allergens. Furthermore, patients with an allergy to pollen were equally distributed over the two groups.

\subsection*{Design}

This study was a prospective, single-blind, placebo-controlled trial, which started with a baseline period of 2 weeks followed by an intervention period of 6 weeks. The study took place in the spring of 1993. Patients were entered into the study concurrently and after the baseline period they were randomly allocated to the allergen avoidance group or to the placebo group. Allocation was done after stratification based on the type of floor covering in the bedroom (textile versus smooth) and on the initial FEV1 \% reference value. Patients were unaware of their allocation to the treatment group or the placebo group (single-blind). All patients were asked to clean the floors of their living room and bedroom with a vacuum cleaner and to wash the bedding once a week to standardize the cleaning conditions of the indoor environment.

During the following 6 weeks, we assessed whether the allergen avoidance measures had an effect on asthma symptoms and peak flow parameters.

\subsection*{Mite avoidance measures (treatment group)}

In the treatment group \((n = 16)\), the acaricide benzyl benzoate powder Acarosan was applied to the bedroom and living room floor coverings according to a standard procedure. It was brushed in firmly after the removal of furniture from the floor and was removed by intensive vacuuming 3 hours after application. Mattresses, pillows, and duvet were all encased with covers (Allergy Control) that are impermeable to house dust mites and house dust mite allergens. We have shown earlier that these active covers are quite effective.\textsuperscript{26}

\subsection*{Placebo measures (placebo group)}

In the placebo group \((n = 13)\), textile bedroom and living room floor coverings were sprayed lightly with water from a

\begin{table}[h]
\centering
\caption{Characteristics of the study population}
\begin{tabular}{|l|l|l|l|}
\hline
Population characteristics & Treatment group & Placebo group & \textit{p} Value \\
\hline
\textbf{Number} & 16 & 16 & 0.93 \\
\textbf{Gender (% male)} & 38 & 46 & 0.93 \\
\textbf{Age (yr)} & 32.4 (11.5) & 23.5 (6.3) & 0.04 \\
\textbf{Morning peak flow (L/min)} & 488.9 (109.9) & 500.1 (85.2) & 0.77 \\
\textbf{Evening peak flow (L/min)} & 508.1 (102.4) & 511.2 (84.2) & 0.93 \\
\textbf{Peak flow variability (\%)} & 6.2 (4.0) & 3.9 (2.1) & 0.06 \\
\hline
\textbf{Asthma symptom scores:*} & & & \\
\textbf{Breathlessness} & 1.19 (1.3) & 0.48 (0.7) & 0.09 \\
\textbf{Disturbed sleep} & 0.73 (1.2) & 0.37 (0.5) & 0.28 \\
\textbf{Wheeze} & 0.60 (1.2) & 0.26 (0.5) & 0.31 \\
\textbf{Overall symptom score} & 1.88 (1.2) & 1.49 (1.3) & 0.40 \\
\textbf{(square root)} & & & \\
\hline
\textbf{Reversibility (\% of baseline)} & 4.84 (3.86) & 2.78 (3.42) & 0.14 \\
\textbf{FEV1 \% predicted} & 99.1 (9.5) & 99.1 (12.2) & 0.99 \\
\textbf{Allergy to:} & & & \\
\textbf{P}ets (\%) & 56.2 & 53.8 & 1.00 \\
\textbf{P}ollen (\%) & 50.0 & 46.2 & 1.00 \\
\textbf{Potential confounders:} & & & \\
\textbf{T}extile \textbf{b}edroom \textbf{c}overing \textbf{(%)} & 68.7 & 61.5 & 0.99 \\
\textbf{S}moking behavior \textbf{(%)} & 25.0 & 23.1 & 1.00 \\
\textbf{P}ets (\%) & 62.5 & 76.9 & 0.67 \\
\hline
\end{tabular}
\end{table}

Data reported as mean ± SD.

* Borg score.

