

Natural rubber pharmaceutical vial closures release latex allergens that produce skin reactions

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Background: The release of allergenic proteins from natural rubber vial closures (stoppers) into aqueous pharmaceuticals may induce allergic reactions in individuals with latex allergy (LA) receiving medications from such vials.

Objective: The goal of this study was to determine whether solutions stored in vials containing natural rubber closures release allergenic proteins detectable by skin testing of subjects with LA.

Methods: Five pharmaceutical vial closures (2 natural rubber and 3 synthetic) were coded, inserted onto vials containing phenol-saline-human serum albumin, and stored in an inverted position before use. Twelve volunteers with and 11 volunteers without LA underwent skin testing with solutions from each of the 5 vials, either those not punctured (0P) or those punctured 40 times with a 21-gauge needle 12 to 24 hours before testing (40P). **Results:** All intradermal skin test responses in the group without LA were negative. Two and 5 of the 12 subjects with LA had positive intradermal skin reactions to 0P and 40P solutions, respectively, from vials containing rubber closures. Two subjects with LA had inexplicable, positive, nonreproducible intradermal skin test reactions to solutions from vials containing bromobutyl but not vials with isoprene synthetic closures. *In vitro* inhibition analysis detected 6 to 7 AU/g latex allergen in extracts of cut natural rubber containing closures but not in extracts of synthetic closures.

Conclusion: Natural rubber vial closures released allergenic latex proteins into the tested solutions in direct contact during storage in sufficient quantities to elicit positive intradermal skin reactions in some individuals with LA. These data support a recommendation to eliminate natural rubber from closures of pharmaceutical vials. (*J Allergy Clin Immunol* 2001;107:958-62.)

Key words: *Natural rubber, latex allergy, pharmaceutical vial closures, skin testing*

Abbreviations used

FDA: Food and Drug Administration

LA: Latex allergy

Allergy to natural rubber latex is an established health problem, with a prevalence of 1% to 6% in the general population,¹⁻⁴ 8% to 16% in health care workers,^{5,6} and up to 50% in children with spina bifida.⁷ The symptoms range from mild local cutaneous reactions to generalized urticaria, angioedema, allergic rhinitis, respiratory symptoms, and life-threatening or fatal anaphylaxis. The severity of symptoms is dependent on an individual's susceptibility but also on the mode and route of latex allergen exposure, with mucosa, visceral, and parenteral exposure being associated with the greatest risk for the development of severe systemic reactions.⁸

Avoidance of exposure to natural rubber latex products is the primary method for preventing allergic reactions. Latex products can be classified into 2 types on the basis of their manufacturing processes. Dipped latex products refer to those manufactured by means of dipping a porcelain form into liquid latex. Exposure to dipped products (eg, gloves, balloons, and condoms) causes most of the observed immediate-type reactions. Dry or natural rubber refers to products that are made from hardened sheets of *Hevea* latex. They generally release less latex proteins on extraction than dipped products.⁹ Vial stoppers (hereafter called closures) are natural rubber products. There has been widespread concern that latex allergen may leach from natural rubber closures into medications, with potential for causing a life-threatening allergic reaction if injected into an individual with latex allergy (LA).

In this study the release of latex proteins into solutions stored in vials containing natural rubber and synthetic closures was investigated by using intradermal skin testing of individuals with documented LA and control subjects without LA, as well as by using *in vitro* inhibition analysis.

METHODS

Subjects

Two groups of subjects 18 years of age or older (18 with LA and 11 without LA) were recruited from the Johns Hopkins and University of Maryland Allergy Clinics by means of advertisements and

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TABLE I. Properties of the five 13-mm vial closures evaluated in the study

Parameter*	Closure A	Closure B	Closure C	Closure D	Closure E
Closure formulation [†] (natural rubber or synthetic)	Synthetic (bromobutyl)	Natural rubber (gum/crepe)	Natural rubber (crepe)	Synthetic (isoprene)	Synthetic (gum/isoprene)
Lot number [‡] and color of closure	G802/1433 (gray)	PD8301-002 (brown)	390-98 (gray)	393-98 (gray)	PD8301-001 (tan)
Percentage weight of natural rubber content reported in formulation [†]	0	95.3	66	0	0
Latex allergen content in 0P and 40P solutions (AU/mL)	<0.5	<0.5	<0.5	<0.5	<0.5
Latex allergen content extracted from cut closures (AU/g)	<0.5	7.4	6.7	<0.5	<0.5

AU, Allergen units assigned by RAST inhibition analysis with natural rubber latex (E8-FDA) as a standard, with 100,000 AU/mL undiluted.

