

Safety of intradermal skin tests for inhalants and foods: a prospective study

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Background: Intradermal skin testing is a useful allergy diagnostic tool. Although considered safe when properly performed, systemic reactions have been reported. This is the first large, prospective study to record and evaluate all systemic reactions from intradermal skin testing (IDT) to inhalant or food antigens.

Methods: A 24-month prospective study by 40 physician practices, recording all IDT tests, including reactions, symptoms, severity, time after injection, and reaction treatments.

Results: Eighty systemic reactions (22 major) occurred among 20,530 patients (878,583 wheals). Nine had epinephrine treatment, 4 were observed in an emergency department, and there were no hospitalizations or fatalities. The overall systemic reaction risk was 0.009%. The

risk of having a major reaction was 0.003%, or 1 reaction per 933 patients.

Conclusion: Intradermal skin tests for inhalants or foods, when performed with appropriate precautions, have a safety profile comparable to skin prick tests. © 2012 ARS-AAOA, LLC.

Key Words:

intradermal skin tests; skin test safety; anaphylaxis; non-IgE-mediated food allergy; food allergy; inhalant allergy; subcutaneous immunotherapy

How to Cite this Article:

Gordon BR, Hurst DS, Fornadley JA, Hunsaker DH. Safety of intradermal skin tests for inhalants and foods: a prospective study. *Int Forum Allergy Rhinol.* 2012; 00:X-XX.

Skin testing and subcutaneous immunotherapy (SCIT) are widely used in the United States,¹ and skin prick tests (SPT) and intradermal skin testing (IDT) are used to diagnose aeroallergen, food, and other allergies. These injections are considered safe, although fatalities have occurred. Most U.S. allergy reaction reports combine data from both skin testing and SCIT. Prior to 1970, fatalities were likely related to horse sera reactions and to insufficient epinephrine use. In Mexico, no fatalities have been reported for SCIT, SPT, or IDT.² A 2007 Cochrane Systemic Review

of pollen SCIT studies reported overall systemic reaction rates of 0.13% for active therapy vs 0.01% for placebo.³

In recent decades, use of IDT has been criticized. For example, inhalant testing guidelines, from Global Allergy and Asthma European Network (GA²LEN) and Allergic Rhinitis and its Impact on Asthma (ARIA) recommended that IDT should not be used because of lower safety and uncertain clinical benefit.⁴ On the other hand, Calabria and Hagan⁵ concluded that IDT may be helpful when the SPT result is negative yet there is a history of symptoms on exposure. IDT, in this circumstance, may identify patients with low levels of clinical sensitivity in whom a positive test result may be clinically very relevant. Demoly and Bosquet⁶ concur: "The value of prick-puncture tests is limited by low-potency extracts inducing false negative results . . . in patients with low sensitivity, intradermal skin tests may produce the only positive results." IDT has been found to correlate with nasal antigen challenge in patients who were SPT negative.⁷⁻⁹ IDT also has better reproducibility than SPT due to the greater accuracy of syringe measurement.¹⁰

IDT is therefore of value, but only if no excess testing risk exists. The critical difference between using SPT and using IDT is the *absolute need for screening for high sensitivity* prior to placing any high concentration IDT tests. IDT must be preceded by SPT, in vitro tests, or a serial dilution of

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Funding sources for the study: American Academy of Otolaryngic Allergy Foundation.

Potential conflict of interest: None provided.

Presented at the Annual Meeting of the American Academy of Otolaryngic Allergy Foundation, September 9, 2011, San Francisco, CA

Received: 6 March 2012; Revised: 7 June 2012; Accepted: 3 June 2012

DOI: 10.1002/alr.21091

View this article online at wileyonlinelibrary.com.

IDT from extremely dilute antigen, allowing time for initial reactions to be evaluated before proceeding. This study was designed to determine if IDT tests, with proper precautions, produced a different risk from that reported for SPT.

Patients and methods

Practice demographics and data collection

This was a 24-month prospective study conducted in 40 U.S. medical offices of board-certified otolaryngologists who had been in practice for at least 5 years, and adhering to the educational precepts of the American Academy of Otolaryngic Allergy (AAOA).¹¹ Demographics, including testing method and safety precautions, were obtained from these geographically diverse, academic, military, and private practice sites. A standard report form recorded number of patients tested, number of skin wheals placed, location and circumstances for testing, and whether the testing was to inhalants or foods. Every reaction requiring medical intervention was separately reported on a standardized incident report form that recorded patient symptoms, treatment rendered, time of onset, and possible comorbidity factors. Reports were sent monthly, collated, verified, and stored for analysis.

