

Reliability of skin prick tests during terfenadine treatment in adults with pollen rhinitis

A clinical study

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The variation in skin prick test (SPT) results was evaluated clinically during terfenadine treatment in 39 adult patients with pollen rhinitis. A change in the perceived state of the patient as regards sensitization to a specific pollen allergen or atopic constitution was judged to be clinically important. A randomized, double-blind, crossover design was used, comprising 2 weeks on terfenadine 120 mg once a day and 2 weeks on placebo. SPT for two pollen allergens and histamine (10 mg/ml) were evaluated at the start of the study and at the end of each period. When SPT was used as a discovery test and liberal definitions were applied, predictive values for a positive test were 100%. Sensitivity ranged between 10 and 54% with substantially lower values when a histamine wheal reaction was noted. The inhibitory effect of terfenadine was detectable 2 weeks after withdrawal as a reduction in the median of the mean diameter for the histamine-induced wheal response of 1 mm (0–1.5). The data implied that a *positive* SPT is reliable when liberal definitions are adopted for sensitization and atopy; a *negative* SPT is presumably reliable when the measurement artifact is considered and the wheal reaction to histamine is detectable.

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To achieve unbiased skin prick test(s) (SPT), one should withdraw systemic antihistamine treatment before testing (9); with terfenadine, at least 3 days is advised (2, 10, 12). The withdrawal period disturbs rational planning of test application and may inconvenience patients. It might be interesting to find out how much clinical information is actually lost by doing SPT during terfenadine treatment. The main purpose of the present study was to determine the loss in clinical information by doing SPT in adult patients with pollen rhinitis during treatment with terfenadine.

Material and methods

Patients

Forty patients were selected from the files of the allergy clinic of the Department of Respiratory Medicine, Aalborg Hospital, Aalborg, Denmark. *Inclusion criteria* were as follows: 1) seasonal rhinitis;

2) positive SPT to at least two pollen allergens, including the clinically suspected allergen(s) and no reaction to a negative control shown *within the last year*; 3) age between 17 and 55 years; 4) no major complicating diseases; 5) no pregnancy or breastfeeding; 6) no antihistamines, systemic or local steroids, tricyclic antidepressants, or systemic β_2 -agonists administered within the month before the trial; and 7) informed consent given in accordance with the Helsinki Declaration. *Exclusion criteria* were as follows: 1) adverse reactions to terfenadine, 2) pregnancy, 3) recent disease or need for medical treatment interfering with SPT, 4) informed consent withdrawn, or 5) lack of compliance with the study protocol.

Design

The study was conducted out of the pollen season (October–December 1990) as a randomized placebo-

controlled, double-blind, crossover study. The patients were divided into two groups; by an envelope method, half the patients within each group was assigned to a sequence of 2 weeks on terfenadine – two tablets of 60 mg in the morning – immediately followed by 2 weeks on placebo tablets; synchronously, the other half of the patients was assigned to the opposite sequence. Medicine compliance was measured by tablet counting.

Skin prick test

SPT was done thrice in each patient: in the normal situation at the start of the trial (occasion N) and at the end of the terfenadine and placebo periods (respectively, occasions T and P). In each patient, SPT were done as a single application of 10 common pollen allergens (Phazet, Pharmacia) before two allergens only were chosen for further consideration. Negative and positive controls (Phazet, histamine 10 mg/ml) were done routinely; in all respects, standard procedures and routine conditions were aimed at. The tests were done at the same time of the day.

Evaluation of SPT. The wheal area was computed as the product of the largest diameter and its midpoint orthogonal diameter; a wheal area $\leq 7 \text{ mm}^2$ was deemed to be insignificant (5). The result of SPT was stated as a *score class*, defined by the ratio between the wheal areas for the specific allergen in relation to the histamine control. A ratio between 0.75 and 1.25 defined score class 2 as the reaction equivalent to the histamine control; a larger or smaller ratio defined score classes 3 or 1, respectively; score class 0 was used for an insignificant reaction to a specific allergen. Score class 3 was also used when a significant reaction to a specific allergen occurred with an insignificant reaction to histamine.

Arbiter for SPT. The standard or “true” score class was defined by the combined score class achieved at occasions N and P, as shown in Table 1, left column.

