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Seasonal variability in nasal sensitivity to house dust mite extract

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SUMMARY

Nine patients with a house dust mite (HDM) allergy were monitored for one and a half year starting in Spring 1983 during immunotherapy with aqueous alum precipitated HDM extract. Evaluation included nasal provocation tests with HDM extract and histamine chloride. Nasal responsiveness was assessed by measurement of the nasal airway resistance, by counting the number of sneezes and measuring the amount of secretion.

During the one and a half year hyposensitization a decrease in nasal sensitivity to HDM extract is found when measurements are compared at yearly intervals (Spring 1983–1984 and Autumn 1983–1984).

However, nasal reactivity to HDM extract is elevated in autumn compared with spring (not significant in 1983, but significant in 1984).

Changes in nasal sensitivity to histamine are not so obvious except for the interval between Spring 1983 and Autumn 1983.

The fluctuations in nasal sensitivity could not be attributed to baseline variation in nasal resistance during the trial.

We conclude that seasonal variation in sensitivity to HDM can influence the results of immunotherapy with HDM extract, and should be considered when evaluating such treatment.

INTRODUCTION

In 1969 Voorhorst et al. showed that there is considerable variability in the prevalence of D.Pteronyssinus in house dust samples at different times of the year. Peak counts were observed from August until October. Studies elsewhere failed to show consistent seasonal fluctuations (Murray and Zuly, 1979), or in a study in Ohio, USA, showed peak values in the warm humid months in summer (July-October) (Arlian et al., 1982).

If present, a seasonal variation in the count of house dust mites (HDM) could influence the clinical evaluation of immunotherapy with HDM extract. There have been several placebo-controlled studies of immunotherapy in rhinitis patients where no mention has been made whether the time of the year has any

influence on therapy (D'Souza et al., 1973; Gabriel et al., 1977; Blainey et al., 1984). Recently Pauli et al. (1984) distinguished two different periods of complaints in asthmatic patients who participated in a double-blind placebo-controlled study of immunotherapy with HDM extract. Few medications were used in the treated group until July while increased doses were given in September and October. In the placebo-treated group the mean number of medications did not change during the trial. The present paper describes a small open study of patients with clinical features of allergic rhinitis who underwent immunotherapy with HDM extract.
The results of this study suggest that there is a seasonal fluctuation in nasal sensitivity to HDM extracts and histamine.

MATERIALS AND METHODS

Patients

Thirteen patients (age range: 16–38 years) with perennial rhinitis due to HDM allergy entered the trial. Diagnosis of HDM allergy was confirmed by history, intradermal skin tests and radioallergosorbent test (RAST). No one had previously undergone immunotherapy. Other allergies (to pollen and pets) were not present.

Study protocol

The investigation period had a duration of one and a half years. Nasal provocation tests, skin tests and laboratory investigations were carried out both before the start of immunotherapy (Februari-April 1983; Spring) and at half year intervals. Immunotherapy was started with weekly injections until a top dose was reached, the highest dose being repeated at two-weekly intervals.

Allergen extracts

Lyophilized HDM extract was obtained from the Diephuis Laboratory (Groningen, The Netherlands). The concentration of HDM extract was expressed in Noon Equivalent Units (NEU) as described by Voorhorst et al. (1969). The concentration used in the skin test were: 0.001, 0.01, 0.1, 1,.10 and 100 NEU/ml. For the nasal provocation tests: 1, 10, 100, 200 and 1000 NEU/ml were used. Alum precipitated HDM extract (Diephuis) was used for immunotherapy with a starting dose of 0.1 ml of 10 NEU/ml and a topdose of 1 ml of 10000 NEU/ml. All experiments were carried out using the same batch of lyophilized HDM extract, and care was taken to ensure that the extract remained the same strength throughout the trial by storing it at a temperature of $-20\,^{\circ}C$.

Histamine chloride

For nasal provocation tests histamine chloride 0.25, 0.5, 1.0, 2.0 and 4.0 mg/ml was used.

