

Effects of house dust mite avoidance measures on Der p 1 concentrations and clinical condition of mild adult house dust mite-allergic asthmatic patients, using no inhaled steroids

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Summary

Background Exposure to house dust mite (HDM) allergens often results in worsening of asthma. Therefore, avoidance of exposure to HDM allergens is often proposed. Unfortunately, the most effective and feasible avoidance strategy is still not completely assessed. Consequently, we investigated the effects of a combined HDM avoidance strategy on HDM allergen concentrations and clinical condition of allergic, mild asthmatic, patients using no inhaled steroids.

Methods Asthmatic patients, allergic to HDM, using no inhaled corticosteroids, were randomly allocated to an active ($n = 76$) or a placebo allergen-avoidance group ($n = 81$). Avoidance measures consisted of applying Acarosan® (placebo: water) to the living room and bedroom floors, and the use of HDM-impermeable covers for mattresses and bedding (placebo: cotton covers for mattresses only). Effects on allergen concentrations (Der p 1), FEV₁, bronchial hyperresponsiveness, peak flow parameters and asthma symptom scores were studied during 20 weeks and controlled for the allergic status of the patients.

Results The active covers reduced Der p 1 concentrations to 9.4% ($P = 0.0001$), and were always significant lower than in the placebo group ($P = 0.0002$). Acarosan® resulted in slight but significant decreases (twofold, $P = 0.0001$), both on living room and bedroom floors, but concentrations were never significantly lower than the placebo group. Although the combined avoidance strategy resulted in a considerable reduction in allergen load in the active group, no differences were seen between the two groups in any of the clinical parameters during the follow-up period in this group of allergic asthmatics, using no inhaled corticosteroids. Corrections for the allergic status did not alter these results.

Conclusions The combined avoidance strategy was effective in reducing HDM allergen concentration. This was especially achieved by the allergen-impermeable covers, while the effects of Acarosan® were only marginal. However, this allergen reduction was not reflected in a convincing improvement in clinical condition in this group of mild allergic asthmatics, using no inhaled steroids. Perhaps, a longer follow-up period would have resulted in more pronounced effects.

Keywords: acaricide, allergen avoidance, allergic asthma, bronchial hyperresponsiveness, covers, Der p 1, FEV₁, house dust mite

Clinical and Experimental Allergy, Vol. 29, pp. 1336–1346. Submitted 2 November 1998; revised 29 December 1998; accepted 22 February 1999.

Introduction

Exposure to house dust mite allergens (HDMAs) is considered to be an important trigger for the worsening of asthma [1–3]. Transferring HDM-allergic asthmatics to mite-free environments (hospital rooms, high altitude), improved bronchial hyperresponsiveness (BHR) [1,4]. Consequently, it is widely recognized that avoidance of HDMA improves health status in mite-allergic asthmatics [5,6]. Since transferral of patients out of their familiar habitation is impractical, several alternatives to reduce HDMA exposure in the domestic environment have been proposed. These alternatives included intensified cleaning habits (e.g. vacuum cleaning), removal of textile objects (e.g. upholstered furniture), climatic control, acaricidal chemicals and allergen-impermeable covers [6]. Encasing of mattresses and bedding have thus far shown to be the most effective measure to reduce HDMA exposure [7,8]. Acarosan® is very effective in reducing allergen concentrations in laboratory, but the effectiveness in domestic environment, however, is still the subject of debate [8–11]. Several studies investigating these measures separately, showed improvements in clinical parameters [2,8,12–14], whereas other studies failed to demonstrate this [11,15–18]. This contradiction can partly be explained by differences between studies, for instance, in the procedure of the avoidance measures applied, the severity of asthma in the study-population, differences in medication use (especially inhaled corticosteroids [IC]) before the study but also during the study and confounding of other allergies. Methodological aspects such as differences in population-size and the chosen effect parameters may also play a role. Most studies do not correct for these factors, although they might have important consequences. Because use of ICs has shown the most pronounced effects on clinical parameters, this might especially confound the effects of the avoidance measurements. It is interesting to know what the effects of HDMA avoidance measures are in patients who use no ICs during the time of follow-up. Likewise, interference of the existence of other allergies and exposure to the relevant allergens besides HDMA probably plays an important interfering role, and therefore it is important to correct for this factor as well. Another important aspect concerning the effectiveness of mite avoidance measures is to combine several avoidance measures [19]. This option might result in more pronounced effects on clinical parameters, but has hardly been studied so far. Recently Carswell *et al* [7,20] showed that the combined use of Acarosan® and encasement of mattresses and bedding was effective in both

