

Latex allergy : a challenge for anaesthetists

J. DEMAEGD (*), F. SOETENS (**) and L. HERREGODS (***)

Summary : First reported in 1979, anaesthetists now encounter more and more patients with latex allergy. Several risk groups prone to develop this allergy have been identified. A thorough preoperative interview is necessary to detect high-risk patients. For them, the perioperative period is very dangerous because of the many possibilities of contact with latex-containing materials. There is no cure for latex allergy. Absolute avoidance of contact with latex is the only safe way to treat those who belong to a risk group or who are already allergic. The diagnosis of latex allergy must be kept in mind in every case of perioperative anaphylaxis, even if the patient does not belong to a risk group. In the future, desensitization will probably be useful in helping patients with latex allergy.

INTRODUCTION

Anaphylactic and anaphylactoid reactions occurring during anaesthesia remain a major cause of concern for anaesthetists. The incidence of severe anaphylaxis during general anaesthesia is 1/6000-1/10000. Mortality is about 6% (1). The most common causes of anaphylaxis are neuromuscular blocking agents (58.2%), latex (16.7%) and antibiotics (15.1%) (2).

Since its first recognition in 1979 (3), anaesthetists are encountering latex allergy much more frequently (4). Latex is now the second most common cause of anaphylaxis during anaesthesia. In children with spina bifida, it is the most important cause of anaphylactic reactions (5, 6).

ORIGIN NATURAL RUBBER LATEX (NRL)

NRL is a milky fluid obtained primarily from the rubber tree, *Hevea brasiliensis*; 95% of the world's natural rubber supply is produced in Asia (7). Liquid NRL comprises water (55-65%), *cis*-1,4-polyisoprene rubber (34%), proteins (2-3%) and small amounts of sugars, sterol glycosides, resins and ash. The proteins cause the IgE-mediated latex allergy (8).

NRL ALLERGENS

Hevea brasiliensis (Hev b) latex contains several well-characterized proteins; 13 Hev b proteins are known at present (Hev b1-b13) (9). Hev b1 and b3 are the most important allergens for patients with spina bifida and other congenital disorders that require multiple operations in childhood (10, 11). Healthcare workers are more frequently sensitized to Hev b2, b4, b5 and b6 (12, 13).

NRL IN HOSPITAL

To reduce the spread of HIV, hepatitis B and C in the 1980s, the Food and Drug Administration (FDA) recommended that healthcare workers should wear gloves to protect themselves. At the same time the incidence of latex allergy increased. Latex gloves are the main source of latex proteins and are implicated in most cases of latex-mediated reactions (14-20). There are enormous variations in the amount of latex proteins in gloves from different manufacturers and even in gloves from the same manufacturer (14, 21-24). There are no government regulations that require glove companies to label the protein content. Cornstarch, the powder in latex gloves, is not itself allergenic, but binds latex proteins and acts as a vector for the aerogenic spread of latex proteins. At the time of putting on and especially pulling out the gloves, the cornstarch particles with the latex proteins are released into the air, are inhaled and may lead to conjunctival, nasal and respiratory symptoms, and even to an anaphylactic reaction (25). The air of rooms where powdered latex gloves are used contains high concentrations of latex allergens. These concentrations are lower

J. DEMAEGD, M.D. ; F. SOETENS, M.D. ; L. HERREGODS, M.D.
(*) University Hospital, Dept of Anaesthesia, De Pintelaan 185, B-9000 Ghent.
(**) St Elisabeth Hospital, Dept of Anaesthesia, Rubensstraat 166, B-2300 Turnhout.
(***) Prof. Anaesthesia, University Hospital, Dept of Anaesthesia, De Pintelaan 185, B-9000 Ghent.

when non-powdered latex gloves are used (17, 18). Latex is also found in many other materials used perioperatively (Table I).

Table I
Medical products that may contain latex protein (26)

Gloves (surgical gloves, non-sterile examination gloves etc.)
Intravascular devices
- Balloon catheters
- Intravenous perfusion sets / intravenous tubing ports
- Syringe plungers
- Embolectomy catheters
- Swan-Ganz catheters
Airway equipment
- Nasopharyngeal airway
- Masks / elastic straps
- Endotracheal tubes
Tourniquets
Blood pressure cuffs / tubing
ECG leads
Pulse oximeter probes
Multidose medication tops
Condoms
Bladder catheters
Heating blankets
Gastrostomy devices
Blakemore tube
Tape

Owing to the increasing knowledge and concerns about latex allergy, the industry has reduced the amount of latex proteins in gloves and other materials. Powdered gloves are less used. The removal of the cornstarch powder is important because it greatly reduces the concentration of latex aeroallergens (27-33). For many products, latex-free alternatives are available (34).

