
Systemic reactions to allergy skin tests

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Background: Skin testing is a common diagnostic tool in allergy. It is considered a safe procedure, although systemic reactions have been reported.

Objective: To identify the systemic reaction rates of allergy skin tests and to determine the clinical outcome of such reactions.

Method: This retrospective study used a computerized database at the Mayo Clinic to identify patients who developed systemic reactions to skin tests. Altogether 497,656 skin tests were performed on 18,311 patients from January 1992 to June 1997. Skin puncture tests were performed on 16,505 patients. Skin puncture and intradermal skin tests were performed on 1,806 patients. Systemic reactions were evaluated and treated by physicians.

Results: There were 6 systemic reactions, an overall rate of 33 systemic reactions per 100,000 skin tests. All six patients had asthma. The systemic reaction rates for latex skin testing was 152 or 228 reactions per 100,000 latex skin tests, to penicillin and antibiotics 72 reactions per 100,000 penicillin and antibiotics skin tests, and to aeroallergens 15 or 23 reactions per 100,000 aeroallergen skin tests. The systemic reaction rate for skin puncture test was 30 reactions per 100,000 skin puncture tests, for skin puncture and intradermal skin tests, the rate was 55 reactions per 100,000 skin puncture and intradermal skin tests. All 6 patients were treated and dismissed within 1 hour after treatment.

Conclusion: The systemic reaction rate to skin tests was very low. Systemic reactions were mild and all patients recovered fully within 1 hour.

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INTRODUCTION

Since their introduction over a century ago, allergy skin tests have been an important diagnostic tool in allergic diseases. The number of allergens used in clinical practice has grown to include extracts derived from many pollens and molds, dusts, latex, insects, domestic and fur-bearing animal pelts, foods, antibiotics, bacterial vaccines, and antigens. There are several hundred skin testing reagents available today.

Allergy skin tests are considered safe. Lin et al reported 2 patients who had systemic allergic reactions to skin testing for respiratory allergies in 10,400 patients tested from June 1976 to December of 1989.¹ Between 1895 and 1968, more than 70 deaths were

reported after skin tests, mostly caused by antigens no longer in common use (horse serum-derived tetanus or diphtheria antitoxin and pneumococcal antiserum).² Lockey et al³ reported six deaths associated with skin tests from 1964 to 1983; all six subjects had intradermal skin tests. Reid et al,⁴ in a questionnaire survey study from practicing allergists, reported no fatalities with skin testing for the years 1985 to 1989. Our retrospective study from January 1992 to June 1997 of over 18,000 patients found 6 systemic reactions, but no fatalities.

METHODS AND MATERIALS

Patients

In this retrospective study we used a computerized data base at the Mayo Clinic to identify patients who developed systemic reactions to skin tests. As shown in Table 1, we performed 497,656 skin tests to various allergens on 18,311 patients evaluated for allergic diseases from January 1992 to June

1997 (average of 27.2 skin tests/patients). There were 11,258 females and 7,053 males. Sixteen thousand five hundred and five patients received skin puncture tests. Two hundred sixty-nine patients (Hymenoptera), 1,383 patients (penicillin and other antibiotics), and 154 patients (other drugs) received skin puncture tests followed by intradermal skin testing (15 minutes after skin puncture test). This study was approved by the Institutional Review Board at the Mayo Clinic.

