

Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite

GLENIS K. SCADDING and J. BROSTOFF

Department of Immunology, Middlesex Hospital Medical School, London, W1P 9PG

(Received in original form 4 December 1985 and in revised form 25 April 1986; accepted for publication 28 April 1986)

Summary

In a double-blind placebo-controlled cross-over trial, low dose sublingual therapy with house dust mite was effective in relieving symptoms in 72% of the group of patients with perennial rhinitis due to house dust mite ($P < 0.03$). Following active treatment, there was a significant increase in morning peak nasal inspiratory flow rate ($P < 0.01$) in those who improved (thirteen out of eighteen) and resistance to nasal provocation with house dust mite also increased, in some cases up to 1000-fold ($P < 0.05$). Oral therapy is safe and avoids the side effects of desensitizing injections which can be serious. The potential for oral desensitization is great and further studies on this form of treatment are needed.

Introduction

Allergic rhinitis, although not life threatening, is a troublesome condition, and when perennial can be associated with recurrent sinusitis and secretory otitis media [1]. Symptomatic treatment can be effective, as can desensitization. Classical incremental dosage desensitization, where the dose of allergen injected subcutaneously is increased to the maximum tolerated, does relieve symptoms but can be associated with local [2] and general [3] reactions and even death [4,5].

Desensitization to allergens has been achieved via other routes including transepidermal [6], following bronchial challenge [7] and also following oral administration of allergen extracts. Treatment can also be given either before or during the season [8]. Dosage of allergen also varies widely; low dose treatment was first described by Noon [9] and Freeman [10] in 1911 and was shown to be effective by quantitative provocation testing with the relevant antigen.

Correspondence: Dr J. Brostoff, Department of Immunology, Middlesex Hospital Medical School, Arthur Stanley House, 40–50 Tottenham Street, London, W1P 9PG.

The classic experiments of Mitchison [11] have shown that low zone tolerance is a reliable immunological phenomenon and we decided to test whether such low dose treatment could also be effective in humans using the Miller [12] method of intradermal testing to determine the dose of antigen to be used. We approached this problem using a double-blind cross-over placebo-controlled trial and have shown that low dose sublingual house dust mite treatment is effective both subjectively and objectively in patients with allergic rhinitis.

Patients, materials and methods

Patients

Twenty patients (ten male) aged 18–57, with a history of perennial rhinitis who showed positive skin-prick tests to house dust mite (HDM) allergen and/or who showed symptoms following nasal provocation with HDM were selected. Patient details are given in Table 1. For 2 weeks before and during the trial period, no other medication was taken, with the exception of one patient who took nasal sodium cromoglycate throughout the trial period. The trial took place between February and May, 1985, thus avoiding the peaks of the house dust mite and pollen seasons. None of the patients was sensitive to tree pollen.

Protocol for the study

The protocol is illustrated in Fig. 1. Quantitative nasal provocation tests were performed at the beginning of the control introductory period and before and after both treatment periods [1–5]. Nasal inspiratory peak flow was measured daily throughout the trial period using the Youlten peak nasal inspiratory flow meter (Clement Clarke International Ltd).

Treatment with active (A) or placebo (P) preparations was randomized, neither the patient nor the physician assessing the results being aware of which preparation was being used. At the end of the whole study period the patients were asked to choose which preparation (A or P) relieved their symptoms better. Objective assessments were then correlated.

Allergen

Throughout the study, a single batch (lot no. IM 31340) of Pharmacia purified house dust mite allergen was used for all testing. The freeze-dried material was reconstituted immediately before use by a technician (Y.L.).

Quantitative nasal provocation test

Nasal inspiratory peak flow (NIPF) was measured in triplicate before and after saline instillation as control and then following 10, 100, 200, 1000, 2000 and 10 000 U/ml of house dust mite extract. On each occasion a single measured amount of HDM was blown into both nostrils using a metered aerosol, with the patient in full inspiration to avoid bronchial provocation. The dose causing a 20% fall in NIPF was then calculated (Fig. 2).