CLINICAL MANIFESTATIONS OF LATEX ALLERGY

Three different types of reactions can occur in patients exposed to latex-containing materials :

1. *Irritant contact dermatitis*

The most frequent reaction associated with latex gloves is irritant contact dermatitis, a non-allergic reaction of the skin to an irritant. The alkaline pH of most powdered gloves, sweating, the use of disinfectants, mechanical irritation by the powder and scrubbing are the most plausible causes for this reaction (35). It can develop minutes to hours after exposure to powdered latex gloves. It can show up with the first exposure but is never life threatening. The lesions are limited to the surface of contact. Symptoms include itching, skin rashes or flakiness, burning sensations, inflammation or

blister formation (36). The extent of the reaction depends on the duration of exposure and the skin temperature.

2. *Allergic contact dermatitis or delayed cell-mediated hypersensitivity reaction (Type IV)*

This delayed immunological reaction is the result of a T-cell mediated sensitivity to the chemical additives (antioxidants and accelerators), which are absorbed through the skin. The lesions can extend outside the surface of contact. This reaction is not life threatening and is more frequent than the life threatening type I reaction. On repeated exposure, the reaction starts 24-48 h after contact and peaks after 48-72 h. Its clinical features resemble those of irritant contact dermatitis. Symptoms usually resolve within three to four days after exposure (37, 38). Each exposure may lead to increased sensitization and a more severe reaction (9). Diagnosis is made by patch tests to one of the antioxidants or accelerators (39).

Neither irritant nor allergic contact dermatitis are caused by latex proteins, but these two forms of contact dermatitis damage the barrier function of the skin and can promote and accelerate sensitization to latex proteins (40).

3. *IgE-mediated hypersensitivity reaction (Type I) : the real latex allergy*

This is the least frequent but most dangerous reaction, and the only latex-associated reaction caused by the latex proteins. During first exposure, IgE antibodies to Hev b proteins are produced by B-lymphocytes. These IgEs bind to the surface of tissue mast cells and blood basophils. Upon re-exposure to latex, Hev b proteins cross-link membrane-bound IgEs, leading to degranulation of the sensitized mast cells and basophils. Preformed mediators such as histamine and tryptase, and newly generated arachidonic acid metabolites (prostaglandins and leukotrienes), are released, leading to symptoms (41-45).

IgE-mediated latex allergy presents with symptoms that differ between individuals. The reaction ranges from mild symptoms (pruritus, cutaneous rash, urticaria, oedema of the eyes, rhinitis, conjunctivitis, slight hypotension and tachycardia) to a potential life threatening anaphylactic reaction (laryngeal oedema, bronchospasm, asthma, angio-oedema, cardiovascular collapse with bradycardia, cardiac arrest and death) (2, 37). Several of these symptoms often coincide, but they can also occur in

isolation (2). The severity of the consecutive reactions within one individual is unpredictable.

The moment of development of the IgE-mediated reaction depends on the route of exposure to the latex allergens. After inhalation of airborne particles, the proteins are absorbed slowly so symptoms develop after a delay of 30 to 60 min. Most of the mild reactions such as local urticaria, rhinitis, conjunctivitis and mild shortness of breath are the result of inhalation of airborne latex particles. Quick and severe reactions usually occur shortly after parenteral or mucous membrane exposure to latex proteins (mouth, vagina, urethra, rectum, internal tissues during surgery) (46, 47). In extremely allergic patients, inhalation of only very small doses latex allergens causes a severe anaphylactic reaction (17, 48).

RISK GROUPS FOR LATEX ALLERGY

The prevalence of latex allergy in the general population is less than 1% (49, 50) and the prevalence of latex sensitization is between 5.4% and 7.6% (51). Unfortunately, many of these people do not know they are sensitized to latex.

Several risk groups have a higher prevalence for latex sensitization or allergy (Table II). In persons with a history of atopy, a prevalence up to 17% has been reported (54). Atopic persons frequently have contact dermatitis and it is possible that this may facilitate the transcutaneous passage of latex proteins. Persons who have an allergy to tropical fruit (such as avocado, kiwi, banana, mango, melon, pineapple, papaya) and chestnut or hazelnut, are at increased risk for latex allergy (prevalence of 11%) (34). These fruits contain proteins that are structurally similar to latex proteins; as a consequence cross-sensitization can occur (53, 54). This is called the latex-fruit syndrome.