reducing allergen concentrations and improving the asthmatic condition in children. However, Marks *et al* [15] failed to demonstrate a significant improvement in asthmatic condition by combining avoidance measures (acaricidal treatment of floor covering and encasement of mattresses) in a population of adult asthmatics. This might have been due to small population size and ineffectiveness of the applied chemical treatment on carpets. Hence, the objective of this study was to evaluate the effectiveness of a domestic avoidance strategy in improving clinical condition in a large group of adult HDM-allergic asthmatic patients, who used no steroids during the study. Furthermore, allergies besides HDM were registered and all analyses were corrected for the presence of these other allergies. This study was part of a greater study which also assessed the interactive effects of bronchodilator use and allergen exposure [21] on BHR. Therefore, the use of bronchodilators was carefully controlled and registered. The avoidance measures consisted of acaricidal treatment of textile floor covering, and encasement of mattresses, duvets and pillows with HDMA-impermeable covers, which is a combination of avoidance measures which to our knowledge has not been tested for its clinical relevance in a large group of adult asthmatics before. It is expected that by (1) selecting a group of patients who did not use steroids during the study, (2) defining additional criteria to reduce exposure to relevant allergens, and (3) correcting analyses for the existence of other allergies, a lot of confounding in the study is avoided and that in this way the (clinical) effects of HDM allergen avoidance might become more clear.

Methods

Patients

We selected HDM-allergic asthmatics, who used no ICs or were able to cease them. As in the recruitment phase, privacy rules had to be taken into account, a complex three-step selection procedure was necessary. First, patients who were found to be allergic to house dust mite at an allergy laboratory during the last 5 years ($N=3343$) were selected and reported to their GP. Secondly, the GP checked whether the patient was eligible for the study, according to criteria: (1) age between 16 and 60 years, (2) existence of lower airway complaints, (3) no use of oral steroids, and (4) no dependency on ICs. Eligible patients were informed about this study by their GP and asked to participate ($n=1541$). If patients (willing to participate, $n=541$)

were under treatment of a pulmonologist, this pulmonologist was asked whether the patient could participate in this study. Eventually, 456 patients visited our lung function laboratory for an inclusion assessment, which was the third selection step. The following inclusion criteria were used: (1) $FEV_1 > 50\%$ of predicted and $> 65\%$ after inhalation of $400 \mu\text{g}$ salbutamol; (2) PC_{20} on histamine $\leq 8 \text{ mg/mL}$ and/or reversibility of obstruction $\geq 15\%$ after inhalation of $400 \mu\text{g}$ salbutamol (compared with baseline FEV_1); and (3) a positive intradermal allergen test for HDM. Additional selection criteria to avoid possible confounding of exposure to relevant allergens were defined: (1) patients with a reaction to pets other than cats, which was stronger than the reaction to HDM were excluded if these pets were present in the domestic situation; (2) patients allergic to cats, irrespective of the magnitude of the reaction, were excluded when the cat was present in the domestic situation at that moment, or had been within 1 year before the start of the study. Eventually, 258 patients met these criteria, of which 204 were randomized. The remaining 54 patients did not start the study mainly because of a lack of motivation and moving houses ($n=39$), deterioration in pulmonary condition or they were advised to (re)-start treatment with ICs ($n=15$). The study protocol was approved by the Medical Ethical Committee of the Medical Centre Dekkerswald, University of Nijmegen, and all patients gave a written informed consent.

Study design

Patients were included in the study between October 1993 and September 1996. The study period started with a baseline period of 4 weeks (Fig. 1). After those 4 weeks, patients were randomly allocated to an active or a placebo allergen-avoidance group (blinded for the patients and lung function

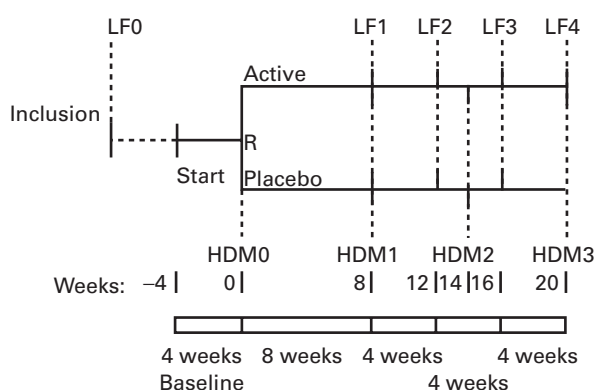


Fig. 1. Study scheme. LF = lung function measurement, HDM = dust sampling, R = point of randomization. During HDM0, baseline dust samples were taken, where after the avoidance measures were performed.

technicians). At the end of baseline period, active and placebo avoidance measures were carried out. At the same time, patients who still used pulmonary medication, but who were expected to be able to stop their treatment according to the GP or pulmonologist, were instructed to cease their own medication (ICs, cromones and antihistaminics). Furthermore, all patients were instructed to use only bronchodilators in a standardized way, of which the use was carefully controlled and registered. After the avoidance measures were performed, patients were followed for a period of 20 weeks. If patients had an exacerbation, as judged by their GP, they were treated with an oral prednisone course and, if necessary, with antibiotics in a standardized way. If this treatment was not sufficient and patients had to restart their old medication (i.e. ICs), because of a further deterioration of their asthma, this was considered as an endpoint, as these patients did not meet the inclusion criteria. These patients were withdrawn.

Intradermal skin testing

During the inclusion assessment an intradermal allergy test was performed with 16 common aeroallergens: house dust mites, pets, feathers, pollen and moulds (all ALK, Groningen, The Netherlands), as previously described [22]. Because having other allergies besides HDM allergy might confound our data, three parameters were calculated to express the allergic status of each patient: (1) the number allergies besides HDM-allergy (0–15); (2) sum of the proportions of the weal size of each allergen compared with the weal size of the positive control; and (3) having a mono-allergy for HDM (yes/no).