Skin Test Methods

For skin puncture tests, the commercially available glycerinated allergenic extracts were applied on the volar surface of the forearm in droplets one inch apart by 9 nurses. The skin was punctured by a bifurcated needle (Allergy Labs of Ohio, but for the past 2 years Duotip-test, Lincoln Diagnostics, Inc) at perpendicular angle through the droplets with downward pressure on the skin. For penicillin and other antibiotics, other drugs, and venom skin tests, both skin puncture tests and intradermal skin tests were performed. The intradermal tests were performed by injecting the testing reagent intracutaneously using a sterile plastic disposable 1-mL tuberculin syringe through a 26-gauge or 27-gauge needle. For venom intradermal skin testing, approximately .02 to .03 mL of testing reagent was injected to create a 5 × 5 millimeter superficial bleb. For penicillin and other antibiotics and other drugs, approximately .01 to .02 mL of testing reagent was injected to create a 2 × 2 millimeter superficial bleb. The wheal-and-flare reaction was measured and recorded 15 minutes after the application of the testing reagent. The patients would report any systemic reactions to the nurses. All the systemic reactions were evaluated by physicians. The physicians initiated

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Table 1. Types of Skin Test

Types of Testing	Techniques	Females	Males	Total
Aeroallergen	SPT	7,187	5,031	12,218
Aeroallergens/ingestants	SPT	716	284	1,000
Food/ingestants	SPT	1,332	639	1,971
Latex	SPT	1,012	304	1,316
Penicillin and other antibiotics	SPT & ID	732	651	1,383
Hymenoptera venoms	SPT & ID	145	124	269
Other drugs	SPT & ID	134	20	154
Total		11,258	7,053	18,311

SPT = skin puncture test and ID = intradermal skin test.

Table 2. Skin Test Methods and Systemic Reaction Rates

Skin Test Methods	Subjects Tested	Subjects With SR	Rates per 100,000	CI (95%)
SPT	16,505	5*	30.3	9.8–70.7
SPT & ID	1,806	1*†	55.4	1.4–308.5
Overall	18,311	6	32.8	12.0–71.3

Definitions: SPT = skin puncture test, ID = intradermal skin test, SR = systemic reaction, and CI = confidence intervals.

* $P = .4637$ (Fisher's exact test).

† Patient 6 (Tables 4, 5, and 6) had a systemic reaction to the intradermal skin test after a negative skin puncture test to penicillin.

Table 3. Types of Skin Test and Systemic Reaction Rates

Types of Skin Test	Patients Tested	Patients with SR*	Rates per 100,000†	CI (95%)
Latex	1316	2 or 3	152 or 228	18.4–549.0 or 47.0–666.2
Penicillin and antibiotics	1383	1	72.3	1.8–402.9
Aeroallergens	13218	2 or 3	15.1 or 22.7	4.7–66.3 or 1.8–54.7
Others‡	3394	0	0	0–108.7

Definitions: SR = systemic reaction and CI = confidence intervals.

* Patient 3 (Tables 4, 5, and 6) tested positive to both aeroallergen and latex.

† Ranges of systemic reaction rates for latex and aeroallergens skin tests with and without patient 3.

‡ Other drugs, Hymenoptera venoms, foods, and ingestants.

treatment of the systemic reactions and made the clinical decision to dismiss the patients after recovery.

Extracts

We used the commercially available allergenic reagents (except for latex reagent which was prepared in our laboratory) in 50% glycerin diluent. Latex reagent in 50% glycerine diluent was prepared to a concentration of 0.23 mg/mL of total protein from Body Guards gloves, T. K. Glove Products Co. LTD. The reagents were refrigerated at 4°C.

Interpretation of Skin Test Results

With the skin puncture test, we considered both a wheal diameter larger than 3 mm surrounded by an erythema (flare) to be positive. Pseudopods, irregular extensions of the wheal, were indicative of high allergenic sensitivity. For an intradermal skin test, we considered a wheal of at least 5 mm in diameter and a surrounding flare to be positive.

Systemic Reactions

The symptoms and signs of a possible systemic reaction were observed and

recorded by nurses and physicians. These subjective and objective manifestations included the following; pruritus or flushing, urticaria and angioedema; asthmatic symptoms such as, cough, chest tightness, wheezing, and dyspnea; as well as hay fever symptoms such as eye itching, nasal congestion and sneezing.

Statistics

Fisher's exact test was used to test if the systemic reactions rates are different between skin testing techniques and gender. A P value of $<.05$ was considered significant. Confidence limits of the systemic reaction rates were calculated based on Poisson distribution at 95%.

