

Toxicity and immediate allergenicity of latex gloves

L. CORMIO, K. TURJANMAA*, M. TALJA†, L. C. ANDERSSON‡
and M. RUUTU

*Fourth Department of Surgery, Helsinki University Central Hospital, *Department of Dermatology, Tampere University Hospital, †Department of Surgery/Urological Unit, Kuopio University Hospital and ‡Institute of Pathology, Helsinki University; Finland*

Summary

Surgical latex gloves and a natural rubber latex (NRL) catheter were evaluated for biocompatibility by cell culture methods and Type I allergic reactions in operating room personnel using latex gloves. The prevalence of relevant immediate allergy to NRL was 5.2% when using eluates made from different latex gloves as allergens and the skin-prick test methodology. The reliability of a questionnaire in detecting the sensitized persons was limited. Weak positive skin test reactions to surgical latex glove eluates were found to be unreliable as compared with challenging with the corresponding glove. Latex gloves exhibited more toxicity in cell culture than non latex gloves but, inversely, the toxic catheter gave weak positive skin-prick test reaction in only one sensitized person, confirming that the allergenicity and toxicity of natural rubber products do not refer to the same properties of the products. Catheters exhibiting toxicity in cell culture have earlier been found to cause significant clinical symptoms in operated patients, but in the case of surgical gloves this relationship is not clear. One glove brand with a low content of known sensitizing rubber chemicals caused clear toxicity in cell culture but was well tolerated by the hospital personnel.

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Introduction

The biocompatibility of natural rubber latex (NRL) devices, including surgical gloves, urinary catheters, rectal probes, clamp covers, drainage and suction tubes, etc., is an increasing problem within the health care sector because of their wide use in medical practice [1–3].

Natural rubber latex is a fluid substance derived from the rubber tree (*Hevea brasiliensis*) containing water-soluble proteins which cannot be eradicated completely during the manufacturing process. The proteins may be eluted from the final NRL products and induce IgE-mediated Type I allergy [4]. Rubber chemicals such as accelerators and anti-oxidants, added to NRL during the manufacturing process, are known contact sensitizers capable of eliciting cell-mediated Type IV allergy [5]. However, the most common side-effects connected with the use of different rubber products are of a toxic nature.

Sensitization to NRL proteins and to the added rubber

chemicals is a consequence of repeated exposure to the allergens, such as prolonged use of latex gloves for cleaning and medical purposes [6], repeated urethral catheterization [7] and multiple operations [8]. Consequently, health care workers represent a major risk group.

The overall incidence and prevalence of the immediate allergy to NRL, either in the hospital personnel or in the whole population, are not known. In a study on 512 hospital workers using gloves, 3% exhibited immediate NRL allergy [6]. In the same study, 25% of the workers complained of irritation when using gloves although no allergy could be confirmed. The occurrence of allergy was higher in the operating unit personnel, 5.6% for nurses and 7.4% for surgeons. Almost two-thirds of sensitized people were atopic, which was defined as previous or present atopic dermatitis and/or rhinitis and/or asthma. In a group of 907 French hospital employees, sensitization to NRL was observed in 2.5% [9]; in another study, 10.7% of the operating room [OR] nurses showed immediate allergy to NRL [10].

While the only symptom of Type IV sensitization to rubber chemicals is eczema, in the case of glove allergy

Correspondence: Dr L. Cormio, Fourth Department of Surgery, Helsinki University Central Hospital, Kasarmikatu 11-13, FIN-00130 Helsinki, Finland.

located on the dorsum of the hand and fingers often with clear cut-off above the wrist, the clinical picture of the Type I allergy to NRL proteins is variable, ranging from local urticaria to death by anaphylaxis. The most frequent clinical symptom, contact urticaria, appears in a few to 30 min after skin contact with NRL, sensitized people developing itching, erythema and weal and flare reaction, which disappear spontaneously in 1–2 hr without treatment [11]. In some sensitized people skin and/or aerogen challenge via NRL-contaminated glove powder can elicit other symptoms, such as rhinitis, asthma and generalized urticaria [12]. Even anaphylaxis has been described after the latex glove use test on eczematous skin [13].

Contact with mucosal surfaces is more likely to cause generalized symptoms. Several cases of anaphylactic reactions occurring in sensitized people during delivery [14], surgery [8] and even during vaginal examination [15] have been reported. Latex balloon-equipped enema tips have been recently recalled by the United States Food and Drug Administration (FDA) because of the increasing number of anaphylactic reactions and even deaths during barium enema examinations [16].

