Original Article

Performance and Pain Tolerability of Current Diagnostic Allergy Skin Prick Test Devices

Jody R. Tversky, MD[a], Yohalakshmi Chelladurai, MD[b], John McGready, PhD[b], and Robert G. Hamilton, PhD[a]
Baltimore, Md

What is already known about this topic? Allergen skin prick test (SPT) remains one of the primary and essential tools for diagnosing atopic disease and guiding treatment. Previous studies have pointed to performance differences among older SPT devices.

What does this article add to our knowledge? Modern day SPT devices vary in the size of the wheal and flare response, sensitivity, and pain. Devices with the greatest signal to noise ratio may also result in more false-positive reactions if solely defined by a 3-mm wheal threshold.

How does this study impact current management guidelines? The 3-mm wheal threshold should not be arbitrarily used as a positive threshold for certain SPT devices. Histamine (1 mg/mL) may be appropriate for use with some but not all SPT devices.

BACKGROUND: Allergen skin prick testing remains an essential tool for diagnosing atopic disease and guiding treatment. Sensitivity needs to be defined for newly introduced devices.
OBJECTIVE: Our aim was to compare the performance of 10 current allergy skin prick test devices.
METHODS: Single- and multiheaded skin test devices (n = 10) were applied by a single operator in a prospective randomized manner. Histamine (1 and 6 mg/mL) and control diluent were introduced at 6 randomized locations onto the upper and lower arms of healthy subjects. Wheal and flare reactions were measured independently by 2 masked technicians.
RESULTS: Twenty-four subjects provided consent, and 768 skin tests were placed. Mean wheal diameter among devices differed from 3.0 mm (ComforTen; Hollister-Stier, Spokane, Wash) to 6.8 mm (UniTest PC; Lincoln Diagnostics, Decatur, Ill) using 1 mg/mL histamine ($P < .001$) and 4.8 mm (GREER Pick; Greer, Lenoir, NC) to 8.4 mm (Duotip-Test II; Lincoln Diagnostics, Decatur, Ill; and Sharp-Test; Panatrex, Placentia, Calif) using 6 mg/mL histamine ($P < .001$). The false-negative rates ranged from 0% to 45% with 1 mg/mL histamine. The analytical specificity was 100% for all devices tested. All devices were well tolerated, with average pain score of less than 4 on a 10-point visual analog scale. Pain scores were higher among women, but this did not reach statistical significance. The Multi-Test PC and the UniTest PC had the lowest pain scores compared with the other devices.
CONCLUSIONS: All 10 skin prick test devices displayed good analytical sensitivity and specificity; however, 3 mm cannot arbitrarily be used as a positive threshold. The use of histamine at 1 mg/mL is unacceptable for certain devices but may be preferable for the most sensitive devices. On average, there was no pain score difference between multiheaded and single-head devices. **(J Allergy Clin Immunol Pract 2015;3:888-93)**

Key words: *Skin test; Diagnostic; Device; Sensitivity; Performance; Pain; Histamine*

Percutaneous skin prick test (SPT) is 1 of 2 principal diagnostic tests used to confirm sensitization in the evaluation of allergic disease. When proper technique and reliable allergen reagents are used, the SPT performs well in comparison to *in vitro* serological testing.[1-5] The Joint Council of Allergy, Asthma & Immunology and the European Academy of Allergology and Clinical Immunology recommend SPT in the selection of allergens for inclusion in immunotherapy, and they point to some advantages and limitations when compared with *in vitro* testing.[6,7] The allergen skin scratch test was first introduced by Sir Charles Blackley more than 140 years ago. The technique was modified in 1924, and today, SPT remains an essential clinical diagnostic tool for allergists, otolaryngologists, and researchers around the world.

Clinicians need to fully understand the manufacturer's recommended methodology for each puncture skin test device and

[a]Division of Allergy and Clinical Immunology, Department of Medicine, Johns Hopkins University, Baltimore, Md
[b]The Johns University Bloomberg School of Public Health, Baltimore, Md
Conflicts of interest: J. McGready has received research support from Johns Hopkins University as a Clinical/Translation Research Grant, and the Johns Hopkins Bloomberg School; has received payment for developing educational presentations from Johns Hopkins Bloomberg School; and travel support from Johns Hopkins Bloomberg School, Department of Biostatistics. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication January 14, 2015; revised July 24, 2015; accepted for publication July 30, 2015.
Corresponding author: Jody R. Tversky, MD, Division of Allergy and Clinical Immunology, Johns Hopkins University, 5501 Hopkins Bayview Circle, Baltimore, MD 21224. E-mail: jodytversky@jhmi.edu.
2213-2198

http://dx.doi.org/10.1016/j.jaip.2015.07.022

Abbreviation used
SPT- skin prick test

how to optimally interpret its resultant response on the basis of available evidence.[8,9] In the case of patients with severe asthma or anaphylaxis to a food, a false-negative result may have life-threatening consequences. However, misdiagnosis of food allergy has been reported to result in inappropriate food avoidance with a possible consequence of severe malnutrition.[10]

SPT device performance depends greatly on the methodologies and reagents used in the testing protocol as well as the quality of the technician's training.[8,9,11,12] Significant variation has been reported in the measured wheal and flare responses even among experienced allergists at different centers.[12] Therefore, knowledge about the attributes of each device and the methods used to achieve reproducible results are essential.