*Closure designation code (A-E) arbitrarily specified by the Parenteral Drug Association before insertion into vials for use in study.

[†]Defined by manufacturer.

direct invitations. At the screening visit, a clinical history and blood samples were collected. Subjects were recruited into the LA group if they had a positive history for IgE-mediated LA and a positive latex-specific IgE serology (>1 kIUa/L, Pharmacia CAP System). Control subjects were recruited with a negative LA history and a negative latex-specific IgE serology (<0.35 kIUa/L). Subjects were not qualified by means of skin testing because of the unavailability of a Food and Drug Administration (FDA)-approved latex extract.

Study vials

Five 13-mm pharmaceutical vial closures were manufactured for this study by American Stelmi (n = 1), West Pharmaceutical Services (n = 2), and Tompkins Rubber Company (n = 2) by using natural rubber (n = 2) or synthetic (n = 3) formulations (Table I). All closures were sent by the manufacturers to the Parenteral Drug Association (Washington, DC), where they were randomized and coded from A to E. The coded closures were then sent to the Chesapeake Biological Laboratories (Baltimore, Md), where good manufacturing practices were used to wash, sterilize, and insert the closures into washed and sterilized 3-mL borosilicate pharmaceutical-grade vials containing 1 mL of saline-0.03% human serum albumin-0.4% phenol (FDA-licensed intradermal skin testing diluent from Greer Laboratories, hereafter called saline). All vials were capped, inverted after manufacturing, and quarantined for at least a month before being released as sterile. They were stored inverted at room temperature until their use within a 9-month period.

Study protocol

Twelve to 24 hours before each study visit, a set of 5 vials (A-E) was punctured 40 times with a 21-gauge needle while inverted and denoted as 40P. Saline removed from the nonpunctured vials after removing their closure was referred to as the 0-puncture (0P) solution. All solutions (saline negative control, histamine positive control, and 0P and 40P solutions from vials A-E) were drawn up into their own labeled 27-gauge needle-equipped tuberculin syringe containing synthetic plunger seals (Becton-Dickinson) 30 to 60 minutes before use.

For safety reasons, a puncture skin test was initially performed, as previously described.¹⁰ If the reaction was negative, single intradermal skin tests were then performed¹⁰ with all 0P solutions and repeated in duplicate if positive at 15 minutes. Next, intradermal skin tests were performed with all 40P solutions in duplicate and read at 15 minutes. The Norman grading criteria¹⁰ were used to define positive or negative results. Individuals with positive (>5-mm wheal or >10-mm erythema) skin reactions to the diluent negative control were excluded from further study. If the initial duplicate

intradermal skin tests produced discrepant results, the same solution was retested in duplicate until an unequivocal result was obtained. The project was approved by the Johns Hopkins Bayview Institutional Review Board.

Laboratory analyses

Whole blood was collected from all subjects for measurement of latex-specific IgE levels, total serum IgE levels, and a multiaeroallergen screen (Phadiatop¹¹) by using the CAP System (Pharmacia). The 5 closure types (A-E) were evaluated for the presence of extractable latex allergen by means of CAP inhibition analysis. Five grams of each vial closure (each cut in half) were extracted in duplicate overnight at room temperature with rotation by using 5 mL of PBS containing 1% BSA and 0.01% thimerosal. All closure extracts were centrifuged, sterile filtered, and, together with the 0P and 40P solutions from all 5 vials types, analyzed by means of CAP inhibition analysis. The assay used nonammoniated latex (E8) from the FDA (CBER; neat = 100,000 AU/mL) as the reference and an IgE anti-latex containing a human serum pool known to contain Hev b 1 to Hev b 7-specific IgE antibody. The analytic detection limit of the CAP inhibition assay was 0.5 AU/mL.

