

Immunotherapy with dog and cat extracts in children

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Hypersensitivity to dogs and cats causes asthma in many children. In this open controlled clinical study we wanted to establish whether immunotherapy can be recommended as a supplement to conventional medical therapy in dog- and cat-induced asthma in children. Twenty-seven children with mean age 10 7/12 years and with allergy to dog or cat according to anamnesis, skin prick test (SPT), specific IgE (RAST) and bronchial provocation test (BPT) entered the study. On the basis of age and bronchial sensitivity they were randomly allocated to either immunotherapy with dog or cat extract (active group, $n = 14$) or conventional medical therapy (control group, $n = 13$). Immunotherapy comprised subcutaneous injections with an alum-adsorbed depot extract (Alutard-SQ), and a maintenance dose of 100,000 SQ-U or the maximum tolerated dose. Before entering the study and after 9 months' therapy the patients were evaluated by BPT, SPT, RAST – and IgG₄ analyses. The active group showed statistically significant change in bronchial tolerance ($P < 0.02$), whereas no such change was found in the control group ($P > 0.05$). The change in skin sensitivity was significantly greater in the active group than in the control group ($P < 0.05$), whereas no significant differences were found in RAST and IgG₄. However, a significant ($P = 0.05$) increase in IgG₄ was seen in the active but not in the control group. Frequency and degree of side effects in this study were acceptable.

Key words: BPT; cat allergy; dog allergy; hyposensitization; IgG₄; immunotherapy; RAST; SPT; standardized extracts.

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CLINICAL ASPECTS

Based on results of BPT and SPT, immunotherapy with standardized dog and cat extracts can be recommended as a supplement to conventional medical therapy under the conditions of this study.

Hypersensitivity to dogs and cats is an important cause of asthma in many allergic children. Since elimination and conventional pharmacologic therapy is not always sufficient, a treatment supplement is sometimes needed.

The effect of immunotherapy is well documented in cases of allergy to pollen (14),

house-dust mites (7) and insects (3). According to new reports (5, 6, 8) the results of hyposensitization with standardized dog and cat extracts also appear satisfactory.

The aim of this open controlled clinical study was to establish whether therapy can be recommended as a supplement to conven-

Table 1
Inclusion and exclusion criteria

Inclusion criteria:

- history of allergy to dog or cat
- positive skin prick test (SPT) to dog or cat
- positive RAST to dog or cat
- positive bronchial provocation test (BPT) to dog or cat

Exclusion criteria:

- previous immunotherapy with dog or cat extracts
- simultaneous immunotherapy with other extracts
- allergy to dust mite more important in causing symptoms than dog or cat
- other chronic lung disease or immunologic disease

tional medical therapy in dog- and cat-induced asthma in children.

MATERIAL AND METHODS

Patients

Twenty-nine children, from two paediatric departments, were included in the study. Two were withdrawn because of non-cooperation. Twenty-seven children (14 boys, 13 girls) completed the trial. Their mean age was 10 7/12 years ranging from 7 to 15 5/12 years. Inclusion and exclusion criteria are presented in Table 1.

Patients had to fulfil all inclusion criteria. A positive history of allergy to dog or cat was defined as information of asthma attacks elicited by contact with dog or cat on repeated occasions. Skin prick test was considered positive, when skin index $\geq 1,0$ (skin index = $(d_e \times D_e)(d_H \times D_H)$. d = smallest diameter; D = largest diameter; e = extract of dog or cat (1.0 HEP); H = histaminechloride (1 mg/ml)). A positive RAST was defined as class 3–4 (12). A positive BPT was defined as a fall in FEV₁ of > 20 % from basic FEV₁ and/or stethoscopic ronchi and bronchospasms elicited by inhalation of dog/cat allergen.

Patients and their parents gave informed consent to participate in the study.

On the basis of age and bronchial sensitivity, the children were randomly allocated to either immunotherapy with dog or cat extract supplemented with conventional medical ther-

apy (active group $n = 14$) or exclusively conventional medical therapy (control group $n = 13$).

There was no statistically significant difference in bronchial sensitivity to dog or cat between the groups before entering the study. Neither was there any difference between the treatment groups as regards number of other allergies: according to anamnesis, SPT and/or RAST analyses seven of the children had no other allergies, eight had one, 13 had two or more allergies, mostly other pelt animals or pollen.

Treatment

Immunotherapy comprised subcutaneous injections with a standardized alum-adsorbed depot extract (Alutard®-SQ, ALK, Copenhagen, Denmark). In allergy to both dog and cat, the allergen of most importance according to anamnesis and the *in vivo* and *in vitro* tests mentioned below was used.

