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The incidence and features of systemic reactions to skin prick tests

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ABSTRACT

Background: Skin prick testing (SPT) has been regarded as a safe procedure with few systemic reactions. **Objective:** To evaluate the rate of systemic reactions and their associations after SPT in the largest population to date.

Methods: In this study reactions were recorded prospectively in a specialist UK allergy clinic for 6 years (2007–2013). An estimated 31,000 patients underwent SPT.

Results: Twenty-four patients (age range 7 months to 56 years, mean 23.5 years, 17 female patients, 12 with asthma) had systemic reactions. The rate of systemic reactions to SPT was 0.077%. The likely allergens causing the reaction were foods (18; peanut, 7; walnut, 1; Brazil nut, 2; pistachio, 1; lupin, 1; cow's milk, 2; shrimp, 1; spinach, 1; legume, 1; soy, 1), aeroallergens (4; rabbit, 1; rat, 1; ragwort, 1; grass pollen, 1), wasp venom (1), and Tazocin (1). The causative SPT wheal was larger than 8 mm in 75%. The reaction to Tazocin was severe, with anaphylaxis occurring minutes after SPT. Reactions were treated immediately in the clinic and did not require further medical care.

Conclusion: In this largest single-center study, the rate of systemic reactions after SPT was 77 per 100,000 patients. It is the first study to identify foods as a common and important cause (75%), with nuts posing the highest risk. This study reports the first systemic reaction to venom SPT and the first anaphylactic reaction after drug SPT. There was an association with a history of severe reactions and large skin test reaction. There are risks, albeit small, when undertaking SPT.

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Introduction

Skin prick testing has been used widely in the diagnosis of IgE-mediated hypersensitivity for longer than a century. It was first described by Blackley in 1873¹ and remains popular because it is inexpensive, minimally invasive, and results are available during the consultation. It is considered a reliable and safe procedure.

However, previous studies have challenged the safety of skin prick tests (SPT). From 1895 to 1968, there were more than 70 deaths reported after SPT, but these were caused mainly by allergens no longer in use (eg, horse serum-derived tetanus or diphtheria antitoxin).^{2–4} Since then, most deaths have occurred secondary to intradermal testing because the allergen is injected intracutaneously and therefore carries a higher risk of systemic reactions. There have been 6 deaths from intradermal testing and 1 from SPT.^{2,5}

It is not clear why patients have systemic reactions after SPT. Studies from the early 1990s reported SPT to aeroallergens as a common cause for systemic reactions. Lin et al⁶ prospectively evaluated systemic reactions after SPT from 1976 to 1989. Patients with only respiratory allergies were included in the study. Ten

thousand four hundred patients had SPT and intradermal testing, with 2 having systemic reactions. These patients had positive reactions to aeroallergens, yielding a rate lower than 0.02%. Valyasevi et al⁷ reported on 5 patients who had systemic reactions after SPT alone, yielding a rate lower 0.03%. These patients had positive reactions to aeroallergens and latex. However, since the millennium, there has been an increase in systemic reactions to foods.^{8,9} Other possible factors reported have been asthma and a young age.^{2,7,10}

Most previous studies have been performed in the United States and examined SPT and intradermal testing. The present study is the first carried out in the United Kingdom and was triggered by noting reactions to SPT that had been extremely rare during 30 years of allergy practice in a major allergy center. This study determined the rate of systemic reactions to SPT alone (not including intradermal tests). It is in the largest population to date in a specialist allergy practice covering a comprehensive range of disorders and using a wide range of allergens, including food, drugs, and venom. Foods were the commonest cause of systemic reactions. This study identified the first systemic reaction to wasp venom SPT alone and the first severe reaction to drug SPT.

Methods

A retrospective study was performed in which reactions were sought prospectively and recorded as they occurred in a specialist

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allergy clinic at Addenbrooke's Teaching Hospital (Cambridge, United Kingdom) during 6 years (2007–2013) to determine the rate of systemic reactions after SPT. Patients are from a wide (regional) geographic area (urban and rural) with a diverse ethnic and social class mix. Approximately 30% of patients are local (derived from a population of 1 million), 65% are regional (from a population of 7 million), and 5% are national. This study was exempt from institutional review because the data were collected from hospital records of a routine clinical practice. Of 42,000 patients seen, an estimated 31,000 patients underwent SPT.

Patients were referred to the allergy clinic at varying intervals, from the original reaction or from the onset of symptoms ranging from a few days to many years. The usual interval was months to years.