Reaction definitions

A reaction was considered major systemic if it produced any substantial symptoms at a location distant from the injection site, including: persistent wheezing, a feeling of tightness in the throat or chest, general rash or urticaria, angioedema, throat edema, dyspnea, hypotension, or any reaction requiring use of epinephrine and/or treatment in an emergency room (ER) or department. Minor systemic reactions included: local swelling, urticaria, wheal >2 cm, or rash, accompanied by itching, lightheadedness, dizziness, headache, or anxiety. Reactions were considered to be nonsystemic if no medication was given and there were no systemic symptoms. Vagal response or panic attack was considered nonsystemic. All reactions were classified according to these criteria.

Testing methods and safety precautions

Patients underwent appropriate medical screening and informed consent. Emergency equipment and qualified personnel were on site for all testing. Patients were tested for inhalants (pollens, molds, and indoor allergens) and/or foods. Inhalant testing, from either standardized or 1:20 weight per volume (wt/vol) commercial extracts, was initiated either with SPT, followed by a #2 dilution, 1:500 wt/vol IDT wheal (modified quantitative testing [MQT]),¹² or by 5-fold IDT titration, beginning with dilution #6 (1:312,500 wt/vol), or, in less sensitive patients, with dilution #4 (1:12,500 wt/vol).^{10,13} Food allergy patients were all regularly eating all foods to be tested, and ate those foods within 24 hours of being tested, whereas foods known or suspected to be anaphylactic, or foods already being

TABLE 1. Number of patient encounters, treatment injections, and systemic reactions

	Inhalants	Foods	Total	Severe
Reactions	72	8	80	22
Patient encounters (n)	18,822	1,708	20,530	20,530
Injections (n)	834,983	43,600	878,583	878,583
Per 100,000 patients	382	468	390	107
Per 100,000 injections	8.62	18.3	9.1	2.5
Patients for 1 reaction (n)	261	214	257	933
Injections for 1 reaction (n)	11,597	5,450	10,982	39,935
Reactions per patient (%)	0.38	0.47	0.39	0.11
Reactions per injection (%)	0.009	0.018	0.009	0.003

TABLE 2. Major systemic symptoms during immediate and late reactions*

Symptom	Patients showing symptom (n)		
	Immediate	Late	Total
Throat/chest tightness	28	0	28
Wheezing	9	0	9
General urticaria	9	0	9
Angioedema	6	0	6
General rash	3	0	3
Hypotension	2	0	2
Major symptom total	57	0	57

*N = 22 patients.

avoided, were not tested. Testing with commercial 1:10 wt/vol food concentrates, was usually initiated at #3 dilution, (1:1,250 wt/vol), and in less sensitive patients, with #1 dilution, (1:50 wt/vol).¹⁰

Results

Reaction types

During this study, 20,530 patients experienced 72 reactions during 834,983 inhalant tests, and 8 reactions during 43,600 food tests (Table 1). Most patients experienced multiple symptoms: 22 patients with major reactions experienced 57 symptoms (Table 2), whereas 58 minor reaction patients experienced 123 symptoms (Table 3). There were no fatalities or hospitalizations. Overall reaction rates were 0.40% per patient, 0.009% per injection, or 1 systemic reaction per 933 patients.

Time to reaction

Eighty-two percent of reactions occurred within 20 minutes, 18% had delayed symptoms, and 4 of these

TABLE 3. Minor systemic symptoms during immediate and late reactions*

Symptom	Patients showing symptom (n)		
	Immediate	Late	Total
Wheal >2 cm	7	41	48
Mild sneezing	19	14	33
Local swelling/urticaria	7	13	20
Limb rash/urticaria	9	0	9
Minor headache	0	8	8
Vagal/anxiety responses	2	3	5
Minor symptom total	44	79	123

*N = 58 patients.

experienced very delayed symptoms 2 to 48 hours after testing. The percent reacting within 20 minutes was similar to that previously reported for SCIT reactions.¹⁴ Sixty-six patients reacted in the office, 12 at home, and 2 in their automobile. Symptoms observed during reactions are listed (Tables 2 and 3).

Responsible antigen

Seventy-two reactions were ascribed to inhalants (49 in season), and 49 reactors also had mold testing, either alone, or with other inhalants. Only 8 patients reacted after food testing. The reaction rate per patient for inhalant tests was 0.38%, and for foods was 0.47% (Table 1). These were not statistically significantly different. (chi square with Yates correction, $p = 0.73$)

Response to reactions

ER visits

Four patients were classified as major reactors due to ER visits. Patient A received office epinephrine, then was observed in the ER for 2 hours and released with no further treatment. Patient B was treated with office albuterol inhalation, then sent to the ER for observation. She was diagnosed with a panic attack, and received no additional antiallergic treatment. Patient C had no office symptoms, then spent 3 hours in a hair salon. She went to the ER at 3:00 AM because of chest tightness, was diagnosed as chemically sensitive, and received epinephrine. Patient D had no office symptoms, and had an auto accident on his way home. In the ER, the neurologic exam was nondiagnostic, with no allergic signs or symptoms, and no allergic treatment was given.