\textsuperscript{25}
siphon with a label of an acaricide, after the furniture was removed from the floor. After 15 minutes the floors of the bedroom and living room were vacuumed. For mattresses, placebo covers permeable for the house dust mite were used. Patients were given the impression that these measures were part of the active avoidance measures.

Clinical features

Patients were provided with peak flow meters (Pocket Peak Flow Meter, Micro Medical, Rochester, Kent) and were trained in recording three readings each morning before breakfast and each evening before dinner. The highest of the three (both in the morning and the evening) were recorded. Patients also scored symptoms of cough, breathlessness, wheezing, expectation, tiredness, and disturbed sleep (due to cough, wheeze, or breathlessness at night) on a modified Borg scale (0 = no symptoms to 10 = severe symptoms). The peak flow values and symptom scores were recorded daily on a diary card during the study. Before the start of the study, patients were trained to measure and record their peak flow and symptoms. During the 2-week baseline, the diary cards were also filled in to obtain initial values of all parameters. To avoid learning effects, only the data from the second week were taken for the baseline period.

During the first home visit, information about the bronchial symptoms, smoking habits, occupation, and frequency of house cleaning was obtained by a questionnaire.

Statistical analyses

Sample sizes were estimated based on peak flow morning values with an α of 0.05 and a β of 0.80. The minimal clinical relevant difference to be detected was set at 15 L/min (with a standard deviation of 15 L/min), because no asthma had been diagnosed and consequently little room for improvement was possible. Sample sizes were estimated at 15 patients per group. All p values were assessed with two-sided tests.

Values for morning and evening peak flow, peak flow variability, measured as ([highest peak flow − lowest peak flow]/[highest peak flow] × 100), and asthma symptom scores were calculated as means during 1 week before intervention and for each consecutive week after intervention. Changes between each week of follow-up and baseline were calculated for all parameters, resulting in mean changes (± standard error). An overall symptom score was calculated by adding up the separate symptom scores for each mean of the week followed by square root transformation to achieve a normal distribution.

Within-group comparisons were made by testing differences after 1, 2, 3, 4, 5, and 6 weeks with the baseline value for all parameters by Student’s paired t test. A cross-sectional comparison of the changes compared with baseline between the two groups was made by means of the Student unpaired t test. When baseline values differed (p < 0.10), a correction for baseline values was made by MANOVA. Drop-outs were included in the analyses as far as they completed the study (intention to treat protocol). An explanatory analysis was also done with only patients who completed the study.

RESULTS

Patient characteristics

Twenty-nine patients were included in the study. After randomization and stratification, a slightly unbalanced distribution was achieved, with 16 patients in the treatment group and 13 patients in the placebo group. Patient characteristics are shown in Table I. Only age differed significantly between the groups, in that the treatment group was older than the placebo group (31 vs 24 years). In all analyses, the difference in age had no influence on any of the effects studied (p values always >0.05). All parameters studied were normally distributed.

Only a few patients used pulmonary medications: five patients used a β-agonist on demand (three in the treatment group and two in the placebo group), and five patients used antihistaminics (three in the treatment group and two in the placebo group).

In both groups some patients dropped out. As baseline values of peak flow parameters and asthma symptom scores of the dropouts and those who completed the study were not different, the act of dropping out appeared not to be selective. The treatment group started with 16 patients. During weeks 1, 2, and 3 no dropouts occurred, in week 4 one patient dropped out, and in week 5 one also dropped out. Three patients dropped out in week 6, so the treatment group ended with 11 patients. The placebo group started with 13 Patients. During the first 3 weeks no dropouts occurred. In week 4 three patients dropped out and in week 5 two patients dropped out. In week 6 the placebo group ended with 7 patients. Patients left the study because of motivational factors not related to the study objective, and factors did not differ significantly between the two groups. Furthermore, the explanatory analyses showed no real differences compared with the intention to treat analyses.

