Patch Testing with Natural Rubber Latex: The Mayo Clinic Experience

Margo J. Bendewald, Sara A. Farmer, and Mark D. P. Davis

Background: **Delayed hypersensitivity reactions to natural rubber latex (NRL) have been recognized. These reactions may contribute to allergic contact dermatitis. We therefore have undertaken patch testing of patients with NRL if they are suspected to have allergic contact dermatitis to rubber.**

Objective: **To review results of patch testing with NRL (January 1, 2000, through December 31, 2007).**

Methods: **Patients suspected of having allergic contact dermatitis from rubber who underwent patch testing with NRL were identified retrospectively. For safety reasons, patients with immediate hypersensitivity to NRL were excluded from patch testing.**

Results: **Of 148 patients patch-tested with NRL, 3 (2.0%) had an allergic patch-test reaction.**

Conclusions: **NRL is as common a cause of allergic contact dermatitis as many of the other allergens included in a specialized rubber allergen series. Patients suspected to be allergic to rubber should be patch-tested with NRL (provided they do not have type 1 hypersensitivity to NRL).**

LATEX is a milky liquid derived from the sap of the rubber tree, *Hevea brasiliensis*. Several additives are combined with the liquid during processing to create a latex polymer termed natural rubber latex (NRL). NRL is frequently found in household and medical products and is now recognized as an important occupational and environmental allergen. Health care workers have allergies to NRL and rubber more frequently than the general population; this increased sensitivity may be due to increased exposure in the work environment.[1,2]

Immediate hypersensitivity reactions to NRL were noted in epidemic proportions in the 1980s and 1990s. This increase was concurrent with increased use of latex gloves and other latex preparations, but the incidence rate has waned with decreased use of NRL.[2–4] Delayed hypersensitivity reactions to latex have been recognized more recently (Table 1).[5–10] We sought to characterize the Mayo Clinic experience of the frequency of allergic patch-test reactions (delayed hypersensitivity) to NRL.

From the Department of Dermatology and Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, and the University of Wisconsin Hospitals and Clinics, Madison, WI.

Address reprint requests to Mark D.P. Davis, MD, Department of Dermatology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905. E-mail: davis.mark2@mayo.edu

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Methods

Patients

This study was approved by the Mayo Clinic Institutional Review Board. We retrospectively examined medical records to determine the results of patch testing with NRL. Patients were identified with the institution's patch-test database (Sybase, Inc, Dublin, CA), which combined data from all Mayo Clinic sites (Rochester, MN; Jacksonville, FL; Scottsdale, AZ). Patients with suspected allergic contact dermatitis from rubber first were screened to exclude those with immediate hypersensitivity reactions to NRL (detailed below). If the screening result was negative, patients then underwent patch testing with NRL, which was part of a specialized series of rubber allergens. Testing was conducted from January 1, 2000, through December 31, 2007. Patients who withheld research authorization were excluded from this study.

Source of NRL

The NRL serum used for patch testing was made at a laboratory within the Division of Allergic Diseases at Mayo Clinic. Raw latex (Johnson & Johnson, New Brunswick, NJ), stored in ammonia to prevent coagulation, was centrifuged, and the middle "latex serum" layer was saved (the top rubber pellet and a small amount of precipitate were discarded). The serum contained 39.2 mg/mL of protein, as measured by

Table 1. Comparison of Natural Rubber Latex Patch-Test Studies

		Positive Reactions to NRL	
Study	*Reference*	*No. of Patients*	*%*
Wakelin et al	7	24/608	3.9
Nettis et al	8	2/497	0.4
Nettis et al	9	2/61	3.3
Sommer et al	5	27/2,738	1.0
Miri et al	10	8/48	16.7
Wilkinson and Burd	6	7/117	6.0
Our study*	—	3/148	2.0

NRL = natural rubber latex.
*Only patients who did not immediately react to NRL (negative results on skin-prick test or radioallergosorbent test) underwent patch testing.

the Ninhydrin protein assay, and did not contain glycerin (Yunginger JW, personal communication, June 2008). It is unknown whether this contained any accelerators.

