

Short communication

Clinical effects of benzyl benzoate in the prevention of house-dust-mite allergy

Results of a prospective, double-blind, multicenter study

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The efficacy of the acaricide benzyl benzoate as an additive to a chemically and technically defined cleaning substance (Acarosan®) was tested in a multicentric, prospective, randomized, controlled study on 118 outpatients with bronchial asthma due to house-dust-mite allergy. Subjective reports from patients and doctors revealed an improvement in clinical complaints in more than 50%, with only small differences between the verum and the placebo group. Objective parameters such as titrated skin tests, RAST, and bronchial challenge tests with histamine and *Dermatophagoides pteronyssinus* (*D. pt.*) did not reveal any significant changes either during the year of testing or between the two groups. A clinical improvement as observed in either group could not be assessed by objective parameters. Additional questions as to the merits of the possible prophylactic use of benzyl benzoate over more than 1 year remain unanswered.

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Conventional cleaning methods have been recommended for decades to avoid or decrease the numbers of house-dust mite: thorough vacuum cleaning, replacement of feather bedding by synthetic materials, frequent washing of bedclothes, reduction of textile objects in living and sleeping areas (rugs, upholstered furniture), good airing, and less humidity in homes (1, 2). Studies on the clinical efficacy of conventional cleaning procedures to reduce mite exposure have provided different results. Some authors report a favorable effect (3–7); other studies (8, 9) did not find such positive results. Furthermore, bed encasings have been tested, found to show positive effects on the clinical course of atopic diseases, and could reduce mite-allergen levels in beds (10–12). In addition to conventional mite avoidance, various acaricide measures have been tested for years to combat the settling of house-dust mites in home living areas. Ten different acaricide substances have been presented and tested in Europe over the last few years.

The product Acarosan® (containing benzyl benzoate) has aroused considerable interest. It has been shown that benzyl benzoate can reduce mite allergen levels (13–14). Since 1986, several studies

have reported on the clinical efficacy of Acarosan. In most of these, however, the authors usually referred to a very small number of cases examined in uncontrolled studies. Hide et al. (15) showed an effect on atopic eczema, but no effect on asthma. Some studies found only a short-term effect (16, 17), and it was suggested that more cleaning time was necessary than recommended in the manufacturer's instructions (18, 19).

In a double-blind clinical study on 20 patients with allergic rhinitis (matched pairs) (20), the efficacy of Acarosan was reported to be high. In another double-blind study on 12 patients, the acaricide failed to prove its effect (21). Sette et al. (22) also showed that benzyl benzoate spray was no more effective than placebo in reducing the level of house-dust mite in patients' mattresses, or in reducing bronchial hyperreactivity.

This multicenter study by the Wissenschaftliche Arbeitsgemeinschaft für die Therapie von Lungenkrankheiten e.V. (WATL) (Scientific Study Group for the Therapy of Lung Diseases) aimed to investigate the possible clinical benefit of using Acarosan on house-dust-mite asthmatics in a prospective, double-blind method.

Material and methods

Patients

A total of 118 patients, aged 8–50 years, participated in the study. All patients had bronchial asthma with or without clinical symptoms, but required regular antiasthmatic therapy. Sensitization to *Dermatophagoides pteronyssinus* (*D. pt.*) had been shown by skin test and RAST. The clinical relevance was proven by bronchial challenge tests. Patients with other relevant allergies were excluded. Only nonsmokers or ex-smokers for at least 5 years were included. The patients were randomized individually in each participating center. Biographic background data did not differ significantly between the placebo and the verum group (Table 1).

