Review

Systemic reactions from skin testing: literature review

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Summary. The skin prick test (SPT) is the most appropriate diagnostic approach to identify IgE sensitization to aeroallergens, foods, hymenoptera venom and some pharmacological compounds. SPT is considered a safe diagnostic approach, but several fatal or near-fatal reactions have been described. Based on the literature, the occurrence of systemic reactions with inhalant allergens has diminished over the last thirty years, whereas fresh food, hymenoptera venom and antibiotic SPT still carry some risk. In general, the risk of systemic reactions is lower with SPT than with intradermal testing.
Some patients (history of previous anaphylactic reactions, small children, pregnant women, uncontrolled asthma, high degree of reactivity) should be considered at higher risk of systemic/anaphylactic reactions.
Based on the literature, the risk of fatality due to SPT is extremely remote, and severe/anaphylactic reactions are rare. Nevertheless, this risk cannot be completely excluded, especially in highly susceptible subjects. Physicians who perform SPT should be aware of this and apply simple precautional rules.

Key words: Anaphylaxis, allergy, skin prick test(ing), systemic reactions, fatality.

Resumen. La prueba cutánea prick es el enfoque diagnóstico más adecuado para identificar la sensibilización de la IgE a aeroalérgenos, alimentos, veneno de himenópteros y algunos compuestos farmacológicos. El prick test se considera un enfoque diagnóstico seguro, aunque se han descrito diversas reacciones fatales o casi fatales. Según la literatura, en los últimos treinta años ha disminuido el número de reacciones sistémicas con alérgenos inhalantes, mientras que los alimentos frescos, el veneno de himenópteros y el prick test con antibióticos aún conllevan cierto riesgo. En general, el riesgo de reacciones sistémicas es menor con el prick test que con la prueba intradérmica.
Algunos pacientes (historia de reacciones anafilácticas previas, niños pequeños, mujeres embarazadas, asma incontrolada o elevado grado de reactividad) deberían considerarse con mayor riesgo de reacciones anafilácticas/sistémicas.
Según la literatura, el riesgo de mortalidad por prick test es extremadamente remoto y las reacciones anafilácticas/graves son muy poco frecuentes. Sin embargo, este riesgo no puede excluirse por completo, especialmente en personas altamente susceptibles. Los médicos que realizan los prick test deberían ser conscientes de esto y aplicar simples normas de precaución.

Palabras clave: anafilaxia, alergia, prick test, reacciones sistémicas, mortalidad.

General aspects

Skin tests (ST), including skin prick test (SPT) and intradermal test (IDT), are used to diagnose *in vivo* IgE-mediated sensitizations for allergies induced by aeroallergens, foods, hymenoptera venoms and drugs. SPTs are generally recommended as the first choice in the diagnostic workup. SPT have a global efficiency comparable to specific IgE assays (RAST and related methods). SPTs are easy to perform, cheap, and provide a positive/negative response within a few minutes. The number of allergen extracts for diagnostic purpose include nowadays materials derived from many sources such as pollens, moulds, dusts, stinging insects, latex, antibiotics, anaesthetics and foods. The commercially available diagnostic extracts for SPT are of high quality and standardized either biologically or immunologically.

Skin tests are considered a safe diagnostic procedure. The few fatalities associated with their use, reported from 1895 to 1980 were associated with biologic products that are no longer used such as horse serum-derived tetanus or dyphtheria toxins or pneumococcal antiserum [1-10].

Table 1. Surveys on the risk from SPT.

AAAI Surveys	
Lockey (13)	5 fatalities by IT + 1 by SPT
Bernstein (15)	1 death following SPT (scratch, multiple food allergens)
Reid (17)	No fatality
Lockey (18)	45 systemic reactions after SPT to stinging insects
Sullivan (19)	No fatality
Other surveys	
Nhanes (20)	
Lin (12)	0.02% nonfatal reactions
Valyasevi (21)	33/100.000 nonfatal reactions
Devenney (22)	6 nonfatal reactions by fresh food in children < 6 yrs
Valyasevi (24)	1710 pts 0.12; and 2.3% for the penicillin skin test+
Cantani (23)	no reactions in children
Rodríguez pérez (25)	3 slight reactions by SPT
Liccardi (11)	1 anaphylaxis in 55,000 pts

In the last thirty years the occurrence of systemic reactions, at least with SPT for inhalant allergens extracts, has decreased dramatically [11]. The recent surveys suggest that the overall risk of inducing anaphylactic reactions by SPT is less than 0.02 % [12, 13], whereas IDT is more likely to induce systemic reactions. In a survey by Lockey et al [13], 5 of the 6 reported fatalities were associated with IDT is some additional cases were described by Lin et al [12]. Given the lower specificity [14] and increased risks, IDT is no longer recommended as first-choice, but for selected diagnostic procedures.

Overview of the recent literature

The literature from 1980 through 2005 was searched via MEDLINE using the following keywords: *skin prick test [AND] systemic reactions [OR] anaphylaxis*. A further review of all related articles and links was also performed. Numerous articles were found including: surveys by the American Academy of Allergy and Immunology [13, 15 - 19], the National Health and Nutrition Examination Survey (NHANES II)[20], spontaneous surveys [11, 12, 21-25], case reports [11, 26-41] and some editorials or commentaries [42-45]. The surveys are summarized in Table 1, whereas Table 2 illustrates the main features of the published case reports.

