

Intradermal testing for food and chemical sensitivities: A double-blind controlled study

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Background: Confirming adverse reactions to foods and chemicals is fundamental in providing a basis for diagnosis and treatment of patients with reported environmental sensitivities. Provocation-neutralization testing is widely used in this respect but has not been thoroughly evaluated, therefore remaining a controversial and unproven technique.

Objective: This study investigated the validity of intradermal testing for evaluation of reported adverse reactions to a variety of incidents within the patient population at the Nova Scotia Environmental Health Centre.

Methods: A total of 132 people who were referred to the Nova Scotia Environmental Health Centre, a dedicated government-funded research and treatment facility for suspected environmental sensitivities, were tested by the technique of provocation-neutralization by the guidelines set out by the American Academy of Environmental Medicine. A panel of 13 foods, 9 chemicals, and 4 placebos (normal saline solution) was evaluated in a double-blind, randomized study. Symptoms and skin reactions were recorded, and response rates were determined for all substances, including saline solution injections.

Results: Seventy percent of the patients reported symptoms to 1 or more of the 4 saline solution injections. In comparison, 15% of patients experienced a skin reaction (wheal) to 1 or more injections of saline solution. Only 5% of individuals experienced a wheal to more than 1 saline solution injection, although 40% of the patients reported symptoms to more than 1 saline injection. Patients who experienced 1 or more reactions (wheal or symptoms) to saline solution were more reactive to injected allergens, on average reacting to 67% of active substances. Patients who experienced no reaction to the saline solution did experience a reaction to 48% of injected substances on average. Reaction by symptoms to foods, chemicals, and normal saline solution showed a random pattern, although wheal reactions showed a distinct pattern. Subsequent observations have indicated that experiencing no reaction to previous saline solution injections does not accurately predict response to saline solution in later testing. Some individuals who did not experience a reaction to saline solution in an initial screening later experienced a reaction to saline solution during further testing.

Conclusions: Provocation of symptoms in usual testing conditions is not a useful tool for discriminating between reactions to saline solution and reactions to specific chemicals or foods. Skin response alone may be a more reliable indicator and will require cross-validation with other tests, such as oral and inhalation challenges and comparison with a control population. Heightened sensitivity and chaotic responses may be a feature of chemical sensitivity. Meanwhile, the results of provocation-neutralization testing, using symptoms alone as an indicator of neutralization, should not be used as a basis for clinical intervention. (*J Allergy Clin Immunol* 1999;103:907-11.)

Key words: Diagnostic techniques and procedures, double-blind method, environmental illness, intradermal tests, multiple chemical sensitivity, placebos, provocation neutralization, skin tests

The development of adverse reactions to chemicals such as fragrances appears to be an increasingly common problem. Approximately 4% of the population reports everyday problems with reactions to chemicals.¹ Information from a provincial health survey supports this result,² with 3% of the adult population reporting environmental illness as a chronic condition in Nova Scotia, Canada.

One challenge facing the physician working with this patient population is difficulty in objectively confirming the reported reactions, even in the presence of classic allergies.^{3,4} As a prelude to desensitization therapy for inhalants, serial dilution end point titration has been identified as "a useful and effective measure of sensitivity."⁵ Confirmation of adverse reactions to foods and chemicals has been more challenging because many of these reactions are not believed to be immunologically mediated.⁶

Lee⁷ originally described skin testing for identification of adverse reactions to food (allergies and intolerance), with others⁸⁻¹¹ confirming this testing and modifying his method. The technique became known as *provocation-neutralization*. It was reported that an intradermal injection could produce symptoms similar to the oral food challenge. Lee⁷ also reported that injection of the first dose that failed to produce a wheal resulted in the disappearance of provoked symptoms. This observation led to the use of provocation of symptoms as an indicator of sensitivity. A double-blind investigation into this method showed that a positive skin test was significantly associated with oral challenge food tests.¹²

Production of a wheal is recorded as a positive result

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TABLE I. Percentage of individuals who experienced a reaction* (wheal or symptom) to 1 or more normal saline solution injections

	Wheal (%)	Symptom (%)
Reaction to saline solution		
Yes	15	70
No	85	30

*N = 132. Reaction (wheal or symptoms) is not mutually exclusive; individuals may express both wheal and symptoms for a single injection.

in traditional testing of foods. Use of symptom provocation as a means to detect food sensitivity has been investigated in a double-blind controlled manner.¹³ Although this article is widely quoted, there were design issues, the main one being that the authors did not test the methods commonly used by physicians.

