

The rate of epinephrine administration associated with allergy skin testing in a suburban allergy practice from 1997 to 2010

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ABSTRACT

Allergy skin testing is considered a safe method for testing for IgE-mediated allergic responses although anaphylactic events can occur. Reported rates of anaphylaxis per patient are not consistent and range from 0.008 to 4%. The aim of this study was to determine the rate of epinephrine use associated with allergy skin-prick testing (SPT) and intradermal testing (IDT) in a suburban practice over 13 years. This retrospective chart review used billing and procedure coding records during the time period from January 1997 to June 2010 to identify encounters where epinephrine was administered after SPT or IDT. Patient encounters with procedure codes for skin testing plus either parenteral epinephrine, corticosteroid, antihistamine, or i.v. fluid administration were identified. These patient charts were reviewed to determine if epinephrine was administered, whether systemic reactions developed, and rates of epinephrine administration were calculated. There were 28,907 patient encounters for SPT and 18,212 for IDT. Epinephrine was administered in six patient encounters (0.02%) where SPT was performed; no IDT encounters led to epinephrine administration. There were no fatalities. Allergy skin testing to a variety of allergens, when administered by well-trained personnel, is a safe procedure. This study, involving the largest population to date, showed a rate of systemic reactions requiring epinephrine of 20 per 100,000 SPT visits. No epinephrine was given after IDT.

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Skin-prick testing (SPT) and intradermal testing (IDT) are frequently used to assess IgE-mediated sensitivity to a variety of allergens. Despite years of experience in administering allergy skin tests, the reported rates of systemic reactions to these tests are inconsistent.¹ Previous studies have been hampered by short study periods, use of physician surveys that can lead to inaccurate estimates of anaphylaxis, and risk estimation based on testing to a single class of allergen (e.g., aeroallergens).

To date, the largest number of patients evaluated was in a study performed by Valyasevi *et al.*² that included 18,311 patients (16,505 SPT and 1806 IDT) from 1992 to 1997. The rate of systemic reactions was 0.03% for SPT and 0.06% for IDT. The longest period of time that has been studied was in a prospective study by Lin *et al.*,³ from 1976 to 1989. This study included 10,400 patients who were evaluated for aeroallergen

sensitization only and reported a rate of anaphylaxis of 0.02%. Other studies have disagreed with these findings,¹ with reported rates as high as 0.4% for SPT and 3.2% for IDT.

Given the diversity of reagents used for skin testing in clinical practice and recently refined definitions of anaphylaxis,⁴ a review of a large population over a long time period would be helpful to reassess risks associated with skin testing. This study aimed to define the rate of epinephrine administration due to systemic reactions to allergy skin testing in the largest population yet to be evaluated, over a 13-year period of time.

METHODS

This was a retrospective study to determine the rate of epinephrine administration after skin testing over 13 years in a single, suburban allergy/immunology practice. The practice's electronic billing database was queried for all patient encounters from January 1997 through June 2010 that carried the procedure codes for SPT and IDT. Encounters were then cross-referenced with procedure codes for the administration of parenteral epinephrine, diphenhydramine, corticosteroids, or i.v. fluids. Demographic data including age and gender were collected from the database. Patient charts for encounters that included at least one SPT and one medication administration code were manually reviewed to characterize types of skin tests performed, number of skin tests performed, number of positive

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tests (defined as a wheal ≥ 3 mm larger than negative control for both SPT and IDT with associated erythema), timing and type of symptoms developed, administration of medications, and occurrence of fatality. Anaphylaxis was defined as a systemic reaction treated with epinephrine and/or fulfilling criteria for diagnosing anaphylaxis as set forth by the World Allergy Organization.^{4,5}

