

Comparative performance of five commercial prick skin test devices

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Five commercially available devices for performing prick skin testing were compared for reproducibility, patient acceptance, occurrence of false-negative skin test results, and size distribution of reactions at the negative control sites. Reproducibility of skin testing with 10 mg/ml histamine base, as expressed by coefficient of variation, was similar. However, a clear range of trauma to the skin was produced by the devices. This trauma was least with the Hollister-Stier and ALK Laboratories lancets, intermediate for the bifurcated needle by either prick or puncture, and greatest for the Multi-Test and DermaPIK devices. The more traumatic devices produced larger mean wheals and more frequent and large reactions at saline control sites, and were less acceptable to subjects. However, except for the Multi-Test device, they less often yielded false-negative responses. It is proposed that for each device a different size of wheal must be produced at the allergen site to have confidence that it exceeds the control site. The wheal size necessary for 99% specificity were as follows: Hollister-Stier lancet, 2 mm; ALK lancet, 3.0 mm; bifurcated needle prick, 4.0 mm; bifurcated needle puncture, 4.5 mm; Multi-Test device, 5.0 mm; and DermaPIK device, 5.5 mm. An additional observation was the presence of a significant gradient of reaction size on the back to both histamine and allergen ($p < 0.0001$), with the smallest reactions in the upper third and the largest in the lower third of the back. (J ALLERGY CLIN IMMUNOL 1993;92:750-6.)

Key words: Skin tests, devices, prick, puncture, false positive, false negative, reproducibility

The trend in recent years in clinical allergy has been to employ prick skin testing as the primary means of establishing the presence of immediate hypersensitivity to foods and inhalant allergens. In part this practice reflects an appreciation that the degree of sensitivity demonstrated by prick testing correlates better with the presence of clinical symptoms than does that elicited by intradermal testing at the concentrations customarily employed.^{1, 2} Furthermore, prick testing is safer, more rapid, and less uncomfortable to the patient.³

Traditionally, prick testing was performed either by the scratch method or by pricking through a drop of extract with a solid bore⁴ or hypodermic needle.⁵ Recently, however, a number of devices have been introduced that are designed to pro-

Abbreviations used

ANOVA: Analysis of variance
CV: Coefficient of variation ($[(SD \div \text{Mean}) \times 100]$)
SD: Standard deviation

duce greater uniformity in penetration of the skin and hence better reproducibility of the test results. The majority of these instruments are designed to be used with downward pressure and are provided with a handle, which provides a secure grip and a widening above the point, which limits penetration of the point into the skin.

A number of studies reported the performance of individual devices⁶⁻¹⁰ or have compared several devices in use in the United States or Europe.¹¹⁻¹⁶ None has compared all the devices that have recently become commercially available in the United States. The purpose of this study was to make such a comparison. The specific aims were to compare the reproducibility, the rate of false-negative reactions, the size of reactions induced at negative control sites, and acceptability to subjects of these devices.

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METHODS

Devices

Five devices were compared by prick skin testing, one by two methods. Devices employed with downward pressure included the lancet (ALK Laboratories, Inc., Milford, Conn.), the prick lancetter (Dome Allergy Products, Spokane, Wash.), and the Multi-Test (Lincoln Laboratories, Decatur, Ill.). The DermaPIK (Greer Laboratories, Lenoir, N.C.) was pressed gently into the skin and rotated approximately a quarter turn as advocated by the manufacturer. The bifurcated needle (ALO Laboratories, Columbus, Ohio) was employed both with downward pressure as recommended by the distributor and in the classic upward prick motion, to allow comparison with the results obtained in a previous study in which it was employed by that method.¹⁷

Subjects

Two groups of subjects were recruited. In 12 subjects the reproducibility of the devices was compared by repeated testing with histamine phosphate. In 21 allergic subjects with at least one large reaction to an allergen extract on preliminary prick skin testing the devices were employed to assess the size of reactions at glycerosaline negative control sites, and the occurrence of false-negative skin tests with either histamine or allergen. Subjects with dermatographism were excluded from participation. No antihistamine or antidepressant treatment was allowed within 1 week of skin testing. Astemizole treatment was not allowed within 3 months of skin testing.