Provocation-neutralization is still widely practiced as a testing technique. The technique is controversial, because the American Academy of Allergy, Asthma and Immunology regards it as unproved and does not recommend its use as a diagnostic tool.¹⁴ We have examined the efficacy of provocation-neutralization testing for patients referred to the Nova Scotia Environmental Health Centre, using the technique of the American Academy of Environmental Medicine.

METHODS

Patients

A total of 132 patients were included in the study. These patients were referred by their primary care physician or another specialist to the Nova Scotia Environmental Health Centre for consultation. The patients were noted to have symptoms that were disruptive to their normal life and that were of a degree of severity that justified early consultation. Patients were unable to either work or attend school because of their symptoms, were suicidal because of their illness, or experienced life-threatening anaphylaxis. The age range was from 9 to 78 years, and 78% were female. Not all patients were thought to have chemical sensitivity after initial consultation, and only those patients who were identified with possible or probable chemical sensitivity were referred for testing.

Testing

Patients with a history of anaphylaxis or refractory angioedema received in vitro testing by a modified RAST. The RAST was limited to those substances thought to have provoked the anaphylaxis.

Intradermal testing was used for all patients. The allergens used for testing were prepared by the Environmental Health Center-Dallas and were preservative free. Various chemicals were used, and organic foods were prepared by extraction with Coca's solution. Neither glycerine nor phenol was added. A panel of 13 foods (banana, beef, baker's yeast, brewer's yeast, cane sugar, chicken, chocolate, corn, cow's milk, egg, soy, tomato, and wheat), 9 chemicals (cigarette smoke extract, ethanol, formaldehyde, orris root, phenol, grass terpene, pine terpene, unleaded/diesel and either fire-place ash extract or women's cologne or men's cologne or cedar terpene) and 4 placebos (normal saline solution) was set up, with individual vials identified only by a letter and number. Each allergen was set up as a series of 1 in 5 dilutions from the stock solutions identified as 1 (1 in 5) to 5 (1 in 3125). The saline solutions were labeled 1 through 5, but each was identical (normal saline solution).

TABLE II. Percentage of individuals who experienced a reaction* (wheal or symptom) to 1 or more injections of normal saline solution and the number of reactions to saline solution

Reactions to saline solution (n)	Wheal (%)	Symptom (%)
1	10	30
2	4	17
3	1	17
4	0	6

*N = 132. Reaction (wheal or symptoms) is not mutually exclusive; individuals may express both wheal and symptoms for a single injection.

The panel was set up by 1 individual, and the different test substances were randomly assigned. The codes were held by 1 investigator and were not known by the testing nurse nor by the patient. The code was broken for the physician by the research staff when all testing on the patient was complete. The testing nurse remained unaware of the code.

The panels were changed 5 times during the 17-month study period. Patients were tested with a single "substance" (food, chemical, or normal saline solution) at a time. The response was assessed over 10 minutes. Testing was performed over several days, with an average of 2.5 days to complete the full panel. During testing there were up to 8 patients being tested at the same time. A positive result was recorded if, within 10 minutes, there was a growth in the size of the wheal by 2 mm, measured on a vertical and horizontal axis. The endpoint was recorded as the dilution for the first negative wheal. If the patient perceived symptoms developing, these were recorded. Incremental doses of 0.05 mL were injected at 10-minute intervals until symptoms disappeared. The neutralization point was recorded as the total volume injected at the final dilution when symptoms disappeared. If, within 24 hours, the patient experienced a wheal/papule at the site of an injection that was negative during testing, this was recorded as a delayed response. A neutralization point for this allergen was the first negative dilution that did not cause such a delayed response. Delayed responses were reported by the patients phoning the Centre the next day. Testing for the allergen that elicited the delay would continue until the neutralization point was found. For the purpose of the article, a reported delay was not recorded as a positive response.