During the time period studied, five practitioners were involved in skin testing. Both DermaPICKII (Biomedix, Spokane, WA) and blood lancets were used as devices for SPT on the upper back or volar aspects of the forearms. IDT was performed using a hypodermic needle and syringe to inject ~ 0.05 mL of extract in the upper arm. Aeroallergen, food, and venom extracts were purchased from available manufacturers, and in-office prepared drug extracts were used during the study period. Fresh food was also used in the practice, using the “prick-by-prick” method. PrePen (Alk-Abello, Round Rock, TX), when available, was used for penicillin testing. Institutional Review Board approval was obtained through the University Hospitals/Case Medical Center Institutional Review Board. Rates of epinephrine administration were calculated as number of patient visits where epinephrine was given, divided by the total number of patient visits for that particular skin test. Events that fulfilled criteria for anaphylaxis, without epinephrine administration, were also included to ensure that cases with clinical features of anaphylaxis were noted.

RESULTS

During the time period studied, 28,907 patient visits for SPT and 18,212 visits for IDT occurred. The demographics of this patient population and skin test details are summarized in Table 1. On average, 37.2 individual percutaneous SPTs and 11.7 IDTs were performed per visit. Based on procedure codes, skin tests were categorized into two types: those performed to drugs and/or venoms, and those performed to all other allergens. From all patient visits, 101 charts where SPT and 27 charts where IDT resulted in medication administration were identified for manual review. From these reviews, six patient visits for SPT and zero visits for IDT resulted in epinephrine administration. This resulted in a rate of epinephrine administration of 20 per 100,000 SPT visits (0.02%). All six patients received epinephrine and there were no fatalities. One patient also received i.v. fluids. No episodes of anaphylaxis were identified where epinephrine was not given. None of the patients were concurrently receiving immunotherapy. Table 2 summarizes the characteristics of each patient and the types of tests that were used in each patient’s case.

Patient 1 was a 38-year-old woman with a history of allergic rhinoconjunctivitis, multiple food allergies

Table 1 Chart review data summary and demographics

	SPT	IDT
No. of visits*	28,907	18,212
Median no. of tests/visit (interquartile range)	30 (14, 56)	12 (9, 16)
No. of drug/venom visits (%)	667 (2.3)	2279 (12.5)
Male (%)	15,987 (55)	7572 (42)
Median age, yr (interquartile range)	20.7 (7.3, 44.4)	33.2 (13.6, 49.1)

*Includes patients with multiple visits and both types of testing in same visit.

IDT = intradermal testing; SPT=skin-prick testing.

with anaphylaxis, medication allergies, latex allergy, anaphylaxis to immunotherapy, and asthma. She presented in February 2010 for reevaluation of her food allergies. SPT for 71 foods was conducted and the patient showed sensitizations to 11 foods. Her systemic reaction was not documented. Thirty minutes after skin testing was performed, administration of 0.3 mg of intramuscular epinephrine was documented, and the patient was discharged home.

Patient 2 was a 39-year-old woman with a history of multiple drug hypersensitivities, latex allergy, anaphylaxis to Hymenoptera, anaphylaxis to shrimp, urticaria, and angioedema. She presented in October 2010 for testing. SPT to 71 foods, penicillin G, benzylpenicilloate, ampicillin, and cephalosporin was conducted. The patient was found to have sensitization only to one food (shrimp). Approximately 50 minutes after skin testing, the patient received 60 mg of oral methylprednisolone. Five minutes later the patient received 0.3 mg of epinephrine intramuscularly. A tryptase was drawn during the reaction and was found to be 7 ng/mL (normal, <11.4 ng/mL). The details of the anaphylactic reaction were not documented in the chart.

