

Short communication

The presence of latex can induce false-positive skin tests in subjects tested with penicillin determinants

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Latex allergens are ubiquitous, and exposure may occur from different sources in the medical environment and in daily life. The observation that subjects with latex allergy were skin test positive to major and minor determinants of penicillins led our group to carry out an investigation to try to explain these findings. A group of 20 subjects with a history of allergy to latex and with positive skin tests for, but good tolerance of, penicillins was studied. The presence of latex contaminants was studied by RAST and RAST inhibition. Sixteen of the subjects were positive to at least one of the penicillin determinants used, and 14 (87%) of these were positive to at least two determinants. Repetition of skin tests using the container without a stopper changed the skin test results to negative in almost all cases, indicating that some trace contaminants had still been present. RAST-inhibition studies showed that in all penicillin determinants there were trace amounts of latex allergens varying between 3 and 0.03 µg/ml. These results indicate that skin tests with penicillin in subjects allergic to latex may give false-positive results and lead to such patients being falsely diagnosed as allergic to betalactams when penicillins are stored in containers with rubber stoppers.

Key words: latex allergy; penicillin determinants; skin testing.

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Allergy to latex has increased because of the ubiquitous presence of this product. Particular groups of subjects have an increased incidence of allergic reactions to latex products. The prevalence of sensitivity to latex in spina bifida is as high as 64% (1, 2). In medical personnel exposed to products containing latex, the incidence of latex sensitization varies from 7% to 17% (3, 4). The latex exposure may occur by cutaneous, mucosal, and parenteral routes (5, 6). Various sources of exposure have been reported: gloves, catheters, adhesives, tourniquets, drains, and anesthetic equipment (3, 7).

The initial observation by our group and others (8) that some patients allergic to latex have a positive skin response to penicillin determinants, despite an unconvincing history of penicillin allergy, led us to consider the possibility of the presence of

latex allergens in the supernatant of penicillin solutions, cross-reactivity, or some association. Skin tests with major and minor determinants of different penicillins, RAST-inhibition studies, and controlled challenge showed that the patients had good tolerance of penicillin derivatives, and that the positive skin test was due to the presence of latex contaminants in the supernatant of the penicillin solutions. The relevance of these findings is discussed.

Material and methods

Subjects

A group of subjects with a history of allergy to latex and good tolerance of penicillin were selected for the study. An age- and sex-matched group of

subjects with no history of allergy to penicillins or to latex and good tolerance of penicillins was used as a negative control group.

Sera collection

A volume of 20 ml of blood was taken from each subject for *in vitro* studies. Serum samples were frozen at -20°C until assayed.

Skin tests

The latex allergen for skin testing was provided by Abelló at a final concentration of 2 mg/ml and was prepared as follows. Raw, ammoniated latex (in 0.7% ammonia solution, pH 10.8) was diluted in distilled water (30% v/v). Acetic acid was added stepwise until two phases were formed. The supernatant (serum latex) was taken out and neutralized with NaOH and then adjusted with 0.2 M phosphate buffer until a concentration of 25 mM was reached. This was passed through a glass fiber prefilter and dialyzed in distilled water, pH 7.5, using a dialysis membrane with a cutoff of 3.5 kDa. Then it was passed through the glass fiber again, and the protein concentration was determined by Bradford's method. The extract was lyophilized and reconstituted in NaCl until a final concentration of 1.8% w/v was reached. For skin testing, the extract was prepared as previously described (9). For penicillin testing, the following determinants were used: benzylpenicilloyl polylysine (BPO) 5×10^{-5} M and minor determinant mixture (MDM) 10^{-2} M, both provided by Allergopharma (Merck); amoxicillin (AX) 20 mg/ml, provided by Beecham, Toledo, Spain; and ampicillin (AMP) 20 mg/ml, provided by Antibiotic SA, León, Spain. All penicillin reagents were diluted in phosphate-buffered saline with and without the container stopper (the latex content of the stoppers was unknown). Latex allergens were tested by prick. Intradermal tests were carried out for the penicillin determinants (10). The criteria for positivity on prick testing were as previously reported (11), a papular area greater than 3 mm being considered positive.

RAST

Specific IgE antibodies to latex were determined by a commercially available assay (CAP, Pharmacia), and those to penicillin derivatives were determined by RAST, as described elsewhere (12).