Skin test materials

Histamine phosphate was prepared by the institution's pharmacy at 10 mg/ml histamine base (27 mg/ml histamine phosphate) dissolved in 50% glycerosaline solution. This concentration of histamine was employed to produce large and more reproducible wheals.¹⁸ The allergen extracts were diverse and depended on the subject's sensitivity during preliminary skin testing. Allergen extracts were tested in the highest concentration available (1:10 or 1:20 wt/vol, 100,000 allergen units/ml), dissolved in 50% glycerosaline solution. The negative control was 50% glycerosaline solution.

Study plan

Part I. Twelve subjects were tested with histamine phosphate. Tests were performed on the back and employed a template with five columns of six rows each. All sites tested with individual test devices were 5 cm apart. Multi-Test, when employed, was substituted for two of the six rows in either columns 1 and 2, or columns 4 and 5.

Each subject was tested with histamine applied five times with each of the five individual devices and five times with a Multi-Test device. Glycerosaline solution was applied with the remaining three heads of the

Multi-Test, and a single glycerosaline negative control was applied at the thirtieth site to rule out the presence of dermatographism. The areas of the back used for each device were varied in a rotating manner during the course of the study. New devices were employed for each test.

The reactions to saline solution with the use of three heads of the Multi-Test device were read at 10 and 20 minutes.

At the end of each testing session the subjects were asked to rate blindly on a scale of 1 (lowest) to 4 (highest) the degree of acceptability of each of the devices.

Part II. Twenty-one subjects participated in Part II, which was designed to examine the incidence of false-positive and false-negative test results. Alternating positive and negative stimuli were applied with the use of the same 30-site template that was employed in Part I, with individual sites separated by 5 cm. Each subject participated in two skin test sessions on two separate days, with the following combination of positive and negative skin tests: (1) histamine phosphate and glycerosaline solution and (2) an allergen selected on the basis of a wheal greater than 8 mm on preliminary prick skin testing, and glycerosaline solution.

Each of the five individual devices was used to apply skin tests in one column, in rotating order. Again, Multi-Test was substituted at each of the levels in column 1 and 2, or 4 and 5. When the Multi-Test was employed, five heads were loaded with the positive skin test stimulus and three with the negative stimulus.

The Multi-Test device was tested 15 times in 15 subjects in sites evenly distributed among upper, mid, and lower portions of the back. Each of the other devices was tested equally in each third of the back.

At the end of the first testing session each subject was asked to rate blindly the degree of acceptability of each of the devices on the same scale of 1 to 4 as used in Part I.

Recording

All skin testing was applied by the same experienced technician (D.M.R.), and the results were recorded by a second experienced technician (L.I.M.) without knowledge of the device employed except in the case of Multi-Test, where the characteristic pattern prevented blinding. Recording was performed with the reader blinded to the test solution at each site in all cases, including the Multi-Test.

Skin test reactions were outlined with a felt-tip pen and transferred with transparent tape to a permanent record. The longest and orthogonal diameters were measured and the mean diameter employed for analysis. Skin test reactions to histamine and saline solution were recorded at 10 minutes; allergen and saline tests were recorded at 20 minutes. Wheal and erythema were recorded, but only the wheal was employed for interpretation¹⁸ because the results have been shown to be

TABLE I. Size and reproducibility of skin testing with 10 mg/ml histamine base

Device	n	Wheal (mm)*		Mean CV (%)
		Mean	SD	
HS lancet	60	6.2	1.0	15
ALK lancet	60	6.9	1.1	16
BN prick	60	7.0	1.4	19
BN puncture	60	7.2	1.3	19
Multi-Test	60	9.2	1.5	17
DermaPIK	60	9.9	1.7	17

BN, Bifurcated needle; HS, Hollister-Stier.

*Differences among means are significant ($p < 0.0001$); differences among SD values are significant ($p < 0.05$).

TABLE II. Subject acceptability of devices, in order of acceptability

	1	2	3	4
HS lancet	0	5	16	11
BN prick	0	7	15	10
ALK lancet	2	8	17	5
BN puncture	7	15	7	3
Multi-Test	9	8	8	1
DermaPIK	16	13	3	0

On completion of testing, subjects (26 for Multi-Test and 32 for all others) rated the acceptability of the devices. There was a marked and highly significant difference in the perceived acceptability ($p < 0.0001$) among the devices. Scale: 1 = least comfortable; 4 = most comfortable.