Healthcare workers are also a high-risk group because of frequent occupational contact with latex-containing materials. Studies in healthcare workers show a prevalence of sensitization of up to 17% (25, 55, 56). An atopic healthcare worker is at even higher risk (57).

Non-healthcare workers with occupational exposure to latex, such as hairdressers (sensitization prevalence 9.7%) (58), greenhouse workers (59), latex glove manufacturers (sensitization prevalence 11%) (60, 61), housekeeping personnel and textile workers, are also high risk.

Any individual who has ever developed a type I reaction is at increased risk.

Children who have undergone multiple operations are at increased risk for latex sensitivity or allergy (62-64). The younger the child at the time of surgery, the higher the risk of developing latex allergy. For that reason, children likely to require surgical interventions during infancy should be managed latex free from the very beginning of life (65). Whether a patient, who has been operated on frequently as an adult, is at increased risk, is still matter of debate (59, 66-68). Spina bifida, even in the absence of multiple surgical procedures, seems to be an independent risk factor for latex sensitization (69). Spina bifida patients show sensitization prevalences ranging from 34% to 72% (66, 70).

Table II

Risk groups for latex sensitization/allergy

1. Patients who have a history of atopy, in particular those with asthma, dermatitis or food allergy
2. Patients exposed to repeated bladder catheterization. This group includes children with neural tube defects (spina bifida) or urogenital malformations
3. Healthcare workers and other occupations frequently exposed to latex
4. Patients with a history of anaphylaxis of uncertain aetiology, especially if associated with previous surgery, hospitalizations or dental visits
5. Patients who have been operated on frequently at young age

DIAGNOSIS OF LATEX ALLERGY

1. *The need for a good preoperative interview*

To assess the risk for latex sensitization and allergy, a specific preoperative interview is crucial. Questions about the patient's occupation, family history of latex allergy, the presence of atopic symptoms and symptoms such as itchiness, urticaria, conjunctivitis, rhinitis, asthma and angioedema after contact with latex-containing products (for example, after blowing up a balloon) are essential. Any history of fruit allergy should also be looked for. Asking about spina bifida and surgical procedures at young age is also important because of the link with the development of latex allergy.

2. *Peroperative symptoms of latex allergy (vide supra)*

Unlike anaphylaxis to anaesthetics, anaphylaxis to latex during anaesthesia usually presents 30 to 60 min after induction, coinciding with the absorption of airborne allergens or with mucous membrane exposure at the beginning of the surgical procedure. Cutaneous symptoms (such as rash, urticaria and angioedema) are often masked by

surgical drapes, while mild bronchoconstriction or hypotension is often attributed to the administration of medication or to normal physiological reactions that can occur during anaesthesia. Consequently, during anaesthesia, bronchospasm and cardiovascular collapse are often the first signs of an anaphylactic reaction.

Table III

Symptoms of latex exposure and possible anaphylaxis (9)

Conscious patient	Anaesthetized patient
Itchy eyes	Facial oedema
Generalized pruritus	Urticaria
Shortness of breath	Rash
Sneezing	Skin flushing
Wheezing	Bronchospasm
Nausea and/or vomiting	Laryngeal oedema
Faintness	Oedema
Abdominal cramping	Hypotension
Diarrhoea	Tachycardia
Feeling of impending doom	Cardiac arrest

The diagnosis of latex allergy should be considered in all cases of perioperative anaphylaxis, even in patients without risk factors for latex allergy, and all latex-containing materials should be removed (71, 72).

3. Diagnostic tests

Preoperative testing is only done when there is a family history of reactions or when patients experience symptoms such as a rash, swelling or wheezing when exposed to latex. The investigation of a suspected anaphylactic reaction is based on laboratory tests done during or shortly after the reaction and on tests done days or weeks later.

3.a. Plasma concentrations of tryptase (RIA-tryptase)

Several radioimmunoassay tests for the detection of histamine and tryptase are available (2).

The serum histamine concentration is not a good test. An elevated plasma histamine does not establish the mechanism of the reaction (73). In addition, because of its short biological half-life, the rise is usually transient and sampling must be done at a time when resuscitation is a priority.

