

Atopy patch test with different vehicles and allergen concentrations: An approach to standardization

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Background: In some patients with atopic eczema, eczematous skin lesions can be induced by patch testing with aeroallergens.

Methods: To establish a standardized system for the atopy patch test (APT), 36 patients with atopic eczema, four patients with rhinoconjunctivitis and 10 healthy control subjects were epicutaneously tested with allergen extracts from house dust mite, cat dander, and grass pollen. APTs were performed on nonabraded, uninvolved skin with 1000 and 10,000 protein nitrogen units (PNU)/gm allergen in petrolatum or hydrogel. Reactions were evaluated after 48 and 72 hours and compared with skin prick and specific serum IgE (CAP-RAST; Pharmacia, Uppsala, Sweden).

Results: After 48 hours, 57 clear-cut positive reactions with eczematous, often follicle-bound, appearance were diagnosed from a total of 432 test sites. Seventy-two percent of these positive reactions in patients with atopic eczema developed with 10,000 PNU/gm and 28% with 1000 PNU/gm. Sixty-seven percent of reactions were elicited with allergens in petrolatum versus 33% when hydrogel was used as vehicle. Allergen-specific concordances of APT (10,000 PNU/gm, petrolatum) ranged from 0.39 to 0.53 (prick test) and 0.42 to 0.69 (CAP-RAST). In healthy control subjects and patients with rhinoconjunctivitis without atopic eczema, no clear-cut positive APT reaction was seen.

Conclusions: Petrolatum as vehicle and an allergen concentration higher than 1000 PNU/gm may lead to improved APT results on unchanged skin. In the future, the clinical relevance of an IgE-mediated sensitization for eczematous skin lesions may be evaluated by the APT. (*J ALLERGY CLIN IMMUNOL* 1995;95:677-84.)

Key words: Aeroallergens, patch test, atopy patch test, standardization, atopic eczema

The role of allergy in the pathophysiology of atopic eczema, a disease with inflammatory, chronic, or relapsing skin lesions with intense pruritus and various skin symptoms and signs, is still a matter of controversy.¹⁻³ Yet, IgE-mediated reactions to aeroallergens have been shown to play a role in a subgroup of patients with atopic eczema.^{4,5} It is a clinically well-known observation that some patients with atopic eczema experience exacerbation of their skin lesions after contact with certain aeroallergens (e.g., animal dander). An

Abbreviations used

APT: Atopy patch test
PNU: Protein nitrogen unit
SLS: Sodium lauryl sulfate

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increasing number of reports demonstrate that in certain patients, eczematous skin lesions can be induced after epicutaneous patch testing with aeroallergens (e.g., house dust mite).^{3, 6-22} For this procedure, namely an epicutaneous patch test with allergens known to elicit IgE-mediated reactions and the evaluation of eczematous skin lesions, we have proposed the term *atopy patch test* (APT).^{3, 5, 17}

Studies of patch tests with aeroallergens, beginning with the study by Mitchell et al.¹³ in 1982, have varied widely in the methods used. Skin abrasion,^{10, 13, 14} tape stripping,^{7, 22} and sodium lau-

ryl sulfate (SLS) application²⁰ were frequently used to enable allergen penetration. However, studies with APT on nonabraded, nonpretreated skin were also performed^{3, 17, 21, 23} with different numbers of positive reactions, which were obviously related in part to different allergen content in the preparations used. We have obtained positive APT reactions in 30% of tested patients by using standard skin prick test solutions without clear-cut correlation to skin prick test or RAST results.³

To establish a standardized system for the APT, we performed comparative epicutaneous tests with three aeroallergens in two concentrations and in two easily applicable vehicles differing in water binding capacity.

METHODS

Patients and control subjects

Thirty-six patients (27 female and 9 male), aged 3 to 69 years (mean age, 29 ± 16 years) with moderate to severe atopic eczema (approximately 15 to 90 points in the SCORAD system²⁴) were included in the study. These patients were divided into two subgroups according to their history: 16 patients reported an exacerbation of eczematous skin lesions after exposure to at least one of the three allergens tested, and 20 patients were not aware of such associations. Twenty-two patients in both groups also had allergic rhinoconjunctivitis, and seven also had bronchial asthma. Patients who had received phototherapy in the last 12 months or antihistamines with prolonged half-lives in the last 6 months were not included in the study.