RESULTS

Table I shows that 15% of the subjects experienced a reaction to 1 or more of the saline solution injections by the development of a wheal. No wheal was produced to any of the 4 saline solution injections in 85% of the people tested. Only 2 individuals reported a delayed skin response to saline solution. Table II shows the number of saline solution injections to which patients experienced a reaction. A reaction to more than 1 saline solution injection by the production of a wheal was rare (5%). In contrast, 40% of the patients experienced a reaction to more than 1 saline solution injection by the development of symptoms.

Fig 1 summarizes the results of food testing by the production of wheal growth and the provocation of symptoms. Comparison between the 36 patients who did not experience a reaction to any of the 4 saline solution injections and the 96 patients who did is made by examining the top and bottom graphs in the figure. It can be

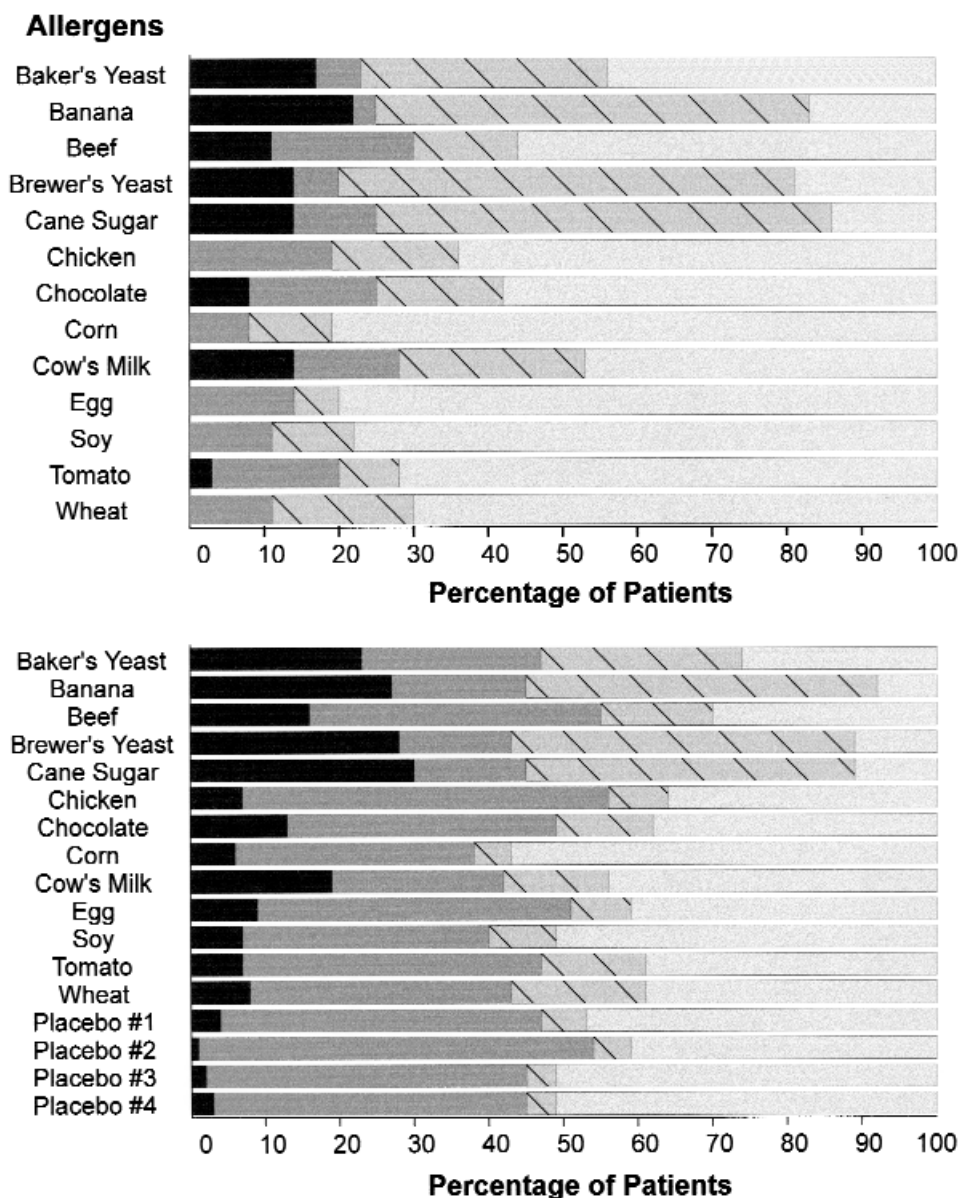


FIG 1. A, Reactions to food injections by patients who experienced no reaction to saline solution ($n = 36$) and **(B)** by patients who experienced a reaction to 1 or more saline solution injections ($n = 96$). Data are for patients who experienced a reaction with both symptoms and wheal (solid black bar), symptoms only (dark gray bar), wheal only (hash-marked bar) or no reaction (light gray bar).

seen that differences exist between those individuals who experienced a reaction with symptoms to saline solution and those who did not. The rate of positivity by symptoms was much higher in those patients who experienced a reaction to saline solution injections.

A similar comparison can be made for the response rate to chemicals as shown in Fig 2.

DISCUSSION

Approximately three fourths of the patients tested experienced a reaction to 1 or more saline solution injections by the production of symptoms. Furthermore, if one

looks at the rate of symptoms produced by the various foods and chemicals in the panel, the distribution resembles a random variation around a mean. It appears that the production of symptoms is a random event bearing no relationship to the nature of the substance injected.

The current practice of environmental medicine advocates this technique to advise patients about what they should and should not eat and what to avoid in terms of environmental exposures. Subsequently, these tests and their unreliable endpoints are being used to prescribe injections for neutralization of symptoms after an exposure or for desensitization. The practice of repeatedly injecting potentially toxic chemicals and substances,