Patient 3 was a 23-year-old woman with a history of opioid/nonsteroidal anti-inflammatory drug-induced anaphylactoid reactions and idiopathic anaphylaxis requiring intensive care admission who presented in November 2008 for skin testing. SPT to 71 foods and 12 aeroallergens was performed. The patient showed one positive aeroallergen sensitization (mold mix). The patient developed erythema of her neck and chest, lip tingling, chest pain, and dyspnea. She received 0.3 mg of intramuscular epinephrine, an i.v. bolus of normal saline, and 2 additional doses of epinephrine. The pa-

Table 2 Patients who received SPT and epinephrine: Summary data

Patient no.	1	2	3	4	5	6
Age, yr	38	39	23	7	8	4
Sex	F	F	F	F	M	M
Race	C	C	C	C	A	C
Total no. of tests	71	75	83	27	38	53
Percent positive tests	15%	1%	1%	4%	87%	79%
No. of aeroallergen (no. positive)	0	0	12 (1)	0	12 (9)	42 (36)
No. of foods (no. positive)	71 (11)	71 (1)	71 (0)	27 (1)	26 (24)	11 (6)
No. of drug/venom (no. positive)	0	4 (0)	0	0	0	0
History of asthma	Yes	No	No	No	Yes	Yes
History of anaphylaxis	Yes	Yes	Yes	Yes	Yes	No

C = Caucasian; A = African American; SPT = skin-prick testing.

tient was then transferred to a local emergency room in stable condition. During the anaphylactic event the patient's tryptase was found to be 3.7 ng/mL (normal, <11.4 ng/mL) and histamine was 52 ng/mL (normal, 20–200 ng/mL).

Patient 4 was a 7-year-old girl with a history of peanut-induced anaphylaxis who presented for retesting in June 2007. SPT to 27 foods was performed, and the patient had one positive response (peanut). Although no symptoms were documented, the patient required 0.3 mg of intramuscular epinephrine 1 hour after the test was performed. She was stable on discharge home.

Patient 5 was an 8-year-old boy with a history of asthma, multiple food allergies with anaphylaxis, and eczema who presented in May 2010 for reevaluation of his food allergies and allergic rhinitis. SPT was performed for 12 aeroallergens, 16 fish/shellfish, and 10 nut/peanut extracts. The patient was found to have sensitizations to 9 aeroallergens and 24 foods. His systemic reaction was not documented. Approximately 30 minutes after testing, the patient required intramuscular epinephrine at 0.3 mg.

Patient 6 was a 4-year-old boy with a history of asthma, eczema, allergic rhinoconjunctivitis, and food allergies (angioedema to peanuts and egg) who presented in June 2010 for reevaluation of his allergic rhinitis and food allergies. The patient showed sensitizations to 36 aeroallergens and 6 foods on SPT (53 total tests were placed). Approximately 5 minutes after skin testing was performed the patient developed generalized urticaria, dyspnea, and throat tightness. The patient received 0.15 mg of epinephrine intramuscularly. The patient's symptoms resolved and he was sent home in stable condition.

DISCUSSION

Skin testing is an efficient and important tool that can help confirm allergic sensitization in patients who ex-

hibit clinical symptoms of IgE-mediated allergy. These benefits are counterbalanced by the potential risk of inducing a systemic reaction such as anaphylaxis. These reactions have been shown by several studies to be rare^{1,2,6–11}; however, the exact rates of systemic reactions to skin testing have not been clarified because of difficulties within individual studies that include study population size, data collection technique (*i.e.*, surveys), and/or testing to only a single class of allergen (*e.g.*, aeroallergens). A review of pertinent studies, using PubMed search terms "systemic reaction," "anaphylaxis," "skin testing," and "intradermal testing" was performed, and bibliographies were cross-referenced. References comparable with the current study are presented in Table 3.

Chart Reviews

Chart reviews have described anaphylactic rates due to SPT of 0.008–4%, depending on the types of antigen and skin testing used. These reviews encompassed a number of patients ranging from 740 to 18,311, and a time period from 6 months to 13 years (Table 3). Vallyasevi *et al.*² studied 18,311 patients' charts (representing 497,656 skin tests), covering a time period from 1992 to 1997. Of these patients, six had systemic reactions, five of which were from SPT. This translated to a reaction rate of 0.03% of SPT and 0.06% of both SPT and IDT. Chacko *et al.* reviewed charts of 792 subjects over 6 months in 2006, finding an overall rate of systemic reaction (SR) to skin testing of 4%.¹² Other studies have described rates of systemic reactions to venom,⁶ penicillin,^{7,13} and food^{14,15} skin testing, albeit in smaller populations.