Inhibitory effect of terfenadine. A mean diameter for the wheal reaction was calculated to evaluate the inhibitory effect: the largest diameter (d) and its midpoint orthogonal diameter were averaged: $(d_1 + d_2)/2$.

Definitions

Clinical information. The purpose of doing SPT was believed to be dual: to look for a sensitization to a specific allergen and to reveal an atopic constitution. Thus, a change in clinical information referred to a substantial change in either the sensitization to a

Table 1. Distribution of score classes for 78 SPT in 39 adult patients with pollen rhinitis on three occasions: normal situation, after placebo treatment, and after terfenadine treatment. Spaced column between score classes 1 and 2 denotes cutoff level for positive SPT. Two spaced rows denote two cutoff levels for “true” status of SPT achieved on occasions N and P; respectively, upper and lower levels refer to strict or liberal definition (see text)

Occasion						
Normal and placebo (score classes)	Terfenadine (score classes)				Total	% Suppressed
	3	2	1	0		
3-3	11	1	0	6	18	33
3-2	10	1	1	6	18	33
2-2	3	0	0	4	7	57
3-1 or 3-0	3	0	0	5	8	63
2-1	0	0	0	2	2	100
1-1, 1-0, or 0-0	0	0	0	25	25	100
Total	27	2	1	48	78	

specific allergen or the atopic condition as identified by a substantial change in SPT (see below).

Sensitization to a pollen allergen. A *positive SPT* was defined by at least score class 2, and a *negative SPT* by score class 0 or 1. The “true” SPT was deemed to be positive (negative) if positive (negative) at occasion N or P (liberal criterion) or N and P (strict criterion). A clinically substantial *change* was defined as a change between positive and negative SPT.

Atopic status. Atopy was present if at least one of the two SPT was positive; “true” atopy was defined as present (absent) if present (absent) at occasion N or P (liberal criterion) or N and P (strict criterion). Any *change* in status was considered to be clinically important.

Test evaluation. Reliability was here defined as the trustworthiness of a test to serve the clinical purpose for which it was done. Thus, a defined “true” status or standard was a necessity. The evaluation followed recommended procedures and terms (4, 6). *The quantity of interest was a change in sensitization to a specific allergen or atopic condition during terfenadine treatment.*

The tests used were SPT and atopic condition as two-class tests. The predictive value of a positive (or negative) test PV_{pos} (PV_{neg}) was the percentage of all positive (or negative) test results which were verified as “true” positive (or negative) results. 1-Sensitivity was the percentage of false negative test results among all verified “true” positive states (sensitization to a specific allergen or atopic condition) in the study.

Statistics

Differences between rates were tested by Fisher’s exact test, paired data by Pratt’s test, and unpaired data by the Mann-Whitney test (11). Tests were done two-tailed with a chosen significance level of 0.05; for comparison of medians among several groups, mass significance was dealt with by the method of Bonferoni, and tests were done one-tailed (7). In the following data, figures in square brackets denote 95% confidence intervals (97.5% at the extremes), binomial distribution assumed.

Results

Thirty-nine patients completed the study; one patient was excluded for lack of compliance. No indication of poor medicine compliance was found.

At occasion T, after 2 weeks of terfenadine treatment, insignificant wheal reaction to histamine was noted in 27 patients (69% [52–83]), and a detectable reaction was seen in 12 (partly suppressed in nine (23% [11–39]) and unchanged in three patients (8% [2–21])); in 11 of the patients with insignificant histamine reaction, at least one positive SPT was noted.

Score classes

Within each of the two patient groups, no statistically significant *period effects* were found: no *carry-over effect* was present when the sequences P,T and T,P were tested.

Table 1 shows the changes in “true” score classes after terfenadine treatment: 48 of 78 SPT (62% [50–72]) were fully suppressed, including nine SPT which also had score class 0 at occasions N and P; 20 SPT remained unchanged at all three occasions (26% [16–37]). With decreasing “true” score class, an increasing fraction of SPT was fully suppressed ($P < 0.05$).