Measurement of clinical parameters

During the total study period patients completed diary cards, in which medication use, asthma symptoms and peak flow values (Pocket Peak Flow Meter, Micro Medical, Rochester, UK) were recorded. Patients were trained in performing peak flow manoeuvres preceding the study period. Three readings were performed each morning before breakfast and each evening before dinner. The highest of the three (both in the morning and the evening) were recorded. Asthma symptoms included cough, breathlessness, wheezing, expectoration, tiredness, and sleep disturbance (due to nocturnal asthma symptoms) and were scored on a modified Borg scale (0 = no symptoms to 10 = severe symptoms) [23]. Furthermore, at inclusion, and during each subsequent visit to the lung function laboratory (Fig. 1) FEV_1 and $15'$ reversibility of FEV_1 after inhaling $400 \mu\text{g}$ of salbutamol were measured (Microspirometer HI-298, Chest Corporation, Tokyo, Japan [24]). BHR was determined by step-wise inhalation of increasing concentrations of histamine

solution, according to the ERS-standard [25]. The dose of inhaled histamine, causing a 20% fall in FEV₁ with regard to baseline was obtained from the log-dose response curve by linear interpolation (PC₂₀). After spontaneous recovery to $\geq 90\%$ of the prehistamine value, bronchodilator response was measured before and 15 min after 400 μ g salbutamol (m.d.i.). Reversibility of FEV₁ was calculated as the percentage change compared with the prebronchodilator value.

House dust avoidance measures

The active allergen-avoidance measures consisted of treatment of carpets and rugs in bedroom and living rooms with an acaricidal moist powder (Acarosan[®], benzylbenzoate 5% (w/w), Allergopharma, J. Ganzer KG, Hamburg, Germany), following the instruction of the manufacturer. Smooth floors (e.g. parquet, flagstones) were not treated. Mattresses, duvets and pillows were enclosed in covers impermeable to house dust mite and its allergens (Intervent^{*} Bedding Systems[®], W. L. Gore & Associates Ltd, Livingston, UK).

The placebo intervention consisted of spraying a small volume of water on the carpets and rugs from a bottle with an acaricidal superscript, and encasement of mattresses with mite- and allergen-permeable cotton covers (specially designed for easy penetration by house dust by Intervent^{*} Bedding Systems) [26].

Dust collection, extraction and Der p 1 assessment

Dust samples were collected at end of the baseline period (before avoidance measures), and 8, 14 and 20 weeks later, to assess HDMA (Der p 1) concentrations (Fig. 1). During each visit three samples were taken: (1) living room floor, (2) bedroom floor, and (3) mattresses. For all samples the same type of vacuum cleaner was used (Philips Turbo Exclusive TC836, 1400 Watt, Philips, Eindhoven, The Netherlands). Dust was collected in paper bags (floor samples), and was equipped with a nozzle containing a collector with a filter paper for mattress samples. Floors were vacuumed totally, except on places with heavy furniture (e.g. cupboards), in a standardized way (intensity: 1 min/m [2]). Both the upper surface of the bare mattress (or after encasing directly on the covers) of the patient and the partner (if applicable) were sampled, again in a standardized way (intensity 5 min/m [2]).

The amount of fine dust was weighed (floor samples: after sieving [pores 0.35 mm]) and a 10% (w/v) extraction in 0.01 mol/L NH₄HCO₃ buffer was performed by overnight rotation at 4°C. The samples were centrifuged and the supernatants were stored at -18°C until Der p 1 concentrations were measured. Detection of Der p 1 was performed by ELISA as described by van der Heide *et al* [27], and expressed as ng/gram dust.

Data analyses

Der p 1 concentrations were ln-transformed before analysis to achieve a normal distribution. PC₂₀ values were ²log transformed, so that differences can be interpreted as doubling doses. FEV₁ was presented as percentage of the predicted value (ERS/ECSC standard) [28]. 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 the mean during the 3 weeks before the intervention (the first week was left out, to avoid learning effects) and as the mean for each consecutive week after the intervention. Furthermore, an overall symptom score was calculated by adding up the separate symptom scores of each day, which resulted in a mean overall symptom score per week.

Repeated measurement analysis of variance testing for both within-subject factors and between-subject factors was used to investigate changes in Der p 1 values and clinical parameters from baseline. Repeated measurement-models contained the following independent variables: group (active/placebo avoidance), time (0-4 for spirometric parameters, 0-3 for Der p 1 parameters, and 0-20 for peak flow and symptom parameters) and group × time interaction term, resulting in the following model:

$$\text{dependent variable} = \alpha + \beta_1 \times \text{group} + \beta_2 \times \text{time} + \beta_3 \times \text{group} \times \text{time}$$

If the estimate for β_1 is significant, it means that there is a significant difference between the active and placebo group during the whole follow-up period. If the estimate for β_2 is significant, it means that measurements in time are significantly different. If β_3 is significant, it means that the course in time in the active group of the dependent variable is significant different compared with the course in time in the placebo group. The analyses for the pulmonary parameters were all adjusted for the allergic status factors of the patient; all three calculated factors were included independently in the analysis.