An initial dose of 20 SQ-units was given and thereafter, at weekly intervals, increasing concentrations (according to the dosage schedule recommended by ALK) until a maintenance dose of 100,000 SQ-U or the maximum tolerable dose was obtained. Hereafter injections were given with 4–6 week intervals. When needed, the patients could use conventional medical therapy.

The control group received exclusively conventional medical therapy (B₂-agonists, methylxanthines, topical steroids, sodium cromoglycate).

Methods

Bronchial provocation test (BPT) was performed in all patients before and after 9 months therapy according to a standardized procedure (15). Dissolved freeze-dried extracts of cat or dog allergen (Aquagen®-SQ) of 10-fold increasing concentrations from 10 SQ-U to 100,000 SQ-U were inhaled using an Optimist or Pari nebuliser. After inhalation of 1 ml of each con-

centration, lung function was evaluated by chest auscultation and forced expiratory volume in 1 s (FEV₁) on a Dräger spirometer. The lowest concentration causing a $\geq 20\%$ fall in FEV₁ compared with baseline values and/or bronchospasms on auscultation was recorded as the bronchial sensitivity threshold dose.

To exclude unspecific bronchial reactions, a bronchial provocation with an allergen which did not result in a positive BPT was carried out on a separate day, and BPT were done blinded to the patients.

On days when BPT was performed the patients had no signs of asthma (normal chest auscultation, basis FEV₁ $\geq 80\%$ of the predicted value). Patients were not allowed to use topical steroids or sodium cromoglycate 3 weeks before and bronchodilators 48 h before the BPT.

Reproducibility of the BPT was evaluated in a separate trial. Under identical standardized conditions, bronchial provocation with dog (in 4 children) or cat (in 5 other children) allergen was performed twice, with an interval of 2 weeks. There was no difference in bronchial sensitivity threshold dose between the two provocations, evaluated by Wilcoxon matched-pairs signed-ranks test (2-tailed $P = 0.317$) as well as paired samples t-test (2-tailed $P = 0.347$). So the reproducibility was high.

Skin prick test (SPT) was performed in all patients before and after 3 and 9 months' ther-

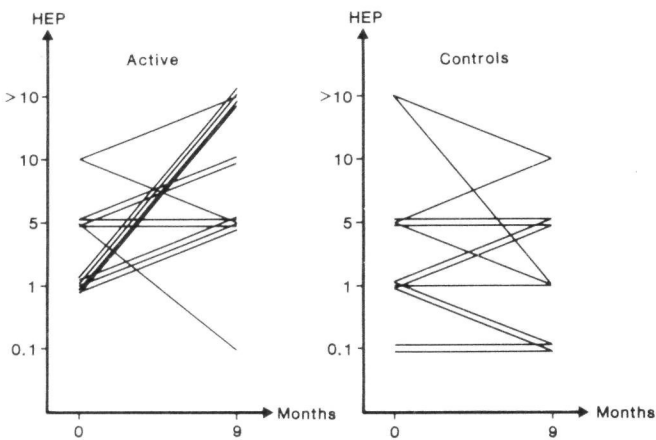


Fig. 2. Skin prick test (SPT) before and after 9 months of therapy. Values indicate the lowest allergen concentration to give a skin reaction $\geq$ the positive control (skin sensitivity threshold).

apy. A 50 % glycerol solution (Soluprick®-SQ) of dog and cat extracts was used in concentrations 0.1, 0.5, 5.0 and 10 HEP (Histamine Equivalent Prick). Histamine hydrochloride (1 mg/ml) served as positive control, and glycerol containing buffer as negative control. A droplet of each concentration was applied to the volar forearm. A 1.0 mm prick lancet (13) (DHS-allergy pricker) was passed through the droplet and the underlying skin was punctured with the tip of the needle. After 5 min the drops were wiped off and after 15 min each wheal was measured and recorded. The allergen concentration which gave a skin reaction $\geq$ the positive control was recorded as the skin sensitivity threshold concentration.

Serum-specific IgE (RAST) was measured in all patients before, and after 3 and 9 months therapy by AL-RAST (aluminium-radio-allergo-sorbent-test) according to Weeke (12). Serum-specific IgG₄ was determined before, and after 3 and 9 months of therapy according to Hamilton et al. (1).

Before and after 9 months of therapy, dust samples from the homes of all patients were analysed. The results were given in titers showing the amount of allergen in the patient's home (4).

The same batch of dog and cat allergen extract was used for all *in vivo* and *in vitro* analyses.

