

Latex allergy in operating room nurses

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Objective: To determine the prevalence of allergy to natural rubber latex and potential crossreacting foods in operating room nurses.

Method: Two hundred forty-seven operating room nurses completed a latex allergy questionnaire. They were questioned about symptoms of latex reactivity and about other allergies particularly to foods that may crossreact with latex. Informed consent was obtained and skin prick testing was performed with natural rubber latex and five latex extracts representing low (0.08 to 0.25 $\mu\text{g/mL}$) and high (18 to 106 $\mu\text{g/mL}$) natural rubber latex protein gloves. Skin prick tests were done with four potentially crossreacting foods (banana, avocado, kiwi, and potato), saline, and histamine controls.

Results: One hundred thirty-five (54.7%) nurses described allergic symptoms they attributed to latex exposure. Of these 12 (4.9%) tested positive to latex extracts alone, 12 (4.9%) tested positive to food extracts alone, and 5 (2.0%) tested positive to both latex and crossreactive foods. Three of the 17 (17.6%) nurses testing positive to latex gave no history of reactivity to latex. Indirect latex ELISA was done on the serum of skin test-positive patients with a 70.6% sensitivity.

Conclusion: Of the nurses tested, 6.9% had positive skin prick tests to latex extracts; 17.6% of these were asymptomatic and 29.4% had associated food positive skin prick tests.

Ann Allergy Asthma Immunol 1998;80:252–6.

INTRODUCTION

Since 1979¹ there have been many reports of natural rubber latex allergy. Health care workers who frequently use disposable latex gloves are at risk for allergic reactions to natural rubber latex. Studies have estimated that the prevalence of latex allergy ranged from 2.9% up to 17% of health care workers.^{2–5} Latex hypersensitivity poses a serious problem for latex-allergic patients and caregivers. Allergic

reactions to latex include contact eczema, urticaria, rhinitis, conjunctivitis, asthma, and anaphylaxis. Depending on the severity of symptoms, some healthcare workers may have no choice but to leave their chosen occupation. Manufacturers of latex medical devices are investing significant time and resources to reduce the amount of allergenic protein in their latex products. These measures should reduce the rate of latex sensitization.

This study evaluated the prevalence of latex allergy in operating room nurses. Reactivity with glove extracts of variable protein content and the prevalence of associated positive skin prick tests to potential crossreactive foods was also assessed. Latex-specific IgE ELISA was done on latex skin prick test-positive patients.

MATERIALS AND METHODS

Subjects

Subjects were recruited from the Operating Room Nurses Association of Canada (ORNAC) annual meeting.

The protocol and consent was approved by the ethics committee of the University of British Columbia. Two hundred forty-seven nurses signed informed consent and participated in the study. Mean age was 44.2 years (± 8.0 SD). Mean duration of natural rubber latex exposure was 17.4 years (± 8.7 SD years) and the mean number of hours exposed each day at work was 4.9 hours (± 2.0 hours SD).

Questionnaire

A standard questionnaire was completed by all subjects. Natural rubber latex-related questions included the type of glove, total duration of regular glove use, and the total hours per day that the gloves were worn. Symptoms of latex allergy and latex products to which the patient had possible allergic reactions were obtained. A previous history of food and other inhalant allergy was also determined. All medications taken by the participant were recorded.

Skin Prick Testing

All 247 nurses underwent skin prick testing. Epicutaneous skin prick testing was done using histamine (1/1000 Bencard Laboratory) and saline as positive and negative control reagents, respectively. Extracts of five latex gloves were tested (see below). A commercially available natural rubber latex extract (Bencard Laboratory, Mississauga, Ontario), 1/10 dilutions of banana, kiwi, avocado, and potato were tested. Skin testing was performed on the forearm by placing a drop of extract and pricking through this with a skin test lancet (Bayer Laboratories, Etobicoke, Ontario). Positive results were defined as wheals 4 mm $\geq$ saline control and were recorded directly by outlining the wheal which was transferred with transparent tape as a permanent record.

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Supported by a grant from Ansell Cares.

Received for publication May 12, 1997.

Accepted for publication September 12, 1997.

Glove Extract Solutions

Test solutions were prepared by extracting gloves for 15 minutes at 37 °C under sterile conditions, using 5 milliliters of saline per gram of latex glove. Five gloves from each brand were sampled to reduce variability.

