

Atopic dermatitis or eczema is a disease of the skin that results in significant physical and emotional morbidity. Chronic atopic dermatitis is characterized by means of lichenification of the skin with a hyperplastic epidermis, prominent hyperkeratosis, and minimal spongiosis. An increased number of IgE-bearing Langerhans cells, T_H1 cells, T_H2 cells, eosinophils, and mast cells with higher levels of the cytokines IL-4, IL-5, GM-CSF, IL-12, IL-13, and IFN- γ are present in the chronic disease.¹ GM-CSF is important in sustaining the function and survival of Langerhans cells, monocytes-macrophages, and eosinophils. There are increased numbers of IgE-bearing Langerhans cells that seem to be important in antigen presentation to T_H2 memory cells, as well as in causing differentiation of naive T_H0 cells to T_H2 cells. IgE binds to the high-affinity Fc ϵ RI receptors on Langerhans cells, facilitating antigen presentation. The level of binding has been correlated with serum IgE levels. Low levels of Fc ϵ RI expression on Langerhans cells are found in normal individuals and individuals with respiratory allergy, whereas high levels are present in atopic dermatitis.¹ Therefore the treatment modality must affect these different immunologic parameters to successfully treat atopic dermatitis.

Although various treatment modalities are used to treat atopic eczema, until recently, the only successful treatment for severe atopic dermatitis has been the use of systemic glucocorticosteroids or oral cyclosporin A, both of which can lead to considerable side effects. Topical tacrolimus is at least as effective as topical glucocorticosteroids, without the concomitant side effects.² Tacrolimus (FK506) interferes with intracellular signaling of T cells by binding to FK506-binding protein and thereby inhibiting the phosphatase activity of calcineurin. This prevents dephosphorylation of nuclear factor of activated T-cell protein, blocking migration of this protein into the T-cell nucleus and preventing the transcription of IL-2, IL-3, IL-4, TNF- α , IFN- γ , and GM-CSF.³ Panhans-Gros et al⁴ have also shown that tacrolimus decreases Fc ϵ RI expression on Langerhans cells. Hauk and Leung⁵ demonstrated that tacrolimus blocks *Staphylococcus aureus* superantigen-induced T-cell activation, which glucocorticosteroids do not affect. Thus tacrolimus has been shown to target multiple links in the pathogenesis of atopic dermatitis.

Systemic tacrolimus has been successfully used for patients undergoing both kidney and liver transplantation. The principal side effects include tremor, headache, diarrhea, hypertension, nausea, and renal dysfunction. Hyperkalemia, hypomagnesemia, hypophosphatemia, and diabetes mellitus have been reported. There is also an increased risk of non-Hodgkin lymphoma and skin malignancies. Routine tests and laboratory studies should include measurements of the following: blood pressure, serum blood urea nitrogen, creatinine, potassium, and glucose. Klein et al,⁶ in a study on healthy subjects, showed that tacrolimus had no effect on renal function and blood pressure over a 2-week period, whereas cyclosporine, another treatment for severe refractory der-

matitis, caused a statistically significant decrease in renal function and increase in blood pressure.

There are numerous reports showing the efficacy of topical tacrolimus for treatment of atopic dermatitis; however, there are no reports demonstrating the efficacy of systemic tacrolimus. Treatment with topical tacrolimus failed in our patient, and therefore he was started on systemic tacrolimus treatment because of the debilitating effects of the continued use of glucocorticosteroids. The patient greatly prefers tacrolimus therapy over glucocorticosteroid therapy. While taking systemic tacrolimus, his eczema has improved at least 80%, he has stopped taking systemic glucocorticosteroids, and he is now able to attend college and participate in many activities appropriate for his age. Double-blind, randomized controlled trials are necessary to show that tacrolimus is an effective and safe treatment for severe, refractory, steroid-dependent atopic dermatitis and that the risk/benefit ratio is better than that with long-term use of oral glucocorticosteroids and cyclosporine. Such therapy should be the last option for individuals who have exhausted all other forms of therapy.

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Anaphylaxis caused by skin prick testing with aeroallergens: Case report and evaluation of the risk in Italian allergy services

To the Editor:

Skin prick testing (SPT) is the first-line diagnostic method of demonstrating an IgE-mediated hypersensitivity, especially for inhalant allergens. The number of allergenic products for diagnosis has increased in the last years, and their quality has improved as well. Now we have commercial extracts derived from many sources, including mites, pollens, stinging insects, domestic animals, foods, antibiotics, latex, and other less common allergens.

SPT is generally considered a safe procedure. The frequency of systemic reactions caused by extracts of

TABLE I. Results of the survey on the use of SPT with aeroallergens

Center	No. of patients	Age range	Male (%)	No. of allergens tested	Allergens per patient (mean)	Systemic reaction
Verona	19,759	4-60	43.5	278,626	14.1	0
Genoa	13,151	3-67	40.0	133,510	10.2	0
Naples University	10,640	6-72	45.2	108,400	10.2	0
Naples Hospital	11,555	3-72	41.1	163,770	14.2	1
Total	55,105	3-72	43.8	684,306	12.4	1

inhalant allergens is extremely low, whereas it is slightly increased if food, latex, drug, or hymenoptera venom extracts are used.¹ The available literature suggests that the overall risk of inducing anaphylactic reactions by SPT is less than 0.02%.² On the other hand, intradermal testing might induce systemic reactions more frequently than SPT. In fact, in a survey by Lockey et al,³ 5 of the 6 fatalities described were associated with intradermal testing. To our knowledge, no evaluation of the risk of anaphylactic reactions induced by SPT has ever been carried out in Europe, despite the wide use of the test. This is probably a result of the almost complete absence of systemic severe adverse events.