Testing for Immediate Hypersensitivity

To ensure that patients with immediate hypersensitivity to latex were not patch-tested with NRL, candidates for patch testing were first screened with a latex skin-prick test (Mayo Clinic Rochester) or a radioallergosorbent test (Mayo Clinic Scottsdale, Mayo Clinic Jacksonville). Skin-prick testing was performed, as previously described, and validated.[11,12] Tested compounds were a latex 1:10 solution (compounded by the Mayo Clinic pharmacy), a histamine control, a glycerin control, and a cornstarch control; a prick-only control was also used. If the latex site was negative after a 15-minute interval, concentrated latex polymer (''latex neat'') was applied over the test site. A negative result was defined as no reaction to either the latex solution or to latex neat. A positive result was characterized by a wheal ($>$ 3 mm) with flare and clinical relevance, as interpreted by an allergist. Only patients with negative test results (skin-prick test or radioallergosorbent test) were subsequently patch-tested with NRL.

Patch Testing

Patch testing was conducted in a standardized fashion as previously described.[13–16] Testing was performed with Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster Aksjeselskap, Vennesla, Norway). Patches were applied to clean dry skin on the upper back and were removed after 48 hours. Readings were taken at 48 to 72 hours and at 96 to 168 hours after application.

Patients generally were tested concurrently with a standard allergen series and a specialized rubber allergen series that included NRL. Results to patch testing with the rubber series are reported separately.[17] Patients were patch-tested with NRL serum.

Reactions were graded according to the following scale: negative reaction = 0, macular erythema = 1, weak reaction = 2, strong reaction = 3, and extreme reaction = 4. A weak reaction consisted of nonvesicular erythema, infiltration, or occasionally papules. A strong reaction was indicated by the presence of edematous or vesicular lesions. An extreme reaction was indicated by bullous or spreading reactions. Results were assessed for relevancy as determined by the likelihood of exposure to the chemical in the work or home environment. Relevancy was characterized according to the following scale: I (irritant); N (allergic, not relevant); Q (allergic, questionable relevance); P (allergic, formerly relevant); and R (allergic, relevant). Reactions that were present at the initial reading but that diminished or were absent at the second reading were characterized as irritant reactions. For the purposes of this study, a positive patch-test reaction was classified as a weak, strong, or extreme reaction at the last reading; macular erythema reactions were considered positive if the results were relevant. A reaction was considered relevant if it was characterized as being of past, current, or questionable relevance.

Statistical Analysis

All statistical analyses were performed using the *Statistical Analysis System* software package, version 8.2 (SAS Institute Inc., Cary, NC).

Results

Skin-prick test results were available for 245 patients. Of these patients, 17 (6.9%) had positive reactions to NRL and were excluded from patch testing with NRL.

We identified 148 patients who underwent patch testing with NRL during the study period. One hundred five patients (70.9%) were female, and 127 (85.8%) were white. Mean patient age was 41.9 years (range, 11–75 yr). The most common sites of dermatitis were the hand (n = 93 [62.8%]), limbs (n = 34 [23.0%]), and trunk (n = 16 [10.8%]). Forty-five patients (30.4%) were health care workers, and nursing was the most commonly listed career (n = 32 [21.6%]).

Of the 148 patients patch-tested with NRL, 3 (2.0%) had a positive reaction (Table 2). One of the three patients

