

Evaluation of a Self-Test Device Used in Allergic Contact Dermatitis

Peter Elsner^a Henriette Bjarnøe^c Werner Aberer^d Jochen Brasch^b

^aDepartment of Dermatology, University Hospital Jena, Jena, ^bDepartment of Dermatology, University Hospital Kiel, Kiel, Germany; ^cSmartpractice, Hillerød, Denmark; ^dDepartment of Dermatology, Medical University Graz, Graz, Austria

Key Words

Contact dermatitis · Patch testing · Self-test · Diagnostic device

Abstract

Considering the scarcity of dermatologic resources in many parts of the world, self-testing by patients is not only of interest for internal medicine but also for dermatology. In this open, nonrandomized, multicenter diagnostic trial involving subjects with suspected contact sensitization to nickel and/or a fragrance mix, we assessed the agreement of self-testing by subjects with readings made by dermatologists. The self-test product (NixemaTM) is based on Thin-Layer Rapid Use Epicutaneous Test (TRUE Test[®]) technology. One hundred and sixty-five subjects self-tested the ready-made patch-test product. The test was applied for 48 h and then read after 3 or 4 days. It was also evaluated independently by experienced dermatologists after 3 or 4 days. In the 162 evaluable subjects, the proportion of agreement for both allergens together was 89.5% [95% confidence interval (CI) 83.7–93.8], the sensitivity was 97.5 % (95% CI 86.8–99.9) and the specificity was 86.9% (95% CI 79.6–92.3). Cohen's kappa was also high at 0.749 (95% CI 0.637–0.862). Discrepancies between

the subjects' readings and the dermatologists' readings were mainly due to the subjects interpreting reactions of 'irritant' or 'doubtful' as 'positive'. Apart from itching and burning sensations and tape irritation, no side effects were observed. In conclusion, this study showed a high rate of agreement between the self-reading of the upper arm and the readings made by the dermatologists. The upper arm proved to be an appropriate area for self-testing. Self-testing may improve the screening for contact sensitization for patients, particularly where dermatologic health resources are scarce.

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Introduction

Patch self-testing is widely practiced in medicine. Diabetic patients test their own blood glucose in order to adjust insulin dose [1], and patients on anticoagulation medication test their international normalized ratio [2]. For assessing field loss in glaucoma patients, a computer-based FDA-registered perimetry device for self-testing by patients is available, which shows a high degree of correlation with the standard Humphrey visual-field analyzer [3]. In infectious medicine, self-testing has the potential

to be an innovative component of HIV-prevention strategies in communities [4].

Self-testing is of proven benefit where the involvement of the patient is necessary for the management of chronic diseases such as diabetes or coagulopathy. It may also be beneficial in the screening for diseases when the quantity or quality of medical resources is not sufficient to satisfy the demand. This is the case in many countries that have long waiting lists for dermatologic services for contact dermatitis sufferers. The mere existence of waiting lists may deter patients from seeking medical advice. Only about half of the women believed to be suffering from an allergy to nickel or fragrances consult their general practitioner with the problem, and only about 22% of these are referred to a dermatologist for further evaluation [5]. In 5 countries in the European Union where this issue has been investigated, the number of subjects referred to dermatologists varies between 14% (UK) and 45% (Spain). There seems to therefore be an underdiagnosed group of a considerable size. Patch self-testing is a potential way to tackle problems due to allergies as well as reducing numbers on waiting lists and enabling dermatologic care to focus on patients with greater needs.

An over-the-counter product for patch self-testing by patients has been developed on the basis of the Thin-Layer Rapid Use Epicutaneous Test (TRUE Test®) introduced by Fisher and Maibach [6] in 1985. In this test, the allergens are incorporated into a thin, flexible, solid vehicle on a water-impermeable backing. The TRUE Test produces an exact dosage, an even surface spread and high bioavailability for the allergens. It is a ready-made, easy-to-use test that has been employed extensively in patch testing by dermatologists for 2 decades, and extensive documentation is available on its safety, sensitivity and specificity [7].

The 2 allergens that are most frequently patch-test-positive in the European population are nickel and fragrance mix. These allergens were incorporated into the new patch self-test.