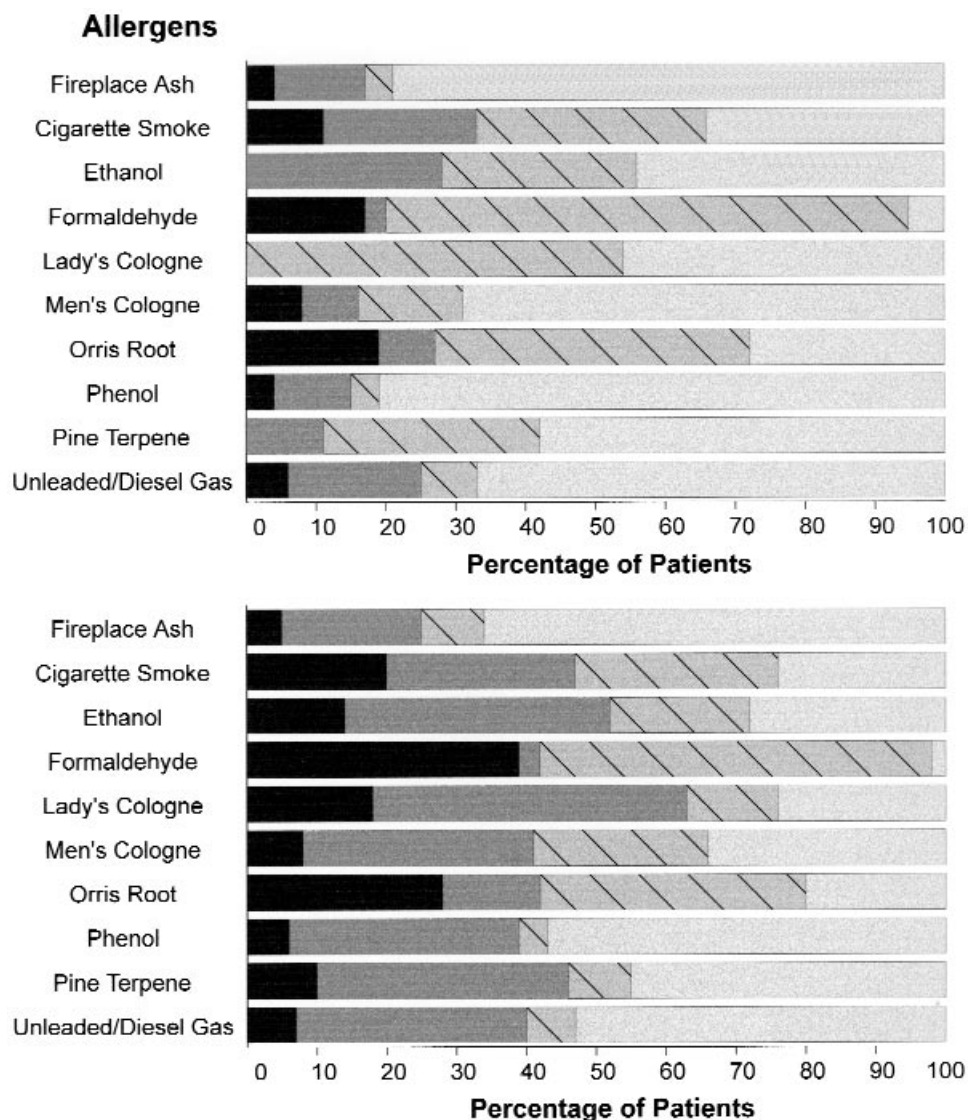


FIG 2. A, Reactions to chemical injections by patients who experienced no reaction to saline solution and **(B)** by patients who experienced a reaction to 1 or more saline solution injections. Data are for patients reacting with both symptoms and wheal (solid black bar), symptoms only (dark gray bar), wheal only (hash-marked bar) or no reaction (light gray bar).

although at a very low dose, needs to be questioned in terms of toxicity and sensitizing effect.

There were no obvious clinical differences between the 20 patients who experienced the development of a wheal with saline solution injections and the rest of the patients. The major clinical manifestation in these patients was a disturbed function of the nervous system, which is usually manifested by the clinical complaints of profound fatigue, cognitive dysfunction, difficulty in concentrating, emotional lability, and autonomic nervous system dysfunction. However, in 2 patients these symptoms were not prominent; 1 of these patients experienced anaphylaxis, and the other patient experienced a burning throat and discomfort in the presence of chemicals. All but 1 of these individuals have been disabled and unable to work.

We have observed a substantial difference in the rate of positive reactions (wheal) between various chemicals and foods. These positive skin reactions may indicate allergy, intolerance, or a low threshold for irritant effects to the substance being tested. Irritant substances may produce a wheal by direct action on the effector cells, and it is likely that a nonimmunologic skin response to certain chemicals and foods is of this type.

Other than a purely psychologic response, it could be hypothesized that these patients are in a state of heightened sensitivity as the result of the chronic irritation by various environmental components and other external and internal stressors. Such individuals might experience continuous stimulation and arousal of the nervous system. In this situation with high background noise any

additional stimulus, whether derived from the internal state of anxiety or from the external skin prick or the odor of detergent from the patient next to them, could be a sufficient stimulus to cross the threshold and trigger a response. If such an event requires a combination of factors, it may appear to be random in nature. This phenomenon of stochastic resonance has been described for threshold responses, including the neurologic influence on contact dermatitis.¹⁵

These data suggest that, under the usual testing conditions, skin tests that rely on the provocation of symptoms to determine whether a patient is sensitive should not be used to make diagnostic or therapeutic decisions.

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