SPT Method

Skin prick testing was carried out by 4 specialist allergy nurses. The reagent was applied to the volar aspect of the forearm and a lancet (ALK-Abelló, Copenhagen, Denmark) was used to puncture the skin through the droplets at a perpendicular angle.

All new adult patients and most children older than 5 years underwent SPT to 10 commercial allergens, which included house dust mite, grass pollen, *Alternaria alternata*, cat, egg, milk, wheat, tree pollen mix, shrubs and weeds (Allergy Therapeutics, Worthing, United Kingdom; and Allergopharma, Reinbek, Germany), *Cladosporium herbarum* (Stallergenes, Antony, France) with negative (Allergy Therapeutics) and positive (ALK-Abelló) controls, and peanuts and tree nuts (ALK-Abelló) with additional SPT performed according to the patient's history. Bee and wasp venom SPT was performed using ALK-Abelló extracts. Prick-prick testing was carried out to fresh fruit, vegetables, shellfish, and other allergens if the history was applicable. Tazocin (piperacillin and tazobactam) SPT was performed using undiluted therapeutic concentrations of 200 mg/mL of Tazocin (Pfizer, New York, New York), 150 mg/mL of benzylpenicillin (Genus, Berkshire, United Kingdom), and 200 mg/mL of amoxicillin (Wockhardt, Wrexham, United Kingdom). All reagents were refrigerated at 4°C.

Young children (<5 years old) were tested to fewer allergens, which were selected according to clinical history. No procedures were performed outside the authors' routine clinical practice, and all patients (adults and parents of children) gave verbal consent for SPT to be carried out and photographs to be taken if necessary. The wheal and flare were measured 10 minutes after application. A wheal equal to or larger than 3 mm in diameter (larger than the negative control) with flare was considered a positive reaction. The severity of the original reaction and systemic reactions to SPT were graded according to a published system (Table 1). Grades 1 and 2 consisted of localized (eg, urticarial and erythema of the torso) and generalized (widespread) cutaneous symptoms; grade 3 included cutaneous symptoms with or without gastrointestinal symptoms or rhinoconjunctivitis. Grade 4 included mild asthma and laryngeal edema, and grade 5 included profound dyspnea or hypotension.¹¹ Asthma was considered not optimally controlled if the forced



Figure 1. Severe skin prick test reaction to the drug Tazocin, showing a rapidly extending wheal with widespread erythema.

expiratory volume in 1 second was less than 80% despite corticosteroid inhaler treatment or if frequent exacerbations occurred irrespective of therapy. The allergen considered most likely to have caused the systemic reaction to SPT was identified based on the severity of allergy (assessed by history) combined with a large or largest SPT wheal and, when present, clear evidence of the reaction emanating from a particular skin test site.

Results

Twenty-four patients (age range 7 months to 56 years, mean 23.5 years, 17 female patients, 12 with asthma) had systemic reactions. Six of these patients were children (<16 years old). The rate of systemic reactions to SPT was 0.077% (ie, 77 systemic reactions per 100,000 patients). In patients who reacted to SPT, the number of SPTs undertaken was 2 to 20; the median number of positive results was 6 (range 2–12); and the median number of wheals larger than 8 mm was 2. Data on the number of SPTs performed in patients who showed no reaction to SPT were not collected (the hospital operates on a paper-based system) but the normal range would be 2 to 24, with most patients having at least 10 allergens tested. The likely allergen causing the reaction was peanut (6), walnut (1), Brazil nut (3), pistachio (1), lupin (1), cow's milk (2), shrimp (1), spinach (1), legume (1), soy (1), wasp venom (1), rabbit (1), rat (1), ragwort (1), grass pollen (1), and Tazocin (1). Foods caused 75% (18 of 24) of the systemic reactions to SPT and nuts accounted for 61% of these (11 of 18).

There was 1 severe reaction to a drug SPT. A nurse developed conjunctivitis, dyspnea, and lightheadedness after splashing Tazocin on her skin at work. SPT were carried out to penicillins and Tazocin. Reactions were positive to benzylpenicillin, amoxicillin, and Tazocin (Fig 1). Within minutes she developed rhinoconjunctivitis, wheeze,

Table 1
Grading of patients' allergy and systemic reactions to skin prick testing⁶