In order to evaluate the suitability of the test as an over-the-counter product, this study aimed to examine the agreement of the subjects' self-readings on the upper arm with readings made by dermatologists.

Materials and Methods

Study Design

The study was an open, phase IV, nonrandomized, multicenter, diagnostic trial, carried out in Jena and Kiel in Germany and Graz in Austria. The subjects served as their own control, i.e. they were tested with 2 identical test tapes at the same time. The readings of

the subjects were compared with the readings of the investigators. The study was approved by the ethical commissions of the study centers involved.

Subject Population

Eligible subjects were found by advertising in local newspapers. People of either sex, aged ≥ 18 years, with self-suspected allergy towards fragrance and/or nickel were recruited after providing oral and written informed consent.

All subjects were excluded who had previously had positive patch tests to fragrance and/or nickel, were on topical treatment with corticosteroids in the 2 weeks prior to the study (on or near the test area), had been on systemic treatment with corticosteroids, antihistamines and/or immunosuppressive agents during the last 7 days or had received ultraviolet light treatment during the last 3 weeks, had dermatitis on the test area or widespread active dermatitis, were breast-feeding or pregnant and also those who had shown a lack of cooperation or participation in other clinical trials during this study period and 3 weeks prior to inclusion.

It was planned that 200 subjects would be included who were suspected of suffering from allergic contact dermatitis caused by fragrances ($n = 100$) or nickel ($n = 100$).

Allocation of Subjects

Subjects were allocated to the fragrance-mix or nickel group on the basis of their own evaluation of symptoms. They were asked by the investigator what symptoms they had and if they believed they were sensitive to fragrances or nickel. Those who believed they were sensitive to both fragrance mix and nickel were allocated to the fragrance-mix group. No randomization took place.

Test Materials

The test panel consisted of surgical tape, approximately 5 cm $\times$ 5.5 cm, with 4 patches fixed to it. Each patch measured 0.81 cm² and contained either nickel sulfate (0.20 mg/cm²) or a fragrance mix (0.43 mg/cm²: geraniol, cinnamaldehyde, hydroxycitronellal, cinnamyl alcohol, eugenol, isoeugenol, α -amyl-cinnamaldehyde and oak moss) incorporated into a gel coated onto a polyester sheet. Two of the patches were without allergens (negative controls). The test panels were provided by the manufacturer Mekos Laboratories AS, Hillerød, Denmark.

Test Procedure

Two test tapes were applied for 48 h, which is the recommended exposure time for patch testing [8]. One was applied on the upper arm and one on the upper back.

The subject applied and removed the test panel on the outer upper arm by following written instructions and without support from the investigator or other health professionals. They filled in a questionnaire with details: the time of application and removal of the patch, side effects, results and any comments regarding the instruction material. They removed the test tapes after 48 h and read and noted the test results after 3–4 days (i.e. 72–96 h).

Concurrently with the application of the test tape on the upper arm, the investigator applied the test panel on the back of the subject, removed it after 2 days (approx. 48 h) and then read the result after 3–4 days (72–96 h). Reading and noting the result of the test patch on the upper arm were performed by the investigator during the visit before they read the results of the test patch on the back.

Reading of the Patch Tests

The reading of the patch test on the upper arm was performed by the subjects according to the written instructions provided with the patch test. No further instruction was given by the investigators.

All readings by the investigators of patch-test sites were graded according to the recommendations of the International Contact Dermatitis Research Group with the only difference that the reading '+' was omitted in order to make it possible to compare the investigator's reading with the subject's, as subjects only had the possibility to answer 'positive' or 'negative'.

Primary End Point

The investigator evaluated the subject's upper arm and scored each of the 4 patches as 1 of the following: 'negative', '+', '++', '+++', 'irritant' (5 levels). These 5 levels were reduced to 2: negative (negative/irritant) and positive (+/++/+++), in order to compare the results read by dermatologist and subject. The subject scored each of the 4 patches on the upper arm as either 'positive' or 'negative' (2 levels).

The primary end point was considered a success when the corresponding evaluations from the subject and the dermatologist were obtained.

