

Evaluation of the Phadiatop[®] test in an epidemiological study

A. M. J. WEVER,¹ J. WEVER-HESS,¹ C. P. VAN SCHAYCK² & C. VAN WEEL²

¹Department of Pulmonology, University Hospital, Leiden, and ²Department of General Practice/Family Medicine, University of Nijmegen, The Netherlands

Sera from 204 adult patients with chronic airways obstruction were analysed with the Phadiatop[®], a new allergosorbent test with a paper disc containing the most relevant inhalant allergens, the PRIST for total IgE determinations, and a panel of seven RAST tests with the common inhalant allergens in The Netherlands as reference. The aim was to evaluate the Phadiatop as screening test in the *in vitro* diagnostic procedures in an epidemiological setting. The Phadiatop was classified positive or negative according to percentage binding, total IgE was considered elevated at values >100 kU/l and the RAST panel positive when at least one RAST result was class >1. The prevalence of inhalant atopy came to 27.9%. The predictive value of the Phadiatop for a positive RAST panel was 96.4%, and for a negative RAST panel 97.3%. For the PRIST these values were 51.9% and 87.2% respectively. The correlation between the log percentages binding of the Phadiatop and the RAST panel was 0.93. It is concluded that the Phadiatop is a valuable test for the screening of inhalant atopy, and as the percentage binding of the Phadiatop may reflect the degree of sensitization it could also be applied as a quantitative measure especially for epidemiological purposes.

Key words: epidemiology; inhalant allergens; Phadiatop[®]; PRIST; RAST; specific IgE; total IgE.

Accepted for publication 26 August 1989

Since the discovery of immunoglobulin E (IgE) in 1966, the diagnostic possibilities of IgE mediated allergy have markedly increased (2, 15). Publications have recently appeared on a new *in vitro* test based on a radio-allergo-sorbent test (RAST)-principle. This new test, the Phadiatop[®], is a single screening test for IgE antibodies against inhalant allergens. The Phadiatop results showed very good correlations with the results of a RAST panel, both in children (11, 12) and in adults (13, 17, 23). The sensitivity and specificity of the Phadiatop for a clinically diagnosed inhalant allergy also proved to be high (3, 11, 14). In The Netherlands a regional intervention study in patients with chronic airways obstruction was started in 1987. In this population, in which, by

contrast, a low prevalence of inhalant atopy was expected, the Phadiatop was evaluated as screening test beside other *in vitro* diagnostic procedures to determine whether atopy for inhalant allergens existed.

PATIENTS AND METHODS

Patients

Serum was obtained from adult patients (minimum age 30 years in the study period) treated in general practice for chronic airways obstruction, based on ATS criteria (1). The patients were recruited for a medication intervention study, conducted in the eastern

part of The Netherlands. Inclusion criteria with respect to lung function and non-specific bronchial hyperreactivity were: FEV₁ < reference value minus 2x SD, and/or FEV₁/VC < reference value minus 2x SD, and/or FEV₁ showing a rise of > 15 % after broncho-dilatation, and/or histamine threshold (PC₂₀) < 8 mg/ml, and baseline FEV₁ > 50 % reference value.

Laboratory tests

The following tests were performed: Phadiatop test for determination of IgE antibodies against a balanced mixture of relevant inhalant allergens not further specified by the manufacturer (18), paper-radioimmunosorbent test (PRIST) for determination of total serum IgE, and RAST for determination of specific IgE antibodies against the following inhalant allergens common in The Netherlands: house dust mite,

Table 1		
Allergens used in the RAST		
D1 House dust mite:	<i>Dermatophagoides pteronyssinus</i>	
Gx1 Grass pollen mix:	G3	Cocksfoot
	G4	Meadow fescue
	G5	Rye-grass
	G6	Timothy
	G8	Meadow grass, Kentucky blue
E1 Cat dander		
E5 Dog dander		
Wx3 Weed pollen mix:	W6	Mugwort
	W9	English plantain, Ribwort
	W10	Goosefoot, Lamb's quarters
	W12	Golden rod
	W20	Nettle
Tx9 Tree pollen mix:	T2	Grey alder
	T3	Common silver birch
	T4	Hazel
	T7	Oak
	T12	Willow
Mx1 Moulds mix:	M1	<i>Penicillium notatum</i>
	M2	<i>Cladosporium herbarum</i>
	M3	<i>Aspergillus fumigatus</i>
	M6	<i>Alternaria alternata (tenuis)</i>