Patients who restarted the use of ICs were not included in the analysis. Other dropouts were included in the analyses as long as they participated in the study (intention to treat protocol). An explanatory analysis was also done with only patients who finished the study completely. When there were no differences in outcome between those two analyses, the intention to treat results are presented.

Results

Patients characteristics

After inclusion, 204 patients started the study, 105 in the active group and 99 in the placebo group. Firstly, 42 patients

	Active <i>n</i> (%)	Placebo <i>n</i> (%)	Total <i>n</i> (%)
Start (washout)	105 (40)	99 (32)	204 (36)
Dropout before 1st follow-up (8 weeks)	25 (52)	17 (94)	42 (69)
Due to motivation	14	5	19
Due to restart ICs	11	12	23
Remained after 1st follow-up (8 weeks)	80 (36)	82 (20)	162 (28)
Dropout after 1st follow-up	11 (45)	5 (20)	16 (38)
Due to motivation (ITT)*	7	4	11
Due to restart ICs (excluded)	4	1	5
Remained after 20-weeks follow-up	69 (35)	77 (19)	146 (27)
Suitable for intention to treat	76 (32)	81 (19)	157 (25)

Table 1. Numbers (*n*) of subjects after randomization. Percentage of subjects that had to stop using their ICs at the start of the study in parenthesis. Subjects who dropped out because of motivational factors after 8 weeks (first follow-up assessment [*n* = 11*]) were included in the intention to treat analysis (ITT)

dropped-out before the first follow-up measurement (Table 1) and were therefore not included in the analysis. Secondly, another 16 subjects dropped out after the first follow-up measurement, of which 11 could be included in the intention to treat analysis. Finally, 146 patients completed the entire study and 157 (146 + 11) patients were included in the intention to treat analysis, 76 in the active group vs 81 in the placebo group. Patient characteristics

(Table 2) showed no significant differences between the two groups at the start of the study. The dropout after randomization in each of the two study groups was not selective. Of the remaining 157 patients, nine were treated with one course of oral prednisone (active: four, placebo: five). One subject in the active group received two oral prednisone courses. Furthermore, 17 subjects (22 measurements, active: 13, placebo: nine) had an FEV₁ lower than 50% of predicted

Table 2. Characteristic of the study population. Means and standard deviations or the absolute distribution (dichotomous parameters) are given

	Active <i>n</i> = 76	Placebo <i>n</i> = 81	<i>P</i> -value
Gender (M/F)	39/37	43/38	0.824
Age (years)	32.7 (11.0)	33.9 (11.1)	0.510
FEV ₁ prebronchodilator (mL)	3269.5 (770.7)	3234.1 (684.8)	0.761
FEV ₁ post-bronchodilator (mL)	3553.4 (772.9)	3538.4 (727.4)	0.900
Reversibility (%)*	7.51	8.17	0.473
FEV1% predicted (pre)	86.6 (15.9)	86.3 (14.9)	0.920
FEV1% predicted (post)	93.9 (13.9)	94.4 (14.1)	0.834
PC ₂₀ histamine (mg/mL)†	0.58 (0.38–0.88)	0.68 (0.46–1.00)	0.607
Number of allergies (besides HDM)	5.4 (3.5)	4.7 (3.4)	0.185
Peak flow morning (L/min)	523.2 (132.0)	532.3 (125.9)	0.663
Peak flow evening (L/min)	543.3 (127.8)	540.7 (123.1)	0.898
Peak flow variability(%)	6.44(4.06)	5.37(3.13)	0.068
Overall symptom score (sum of Borg-scores)	6.0 (6.1)	6.8 (6.7)	0.493
Smoker? (yes/no)	12/64	17/64	0.402
Der p 1 mattresses† (ng/g)	860 (537–1376)	931 (602–1439)	0.806
Der p 1 on bedroom floor† (ng/g)	1000 (684–1462)	675 (470–970)	0.136
Der p 1 living room floor† (ng/g)	937 (625–1403)	563.1 (375.2–845.1)	0.078
Floor covering in living room (textile/smooth)	58/18	58/23	0.502
Floor covering in bedroom (textile/smooth)	51/25	52/29	0.701
Age of mattress (months)	62.5 (42.8)	66.6 (48.5)	0.579

*Median (tested by Mann–Whitney *U*-test). †Geometric means (with 95% confidence interval).

during one or more spirometric measurements. Consequently, no BHR was measured. Although subjects were instructed not to change their domestic environment during the study, in total six subjects (active: three, placebo: three) made substantial changes (e.g. new mattresses, changing textile floors into smooth floors, moving houses). These subjects were removed from the analysis from the moment the changes took place.

Effect of allergen-avoidance measures on Der p 1 concentrations

Repeated measurement analysis showed that during the follow-up period, Der p 1 concentrations on mattresses

were always significantly lower in the active group compared with the placebo group ($P=0.0001$, Fig. 2). At the end of the study period Der p 1 concentrations of mattresses within the active group decreased significantly to 9.4% ($P=0.0001$) of the baseline value. Concentrations in the placebo group also decreased significantly (to 68.5%, $P=0.0153$). Thus, the reduction achieved with the active covers was much greater (10-fold) compared with placebo covers (1.5-fold).