Glove Extract Total Protein Levels

Protein levels were determined according to the American Society for Testing and Materials (ASTM) standard test method D5712-95 that incorporates a precipitation step to reduce the interfering substances in latex extracts prior to analysis by the Lowry assay. In brief, the precipitation step was performed on 0.5 mL of each sample by adding 50 μ L of 0.15% (wt/vol) sodium deoxycholate and incubating the sample at room temperature for ten minutes. Next, 50 μ L of 72% (wt/vol) trichloroacetic acid and 50 μ L of 72% (wt/vol) phosphotungstic acid were added and the samples incubated at room temperature for an additional 20 minutes. The samples were centrifuged for 15 minutes at 6,000 *g*, the supernatant discarded, and the pellet dissolved in 125 μ L of 0.1 M NaOH (yielding a 4-fold concentration of each sample). Protein was determined using the Detergent Compatible protein assay (Bio-Rad Laboratories, Hercules, CA). Each sample was tested in duplicate using four 2-fold serial dilutions. The optical was read at 700 nm and the concentration of protein determined by comparing the optical density of unknowns to the ovalbumin protein standard. The limit of detection for the assay was 2.5 μ g/mL and the reporting limit for the method was calculated as 9.3 μ g/mL (46.5 μ g/g using a 1:5 weight to volume extraction ratio).

Glove Extract Antigen Levels

Antigen levels in the glove extracts were quantitated by an indirect enzyme-linked immunosorbent assay (ELISA) using the latex ELISA for antigenic protein (LEAP) as described previously.⁶ In brief, latex protein standard and sample extracts were added to 96-well, high protein-binding polystyrene ELISA plates (Corning, Corning,

NY) and incubated at 37 °C for four hours. The plates were washed once with phosphate buffered saline at pH 7.2 containing 0.1% Tween 20, after which the unreacted sites were blocked with 2% bovine serum albumin (BSA) in PBS for one hour. After blocking, the plates were washed, incubated overnight at 37 °C with rabbit anti-latex protein antiserum, washed three times and then reacted with peroxidase-labeled goat anti-rabbit IgG (Sigma, St. Louis, MO) for one hour at 37 °C. After a final wash, a colored reaction product using *o*-phenylenediamine (1 mg/mL) in H₂O containing 0.1% H₂O₂. The reaction was stopped by the addition of 4 N sulfuric acid. The reaction product was quantitated by reading the absorbance at 490 nm using an MR 5000 ELISA plate reader (Dynatech, Chantilly, VA). The concentration of latex protein in the samples was determined by comparing absorbance units of unknowns to the latex protein standard curve at three consecutive dilutions using a customized computer spreadsheet. The lower part of the calibration curve was used to avoid interferences. The assay has a detection limit of 0.03 μ g/mL and a reporting limit of 0.06 μ g/mL (0.3 μ g/g using a 1:5 extraction ratio).

Enzyme-Linked Immunosorbent Assay (ELISA) IgE to Glove Antigens

Sera from subjects with positive skin prick tests to latex (*n* = 17) were evaluated. Sera from skin test negative subjects (*n* > 300) were used as controls.

Wells of polystyrene microplates (Immulon 2, Dynatech Laboratories, Chantilly, VA) were coated with the glove extracts after making dilutions in phosphate buffered saline.⁷⁻⁹ The plates were incubated at room temperature for three hours followed by overnight incubation at 4 °C. After washing and blocking the wells, serum samples were added and incubated for two hours at room temperature. This was followed by the addition of goat anti-human IgE, biotinylated rabbit anti-goat IgG, and streptavidin peroxidase. The plates were incubated at room temperature for one hour each

with different reagents and washed with phosphate buffered saline-Tween in between the addition of the reagents. Ortho-phenylenediamine substrate was added, and the color developed was measured in an automatic ELISA reader with a 490-nm filter (Dynatech Laboratories, Chantilly, VA). The optical density values were compared with known positive and negative samples run with each plate. Similarly processed crude antigen-coated plates (5 μ g/mL) were also compared. All reagents were standardized by checkerboard titration with previously determined positive and negative sera.

RESULTS

Questionnaire

Symptoms attributed to latex exposure were recorded by 135/247 (54.7%) of the participants. The most common symptom was a rash on the hands, itching, and scaling. Eleven of 17 (64.7%) nurses testing positive to latex had symptoms referable to two or more of either skin (hives, skin rash, itching, or blisters), ocular (swollen, burning or itchy eyes), or respiratory (rhinorrhea, nasal congestion, or itch and wheezing) systems compared with 43/230 (18.7%) of non-reactors (Table 1). The pattern of skin symptoms differed greatly between the latex-reactive and non-reactive groups (Table 2). Ten (58.8%) of the latex-reactive subjects complained of localized itch and nine (52.9%) in this group complained of localized hives. In contrast, only 63/230 (27.4%) of the non-reactors complained of itch and 5/230 (2.2%) noted hives (Table 1).