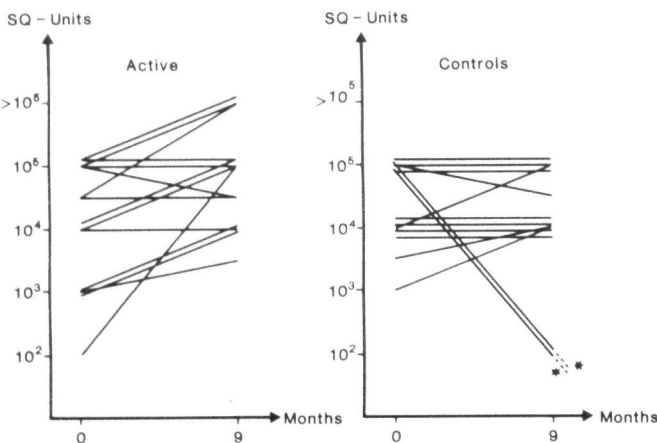


Fig. 1. Bronchial provocation test (BPT) before and after 9 months of therapy. Values indicate the lowest allergen concentration to give a positive BPT (bronchial threshold).
*too many symptoms to undergo BPT.

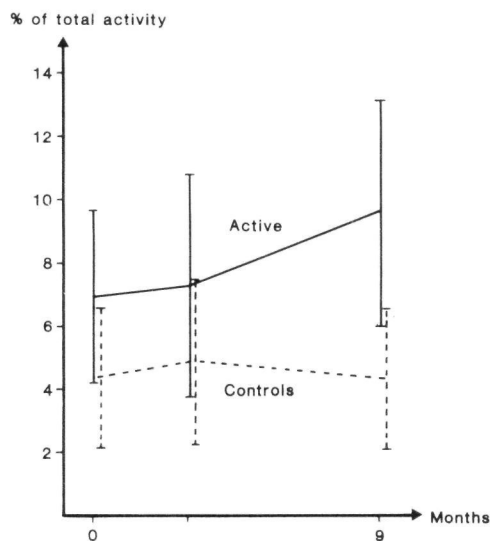


Fig. 3. IgG₄ (mean values) before and after 3 and 9 months of therapy.

Statistics

All data were evaluated by non-parametric tests. Mann Whitney test was used for significance of difference between mean values of groups. Wilcoxon two-tailed t-test was performed to evaluate difference in each group between start of therapy and 9 months results. Rank correlation tests were performed by Spearman test. A *P*-value of less than 0.05 was considered significant.

RESULTS

The results of the BPT before and after 9 months of therapy are shown in Fig. 1. Two patients in the control group had so persistently marked symptoms that they could not go through the 9 months control BPT. They are included as having decreased tolerance to dog or cat. The active-treated group showed significant increase in bronchial tolerance to cat or dog provocation (*P* < 0.02). An “average” patient tolerated approximately 5 times more allergen after 9 months of active treatment. No change was found in the bronchial tolerance in the control group.

The change in allergen-specific bronchial sensitivity correlated to a change in the basic FEV₁ value (*P* < 0.05) in the active group.

Fig. 2 shows the results of the SPT before and after 9 months of therapy. The active group showed a significantly larger change in skin sensitivity than the control group after 9 months (*P* < 0.05).

The efficacy of hyposensitization with dog extract did not differ from the efficacy of cat extract as far as BPT or SPT were concerned.

The results of serum-specific IgE (RAST) showed no significant difference either at 0, 3 or 9 months between the groups or from start to 9 months of therapy in the two groups (*P* > 0.05).

Fig. 3 shows the results of the serum-specific IgG₄ analyses. During 9 months of treatment no change was observed in the control group (*P* > 0.05), whereas a significant increase was seen in the hyposensitized children (*P* = 0.05).

The content of dog or cat antigen in dust samples from the patients’ homes was rather constant before and after 9 months of therapy except for three patients in the active and one in the control group who were apparently exposed to increase amounts of allergen. One of the patients in the active group had practically eliminated animal dander antigen from the home.

Fig. 4 shows the maintenance dose per injection at 9 months in each patient correlated to the effect of therapy seen in BPT and SPT. Six patients reached a maintenance dose of 100,000 SQ-U, five of whom had increased bronchial and skin tolerance. In six patients a dose of 50,000–80,000 SQ-U was obtained, two of these had increased bronchial and skin toler-