To assess the effects of Acarosan®, only dust samples of floors with textile covering (wall to wall, or rugs) were included in the analysis, since not all participants had textile floor covering in their living room and/or bedroom (Table 2). There were no significant differences in living room Der p 1

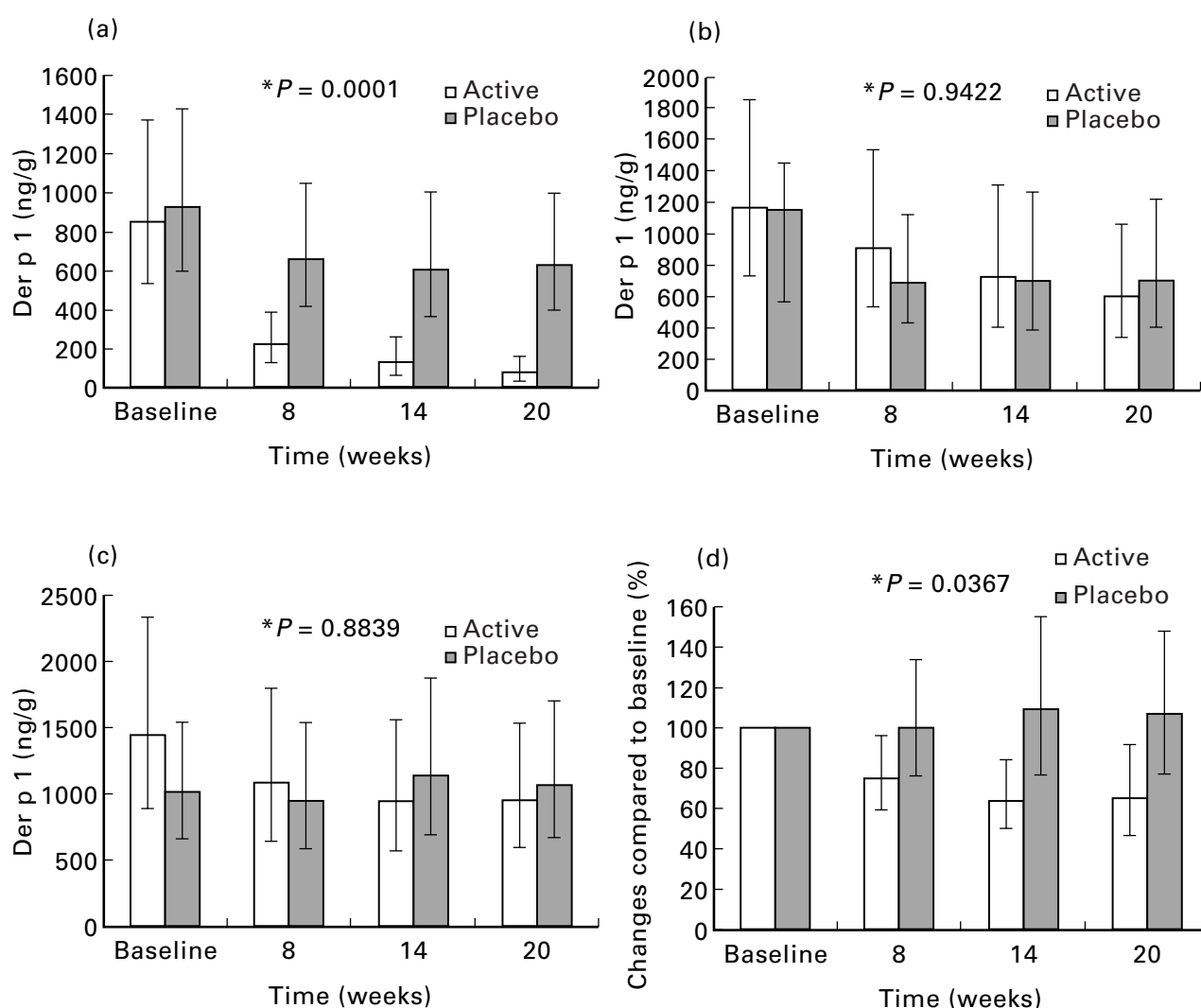


Fig. 2. Der p 1 concentrations (ng/g) on (a) mattresses, (b) living room, and (c) bedroom floors, for the active and placebo group during the study. Only patients who had textile floor covering or rugs were included in the analysis for living room and bedroom floors. Geometric means (95% confidence interval) are presented. *P-values between groups after the intervention. Reductions are also presented for (d) bedroom floors.

concentrations between the groups during the whole follow-up period ($P=0.9422$, Fig. 2). However, within the active allergen-avoidance group a significant decrease in living room Der p 1 concentrations was seen to 51.5% ($P=0.0004$). The placebo group showed no changes. Der p 1 concentrations on the bedroom floor showed the same tendency: no significant differences in bedroom Der p 1 concentrations (absolute) between the active and placebo group during the follow-up period ($P=0.8839$, Fig. 2) were seen. However, when reductions were analysed, a significant difference between the active and placebo group (active greater reductions, $P=0.0367$) was seen. Significant decreases in bedroom Der p 1 concentrations were seen to 66.5% ($P=0.0036$) in the active avoidance group. No significant changes compared with baseline were seen in the placebo group.