Quantitative intradermal skin testing

House dust mite extract (0.05 ml) was injected intradermally into the outer aspect of the upper arm, starting with a concentration of 0.8 U/ml. The weal was measured immediately and again exactly 10 min later. Intradermal injections of five-fold

dilutions of the standard extract were made until a dilution was reached where no growth of the weal was seen at 10 min. This was defined as the 'end-point' for the patient. End-point concentrations ranged from 2×10^{-6} to 8×10^{-1} U/ml.

Nasal inspiratory peak flow (NIPF)

Daily measurements of NIPF were made in the morning and evening throughout the trial period. Three measurements were recorded on each occasion and the best used in subsequent calculations.

Serum IgE

Blood was taken before and after each treatment period, spun down and the serum stored at -20°C . At the end of the trial serum total IgE was measured by ELISA using goat anti-rabbit IgE (Dako) at $10 \mu\text{g/ml}$ as both the bottom and top layer. House dust mite specific IgE was measured by the RAST technique, courtesy of Pharmacia Ltd.

Table 1. Clinical and laboratory details of patients

Patient no.	Age	Sex	Skin-prick tests	PC20 of initial nasal provocation		Total IgE		RAST		Preference A = active P = placebo
				(1)	(2)	pre-	post-active	pre-	post active	
1	30	F	HDM+, Cat+	160	100	270	300	12.1	13.8	A
2	44	M	—	7,	10	62	60	0	0	A
3	41	F	HDM+	8,	6	70	56	0	0	A
4	18	M	HDM+ multiple+	8,	55	620	900	>17.5	>17.5	A
5	18	F	HDM+mould+	160,	6	110	110	0,	14.1	A
6	25	M	HDM+, GP+	37,	5	140	180	0	0	A
7	22	M	multiple+GP+, HDM+	10,	3	>1000	>1000	>17.5	>17.5	A
8	57	M	—	8,	8	54	ND	0	ND	A
9	29	F	HDM+, GP+	5,	8	540	540	14,	12.2	A
10	39	M	HDM+, Cat+, GP+	200,	200	>1000	220	2.2,	0	P*
11	20	M	HDM+, GP+, milk+	10,	5	820	800	>17.5	>17.5	A
12	38	M	HDM+, multiple+	4,	5	1000	>1000	3.8	3.8	P
13	24	M	HDM+, Cat+, GP+	10,	100	310	480	>17.5	>17.5	P
14	24	F	HDM+	77,	145	520	720	12.3	11.3	A
15	32	F	HDM+	153,	200		N.D.		N.D.	A
16	25	F	HDM+	90,	100	270	240	>12.5	>12.5	A
17	36	F	HDM+	132,	120	80	56	16.7	12.5	A = P
18	28	F	HDM+	10,	10	330	270	>17.5	>17.5	P

* On Rynacrom throughout.

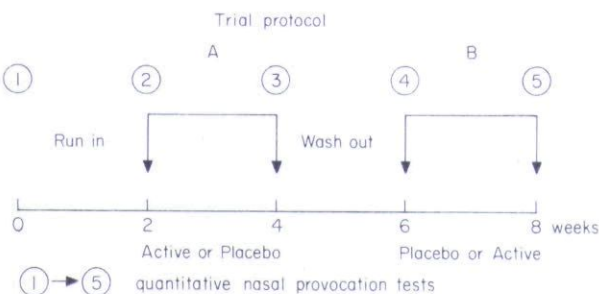


Fig. 1. Protocol for the trial.

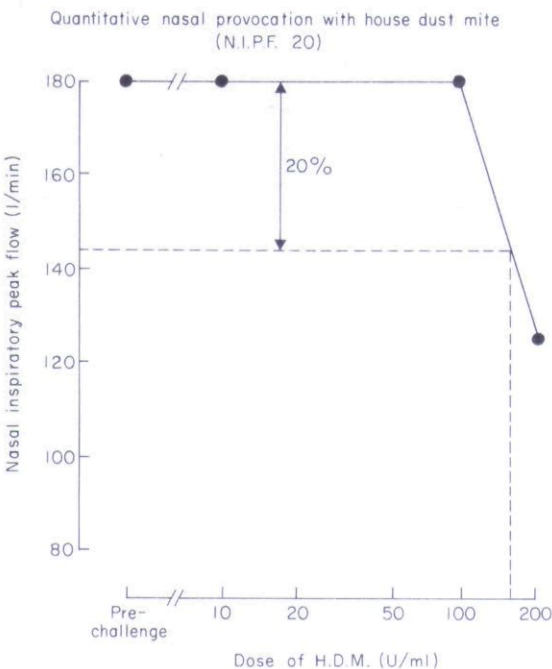


Fig. 2. Nasal inspiratory peak flow (NIPF) was measured after sequential nasal provocation tests with HDM. The dose leading to a 20% fall in NIPF was then calculated.