Adverse Events

At all visits, subjects were questioned regarding adverse events, worsening of preexisting disease and changes in concomitant medication.

Dropouts

A subject could be withdrawn from the study if, in the investigator's opinion, this was in the interests of the subject, unacceptable adverse events occurred or the subject requested it. If a subject did not appear at the appointed visit, the investigator was to try to contact the subject in order to make a new appointment within the time frame of the study. The reason for withdrawal from the study was clearly described on the case-report form and in the screening log.

Statistical Methods

Statistical Evaluation

The data were summarized as the number and percentage of patients at each center and in each allergy group as well as across centers and allergy groups. The primary end point was analyzed by means of a 2×2 cross tabulation of the dermatologist's and the patient's classification of the reactions as positive or negative. For each such table, the proportion of agreement, sensitivity and specificity with 95% confidence intervals (CIs) based on binomial distributions were calculated. As an alternative measure of the agreement between the readings made by the dermatologist and the patient, Cohen's kappa with 95% CI was calculated. The difference between the proportions found positive by the investigator and the patient was tested by McNemar's test.

The analysis was performed on a 2×2 table of the patients with a suspected allergy to nickel (based on readings of patch 1) and another of the patients with a suspected allergy to fragrances (based on readings of patch 6) as well as both of these tables combined. In this way, only the reading from 1 patch from each patient was included. This secured statistical independence and valid tests and CIs. In addition, it was considered of interest to

evaluate the 2×2 tables of the readings of both patch 1 and patch 6. This was done separately for the nickel and fragrance-mix allergy groups as well as for both groups combined. In this way, 2 readings were included from each patient, and it is open to question whether 2 such readings are statistically independent. Therefore, we had some reservations about the validity of the tests and CIs. The different estimates of the agreement between the readings made by the dermatologist and the patient were, however, not influenced by this problem. Finally, the 2×2 tables constructed from the readings of all 4 patches were also analyzed; the uncertainty persisted as to whether the 4 readings by the dermatologist or the patient could be regarded as statistically independent.

The first secondary end point was analyzed in essentially the same way as the primary one. It was, however, not considered meaningful to calculate estimates of sensitivity or specificity of the dermatologist's readings of the patches on the arm relative to those on the back or vice versa. Thus, only the proportion of agreement and the kappa value with 95% CIs as well as McNemar's test were calculated. With regard to the second secondary end point, the rates of false-positive and false-negative readings were calculated for the patient's readings of the patches on the arm relative to the dermatologist's readings of the corresponding patches on the back. The proportion of agreement was also calculated, and 95% CIs were calculated from the binomial distributions. When these secondary end points were analyzed based on readings of >1 patch, there was again the issue of statistical independence, giving rise to our reservations about the tests and CIs.

The last secondary end point regarding the adhesiveness of the test tape was analyzed by comparing the frequency of observed loosening, reinforcement or falling-off of test tapes from two suppliers. These analyses were made by Fisher's exact test.

Determination of Sample Size

A clinically relevant proportion of agreement was judged to be 85%. From a binomial distribution ($n = 200$), the lower 95% confidence limit of the proportion of agreement was calculated. Given the alternative that the true proportion of agreement was 85%, the estimate fell >75% with a power of at least 85%.

Results

The study was planned to include 100 patients with a suspected allergy to nickel and 100 with a suspected allergy to fragrances, in order to secure sufficient power to detect a proportion of agreement exceeding 75% when the true proportion was 85%. However, it was decided to stop at 165 patients because the rate of recruitment became unacceptably slow.

One hundred and sixty-five subjects, all Caucasian, were included in the study, i.e. 133 women (81%) and 32 men (19%) were tested; 163 of these completed the study and 2 were lost to follow-up, 1 because the test tape fell off after 2.5 h and the other did not return after the first visit (for undetermined reasons). One subject did not per-

Table 1. Agreement between the dermatologists' and the subjects' readings of the nickel patch

Patients' readings	Dermatologists' readings, n (%)		
	positive	negative	total
Positive	34 (39)	7 (8)	41 (47)
Negative	1 (1)	46 (52)	47 (53)
Total	35 (40)	53 (60)	88 (100)
			95% CI
Proportion of agreement		90.9%	82.9–96.0
Sensitivity		97.1%	85.1–99.9
Specificity		86.8%	74.7–94.5
Cohen's kappa		0.816	0.694–0.937
McNemar's test: H ₀ = equal rates of positive readings. p = 0.034			

form the required self-reading of the patch test, so a total of 162 patients were included in the efficacy analysis, i.e. 74 from the fragrance-mix group and 88 from the nickel group. The analysis set thus consisted of all patients who did not violate the protocol or withdraw before the efficacy assessments were performed.