Grade of reaction	Clinical features
1 (mild)	Localized cutaneous symptoms, urticaria, angioedema, oral pruritus
2 (mild)	Generalized cutaneous symptoms, urticaria, angioedema
3 (mild)	At least grade 1 or 2 plus gastrointestinal symptoms or rhinoconjunctivitis
4 (moderate)	Mild laryngeal edema (voice change, tightening of throat), mild asthma
5 (severe)	Pronounced dyspnea, hypotensive symptoms (lightheadedness, collapse, loss of consciousness)

Table 2

Clinical details of patients with systemic reactions to skin prick testing

Patient number	Age (y)	Sex	Diagnosis	Original reaction grade	Asthma	Controlled
1	0.56	F	Cow's milk	3	N	
2	7	M	BN + persistent cow's milk allergy	2 ^b	Y	Y
3	8	M	TN, sesame, PN, kiwi allergy	2	Y	Y
4	11	M	PN, TN, shellfish allergy	2	Y	Y
5	11	M	Severe BN allergy	2 ^a	N	
6	15	F	Severe cow's milk; nut + egg	5	Y	N
7	16	F	PN	3	N	
8	16	F	Soy anaphylaxis	4	Y	N
9	17	F	PN + TN, asthma	1 ^a	Y	Y
10	18	M	Life-threatening PN anaphylaxis	5	N	
11	18	F	Severe PN, OAS, rhinitis	3 ^a	Y	
12	19	F	PN allergy	3	N	
13	19	F	TN allergy	3	N	
14	22	F	Rhinitis and asthma due to rat, HDM rhinitis ^c	4	Y	Y
15	23	M	Pea, lentil allergy	4	N	
16	29	F	Lupin anaphylaxis	4	Y	Y
17	29	F	Shrimp allergy	4	N	
18	31	F	Spinach allergy (pork–cat syndrome)	3	Y	Y
19	32	M	Ragwort anaphylaxis	5	N	
20	38	M	TN allergy	5	N	
21	38	F	Rabbit anaphylaxis	5 ^a	Y ^d	d
22	45	F	Wasp venom allergy	2	N	
23	47	F	Perennial + seasonal rhinitis (HDM + GP)	3 ^b	Y	Y
24	56	F	Drug anaphylaxis (Tazocin)	5	N	

Abbreviations: BN, Brazil nut; F, female; GP, grass pollen; HDM, house dust mite; M, male; N, no; OAS, oral allergy syndrome; PN, peanut; TN, tree nut; Y, yes.

^aCutaneous reaction to trace exposure (eg, contact with foods or minor amounts of inhaled allergen).^bRhinitis only.^cPatient also sensitized to GP, weed pollen, and cat.^dSevere asthma at minimal rabbit exposure (distant from rabbits in an adjacent field); asymptomatic and no treatment when away from animals.

dyspnea, and tachycardia and was treated with intramuscular epinephrine, intravenous antihistamines, intravenous steroids, and nebulizers.

The severity of the original episode was grade 5 (severe) in 4, grade 4 (moderate) in 5, grade 3 (mild) in 5, and grade 2 (mild) in 2 (Table 2). Six were reactions to trace exposure; therefore, the true severity of the patients' allergy was much greater than indicated by the grade derived from the symptomatology. One patient had anaphylaxis despite trace exposure. Five had cutaneous symptoms to trace exposure, 1 of these also having rhinitis. One patient's original reaction was allergic rhinitis. Several patients had severe anaphylaxis (eg, a near fatal reaction) to peanut. Patient 19 had anaphylaxis to ragwort. This occurred after pulling out large quantities of ragwort from the ground, with exposure to sap that was absorbed systemically through scratches on the arm and leading to intense itching of arms, localized and then generalized erythema, perioral edema, severe dyspnea, disorientation, and lightheadedness.

Of the reactions to SPT, more than half were mild cutaneous reactions but 10 were severe, with airway involvement or hypotension (Table 3).

The suspected allergen was identified using criteria and patients were grouped accordingly: 19 with a clinical history of severe reaction, with the largest positive reactive wheal usually exhibiting spreading erythema from the SPT site; 4 with a large positive reactive SPT wheal; and 1 with a history and a positive SPT reaction. The reactive SPT wheal to the suspected allergen was larger than 8 mm in 75% (18 of 24).

Discussion

Skin prick tests are considered a fairly safe diagnostic procedure and there have been no reported fatalities from SPT in the past 14 years. The present study is the largest to date and involves all types of allergic disease in a specialist setting where a full range of allergens was tested.