Reactions and treatment

Medication treatments (Table 4) included: 9 injected with epinephrine (14%), 13 who inhaled albuterol (20%), and 42 given oral corticosteroids (65%). Identified risk factors

TABLE 4. Treatments for major and minor reactions

Treatment given	Number of treated patients			
	22 Major reactions	58 Minor reactions	Total	Percent
Resuscitation	0	0	0	0
Emergency department visit	4	0	4	5
Drug treatment	21	19	40	50
Oral antihistamine	21	19	40	—
Oral steroid	11	10	21	—
β -agonist inhaler	13	0	13	—
Intravenous heparin	1	0	1	—
Intramuscular epinephrine	9	0	9	—
Observation only	0	36	36	45

for reactions included asthma (13.8%), previous history of reaction (8.8%), and beta blockade (2.5%).

Discussion

Reported risk from prick tests

It is difficult to obtain accurate data on SPT risk. Differing definitions of reaction types, retrospective surveys and reviews, and combination of testing with immunotherapy data add complexity. Prick tests appear to have an overall systemic reaction risk of about 0.02%,¹⁵ with very few deaths recorded. A retrospective study of inhalant SPT found 1 reaction in 55,000 patients, a risk of 0.002%.¹⁶ A second retrospective review of 18,000 patients found 2 aeroallergen patients reacting to SPT, none to combined SPT with IDT, and, including tests for latex and antibiotics, the overall SPT systemic reaction rate was 0.03%.¹⁷

Reported risk from intradermal tests

The 1987 report by Lockey et al.¹⁸ has often been cited as reporting a high risk from IDT, but this work actually reports that deaths can occur *from the incorrect use of IDT*. Regrettably, in subsequent guidelines, it is this single, dated report that is cited as the basis for blanket condemnation of intradermal testing. Of 46 deaths in the U.S. from 1945 to 1984, only 6 were documented to have occurred from skin testing. In 5 of those deaths, IDT was done *without prior SPT or equivalent low dose IDT*. Therefore, these cases actually reveal the risk of improperly performed IDT.¹³ Lockey¹⁹ recognized this fact, and stated: "Risk factors identified for skin testing included IDT without preceding prick, puncture, or scratch testing [. . .] Prick, puncture, or scratch testing should precede intradermal testing (unless very dilute intradermal tests are done initially)". There are no prospective data to support the contention that IDT is more hazardous than any other form of allergy skin test.

TABLE 5. Mortality reports since 1985 from intradermal testing or immunotherapy

Author	Study date	Study type	SCIT deaths	IDT deaths
Reid et al. ²⁰	1985–1989	S	17	2
Valyasevi et al. ¹⁷	1992–1997	R	na	0
Bernstein et al. ²¹	1990–2001	S	41	1
Cook et al. ²²	1994	S	6	0
Hurst et al. ¹⁴	1993–1995	P	0	na
Gordon (this study)	2012	P	na	0
Deaths since 1985			64	3

IDT = intradermal skin testing; na = not applicable; P = prospective; R = retrospective; S = survey; SCIT = subcutaneous immunotherapy.

TABLE 6. Comparison of major reaction incidences: immunotherapy vs intradermal testing

	Prior SCIT safety study ¹⁴	This IDT safety study	Relative risk of IDT vs SCIT
Major systemic reactions	31	22	–
Patient encounters (n)	276,678	20,530	–
Injections (n)	646,012	878,583	–
Patients for 1 reaction (n)	8,925	933	9.6
Injections for 1 reaction (n)	20,839	39,935	0.52

IDT = intradermal skin testing; SCIT = subcutaneous immunotherapy.

Reaction risk comparison of intradermal tests with immunotherapy injections

Since 1985, 64 U.S. deaths have been reported following SCIT compared with only 3 following IDT (Table 5).^{16,17,19–23} The relative numbers of these reports suggest that SCIT is more hazardous than IDT; however, the denominators are unknown. Also, these reports are retrospective or based on questionnaire surveys, and thus subject to significant potential systematic errors due to both recall and response biases. In contrast, this report is now the second prospective study not subject to these biases. Hurst et al.¹⁴ prospectively reported 1.14 million SCIT inhalant immunotherapy injections: SCIT was found to be safe, with no reported fatalities. In that study, only 31 major systemic reactions were observed among 277,000 patients receiving SCIT for 1 year, a frequency of 1 per 21,000 injections or 1 per 8900 patients per year (Table 6).