Diagnostic procedures

Uniform batches of *D. pt.* were used for skin tests, RAST, and provocation tests. At the beginning and the end of the study, we used the same batch (specially manufactured and supplied by Allergopharma, Joachim Ganzer KG, Reinbek, Germany). For the skin prick tests, we used the Allergy Pricker, according to Østerballe. The skin titration was made with 30, 100, 300, and 1000 PNU twice on both arms in counterrotatory design (Kjell Aas method) at the beginning of the study and after 12 months. The test reaction was documented with tape and planimetry of the area with a Digicon. The allergen concentration causing a wheal of the size of the histamine control or greater HEP (histamine equivalent prick) was calculated. The specific IgE against *D. pt.* was measured by the Phadezym method (Pharmacia, Uppsala, Sweden). The RAST was done at the beginning and after 12 months. Only patients with RAST class 3 or 4 were included. Bronchial provocation tests with histamine and *D. pt.* were done at the start and after 12 months. Histamine provocations were performed to determine the bronchial hyperreactivity. The following histamine concentrations were used in increasing doses: 0.03, 0.3, 3.0, 6.0, and (in some cases) 15.0 mg/ml. Bronchial challenge tests were carried out with *D. pt.* extract (Allergopharma, Joachim Ganzer KG, Reinbek, Germany) in the following concentrations: 1:1000, 1:100, 1:10, 1:2, and (in some cases) 1:1. The PC₂₀ histamine/*D. pt.* value was gained by linear regression to the decreasing FEV₁ values.

Cleaning procedures

The cleaning products were used according to the manufacturer's precise written instructions: admini-

Table 1. Biographic background data from randomized patients. Column at right shows results of chi-square tests (NS: no significant difference)

	Control	Verum	Chi-square test
Sex			
M	33	34	0.7158
F	30	21	NS
FH ¹ positive for atopy			
No	32	29	0.0006
Yes	31	26	NS
Asthma grade ²			
2	48	43	0.1748
3	15	10	NS
Rhinitis			
No	23	25	0.6385
Yes	40	30	NS
Atopic dermatitis			
No	53	50	0.6828
Yes	10	5	NS
IT			
Never	36	33	0.3681
Formerly	17	12	NS
Now	9	7	

¹FH: family history.

²Asthma grade 2: regular antiasthmatic therapy without symptoms; asthma grade 3: regular antiasthmatic therapy with symptoms.

IT: immunotherapy.

stration, respectively, of the placebo and the verum preparation at the start and after 6 months. The control group received a placebo cleaning product without the acaricide, but which was otherwise identical to the verum product. Patients were also instructed by their doctors on how to perform cleaning procedures in their homes. It was decided not to have professional health workers do the cleaning in order to gain a realistic view of practical allergology.

Statistical methods

The statistical evaluation was carried out with the SPSS software package. The chi-square test and nonparametric tests were used. The significance level was 0.05.

Results

A total of 118 patients participated in the study. Data from 78 patients were available for final analysis. The dropouts were based on patient or medical decision. Dropouts also occurred because of protocol violation and loss to follow-up. There was no difference between the two groups (control/verum) in incidence of and reason for dropout.

Side-effects

None of the users mentioned significant side-effects. Three patients reported a subjective "strange smell".