Corn starch powder, used in the manufacture of latex gloves, has been suspected of causing the immediate-type allergy in connection with the use of latex gloves [17–22]. However, the published results are controversial, since sensitization to NRL proteins has not been exhaustively excluded and the origin of the corn starch powder is not clearly indicated in the published studies. Maize proteins can be present as impurities in corn starch powder and cause Type I symptoms in people already sensitized to corn, e.g. by eating, but none of the published 'corn starch-allergic' persons showed specific IgE to maize. Glove powder taken from a glove has been shown to be contaminated by the allergens of NRL not found in corn starch powder delivered directly from the manufacturer without previous contact with NRL [23].

Urethral strictures caused by NRL catheters have been reported since 1982 [24–26]. The role of the combination of diminished urethral blood circulation and toxic substances leaching from the catheters has been shown to be essential in the development of severe urethritis and scarring [27–28].

The manufacture of urinary catheters is a long process during which many chemicals are added to the NRL base. The toxicity of these substances, the full character of which is not completely understood, has been confirmed in cell culture tests [29]. Latex gloves and urinary catheters share, at least in part, common manufacturing processes and, consequently, the irritative symptoms described by many glove users may have the same aetiology as in the case of urinary catheters.

The aim of this study was to confirm this hypothesis

Table 1. Trade names and manufacturers of the examined items

Latex gloves

Biogel starch-free, LRC Co. Ltd, London, U.K.
Opett, Semperit Co., Vienna, Austria
Triflex, Bacter S.A. Lessines, Belgium

Non-latex gloves

Elastyren, Danpren AS, Albertslund, Denmark
Neolon, Becton Dickinson, Franklin Lakes, U.S.A.

Latex catheter

Silkolax, Rusch Co., Germany

and to assess the biocompatibility of surgical latex gloves by testing both their toxic and allergenic properties *in vitro* and *in vivo*.

Materials and methods

The biocompatibility of several surgical gloves (Table 1), used in the operating unit of the Fourth Department of Surgery, Helsinki University Central Hospital, was assessed by evaluating their toxicity and immediate allergenicity.

The toxicity was studied *in vitro* by means of a cell culture test. The continuous human cell line JM (T-cell leukaemia) was chosen because of its stable growing properties. The cell concentration was 200 000/ml. Under sterile conditions, non-prewashed pieces of glove material, 5 cm²/ml, and urinary catheter, 0.15 g/ml, were eluted in RPMI-1640 culture medium at 37°C for 24 hr. After removing the pieces, the eluates were centrifuged at 1000 rev/min for 5 min in order to separate the glove powder. The eluates were then supplemented with 10% fetal calf serum and added at 3, 10, 30, 60 and 100% concentrations to cell cultures. The culture medium itself was used as a negative control. A urinary catheter known to be toxic was used as a positive control. After culturing for 3 days at 37°C, cell proliferation was measured by adding 20 µCi Htdr (tritiated thymidine) 6 hr before the termination of culture and the incorporated radioactivity was quantified by scintillation counting. Triplicate determinations were made and the medians were used as representative values [26].

The allergenicity was studied *in vivo* by skin-prick testing (SPT), which is the method of choice in diagnosing the immediate allergy to NRL products [30,31]. The test material consisted of non-prewashed glove material cut into pieces of 5 cm²/ml and of urinary catheter material, 0.15 g/ml, eluted in sterile physiological saline at 37°C for 24 hr. Saline stored in a plastic bag was chosen in order to

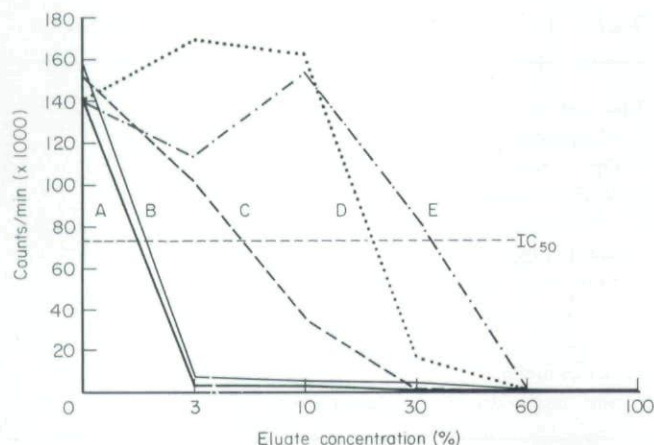


Fig. 1. Cell culture test: counts per minute at different eluate concentrations of the tested brands. A, Biogel; B, Opett; C, Triflex; D, Neolon; E, Elastyren.

avoid contamination from rubber bungs. After incubation, the pieces were removed and the eluates were stored in sterile bottles at 4°C. Histamine hydrochloride, 10 mg/ml (Allergologisk Laboratorium, A.S., Copenhagen, Denmark), and physiological saline were used as positive and negative controls, respectively.