BN, Bifurcated needle; HS, Hollister-Stier.

similar with either parameter¹⁷ and the wheal is more widely employed in clinical practice.

Statistical analysis

Reproducibility. The mean wheal sizes produced by testing with histamine were compared by two-way analysis of variance (ANOVA), including a blocking effect for subjects but ignoring the location of the test on the back. Pooled estimates of the variance for each device were computed by removing the variance between subjects. Variances were compared between devices with Cochran's test for homogeneity and variance.¹⁹ Reproducibility for each device was expressed as the mean, standard deviation (SD), and coefficient of variation (CV) derived from repeated testing with histamine in Part I. The CV was calculated by dividing the SD by the mean.

Difference between 10- and 20-minute reactions to saline solution. The reactions with Multi-Test at the three saline-treated sites were compared at 10 and 20 minutes by a one-sample *t* test on the mean difference between times for each subject.

Acceptability. Differences in acceptability among devices were compared by a Pearson chi-square test for association in a two-way classification.

Location. Reactions at different locations on the back to histamine and allergen were compared by

three-way ANOVA to test the effects of subject, device, and location, and the device by location interaction. Specific presumptive tests for a linear trend across locations were performed by linear contrasts. The Multi-Test device was excluded from this analysis because the pattern of application differed from that of the individual devices.

False-negative test results with histamine and allergen extract. A skin test was considered falsely negative if the mean wheal diameter was less than 3 mm for histamine phosphate or less than 3 mm for an allergen extract, if the duplicate test in the same portion of the back, of the same subject, with the same device yielded a wheal of 5 mm or greater diameter.

Size of reaction at negative test sites. The distributions by size of reactions to glycerosaline solution adjacent to histamine and allergen skin test sites were compared for the different devices other than Multi-Test by a three-way ANOVA testing the effects for subjects, device, and location. Quantiles corresponding to probabilities of 0.95 and 0.99 were computed for the distributions of the sizes of the saline solution reactions. Differences resulting from subject and location were ignored. These quantiles estimate wheal size criteria required to achieve 0.95 and 0.99 specificity, respectively. The specificity achieved by using the standard 3 mm cutoff was also computed for each device.

TABLE III. Wheal size by device and region of back (excluding Multi-Test)

Region of back	Diameter of wheal (mm)*				
	HS lancet	ALK lancet	BN prick	BN puncture	DermaPIK
Top					
n	21	19	20	18	17
Histamine (mean $\pm$ SEM)	6.1 $\pm$ 0.3	6.6 $\pm$ 0.3	6.6 $\pm$ 0.3	7.3 $\pm$ 0.5	9.5 $\pm$ 0.6
Allergen (mean $\pm$ SEM)	7.2 $\pm$ 0.9	7.5 $\pm$ 0.8	8.7 $\pm$ 1.2	7.2 $\pm$ 0.9	8.5 $\pm$ 1.2
Middle					
n	19	17	21	20	18
Histamine (mean $\pm$ SEM)	6.5 $\pm$ 0.4	7.3 $\pm$ 0.4	8.4 $\pm$ 0.4	8.4 $\pm$ 0.5	10.3 $\pm$ 0.5
Allergen (mean $\pm$ SEM)	10.1 $\pm$ 1.1	9.8 $\pm$ 1.2	11.2 $\pm$ 1.2	9.4 $\pm$ 1.0	11.5 $\pm$ 1.3
Lower					
n	17	18	19	21	20
Histamine (mean $\pm$ SEM)	7.9 $\pm$ 0.6	8.0 $\pm$ 0.4	8.6 $\pm$ 0.5	9.4 $\pm$ 0.6	10.9 $\pm$ 0.6
Allergen (mean $\pm$ SEM)	9.7 $\pm$ 1.0	9.6 $\pm$ 0.9	12.7 $\pm$ 1.3	11.5 $\pm$ 1.1	12.1 $\pm$ 1.4

BN, Bifurcated needle; HS, Hollister-Stier.

*Gradient of response is highly significant ($p < 0.0001$) with the smallest reactions in the upper third and the largest reactions in the lower third of the back.

All tests of hypotheses were two-tailed at the 0.05 level of significance. All analyses were performed with JMP Version 2.0.4 software on a Macintosh Quadra 700 computer.