% of patients

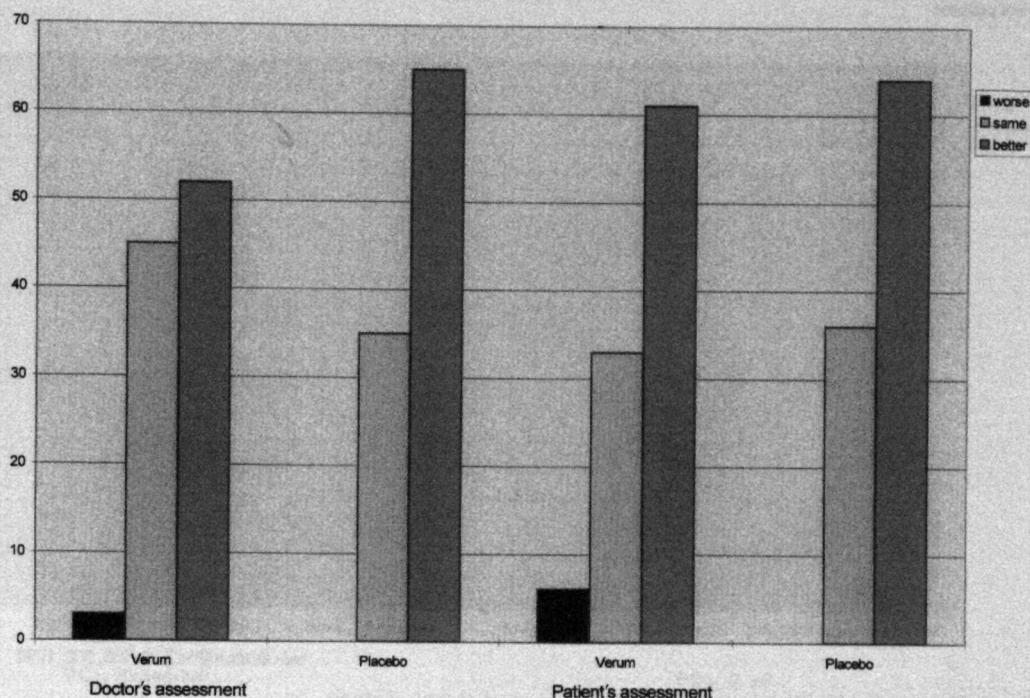


Fig. 1. Clinical outcome: assessment of symptoms.

The spotty bleaching of upholstery was reported in one case. Both the use of the preparations and the cleaning instructions were regarded favorably.

Clinical assessment by the patient and attending physician

At the end of the study, both the patient and the attending physician assessed the patient's clinical well-being as compared to the beginning of the study. The patients' assessment and that of their doctors corresponded in 84% of the cases. A high percentage of improvement became apparent in these clinical parameters. Neither the patient's assessment ($P=0.098$) nor the doctor's assessment ($P=0.696$) revealed any significant differences between control group and verum group (Fig. 1). (The assessments "worse" and "same" were grouped together to form one category in the statistical analysis.)

RAST examination

The changes of the RAST data from the beginning to the end of the study showed no differences between the control and the verum group.

Skin titration (skin prick test)

Changes in skin titration (HEP) values from the beginning to the end of study are shown in Fig. 2.

No difference existed between the control and verum group.

PC₂₀-histamine and PC₂₀ D. pt.

Fig. 3 shows the PC₂₀ data for challenge tests with histamine and *D. pt.* There was no difference between the two groups in the histamine and the *D. pt.* provocation, either at the beginning or at the end of the study.

Discussion

This study showed subjective improvement of symptoms as assessed by the patients and by the doctors, at the end of the cleaning period, with no difference between the verum and the placebo group. There was no change in allergologic data (skin end-point titration, RAST, bronchial challenge with histamine, and *D. pt.* PC₂₀) during the study.

Clinical assessment by the attending physician and self-assessment by the patient

The opinion on general well-being by both the patient and the attending physician revealed a roughly 50% improvement in both the verum and the control group – a highly satisfactory statement of clinical importance. The breakdown between the control and the verum group did not reveal any

