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The nasal provocation test in the diagnosis of allergic rhinitis. II. Comparison with other diagnostic tests

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SUMMARY

We standardized the NPT by means of AAR, and in the present study, we compared this technique with skin testing and the RAST test. Using Alternaria tenuis and cat epithelium, the NPT was found to be more specific than skin testing; in the case of Phleum pratensis, no differences were observed. We conclude that the NPT is an excellent diagnostic technique.

INTRODUCTION

The NPT has been widely employed in the diagnosis of allergic rhinitis. But this technique has by no means been completely standardized; and studies comparing it with other diagnostic parameters have rarely been carried out.

In allergology, therefore, the clinical history, skin testing and the RAST test are still the principal methods of diagnosis.

The aim of our study is to analyse the RAST test, skin testing and the NPT is order to evaluate their diagnostic efficacy. We will show that the NPT is of fundamental importance in the diagnosis of allergic rhinitis.

MATERIAL AND METHODS

1. *Patients*

Our study involved 36 patients (8 allergic to Alternaria tenuis, 14 to Phleum pratenis, and 14 to cat epithelium). They all gave positive results (greater than the control) on standard prick testing. The characteristics of the population are shown in Table 1.

2. *Investigations*

A clinical history was obtained from each patient in order to determine whether he or she had a positive or negative history. Skin testing (Pharmalgen prick) was carried out with serial dilutions (100-100,000 BU/ml.), a control (diluent) and histamine chlorhydrate (mg/ml). A skin test was considered positive when the papule produced was equal to or greater than that obtained using histamine. In both skin testing and the NPT, the same batches were always used (HF 27.250 for

Table 1. Characteristics of our population.

		ages	
allergen	M/F	average	SD
alternaria	1.66	17.5	± 9.036
cat epithelium	0.27	25.93	±13.06
phleum	0.27	27.07	± 9.47

cat epithelium; IF 31.192 for Phleum; and IC 31.024 for Alternaria). In addition, serum was obtained from each patient by sedimentation of 5 ml of whole blood at room temperature. The serum samples were frozen to −40°C, and later reconstituted for the RAST test (Phadezym - RAST) by an enzymatic system. All the samples were studied simultaneously.

3. *NPT*

The technique is described at length in (Olive, 1988). We employed a double-channel Sibel rhinomanometer (AAR technique), with simultaneous recording of ΔP and $\dot{V}$. The results were obtained in mm H_2O and l/min. respectively; these were then converted to cm H_2O and l/sec.

In accordance with Eichler and Lenz (1985), we calculated the following values:

$$R=\frac{\Delta P}{\dot{V}} \qquad W_{1.85}=\frac{\Delta P}{\dot{V}^{1.85}} \qquad W=\frac{\Delta P}{\dot{V}^{2}}$$

Administration of the allergen was performed using a standardized outlet which released 0.1 ± 0.05 ml per pulsation; this was carried out during apnea. There was an accumulative effect: the allergen concentration being between 10 and 100,000 BU/ml. The test was considered positive where there was a 100% increase in ΔP or R or $W_{1.85}$ or W_2, with respect to the baseline values. Patients who demonstrated a 25% increase in these values following inhalation of the diluent were excluded.

4. *Statistical analysis*

Following Vecchio (1966), we calculated the following parameters:

$$\text{Clinical sensitivity}=\frac{\text{Patients with positive test}}{\text{Total number of patients studied}}$$

$$\text{Clinical specificity}=\frac{\text{Healthy subject with negative test}}{\text{Total number of healthy subjects studied}}$$

$$\text{Predictive value of a positive result } (PV_{pos.}) = \frac{\text{Patients with positive test}}{\text{Total number of negative tests}}$$

$$\text{Predictive value of a negative result } (PV_{neg.}) = \frac{\text{Healthy subjects with negative tests}}{\text{Total number of negative tests}}$$

Given the method of calculation and presentation, we carried out, in turn, a proportional analysis for the same population and a comparative proportional analysis - in a binomial distribution - at the 95% confidence limit.

RESULTS

1. *Skin testing*

The results are shown in Table 2. The statistical analysis revealed no significant differences in the sensitivity, specificity, $PV_{pos.}$ and $PV_{neg.}$ of the skin tests using the different allergens.