RAST inhibition

In a pool of five serum samples from subjects allergic to latex, ranging from 5 to 55 kU/l, RAST

inhibition was done with RAST disks coupled to latex allergens in the solid phase, and in the fluid phase with allergens from latex and the same penicillin reagents used for skin testing. The concentrations used were as follows: for latex allergen, 30, 3, 0.3, and 0.03 $\mu\text{g/ml}$ of protein; for AX and AMP, 50, 5, 0.5, and 0.05 $\mu\text{g/ml}$ of drug; for BPO-PLL, 300, 30, 3, and 0.3 $\mu\text{g/ml}$ of conjugate; and, for MDM, 2000, 200, 20, and 2 $\mu\text{g/ml}$ of drug.

Challenge tests

In all patients with positive skin tests to any of the penicillin determinants, a controlled challenge test with the same derivative was made in order to exclude sensitization. The challenge procedure was carried out as previously described (10).

Results

A total of 20 subjects were included in the study. The clinical data are presented in Table 1. All subjects reported having had allergic symptoms after latex exposure. Eleven had nasal or nasoconjunctival symptoms, and four of these had developed asthmatic episodes after exposure. These cases were confirmed by environmental exposure. This means that all patients had had a reaction after exposure at their workplace, but they were not challenged. Patients 2, 5, 8, 17, and 18 experienced a fall in FEV_1 of 20%, 20%, 29%, 25%, and 24%, respectively, after handling gloves. Three (patients

Table 1. Clinical data, skin tests, and RAST of patients included in study

Patient no.	Age (years)	Sex	Occupation	Diagnosis	Skin test	RAST
1	32	F	Housewife	U, ANA	+	2
2	39	F	Nurse	RC, AS, U	+	3
3	30	M	Nurse	RC, U	+	1
4	31	F	Nurse	RC, U	+	2
5	32	F	Nurse	RC, AS, ANA, U	+	3
6	40	F	Nurse	R, U	+	3
7	32	M	Nurse	U	+	2
8	42	M	Medical doctor	U, R, AS	+	3
9	41	F	Housewife	U, ANA	+	1
10	17	M	Nurse	U	+	3
11	35	F	Nurse	U, R	+	0
12	28	F	Housewife	U	+	5
13	34	F	Nurse	U, R	+	5
14	36	F	Nurse	U	+	2
15	23	F	Housewife	U	+	1
16	36	F	Nurse	U, ANA	+	2
17	34	F	Nurse	U, R, AS	+	3
18	42	F	Housewife	U, AS	+	1
19	30	F	Nurse	U, R	+	2
20	26	M	Nurse	RC, U	+	3

U: contact urticaria; R: rhinitis; RC: rhinoconjunctivitis; AS: asthma; ANA: anaphylaxis.

5, 9, and 16) had suffered from anaphylactic shock after surgical intervention and one patient had anaphylactic shock after colonoscopy (patient 1). In addition to these symptoms, all patients developed urticaria after contact with gloves or products containing latex (Table 1).

The RAST value for latex determined by CAP-FEIA can be seen in Table 1. It was class 5 in patients 12 and 13, class 3 in seven patients (nos. 2, 5, 6, 8, 10, 17, and 20), class 2 in six patients (nos. 1, 4, 7, 14, 16, and 19), class 1 in four patients (nos. 3, 9, 15, and 18), and negative in patient 11.

The skin test results for BPO, MDM, AX, and AMP are shown in Table 2. Sixteen patients were positive to at least one of the penicillin determinants tested. In patients 12 and 13, the skin tests were positive to the four determinants tested. In three patients (nos. 10, 15, and 19), the skin tests were positive to three determinants, BPO, MDM, and AX. Skin tests were positive to two determinants, BPO and MDM, in nine patients (nos. 1, 2, 4, 5, 8, 16, and 20); to MDM and AMP in patient 9; and to MDM and AX in patient 17. In patients 3 and 6, RAST was positive only to MDM. The skin tests were repeated with the same container without the stopper in 10 of the subjects. All of the tests were then negative, except for patient 9, whose test remained positive to AMP, and patient 10, whose test remained positive to AX.