Treatment

Using the end-point concentration, a vaccine was prepared for each patient. The dose was 0.1 ml sublingually four times a day for the treatment period. Control (placebo) drops were indistinguishable from the active preparation.

Results

Eighteen of the twenty patients completed the trial. Two dropped out, one because of a car accident and one because of acute renal colic.

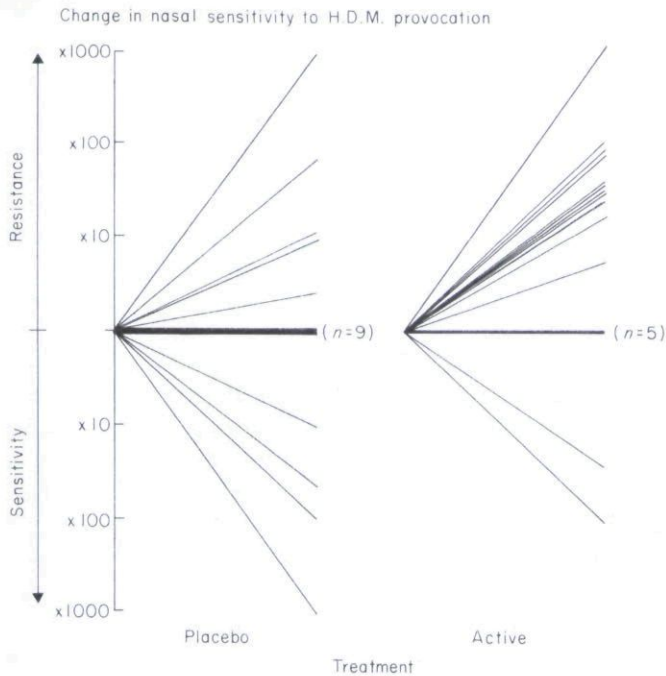


Fig. 3. There was a significant increase in nasal resistance to challenge after the active compared with placebo treatment period ($P < 0.05$; Chi-squared test).

Preference for treatment

Thirteen out of the eighteen patients preferred the active preparation as their overall symptoms were improved by this treatment. Four preferred placebo (as their symptoms were made worse by the active treatment), and one was undecided and therefore for statistical purposes was counted as having preferred placebo. These results are statistically significant in favour of the active preparation $P < 0.03$ (Binomial probability theorem).

Quantitative nasal provocation test

The change in nasal sensitivity to provocation with HDM following active and placebo treatment is shown in Fig. 3. During the placebo period, nine subjects showed no change, four became more sensitive and five less. During the active HDM treatment, only five subjects showed no change, two were more sensitive and eleven less. These results are significantly in favour of the active treatment reducing the nasal sensitivity to HDM; $P < 0.05$ (Chi-squared test).

Nasal inspiratory peak flow (NIPF) (Table 2)

The morning nasal peak inspiratory flow rate was significantly increased in those patients who were improved by the active treatment from 111 ± 28 to 124 ± 37 l/min (paired t -test; $P < 0.01$). However, those patients who were made worse by the active treatment showed a reduction in nasal peak flow from 129 ± 56 to 104 ± 45 l/min ($P < 0.02$).

It is interesting to note that in the group overall, the mean of the morning NIPF was significantly less than the evening figure (a.m.: 117 ± 37 l/min; p.m.: 134 ± 22 l/min).

Furthermore, the improvement seen in NIPF was in the morning values only—the evening figures remaining unchanged. This suggests that the morning dip is mainly due to night time exposure to HDM in the bedding rather than accentuation of normal variations in nasal airway calibre.