Table 2. Skin testing: parameters of diagnostic efficacy.

	alternaria	cat epithelium	phleum
sensitivity	0.75	0.86	0.7
specificity	0.25	0.43	0.5
$PV_{pos.}$	0.75	0.6	0.78
$PV_{neg.}$	0.5	0.75	0.4

2. *RAST*

The results are shown in Table 3. There are no differences as regards either sensitivity or specificity. Phleum displays a $PV_{pos.}$ which is inferior to that of Alternaria ($p = 88.26\%$), but the difference is not significant. There are also no differences in the $PV_{neg.}$.

Table 3. RAST: parameters of diagnostic efficacy.

	alternaria	cat epithelium	phleum
sensitivity	0.57	0.88	0.92
specificity	0.66	0.75	0.5
$PV_{pos.}$	0.57	0.8	0.92
$PV_{neg.}$	1	0.75	0.5

3. *NPT*

With regard to the sensitivity of the parameter ΔP, there are no significant differences in testing with the different allergens; but the resistances R - as well as $W_{1.85}$ and W_2 - are more sensitive for Phleum than for Alternaria, although not at

a significant level. As regards the specificity of ΔP, there were no significant differences between the allergens; this was also the case for R, but $W_{1.85}$ and W_2 were found to be more specific for cat epithelium than for Alternaria ($p<0.05$). Analysis of both the $PV_{pos.}$ and the $PV_{neg.}$ revealed no significant differences between the allergens. The results of the NPT are shown in Table 4.

Table 4. NPT: parameters of diagnostic efficacy.

	alternaria				cat epithelium				phleum			
	ΔP	R	$W_{1.85}$	W_2	ΔP	R	$W_{1.85}$	W_2	ΔP	R	$W_{1.85}$	W_2
sensitivity	0.29	0.71	0.71	0.71	0.78	0.78	0.89	0.89	0.67	1	1	1
specificity	0.857	0.286	0.286	0.286	0.73	0.73	0.82	0.82	0.875	0.75	0.75	0.75
$PV_{pos.}$	0.67	0.83	0.83	0.83	0.75	0.77	0.77	0.77	0.875	0.92	0.85	0.85
$PV_{neg.}$	0	0	0	0	0.5	0.6	0.6	0.6	0.15	0	0	0

4. *Allergen comparison*

A. Alternaria: The results are shown in Table 5. Statistical analysis indicates that (1) skin testing is significantly more sensitive than the RAST test and the variations in ΔP ($p<0.05$); (2) there are no significant differences between skin testing and the RAST test and regards specificity; (3) the ΔP value is significantly more specific than skin testing and the increase in resistance; and (4) in the case of the $PV_{pos.}$ there are no significant differences. Given the small size of the sample it was not possible to analyse the $PV_{neg.}$.

Table 5. Parameters of diagnostic efficacy - with alternaria.

	skin T.	RAST	ΔP	R	$W_{1.85}$	W_2
sensitivity	0.75	0.57	0.29	0.71	0.71	0.71
specificity	0.25	0.66	0.857	0.286	0.286	0.286
$PV_{pos.}$	0.75	0.8	0.75	0.77	0.77	0.77
$PV_{neg.}$	0.5	0.75	0.5	0	0	0

B. Cat epithelium: There are no differences between the sensitivity of the different tests and the parameters of the NPT for this allergen. But the resistances $W_{1.85}$ and W_2 are significantly more specific than skin testing ($p<0.05$). With regard to the $PV_{pos.}$, and the $PV_{neg.}$, the differences are not significant. The results are shown in Table 6.

Table 6. Parameters of diagnostic efficacy - with cat epithelium.

	skin T.	RAST	ΔP	R	$W_{1.85}$	W_2
sensitivity	0.86	0.88	0.78	0.78	0.89	0.89
specificity	0.43	0.75	0.73	0.73	0.82	0.82
$PV_{pos.}$	0.6	0.8	0.75	0.77	0.77	0.77
$PV_{neg.}$	0.75	0.75	0.5	0.6	0.6	0.6

C. Phleum: The differences in sensitivity between the tests and the parameters of the NPT are not significant; neither are the differences in specificity, $PV_{pos.}$ and $PV_{neg.}$. The results are shown in Table 7.