Table 2. Characteristics of Patients Allergic to Natural Rubber Latex

Patient	*Sex*	*Age (yr)*	*Health Care Worker?*	*Occupation*	*Allergen*	*Grade of Reaction*	*Relevance of Reaction*	*Other Allergens Causing Positive Reactions*
1*	M	49	No	Launderer/dry cleaner	Centrifuged latex serum	Macular erythema	Q	Budesonide 0.1%, methyldibromoglutaronitrile/phenoxyethanol 1.5%
2	F	43	No	Technician	Centrifuged latex serum	Macular erythema	R	Carba mix 3%, thiuram mix 1%, dipentamethylenethiuram disulfide 1%, tetraethylthiuram disulfide 1%, tetramethylthiuram disulfide 1%, tetramethylthiuram monosulfide 1%, zinc diethyldithiocarbamate 1%, N-(cyclohexylthio)phthalimide 1%, natural fragrance mix 2%
3*	F	42	Yes	Optician	Centrifuged latex serum	Strong	R	Carba mix 3%, thiuram mix 1%, hexamethylenetetramine (methenamine) 2%, tetraethylthiuram disulfide 1%, tetramethylthiuram disulfide 1%, tetramethylthiuram monosulfide 1%, zinc dimethyldithiocarbamate 1%, 4,4-dithiodimorpholine 1%, balsam of Peru 25%, colophony 20%, DMDM hydantoin 1%, ethyleneurea-melamine formaldehyde mix 5%, formaldehyde 1% aq, methyldibromoglutaronitrile/phenoxyethanol 1.5%, quaternium-15 1%, *Compositae* mix 5%, natural fragrance mix 2%

aq = aqueous; DMDM = 1,3-dimethylol-5,5′-dimethyl; F = female; M = male; Q = questionable relevance reaction; R = current relevant reaction.
*Follow-up information was available for this patient.

Table 3. Results of Patch Testing in Patients Allergic to Natural Rubber Latex

Allergen	Allergen Series	Patients Tested	Positive (Relevant) Reactions*		No. of Reactions, by Strength†								
					1			2 & 3			4		
			No.	%	P	Q	R	P	Q	R	P	Q	R
Balsam of Peru	Standard	3	1	33	0	0	1	0	0	0	0	0	0
Budesonide 0.1%	Standard	3	1	33	0	1	0	0	0	0	0	0	0
Carba mix 3%	Standard	3	2	67	0	0	0	0	0	2	0	0	0
Colophony 20%	Standard	3	1	33	0	0	0	0	1	0	0	0	0
DMDM hydantoin 1%	Standard	3	1	33	0	0	0	0	0	1	0	0	0
Ethyleneurea-melamine formaldehyde mix 5%	Standard	3	1	33	0	0	0	0	1	0	0	0	0
Formaldehyde 1%	Standard	3	1	33	0	0	0	0	0	1	0	0	0
MDBGN/PE 1.5%	Standard	3	2	67	0	1	0	0	1	0	0	0	0
Quaternium-15 1%	Standard	3	1	33	0	0	0	0	0	1	0	0	0
Thiuram mix 1%	Standard	3	2	67	0	0	0	0	1	1	0	0	0
Compositae mix 5%	Standard	1	1	100	0	0	0	0	0	1	0	0	0
Natural fragrance mix 2%	Standard	3	2	67	0	1	0	0	0	1	0	0	0
Dipentamethylenethiuram disulfide 1%	Rubber	3	1	33	0	0	1	0	0	0	0	0	0
Hexamethylenetetramine (methenamine) 2%	Rubber	3	1	33	0	0	0	0	1	0	0	0	0
Tetraethylthiuram disulfide 1%	Rubber	3	2	67	0	0	1	0	1	0	0	0	0
Tetramethylthiuram disulfide 1%	Rubber	3	2	67	0	0	1	0	0	0	0	1	0
Tetramethylthiuram monosulfide 1%	Rubber	3	2	67	0	0	1	0	1	0	0	0	0
Zinc diethyldithiocarbamate 1%	Rubber	3	1	33	0	0	1	0	0	0	0	0	0
Zinc dimethyldithiocarbamate 1%	Rubber	3	1	33	0	0	0	0	0	0	0	1	0
N-(Cyclohexylthio)phthalimide 1%	Rubber	3	1	33	0	0	1	0	0	0	0	0	0
4,4-Dithiodimorpholine 1%	Rubber	1	1	100	0	1	0	0	0	0	0	0	0

DMDM = 1,3-dimethylol-5,5′-dimethyl; MDBGN/PE = methyldibromoglutaronitrile/phenoxyethanol; P = past relevant reaction; Q = questionable relevance reaction; R = current relevant reaction.

*Calculated by summing the number of reactions with past, questionable, or current relevance. Relevance was considered only for positive reactions (irritant reactions were not considered positive reactions). None of the positive reactions were categorized as ''not relevant.''