Peak flow morning values and peak flow variability

Fig. 1 shows the changes in the weekly mean values compared with the pretreatment week for peak flow morning values, peak flow evening values, and peak flow variability.

Improvements in peak flow parameters were seen only in the treatment group. Peak flow morning values showed significant increases from +13.2 ± 5.4 L/min in week 4 (p = 0.029) to +18.2 ± 6.9 L/min in week 6 (p = 0.030). Peak flow evening values also showed an increase. This increase became significant in week 4 (+8.57 ± 4.3 L/min, p = 0.027), which tended to continue in weeks 5 and 6 (+8.57 ± 4.3 L/min [p = 0.070] and +21.89 ± 9.7 L/min [p = 0.054], respectively). Peak flow variability showed no statistically significant differences, although it tended to decrease in week 3 (−1.36% ± 0.7%, p = 0.080) up through week 6 (−2.18% ± 1.0%, p = 0.064).

Asthma symptom scores

The treatment group showed an improvement in the symptom scores for disturbed sleep, breathlessness, wheeze, and the overall symptom score (Fig. 2).

Patients in the treatment group had less disturbed sleep in week 4 (−0.52 ± 0.3 on the Borg score, p = 0.063) and week 5 (−0.45 ± 0.2 on the Borg score, p = 0.050). In the placebo group, no significant changes in disturbed sleep were seen.

The symptom score for breathlessness tended to de-
FIG. 1. Mean ± SEM changes in peak flow morning values (A), peak flow evening values (B), and peak flow variability (C) compared with baseline for the treatment group (■) and the placebo group (▲). A, Significant increases in peak flow morning values compared with baseline occurred only in the treatment group during weeks 4 (*p = 0.029), 5 (#p = 0.024), and 6 ($p = 0.030). B, In the treatment group, a significant increase in peak flow evening values compared with baseline was also seen during week 4 (*p = 0.027). This tendency was also seen during weeks 5 (#p = 0.070) and 6 ($p = 0.054). C, Peak flow variability tended to decrease in the treatment group. This tendency was most pronounced in week 6 (*p = 0.064).

crease in the treatment group. This tendency became significant in week 5 (−0.47 ± 0.19 on the Borg score, p = 0.024) and week 6 (−0.84 ± 0.3 on the Borg score, p = 0.020).

An improvement was also seen for the symptom score for wheeze in the treatment group; it was significant in week 5 (−0.31 ± 0.1 on the Borg score, p = 0.032). The decrease in Borg score in the treatment group in week 5 differed significantly from the increase in the placebo group in week 5 (change was 0.53 ± 0.24 on the Borg score, p = 0.038).

The overall score (square root) decreased in weeks 4, 5, and 6. These decreases were −0.41 ± 0.2 (p = 0.039), −0.54 ± 0.2 (p = 0.005), and −1.02 ± 0.2 (p = 0.002), respectively.

DISCUSSION

Sufficient evidence has accumulated to confirm a close relation between sensitivity to mite allergens and asthma. A causal relationship between mite allergen sensitization and the development of asthma seems plausible. Consequently, in some patients allergy might be an indication of a genetic disposition for asthma; in other words, allergy might be considered in these patients as a subclinical (early) expression of asthma. Therefore, in these patients, preventing further development from subclinical to clinical asthma by reducing the exposure to allergens is important. Because house dust mite allergens are one of the most important allergens in asthma, preventive measures should be especially focused on avoidance of these allergens. The prevention of asthma is difficult to study, because the assessment of the development of asthma would need a very long-term observation of objective variables in controlled circumstances. Because of the relatively short follow-up period and small number of patients, this short-term study can only serve as a preliminary report in investigating possibilities of preventing the development of asthma.