Serum IgE (Table 1)

This did not change significantly in seventeen patients; one who was taking nasal sodium cromoglycate showed a steady fall in serum IgE which started during the run-in period. HDM-specific IgE did not show any consistent change on treatment.

Discussion

In a double-blind cross-over trial, we have clearly shown that low dose immunotherapy with HDM allergen given sublingually has improved the symptoms of 72% of our group of patients with allergic rhinitis. Following active treatment, nasal air flow improved and the nasal resistance to allergen provocation was increased in some patients up to 1000-fold. The effect of this form of therapy appears quickly (2–4 days), but wears off over a week after stopping the drops.

The patients entered into the trial were those who were able to give a reading above 50 on the nasal inspiratory peakflow meter, whilst on no treatment. This was to ensure that we could obtain objective measurements of nasal obstruction. Thus, their nasal obstruction was not severe, but all patients had symptoms, including sneezing and rhinorrhoea which drove them actively to seek treatment. We have subsequently treated patients with severe disease, with success.

The criteria used for patient selection were a clinical history suggestive of HDM sensitivity and a positive nasal provocation test with or without a positive skin-prick test. Only one individual who fulfilled these criteria did not give a clearly positive response to intradermal HDM antigen with decrease in weal size on increasing dilution. She was not entered into the trial.

Absorption of drugs through the buccal mucosa is remarkably rapid and effective therapeutically [13,14], in some instances more rapid than when the drug is given subcutaneously or intramuscularly [15].

Table 2. Morning and evening nasal inspiratory peak flow (NIPF)

	Treatment	
	Placebo	HDM
Mean of morning NIPF		
total group ($n=14^*$)	117 ± 37	113 ± 38 ($P=N.S.$)
patients who improved ($n=9$)	111 ± 28	124 ± 37 ($P<0.01$)
patients who did not improve ($n=5$)	129 ± 50	104 ± 45 ($P<0.02$)
Mean of evening NIPF		
total group ($n=14$)	134 ± 22	133 ± 25 ($P=N.S.$)
patients who improved ($n=9$)	129 ± 11	136 ± 18 ($P=N.S.$)
patients who did not improve ($n=5$)	142 ± 34	129 ± 37 ($P=N.S.$)

* We were unable to provide nasal inspiratory peak flow meter to all our patients.

In classical, incremental subcutaneous desensitization, 'symptoms are alleviated but infrequently cured' [2]. Where classical desensitization achieves this only after many months of therapy, the sublingual route with titrated doses offers an immediate clinical response. There is a further very substantial advantage with the sublingual route and that is the lack of serious side effects. Local [2] and general reactions [3] are not infrequent with classical desensitization and anaphylactic death has been reported following allergen injections [4,5]. These problems are avoided with sublingual therapy. Our trial was not designed to assess long term efficacy of low dose treatment, and it is conceivable that prolonged administration would produce superior clinical results.

Lessof [16] has commented that oral desensitization is of value for some food allergens [17] using very high dilutions of allergen and there is other evidence to suggest that this approach is clinically effective [18–22]. Schiff *et al.* [23] using cat and dog dander have shown that injection of low dose allergen attenuates the response to bronchial challenge with the same allergen.

There is controversy about the value of limiting dilution desensitization (also called the Miller technique or provocation/neutralization). The literature on this subject has been well reviewed recently by Freed [24], who concludes that there are now more scientifically based favourable reports than unfavourable ones. The negative studies of low dose desensitization to ragweed by Hirsch [25] and Van Mettre [26,27] used a different technique (Rinkel) employing doses of antigen some 5–125 times higher given by a different route (subcutaneous injection). These studies are therefore not comparable to this one.

The mechanism of action of this form of desensitization is not yet understood but there are a number of possible explanations. This could be a form of oral tolerance, with the production of suppressor T cells in the circulation and IgA in the secretions [28]. However, the state of tolerance is usually prolonged and in our patients it was not. The quick onset of diminished sensitivity to HDM is also against this explanation.

Our current hypothesis is based on desensitization of basophils. In the nose, basophils are found in blown secretions [29] and appear rapidly after challenge [30], whereas mast cells are mainly submucosal [31] where access of inhaled protein is prevented by tight junctions between epithelial cells. The late phase reaction (LPR), coming on 3–8 hr after challenge is thought to be involved in the production of nasal hyper-reactivity and chronicity [32] as it does in asthma [33].