Looking at the literature, the occurrence of fatalities with SPT is extremely low. In fact, only 7 deaths following skin testing procedures were reported in the largest available surveys conducted in the USA, but five of them were due to IDT, and no other fatality due to SPT has ever been reported. In one of the fatal cases scratch tests with 90 commercial food antigens (including fish, egg, shellfish, nut, and peanut) [15] were employed. Some nonfatal but severe reactions, mainly anaphylaxis, were described by some authors over the last 30 years (Tables 1, 2), but only few were due to aeroallergens [11, 21, 27, 34, 38, 41], and in one of these patients a documented latex allergy was present. Two case reports described anaphylaxis due to allergen contact with either intact [46] or damaged skin [47].

Taking into account the available literature, SPT remains a safe diagnostic procedure, although a theoretical

Table 2. Case reports on anaphylaxis/severe reactions by skin testing.

Liccardi (11)	1 anaphylaxis with inhalant SPT
Novembre (26)	2 anaphylaxis with kiwi and fish SPT
Gale (27)	1 anaphylaxis with inhalant SPT
Pinkowski (28)	Anaphylaxis by chymopapain SPT
Schiavino (29)	Asthma-anaphylaxis by phytohemagglutinin SPT
Alonso (30)	Anaphylaxis by penicillin SPT (negative)
Nicoloau (31)	Anaphylaxis by latex SPT
Nettis (32)	Anaphylaxis by latex SPT
Mansfield (33)	Anaphylaxis by tetanus toxoid SPT
Kruszewski (34)	Anaphylaxis by aeroallergen SPT
Vincent (35)	Anaphylaxis by gallamine intradermal test
Koshak (36)	Anaphylaxis by penicillin SPT
Van de Scheur (37)	Anaphylaxis by fresh pine nut SPT
Eleuterio González (38)	Asthma-urticaria by aeroallergen SPT
Geller (39)	Anaphylaxis by trycophytin SPT
Gaig Jane (40)	Anaphylaxis by amoxicillin SPT
Vanin (41)	Anaphylaxis by aeroallergen SPT

Table 3. Recommendations to minimize the risk of systemic/anaphylactic reactions with skin testing.

CATEGORIES OF PATIENTS
– Pay special attention to very young children, patients with a history of previous systemic/anaphylactic reactions, high degree of reactivity.
– Patients with spina bifida may be at higher risk of systemic reactions with latex SPT.
– In pregnant women, postpone SPT. If there is immediate diagnostic need, prefer serological assay.
GENERAL RULES
– Use, when available, standardized diagnostic extracts (50).
– Avoid concomitant use of beta-blocking agents, if possible (51).
– Minimize the number of allergens to be tested during the SPT procedure.
– Avoid IDT as first choice.
– SPT should be performed by trained and qualified personnel, under physician supervision.
– Adequate equipment to treat anaphylaxis must be available.
– A 20-minute waiting period appears to be adequate (12,16).
– In patients at risk, consider the possibility of diluting allergenic extracts before use (46), or in the case of fresh foods, before prick-by-prick apply the food on intact skin for some minutes (44).

and remote risk is in principle present. Due to the rarity of severe reactions by SPT, it is difficult to clearly identify all the possible risk factors in the general population, but some basic recommendations can be suggested.

Recommendations

Very young children require particular caution, since the risk factors in this group are different and more relevant than in adults. It has been previously suggested to avoid duplication of skin tests (which increase antigen load locally), especially when food allergens are used and when children suffer from extensive eczema [22]. In some highly susceptible subjects cow milk may induce systemic reactions also as a consequence of a simple contact with intact skin [46] or after SPT [44]. In addition, little children cannot effectively verbalize early symptoms of an allergic reaction (e.g apprehension, generalized itch, feeling of asphyxiation, tightness of chest, and dizziness)[45]. Another important aspect is the interpretation of results. It should be considered unethical to perform SPT in this group of patients if the physician cannot correctly interpret the results so as to benefit the patient [45].

Pregnant women are another category of patients requiring some caution in performing SPT [48]. Although SPT is not contraindicated in pregnancy, it is unanimously considered prudential to postpone SPT, in order to avoid possible reactions, even if rare, and consequently aggressive therapies. In the case of an immediate clinical need to assess allergic sensitization in pregnant women, specific IgE assays should be preferred.

The rate of systemic reactions to hymenoptera venom was reported to be 1.4 % (only 0.025 % severe reactions) in patients with previous hymenoptera-induced systemic reactions [18]. This is similar to what is observed (1%) with penicillin skin testing [19]. Latex allergens may induce systemic/anaphylactic reactions in highly sensitive patients, such as those with spina bifida. In this condition SPT performed with latex allergenic extract is considered risky [49].

Turkeltaub and Gergen [20] evidenced that some highly anxious subjects might experience systemic but non-allergic reactions such as malaise and syncope. This type of reaction is common in clinical practice; thus it would be recommendable to put anxious patients supine when SPTs are performed. In general, patients with previous anaphylaxis or ascertained high degree of reactivity may be considered at higher risk of systemic reactions, although the rate of systemic reactions remains extremely low.

In *conclusion*, the relatively few but consistent data suggest there is a potential risk of systemic reactions/ anaphylaxis by using the SPT technique. Physicians/ specialists who perform SPT should be aware of this, should be prepared to recognize and treat reactions [50, 51] and should apply some rules of caution (Table 3).

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