Control groups consisted of four patients with allergic rhinoconjunctivitis only without previous or actual skin changes (2 women and 2 men, aged 32 to 54 years) and 10 nonatopic healthy volunteers without a history of allergic rhinoconjunctivitis, bronchial asthma, or atopic eczema (9 women and 1 man, aged 32 to 66 years). One of these volunteers had elevated total serum IgE, and another one elevated RAST values in response to *Dermatophagoides pteronyssinus* without any history of atopy ("latent atopic individuals"). The remaining eight healthy subjects had normal IgE (total and specific). All healthy volunteers were free of skin signs of atopy (i.e., duplicated infraorbital fold, hyperlineated skin of palms, white dermatographism). The patients with atopic eczema were all in a stable phase of partial or complete remission (i.e., not requiring systemic medication or topical steroids). Most of them had few remaining eczematous skin lesions on other parts of the body (not on the back skin). Informed consent was obtained from each patient or the parents before the study.

Materials

Patch tests were performed with three lyophilized common aeroallergens: house dust mite (*D. pteronyssinus*), cat dander, and grass pollen (Allergopharma,

Reinbek, Germany). These allergens were used in concentrations of 1000 protein nitrogen units (PNU)/gm and 10,000 PNU/gm of test substance in two different vehicles: (1) white petrolatum/10% isopropyl myristate and (2) methylcellulose hydrogel/10% propylene glycol.

The lyophilized grass pollen extract contained a mixture of *Holcus lanatus*, *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*, and *Festuca pratensis*. The test preparations (not commercially available) were kindly prepared by Hermal Company (Dr. Matthies), Reinbek, Germany. Because lyophilized allergens were used, no potentially irritating diluents were contained in the test substances or controls.

APT

After antihistamines and systemic and topical (test area) steroids were discontinued for at least 7 days, the test substances were applied for 48 hours in large Finn chambers (Epitest Ltd., Oy, Finland; diameter = 12 mm) on clinically uninvolved, untreated back skin. Evaluation was performed after 48 and 72 hours. Grading of positive APT reactions was principally similar to the criteria used in conventional contact allergy patch testing: (+) represented a questionable reaction (i.e., only erythema); $\pm$ was graded when erythema, infiltration, none or few papules occurred. Erythema, intensive infiltration, many papules, occasionally vesicles were represented by ++ and densely aggregated papules and vesicles were represented by ++++. In control areas, vehicles without allergens were tested; the vehicle additives propylene glycol and isopropyl myristate (10% each) and a 0.5% solution of SLS as irritant were also included in the test panel.

Skin prick test

Prick tests with *D. pteronyssinus*, cat dander, and grass pollen mixture (Bencard, Neuss, Germany) were performed before APT in each subject tested.

Total and specific serum IgE

Serum levels of total IgE and aeroallergen-specific IgE were measured by the CAP-RAST system (Pharmacia, Uppsala, Sweden). The serum samples were taken on the first day of the APT from each patient and control subject.

Statistical analysis

Statistical analysis was performed with Wilcoxon's matched-pairs signed-rank test.

RESULTS

Twenty-seven of 36 patients with atopic eczema showed at least one positive reaction at APT sites when doubtful, (+), reactions were included and reactions at 48 and 72 hours were merged (Table I). The reactions of 17 patients were graded as clear-cut positive ($47\% \geq +$).