The reaction rate (0.07%) was higher than in 2 studies of comparable size and duration in the United States with rates of 0.02% and 0.03%, respectively.^{8,9} Bagg et al⁹ reported a higher rate of 0.4% in a small sample of 1,456 patients. A possible reason for the high rate in the present study is that as the only specialist allergy center covering the east of England, the cohort of patients in this clinic could be more severely allergic. Although the overall reaction rate is higher than in comparable studies, the rate of reaction after aeroallergen SPTs only in the present series was 0.013, similar to that described by Lin et al,⁶ but in the present series aeroallergens were the cause in a minority. A weakness of this study is that the total number of patients undergoing SPT was estimated from attendance rates.

To the authors' knowledge, this is the first study to report on a case of a reaction to venom SPT and the second case (first severe case) of a reaction to drug SPT.^{12,13} Lockey et al¹² reported systemic reactions to venom SPT, although all patients had undergone SPT and intradermal testing. A patient in the present study developed erythema and lightheadedness after wasp SPT. In a large venom allergy practice of several thousand patients, no other patient has reacted to skin prick and intradermal testing with venom. Sullivan et al¹³ described 4 cases of rash after SPT to penicillins, of which only 1 was from SPT. In the present case, the reaction to penicillin SPT was more severe. Her index reaction (anaphylaxis after splashing Tazocin) also highlighted that she can react to SPT and therefore should take precautions, such as dilute concentrations of the drug, for SPT to prevent adverse reactions.

Foods were highlighted as the commonest cause of reactions to SPT (75%). More than half of those cases were due to nut (mainly peanut). Swender et al⁸ and Bagg et al⁹ each found that 5 of 6 cases were secondary to a combination of food and aeroallergens, and Valyasevi et al⁷ reported no reactions to food SPT. The rate of reaction to food was high at 0.05% in the present study. The prevalence of nut allergy has become more predominate since the mid-1990s and peanut allergy affects 1.5% of children and, hence, was not observed in the study by Valyasevi et al.^{7,11} The present rate was higher than the rate reported by Bagg et al⁹ because a small population was examined for a shorter period (12 months).

Table 3
Systemic reactions to skin prick testing^a

Patient number	No positive SPT reactive wheal ≥ 3 mm	SPT with reactive wheal >8 mm	Cause of reaction (size of SPT wheal if <8 mm)	SPT reaction severity grade	Treatment
1	2	None	Milk (5 mm)	1	Oral AH, top S
2	5	Milk, BN	BN	1	Oral AH
3	7	CN, Pis, BN	Pis	1	Oral AH
4	12	PN, BN, HDM, cat	PN [BN]	1	Oral AH
5	6	BN, WN	BN	1	Oral AH
6	2	Milk	Milk	1	Oral AH
7	5	PN	PN	1	Oral AH
8	8	None	Soy (3 mm)	4	Oral + IV AH, S + Ep + nebs
9	7	PN, HN	PN	1	Oral AH
10	6	PN, BN	PN	4	Oral AH
11	9	PN, TP, GP, horse	PN	1	Oral AH
12	8	PN, GP	PN	1	Oral AH
13	5	BN, WN, HN, almond, GP	WN [BN]	2	Oral AH, inhalers
14	9	HDM, GP, cat	Rat (6 mm)	2	Oral AH, inhalers
15	7	Pea (pp), pea (sol), lentil, HDM, GP	Pea + lentil	2	Oral AH, inhalers
16	5	Lupin, sesame	Lupin	2	Oral AH
17	6	Shrimp, crab, lobster, HDM	Shrimp	4	Oral AH, neb Ep
18	11	Spinach, cat, HDM, TP	Spinach	1	Oral AH, top S
19	2	None	Ragwort stems (5 mm), leaf (4 mm)	5	Oral AH + S
20	9	BN, CN, Pis, cat, GP	BN	3	Oral AH, IV S
21	3	None	Rabbit (5 mm)	5	Oral AH, IV AH, inhalers
22	4	None	Wasp (3 mm)	5	Oral + IV AH + S
23	5	GP	GP	1	Oral AH
24	3	Tazocin, amoxicillin, BP	Tazocin	5	Oral + IV AH, S + Ep + nebs

Abbreviations: AH, antihistamine; BN, Brazil nut; BP, benzylpenicillin; CN, cashew nut; Ep, epinephrine; GP, grass pollen; HDM, house dust mite; HN, hazelnut; IV, intravenous; nebs, nebulizers; Pis, pistachio; PN, peanut; pp, prick prick; SPT, skin prick testing; S, steroid; sol, solution; top S, topical steroid; TP, tree pollen; WN, walnut.

^aAllergens in brackets are less likely suspected causes of reaction.