Effects on lung function parameters

There were no significant differences between baseline values for each of the clinical parameters (Table 2). No significant differences were found during the follow-up period between the groups in FEV₁%pred. ($P=0.8206$, Fig. 3). Both the active group and the placebo group showed a significant decrease in FEV₁% predicted within each group (active group: 5.3%, $P=0.0001$, placebo group: 6.1%, $P=0.0001$). During the follow-up period, no significant differences in PC₂₀ values between the active and placebo allergen-avoidance group were seen ($P=0.1291$, Fig. 3). No changes could be demonstrated within the active group. The placebo group showed a slight improvement (less than one doubling dose) during the follow-up period ($P=0.0271$). When analyses are done at each follow-up measurement separately in time, a significant improvement was only seen after 8 weeks (0.85 doubling dose, $P=0.007$) but disappeared during the rest of the follow-up period.

Peak flow parameters

Baseline values of peak flow parameters (morning, evening and variability) were comparable for both groups (Table 2). Repeated measurement analysis showed no significant effects between the two groups at any time point during the follow-up period for changes in peak flow morning values ($P=0.1203$, Fig. 4), peak flow evening values ($P=0.5144$) and peak flow variability ($P=0.6222$). Changes in peak flow morning values tended to rise in the active group, although this never reached significance (Fig. 4). Peak flow morning values in the placebo group showed a slight decrease, but this was not significant as well. Furthermore, no significant changes within groups in time were seen for peak flow evening values or peak flow variability.

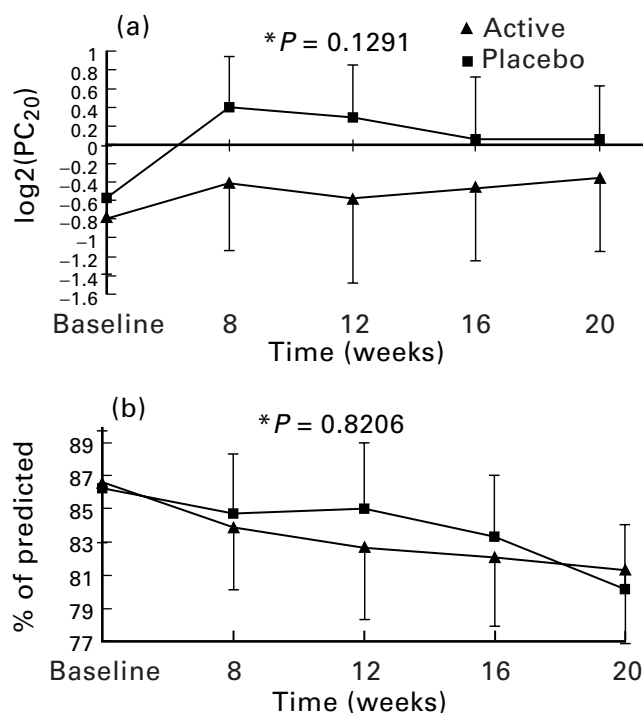


Fig. 3. BHR (a) and FEV₁ (b), for the active and placebo groups during the study. Means (95% confidence interval) are given, * P -values between groups after the intervention.

Asthma symptom scores

Baseline values of asthma symptom scores showed no significant differences between the two groups (Table 2). Because all symptom scores showed the same tendency, only the overall symptom score was presented. No significant effects between the two groups at any time during the follow-up period for changes in overall symptom scores could be demonstrated ($P=0.5474$, Fig. 5). Furthermore, no

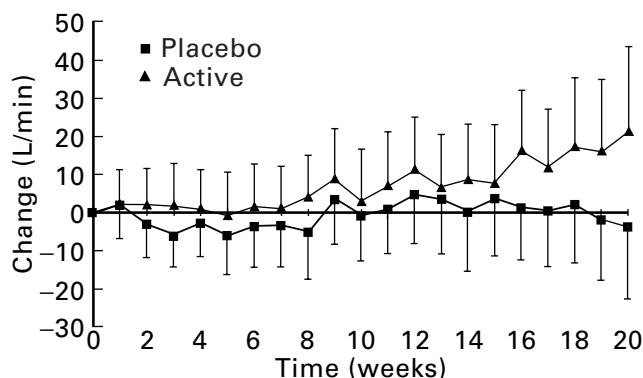


Fig. 4. Changes in peak flow morning values (mean [95% confidence interval]) compared with baseline for the active and placebo group. $P=0.1203$ between groups after the intervention.