Table 7. Parameters of diagnostic efficacy - with phleum.

	skin T.	RAST	ΔP	R	$W_{1.85}$	W_2
sensitivity	0.7	0.92	0.67	1	1	1
specificity	0.5	0.5	0.875	0.75	0.75	0.75
$PV_{pos.}$	0.78	0.92	0.875	0.92	0.85	0.85
$PV_{neg.}$	0.4	0.5	0.17	0	0	0

DISCUSSION

The results of most of the studies are expressed as the frequency of positive results. Lynch et al. (1975) have demonstrated good concordance in the frequencies of positive and negative results from the NPT and the RAST test with Alternaria. With dog dander, Vanto et al. (1983) found a lack of agreement between the results of the two afore mentioned tests.

We believe that the analysis of our results is more useful, as they provide us with some indication of the sensivity and specificity of the technique, and permit evaluation of the results in the light of the clinical history. In addition, the $PV_{pos.}$ expresses the likelihood of obtaining a positive test among patients allergic to the particular allergen, and the $PV_{neg.}$ expresses the likelihood of obtaining a negative test among healthy subjects. The expression of these parameters, as proposed by Romar (1984), is more informative, but it requires knowledge of the prevalence of these allergens in our population. Although the prevalence in our sample is known, its comparison with the prevalence in the general population is speculative - as we showed in the case of Parietaria (Olive et al., 1986).

Our study, involving the performance of the NPT using AAR, shows that, for the sensitivity and the specificity, the results are not inconclusive (with respect to the different allergens, there are no significant differences). A comparison of the results of the NPT, using the variations in ΔP and the variations in R, $W_{1,85}$ and W_2 as the criteria for a positive result, reveals that these parameters are as sensitive as skin testing, and that, with Alternaria, the variations in ΔP are more specific. Consideration of the fact that the allergen was the same, and from the same batch, and that its potency was checked every three months by RAST inhibition (Olive, 1986), should lead one to conclude that the greater specificity was a result of the technique. In this respect, one should mention the finding of a significantly lower $PV_{neg.}$; but, given the results and the small size of the sample - due to the low incidence of this aetiology in our population -, we cannot offer any conclusions on the $PV_{neg.}$.

In the case of cat epithelium the specificity of the increase in resistances is greater than that of skin testing; no significant differences were found in the other cases. As the extracts of this allergen were also from the same batch the lower specificity must be due to the technique.

No differences were found in the case of Phleum. A possible explanation for such findings might be the fact that both Alternaria and cat epithelium are perennial allergens, whereas Phleum has a very short seasonal occurrence. The first two allergens, therefore, could cause latent sensitization - not manifested clinically - with positive skin tests and a negative NPT; this would not occur in the case of Phleum. Another possible explanation would be the existence of cross reactions. These have been described for Alternaria (Aukrust et al., 1985) and other fungi (Yunginger et al., 1980), but their clinical relevance to our work has not been determined. It has been suggested that a cross reaction occurs between cat epithelium and D. pteronyssinus, via Otodectes cyanotis (Larkin, 1981), but further confirmation is required. What we do know is that there exists a greater frequency of positive skin tests to cat epithelium among positive D. pteronyssinus patients, but not vice versa.

Another related finding is the existence of cross reactivity between epithelial allergens. In a study on the diagnostic value of the RAST test, using cat epithelium and involving 61 patients, of whom 26 had a clear history of allergy to cat epithelium, it was found that the sensitivity of the RAST test was of the order of 0.962 and that of the $PV_{pos.}$ was of the order of 0.41 in the group of patients who were allergic to cat epithelium; in this study the group of patients who were not allergic to cat epithelium was also not allergic to either dog or other animal epithelia (Granel et al., 1985), or to mites. This phenomenon, although not completely understood would account for the low specificity of skin testing with cat epithelium. Phleum, on the other hand, only cross reacts with the Gramineal pollens, so that a "positive history to Phleum" would also indicate a "positive history to Gramineal pollens", as they are indistinguishable.

Whereas skin testing (and also the RAST test) demonstrates the existence of specific antibodies (sensitization), the NPT demonstrates the existence of specific antibodies in the mast cells of the nasal submucosa, a positive NPT is highly suggestive as regards the aetiology.

All these findings indicate that the NPT is an excellent diagnostic technique which can - taking into account the proposed standardization - replace those techniques normally employed in the diagnosis of allergic rhinitis - techniques to which the NPT is without doubt superior.

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