Nasal provocation tests

Medication was withheld two days before the test. None of the patients had an airway infection during the two weeks preceeding the challenge. On each occasion patients waited half an hour before the test to allow the nasal mucosa to become acclimatized. After rhinoscopy 0.2 ml of solution was sprayed into each nostril with a De Vilbiss atomizer connected to a pressure pump. In the morning provocation with increasing doses of histamine chloride was performed at 10 minutes intervals. In the afternoon subjects were challenged with HDM extract at 15 minutes intervals. Two patients had the HDM provocation tests the morning after the histamine challenge throughout the entire study. The results with these patients did not differ from the results obtained with the other patients.

Before histamine or HDM was applied, a control solution (PBS containing HSA 0.03% and benzalkonium chloride 0.05%) was used.

The nasal resistance of each nostril was measured using a passive anterior rhinomanometer as previously described by Clement et al., 1978. This entailed blowing an airstream with a fixed flow at 0.25 l/sec into each nostril. The anterior nasal pressure of each side was measured. The resistance for the left (R_l) and the right (R_r) cavity was calculated by dividing the nasal pressure by the nasal flow. The total nasal resistance was computed from the formula:

$$R_{tot} = R_l \times R_r/(R_l + R_r).$$

The lowest concentration which doubled the total nasal resistance compared with the initial value, was taken as the end-point. As some patients reacted with secretion or sneezing instead of nasal blockage an arbitrarily chosen amount of secretion of 0.5 ml or more (collected as described before by Borum, 1978), or a total of at least 5 sneezes within 15 minutes was also taken as the end-point in these patients.

Skin tests

Intradermal skin tests were performed by injecting 0.02 ml of increasing concentrations of HDM extract. Skin reactions were read after 20 minutes and expressed using standardized plus signs following the grading system devised by Norman (1980). The plus signs were added up for each patient (Voorhorst et al., 1969; Dieges, 1983) in order to evaluate the changes in skin reactivity during the course of the trial.

Total IgE and Radioallergosorbent Test (RAST)

Total IgE was determined by a noncompetitive binding assay (Stallman and Aalberse, 1977). Specific IgE was determined by RAST (Radioallergosorbent Test) using agarose beads as an allergen-support (Adkinson, 1980) as previously described (Van Toorenenbergen et al., 1981).

The relative amounts of HDM-specific IgE were calculated from the horizontal distance between patient serum and the reference serum dilution curves, as described by Adkinson (1980).

Statistical analysis

For paired observations the Wilcoxon non-parametric signed rank test was used. Correlations were calculated using the Spearnman rank correlation test. The end-point concentration in the histamine provocation test was expressed as a power of two. End-point concentration in the allergen provocation test was expressed as a power of ten (i.e. as the logarithm).

RESULTS

Four of the thirteen patients were withdrawn from the trial. Two stopped because of the time consuming character of the investigations, one because of large local reactions caused by the injections and one because of severe nasal blockage, which made nasal provocation tests impossible.