RESULTS

Table 1 summarizes the types of allergens tested, the techniques used and the gender profiles of the patients. There were 6 systemic reactions in 6 patients (average age 30 years) out of 18,311 patients who had skin tests. The overall rate of systemic reactions to allergy skin test was 33 systemic reactions per 100,000 allergy skin tests (Table 2). Five out of 6 patients with systemic reactions had skin puncture tests; the rate of systemic reaction to skin puncture test was 30 systemic reactions per 100,000 skin puncture tests. One patient (patient 6 in Tables 4, 5, and 6) developed a systemic reaction following intradermal skin tests (after negative skin puncture tests). The rate of systemic reactions to intradermal skin testing was therefore 55 systemic reactions per 100,000 Intradermal skin testing. Two patients with systemic reactions had positive skin puncture tests to aeroallergens. Two patients with systemic reactions had a positive skin puncture test to latex. One patient (patient 3 in Table 4, 5, and 6) was tested who had positive skin puncture tests to both aeroallergens and latex. As shown in Table 3, the rate of systemic reactions to latex skin puncture test was 152 or 228 systemic reactions per 100,000 latex skin puncture tests, depending on whether patient 3 was considered to have a

Table 4. Patient Profiles

Pat.	Date	Sex	Age	Clinical Diagnoses	Medications
1	7/21/92	F	31	Asthma (asymptomatic), allergic rhinitis, migraine	Beclomethasone nasal spray, terfenadine, theophylline
2	10/21/94	F	30	Asthma (faint wheezing, FEV ₁ = 116%), allergic rhinitis	Prednisone (oral) 10 mg a day, theophylline, albuterol (oral), bitolterol MDI BID, albuterol aerosolized once a day
3	10/9/95	F	35	Asthma (asymptomatic, FEV ₁ = 81%), allergic rhinitis	Beclomethasone MDI, albuterol MDI, salmeterol MDI
4	1/14/94	F	23	Asthma (exercise induced), tracheostomied for vocal cord dysfunction, deep vein thrombosis	Diphenhydramine, warfarin
5	6/19/97	F	54	Asthma (wheezing, coughing, dyspnea, FEV ₁ = 91%), hypertension, anaphylaxis	Triamcinolone MDI, cetirizine, albuterol MDI, verapamil
6	6/1/95	M	9	Upper respiratory tract induced asthma (asymptomatic), cerebral palsy	Albuterol aerosolized as needed, Phenobarbital

Pat. = patient, F = female, M = male, MDI = metered-dose inhaler, BID = twice a day, and FEV₁ = force expiratory volume at 1 minute.

reaction to latex. The rate of systemic reactions to aeroallergens skin puncture test was 15 or 23 systemic reactions per 100,000 aeroallergens skin puncture tests depending on whether patient 3 was considered to have a reaction to aeroallergen skin tests. One patient developed a systemic reaction after a positive intradermal skin test (after a negative skin puncture test to penicillin). The rate of systemic reaction to penicillin and other antibiotics skin testing was 72 systemic reactions per 100,000 penicillin and other antibiotics skin tests.

As shown above in Table 1, 11,258 females and 7,053 males were skin tested (Table 1). Of the 6 patients who had systemic reactions, 5 were females and 1 was male ($P = .4185$). Only about 11% of all patients who were skin tested had asthma listed as a diagnosis. All patients with systemic reactions had asthma; two of these patients had evidence in their medical records that their asthma was not optimally controlled at the time of the skin test (Table 5). They were wheezing during their physical examination prior to skin testing.