A total of 432 APT areas (excluding control

TABLE I. Positive APT reactions in different groups of patients

Group	n	APT (+)	APT ≥ +
Atopic eczema (total)	36	10	17
Atopic eczema with "aeroallergen history"	16	7	8
Atopic eczema without "aeroallergen history"	20	3	9
Allergic rhinoconjunctivitis	4	0	0
Nonatopic control subjects	8	0	0
"Latent" atopic individuals	2	1	0

TABLE II. Intensity of positive APT reactions after 48 hours with different allergen concentrations and vehicles in 36 patients with atopic eczema

	Number of reactions				Total ≥ +
	(+)	+	++	+++	
Allergen concentration in petrolatum					
1,000 PNU/gm	19	9	2	0	11 (19.3%)*
10,000 PNU/gm	12	13	11	3	27 (47.4%)*
Total in petrolatum	31	22	13	3	38 (66.7%)*
Allergen concentration in hydrogel					
1,000 PNU/gm	8	2	3	0	5 (8.8%)*
10,000 PNU/gm	10	5	7	2	14 (24.6%)*
Total in hydrogel	18	7	10	2	19 (33.3%)*
Total	49	29	23	5	57 (100%)*

*Excludes questionable reactions.

areas with vehicles) were evaluated in the 36 patients. One hundred six of these test areas were graded as at least questionably positive in 27 of 36 patients. At the time of removal of the test chambers after 48 hours, in 57 areas clear-cut positive reactions had developed, whereas another 49 areas were graded as questionable, (+), (Table II). After 72 hours, the number of clear-cut positive reactions had declined to 41. APT reactions showed a different time course compared with classic patch tests with contact allergens: in all but three cases of 17 patients with clear-cut reactions, the peak severity of APT reactions was reached after 48 hours. After this time, the reactions showed no further increase but rather a decrease, indicating a difference of these reactions compared with responses to classic contact allergy tests. Control patch test sites with vehicles and vehicle additives without allergen remained negative in all test subjects. The following data represent the results obtained from 36 patients after 48 hours. At this time, 23 patients showed at least questionable reactions. A typical example of a ++-positive APT reaction is shown in Fig. 1. With increasing intensity, the reactions showed a prominent, often follicle-bound and pronounced eczematous appearance.

To evaluate and compare nonspecific irritation, SLS was tested. Thirty-three percent of patients and 29% of control subjects had a sharp-lined erythema without papules, which was strictly limited to the edges of the Finn chamber containing the test irritant. These reactions were clearly distinguishable from aeroallergen test sites.

Comparison of different patient groups

The percentage of patients with clear-cut positive reactions was nearly independent of the criterion "aeroallergen-positive history": 8 of 16 patients (50%) compared with 9 of 20 patients (45%) without such a history. When all reactions, including questionable ones, were included, a difference of 94% reactive patients "with history" versus 60% "without history" was noted. No difference was seen between patients who had both atopic eczema and allergic rhinoconjunctivitis and patients who had atopic eczema only. Nonatopic control subjects and patients with only allergic rhinoconjunctivitis experienced no positive reactions, whereas one of the "latent atopic" control subjects with elevated total IgE but negative skin prick test and CAP-RAST responses showed a questionable reaction (Table I).