Table 2			
Predictive values and accuracy of the Phadiatop® for a panel of seven RAST tests in adult patients (n = 204), with panel positive when at least one RAST result class > 1, in parentheses when at least one RAST result class > 2			
Phadiatop®	RAST panel		Total
	positive	negative	
Positive	53 (50)	2 ((5)	55
Negative	4 (2)	145 (147)	149
Total	57 (52)	147 (152)	204
Positive predictive value: 53/55 = 96.4 % (90.9 %)			
Negative predictive value: 145/149 = 97.3 % (98.7 %)			
Accuracy: 198/204 = 97.1 % (96.6 %)			

grass pollen, cat dander, dog dander, weed pollen, tree pollen and moulds (Phadebas RAST D1, Gx1, E1, E5, Wx3, Tx9 and Mx1, Table 1). The tests were carried out with reagents of Pharmacia Diagnostics AB, Uppsala, Sweden, according to the instructions of the manufacturer. The Phadiatop and RAST were performed as single tests, the PRIST as a double test. The percentage binding of the Phadiatop was determined and classified as a positive or negative result. The percentage binding of each RAST was determined and classified semiquantitatively in Phadebas RAST classes 0-4. Total IgE concentration was expressed in kU/l, taking the mean of two determinations, and considered elevated at a value > 100 kU/l (25, 26).

Table 3			
Predictive values and accuracy of total IgE for a panel of seven RAST tests in adult patients (n = 204), with panel positive when at least one RAST result class > 1, in parentheses when at least one RAST result class > 2			
Total IgE	RAST panel		Total
	positive	negative	
> = 100 kU/l	41 (37)	38 (42)	79
< 100 kU/l	16 (15)	109 (110)	125
Total	57 (52)	147 (152)	204
Positive predictive value: 41/79 = 51.9 % (46.8 %)			
Negative predictive value: 109/125 = 87.2 % (88.0 %)			
Accuracy: 150/204 = 73.5 % (72.1 %)			

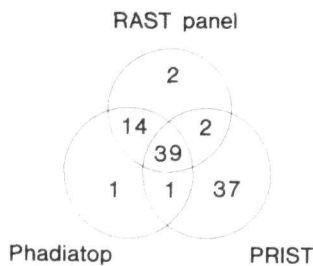


Fig. 1. Venn diagram showing the frequencies of combinations of the *in vitro* results in the patients who were positive for at least one test ($n = 96$).

Data analysis

The RAST panel served as reference. It was considered positive when at least one RAST result was class > 1 and negative when all seven RAST results were class 0. The predictive

values and accuracy of the Phadiatop and the PRIST for the RAST were computed (10). Total IgE concentration and percentage binding of the Phadiatop were expressed as a function of the sum of the RAST results (4). The correlations were calculated between the sums of the percentage binding of the seven RAST tests and the percentage binding of the Phadiatop respectively the total IgE values by the least squares regression method after $^{10}\log$ transformation to obtain a more uniform scatter of the data.

RESULTS

Blood was sampled in 204 patients (115 males and 89 females), mean age 52.8 years, SD 12.5. In this population 57 (27.9%) of the patients were RAST positive. The mean age of the RAST positive group was 45.6 years (SD 10.9) and of the RAST negative group