An increased tryptase concentration in serum is a marker for systemic mast cell activation. Elevated β -tryptase concentrations are considered a highly sensitive indicator of anaphylactic reactions during anaesthesia (74), although they can be elevated in other conditions (75). β -Tryptase concentrations peak between 30 and 60 min; thus they

should be measured approximately one hour after the start of the reaction. The biological half-life is estimated at 2 h, and therefore increased concentrations can be detected for 1-6 h or more after the onset of anaphylaxis. The more severe the anaphylactic reaction, the higher the β -tryptase, but a negative result does not completely rule out anaphylaxis, particularly if sampling is done at the beginning of the reaction, or in mild reactions (74, 76).

The sensitivity of the tryptase test for the diagnosis of anaphylaxis is 64%, the specificity is high: 89.3%. The positive predictive value is 92.6%; the negative predictive value is only 54.3% (2).

The diagnosis of anaphylaxis should not rely on a single test, and patients in whom mast cell tryptase concentrations are not increased still require skin testing or latex-specific IgE measurements (2).

3.b. In vitro test: radioimmunoassay for the detection of latex-specific IgE antibodies

The FDA has approved three different serum tests to detect and to quantify latex-specific IgEs (CAP, ALaSTAT, HYTEC). These tests are highly specific, but their sensitivity is low. They are less sensitive than skin prick tests but can be used safely. The CAP and ALaSTAT have sensitivities that range from 75% to 80%, and specificities that range from 90% to 95% (77-79): approximately 20-25% of IgE-positive patients test as false negative. The HYTEC shows a high sensitivity (90%), but a lower specificity of 68-73% (79, 80): approximately 30% of the results are false positive.

Although classically made several weeks after the reaction, these tests can be done on blood drawn at the time of the reaction (43).

3.c. In vivo test: skin prick

In Europe a standardized fresh latex extract is now available for skin prick tests (Stallergenes, Paris, France); in America clinicians use a home-made latex extract (for example made of latex gloves) or a commercial extract. These extracts have a sensitivity of 70-98% and a specificity of more than 95% (81-83). So the sensitivity of the skin prick test is better than in the detection of the latex-specific IgEs.

Skin prick tests are not without danger and anaphylaxis is reported (84-88). They are best done 4 to 6 weeks after the reaction. Immediately after the anaphylactic reaction there is a depletion of mast cell mediators, which can make the skin prick test false negative.

3.d. Genetic testing

Some gene forms are associated with increased risk for latex allergy (89-92). If the family history is positive, genetic testing is advised to identify persons before sensitization occurs.

3.e. Provocation tests

Several variants of provocation tests have been described (93-94) : for example, wearing of latex gloves, nasal or bronchial inhalation of latex particles. Unfortunately there is no standardization between the protocols, so it is difficult to compare these tests.

Provocation tests should only be done when resuscitation equipment is available. Because of the potential danger, this diagnostic method should be reserved for patients with a clear history of latex allergy, but in whom the skin test and the latex-specific IgE test remain negative (93).

ANAESTHETIC POLICY IN A PATIENT WITH LATEX ALLERGY

Premedication with corticosteroids and H₁- and H₂-antagonists is still controversial because it does not prevent latex-mediated anaphylaxis (95, 96), and it can give the anaesthetist a false sense of security. In high-risk patients, however, premedication can be recommended in addition to latex avoidance since it may temper the severity of the reaction.

Absolute avoidance of contact with latex is mandatory for all not yet sensitized patients belonging to a risk group (primary prevention) and for all sensitized patients (secondary prevention) (97-99). There are specific points of interest in perioperative primary and secondary prevention (9).

1. In every operation theatre, pre-anaesthetic area or post-anaesthesia care unit (PACU), a list of all products containing latex and appropriate latex-free substitutes should be available. This list must be exact and updated frequently.

2. A trolley containing only latex-free materials must be immediately available. It must be well covered to prevent contamination with latex aeroallergens.

3. Write a warning in the front of the patient's file and on the bed : 'This patient has latex allergy'.

4. Inform all healthcare workers preoperatively (anaesthetic department, nurses, surgeon).

5. Schedule the procedure as the first case of the day, when the amounts of latex aeroallergens are least. Prepare the operation room (OR) the evening before (remove all latex-containing materi-

als, put the latex-free trolley and the latex-free surgical materials ready, and inform the surgeon if no latex-free substitute is available). Restrict movements of staff and equipment before and during the surgical procedure to minimize the concentration of aeroallergens in the operation room.

6. If it is not possible to schedule the procedure as the first case, do it in an operating room that has not been used for a minimum of 6 h, to reduce optimally the concentration of latex aeroallergens (97, 100). All upper surfaces should be thoroughly cleaned.