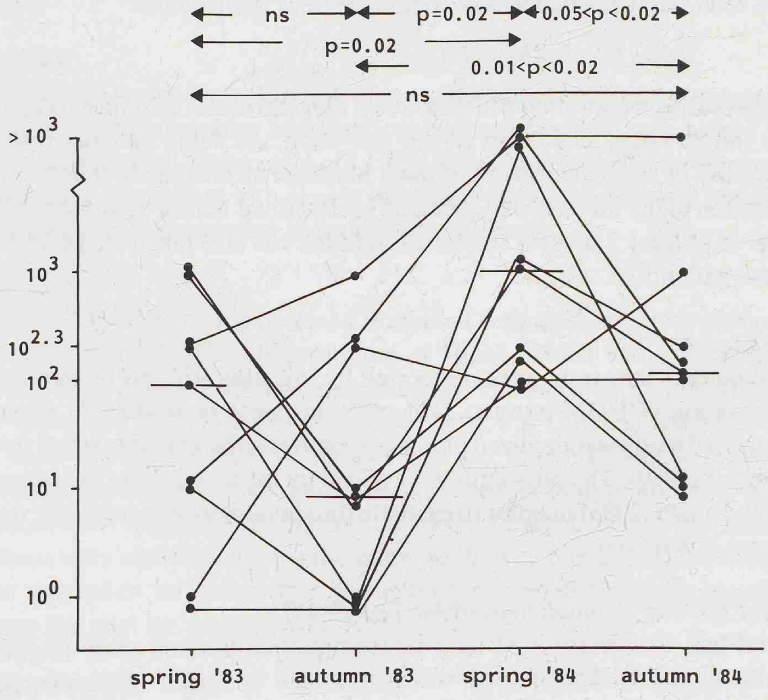

Figure 1. End-point concentrations in nasal provocation tests with HDM extract (NEU/ml) during the trial.

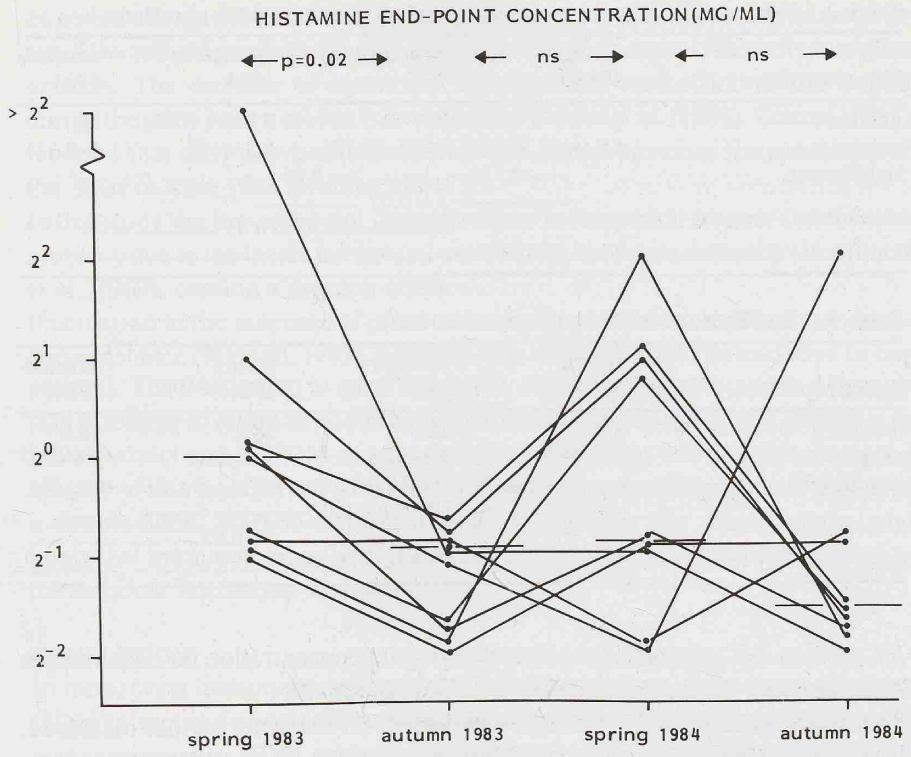

Figure 2. End-point concentrations in nasal provocation tests with histamine (mg/ml) during the trial.

Analysis of HDM end-point concentrations during nasal provocations showed a significant increase in values at one year intervals (Spring 1983–1984 and Autumn 1983–1984; Figure 1). However, median end-point concentrations were lower in autumn than in spring of the corresponding year ($p > 0.05$ in 1983; $p < 0.05$ in 1984). Moreover there was no significant ($p > 0.05$) difference in end-point values between the beginning of the trial (Spring 1983) and the end of the study (Autumn 1984).