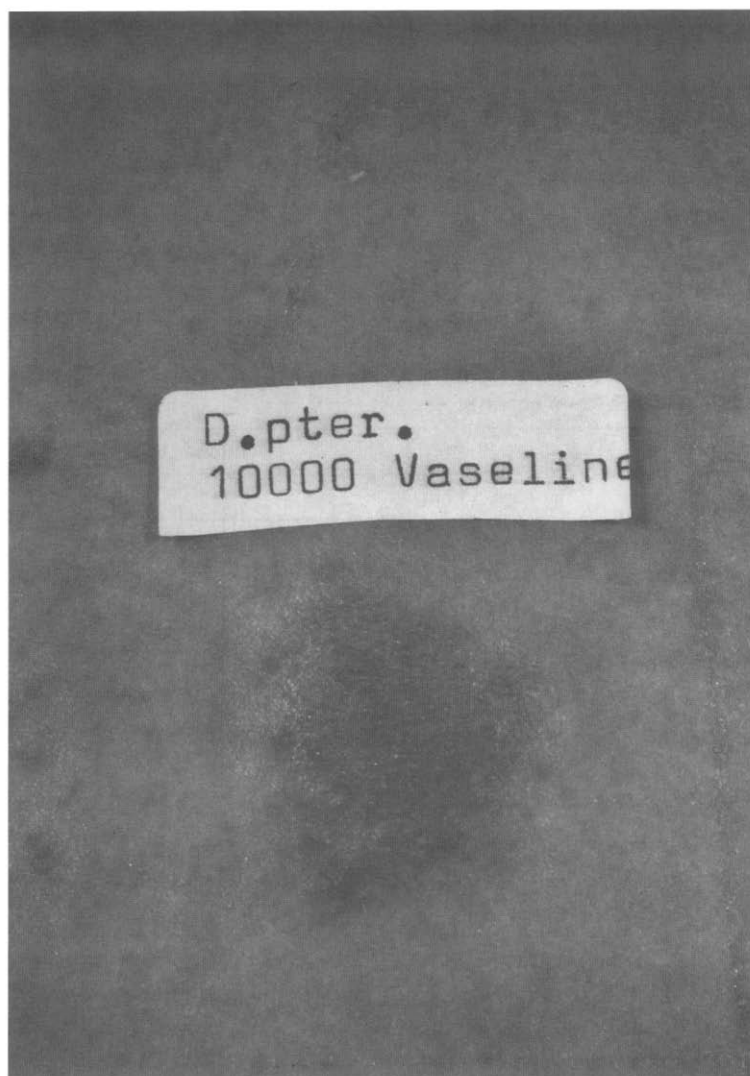


FIG. 1. APT reaction after removal of Finn chambers after 48 hours (detail) in a patient with atopic eczema and a history of house dust-induced exacerbations.

Comparison of the dose-response to two allergen concentrations

There was a clear dose-response relationship between allergen concentration and positive APT reactions. The analysis (Table II) showed that 72% of clear-cut positive reactions were provoked with 10,000 PNU/gm allergen concentration. In contrast, only 28% were already elicited by 1000 PNU/gm. This difference was independent of the vehicle used because similar results were obtained with hydrogel and petrolatum. There was a rate of 56.5% (39 of 69) positive APT reactions with petrolatum and 65% (24 of 37) with hydrogel as vehicle with 10,000 PNU/gm when doubtful reactions were included. In 15 of 23 patients, the yield of at least erythematous APT reactions was in-

creased by the higher concentration ($p = 0.0023$) (Table III).

Comparison of two different vehicles

There were clear-cut differences in the frequency of positive reactions between petrolatum- and hydrogel-formulated allergens: twice as many APT reactions occurred with petrolatum as with hydrogel. This trend remained stable for different reaction intensities and allergen concentrations (Table II).

Seventeen patients had more reactions to allergens in petrolatum than to those in hydrogel. This rate was significantly higher than the number of those patients in which allergens in hydrogel induced more APT reactions (2 patients, Table III).

Allergen specificity

When only clear-cut reactions with 10,000 PNU/gm allergen preparations in petrolatum were analyzed, the allergen that most frequently elicited a positive APT reaction was the house dust mite *D. pteronyssinus* (13 of 36 patients = 36.1%). Reactions to cat dander and grass pollen were seen in 8 of 36 (22.2%) and 6 of 36 (16.7%) patients (Table IV). Nine patients reacted to more than one allergen. Six patients had reactions to two allergens, and three patients had reactions to all three allergens. Isolated clear-cut positive APT reactions to *D. pteronyssinus* occurred in four patients and to cat dander, as well as to grass pollen in one patient each.

Concordance of prick test, CAP-RAST, and APT results

For the correlation of APT and skin prick test or RAST results only clear-cut positive prick test with a grade of + or greater and APT reactions with a grade of + or greater with 10,000 PNU/gm allergen concentrations in petrolatum were considered. CAP-RAST class had to be 2 or greater.

Eight of 20 patients with a positive prick test response to *D. pteronyssinus* had a corresponding APT result, but 5 of 16 patients with negative prick test responses also had a clear-cut positive APT reaction. The correlation of *D. pteronyssinus*-specific IgE and APT was higher. Although 10 of 18 patients with a CAP-RAST class of 2 or greater showed a corresponding APT reaction, only three of 18 without elevated IgE were found to be reactive (Table V).