Statistical analyses

Qualitative differences in the frequency of positive skin test responses between the LA and non-LA groups with solutions from natural rubber (B0P, B40P, C0P, and C40P) and synthetic (A0P, A40P, D0P, D40P, E0P, and E40P) closure-containing vials were assessed by using χ^2 Pearson correlation analysis with SPSS software. Differences in the quantitative mean value (in millimeters) of wheal and erythema responses between the non-LA and LA groups for each of the test solutions (0P and 40P from vials A-E) were evaluated by using ANOVA, with the 2-tailed *t* test for equality of mean (SPSS). Significance was considered at a *P* value of less than .05.

RESULTS

Study population characteristics

Six of 18 subjects with LA were excluded from participation because of a positive intradermal skin test response to the negative control diluent. The remaining 12 subjects with LA (10 female and 2 male subjects) and 11 subjects without LA (10 female and 1 male subject) underwent skin testing with 0P and 40P solutions from each of the 5 test vials. IgE anti-latex levels ranged from 1.0 to 31.9 kIUa/L in the sera of the subjects in the LA

TABLE II. Intradermal skin test reactivity in subjects with solutions from vials A-E

Subject code	Latex-specific IgE		H	Closure A Synthetic		Closure B Natural Rubber		Closure C Natural Rubber		Closure D Synthetic		Closure E Synthetic	
	(kIUa/L)	S		0P	40P	0P	40P	0P	40P	0P	40P	0P	40P
LA-1	1.0	0 × 0	14 × 32	—	—	—	—	—	—	—	—	—	—
LA-2	1.1	1 × 6	10 × 53	—	—	—	5 × 29	—	—	—	—	—	—
LA-3	1.2	0 × 0	13 × 43	—	—	—	—	—	—	—	—	—	—
LA-4	1.6	0 × 0	11 × 48	—	—	—	—	—	—	—	—	—	—
LA-5	1.8	0 × 0	9 × 34	—	—	—	—	—	—	—	—	—	—
LA-6	3.0	0 × 0	12 × 37	—	—	—	8 × 15	—	—	—	—	—	—
LA-7	3.2	0 × 0	10 × 58	6 × 31	—	—	—	—	6 × 39	—	—	—	—
LA-8	4.9	0 × 0	15 × 50	—	—	—	—	—	—	—	—	—	—
LA-9	5.7	0 × 0	11 × 41	—	—	10 × 37	12 × 36	9 × 29	9 × 46	—	—	—	—
LA-10	25.7	0 × 0	19 × 53	—	7 × 25	9 × 37	10 × 28	—	6 × 44	—	—	—	—
LA-11	3.8	0 × 0	12 × 49	—	—	—	—	—	—	—	—	—	—
LA-12	31.9	0 × 0	13 × 13	—	—	—	—	—	—	—	—	—	—
Reactivity of 11 subjects without LA	<0.35	0 × 0 [†]	10 × 37 [†]	—	—	—	—	—	—	—	—	—	—

S, Saline; H, histamine; —, Negative intradermal skin test defined as a wheal of less than 5 mm and erythema of less than 10 mm.

*Mean (millimeters) wheal × erythema of positive intradermal skin test reactions.

[†]Mean results for 11 subjects without LA.

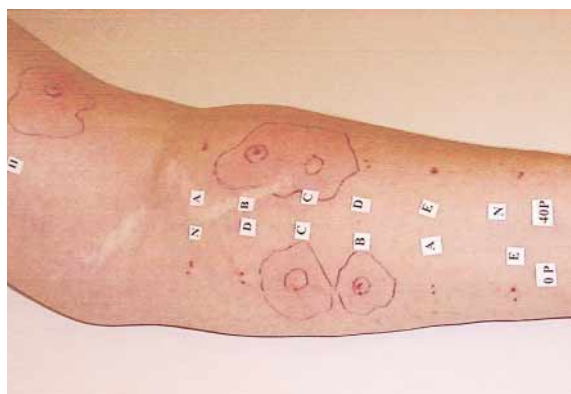


FIG 1. Representative intradermal skin test reactions induced by 0P and 40P solutions from vials containing natural rubber closures B and C on the forearm of subject LA-9. Ink lines demarcate the wheal-and-flare perimeters observed at 15 minutes. H, Histamine positive control; N, saline negative control.

group (Table II). There were no significant differences in the levels of latex-specific IgE antibody or total serum IgE between the 12 subjects with LA included and the 6 individuals with LA excluded from further testing.