7. Mark the OR doors with a clear warning : 'Precautions, latex allergy'.

8. Resuscitation equipment should be immediately available.

9. Use only latex-free materials (gloves, perfusion sets, syringes, blood pressure cuffs, bladder catheter).

10. Release of cornstarch particles into the air must be avoided. Powdered latex gloves must not be opened or taken off in the room where the latex-allergic patient is being treated. Those caring for the allergic patient must wear fresh clothes and wash their hands very carefully to avoid the transfer of latex particles.

11. Use medications from glass ampoules or latex-free vials if available. The use of medications from vials with a latex-containing rubber stopper is still controversial. Latex proteins can be released from the stopper. The stopper must be removed and the medication drawn up with a latex-free syringe (101-103). Do not prick the stopper.

12. Monitor for anaphylactic reactions during the whole procedure because these can occur up to 60 min after the exposure.

13. Inform PACU staff members in advance of the patient's arrival time. The patient is at risk for anaphylaxis upon arrival in the PACU because of aeroallergens or contact with latex particles from the clothes or hands of the nurses. A patient with latex allergy should be treated in a corner of the PACU and should be treated by only one nurse. PACU staff must follow the same hygiene prescriptions as the OR staff.

PEROPERATIVE TREATMENT OF LATEX ALLERGIC REACTIONS

Immediate recognition and aggressive treatment of anaphylaxis is essential because mild symptoms may rapidly progress to severe shock. The removal of the potential triggers of anaphylaxis is necessary. All medication that could be responsible

for the anaphylactic reaction (for example an infusion with antibiotics) must be discontinued and the environment must be converted to latex free.

Intravascular volume expansion with isotonic crystalloid or colloid is indicated for patients with hypotension or shock. Adults receive boluses of 1 L (total 25-50 ml/kg), children boluses of 20 ml/kg (26). Adrenaline is the most important medication for the treatment of anaphylaxis. Its α - and β -adren-ergic effects result in an increase of the systemic blood pressure, a reduction of the urticaria and the angioedema, a relaxation of bronchial smooth muscles, and a decrease of the mediator release of mast cells and basophils. The dose and route used depend on the severity of the episode. During anaesthesia, intravenous administration is preferred. The recommended initial dose is 5-10 μ g IV (0.1 μ g/kg), then titrate to maintain an adequate systemic blood pressure. In the presence of cardiovascular collapse, adrenaline 0.1-0.5 mg IV should be given promptly (104), and continuous infusion of adrenaline and noradrenaline may be required (105).

During local anaesthesia, intubation may be become necessary. Administration of 100% oxygen is mandatory as well as ventilation with positive end-respiratory pressure.

After stabilization of the patient, an H1-blocker, an H2-blocker and a corticosteroid such as hydrocortisone or methylprednisolone should be given to inhibit the effect, the production and the release of mediators (106,107). Histamine mediates the anaphylactic response through H1- and H2-receptors. Corticosteroids are maximally effective 6 h after the reaction and can prevent delayed reactions or the revival of an initially treated anaphylactic reaction. Patients with upper airway obstruction may benefit from an aerosol containing adrenaline. Patients with bronchospasm can receive albuterol as an adjuvant to the adrenaline (26).

In patients taking β -blocking agents, the β -adrenergic agonists have little effect. Glucagon, if available, has proved successful (108,109). The recommended adult dose is 1 mg IV every 5 min until the patient's condition is stabilized, followed by a continuous infusion.

Once the patient is stable, they should be transferred to the intensive care unit and the serum tryptase concentration tested.

DESENSITIZATION AND OTHER IMMUNOTHERAPIES

Several studies of progressive, controlled administration of oral (110), cutaneous (111), subcutaneous (112-114) and sublingual (115) latex

allergens show beneficial results in patients with latex allergy, although these results need to be further investigated. Anaphylactic reactions are reported (116). Latex-specific desensitization remains an experimental treatment. The use of humanized anti-IgE antibodies may play an important part in the future treatment of latex allergy. Others forms of immunotherapy are being studied.

CONCLUSION

The incidence of latex allergy has increased consistently with time. The diagnosis should be considered in all cases of perioperative anaphylaxis, even in patients without risk factors for latex allergy. With every perioperative anaphylactic reaction the environment must be converted to be latex free.

In the future it will probably be possible to desensitize patients with latex allergy. At present, the absolute avoidance of any contact with latex-containing materials is the only way to treat these patients safely.

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