Patient characteristics are another important factor to consider. Skin reactivity to a particular allergen may depend on age, seasonality, and prior medication use as well as the level of allergen-specific IgE antibody. SPTs in children, for instance, are highly effective in the detection of aeroallergen sensitization.[1] In elderly patients, however, one may observe more false-negative SPT responses.[13]

The focus of this study was to evaluate the performance of 10 modern day SPT devices independent of the presence of specific IgE bound to the surface of mast cells in the skin. Thus, histamine at 2 clinically relevant concentrations (1 and 6 mg/mL) and negative control diluent were used as surrogates to assess specific and irrelevant allergen reactivity in the skin. Because histamine rather than allergen extract was used for testing, seasonality and the patients' allergic status were not confounding factors. The goal was to define the analytical sensitivity and specificity of the devices using a randomized single-blinded study design. We also examined the relative pain scores elicited by each of the 10 devices.

METHODS

Study design

A prospective randomized single-blind study of 10 allergy SPT devices was conducted with approval by the Johns Hopkins Institutional Review Board. Skin prick testing was performed on 6 locations on the upper and lower volar aspect of the arm, which were identified as regions I to VI (Figure 1). Each of 4 multiheaded devices occupied 1 of the 6 regions tested. The single-head devices were evenly applied to the remaining 2 regions. Randomization was performed once on the first subject and then sites were sequentially rotated so that each device was equally represented among the 6 regions. Antihistamines were withheld for at least 10 days before testing. Histamine and diluent control solutions were used to assess the analytical performance of each skin test device according to manufacturer-recommended techniques.

Subjects

Twenty-four volunteer subjects aged 18 to 65 years, with or without a history of allergic disease, were included in the study. Of the study subjects, 8% had dark skin. The primary exclusion criteria included the use of antihistamines within the last 10 days of the study, dermatographism, severe atopic dermatitis, or the use of omalizumab. Because allergen extracts were not used for skin testing, patients who previously received immunotherapy were invited to join the study.

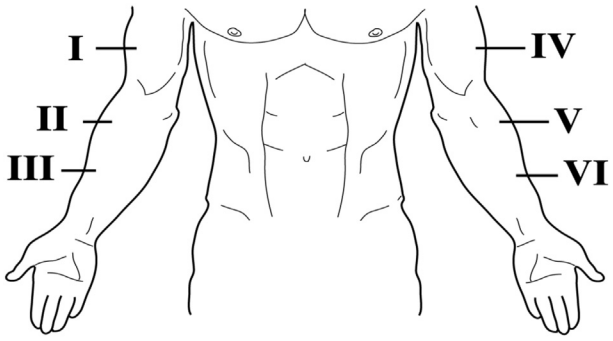

FIGURE 1. SPT sites were randomized to 6 locations on the upper and lower volar aspect of the arm as indicated.

Devices

Ten commercially available skin test devices were evaluated. These included the bifurcated lancet (Precision Medical, Northampton, Pa); Duotip-Test II, UniTest PC, and Multi-Test PC (Lincoln Diagnostics, Decatur, Ill); QUINTIP and ComforTen (Hollister-Stier, Spokane, Wash), Sharp-Test and Quick-Test (Panatrex, Placentia, Calif); and GREER Pick and Skintestor OMNI (Greer, Lenoir, NC) (Figure 2).

Skin test protocol

All manufacturer recommendations were followed in the application of each device. The Duotip-Test II was applied using the twist method. In contrast, the bifurcated lancet was applied through the test solution using the puddle and four-lean technique. All other devices were applied using direct pressure. The multiheaded devices were gently rocked twice along the long axis without lifting the heads off the skin surface. All the 10 devices were tested using 6 mg/mL histamine base (10 mg/mL histamine dihydrochloride) and glycerol-saline (both from Hollister-Stier). Each of the multiheaded devices, as well as the Duotip-Test II and UniTest PC, was also tested with a concentration of 1 mg/mL histamine base. Devices were placed at least 2 cm apart. Space did not permit testing of the 1 mg/mL histamine for all the devices.

After each device was applied to the skin, subjects were asked to subjectively rate their discomfort from 1 to 10 using a Wong-Baker pain rating scale. Subjects were not blinded as to which device was being tested. At exactly 15 minutes, a single technician carefully traced the wheal and flare reactions using a skin-safe marker. The markings were transferred onto a sheet of paper using a 2-inch wide tape. At a later date, 2 technicians (masked as to which device was being evaluated) independently measured the wheal and flare diameter on the transfer tape to a 1-mm precision. Maximum and orthogonal measurements were used to calculate the mean diameter. If any single measurement differed between the 2 technicians by more than 1 mm, a third technician was called upon to perform an additional measurement and the outlier was excluded. A true positive histamine reaction was defined in the present study as a mean diameter of the wheal greater than or equal to 3 mm and at least 2 mm greater than that of the diluent control. A negative reaction was defined as a wheal diameter of less than 3 mm and/or histamine response of less than 2 mm more than that with the diluent control.