Table 1. Initial nasal resistance before HDM provocation.

	spring 1983	autumn 1983	spring 1984	autumn 1984
*Initial resistance**				
median	1.6	1.9	1.7	1.6
range	1.5–2.0	1.2–2.0	1.2–2.1	0.6–1.9
significance	— n.s. —	— n.s. —	— n.s. —	

* expressed in cm H_{20}*1^{-1}*sec.
n.s. = not significant

Table 2. Skin reactivity expressed in total number of standardized plus signs.

skin reactivity	spring 1983	autumn 1983	spring 1984	autumn 1984
median	8	9	7.3/4	7.3/4
range	6.3/4–11.1/2	6.3/4–10.1/4	6.3/4–10	6–9.1/4
significance	— n.s. —	— $p = 0.05$ —	— n.s. —	
	— $p = 0.02$ —			
		— $p = 0.05$ —		
	— $p = 0.02$ —			

Table 3. RAST-results in arbitrary units (see text).

RAST-results	spring 1983	autumn 1983	spring 1984	autumn 1984
median	8.9	12.0	18.2	16.0
range	3.0–36.6	4.2–22.8	3.5–43.6	3.4–41.7
significance	— n.s. —	— $0.02 < p <$	0.01 —	— n.s. —
	— $0.05 < p < 0.02$ —			
		— $p = 0.02$ —		
	— $p = 0.02$ —			

All patients but one had a lower nasal-end-point concentration for histamine in Autumn 1983 than in Spring 1983 ($p = 0.01$; Figure 2).
Statistically significant fluctuations were absent for the other periods measured. In all test periods no significant difference in median nasal resistance could be found before provocation (Table 1; $p > 0.05$).
Analysis of skin tests and RAST results for the trial periods shows a small significant decrease in median of total plus signs and a small significant increase in median RAST values without a seasonal fluctuation (Tables 2 and 3).
No significant correlation was observed between nasal threshold values and total plus signs or RAST results during the test periods ($p > 0.05$).

DISCUSSION

In this study we monitored nasal responsiveness to HDM extract during immunotherapy. The measurement of the nasal resistance after provocation has been considered as the most objective way of assessing the nasal response (Mygind, 1982; Wihl, 1983). As there are three syptoms in nasal response (blockage, sneezing and secretion) we also took an obvious amount of secretion or a certain number of sneezes as end-point.
We showed a marked fluctuation in nasal reactivity to HDM extract, with an increased sensitivity in autumn compared with spring of each year. Changes in nasal sensitivity to histamine were not so obvious except for the interval between Spring and Autumn 1983.

In pollen allergy provocation tests are performed outside the season in order to avoid the influence of natural exposure to pollen on the nasal reactivity to pollen extracts. The increase of sensitivity to histamine, methacholine and pollen during the grass pollen season is described by Borum et al. (1983). Connel (1969) reported that daily provocation with ragweed pollen increases the sensitivity of the nasal mucosa (the "priming effect").
In this study the low end-point concentrations in the period August-October are probably due to the increased natural exposure to the house dust mite (Voorhorst et al., 1969), causing a priming effect.
Fluctuation in the outcome of provocation tests can be due to variation in base-line resistance (Mygind, 1983), however, this variation could be excluded in our patients. The fluctuation in nasal sensitivity could not be attributed to a fluctuation in allergy to HDM as no similar variation could be found in skin reactivity to HDM extract and in HDM-specific IgE. No conclusions can be made about the efficacy of immunotherapy with HDM extract as the study was not carried out in a double-blind, placebo-controlled fashion, however, the results of the trial imply that immunotherapy with HDM extract has to be evaluated with respect to the seasonal fluctuation in amounts of HDM.

CONCLUSION

In monitoring immunotherapy with HDM extract a fluctuation in sensitivity to HDM extract and possibly histamine was seen. Patients have an increase in nasal responsiveness to HDM extract in the period from August till October. This is probably due to the increased exposure to house dust mites in this period which has a priming effect. All evaluations of immunotherapy with HDM extract should thus take this seasonal fluctuation into account.