The SPT was performed on the forearm skin of 77 of 78 surgeons and instrumental nurses working in our operating unit. Reactions were scored after 15 min as mildly positive (2+), when the area of the weal was equal to or bigger than half of that of the histamine, and clearly positive (3+), when equal to or larger than that of the histamine [32].

All tested instrumental nurses and surgeons filled in a questionnaire concerning their history of previous or present hand dermatitis, personal history of atopy defined as present or previous atopic eczema and/or rhinitis and/or asthma, and evidence of symptoms when using surgical latex gloves.

Results

Cell culture test

All the tested substances showed some cytotoxic effect when eluate concentrations of 100 and 60% were used. Significant differences between the tested substances were seen at 30, 10 and 3% eluate concentrations (Fig. 1). All latex materials had a toxic effect at eluate concentrations of 30, 10 and 3%. The IC₅₀ (eluate concentration which inhibits thymidine uptake by 50% of control) ranged from 1 to 5% (Biogel 1, Opett 1, Triflex 5).

The cytotoxicity of the two non-latex glove brands was low at 30% eluate concentration and no cytotoxicity was observed at 10%. Their IC₅₀ ranged from 15 (Neolon) to

35% (Elastyren). The IC₅₀ of the latex catheter was 9, correlating well with our earlier results obtained with the same catheter brand in the same cell culture test [33].

Skin-prick test

The test was performed on 77 employees (40 instrumental nurses and 37 surgeons), representing 99% of the operating staff of our hospital. Clearly positive (3+) SPT reactions were seen in four (5.2%) employees (Table 2), while five (6.5%) presented with a reaction scored as mildly positive (2+) with isolated glove eluates. In order to clarify the relevance of the 2+ SPT results, these five employees underwent a use test. All of them were able to wear the glove which gave the mild positive reaction in SPT for 90 min, proving that smaller reactions may have a low specificity for clinical allergy.

Of the four 3+ positive employees, one showed clearly positive reactions to all three latex gloves, one to two gloves and the other two to one of the latex gloves in addition to 2+ reactions to other latex gloves. Of the seven clearly positive skin test reactions, three were due to the Opett glove, three to the Triflex and one to the Biogel glove. All four sensitized employees resolved the problem of glove-related skin symptoms by using 'better' latex gloves (Biogel in three cases and Ansell Gammex [Ansell Melaka, Malaysia] in one).

According to the questionnaire, 25 (32%) employees were atopic and 38 (49%) employees gave a history of previous skin reactions in connection with wearing surgical latex gloves. These employees included all the four employees found to be allergic to NRL and all of them also suffered from previous hand eczema. No complications occurred as a consequence of the SPT or the use test, and all positive reactions disappeared spontaneously within 3 hr.

Discussion

Natural rubber latex devices are widely used within the health care sector. It is, therefore, important to be aware of their side-effects. Toxic reactions are the most common ones, but the clinical symptoms of allergic and toxic origin are often indistinguishable, which makes the diagnosis difficult [34]. The use of catheters can lead, for example, to strictures due to toxicity, but it is not known whether this kind of symptom could also have an allergic background. In the case of NRL gloves, toxic symptoms are more frequent, but allergic reactions are more important because they may elicit severe symptoms either in hospital employees using latex gloves or in sensitized patients who come into contact with NRL products.

In the present study, where 99% of the workers daily

Table 2. Clinical chart of the sensitized employees

Tested employee	History of atopy	Hand eczema		Prick test						Glove actually used
		Past	Present	Biogel	Opett	Triflex	Elastyren	Neolon	Catheter	
1	—	+	—	—	++	+++	—	—	—	Biogel
2	—	+	—	—	+++	++	—	—	—	Biogel
3	+	+	—	++	+++	+++	—	—	++	Biogel
4	—	+	—	+++	+++	+++	—	—	—	Gammex

using latex gloves were included, the prevalence of immediate allergy to NRL was 5.2%, which is slightly lower than the 5.6% observed in a previous report [6]. These figures are not comparable, since in the previous report all employees were not included and, therefore, it represents only the occurrence of allergy among those using latex gloves. To our knowledge, this is the first report of the prevalence (99% of the whole OR personnel studied) of NRL allergy. In addition, the relevance of mild positive SPT reactions has been only occasionally determined by use tests [6,30,35].