None of the participants had reported anaphylaxis. Thirty-nine of 135 (28.8%) reported reactions to latex products other than gloves. A history of atopy was strongly associated with latex skin prick test positivity. Thirty-five of 230 (15.2%) non-reactors had a history of atopy compared with 9/17 (52.9%) reactors having a history of atopy (Table 1). Twelve of 247 (4.9%) were skin prick test-positive for latex extracts alone, 5/247 (2.0%) were positive for latex as well as cross-reactive

Table 1. Association of Various Characteristics with Latex Skin Test Status

	Latex SPT* Positive (n = 17)	Latex SPT Negative (n = 230)	Odds Ratio	95% CI	P Value (two-tailed)
Symptoms in 2 or more systems	11	43	8.0	2.5–25.9	<.0001
Complaint of itch	10	63	3.8	1.3–11.6	.011
Complaint of hives	9	5	50.6	11.9–233.0	<10 ⁻⁸
History of atopy	9	35	6.3	2.0–19.4	.0007
Food allergy	5	12	7.6	2.0–28.6	.003

* SPT = skin prick test.

Table 2. Frequency of Cutaneous, Respiratory, and Ocular Symptoms in Latex-Reactive and Latex Non-reactive Subjects

	Symptoms			
	Cutaneous*		Respiratory†	Ocular‡
	Itch	Hives		
Latex reactive (n = 17)	10 (58.8%)	9 (52.9%)	11 (64.7%)	10 (58.8%)
Latex non-reactive (n = 230)	63 (27.4%)	5 (2.2%)	33 (14.3%)	22 (9.6%)

* Also includes other rash, scaling, and blistering.

† Includes rhinorrhea, nasal itch, congestion, sneezing, and wheeze.

‡ Includes: swollen, burning or itchy eyes.

foods: banana, avocado, kiwi, and potato. Three of 17 (17.6%) of the subjects testing positive for latex gave no history of latex-associated symptoms.

There was no correlation between reactivity and the total duration of use. Six of 17 (35.3%) of those with positive skin tests and 79/230 (34.3%) of latex non-responders reported using gloves for six hours or more daily. The ages, years of cumulative exposure, and amount of daily exposure in the latex responder and non-responder groups were similar (Table 3).

Table 3. Comparison of Ages, Duration of Use, and Hours of Daily Use of Latex Gloves in Latex Responsive and Non-responsive Subjects

	Latex SPT* Positive	Latex SPT Negative
Average age, yr	43.5	44.9
Duration of use, yr	17.4	17.6
Average hours per day of use	4.5	4.7

* SPT = skin prick test.

Relationship between Questionnaire and Skin Prick Testing

One hundred thirty-five subjects reported symptoms attributable to latex but only 17 tested positive for latex; thus, the positive predictive value of the questionnaire was poor (12.6%). None of the latex skin test negatives gave a history of allergy to any of the crossreactive foods while three of the skin test-positive participants complained of an itchy mouth after eating the implicated food, kiwi in two cases and banana in the other. Three of those positive for foods by skin prick test were latex asymptomatic.

Relationship Between Skin Prick Tests and Various Glove and Food Extracts

Five of 17 (29.4%) of the latex-reactive subjects were skin prick test-positive to either kiwi, banana, avocado, or potato extracts while only 12/230 (5.2%) of the non-reactors reacted to foods (Table 1). The results of skin prick tests to natural rubber latex, latex glove extracts, and commercial extracts of banana, avocado, kiwi, and potato are recorded as size of

wheel in millimetres. These are tabulated in Table 4.

Relationship Between Skin Prick Tests and Latex ELISA

Latex ELISA for IgE was positive in 12/17 (70.6%) patients who were skin prick test positive for latex.

DISCUSSION

In this study latex sensitization was detected in 6.9% of regularly exposed operating room nurses which is comparable to other studies.^{2,4} The large number of subjects attributing cutaneous, ocular, and respiratory symptoms to latex but having negative skin tests has also been previously reported.⁴ The fact that subjects in the study were invited to complete the questionnaire rather than chosen at random may have resulted in the selection of a larger number of people who initially felt their symptoms were caused by latex.