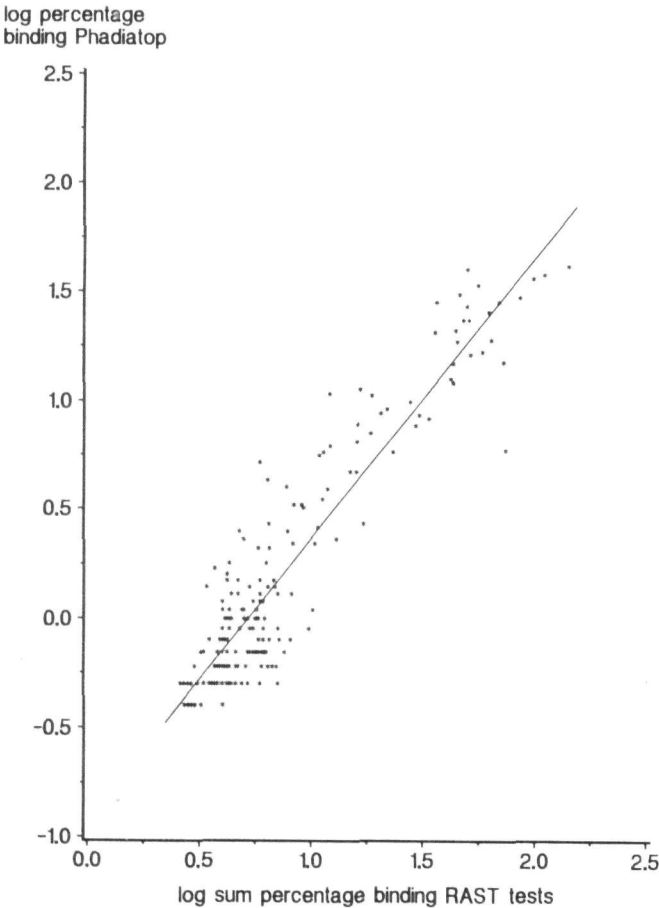


Fig. 2. Scatter diagram showing log of the percentage binding of the Phadiatop against log of the sum of the percentage binding of the seven RAST tests ($n = 204$), correlation coefficient 0.93, slope 1.29 ($P < 0.0001$).

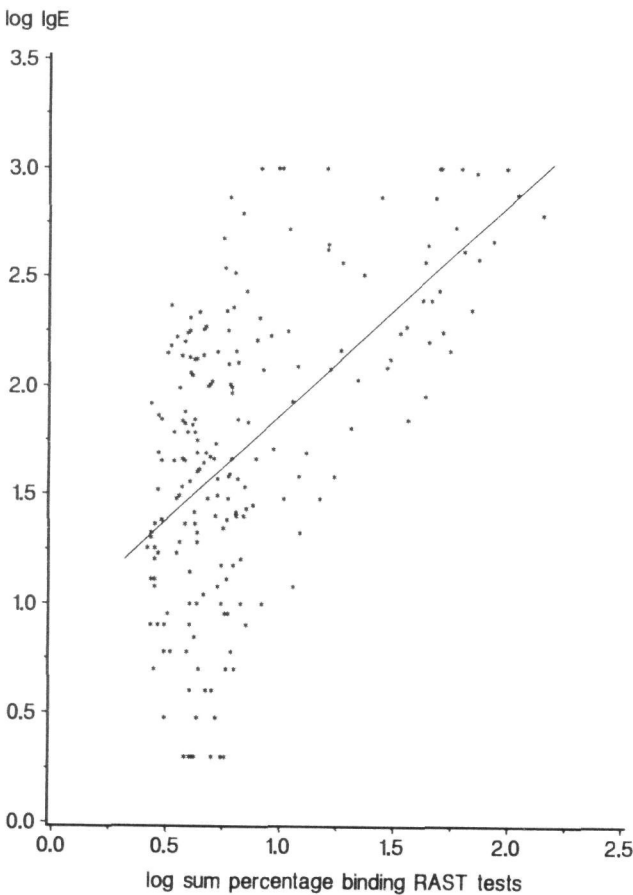


Fig. 3. Scatter diagram showing log of the value of total IgE against log of the sum of the percentage binding of the seven RAST tests ($n = 204$), correlation coefficient 0.57, slope 0.97 ($P < 0.0001$).

55.6 years (SD 12.1) (unpaired *t*-test $P < 0.0001$). No significant sex differences between the RAST positive and negative group were found (35 males and 22 females versus 80 males and 67 females, chi-square test on 2×2 table $P = 0.367$). The predictive value of the Phadiatop for one or more positive RAST results was 96.4% and its predictive value for all RAST results being negative was 97.3%, the accuracy of the test being 97.1% (Table 2). For total IgE these predictive values were 51.9% and 87.2% respectively with the accuracy of the PRIST being 73.5% (Table 3). If class 2 was applied as criterion for RAST positivity (3, 16, 20) then the predictive values of the Phadiatop were 90.9% and 98.7% respectively (accuracy 96.6%) and those for total IgE 46.8% and 88.0% respectively (accuracy 72.1%). The Venn diagram (Fig. 1) shows the frequencies of the combinations of positive test results.

Figs. 2 and 3 show the relationship between the log of the percentage binding of the Phadiatop (Fig. 2), or the total IgE values (Fig. 3), and the log of the sums of the percentage binding of the seven RAST tests, the correlation coefficients being 0.93 and 0.57 respectively.