In this study atopy seemed not to represent a risk factor for developing NRL sensitization. This may be due to the difficulty of obtaining relevant anamnestic data by questionnaires among health care workers who are not familiar with allergic diseases. In many previous reports atopy has been the most common risk factor for immediate allergy to NRL [1–3]. Questionnaires have also proved to be an inappropriate method of revealing allergy to NRL [10]. In the present study, only 4/38 (11%) employees having difficulties in wearing surgical latex gloves were diagnosed as having NRL allergy, which confirms earlier findings [6]. The workers should be carefully questioned about which gloves caused their symptoms, as there are great differences in the allergenicity of latex gloves [31]. Their statements correlated well with the allergenicity of the gloves and many workers managed well with gloves known to contain fewer NRL allergens, such as Ansell Gammex and Biogel [35]. In the present study, the gloves chosen for the test material were those used at our clinic. It is not possible to estimate which NRL product caused sensitization of a specific person, since the challenge to NRL products ranges from pacifiers and balloons to condoms and protective gloves. Concomitant SPT with different rubber products has confirmed that people having symptoms from gloves also show positive SPT to, e.g. condoms and pacifiers [36,37]. The allergenicity of different catheters has not been examined. In the present study a known toxic NRL catheter was chosen as a reference, but it caused a positive SPT reaction in only one of the four sensitized persons.

For SPT we used eluates made from non-prewashed gloves. In large patient studies there is a high correlation between the test results of glove eluates and natural rubber tree sap, confirming that both reactions are due to the allergens in the rubber tree [30, KT, unpublished observation]. This observation has been confirmed by immunoblotting and immunoelectrophoretic methods [38,39].

The present study confirmed the hypothesis that surgical latex gloves may also have toxic effects. In the cell culture test, all latex gloves were more toxic than the non-latex gloves. It has been shown earlier that this finding is of importance when NRL devices come into contact with mucous membranes like urethra [29] or common bile duct (unpublished observations). In this study Biogel proved to be relatively more toxic although it has been defined as 'hypoallergic' which implies a low content of sensitizing rubber chemicals [40]. The term 'hypoallergic' is misleading because it does not give any information about the NRL allergen content of the glove. Biogel also has a low NRL allergen content, and it is well tolerated by health care workers. There is, therefore, an obvious discrepancy between the cell culture results obtained in this study and clinical experience. Irritation of the skin related to the use of gloves is a complex, multifactorial phenomenon, since frequent hand washing in the OR, as well as detergents, scrubbing, glove powder and sweating due to occlusion are also possible eliciting factors. This aspects warrants further investigation.

While the toxicity of the different surgical latex gloves was of the same level, the immediate allergenicity was not: Opett and Triflex gloves induced more allergic reactions than did the Biogel glove. Moreover, several workers allergic to Opett or Triflex gloves currently used Biogel or Ansell Gammex without problems, although these are also NRL gloves [31]. These findings suggest that some manufacturers have managed to eradicate at least part of the allergens from their products.

In conclusion, surgical latex gloves have both toxic and allergenic properties. A significant number of people may become sensitized as a result of the professional use of

NRL devices. The identification of sensitized people is of major importance, as anaphylactic reactions and even death may occur in case of contact of NRL devices with the mucosal surface or eczematous skin. This is especially important when planning to operate on such persons. As a commercial standardized and sensitive allergen for skin testing is available, careful consideration should be given as to whether SPT should be performed routinely, at least in some risk groups.

The prevention of sensitization is the main priority but it is important to recognize that sensitization is not only due to medical interventions, pacifiers, balloons, condoms, household gloves, bands, etc. may also trigger off allergy. The FDA has already organized a conference dealing with these problems [41]. Two major problems still remain to be solved: (i) the manufacturers should develop more effective methods of eradicating as much as possible of the allergenicity of their products, if it is not possible to make totally allergen-free products and (ii) while waiting for these better products, we should develop methods of estimating the allergenicity of NRL products and label the products accordingly. There are already many non-latex alternatives available but, for example, surgical non-NRL gloves are about 10 times more expensive than normal surgical latex gloves and their elasticity is not comparable to NRL products. During recent years the quality of urinary catheters has been improved as a result of product development. Increasing knowledge of NRL-related problems among clinicians will hopefully also lead to more stringent quality requirements for latex gloves.

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