RESULTS

In Part I each of the 12 subjects was tested with histamine phosphate (10 mg base/ml) five times with each individual device and once with Multi-Test with histamine on five of the heads. Mean reaction size, SD, and CV were calculated for each device (Table I). The mean wheal sizes were significantly different ($p < 0.0001$), and the SD values were significantly different ($p < 0.05$), but the CV values were similar.

All 12 subjects were tested with glycerosaline solution on three heads of the Multi-Test. In Part I as a preliminary to Part II the glycerosaline sites were read at both 10 and 20 minutes to determine whether the use of the latter time would give more reliable negative readings. The reactions at the three glycerosaline sites of the 12 Multi-Test devices at 10 minutes became smaller, although they were still present, at 20 minutes. The time effect was significant ($p = 0.002$), with a decrease in mean wheal size from 2.3 mm at 10 minutes to 2.0 mm at 20 minutes (change, -0.3 mm [95% CI, -0.1 , -0.4 mm]). Therefore the 20-minute

reactions were employed at all saline test sites in Part II.

After Part I testing and the first session in Part II, the subjects were asked, without knowing the order in which they were tested, to rate the five or six devices for acceptability on a scale of 1 (most uncomfortable) to 4 (least uncomfortable). A marked difference was found in the rated acceptability of the devices ($p < 0.0001$) (Table II).

When the reactions to both histamine and allergen extract in Part II were examined, a clear difference in reactivity was apparent between the upper, mid, and lower regions of the back to both agents with all the devices being tested, exclusive of the Multi-Test (Table III). For both histamine and allergen the device and location effects were highly significant ($p < 0.002$). For both substances the gradient in response was highly significant ($p < 0.0001$), with the smallest whealing reactions on the upper third and the largest whealing reactions on the lower third of the back.

A false-negative response was considered to be present when the reaction to 10 mg/ml histamine base was less than 3 mm⁷ or when the reaction to an allergen was less than 3 mm at one site and 5 mm or greater at another site in the same region of the same subject's back with the same device.

TABLE IV. Number of reactions at glycerosaline control sites with various devices (at 20 minutes)

Device	Diameter of wheal (mm)						
	0	1-1.5	2-2.5	3-3.5	4-4.5	5-5.5	≥ 6
HS lancet	108	0	5	0	0	0	0
ALK lancet	78	6	18	5	0	0	0
BN prick	63	4	34	12	3	0	0
BN puncture	35	5	55	19	3	1	0
Multi-Test	41	2	15	19	10	2	1
DermaPIK	1	1	20	54	24	10	0

Devices differed significantly in the distribution of the reactions at the control sites ($p < 0.0001$).

BN, Bifurcated needle; HS, Hollister-Stier.

TABLE V. Confidence limits for whealing reactions with different devices

Device	n	Wheal diameter (mm)		Specificity of 3 mm wheal
		0.99 quantile	0.95 quantile	
HS lancet	114	2.0	0.0	1.00
ALK lancet	108	3.0	2.5	0.95
BN prick	122	4.0	3.5	0.87
BN puncture	118	4.5	3.5	0.81
Multi-Test	90	5.0	4.5	0.64
DermaPIK	110	5.5	5.0	0.20

Wheal reactions listed as 0.95 quantile had a specificity of 0.95, whereas those listed as 0.99 quantile had a specificity of 0.99 of being larger than the wheals encountered in testing with saline solution with the same device.

BN, Bifurcated needle; HS, Hollister-Stier.

Overall false-negative results were very few, occurring only one time with the Hollister-Stier lancetter and four times with the Multi-Test.

A marked difference was observed between devices in the number of glycerosaline sites where whealing reactions were present at 20 minutes (Table IV). The pattern is for the fewest and smallest reactions to saline solution to be produced by the lancets, with the bifurcated needle intermediate, and the Multi-Test and DermaPIK producing the most reactions greater than 4 mm. Statistical analysis, omitting Multi-Tests because of its different pattern of application, revealed significant differences for devices ($p < 0.0001$).

To estimate criteria for determining that a reaction to an allergen is truly positive, the 0.95 and 0.99 quantiles of the distributions of reaction sizes to saline solution were tabulated for each device without regard to subject or location (Table V). Depending on the desired degree of certainty that a reaction is not just a response to the trauma of the device, the lower limit of positive skin reactions was 0 to 5.0 mm for 95%

confidence, and 2.0 to 5.5 mm for 99% confidence, depending on the device employed. Also tabulated was the specificity corresponding to the use of a criteria for positivity of a wheal size greater than or equal to 3.0 mm. Again, a wheal of this size would have high specificity only with the lancets among the devices tested.