Histamine, Kinin, TAME and PGD_2 appear in nasal secretions during the acute immediate reaction following provocation, but PGD_2 is absent during the LPR [34]. This suggests that the basophil (which does not produce PGD_2) plays a central role in the LPR, and in maintaining the chronicity of symptoms.

Low dose antigen can produce prolonged unresponsiveness of basophils to subsequent optimal challenge *in vitro* [35, 36] and we feel that this may be the mechanism of the oral hyposensitization seen in our patients. In the model system studied by Mendoza & Minagawa [35], desensitization with low dose antigen was even more effective if small divided doses were given frequently. The same effect was seen clinically by Herxheimer [7] where small but frequent doses of allergen given by bronchial provocation abolished the asthmatic response to the large dose that previously caused an asthmatic attack.

Pre-incubation of basophils of patients with their 'end-point' concentration of allergen followed by challenge with an optimal histamine releasing dose should

provide a model system for this form of desensitization.

The occurrence of positive nasal provocation tests in skin test negative patients has been previously noted [37]. Three patients in this study have had positive skin tests but a negative RAST; this probably reflects the longer half-life of IgE when cell bound (6–8 weeks) rather than in serum (2½ days).

The discrepancies in the nasal sensitivity, skin-prick test and RAST probably reflect the fact that mucosal sensitization is the primary process in HDM sensitivity. Presumably when 'spill-over' of IgE into the general circulation has occurred, the skin and nose would reflect the same immunological sensitivity and tolerance. The reason for using intradermal testing to determine the 'end-point' was that this is the method described by Miller [12] and used extensively in the U.S.A. and in the private sector in the U.K.

We suspect that the mechanism of sublingual therapy is probably not 'hyposensitization' but may reflect subthreshold coating of basophils and/or mast cells by a dose of antigen which is too low to cause degranulation. If this is so, then possibly factors such as basophil/mast cell Fc_ε receptor density, granule releasability, etc. may be relevant and could well be similar in nose and skin. The potential for oral desensitization is great and further studies on this form of treatment are needed.

Acknowledgments

We thank Dr S. Dreborg of Pharmacia for the supplies of house dust mite, and Mrs S. Pack and Miss Y. Latchman for their able technical assistance.

References

- 1 Clemis JD. Identification of allergic factors in middle ear effusions. *Ann Otol Rhinol Laryngol* 1976; 23:234.
- 2 Norman PS. Allergic rhinitis. *J Allergy Clin Immunol* 1985; 75:531–45.
- 3 Fuchs AM, Strauss MB. The clinical evaluation and the preparation and standardization of suspensions of a new water-insoluble whole ragweed pollen complex. *J Allergy* 1959; 30:66.
- 4 Rands DA. Anaphylactic reaction to desensitization for allergic rhinitis and asthma. *Br Med J* 1980; 282:854.
- 5 Ancill R, Wainscott G. Anaphylactic reaction to desensitization. *Br Med J* 1980; 281:1429.
- 6 McEwen L, Nicholson M, Kitchen I, O'Gorman J, White S. Enzyme potentiated hyposensitization IV. *Ann Allergy* 1975; 34:290–5.
- 7 Herxheimer H. Induced asthma in man. *Lancet* 1951; i:1337–41.
- 8 Ganderton MA, Brostoff J, Frankland AW. Comparison of preseasonal and coseasonal Allpyral with Depo-medrone in summer hay fever. *Br Med J* 1969; 1:357–8.
- 9 Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911; i:1572–3.
- 10 Freeman J. Further observations on the treatment of hay fever by hypodermic inoculations of pollen vaccine. *Lancet* 1911; ii:814–17.
- 11 Mitchison NA. The dosage requirements for immunological paralysis by soluble proteins. *Immunology* 1968; 15:509.
- 12 Miller JB. Technique of intradermal testing and subcutaneous injection therapy. *Trans Soc Ophthalmol Otolaryngol Allergy* 1976; 16:154–68.
- 13 Kare M, Schechter P, Grossman S, Roth L. Direct pathway to the brain. *Science* 1969; 163:952.
- 14 Bruntton RL. The Goulstonian Lecture, Royal College of Physicians. 1887. London: Macmillan.
- 15 Gibaldi M. Drug administration: new candidates for buccal administration. *Perspect Clin Pharmacol* 1985; 3:49.
- 16 Lessof MH. Any questions. *Br Med J* 1985; 291:727.
- 17 Shenassa MM, Perelmutter L, Gerrard DM. Desensitization to peanut. *J Allergy Clin Immunol* 1985; 75:177.
- 18 Rapp D. Double blind confirmation and treatment of milk sensitivity. *Med J Aust* 1978; 1:571–2.
- 19 Rapp D. Food allergy treatment for hyperkinesia. *J Learn Disab* 1979; 12:42–50.