% of patients

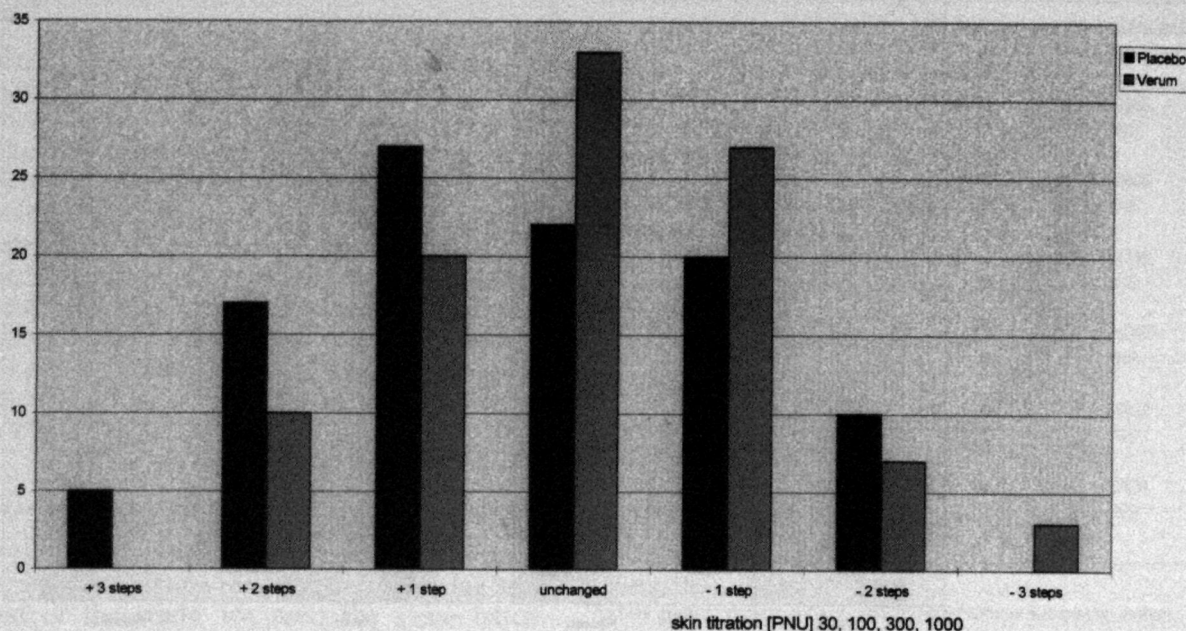


Fig. 2. Changes in skin titration (HEP) values from start to end of study.

significant difference. Morrow-Brown & Merrett (23) evaluated the clinical course of 12 asthmatics after the application of Acarosan, without using a control group. An improvement was noted in four (out of five) asthmatic patients under 30 years of age on the basis of symptom score and drug intake. The condition of four (out of seven) asthmatic patients over 30 years remained unchanged after cleaning with Acarosan. The authors explained this by the fact that hyperreactivity and inflammatory changes may be irreversible in older patients. Our study does not confirm this assumption, as we did not find an age-related difference in subjective improvement. Kniest (20) studied a small group of patients (10 patients each in the control and test group). Of the patients using the verum preparation, 80% improved according to clinical parameters, compared to only 40% in the control group. The same was found by Wirthmüller & Pichler (24) (11 patients in the test group; eight patients in the control group). There was a significant improvement in the symptom scores of rhinopathy and asthma and a reduction in drug intake.

We were unable to determine a similar difference in favor of the acaricide therapy. Our results are comparable to those of Huss et al. (21), who also found no significant changes in lung function or medication score in a randomized, double-blind, placebo-controlled study (six patients each in the control and test groups). When comparing the clinical outcome, one must take into consideration

that Kniest conducted his study on patients with rhinopathy, and Wirthmüller & Pichler (24) had patients with rhinopathy and/or asthma, whereas our group consisted exclusively of patients with clinically manifested bronchial asthma. Morrow-Brown & Merrett refer to the considerable influences of competing antigens, which are not affected by mite-reducing procedures. Wirthmüller & Pichler included 16 patients (total 31) with animal-related allergic symptoms. In our study, we accepted only patients with mite allergy and mite allergen as the only relevant allergen. However, such competing factors as viral infection and psychogenic influence can never be totally excluded.

Allergologic data (prick tests, RAST, bronchial provocation with D. pt.)

A positive skin prick test confirms the presence of specific IgE antibodies against the corresponding allergen in the skin. For assessment of the clinical relevance of this sensitization, additional diagnostic criteria are needed. Reports have been made on fluctuations in allergic reactions to house-dust-mite allergens during the course of a year. Therefore, we tested the hypothesis that avoidance of house-dust mite – if possible – would also lead to a decrease in skin sensitivity (and RAST results) to *D. pt.* The results of the skin titrations and RAST determinations in our study did not confirm this assumption.