ZUSAMMENFASSUNG

Neun Patienten wurden 1,5 Jahre lang hyposensibilisiert mit einem Hausstaubmilbenextrakt. Halbjährlich wurde eine Nassenprovokation mit Histamin und Allergen ausgeführt. Die nasale Reaktion wurde an Hand der Veränderung der Nasenwiderstand, an Hand der Häufigkeit des Niesens, und der Menge der Sekretion, die beide als Folge einer Provokation auftraten, gemessen.
Bei einem Vergleich der Resultate mit einem Abstand von einem Jahr (Frühjahr 1983-1984, und Herbst 1983-1984), konnte eine Verminderung der nasalen Sensibilität gegenüber Allergen konstatiert werden. Die nasale Sensibilität genenüber Hausstaubmilben war im Herbst grösser als im Frühjahr desselben Jahres (1983 signifikant, 1984 nicht signifikant).
Schwankungen in Bezug auf die Histamin-Empfindlichkeit waren - ausser in der Periode vom Frühjahr 1983 bis Herbst 1984 - weniger deutlich. Die konstatierten Fluktuationen konnten nicht einer "base-line" Variation des Nasenwider-

standes zugeschrieben werden. Man kann zur Konklusion kommen, dass eine saisonabhängige Variation bezüglich der Empfindlichkeit gegenüber Hausstaubmilben die Resultate der Hyposensibilisierung beeinflüssen kann. Ausserdem muss man den Zeitpunkt der Auswertung der Therapie berücksichtigen.

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REFERENCES

1. Adkinson NF. Measurement of total serum Immunoglobulin E and allergen-specific Immunoglobulin E antibody. In: Rose NR, Friedman H, Eds. Manual of Clinical Immunology, 2nd ed. Washington 1980; American Society for Microbiology, 808–821.
2. Arlian LG, Bernstein IL, Gallagher JS. The prevalence of house dust mites Dermatophagoides spp and associated environmental conditions in homes in Ohio. J Allergy Clin Immunol 1982; 69: 527–532.
3. Blainey AD, Phillips MJ, Ollier S, Davies RJ. Hyposensitization with a tyrosine adsorbed extract of Dermatophagoides pteronyssinus in adults with perennial rhinitis. A controlled clinical trial. Allergy 1984; 39: 521–528.
4. Borum P. Nasal metacholine challenge. J Allergy Clin Immunol 1979; 63: 253–257.
5. Clement PAR, Dishoeck EA van, Wal RJ v.d., Stoop AP, Hoeck GT, Strik R van. The nose provocation and the passive anterior rhinomanometry (P.A.R.) Acta Oto-rhino-laryngol Belg 1978; 32: 56–63.
6. Connell JT. Quantitative intranasal pollen challenge III. The priming effect. J Allergy 1969; 43: 33–44.
7. Dieges PH. Hyposensitization in pollinosis caused by grass pollen. Rotterdam, Thesis (in Dutch), 1983.
8. Gabriel M, Ng HK, Allan WGL, Hill LE, Nunn AJ. Study of prolonged hypotensitization with D.Pteronyssinus extract in allergic rhinitis. Clin Allergy 1977; 7: 325–336.
9. Murray AB, Zuly P. The seasonal variation in population of house dust mites in a North American city. J Allergy Clin Immunol 1979; 64: 266–269.
10. Norman PS. Skin testing. In: Rose NR, Friedman H, Eds. Manual of clinical Immunology; 2nd ed. Washington: American Society for Microbiology 1980: 789–793.
11. Pauli C, Bessot JC, Bigot H, et al. Clinical and immunological evaluation of tyrosine-adsorbed extract: A double-blind placebo-controlled trial. J Allergy Clin Immunol 1984; 74: 524–535.
12. Stallman PF, Aalberse RC. Estimation of basophil-bound IgE by quantitative immunofluorescence microscopy. Int Archs Allergy Appl Immunol 1977; 54: 9–18.
13. Toorenenbergen AW van, Aalberse RC. IgG_4 and passive sensitization of basophil leucocytes. Int Archs Allergy Appl Immunol 1981; 65: 432–440.
14. Voorhorst R, Spieksma FThM, Varekamp H. House dust atopy and the house dust mite. Leiden: Stafleu's Scientific Publishing Co, 1969.
15. Wihl JA. Methods for assessing nasal reactivity. Eur J Respir Dis 1983; 64, Suppl 128: 128–179.

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