We describe herein an unexpected case of anaphylaxis induced by SPT with commercial extracts and report the results of a retrospective survey on the occurrence of severe systemic reactions in 4 large Italian allergy services.

A 32-year-old woman came to our service because of recent episodes of generalized urticaria-angioedema. She had rhinoconjunctivitis and asthma for 10 years and reported a previous diagnosis of IgE-mediated allergy. Her family history was negative for atopy, and her personal history was negative for atopic dermatitis and drug intolerance. SPT with commercial standardized allergenic extracts (ALK-Abellò Group, Milan, Italy) was performed to better define the diagnosis of respiratory allergy. The panel included the following: house dust mites, *Parietaria* species, grasses, cat and dog dander, olive, birch, *Alternaria alternata*, *Cladosporium herbarum*, and mugwort, plus a positive (1% histamine hydrochloride 1) and a negative (glycerinate solution) control. Skin prick tests were carried out and interpreted according to international guidelines.⁴ Briefly, one drop of each extract was put on the anterior surface of the forearm, and the forearm was pricked with a sterile and disposable 1-mm blood lancet (Artsana SpA, Grandate, Italy). The result was read after 10 minutes and expressed as the major diameter of the wheal and its orthogonal. A skin reaction of 3 mm or greater was considered positive. The patient was symptom free, and she was not taking medications, including H₁-receptor antagonists, β -blockers, or steroids. A positive response (erythema and wheal with pseudopodia) developed with several allergens. The diameters of the wheals and flares, respectively, were as follows: *Parietaria* species, 15 $\times$ 14 mm and 48 $\times$ 46 mm; *Dermatophagoides pteronyssinus*, 13 $\times$ 14 mm and 44 $\times$ 42 mm; *Dermatophagoides farinae*, 13 $\times$ 12 mm and 42 $\times$ 40 mm; grasses, 11 $\times$ 10 mm and 29 $\times$ 23 mm; dog dander, 9 $\times$ 8 mm and 27 $\times$ 25 mm; and positive control, 9 $\times$ 8 mm and 28 $\times$ 29 mm.

After 15 minutes, generalized urticaria, angioedema of the lips and eyelids, cough, and dyspnea appeared and were suddenly followed by profound hypotension. The heart rate was greater than 120 beats/min, and the respiratory rate was 25 breaths/min. The patient was promptly treated with intravenous epinephrine, corticosteroid (methylprednisolone, 500 mg), and antihistamine (chlorphenamine, 10 mg). Inhaled albuterol (400 μ g) and oxygen were also administered. The patient completely recovered in about 20 minutes.

A laboratory evaluation was performed on the day after the episode. Total IgE levels were 224 kU/L; specific IgE (CAP System; Pharmacia, Uppsala, Sweden) results were positive for *Parietaria* species (53.6 kU/L, class V CAP), *D pteronyssinus* (14.4 kU/L, class III CAP), *D farinae* (9.68 kU/L, class III CAP), *Lolium perenne* (1.05 kU/L, class II CAP), *Artemisia* species (0.98 kU/L, class II CAP), and dog dander (1.32 kU/L, class II CAP). No other abnormality was found in routine blood analysis.

To evaluate the frequency of systemic reactions caused by SPT, we performed a retrospective analysis in 4 large allergy services (2 in Naples, 1 in Genoa, and 1 in Verona). The centers were asked to review the records of the patients pricked with inhalant allergens between January 1, 1991, and December 31, 2002, to provide a count of the SPT performed. They were asked to notice and describe any systemic reactions, including urticaria, asthma, rhinitis, gastrointestinal symptoms, hypotension, and anaphylaxis. The results of the survey are shown in Table I. With the exception of the present case, no other systemic or anaphylactic reaction was ever reported.

In general, the international literature about the risks of SPT is very poor. Two cases of nonfatal systemic reaction induced by intradermal skin testing were reported by Lin et al,² and 3 reactions after SPT were described by Valyasevi et al¹ with inhalant allergens. In one of these patients, a concomitant positivity to latex was found. In a large epidemiologic survey Turkeltaub and Gergen⁵ found no anaphylactic reactions after SPT, whereas one single case was recently described in an 8-year-old boy in Italy.⁶ Some other cases of systemic reactions after SPT were indeed reported with foods.^{7,8} Overall, in the last 10 years, systemic reactions with SPT were described only exceptionally. Possible explanations for this fact might be the improved quality of the extracts and the educational effort made by the divulging of practical guidelines. This is the first report of an anaphylactic reaction caused by SPT with inhalant allergens in adults in

Italy, at least in the last 10 years. In our patient it was impossible to identify the culprit allergen because all the skin tests were performed at the same time. In addition, we could not evidence predictive risk factors: the positive reactions elicited were not of exceptional intensity, and it is common to find multiple positive results. We could only suppose that *Parietaria* species or mites had been responsible for the reaction on the basis of the presence of high specific IgE levels. Obviously, the procedure was not repeated for ethical reasons.

This unexpected case of anaphylaxis caused by SPT provided the occasion for evaluating the risk of this procedure. We could survey a 12-year period and more than 55,000 patients (adults and children). The period was chosen because of its reasonable length and because all the centers had followed the same standard procedure for SPT. Our data confirmed that the occurrence of severe systemic reactions after SPT with inhalant allergens is exceptional, but the risk cannot be completely excluded. For this reason, it is essential that allergy services are equipped to treat anaphylaxis and that recommendations^{9,10} are taken into account to decrease the risk.

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