Prospective Studies

Bagg *et al.*¹ conducted a 12-month, prospective review of systemic reactions to skin testing. Fourteen hundred fifty-six patients received skin testing, and 52

Table 3 Overview of selected studies of systemic reactions in allergy skin testing

Author	Time Period	n	Type of Study	SR Rate (%)	Comments
Bagg <i>et al.</i> ¹	2006	1456 Patients	Prospective	3.6 Overall 0.4 SPT 3.2 IDT	Generous definition of anaphylaxis
Lin <i>et al.</i> ³	1976–1989	10,400 Patients	Prospective	0.02 Overall	Longest study to-date; respiratory antigens only
Chacko <i>et al.</i> ¹²	2006	792 Patients	Chart review	4 Overall	No distinction between SPT and IDT; abstract report
Valyasevi ²	1992–1997	18,311 Patients	Chart review	0.06 Overall 0.03 SPT 0.03 IDT	Patients wheezing before SPT
Bernstein <i>et al.</i> ⁸	1990–2001	646 Physician respondents	Survey	n/a (1 fatality)	Reports fatalities only; no SR rate reportable; low respondent rate
Reid <i>et al.</i> ⁹	1985–1989	17 Physician respondents	Survey	n/a (0 fatalities)	Reports fatalities only; no SR rate reportable; low respondent rate
Lockey <i>et al.</i> ¹⁰	1973–1983	60 Physician respondents	Survey	n/a (6 fatalities)	Reports fatalities only; no SR rate reportable; low respondent rate

IDT = intradermal testing; SPT = skin-prick testing; SR = systemic reaction.

(3.6%) developed systemic reactions: 6 (0.4%) from SPT and 46 (3.2%) from IDT. This study's ability to describe the rate of SRs to skin testing was limited by its smaller sample size and shorter study duration.

In the longest reported time period studied to date, Lin *et al.*³ prospectively evaluated 10,400 patients from 1976 to 1989 for the rate of systemic reactions to aeroallergen skin testing. They found a rate of <0.02% in this population. However, this study excluded other important allergens (food, venom, and antibiotics) limiting the breadth of conclusions that can be drawn from it. Since the study was published, much has changed, including the definitions of anaphylaxis⁴ and the type and quality of allergen extracts used in skin testing.¹⁶ A third prospective trial observed the rate of systemic reactions (1.7%) to penicillin skin testing in 776 patients from 1979 to 1985.¹⁷

Survey Data

Bernstein *et al.*⁸ reported the American Academy of Allergy, Asthma, and Immunology survey of its members from 1990 to 2001. This survey captured 646 of 2404 (24%) possible respondents, who reported the number of fatal reactions to skin testing and immunotherapy. One fatality was reported after skin testing multiple (90) food allergens. Although important in highlighting the low risk of death with skin testing, this study can not clarify our understanding of the rate of systemic reactions in skin testing.

Reid *et al.*⁹ surveyed the American Academy of Allergy, Asthma, and Immunology and American Col-

lege of Allergy, Asthma, and Immunology members from 1985 through 1989 regarding skin testing fatalities. Seventeen physician responses were collected. Reports of nonfatal systemic reactions were not collected in this study. In 1987, Lockey *et al.*¹⁰ reported six cases of fatality to skin testing, based on survey data spanning from 1973 to 1983. It is important to note, additionally, that there are several case reports in the literature of isolated systemic reactions in patients receiving skin testing.¹¹

The present study encompassed 13 years and almost 50,000 patient visits—to our knowledge, the largest report of its kind. In comparison with previous studies, this study provides a contemporary, large-scale, long-term view of the rate of epinephrine administration associated with allergy skin testing. By expressing the rate of anaphylaxis in terms of patient visits (rather than per number of individual skin tests), this study provides a clinically meaningful estimate of the risk involved in using these tests.