Primary End Point: Agreement of the Subjects' Readings with the Dermatologists' Readings on the Arm

Table 1 shows the agreement between the dermatologists' and the subjects' readings of the nickel patch on the arm. The proportion of agreement was 90.9% (95% CI 82.9–96.0), the sensitivity 97.1 % (95% CI 85.1–99.9) and the specificity 86.8% (95% CI 74.7–94.5). Cohen's kappa was also high at 0.816 (95% CI 0.694–0.937). A kappa value exceeding 0.80 is considered as indicating very good agreement whereas a value of 0 corresponds to agreement only by chance. McNemar's test results indicated that the subjects' self-reading gave a significantly higher rate of positive results than that made by the dermatologists.

In the group with a suspected allergy to fragrances (table 2), there were relatively few positive cases. Nevertheless, an agreement of 87.8% (95% CI 78.2–94.3), sensitivity of 100.0% (95% CI 54.9–100.0) and specificity of 87.0% (95% CI 76.7–93.9) are still rather high. The kappa value, 0.474 (95% CI 0.152–0.796) was moderate, although still statistically significant. The highly significant outcome of McNemar's test shows that the positive rate of the subjects' readings (19%) was clearly higher than the rate of the dermatologists' readings (7%).

Table 2. Agreement between the dermatologists' and the subjects' readings of the fragrance-mix patch

Patients' readings	Dermatologists' readings, n (%)		
	positive	negative	total
Positive	5 (7)	9 (12)	14 (19)
Negative	0 (0)	60 (81)	60 (81)
Total	5 (7)	69 (93)	74 (100)
			95% CI
Proportion of agreement		87.8%	78.2–94.3
Sensitivity		100.0%	54.9–100.0
Specificity		87.0%	76.7–93.9
Cohen's kappa		0.474	0.152–0.796
McNemar's test: H ₀ = equal rates of positive readings. p = 0.0027			

Assessing both groups together (table 3), the agreement, sensitivity and specificity remained very high, with the kappa value characterized as good and highly statistically significant. McNemar's test became even more statistically significant, indicating that the rate of subjects' positive readings was higher than for the readings made by the dermatologists.

Regarding the primary end point of the study, the results reported in the tables above show that the proportion of agreement (i.e. 'success') was well above 85%. The kappa value may be regarded as a more appropriate estimate of the agreement, since it includes a correction for random agreement. The kappa values were moderate in the group with suspected allergy to fragrances but good for the suspected allergy to nickel and for the test as a whole. Even the lower kappa value for the fragrance-mix patch was statistically significantly different from 0. The estimates of sensitivity were well above 80%. The specificity was also high at 86–87%. Finally, it should be noted that McNemar's test of equal frequency of positive readings clearly showed that the subjects' self-readings gave a higher rate than the dermatologists' readings. This difference will be analyzed further.

Agreement of the Dermatologists' Readings on the Arm and the Back

Table 4 shows the results of analyses of the agreement between the dermatologists' readings of the corresponding patches on the back and upper arm. Overall, the agreement between the dermatologists' readings of the corresponding patches on the back and upper arm was very good according to the kappa values and the propor-

tion of agreement. Moreover, very few of the patches with negative controls to nickel or fragrances were read as positive.

Agreement of the Dermatologists' Readings of the Patch on the Back and the Patients' Readings of the Patch on the Arm

By regarding the reading made by the dermatologist of the patches on the back as the 'true' state of allergy, the rates of false-positive and false-negative patient self-readings were calculated for both allergens combined (table 5). The proportion of agreement was very high at 88.7%. False-negative results were rare (2.9%) and false-positive results were slightly higher (8.3%).