In vivo analyses

All puncture skin test reactions to solutions from vials A to E were negative in both the LA and non-LA groups. Fig 1 illustrates skin reactions produced by intradermal skin testing with solutions from study vials A to E in a representative subject with LA. Table II summarizes the results of intradermal skin testing to the 0P and 40P solutions in the 12 subjects with LA and the 11 subjects without LA. Intradermal skin test reactions with 0P and 40P solutions from test vials A to E were all negative in the 11 subjects without LA. Two subjects with LA had positive skin reactions to

solutions from unpunctured (0P) natural rubber closure-containing vials. Five subjects with LA experienced positive intradermal skin test reactions to 40P solutions stored in vials B, C, or both containing a natural rubber closure. The frequency of skin test positivity with solutions from natural rubber closure-containing vials was significantly higher in the LA group than in the non-LA group ($P = .003$). Moreover, the mean diameter of the wheal and erythema produced by solutions from vial B40P was significantly larger in the subjects with LA than in those without LA ($P = .007$ and $.03$, respectively; range for the group with LA, 5- to 12-mm wheal and 4- to 29-mm erythema). Wheal skin reactions produced by solutions from the other natural rubber closure-containing vials tended to be larger in the LA group than in the non-LA group, but the difference was not statistically significant (B0P, $P = .07$; C0P, $P = .3$; C40P, $P = .1$). Surprisingly, 2 subjects with LA exhibited a positive intradermal skin test reaction to solutions from vial A but not from vials D and E, all of which contained synthetic closures. In subject LA-7, retesting on the same day with a 0P solution withdrawn from a different A-vial caused negative results (data not shown). Subject LA-10 was also retested on a different day with an A40P solution and had a negative reaction (data not shown).

In vitro analysis

After decoding by the Parenteral Drug Association, 3 vial closures were identified as 100% synthetic (A, D, and E), and 2 were reported to contain 95.3% (B) and 66% (C) natural rubber (Table I). RAST inhibition analysis detected 6 and 7 AU of latex allergen per gram in the extracts from closures B and C, confirming that they contained natural rubber. No allergen (<0.5 AU/g) was detected in extracts from synthetic closures A, D, and E or any of the solutions stored in the 0P or 40P vials A to E (<0.5 AU/mL, Table I).

DISCUSSION

Since the medical alert¹² on LA that was issued in 1991 by the FDA, physicians and patients with LA have expressed concerns about the potential for latex allergen exposure from natural rubber closures in pharmaceutical vials and the possibility of allergic reactions after parenteral drug administration. The US Pharmacopeia was prepared in 1996 to ban natural rubber in pharmaceutical vial closures¹³ because satisfactory synthetic butyl and isoprene rubber stoppers were available that contained no latex allergen. This ban was, however, resisted by FDA staff, who believed there was insufficient data to show that natural rubber closures contribute to a significant risk for reactions in individuals with LA (personal communication from Yana Ruth Mille, FDA, to Joseph Valentino, JD, The United States Pharmacopeial Convention, Rockville, Md, February 19, 1997 [Ref. 2-97-001-T]). Their decision was based on the fact that natural rubber vial closures are manufactured from dry rubber that is known to release lower amounts of latex protein than dipped rubber products, such as latex gloves. Total protein tests performed on natural rubber vial closures by the FDA with the insensitive Lowry test failed to detect leached protein. Second, the FDA could only identify 2 reports of allergic reactions presumed to be due to natural rubber vial closures.^{14,15} In both cases further FDA investigation revealed that the vial closures implicated in these studies were in fact synthetic butyl rubber and not natural rubber, as had been previously reported by the authors.

Out of concern for the potential risk for latex allergen exposure from vial closures, hospital staff began removing pharmaceutical vial closures at the bedside of patients with LA and drawing medications into glass or latex-free plastic syringes. Infection control officers were concerned about this practice because it increased the potential for infections. Several hospitals, including our own, adopted a one-stick policy,¹⁶ in which a single puncture was permitted through any vial closure before drug administration to an individual with LA. This practice minimized the risk of leaching from multiple punctures but did not eliminate the possibility that latex proteins may leach slowly from nonpunctured closures into pharmaceuticals during shipping and storage.