DISCUSSION

In recent studies the Phadiatop has been evaluated in populations in which atopy/allergy could be suspected, and accordingly a relatively high prevalence (45–60%) of sensitized patients was found (3, 11, 12, 14, 23). However, in this study adult patients were investigated with chronic airways obstruction, in which atopy was expected to play a lesser role. Based on a panel of seven RAST tests with inhalant allergens common in The Netherlands, atopy occurred in 27.9% of the patients. From the predictive values, which depend on the prevalence of the disease in the population, it can be concluded that also in this population with a relatively low prevalence of inhalant atopy the Phadiatop is a highly efficient test, much more so than the PRIST, in correctly classifying atopic and

non-atopic patients as judged by the reference RAST panel. The four false negative Phadiatop results were all due to a single positive RAST result in the panel (1x class 1 and 2x class 2 for house dust mite, and 1x class 1 for grass pollen mix). There were only two (3.6%) false positive results, but it is possible that the Phadiatop serves a broader panel of inhalant allergens than the above mentioned seven RAST tests in view of the applied panels in other studies (3, 12, 13, 17). Of the 79 patients with an elevated IgE level 38 (48.1%) had a negative RAST panel. To this high percentage of false positive IgE results the habit of smoking might have contributed, as it has been reported that smoking increases the IgE level (6, 21). To investigate this further a stepwise multiple regression analysis was carried out with IgE level (< 100 kU/l / $> = 100$ kU/l) as dependent variable, and age, sex, smoking habit (non-smoker/(ever)smoker and number of pack-years), atopy (RAST panel positive/negative), and also FEV₁% predicted and histamine PC₂₀, as independent variables. Atopy proved to have the greatest predictive value for IgE level, whilst the other variables did not have any additional predictive value. The strong relationship of IgE to atopy and not to smoking is illustrated by the geometric mean IgE in the RAST positive group being 180.8 kU/l in the (ever)smokers ($n = 40$) and 150.8 kU/l in the non-smokers ($n = 17$) ($P = 0.611$), and in the RAST negative group being 35.8 kU/l in the (ever)smokers ($n = 125$) and 26.5 kU/l in the non-smokers ($n = 22$) ($P = 0.373$) (P -values of the *t*-test on the log IgE values). However, the interrelationship between serum IgE, atopy to aeroallergens, smoking and respiratory disorders is a complex one, in which the pathophysiological mechanism(s) are not yet clear (7, 19, 21, 22). Though total IgE might be of use as an epidemiological variable, this study confirms that the Phadiatop is a much more accurate method for screening for inhalant atopy.

Although the Phadiatop has been introduced by the manufacturer as a yes-no test for diagnosing inhalant atopy, the percentage binding might yield further information on the degree

of sensitization. Fig. 2 shows that the log percentage binding of the Phadiatop is predictive of the log sum of the percentage binding of the seven RAST tests. In contrast, the log IgE could not be used to predict the log sum of percentage binding of RAST, although the slope is statistically significantly different from zero (Fig. 3). The degree of sensitization is an important additional fact in view of the interrelationship between atopic status, bronchial hyperresponsiveness to allergen, and bronchial hyperresponsiveness to histamine (5, 8, 9, 24), and could be evaluated in the epidemiological appraisal of patients with chronic airways obstruction.

ACKNOWLEDGEMENTS

We wish to thank Pharmacia Nederland BV for supplying the reagents for the *in vitro* tests, and Dr. J. Hermans for his statistical advice.