There are several weaknesses in this study. Poor documentation of patient signs and symptoms limited our ability to describe the systemic reactions in most of our patients. Documentation of the millimeter size of positive skin tests, as well as the type of prick testing device used, was not available for individual cases. Identification of anaphylactic events relied mainly on billing databases to identify patients who received epinephrine. Given the long time period in this retrospective study, there is the chance that errors in billing/coding and documentation limited the ability to detect

events of epinephrine administration. Also, there may have been milder episodes of anaphylaxis that were not treated with epinephrine and were not detected. Therefore, our data are most reflective of the rate of severe systemic reactions that require epinephrine. We were unable to identify any delayed systemic reactions that developed outside of the office (*e.g.*, emergency room visits after testing).

Despite these limitations, our results are similar to those of previously reported data. Also, the definition of anaphylaxis used in this study was broad, allowing for clinical judgment (epinephrine administration) and published guidelines (World Allergy Organization criteria). By reviewing such a large number of visits and such a long period of time, the effects of such limitations would tend to be minimized.

IDT has been shown to carry a greater risk of SR than SPT.^{1,3} However, the current study did not identify any severe SRs to IDT. Valyasevi *et al.* had similar findings, where fewer patients reacted to IDT than to SPT.² One possible explanation is that IDT is typically performed after SPT, and those patients with a propensity to anaphylaxis will experience it on initial skin testing (thus decreasing the rate of subsequent IDT reactions). Additionally, IDT is typically performed with those allergens that have previously tested negative on SPT, which would skew the rates of anaphylaxis to IDT to be lower (testing with allergens already documented to be negative on SPT).

Two of the six SPT reactors had a large number of positive SPT to foods (patients 1 and 5). This may suggest that large numbers of food SPTs in polysensitized individuals may be a risk factor for anaphylaxis. Indeed, previous reports have suggested that larger numbers of skin tests⁸ and larger skin test responses¹⁸ are associated with an increased risk of SR in skin testing and immunotherapy. Excluding patient 3 (with an underlying history of idiopathic anaphylaxis), the remaining 5 patients all required epinephrine after food SPT. This may suggest that patients receiving SPT to foods are at higher risk of developing adverse reactions that require epinephrine. Two of the patients did not have an elevated tryptase, indicating that their systemic reactions may not have been mast cell mediated. Absence of an elevated tryptase has been observed in food-induced anaphylaxis,^{19,20} and this may also be the case in anaphylaxis triggered by food skin testing.

Another important trend found in our population was that all of the adult patients and all but one of the children had a prior history of anaphylaxis (food or idiopathic). This history may indicate a lower threshold to manifest systemic reactions to small amounts of allergen. It may also indicate the presence of nonspecific sensitivity to immune stimulation. It would be useful to prospectively study such patients and their

rates of anaphylaxis to skin testing compared with patients without anaphylaxis histories.

Four of the six patients who required epinephrine received a large number of skin tests overall (compared with the median number of SPT administered in our population). Thus, placing a large number of skin tests (regardless of allergen type) may place a patient at risk for anaphylaxis. Despite previous reports of higher rates of anaphylaxis with venoms and antibiotics, our study showed that none of the 18,212 IDT visits (2279 of which were tested to drugs/venoms) were associated with epinephrine administration.

This study provides a contemporary, large-scale, long-term view of the rate of epinephrine administration after allergy skin testing in a suburban private allergy clinic. Because of the study's long time period, large population, and inclusion of both SPT and IDT data to multiple types of allergens, it represents a real world view of the rate of severe systemic reactions to allergy testing in a typical allergy practice. Although the rate of severe systemic reactions after skin testing is low, physicians should still take appropriate precautions to manage these complications.

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