% of patients

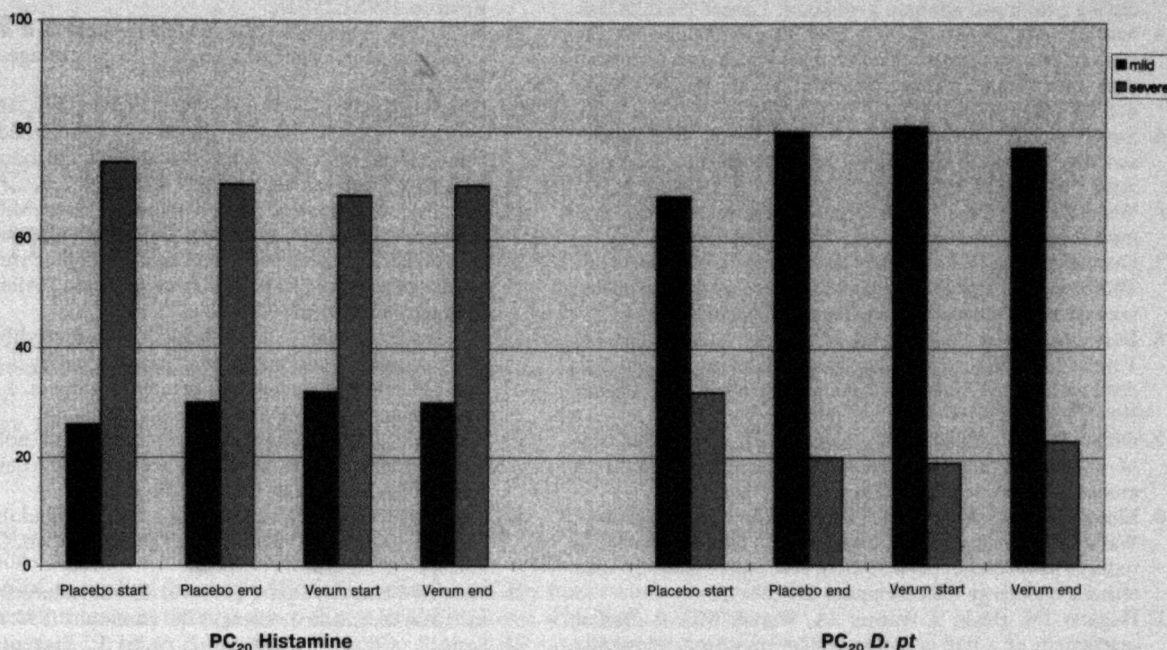


Fig. 3. PC₂₀ histamine/*D. pt.* values after provocation. Comparison of data at start and end of study year.

In our study, the PC₂₀ values in the bronchial provocation test with histamine and *D. pt.* showed no significant improvement after 1 year and no difference between verum and control group. This statement is comparable to the findings of Huss et al. (21), who found no changes in lung function, and Wirthmüller & Pichler (24), who did find an improvement in the patients' self-assessment after Acarosan without statistically significant effect on bronchial hyperreactivity. Sette et al. (22) also found no reduction of bronchial hyperreactivity after spraying benzyl benzoate foam on mattresses. In conclusion:

- 1) This study showed no difference between the verum and control group, either in the patients' or physicians' assessment of the clinical score or in the allergologic data and the PC₂₀ histamine.
- 2) Whereas the clinical score improved in about half of the cases in both groups, the PC₂₀ histamine and the allergologic data (skin end-point titration, RAST, and PC₂₀ *D. pt.*) did not change during the study.
- 3) Several studies provide good evidence that benzyl benzoate is effective in killing mites in a laboratory setting. Our study shows that this does not hold true under practical conditions over the course of 12 months. An acaricidal preparation has to prove its efficacy in the daily life of a patient's family rather than under the guidance of acarologists and professional health workers.

- 4) Further studies would be necessary to determine whether a favorable result with an acaricide could be obtained if applied more frequently and over longer periods.

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References

1. van Bronswijk JEMH. Management of mites and mite allergens in the home. In: de Weck AL, Todt A, editors. Mite allergy – a worldwide problem. Bad Kreuznach, 1–2 Sept 1987. Brussels: UCB Institute of Allergy.
2. Colloff MJ, Ayres J, Carswell F, et al. BSACI Working Group. The control of allergens of dust mites and domestic pets: a position paper. Clin Exp Allergy 1992;22 Suppl 2:1–28.