Although the study by Swender et al⁸ was for a longer period (13 years), the study looked only at the medical notes of patients who were coded to have had SPT and epinephrine administration, thus missing potential adverse reactions that did not require epinephrine.

Other possible associations for adverse reactions included asthma, the severity of allergy, and large reactive skin test wheal. Age did not appear to be associated. In the authors' clinic, approximately 30% of patients are children and one third of SPT reactions occurred in children.

Asthma has been described as an associated risk factor in other studies. Fifty percent of the present patients had asthma, which was poorly controlled in 2. All 6 cases (5 having systemic reactions to SPT and 1 to intradermal testing) reported by Valyasevi et al⁷ had asthma, with poorly controlled asthma in half the cases, and Swender et al⁸ reported that half their patients had asthma. Five of the 6 fatalities reported after intradermal testing had a history of asthma.² Bernstein et al⁵ described a case of respiratory arrest after SPT to 90 food allergens. This patient had severe asthma with an forced expiratory volume in 1 second of 1.7 L (36% predicted) 2 weeks before SPT. Subsequently, it was recommended SPT should be withheld in patients with poorly controlled asthma, but the number of SPTs conducted and the severity of the food allergy are likely to be relevant. The authors run a difficult asthma clinic and a large proportion of patients have asthma as part of multisystem allergic disease; thus, most of these patients with asthma have no systemic reaction to SPT.

The severity of the patients' allergic disease and size of the positive SPT wheal also were noted as associations. Most patients (8 of 11) who had an index reaction of at least grade 4 had a grade 4 to 5 reaction to SPT. This included a patient who had a near fatal reaction to peanut who developed intense pruritus with laryngeal edema 15 minutes after SPT. The original reaction in the patient reacting to ragwort was severe anaphylaxis; and the patient who reacted to rabbit SPT was so allergic that she developed rhinoconjunctivitis and asthma when standing next to a field where

rabbits were running wild. Seventy-eight percent had at least 1 SPT reaction with a wheal of at least 8 mm. However, there was no correlation between the size of the wheal and the grade of the reaction.

The authors identified the allergen suspected to be responsible for the systemic reactions to SPT. The authors were responsible for the clinical care of these patients, knew them well, and were present when the SPT reactions occurred. Therefore, the identification of the suspected allergen responsible was well informed. In most patients, this was based on a history of severe allergy supported by very large or the largest SPT reaction. In most patients, the systemic reaction began with spreading erythema originating from the SPT site to this allergen. For example, patient 16 had a history of anaphylaxis to lupin flour and a large positive reaction to lupin flour (wheal of 10 × 18 mm that became edematous and spread). Her only other allergic reaction was mild rhinitis to house dust mite confirmed by a smaller positive reaction (wheal of 7 mm). In some patients, it was difficult to be certain because there were 2 possible allergens. For example, patient 13 had large positive reactions to walnut and Brazil nut, a definite history of walnut allergy, and a history of suspected Brazil nut allergy (reacting to a chocolate containing a nut). Patient 14 had a history of perennial house dust mite allergic rhinitis since 7 years of age but developed asthma in her 20s after acquiring pet rats that she kept in her bedroom. Skin tests were performed 2 years after the onset of rat allergy and her reaction to SPT mimicked the rat-induced symptoms. Patient 2 had 2 definite allergies clinically, to Brazil nut and milk, and strong positive reactions to each (Brazil nut wheal of 12 × 16 mm and a milk wheal of 10 mm). Based on the criteria used, Brazil nut was the suspected allergen for causing a systemic reaction. This was confirmed by subsequent SPT excluding Brazil nut when there was no systemic reaction despite the same SPT results for all other allergens including milk. Similarly, in patient 20, Brazil nut was identified as the cause and subsequent testing without Brazil nut did not provoke a systemic reaction.

The same highly experienced nurses conducted SPT using the same reagents for the reacting and non-reacting patients and there was nothing to suggest a technical error was responsible.

This is largest single-center study to identify foods as the commonest cause of reactions to SPT and to report the first case of a reaction to venom SPT and the first severe case of a reaction to drug SPT. Asthma, a history of severe reactions, and large SPT reactions were features of the patients who had adverse reactions. Therefore, precautions should be taken in patients with a history of severe reactions and possible diluted concentrations of drugs should be considered for SPT in similar patients. Allergens posing the highest risk were foods, especially nuts. There are risks when undertaking SPT, which should be performed by staff trained to recognize and treat reactions in a setting equipped with emergency medicines.

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