Sensitization to a pollen allergen

Table 2 shows the clinical information on specific sensitization during terfenadine treatment. *Top*: the results in 54 SPT (27 patients) with no histamine reaction were, respectively, for liberal and strict criteria, $PV_{pos} = 100\%$ [79–100] and 81% [54–96], 1-sensitivity = 54% [37–71] and 50% [30–70]. *Bottom*: the results in 24 SPT (12 patients) with detectable histamine reaction were $PV_{pos} = 100\%$ [79–100] and, respectively, for liberal and strict criteria, 1-sensitivity = 28% [10–54] and 24% [7–50]. In the latter patient group (bottom), 1-sensitivity was substantially lower than in the former group for both liberal and strict criteria (respectively, $P = 0.12$ and

Table 2. Sensitization to pollen allergens. “True” status of SPT by liberal criterion and SPT after terfenadine treatment; figures in parentheses refer to result when strict criterion was adopted (see text). Top: result for 54 SPT in 27 patients with no histamine reaction. Bottom: result for 24 SPT in 12 patients with detectable histamine reaction

“True” SPT	Terfenadine treatment		Total
	Positive	Negative	
Positive	16 (13)	19 (13)	35 (26)
Negative	0 (3)	19 (25)	19 (28)
Total	16	38	54

“True” SPT	Terfenadine treatment		Total
	Positive	Negative	
Positive	13 (13)	5 (4)	18 (17)
Negative	0 (0)	6 (7)	6 (7)
Total	13	11	24

0.15); in both situations, a reduction in 1-sensitivity of 26% [about 0–53] was achieved. PV_{neg} was between 50 and 66% in the four situations.

Atopic status

Table 3 shows the clinical information for atopic status during terfenadine treatment. *Top*: the results in 27 patients with no histamine reaction were, respectively, for liberal and strict criteria, $PV_{pos} = 100\%$ [72–100] and 91% [59–99], 1-sensitivity = 50% [28–72] and 47% [24–71]. *Bottom*: the results in 12 patients with detectable histamine reaction were $PV_{pos} = 100\%$ [79–100] and, respectively, for liberal and strict criteria, 1-sensitivity = 18% [2–52] and 10% [1–44]. In the latter patient group (bottom), 1-sensitivity was substantially lower than in the

Table 3. Atopic patient status. “True” status for atopy by liberal criterion and observed status after terfenadine treatment; figures in parentheses refer to result when strict criterion was adopted (see text). Top: result for 27 patients with no histamine reaction. Bottom: result for 12 patients with detectable histamine reaction

“True” atopy	Terfenadine treatment		Total
	Present	Absent	
Present	11 (10)	11 (9)	22 (19)
Absent	0 (1)	5 (7)	5 (8)
Total	11	16	27

“True” atopy	Terfenadine treatment		Total
	Present	Absent	
Present	9 (9)	2 (1)	11 (10)
Absent	0 (0)	1 (2)	1 (2)
Total	9	3	12

Table 4. Reproducibility of 40 SPT from sequence N,P,(T) measured in normal situation and after placebo treatment

		Placebo		Total
		Positive	Negative	
Normal	Positive	22	6	28
	Negative	0	12	12
Total		22	18	40

former group for both liberal and strict criteria (respectively, $P = 0.16$ and 0.10); in both situations, this implies a reduction in 1-sensitivity of approximately 35% [0–64].

PV_{neg} was between 31 and 67% in the four situations.

Reproducibility

Table 4 shows the reproducibility of SPT measured for the sequence N,P,(T) at occasions N and P: kappa = 0.67 [0.46–0.92].

Carry-over effect

The distribution of score class differences P–N and P–T for the sequences N,(T),P and N,P,(T) (not shown) favors positive values in the N,(T),P sequence ($P = 0.04$; difference between rates: 21.6% [4.1–39]).

Table 5 shows the median values for the mean diameters of the wheal reactions induced by histamine and pollen. Allergen I had a median value just above the histamine value, and allergen II just below. *Histamine-induced response:* in the N,(T),P sequence, occasion P was significantly lower than occasion N or the P situation in sequence N,P,(T); in both cases, the difference for the median of the mean diameters

Table 5. Wheal reactions (mm). Median values for mean diameters of wheal reaction measured in 78 SPT from 39 patients with pollen rhinitis. Wheal responses induced by histamine and two allergens are shown in rows. Columns state measurements performed at occasions N and P specified for N,(T),P and N,P,(T) sequences, respectively. Square brackets denote 95% confidence intervals; * denotes $P < 0.05$