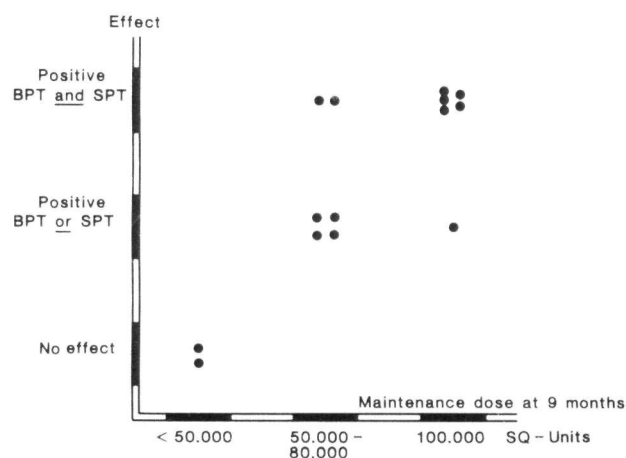


Fig. 4. Correlation between obtained maintenance dose at 9 months and effect in BPT and SPT.

ance, four had either increased bronchial or increased skin tolerance. Two patients only reached a dose of < 50,000 SQ-U. They had neither increased bronchial nor skin tolerance. Moderate local reactions and light systemic side effects as noted in Table 2 were responsible for the reduced maintenance doses.

The allergen dose given at 9 months was significantly correlated to the change in skin sensitivity ($P < 0.01$). No significant correlation could be found between dose and bronchial sensitivity.

DISCUSSION

The treatment of choice in hypersensitivity to dog or cat is strict elimination. However, this is difficult to obtain since indirect exposure to pets among school-mates, friends, family and neighbourhood is responsible for considerable spread of allergens. Vanto (11) found significant amounts of dog dander antigen in dust samples from houses where dogs had never been kept, and claimed that the common presence of dog dander antigen in our environment may induce dog allergy, even without direct exposure to dogs. The same may be applied to cats.

Conventional medical therapy of allergic symptoms may not always be sufficient, so a treatment supplement is needed. Previous results of immunotherapy in dog- and cat-induced asthma have been conflicting. In 1978, however, hyposensitization with a well-defined cat allergen extract showed good results (9), and , recently, other placebo controlled studies (2, 6, 8, 10) have reported good efficacy of immunotherapy using standardized extracts of dog and cat allergen. As the effect of hyposensitiza-

tion with dog and cat allergen is now well documented, we did not consider it ethically correct to use placebo control (5), subjecting children to the stress of having regular injections with an ineffective substance.

However, immunotherapy has some disadvantages: children do not like having to have regular injections for at least 3 years, and the therapy is time-consuming for both parents and children. Moreover, the risk of potentially dangerous systemic reactions must be considered. Correct dosage and injection technique with correct time intervals are essential, and the patient and parents must be well informed. Therefore, to be a recommendable supplement, immunotherapy must add a beneficial effect to that of conventional medical therapy. In this study we have investigated this, using objective methods such as BPT and SPT as effect parameters.

We have preferred objective methods to symptom scores and recording of medical consumption, because these parameters might be influenced by the placebo effect of frequent visits to the doctor and injections. Because of long travel distances our control group only visited the doctor for a clinical check up, and so did not benefit that much from the placebo effect. In both groups medical therapy was adjusted to minimize bronchial symptoms throughout the trial.

We found that the hyposensitized children showed an increased bronchial tolerance compared with the controls, and the same was true for skin tolerance. Our findings are in accordance with those of other authors (2, 6, 8, 10), although we used only 9 months observation in contrast to other authors' 12-14 months. After 9 months of treatment, IgG₄ levels increased in hyposensitized children, but the change showed no correlation with clinical improvement.

The analyses of cat or dog antigens in dust samples from the children's homes indicate that less care may be taken about eliminating allergens from the home when immunotherapy is in progress. The clinician must be aware of this, although the increased allergen content in some of the homes did not seem to influence the effect of the treatment.

Table 2
Side effects

Side effect	No. children
Moderate local reactions	3
Light asthma attacks	3
Urticaria	1
Sneezing	1
Side effects not recorded in control group	

To be an acceptable treatment supplement, immunotherapy must be effective and safe. We did not observe any life-threatening complications. The reported systemic reactions were mild and only seen on one occasion in each child, and all side effects were considered acceptable. Patients who experienced side effects were given a slower dose increase to avoid further complications.

BPT and SPT showed a positive effect of treatment in the 12 patients who reached a maintenance dose of at least 50,000 SQ-U. This was not case for the two patients who reached a smaller dose. Thus it may be recommended to obtain a high maintenance dose.

In conclusion, under the conditions of this study we can recommend immunotherapy as a supplement to conventional medical therapy in dog- and cat-induced asthma in children. Our results indicate that, based on results of BPT and SPT, after only 9 months, hyposensitization adds an antiallergic effect to that obtained by conventional medical therapy.

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