Five systemic reactions occurred within 25 minutes (Table 7), one patient who had a systemic reaction returned back to the clinic 75 minutes after the skin test. All 6 patients with systemic reactions had respiratory complaints of dyspnea or chest tightness and 5 patients with systemic re-

Table 5. Skin Tests and Results

Pat.	Test	Positive Skin Tests
1	SPT	Cat 3 × 5 P F, Cattle 3 × 3 F, Dog 4 × 5 F, Horse 6 × 7 P F, DF 7 × 7 P F, DP 5 × 4 F, KB 5 × 3 F, Tim 3 × 3 F, Birch 10 × 7 P F, Alder 5 × 7 P F, Oak 3 × 4 F, SRW 12 × 7 P F, Pig weed 3 × 5 F, Alt 8 × 6 F, Hormo 4 × 5 F
2	SPT	Cat 7 × 5 F, DF 5 × 6 F P, DP 7 × 8 F P, Alt 5 × 6 F P, Hormo 4 × 5 F P, Mixed smut 4 × 4 F, SRW 9 × 12 F P
3	SPT	Cat 4 × 4 F, Dog 4 × 4 F, Horse 5 × 5 F, Alt 6 × 6 F, Mixed smut 3 × 3 F, BW 5 × 5 F, Oak 4 × 3 F, KB 7 × 8 F P, Orch 10 × 7 F P, Tim 10 × 7 F P, Koch 8 × 6 F P, Pigweed 3 × 3 F, Russian 3 × 3 F, SRW 5 × 5 F, Cornstarch 3 × 3 F, Latex 1:10 3 × 3 F, Latex (Bencard) 1:10 3 × 4 F P
4	SPT	Latex 1:10 25 × 15 F P, Latex 903 10 × 12 F P
5	SPT	Latex 1:10 5 × 6 F
6	SPT & ID	new mix Penicillin G 4 × 4, 10 × 12 F, Benzylpenicilloyl 4 × 4, 12 × 10 F, Penicilloate 3 × 3, 6 × 6

Definitions: Wheal is reported in millimeter, P = pseudopod, F = flare, DF = *Dermatophagoides farinae*, DP = *Dermatophagoides pteronyssinus*, SRW = short ragweed, Alt = *Alternaria*, Hormo = *Hormodendrum*, BW = black walnut, KB = Kentucky blue, Orch = Orchard, Tim = Timothy, Koch = *Kochia*, Russian = Russian thistle, SPT = skin puncture test, ID = intradermal skin test, Pat. = patient.

actions had dermatologic complaints of flushing, itching, or urticaria. All systemic reactions responded to treatment with subcutaneous injection of epinephrine and oral antihistamines. All patients with systemic reactions were discharged within 60 minutes after treatment initiation.

DISCUSSION

This is the largest series of patients (18,311) studied for systemic reactions to skin testing. This is also the largest study involving skin testing for a wide

variety of allergens (ie, aeroallergens, foods, drugs, venoms, and latex).

We report, retrospectively, an overall systemic reaction rate to allergy skin tests of 33 systemic reactions per 100,000 allergy skin tests. In an earlier prospective study the reaction rate to allergy skin tests (skin prick test followed by intradermal skin test if skin prick test was negative) in patients evaluated for respiratory allergies was 19 systemic reactions per 100,000 allergy skin tests.¹ In our report, in addition to respiratory allergy skin test-

Table 6. Systemic Reactions

Pat.	Time* (min)	Symptoms	Treatments	Time† (min)
1	20	Chest tightness, hoarseness, lightheadedness, flushing, shaky feeling	0.2 mL epinephrine, terfenadine 120 mg	60
2	75	Chest tightness, lip swelling & itching, normal blood pressure	0.2 mL epinephrine, terfenadine 60 mg	45
3	25	Dyspnea, localized arm swelling, itching & erythema, itching; throat, ear	0.2 mL epinephrine, terfenadine 60 mg	15
4	10	Large localized arm swelling, dyspnea, normal blood pressure	diphenhydramine 200 mg (oral)§	45
5	0	More wheezing, cough, dyspnea, normal blood pressure	0.2 mL epinephrine, terfenadine 60 mg, prednisone	45
6	10	Dyspnea and urticaria	0.1 mL epinephrine	30

Definitions: Pat = patient and min = minute.