In this study we have demonstrated that latex allergens are released into physiologic solutions in contact with natural rubber vial closures. Two individuals with LA had positive intradermal skin test reactions to solutions from nonpunctured natural rubber closure-containing vials. Five subjects with LA reacted to the solution from punctured natural rubber closure-containing vials. Forty punctures was adopted as a worse-case condition for a multidose pharmaceutical vial (eg, insulin).

Seven of the 12 individuals with LA in the study failed to display positive skin reactions to solutions from vials with natural rubber closures, including the subject with LA with the highest latex-specific IgE levels in the serum. A likely explanation for this is the heterogeneity

of IgE antibody responses to the spectrum of known latex allergens^{17,18} coupled with the possibility of differential leaching of various latex allergens from the natural rubber closures. Noteworthy are the negative skin test results in 4 of 5 subjects with LA with serum latex-specific IgE levels of less than 3 kIUa/L. It is unclear why 2 of the 5 individuals with LA with positive skin reactions to solutions stored in vials containing natural rubber closures also exhibited skin reactions to solutions from vials containing synthetic bromobutyl but not isoprene closures (Table II). Although these skin reactions were not reproducible, they warrant further study and suggest that accelerator chemicals or other ingredients in bromobutyl rubber may induce immediate-type hypersensitivity reactions in the skin. This hypothesis is, however, not supported by any data in the literature.

Two different natural rubber closure sources (B and C) were evaluated in this study. Closure B had a higher latex content as a percentage of weight, and we found higher intradermal skin test reaction rates with solutions from vial B than with those from vial C. One subject with LA reacted to solution from vial C but not from vial B. This suggests that the latex proteins released from the 2 rubber closures may differ.

Other investigators have analyzed solutions stored in vials containing natural rubber closures and syringe plungers for latex allergen content. Thomsen and Burke¹⁹ evaluated 20 solutions from 16% rubber closure-containing vials punctured once and were unable to detect latex allergen with an inhibition immunoassay with a reported analytic sensitivity of 250 ng/mL. Their results are concordant with those from the present study, in which only extracted closures, and not solutions stored in punctured vials, contained detectable latex allergen, as measured by a comparable CAP inhibition assay (Table I). In another study, Jones et al²⁰ evaluated 3 bovine collagen preparations stored for 0, 3, and 45 months in contact with the rubber plungers of syringes for latex allergen content by skin prick testing. They observed that only 1 of 39 subjects with LA and 0 of 31 control subjects without LA had positive skin prick test responses to the collagen solutions stored for 3 and 45 months. This indicates that these injectable collagen syringes may contain low levels of latex allergen. The higher rate of observed positive skin test responses in the present study is attributed to greater sensitivity of the intradermal skin test technique to detect latex allergen in nanogram per milliliter levels while also maintaining diagnostic specificity.²¹ We previously have shown that intradermal skin testing is at least a thousand times more sensitive than puncture skin testing and 100-fold more sensitive than RAST inhibition analysis for the detection of latex allergens.²¹

The percentage of the total number of pharmaceutical vial closures that contain natural rubber has declined in the recent years. Some closures manufactured today contain a mix of natural rubber and synthetic butyl rubber, with a ratio that can be as low as 13.4%.¹⁹ The 2 closures containing 66% and 93.5% natural rubber and 3 synthetic closures used in this study were produced by using

standard formulations by 3 companies who make the majority of closures used in commercial pharmaceutical vials. The problem remains that practitioners have no easy method for determining which products or lots of closures contain natural rubber. This information is often not readily available, even from the pharmaceutical manufacturers themselves.

Data from our study confirm that latex allergen can be released into pharmaceutical solutions simply by direct contact during storage in vials with natural rubber closures. We therefore conclude that both the pop-off and one-stick rule approaches for delivering medications from natural rubber-stoppered vials do not provide adequate protection for patients with LA. Although such contamination may not be hazardous for all individuals with LA, prudence dictates the removal of this allergen source from pharmaceutical closures because suitable latex-free substitutes are readily available. More immediately, however, uniform labeling of the natural rubber content of pharmaceutical closures would serve as a practical interim solution for minimizing risks to patients with LA.

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