In view of the large reactions that occurred at some sites of saline controls (Table V), the reproducibility of the reactions to glycerosaline solution within the same subject with the same device was examined. The two or three negative controls that had been performed in the same testing session with the same device were compared for consistency in size of reaction (Table VI). The reactions clearly are not consistent, and a single control does not reflect the full range of reactions that could occur as a result of trauma in a patient undergoing multiple skin tests.

DISCUSSION

In a previous article we reported our findings with six prick skin testing devices commercially

TABLE VI. Consistency of reactions at glycerosaline sites

Diameter of largest wheal when one control negative*						
Device	n	Wheal (mm)				All positive
		0	1-2.5	3-4.5	≥ 5	
HS lancet	44	39	5	0	0	0
ALK lancet	39	26	10	3	0	5
BN prick	29	17	8	4	0	16
BN puncture	19	6	12	1	0	24
Multi-Test	21	6	4	10	1	7
DermaPIK	1	0	0	0	1	42

*When two or three saline controls were performed on the same subject at the same time with the same device, they could either all result in whealing (all positive) or one could be negative whereas varying reactions occurred at the duplicate sites (one negative). In the latter instances the size of the largest accompanying reaction at a saline site is given.

available at that time.¹⁷ Subsequently one of the devices included in that study, the Multi-Test, was modified by shortened prongs (from 2.4 to 1.9 mm). Several investigators reported highly reliable performance with the restructured device.^{9, 10, 14} We therefore elected to restudy it and to reexamine another of the devices, the bifurcated needle, by the puncture technique, which was recommended by the distributing company. In the interval since the previous study was completed, three new devices had been introduced. Two had been developed in Europe, and prototypes had undergone extensive testing there,^{6, 7} whereas the other had not undergone comparative testing.

We found that the reactions produced by the devices we tested differed significantly in a number of ways. Underlying the differences was the degree of trauma to the skin produced by the device. The greater the trauma, the larger the reaction with histamine or allergen and generally the less the likelihood of a false-negative reaction. On the other hand, the greater the trauma, the greater the likelihood of a whealing reaction at the site of negative controls and the greater the discomfort to the patient.

Because all the glycerosaline skin tests in this study were adjacent to either histamine or allergen extract skin tests, distinguishing reactions caused by the trauma of the device from the effect of a nearby positive skin test was not possible. However, the modest size of the positive reactions and the placement of the sites 5 cm apart suggest that most of the reactions observed were due to trauma from the instrument rather than influence from the nearby positive reactions.²⁰

If the size of the reaction at negative control sites were constant within a patient, it would be possible to modify the interpretation at sites tested with allergy by subtracting the reaction at the negative control site.^{9, 10} However, it is evident (Table VI) that many times the presence of a negative reaction at one glycerosaline control site does not assure lack of nonimmunologic whealing at other sites tested at the same time in the same person with the same device. This variability of reactions at negative control sites limits the possibility of adjusting the interpretation of the reaction at allergen sites by subtracting the results of a single negative control.

The results suggest that the dictum of a 3 mm wheal representing a significant reaction¹⁸ must be reexamined in relation to the newly introduced skin testing devices. Indeed, it appears that a distinct level of significance must be established for each device (Table V). Any reaction at the site of allergen extract testing that is smaller than these limits should be regarded as potentially negative and should be confirmed either with a repeated percutaneous skin test or preferably with an intracutaneous skin test.

Five of the devices tested displayed a consistent and significant trend for larger wheals to occur as testing was performed lower on the back. This was observed with both histamine and allergen extract. Multi-Test was not included in the analysis. However, this device did demonstrate a trend similar to that seen with the others.

In summary, prick skin testing for immediate hypersensitivity is subject to a number of variables, one of which is the device used to introduce the solution into the skin. We demonstrated that

devices commercially available in the United States differ significantly in the size of the reactions they induce, the likelihood of a false-negative reaction, the size of reaction that can occur at a negative control site, and the patient's degree of discomfort. These differences presumably reflect differences in the amount of skin trauma that these devices produce. We also observed a significant trend toward increasing size of whealing reactions as tests were performed lower on the back.

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