†Strength of the reactions was graded as follows: 1 = macular erythema; 2 & 3 = weak or moderate; 4 = severe.

who had positive results was identified as a health care worker. These three patients' positive results of patch tests with other allergens from both the standard allergen series and the rubber series are shown in Table 3. All positive reactions were considered to be of relevance.

Follow-up information was available for two patients (patients 1 and 3 in Table 2). Patient 1 did not report improvement after patch testing. He did not comply with allergen avoidance and declined topical medications except for emollients. Patient 3 improved with wet dressings and allergen avoidance.

Discussion

This report presents our experience of patch testing with NRL. The rate of positive allergic patch-test reactions to NRL in this study (2.0%) was similar to other published reaction rates,[6,9,11] although a wide range of rates have been observed (range, 0.4–16.7%; see Table 1). All three positive reactions in the current study were categorized as relevant when each patient's clinical history was considered (this category included reactions of definite relevance and questionable relevance).

The process of making a diagnosis of delayed hypersensitivity to NRL is challenging. It is theoretically possible to precipitate a type I hypersensitivity reaction (anaphylaxis) by placement of the patch-test material. To avoid this possibility, each patient was tested for type 1 hypersensitivity to latex (by a prick test or radioallergosorbent test) before patch tests were performed; patients with positive results were excluded from patch testing. Others have used different approaches. Miri and colleagues

screened patients with a questionnaire before patch-testing with NRL; patients were asked about type I hypersensitivity symptoms such as runny nose, itchy eyes, or difficulty breathing after exposure to latex products.[10] Nettis and colleagues performed IgE tests to latex after patch testing.[8] In that study, only two patients who had a positive patch-test reaction to NRL then underwent IgE tests to latex.

What form of latex should be used for patch testing? Although licensed commercial preparations of NRL are available in Europe and Canada, such extracts are not available in the United States. Allergists occasionally perform skin testing with in-house preparations of latex glove extracts, but gloves vary widely in their allergen content, and systemic reactions have been reported with the use of unstandardized preparations.

Initially, we used an extract from latex gloves that contained latex and additives; however, determining whether a reaction to the glove extract was attributable to latex or to the additives was problematic. We therefore chose to use a more purified latex product. Because no commercial NRL extract for diagnostic skin testing was available at the time (or even currently), we decided to use the in-house extracts made from raw latex that were provided by Johnson & Johnson. We questioned whether the ammonia storage solution for the latex could be an irritant, but we thought it unlikely because none of the 148 patients tested had an irritant reaction.

We included macular erythema reactions in the calculation of allergic patch-test reactions even though many others do not include such reactions in the analysis. Some advocate repeating patch testing when a macular erythema reaction is noted, but this was not done for patients in this study. We believe macular erythema reactions should be included if they are considered relevant to the patient's clinical presentation.[18,19]

Is it possible that patients become sensitized to NRL by prick testing or patch testing? We are unable to answer this question on the basis of our data. However, to our knowledge, nothing in the literature suggests that this could have occurred.

Limitations of this study include the retrospective review of data, the small sample size, and the overall subjective assessment of the relevancy of a reaction, which is typical for studies reporting results of patch testing. We acknowledge that the population undergoing patch testing comprised individuals suspected of being allergic to NRL; this may have introduced bias in our tested population. Additionally, variation in scoring may have occurred because numerous dermatologists were doing the readings during the study period. The true relevance of a reaction is known only with follow-up data that show whether patients improved with allergen avoidance; thus, the actual relevance of several allergic patch-test reactions remains undetermined.

Conclusion

Allergic patch-test reactions to natural rubber latex (NRL) were identified in 2.0% of patients in the study. This makes allergies to NRL as common as allergies to many of the other substances included in the specialized rubber series. To avoid anaphylaxis caused by patch testing, our practice is to first check for immediate hypersensitivity; patients who are shown to have immediate hypersensitivity to latex are excluded from patch testing. Patients with suspected allergy to rubber should be patch-tested with latex.

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