REFERENCES

1. American Thoracic Society: Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am. Rev. Respir. Dis.* 136, 225-244, 1987.
2. Bennich, H., Ishizaka, K., Johansson, S. G. O., et al.: Immunoglobulin E. A new class of human immunoglobulin. *Bull. W.H.O.* 38, 151-152, 1968.
3. Biot, N., Guilloux, L., Guerrier, G., Carron, R., Ville, G. & Perrin-Fayolle, M.: Un test simple de dépistage de l'allergie respiratoire aux pneumallergènes courants. *Presse Méd.* 17, 376-378, 1988.
4. Björkstén, F. & Johansson, S. G. O.: In vitro diagnosis of atopic allergy. The occurrence and clustering of positive RAST results as a function of age and total IgE concentration. *Clin. Allergy* 5, 363-373, 1975.
5. Bryant, D. H. & Burns, M. W.: Bronchial histamine reactivity: its relationship to the reactivity of the bronchi to allergens. *Clin. Allergy* 6, 523-532, 1976.
6. Burrows, B., Halonen, M., Barbee, R. A. & Lebowitz, M. D.: The relationship of serum immunoglobulin E to cigarette smoking. *Am. Rev. Respir. Dis.* 124, 523-525, 1981.
7. Burrows, B., Halonen, M., Lebowitz, M. D., Knudson, R. J. & Barbee, R. A.: The relationship of serum immunoglobulin E, allergy skin tests, and smoking to respiratory disorders. *J. Allergy Clin. Immunol.* 70, 199-204, 1982.
8. Cockcroft, D. W., Ruffin, R. E., Frith, P. A., et al.: Determinants of allergen-induced asthma: dose of allergen, circulating IgE antibody concentration, and bronchial responsiveness to inhaled histamine. *Am. Rev. Respir. Dis.* 120, 1053-1058, 1979.
9. Cockcroft, D. W., Murdock, K. Y. & Berscheid, B. A.: Relationship between atopy and bronchial responsiveness to histamine in a random population. *Ann. Allergy* 53, 26-29, 1984.
10. Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ont.: How to read clinical journals: II. To learn about a diagnostic test. *Can. Med. Assoc. J.* 124, 703-710, 1981.
11. Guilloux, L., Guerrier, G., Ville, G. & Carron, R.: Phadiatop: un dépistage biologique fiable des troubles respiratoires répétitifs de l'enfant. *Rev. Fr. Allergol.* 27, 129-131, 1987.
12. Gustafsson, D. & Danielsson, D.: In vitro diagnosis of atopic allergy in children. *Allergy* 43, 105-108, 1988.
13. Herold, D. A., Duyan, I. & Kunkel, G.: Phadiatop versus Gesamt-IgE. Teil I. *Allergologie* 10, 276-279, 1987.
14. Herold, D. A., Duyan, I. & Kunkel, G.: Phadiatop versus Gesamt-IgE. Teil II. *Allergologie* 10, 300-303, 1987.
15. Johansson, S. G. O.: In vitro diagnosis of IgE-mediated allergy. In Debelic, M. (ed.): 20 Years with IgE - new prospects. Surrey: Medicom, 35-45, 1987.
16. Merrett, T. G., Pantin, C. F. A., Dimond, A. H. & Merrett, J.: Screening for IgE-mediated allergy. *Allergy* 35, 491-501, 1980.
17. Merrett, J. & Merrett, T. G.: Phadiatop - a novel IgE antibody screening test. *Clin. Allergy* 17, 409-416, 1987.
18. Pharmacia Diagnostics AB: PhadiatopTM RIA. Direction for use. Uppsala, Sweden, 1985.
19. Vollmer, W. M., Buist, A. S., Johnson, L. R., McCamant, L. E. & Halonen, M.: Relationship between serum IgE and cross-sectional and longitudinal FEV1 in two cohort studies. *Chest* 90, 416-423, 1986.
20. Vooren, P. H., Kramps, J. A., Franken, C. & Dijkman, J. H.: Diagnostic relevance of the modified RAST using D_{e2} specific anti-IgE antibodies. *Eur. J. Respir. Dis.* 64, 90-101, 1983.
21. Warren, C. P. W., Holford-Strevens, V., Wong, C. & Manfreda, J.: The relationship between smoking and total immunoglobulin E levels. *J. Allergy Clin. Immunol.* 69, 370-375, 1982.
22. Welty, C., Weiss, S. T., Tager, I. B., et al.: The relationship of airways responsiveness to cold air, cigarette smoking, and atopy to respiratory symptoms and pulmonary function in adults. *Am. Rev. Respir. Dis.* 130, 198-203, 1984.
23. Wever, A. M. J., Wever-Hess, J., Kramps, J. A., Mulder Dzn, J. D. & Dijkman, J. H.: De "Phadiatop-test", een nieuwe in vitro-test voor inhalatie-allergie. (English summary). *Ned. Tijdschr. Geneesk.* 133, 70-73, 1989.
24. Witt, C., Stuckey, M. S., Woolcock, A. J. & Dawkins, R. L.: Positive allergy prick tests associated with bronchial histamine responsiveness in an unselected population. *J. Allergy Clin. Immunol.* 77, 698-702, 1986.

25. Wittig, H. J., Belloit, J., De Fillippi, I. & Royal, G.: Age-related serum immunoglobulin E levels in healthy subjects and in patients with allergic disease. *J. Allergy Clin. Immunol.* 66, 305-313, 1980.
26. Zetterström, O. & Johansson, S. G. O.: IgE concentrations measured by PRIST in serum of healthy adults and in patients with respiratory allergy. *Allergy* 36, 537-547, 1981.

Address:

Dr. A. M. J. *Wever*

Department of Pulmonology

University Hospital, Postbus 9600

2300 RC Leiden

The Netherlands

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.