Safety Evaluation

No adverse events or serious adverse reactions were observed during the 3–4 days of observation.

The only side effects observed were itching and burning sensations at the positive test areas, as anticipated, and also irritation from the surgical tape. Almost all subjects experiencing a positive reaction on the upper arm also reported itching and burning sensations (63/64). All subjects with positive reactions on the upper back reported itching and burning sensations. Of 75 itching/burning sensations reported, none of which required medical treatment, 48 were mild, 16 were moderate and 11 were severe. Fifty-three (33%) subjects experienced tape irritation on the arm and 54 (33%) on the back. Most of the observations, i.e. 37, were weak, 13 were moderate and 4 were severe.

Subjects' Comments on the Test Instructions

One hundred and twenty-five (76%) of the subjects considered the instructions concerning the application and the reading to be adequate and 40 (24%) considered them to be inadequate. The most frequent criticism was that the information on how to apply the test was too detailed, and that the information regarding evaluation of the skin area should be improved.

Discussion

Self-testing serves different purposes. It can be used for self-management of chronic diseases, such as blood-glucose monitoring by patients. With these tests, especially if the results lead to the application of potentially dangerous medication such as insulin injections, the characteristics have to be identical with what is used in profession-

Table 3. Agreement between the dermatologists' and the subjects' readings of the nickel and fragrance-mix patches combined

Patients' readings	Dermatologists' readings, n (%)		
	positive	negative	total
Positive	39 (24)	16 (10)	55 (34)
Negative	1 (1)	106 (65)	107 (66)
Total	40 (25)	122 (75)	162 (100)
95% CI			
Proportion of agreement		89.5%	83.7–93.8
Sensitivity		97.5%	86.8–99.9
Specificity		86.9%	79.6–92.3
Cohen's kappa		0.749	0.637–0.862
McNemar's test: H_0 = equal rates of positive readings. $p = 0.0003$.			

Table 4. Agreement between readings of the corresponding patches on the back and the upper arm made by the dermatologist

<i>Nickel</i>		95% CI
Proportion of agreement	89.9%	81.7–95.3
Cohen's kappa	0.795	0.667–0.922
<i>Fragrance mix</i>		95% CI
Proportion of agreement	97.3%	90.6–99.7
Cohen's kappa	0.819	0.572–1.066
<i>Nickel and fragrance mix combined</i>		95% CI
Proportion of agreement	93.3%	88.3–96.6
Cohen's kappa	0.830	0.734–0.927

McNemar's test: H_0 = equal rates of positive readings. $p = 0.096$ (nickel), $p = 0.16$ (fragrance mix), $p = 0.035$ (in combination of both allergens).

Table 5. Agreement between the dermatologists' readings of the corresponding patches on the back and the upper arm and the patients' readings of the patches on the arm

Patients' readings (arm)	Dermatologists' readings (back), n (%)		
	positive	negative	total
Positive	55 (8)	54 (8)	109 (17)
Negative	19 (3)	520 (80)	539 (83)
Total	74 (11)	574 (89)	648 (100)
95% CI			
False-positive		8.3%	6.3–10.7
False-negative		2.9%	1.8–4.5
Proportion of agreement		88.7%	86.0–91.1

al medical practice, in order to avoid mismedication. Self-testing in such situations requires thorough training of patients by health professionals.

Self-screening by patients for pregnancy or potential disease should have reasonable precision. A low rate of false-negative results is important to avoid misleading the patient into the false perception that they are not pregnant or they are free of disease. False-positive patient self-tests are less critical since they may motivate the patient to seek professional medical help. The damage of a false-positive test is limited to unnecessary use of the health system that the patient might have pursued even without self-screening. These self-screening tests should be easy to use, read and interpret.