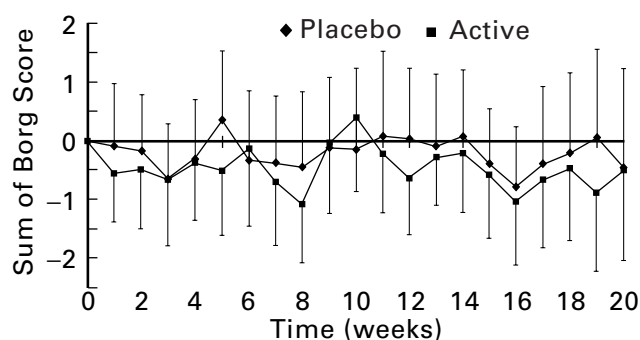


Fig. 5. Changes in overall symptom score (mean [95% confidence interval]) compared with baseline for the active and placebo group. $P = 0.5474$ between groups after the intervention.

significant changes in overall symptom scores within the two groups in time were observed.

Correction for allergic status

Correction for the allergic status of the patients did not result in different outcomes and therefore these results were not presented. This means that the effect of the avoidance measures was not different for the group of subjects with a mono-allergy for HDM ($n = 19$; six active vs 13 placebo) compared with the group of subjects with a multi-allergy. Correction for the severity of allergy (sum of the proportion weal size of allergen reactions divided through the positive control reaction [histamine] or the number of allergies besides HDM) did not influence the effects of the avoidance measurements. Again, patients with the most severe allergic status showed no different reaction on the avoidance measures compared with less allergic subjects.

Discussion

This study has shown that HDM-impermeable covers were capable of reducing the concentration of HDMA on mattresses. A slight effect of Acarosan® on textile floor covering was also seen, but this was only marginal. Although HDMA concentrations were reduced in the active group we found no convincing improvements in clinical parameters. This, despite the fact that we avoid and correct for the effects of two important interfering factors: the use of ICs during the period of avoidance and the presence of other allergies in combination with relevant exposure to other allergens besides HDM. The latter by defining additional selection criteria.

The effectiveness of impermeable covers on HDMA concentrations in this study are in accordance with other studies [2,7,8,29,30]. The placebo covers also caused a significant reduction in Der p 1 concentrations in our

study, which is also observed in other studies [20]. It might be that this kind of cover is relatively new and needs some time to become infested with mites and allergens, although this is not to be expected in this study, because the placebo covers used were of a material that was very permeable for dust and allergens. Vacuuming the mattresses four times intensively during the study period might have also influenced the allergen concentrations, because it is not a normal procedure in daily practice. Furthermore, because this study was focused on allergen loads, patients might have intensified their cleaning habits [6].

Although Acarosan® resulted in significant reductions in HDMA, these reductions were relatively small and HDMA concentrations were never significantly lower than the control group, except when reductions were analysed instead of absolute values. Moreover, these reductions were never more than twofold. Significant effects of Acarosan® are especially found in laboratory settings [9,10,31], while Acarosan® has been found to be less effective in the domestic situation [8,11,16,32,33], which is confirmed by our study. Several factors might explain this. First, the application time might be too short (3 h according to manufacturer's instruction) to gain a relevant effect. There are indications that a longer application time is more effective [31], but this is likely to be impractical for the user. Furthermore, the most important trait of Acarosan® is to kill mites and thus it only partly removes allergens. So, consequently living mites are reduced, but the reservoir of allergens might be preserved. This reservoir might be gradually reduced by vacuuming, on the condition that no new living mites re-infest these carpets. Because in this study the effects of Acarosan® are more pronounced after 14 and 20 weeks, we assume that mites are indeed killed and allergens are reduced to some extent by vacuuming. Re-infestation of mites seems to take more time, resulting in an overall decreased allergen load over time. Seasonal variations in HDMA exposure are not likely to have influenced our results, as patients were included in the trial gradually over a period of 3 years (October 93 to September 96). Active and placebo measures were performed randomly during all months of these years, not in a particular season.

Our baseline allergen concentrations were relatively low compared with other studies in, for example, Australia or South-Africa [15,16]. Although measured Der p 1 concentrations were low, patients in this study were sensitized to HDM, which was confirmed twice (first by recruitment at allergy laboratory and secondly by performing the intradermal skin test) and all these patients were diagnosed as asthmatics. Moreover, although baseline allergen levels were low we achieved significant reductions in allergen concentrations in the active group (especially on mattresses) when compared with the placebo group. Consequently, we

expected the clinical parameters to improve in this group of patients. Especially, because we reduced the influence of two important interfering factors: the use of ICs, and presence of other allergies concomitantly with the exposure to relevant allergens besides HDM. Contradictory to our expectations, we found no convincing evidence for this: Only the morning peak flow showed a non-significant tendency to improvement in the intervention group compared with a slight deterioration in the placebo group. It is important to discuss why we found no evidence of the effects in this well-defined group of allergic asthmatic patients. We selected asthmatic patients who could do without ICs and therefore could be indicated as mild asthmatics [34], with perhaps less room for improvement. However, pulmonary parameters seemed to have room for improvement (PC_{20} below 1 mg/mL and FEV_1 in percentage predicted below 90%, at baseline). Baseline allergen concentrations were relatively low, indicating that patients might already have reached their optimal lung function, especially because their asthma is mild. A further reduction in allergen concentrations may therefore have failed to reach an additional improvement in clinical condition. However, we did achieve a 10-fold reduction within mattresses, which is thought to be sufficient to achieve improvements in clinical parameters [35].