3. Platts-Mills TAE, Tovey ER, Mitchell EB, Moszoro H, Nock P, Wilkins SR. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. *Lancet* 1982;2:675-8.
4. Murray AB, Ferguson AC. Dust-free bedrooms in the treatment of asthmatic children with house dust or house-dust-mite allergy: a controlled trial. *Pediatrics* 1983;71(3): 418-22.
5. Sarsfield JK, Gowland G, Toy R, Norman ALE. Mite-sensitive asthma in childhood. Trial of avoidance measures. *Arch Dis Child* 1974;49:716-21.
6. Walshaw MJ, Evans CC. Allergen avoidance in house-dust mite sensitive adult asthma. *Q J Med* 1986;58:199-215.
7. Dorward AJ, Colloff MJ, MacKay NS, McSharry C, Thomson NC. Effect of house-dust mite avoidance measures on adult atopic asthma. *Thorax* 1988;43:98-102.
8. Burr ML, Dean BV, Merrett TG, Neale E, St Leger AS, Verrier-Jones ER. Effects of anti-mite measures on children with mite-sensitive asthma: a controlled trial. *Thorax* 1980;35:506-12.
9. Gillies DRN, Littlewood JM, Sarsfield JK. Controlled trial of house-dust mite avoidance in children with mild to moderate asthma. *Clin Allergy* 1987;17:105-11.
10. Ehnert B, Lau-Schadendorf S, Weber A, Beutner P, Schou C, Wahn U. Reducing domestic exposure to dust-mite allergen reduces bronchial hyperreactivity in sensitive children with asthma. *J Allergy Clin Immunol* 1992;90:135-7.
11. Hegarty JM, Bevin S, Warner JA, Warner MD. A clinical assessment of a bed covering system on atopic dermatitis patients [Abstract]. *J Allergy Clin Immunol* 1995;95: 249.
12. Tan BB, Weald D, Strickland I, Friedmann PS. Double-blind controlled trial of effect of house dust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996;347:15-18.
13. Pauli G, Dietemann A, Hoyet C, Eckert F, Bessot JC. Effets d'un nouvel acaricide sur les symptomes des asthmatiques allergiques aux acariens et influence sur l'environnement domestique (étude préliminaire). *Rev Fr Allergol* 1989; 29(4):175-80.
14. LeMao J, Liebenberg B, Bischoff E, David B. Changes in mite-allergen levels in homes using an acaricide combined with cleaning agents: a 3-year follow-up study. *Indoor Environ* 1992;1:217-18.
15. Hide DW, Matthews S, Tariq S, Arshad SH. Allergen avoidance in infancy and allergy at 4 years of age. *Allergy* 1996;51:89-93.
16. Lau-Schadendorf S, Rusche AF, Weber AK, Buettner-Goetz P, Wahn U. Short-term effect of solidified benzyl benzoate on mite allergen concentrations in house-dust. *J Allergy Clin Immunol* 1991;87:41-7.
17. Woodfolk JA, Hayden ML, Couture N, Platts-Mills TAE. Chemical treatment of carpets to reduce allergen: comparison of the effects of tannic acid and other treatments on proteins derived from dust mites and cats. *J Allergy Clin Immunol* 1995;96:325-33.
18. Hayden ML, Rose G, Diduch KB, et al. Benzyl benzoate moist powder: investigation of acaricidal activity in cultures and reduction of dust-mite allergen in carpets. *J Allergy Clin Immunol* 1992;89:536-45.
19. Platts-Mills TAE. Environmental control of house-dust mites - new products, what they are and how to use them. *Immunol Allergy Prac* 1991;13:156-8.
20. Kniest FM. Clinical evaluation of a double-blind dust mite avoidance trial with mite-allergic rhinitis patients. *Clin Exp Allergy* 1991;21:39-47.
21. Huss RW, Huss K, Squire EN Jr, et al. Mite allergen control with acaricide fails. *J Allergy Clin Immunol* 1994;94:27-32.
22. Sette L, Comis A, Marucci F, Sensi L, Piacentini GL, Boner AL. Benzyl benzoate foam: effects on mite allergens in mattress, serum and nasal secretory IgE to *Dermatophagoides pteronyssinus* and bronchial hyperreactivity in children with allergic asthma. *Pediatr Pulmonol* 1994;18:218-24.
23. Morrow-Brown H, Merrett TG. Effectiveness of an acaricide in management of house-dust-mite allergy. *Ann Allergy* 1991;61:25-31.
24. Wirthmüller B, Pichler WJ. Einfluß einer Akarizid-unterstützten Hausstaub-Sanierung auf bronchiale Hyperreaktivität bei Hausstaubmilbenallergikern. *Allergologie* 1996;19:282-92.

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