Sequence	Wheal reaction (mm)			
	N,T,P		N,T,P	
	Normal	Placebo	Normal	Placebo
Histamine	6.5 [5.5–7.0]	5.5* [5.0–6.0]	6.5 [5.5–7.5]	6.5 [5.5–6.5]
Allergen I	7.0 [3.0–9.0]	6.0 [4.0–7.0]	8.0 [5.0–9.0]	6.8 [4.5–8.5]
Allergen II	5.0 [0.0–7.0]	4.5 [3.0–5.5]	5.3 [3.5–8.5]	5.5 [3.5–6.5]

was 1 mm [0–1.5]. *Pollen-induced response:* in the N,(T),P sequence, occasion P for both allergens was not significantly lower than occasion N or the P situation in sequence N,P,(T) (in all cases, $0.09 < P < 0.94$); exclusion of the zero values from the calculations did not change the final result.

Discussion

The present study was initiated to solve an everyday clinical problem: how much does antihistamine treatment blur the clinical information yielded by SPT? In all respects, standard procedures and routine conditions were intended to secure a clinically relevant answer; e.g., the use of only a single application of allergen in SPT instead of at least quadruplicate tests, as recommended for scientific purposes. The use of relative quantities and the lack of an external quality-control system require a cautious interpretation (1, 9, 13); furthermore, a conservative attitude should be adopted to the scientific inference of the results from a crossover study (6).

We found insignificant histamine reaction in 69% of the patients during treatment with terfenadine in the recommended dose of 120 mg a day. In a similar study comprising 25 children with pollen rhinitis, 32% of the patients had no reaction to histamine 10 mg/ml during treatment with terfenadine 30 mg twice daily (8). No reaction to histamine 1 mg/ml was seen in 76% of the patients; no relation between body weight and wheal area was found (8). In 12 patients, a significantly greater skin test suppression of mainly histamine was claimed when terfenadine 300 mg twice daily was compared with 60 mg twice daily (3).

No substantial period or carry-over effects were present when the score classes or changes in score classes were considered after the placebo or terfenadine periods, and no period effect was present for occasions N and P. However, a carry-over effect was shown for the differences in score classes between the placebo and normal situation: P–N: fewer positive values in the N,P,(T) sequence than in the N,(T),P sequence were found. As the N,P,(T) sequence model is a regular reproducibility trial, the finding of a skewed distribution must be considered to be the true distribution of the differences in the actual setting. Consequently, the N,(T),P sequence may have too many positive values, suggesting an increased wheal reactivity to specific allergens or a reduced reactivity to applied histamine in the P situation; in fact, the latter was found (Table 5). This finding suggests that the effect of terfenadine is detectable 2 weeks after withdrawal, a period substantially longer than previously reported (2, 10).

Occasions N and P in the N,P,(T) and N,(T),P sequences were placed, respectively, 2 and 4 weeks

apart; we find this bias without importance (Table 2). The data suggest that the wheal reaction induced by histamine or allergen may react differently to terfenadine; however, the study was not designed to address this issue, and improved trials are needed.

The clinical purpose of doing SPT in seasonal rhinitis is assumed to be dual: to identify patients sensitized to a specific pollen allergen or to detect an atopic constitution. Determining the influence of terfenadine on these clinical issues was the primary aim of the study. The verification of the "true" state or standard for these issues is not universally agreed upon, and both liberal and strict criteria were used to reflect the relativity of the arbiters. Irrespective of the purpose, the probability of PV_{neg} was found to equal the tossing of a coin, indicating that the performance of SPT as an *exclusion test* is not worthwhile during terfenadine treatment (Tables 2 and 3).

Perfect values for PV_{pos} were achieved when SPT was used as a *discovery test* and a liberal criterion was adopted, irrespective of the clinical purpose of the test (Tables 2 and 3); the price to be paid is revealed by 1-sensitivity. Substantially lower values for 1-sensitivity were found when the histamine reaction was detectable than when not (Tables 2 and 3; bottom and top), indicating a more reliable result; in fact, in the former situation, measurement artifact alone may explain the deviation from an ideal fit (Table 4).

In conclusion, we think that positive SPT during conventional terfenadine treatment is clinically reliable when a liberal definition of sensitization to pollen allergens and atopy is employed. A negative SPT may be reliable when the histamine reaction (10 mg/ml) is visible and the measurement artifact is taken into consideration.

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