* Interval between application of skin tests and development of symptoms.

† Interval between initiation of treatments and dismissal from clinic.

‡ Epinephrines were given by subcutaneous injection.

§ Patient refused epinephrine subcutaneous injection.

ing (15 or 23 systemic reactions per 100,000 respiratory allergy skin tests), we include skin tests to drugs, venom, latex, and foods and ingestants.

Patients with systemic reactions were predominantly female (5 out of 6), and all had asthma (half of these patients may have had poorly controlled asthma). These differences in reaction rates of males and females is not statistically significant. In earlier reports, women had a higher rate of systemic reactions to skin testing and immunotherapy than men (3.5% for women and 2.2% for men).¹ In a survey study of practicing allergists, Lockey et al, reported 6 fatalities to intradermal skin tests, five of whom had asthma.³ The symptoms and signs of systemic reactions to skin testing in our patients were predominantly respiratory and dermatologic.

The rates of systemic reactions to intradermal skin tests to skin puncture tests were not statistically significant. Earlier studies^{5,6} suggested that intradermal skin tests carried more risk of systemic reactions than skin prick tests.

Previous studies stated that the latex skin prick test was safe and, if per-

formed properly, did not cause an adverse reaction.⁷⁻¹¹ More recent studies^{12,13} reported anaphylactic reactions to the latex skin prick test. Kelly et al¹³ reported 9 out of 107 patients (86 patients with spina bifida, 15 health care workers with symptoms of latex allergy, and 7 patients with symptoms of latex allergy) who had systemic reactions to latex skin puncture tests (Multi-Test, Lincoln Diagnostics, Inc). Only three out of 9 patients who had systemic reactions had prior anaphylaxis when exposed to latex. The use of Multi-test skin puncture tests (serial 10-fold dilutions ranged from 1:1000 to 1:10,000 concentrations and 1:1,000,000 to 1:100,000 concentrations in patients with a history of anaphylaxis) in a high risk group of patients might have contributed to a high rate of systemic reactions in this earlier study. In our study, only one of the three possible patients who had systemic reactions to latex skin puncture tests had a history of a prior anaphylactic reaction upon exposure to latex. Systemic reactions with latex skin testing may perhaps due to its high allergenicity and the non-standardization of latex skin test preparations. Our obser-

vations, together with the earlier findings reviewed above, demonstrated that latex skin prick testing contributed a small but definite risk of inducing a systemic reaction. Systemic reactions to latex skin puncture test may occur, even in the absence of a history of prior anaphylaxis to latex.

The rate of systemic reactions to penicillin skin testing was 72 systemic reactions per 100,000 penicillin skin tests. Gadde et al¹⁴ reported 12 systemic reactions and 1 large local reaction to penicillin skin testing in 5063 patients tested (237 systemic reactions per 100,000 penicillin skin tests) which is still within 95% confidence interval of our finding.

It is noteworthy that there were no systemic reactions to skin tests for foods or venoms. Systemic reactions to both foods and venom skin testings have been reported in the past.^{3,15,16} It is possible that patients at high risk for a systemic reaction to skin testing (eg, patients with a history of life threatening anaphylaxis) either did not undergo allergy testing at all or had in vitro IgE antibody tests instead. We also may be underreporting systemic reaction rates since we routinely observe patients who have allergy skin testing for only 30 minutes. It is possible that systemic reactions that developed after 30 minutes were not called to our attention.

Most of our systemic reactions occurred within 25 minutes of testing. Lockey et al³ reported that all 6 fatalities from intradermal skin testing developed within 20 minutes. Importantly, in our series, systemic reactions were generally not severe and responded quickly and completely to the subcutaneous injection of epinephrine and administration of oral antihistamines. Overall, our results suggest that skin testing is a safe procedure.

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