- 20 O'Shea J, Porter S. Double blind study of children with hyperkinetic syndrome: treatment by multi-allergen extract sublingually. *J Learn Disab* 1981; 14:189-237.
- 21 Rea WJ, Podell RN, Williams ML, Fenyves E, Sprague DE, Johnson AR. Elimination of oral food challenge reaction by injection of food extracts. *Arch Laryngol* 1984; 110:248-52.
- 22 McGovern JJ, Rapp DJ, Gardner RW *et al*. Double-blind studies support reliability of provocative-neutralisation test. *Arch Otolaryngol* 1983; 109:292.
- 23 Schiff M, Boris M, Weindorf S. Injection of low dose antigen attenuates the response to subsequent bronchoprovocative challenge with the same antigen. *Am Rev Respir Dis* 1985; 131:A38.
- 24 Freed DLJ, Foster AS. The neutralisation phenomenon. A Critical literature review with special reference to the position statement of the American Academy of Allergy 1986.
- 25 Hirsch SR *et al*. Rinkel injection therapy: A multicenter controlled study. *J Allergy Clin Immunol* 1981; 68:133.
- 26 Van Metre TE *et al*. A controlled study of the effectiveness of the Rinkel method of immunotherapy for ragweed pollen hay fever. *J Allergy Clin Immunol* 1980; 65:288.
- 27 Van Metre TE *et al*. A comparative study of the effectiveness of the Rinkel method and the current standard method of immunotherapy for ragweed pollen hay fever. *J Allergy Clin Immunol* 1980; 66:500.
- 28 Challacombe SJ, Tomasi TB. Systemic tolerance and secretory immunity after oral immunisation. *J Exp Med* 1980; 152:1459.
- 29 Hastie R, Heroy JH, Levy D. Basophil leukocytes and mast cells in human nasal secretions and scrapings studied by light microscopy. *Lab Invest* 1979; 40:554.
- 30 Okuda M, Otsuka H. Basophilic cells in allergic nasal secretions. *Arch Otorhinolaryngol* 1977; 214:283.
- 31 Okuda M, Kawabon S, Unno T, Otsuka H. Electron microscopic study of the basophilic cells in allergic nasal secretion and mucous membrane. *Rhinology* 1982; 19 (suppl): 115.
- 32 Clement PAR, Stoop AP, Kaufman L. Histamine threshold and nasal hyperreactivity. Belgium: Cauwenberger & Grote, 1983.
- 33 Hargreave FE, Ryan G, Thomson NC *et al*. Bronchial responsiveness to histamine or methacholine in asthma: measurement and clinical significance. *Allergy Clin Immunol* 1981; 68:347-55.
- 34 Norman PS, Naclerio RM, Creticos PS, Togias A, Lichtenstein LM. Mediator release after allergic and physical challenges. *Int Arch Allergy Appl Immunol* 1985; 77:57-63.
- 35 Mendoza GR, Minagawa K. Subthreshold and suboptimal desensitization of human basophils. *Int Arch Allergy Appl Immunol* 1982; 68:101-7.
- 36 Sobotka AK, Dembo M, Goldstein B, Lichtenstein LM. Antigen-specific desensitization of human basophils. *J Immunol* 1979; 122:511-17.
- 37 Huggins KG, Brostoff J. Local production of specific IgE antibodies in allergic rhinitis patients with negative skin tests. *Lancet* 1975; ii:148.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.