This study showed that after 6 weeks of follow-up, small but significant improvements were seen in asthma symptoms (disturbed sleep, breathlessness, wheeze, and overall symptom score) and peak flow parameters in the patients who received a combination of measures to avoid house dust mites. Unfortunately, the actual allergen load was not measured to objectify the effectiveness of the intervention. Nevertheless, we believe that the intervention used has been effective and was not, for
example, a consequence of seasonal variation in house dust mite levels (because patients in the treatment and placebo groups undertook the study at the same time). In particular, the mite-impermeable covers are thought to be largely responsible for a reduction in house dust mite allergens, and reduction was achieved to a lesser extent with the use of Acarosan. It could be possible that especially in this group of patients who had not yet developed asthma, the proposed intervention might be relatively effective. In a group of patients with already clinically manifest asthma, we would probably need a more powerful intervention.

The classification of the patients in this study is very important. It must be clear that these patients do not have a diagnosis of asthma, but rather they have no clinically manifest asthma. Our patients only had some complaints (mainly breathlessness, wheeze, and cough), but peak flow parameters were normal and patients used no anti-inflammatory medication. Furthermore, FEV1 and reversibility of obstruction were also normal. Thus (reversible) airflow limitation seems to be absent in these patients. When peak flow variability is seen as an indication of airway responsiveness, it may be assumed that airway responsiveness is absent in this group of patients. Unfortunately, bronchial hyperresponsiveness was not measured in these patients.

The effects observed were very small, which can be explained by the fact that there was little room for improvement in these parameters because these patients did not have asthma but had only some (early) signs of subclinical asthma. Our results show that with the help of avoidance measures for house dust mite, peak flow variation and symptom scores can be stabilized or improved during a 6-week period. This might implicate a shift in the moment when asthma manifests clinically. Obviously, we cannot predict from these results the extent of this shift in disease manifestation. Questions as to whether the manifestation of asthma will only be delayed, to what extent this delay will happen, or whether the manifestation might actually be prevented can only be answered by studies with a much longer follow-up period and with more patients. In this study, most effects increased toward the end of the 6-week period.
period, which might indicate that a "plateau" in the maximum effect was not reached yet.

To our knowledge, this is the first study that gives more insight in the use of allergen avoidance as preventive measures in adults who do not have asthma (yet). Evidence of a (causal) relationship between the level of exposure to house dust mite allergen and the risk of developing clinical asthma has been achieved in cross-sectional and retrospective studies. Evidence of a (causal) relationship between the level of exposure to house dust mite allergen and the risk of developing clinical asthma has been achieved in cross-sectional and retrospective studies.2-10,29-31 No long-term prospective studies in adults have been reported. Studies dealing with the prevention of asthma are usually performed in children.34-36 These studies try to prevent the sensitization to house dust mite allergens, and as such they are focused on primary prevention of asthma. However, many adult patients have an allergy but do not (yet) have asthma.2 A substantial number of these patients will present to their physicians with some mild, very early asthma-like symptoms. Usually patients with these kinds of symptoms are tested for the presence of (house dust mite) allergy. When allergy is present, preventing the further development of these symptoms toward clinical asthma might be a relevant option. Studies investigating this kind of prevention are urgently needed. Not only is it important to investigate whether prevention is efficacious, but it is also important to determine which (combination of) avoidance measures will yield the best result.

In conclusion, this study investigated the effects of house dust mite avoidance measures in a group of patients with allergy (subclinical asthma). The study was undertaken to gain more insight in the possible preventive capacity of these measures. The study showed that after 6 weeks of follow-up, house dust mite avoidance in patients with allergy but without asthma improves peak flow parameters and asthma symptom scores. These findings might indicate that a shift in the development of clinical asthma is achievable with avoidance measures. These findings are not conclusive because of the relatively short follow-up period and small number of patients. These findings can therefore only serve as an indication that early allergy avoidance might have a favorable effect on the development of asthma. To investigate this hypothesis, we urgently need longer follow-up studies with larger groups. In this way a better understanding of the preventive capacity of house dust mite avoidance measures in the development of asthma can be obtained.

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