Our current observation of 22 major systemic reactions in 20,530 patients following IDT gives a risk of 1 reaction per 40,000 injections or 1 per 933 patients (Table 1). From the perspective of a single patient *injection*, IDT testing for inhalant allergy or non-immunoglobulin E (IgE)-mediated foods has less risk than SCIT treatment (Table 6). An IDT

testing *session* for either inhalant allergy or foods is substantially less risky than a year of SCIT treatment (1 reaction per 933 patients vs 1 reaction per 174 patients, about a 5-fold lower risk). This prospective data confirms our clinical impression that the risk of reactions from IDT for either inhalants or foods is in the same very low range as the risk from both SCIT injections and prick tests. No deaths, hospitalizations, or need for resuscitation were observed in either prospective study, whether for IDT or SCIT, when testing and treatment was done with appropriate precautions.^{10,11}

Reaction risk from food skin tests

Unlike inhalant allergy, food allergies occur in 2 clinical patterns: IgE-mediated and non-IgE-mediated.^{10,24} Oral food challenges are the gold standard used to test whether or not there is allergy of either type. Despite sensitivity differences, in vitro, SPT, and IDT tests are all appropriate diagnostic methods for IgE-mediated food allergy.^{5,25} However, some studies have shown patients with positive oral food challenges to have negative SPT or in vitro tests.^{24,26} The poor correlation of SPT and in vitro tests with clinical symptoms likely reflects the number of people with non-IgE-mediated reactions to foods. In the absence of other sensitive, specific laboratory tests for food allergy, IDT has been used to test for non-IgE-mediated food reactions,²⁷ and avoids the inconvenience and risk of multiple oral challenges. Yet current guidelines state, based primarily on opinion, and not on data, that there is significant risk to food IDT.^{28,29}

IgE-mediated food allergy detection by intradermal tests was once common, but has declined in recent years because of the belief that intradermal tests are more prone to false-positive results than SPT, combined with the belief that IDT is more hazardous than SPT.^{15,29–31} For example, Liccardi et al recommend IDT only for selected diagnostic procedures, where alternatives are not applicable.¹⁵ And, the German and Swiss Allergology organizations' guideline on food skin testing largely agreed.³² Primarily due to perceived risk, they did not suggest IDT, except in rare cases. Despite these opinions, a joint task force report on allergy testing from the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) recently reiterated the reproducibility of IDT and its usefulness when SPT results are discordant with history.²⁸

Risk factors for reactions to skin tests

Severe reactions have occurred during testing for highly reactive allergens, such as antibiotics, latex, venoms, or IgE-mediated anaphylactic foods like peanuts. For such antigens, use of in vitro tests, when available, is often a prudent choice. Many risk factors for SCIT reactions have been identified,¹⁴ and some of these also apply to testing, including: unstable asthma, excessive allergen dose (too many tests), or high dose in pollen or mold season (high allergen load), prior systemic reaction, potent allergens,

inexperienced physician, technical error, current increased symptoms, high sensitivity patient (brittle), β -blocker treatment, and patient age <5 years.

The 1 *critical risk* specific to IDT testing for inhalants or IgE-mediated foods is the risk of not excluding high-sensitivity allergy. IDT must always be preceded by SPT or must proceed only after first testing using a dilute IDT screening strength. Some earlier skin testing guidelines recommended performing SPT, followed, if any SPT were negative, by single, concentrated IDT at 1:1000 wt/vol, or another high strength. This large jump in antigen exposure ignores the precautions cited by Lockett,¹⁹ and adds unnecessary risk. Adhering to more conservative increases in antigen concentration may be 1 important factor that accounts for the very good IDT inhalant and food testing safety reported in this work.

It is impractical to eliminate all risks during skin testing, regardless of technique. It is important to realize that with the reaction incidences that we report, anyone who practices allergy for years will be responsible for administering thousands of tests, and therefore, must expect, and be prepared to treat, at least 1 serious systemic reaction.

Conclusion

We report observations from 878,583 intradermal tests done in 20,530 patients to detect allergy to inhalants or foods. There were 80 systemic reactions, 22 major. Only 9 patients required epinephrine. Eighty-two percent of reactions occurred within 20 minutes. There was no significant difference in rate of reactions to testing for inhalants as compared with foods. The overall systemic reaction risk was 0.009%. The risk of having a major reaction was 0.003%, or 1 reaction per 933 patients (Table 1). From the perspective of a single-patient encounter, IDT testing for either inhalant allergy or foods is substantially less risky than continuing SCIT treatment (Table 2). This prospective study demonstrates that properly performed intradermal tests for both inhalants and foods are safe, with a level of safety comparable to that of SPT. ④

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Acknowledgments

For expert research assistance, we thank the staff from Frazier-Grant Medical Library, Cape Cod Hospital: Jeanie Vander Pyl, MLIS, Director, June Bianchi, Library Assistant, and Deborah Tustin, MLIS, Library Assistant; and also Patty Welles, Office Manager for Dr Hurst, for collating and maintaining the databases.

Appendix A:

Contributing physicians and practice locations

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