There are other studies that failed to demonstrate an improvement in clinical condition, despite reduced allergen concentrations [11,15–18,36]. Most of them concluded that perhaps the reduction was not sufficient to achieve improvements in clinical conditions. Interference of other allergens may also explain this. In the present study, patients with a mono-allergy to house dust mite formed a minority. Most patients were allergic to other allergens besides HDM. Although in this study we have tried to avoid interference of these allergens as much as possible by additional selection criteria, it might be possible that some exposure to these allergens still occurred. However, when we adjusted for the allergic status of the patient, no different results were found. Thus, it is very unlikely that this factor explains these negative results. Although it could be expected that especially the subjects with a mono-allergy for HDM would benefit from these allergen-avoidance measures, this was not seen in our study. Furthermore, in each of the two study groups subjects were instructed to cease the use of their pulmonary medication (if used), except bronchodilators. This might have resulted in a slight deterioration of their clinical condition. Several subjects even had to restart their treatment with ICs and consequently dropped out. Although the dropout during the study was not selective, a tendency towards a more severe group of dropouts can be seen. It might be that only relatively stable patients remained in the study, in which no further improvement was possible. We deliberately selected subjects who could stop using ICs as

otherwise improvements caused by allergen reduction would be masked, because the asthma of these patients already might have been optimally controlled by the use of ICs alone. Moreover, analyses on the subgroup of patients who never used ICs, and consequently did not have to cease this medication for this study, showed no different findings.

We were aware that it would be difficult to show clinical improvement in a group of mild asthmatics, using no ICs. However we think that this group of patients would especially benefit from these avoidance measures, for the following reasons. Avoidance measures might be the first choice of prescription in this group of patients, while in more severe group of patients pharmacological prescriptions, such as inhaled corticosteroids, are of primary interest. Normally, the use of avoidance measures are more or less an additional form of therapy in moderate to severe patients. These facts emphasize that it is very important to assess the effects of allergen-avoidance measures in mild asthmatics.

Some studies that did find an effect on clinical parameters included children [2,7,37]. It might be that in children larger effects are possible when compared with adults. Furthermore, studies that included adults, included patients that still had to use ICs [8,12,15], indicating that these patients were more severely affected by their asthma than our patients. Some of these studies did find effects while others did not. We expected that by selecting patients who used no ICs, and are consequently very mild patients, to observe more pronounced effects. In more severe patients it might be difficult to reverse the developed inflammation in the lung [38–40], just by avoidance of HDMA. Unfortunately, we could not confirm this in this study. Perhaps, effects would be clearer if the follow-up period had been longer, especially if the effects on peak flow parameters at the end of the study were taken into account.

In an earlier study of our group we investigated the effects of the same combination of HDM-avoidance measures used in this study in a group of allergic subjects, without a diagnosis of asthma but with some early signs of asthma [22]. In that study we found that peak flow parameters and asthma symptom scores were stabilized during the follow-up period, suggesting that a delay in the onset of asthma may occur in some allergic subjects [22]. The question is why no positive effects were found in the current group of allergic subjects with already established asthma, but were found in a group that had not developed asthma yet? We hypothesize that allergen avoidance as early prevention has more impact than as tertiary prevention [41]. When asthma is already established, it may be that very small amounts of allergens are sufficient to trigger a deterioration in the patients asthmatic condition [3]. Furthermore, allergen reduction needs some time to reverse the already developed process of inflammation and consequently it needs some

time to observe effects. In allergic patients without asthma, a moderate reduction in allergen load might prevent further development of asthma, because it is easier to slow down the just started process of inflammation in this early stage of the disease. Consequently, effects are probably more rapidly seen. The observation that avoidance measures are more effective in children than in adults [2,7,37] supports this vision. This implies that allergen-avoidance measures have to be applied in an early stage of the disease (secondary or even primary prevention [41,42]). Whether the latter is true requires further investigation. For instance, to investigate the effects of the avoidance strategy used in this study on the course of paediatric asthma in infants and young children.

Summarizing, the combined avoidance strategy used in this study, was effective in reducing allergen load. The reduction was especially achieved in mattresses by the use of allergen-impermeable covers, while the effects of Acarosan® on floor coverings was only marginal. This achieved reduction in allergen load was, however, not reflected in a convincing improvement in the clinical condition of adult allergic asthmatics not using ICs. Correction for the allergic status of the patients did not alter these findings. Perhaps a longer follow-up period would have resulted in more pronounced effects.

Acknowledgements

We would like to thank the research assistants for obtaining the dust samples, Mr H. Hovenga (University Hospital Groningen) for analysing all the dust samples, Prof. Dr R. Aalberse (University of Amsterdam) for kindly supplying the cell line producing monoclonal antibodies against Der p 1, the four lung function technicians for performing all the spirometric measurements, and Mr R. Akkermans for his statistical support.

This study was supported by the Dutch Asthma Foundation, Novartis Pharma, 3M Pharma Industries and Boehringer Ingelheim.

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