In this context, the evaluated self-test system for people who suspect that they are allergic to nickel and/or fragrances seems well-suited for the purpose since it shows an excellent agreement between the evaluations made by the subjects and the dermatologists and a low frequency of false-negatives, but also a higher frequency of false-positives. This can be explained by the fact that it is very difficult for the untrained, and even for the trained, to differentiate between irritant and allergic patch-test reactions. All reactions classified as 'irritant' by the dermatologists were read as 'allergic' by the subjects. In 1992, Brasch [9] proposed the reaction index (RI) which is calculated from the numbers of allergic (a), questionable (q) and irritant (i) reactions as follows: $RI = (a - q - i) / (a + q + i)$. The RI for different allergens varies. Ideally, it would be equal to 1, if all the reactions read were allergic reactions. In contrast, allergens with a high proportion of irritant and questionable reactions will have a low RI approaching 0, becoming negative when only questionable and irritant reactions are observed. According to a study on more than 31,000 patients by the German Contact Dermatitis Research Group, the RI for nickel was reported to be 0.69, while the RI for the fragrance mix was 0.53 [10]. However, this study was performed with petrolatum-based allergens. In the TRUE Test, the RI for nickel was 0.91 [10]. Nevertheless, the lower RI for the fragrance mix explains the higher number of false-positives for this allergen in our study.

We considered the dermatologist's reading as the 'true' state of allergy. It has to be kept in mind, however, that the patch test has inherent biological variability, and that even experienced dermatologists may misclassify patch-test reactions. The reproducibility of the TRUE Test has been reported to be very high (99.2% for nickel sulfate) [11]. Gollhausen et al. [12] reported that 43.8%

of positive patch tests were not reproducible, but that the nonreproducibility for petrolatum-based tests was higher (37.9%) than the TRUE Test (17.9%) [13]. In a comparative study in which TRUE Test allergens were used on both sides of the back, 5% of the nickel and 10% of the fragrance-mix reactions were positive-discordant, i.e. positive only on 1 side of the back [14]; again, this was higher than what was reported for petrolatum-based tests [15].

When self-testing is performed on a wide scale with many healthy patients getting tested, safety concerns become of great importance. It is known that patch testing can induce sensitization to very potent allergens like paraphenylenediamine or acrylates. Therefore, testing of these compounds should be limited to selected patients. However, testing for nickel and fragrance-mix allergies does not seem to pose a significant risk of sensitization. In an unpublished German study on 812 patients, no sensitization was induced by testing with the nickel patch (J. Geier, pers. comm.). There are no systematic study data on fragrance-mix. It may be argued, however, that consumers are exposed to fragrance-mix allergens anyway, since these are used in many cosmetic, perfume and household products, even though they must be labeled in the European Union if they exceed certain levels [16]. Patch self-testing therefore does not add a significant risk for the consumer.

The side effects of patch tests include severe reactions, spreading of reactions outside the test area, flare of dermatitis and postinflammatory hypo- and hyperpigmentation. None of these was observed in our study. The only symptoms were itching and burning sensations at the positive test sites and tape irritation, which was to be expected. Nevertheless, the self-test patch device should be accompanied by a detailed brochure informing users about the risks and how to use it.

It is crucial to provide information for the consumer about which conclusions to draw from a positive self-applied patch test. Considering the potential for false-positive readings, subjects with positive readings should be advised to see a dermatologist for further consultation. Not only is it necessary to confirm positive self-tests made by patients with diagnostic patch testing, it is also important to test the single allergens of the fragrance mix when a positive reaction has occurred. Consumers will benefit from the labeling of fragrance allergens in the European Union [16] only if individual fragrance allergens are identified, thus enabling them to choose products that are free of this specific allergen.

Finally, the self-testing consumer will have to be informed that negative readings to the fragrance test do not exclude a fragrance allergy since there are many more potential fragrance allergens.

In conclusion, our study showed a high agreement rate between self-readings of the upper arm by subjects and the readings made by the dermatologists. In general, self-readings gave a higher rate of positive results than dermatologists' readings. This is in line with a similar study from Sweden [17]. The authors attributed it to the interpretation of 'irritant' or 'doubtful' reactions by patients as 'positive'. Using the upper arm as a test area was as efficient and safe as using the upper back. The self-test device was

easy and safe to use. It could improve allergy testing for patients, particularly in areas with scarce dermatologic health resources.

Acknowledgement

The authors kindly thank statistician Aage Vølund, Denmark, for carrying out the statistical analysis.

Disclosure Statement

No conflicts of interest were declared.

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