The number of systems involved may have a greater predictive value for latex sensitivity. The majority of nurses testing positive to latex had symptoms referable to two or more of either skin (hives, skin rash, itch-

Table 4. Skin Prick Test Responses to Various Glove and Food Extracts (wheal in mm)

Nurse Reacting to Latex Atopy y/n†	Natural Rubber Latex (not assayed)	LEAP* Assay, µg/mL								
		106	18	2.9	3.1	0.28	Banana	Avocado	Kiwi	Potato
1 y	9	5	7	—	—	—	—	—	—	—
2 y	12	6	8	4	—	—	5	8	4	—
3 y	15	8	8	—	3	3	—	—	—	—
4 n	6	—	3	—	4	—	—	—	—	—
5 y	6	4	7	—	—	—	—	—	—	4
6 n	13	5	8	2	—	—	—	—	—	—
7 n	8	—	4	—	—	—	—	—	—	—
8 y	15	3	8	—	—	—	—	—	—	—
9 n	8	—	6	—	—	—	—	—	—	—
10 n	7	5	3	—	—	—	—	—	—	—
11 n	10	4	15	—	—	—	—	—	—	4
12 y	10	—	—	—	—	—	—	—	—	—
13 y	6	—	4	—	—	—	—	—	2	—
14 n	5	4	4	4	—	—	4	2	2	2
15 n	8	—	—	—	—	—	—	4	4	4
16 n	8	—	4	—	—	—	—	—	—	—
17 n	—	—	—	4	—	—	—	—	—	—

* LEAP = latex ELISA for antigenic protein.

† y/n = yes or no.

ing, or blisters), ocular (swollen, burning or itchy eyes), or respiratory (rhinorrhea, nasal congestion, or itch and wheezing) systems compared with non-reactors. The pattern of skin symptoms differed greatly between the latex-reactive and non-reactive groups. The presence of itch was a poor predictor for latex sensitivity while the presence of hives was one of the strongest predictors of type 1 hypersensitivity in the group studied. Latex sensitivity was observed more frequently among atopic individuals than non-atopic individuals, consistent with atopy being known as a risk factor for latex sensitivity.¹²

Whether displaying type I hypersensitivity or not, large numbers of the nurses surveyed complained of symptoms they related to wearing of latex gloves. In such cases both delayed hypersensitivity to latex and irritant dermatitis must be considered. It has been suggested that latex-associated contact dermatitis may predispose to the devel-

opment of latex hypersensitivity. Possible mechanisms for this include the penetration of sensitizing latex proteins across the disrupted cutaneous barrier or latex additives acting as haptens leading to the generation of an IgE response.¹⁰

Crossreactivity between fruit and latex is well recognized.¹³⁻¹⁶ In this study latex-reactive subjects were more frequently skin prick test-positive to either kiwi, banana, avocado, or potato extracts than participants not responding to latex testing. This confirms other studies and the desirability of testing for foods in latex-allergic patients.¹⁶

Sixteen of 17 (94.1%) subjects reacted to the Bencard natural rubber latex solution showing the usefulness of this skin test reagent for assessing suspected natural rubber latex allergy. With one exception, all the subjects who reacted to the low protein latex glove solution responded to all the higher protein latex glove solutions tested. This confirms other studies

demonstrating decreased skin prick test reactivities with low protein gloves.¹⁷ Given the much lower rates of reactivity, both by skin prick testing and serologic testing, the use of low protein gloves provides a reasonable and safer alternative to the use of high protein gloves. The use of low protein powder-free gloves should lead to lower rates of sensitization in those people entering the workplace.

An important finding of this study was that 3/17 (17.6%) subjects reacting to latex gave no history of clinical latex sensitivity. The finding of history-negative, skin prick test-positive latex healthcare workers has been noted previously.² The rate of progression of these patients to symptomatic latex allergy is unknown but there is concern these skin prick test-positive patients are at risk for serious allergic reactions with future exposure. One possible scenario would be an intra-operative reaction during surgery where latex safe precautions are not employed.

This study raises questions concerning routine screening of at-risk individuals to determine asymptomatic latex hypersensitivity. The cost-effectiveness of such screening is uncertain at the present time. Also there is no standardized latex solution available for assessing these individuals. In our study the natural rubber latex reagent (Bencard Laboratories) provided a positive response in 94% of the subjects who also reacted to one or more of the glove extracts. This suggests skin prick testing with a battery of glove extracts of known protein content may be used for accurate evaluation of natural rubber latex allergy. Many of the antigenic proteins in latex have been identified¹⁸⁻²⁰ and the cloning and testing of major antigenic proteins in natural rubber latex has been done.²¹ In the future, a combination of purified natural proteins or recombinant proteins may provide a standardized solution for accurate diagnosis and treatment of latex allergy.

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