Thus patients with *D. pteronyssinus*-positive APT reaction showed in 62% a corresponding positive prick test response and in 77% a corresponding RAST result. The allergen-specific concordance was 0.53 (prick test) and 0.69 (CAP-RAST). For APT with cat allergen, the concordance was 0.5 for prick test and 0.67 for CAP-RAST; whereas for grass pollen APT, concordances of 0.39 (prick test) and 0.42 (CAP-RAST) were observed.

DISCUSSION

The results of this study show that aeroallergens are able to elicit eczematous skin lesions in a group of patients with atopic eczema when applied epicutaneously and that this occurs in a dose-dependent way. Nonatopic individuals and patients with rhinoconjunctivitis showed no clear-cut positive reactions. Other groups have described similar findings^{16, 20, 21} but have not focused on the methodological approach.

TABLE III. APT: Comparison of vehicles and allergen concentration in 36 patients with atopic eczema, reaction grade of (+) or greater after 48 hours

No. of APT reactions to	Patients (n = 36)
Hydrogel = petrolatum	4
Hydrogel > petrolatum	2
Petrolatum > hydrogel	17*
1,000 PNU/gm = 10,000 PNU/gm	6
1,000 PNU/gm > 10,000 PNU/gm	2
10,000 PNU/gm > 1,000 PNU/gm	15*
No reaction	13

* $p < 0.01$.

If the APT should provide a means to evaluate the relevance of a given IgE-mediated sensitization for skin lesions in atopic eczema, standardization of this test procedure is mandatory.^{3, 5, 22} In previous studies there have been methodological differences with regard to allergen extracts, vehicles used, manner of epicutaneous application (including size, location, and pretreatment of test area), application period, and patient selection.

To obtain the highest yield of allergen-specific reactions with a minimum of skin irritation and loss of time, this study was carried out without tape stripping, skin abrasion, or addition of detergents to the test substances. Consequently, irritative reactions were only seen in the SLS areas and in one control subject who had a widespread irritation strictly limited to the skin sites that had been in contact with tape. Isopropyl myristate (in petrolatum) and propylene glycol (in hydrogel) were added in 10% concentration to the vehicles without leading to irritation in our patients. These substances may act as mild enhancers of allergen penetration of the epidermis.

With the use of different allergen concentrations and more or less effective vehicles in each patient, a high rate of questionable "only erythema" APT reactions was observed, and these were counted separately (Table II). However, these reactions were distinguishable from typical irritation: they had no sharp demarcation and mild erythema as compared with the SLS reaction, and they were often follicle-bound.

The allergen-specific nature of APT reactions has been demonstrated by Langeland et al.¹² who were able to transfer APT reactivity in Prausnitz-Küstner test and by van Reijssen et al.²⁵ and Sager et al.,^{23, 26} who characterized allergen-specific T-cell clones derived from skin specimens taken from aeroallergen patch test sites.

TABLE IV. Distribution of APT reactions of 36 patients with atopic eczema related to the allergens used (48 hours)

Allergens	Reactions $\geq +$	Test sites	%	Patients with APT $\geq +^*$
All concentrations and vehicles				
<i>D. pteronyssinus</i>	33	144	22.9	13
Cat dander	13	144	9.0	9
Grass pollen	11	144	7.6	7
Total	57	432	13.2	17
10,000 PNU/gm in petrolatum				
<i>D. pteronyssinus</i>	13	36	36.1	13
Cat dander	8	36	22.2	8
Grass pollen	6	36	16.7	6
Total	27	108	25.0	15

*Nine patients had multiple reactions.