The results of RAST inhibition are shown in Fig. 1. It can be seen that the solution of AMP and AX, when inhibited at 5 µg/ml, contained a concentration of allergen equivalent to 0.3–3 µg/ml of the latex extract used in the inhibition. When the inhibition was carried out with the solutions of BPO, a significant degree of inhibition was obtained only at the maximum concentration of hapten, which was 300 µg/ml, and MDM was inhibited, although to a lesser extent, at the maximum concentration of 2000 µg/ml. This indicated that BPO-PLL and MDM contained trace contaminants of latex of 0.3–0.03 µg/ml. In addition, all patients with a positive skin test to at least one of the penicillin determinants tested were challenged with either benzylpenicillin by parenteral administration or AX by oral administration, and good tolerance was observed in all instances, confirming that skin test results were positive due to latex contamination.

Discussion

Allergic reactions to trace amounts of latex coming from injection ports of intravenous tubing, multidose vials with rubber stoppers, preloaded syringes with rubber-stopper plungers, adhesive tape, and other medical devices have been reported (1, 13–15).

Table 2. Results of skin tests with penicillin determinants in group of subjects allergic to latex

Patient no.	BPO	MDM	AX	AMP
1	+	+	—	—
2	+	+	—	—
3	—	+	—	—
4	+	+	—	—
5	+	+	—	—
6	—	+	—	—
7	—	—	—	—
8	+	+	—	—
9	—	+	—	+
10	+	+	+	—
11	—	—	—	—
12	+	+	+	+
13	+	+	+	+
14	—	—	—	—
15	+	+	+	—
16	+	+	—	—
17	—	+	+	—
18	—	—	—	—
19	+	+	+	—
20	+	+	—	—

BPO: benzylpenicilloyl; MDM: minor determinant mixture; AX: amoxicillin; AMP: ampicillin.

The initial observation of patients with allergic reactions to latex who were skin-test positive to penicillin determinants without previous history of allergic reactions to penicillins led our group to carry out this study in order to determine whether there was an association between latex allergy and allergy to β-lactams, and to test for the presence of latex contaminants in the penicillin reagents used for skin testing. A similar observation has been made by others (8) who have described patients with positive skin tests to BPO and MDM, allergy to latex, and good tolerance of penicillin.

In the 20 patients presented in our study with a diagnosis of latex allergy based on the presence of symptoms after latex exposure, and verified by positive skin test and RAST, skin tests with MDM were positive in 80% of the patients, with BPO in 60%, with AX in 30%, and with AMP in 15%.

RAST inhibition showed that in the shaken vials of AX and AMP there was a latex protein contaminant that produced inhibition equivalent to 0.35–3.5 mg/ml of latex allergen. Furthermore, latex reactivity, although of smaller amount, was also detected in the vials of BPO and MDM. Our results indicate latex contamination exists within the reagent vials.

Repetition of the skin tests with the opened vials where the penicillin determinants were diluted without using the stopper indicated that in most instances skin tests became negative. The positivity of two patients to AX and AMP may indicate a

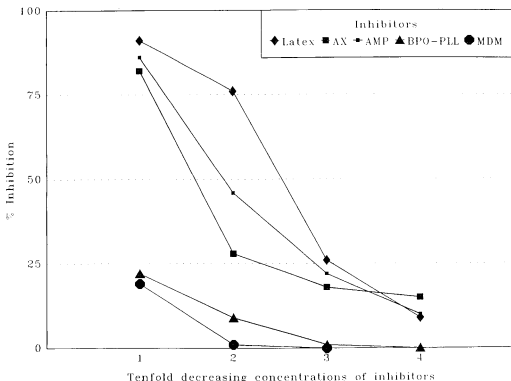


Fig. 1. RAST inhibition study using latex and penicillin determinants. Concentrations used for inhibition are detailed in Material and methods section.

persistent contamination which could have been produced by the plunger of the loaded syringe used for skin testing. Contamination could also have occurred through the puncturing of the stopper by the needle, or the antibiotic powder could have been contaminated by airborne latex particles from the inner surface of the stopper. As we demonstrate, contamination may be avoided if there is no contact with the stopper. More studies are needed in order to quantify the protein released from these medical-device components.

We conclude that when latex-allergic patients are tested for drug allergies the reagents should be kept away from all possible sources of latex release such as stoppers, plungers, and other components, thereby ensuring there has been no latex contamination if a latex-allergic patient has a positive skin reaction to a drug. In order to avoid false-positive skin tests to β -lactams in patients allergic to latex, we recommend the use of glass vials without rubber stoppers.

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