TABLE V. Correlation of clear-cut positive APT reactions (48 hours) with prick test ($\geq +$) and CAP-RAST (≥ 2) results in 36 patients with atopic eczema

	Number of patients with		
	APT +	APT -	Total
<i>D. pteronyssinus</i>			
Prick test +	8	12	20
Prick test -	5	11	16
Total	13	23	36
RAST +	10	8	18
RAST -	3	15	18
Total	13	23	36
Cat dander			
Prick test +	7	17	24
Prick test -	1	11	12
Total	8	28	36
RAST +	5	9	14
RAST -	3	19	22
Total	8	28	36
Grass pollen			
Prick test +	4	20	24
Prick test -	2	10	12
Total	6	30	36
RAST +	4	19	23
RAST -	2	11	13
Total	6	30	36

Test preparation: 10,000 PNU/gm allergen in petrolatum

Some groups have shown that APT results correlate well with elevated levels of specific IgE to certain aeroallergens.^{10, 20, 22} More complex relations between APT reactivity, specific IgE, and morphologic findings were described by Imayama et al.¹¹ who divided patients into four groups: two groups with positive APT reactions and high or low mite-specific IgE and two groups with negative APT reactions, with or without specific IgE. It was noted that clinical morphologic findings were peculiar to three of the groups. The authors conclude

that dust mite antigens may be involved in the development of skin lesions.

The patient's history regarding exacerbation of eczematous skin lesions after aeroallergen contact was of little help in distinguishing patients with positive or negative APT reactions, with regard to either *D. pteronyssinus* or the other allergens. However, only a few patients had isolated reactions to cat dander or grass pollen in this study, whereas the majority reacted to house dust mite, which is not easily recognized as an allergen by

patient's history alone. Our results for a larger group of patients sustain these findings.⁹ Rasp²⁷ found similar difficulties with history for diagnosis of perennial nasal allergy.

Some patients with negative skin prick test responses showed clear-cut positive APT reactions (Table V). They also had low specific IgE levels in their serum. In three of 13 patients with positive APT reactions to mite, the corresponding CAP-RAST result was negative. This shows that a high level of allergen-specific IgE in serum is not mandatory for a positive APT reaction. This allows the conclusion that the APT may provide further diagnostic information in addition to patient's history and prick test and in vitro test results.

The rate of 47% patients with clear-cut positive APT reactions in our data demonstrates that under certain galenic test conditions, allergen penetration is possible without irritating physical or chemical skin alteration such as tape stripping of the stratum corneum or addition of detergents to the test preparations.

Mite allergen in the epidermis under natural conditions,²⁸ as well as in APT sites,^{10, 20} has been demonstrated in proximity to Langerhans cells.

Langerhans cells carry IgE receptors of different classes.^{20, 29, 30} This might explain IgE-associated activation of allergen-specific T cells finally leading to eczematous skin lesions in the APT.

The time course of an APT reaction resembles a 24-hour skin reaction to foreign protein, which was described by Jones and Mote in 1934.³¹ A late-phase allergic reaction may contribute to the clinical picture.

The dose-response analysis shows that 10,000 PNU allergen per gram was superior to 1000 PNU/gm. Depending on the kind of allergen commercially available, prick test solutions contain markedly lower concentrations. Consequently, these solutions may not lead to optimal results. Van Voorst Vader et al.²² also obtained better APT results with high allergen concentrations. Because their study was performed with tape stripping of skin, (8 to 15 times), nonspecific reactions were frequently observed.

The vehicle is obviously critical for the APT. Contrary to one hypothesis that protein allergens might be transported better in a hydrophilic ointment, we found significantly better results with a lipophilic vehicle (petrolatum).

Allergen concentrations of more than 1000 PNU/gm with petrolatum as vehicle seem to improve the yield of positive APT reactions independently of each other. The results show that aeroal-

lergens are able to elicit eczematous skin lesions on unchanged skin in a subgroup of patients with atopic eczema. Clear-cut reactions were seen in patients with atopic eczema only but not in patients with respiratory atopy or control subjects. It can be concluded that the APT may provide further diagnostic information in addition to patient's history and skin prick test and RAST results. With a standardized APT the actual clinical relevance of IgE-mediated sensitizations for the eczematous skin lesions might be evaluated. The reproducibility of this test procedure must be evaluated further and will be proved in a multicenter study, which is in preparation. In addition, the APT will then be validated by double-blind patch test readings and comparison of the APT results of different investigators in the same patient (interobserver variation).

Future studies with specific provocation and elimination procedures must be performed before this instrument can be recommended for routine clinical diagnosis.

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