Latex Anaphylaxis in a Child with a History of Multiple Anesthetic Drug Allergies

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Life-threatening anaphylactic reactions to anesthetic agents are rare in adults and even rarer in children. The unpredictable and rapid onset of the potentially serious circulatory and ventilatory consequences of anaphylaxis demands prompt identification of the causative agent(s) to avoid future recurrence. Recently, latex hypersensitivity has become a recognized etiology for immunoglobulin E (IgE)-mediated anaphylaxis during operative procedures. Presented below is the case of a child with myelodysplasia with repeated episodes of intraoperative anaphylaxis who presented a diagnostic dilemma prior to her diagnosis of latex hypersensitivity.

CASE REPORT

A 7-yr-old girl was admitted for an elective pelvic osteotomy to correct a congenitally dislocated left hip. She was born with a lumbar-sacral myelomeningocele and Arnold Chiari Type II malformation. Physical examination at birth revealed an incomplete sensory and motor deficit below the fourth lumbar spinal segment, congenitally dislocated hips, club feet, and urinary and anal sphincter incontinence. She was able to void spontaneously and did not require bladder catheterization. During the first 2.5 yr of life she had undergone nine surgical procedures uneventfully under general anesthesia. Anesthetic agents and medications administered during these procedures were halothane, nitrous oxide, suxamethonium, pancuronium, methohexital, morphine, fentanyl, atropine, neostigmine, oxacillin, gentamycin, vancomycin, and cephalosporin (Cefadyl). Chronic medications included trimoxazole (Bactrim®) and oxybutynin chloride ( Ditropan®) for long-term urinary tract prophylaxis.

The patient did not have any history of atopic disease, asthma, food, medication, or insect-sting hypersensitivity. The family history was positive for atopic disease. Her father reported a history of childhood asthma, atopic dermatitis, and food hypersensitivity. Her sister had a possible history of asthma, and her mother reported a possible history of Hymenoptera hypersensitivity. An aunt had a history of eczema, and her grandfather experienced allergic rhinoconjunctivitis.

At age 2.5 yr, she underwent a lower extremity osteotomy. She was premedicated with rectal methohexital (30 mg/kg), and anesthesia was induced with nitrous oxide, oxygen, halothane, and pancuronium. Five minutes after the administration of fentanyl and shortly after urethral catheterization, she developed urticaria over the face, trunk, and extremities. The lungs were difficult to ventilate, requiring increased inspiratory pressures from 12 to 35 cmH₂O. Chest auscultation revealed diminished breath sounds bilaterally and wheezing. The systolic blood pressure decreased from 80 to 60 mmHg. Intravenous epi-nephrine (1 μg/kg) was followed by decreased wheezing and an increase in blood pressure. Aminophylline (5.7 mg/kg) followed by 0.5 mg/kg·h⁻¹ intravenously was required to resolve the persistent inspiratory and expiratory bronchial wheezing. The urticaria remained throughout the procedure despite the administration of diphenhydramine (1.6 mg/kg). The trachea was extubated at the end of surgery; no evidence of laryngeal edema was noted. The remainder of the postoperative and hospital course was uneventful.

At age 3 yr, with a presumed history of hypersensitivity to fentanyl, this child underwent revision of a ventriculoperitoneal shunt. She was premedicated with rectal methohexital and anesthetized with intravenous sodium thiopental, isoflurane, nitrous oxide, and pancuronium. Within 2 min of the administration of pancuronium, generalized urticaria were observed, without evidence of wheezing or hemodynamic instability. Diphenhydramine (1.5 mg/kg) was administered intravenously, and the urticaria diminished in severity but persisted without other sequelae. Hypersensitivity to pancuronium was now suspected, and she was referred to an allergist/immunologist for appropriate testing. The parents declined the skin test evaluation because the child had a significant fear of needles.

At age 4 yr, she underwent pelvic osteotomy with uneventful general anesthesia. With a history of possible pancuronium and fentanyl hypersensitivities, she received rectal methohexital, halothane, nitrous oxide, atropine, atracurium, and morphine. She also received repeated doses of ceftazolin sodium during the procedure without adverse sequelae.

At age 5 yr, she was seen by an allergist/immunologist for skin testing with various intravenous anesthetic drugs. Amide local anesthetic testing was also considered after it was revealed that the patient had developed perioral and periorbital edema, a popular pruritic facial rash, and ocular pruritus during a recent dental visit. She had received lidocaine 1.0% (0.6 ml) with epinephrine (1:50,000) for the local anesthetic.

Skin prick and intradermal testing were performed for succinylcho-line, pancuronium, methohexital, sodium thiopental, and ð-tubocurarine. The skin testing, using appropriate positive (histamine phosphate) and negative (normal saline without preservatives) controls re-

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revealed a 2+ positive skin prick reaction to succinylcholine, consistent
with an IgE-mediated sensitivity. Subsequent intradermal testing re-
vealed positive reactions to methohexital and pancuronium. Ra-
dioallergosorbent (RAST) testing performed for the intravenous muscle
relaxants was indeterminate, showing nonspecific reactivity. RAST
binding activity was present at three to four times greater than back-
ground for succinylcholine and thiopental, but RAST inhibition assays
were negative, suggesting that the binding was nonspecific.8 Local an-
esthetic hypersensitivity could not be definitively assessed, with non-
specific skin reactivity present at all concentrations.

At age 7 yr, the patient underwent her 13th surgical procedure, a
pelvic osteotomy. She was anesthetized with halothane, nitrous oxide,
and oxygen. A lumbar epidural catheter was placed uneventfully at
the L2–L3 interspace (above the myelomeningocele) as an adjunct to
general anesthesia to avoid the use of intravenous anesthetic drugs
and to enhance postoperative pain management. Atracurium was ad-
ministered intravenously to facilitate adequate surgical relaxation.
Lido-
caine 1.5% with epinephrine 1:200,000 (2 ml) as a test dose was
followed by 3 ml plain lidocaine 2%. One hour later, a supplemental
dose of bupivacaine 0.5% was given via the epidural catheter.

Five minutes after the administration of bupivacaine and 40 min
after the start of the surgery, a generalized rash occurred, followed
by urticaria. Expiratory wheezing, increased inspiratory pressure, and
decreased ventilatory compliance followed. The systolic blood pressure
dropped from 100 to 65 mmHg, and the heart rate increased from
80 to 110 beats/min. Oxygen saturation by pulse oximetry decreased from
98% to 85%. Repeated doses of intravenous epinephrine (1 µg/
kg) were promptly administered and resulted in resolution of the bron-
chospasm, improvement in ventilation, and restoration of blood pres-
sure and oxygenation status. This episode occurred 1.5 hr after the
initial dose and 0.5 hr after the repeat dose of atracurium. Halothane
was discontinued, and small doses of intravenous morphine were ad-
ministered for the maintenance of the anesthesia and completion of
the procedure. Intermittent doses of epinephrine (0.2 µg/kg) were
necessary to maintain the systolic blood pressure greater than 80
mmHg. Diphenhydramine (1 mg/kg) also was administered later in
the course of the procedure. The rash persisted throughout surgery,
with the development of marked periorbital and facial edema. The
trachea was extubated at the end of the procedure without evidence of
bronchospasm.

The patient's postoperative course was unremarkable. Pain was
managed with a continuous epidural infusion of bupivacaine for 48 h
and parenteral morphine subsequently, without any allergic reactions.

Additional history obtained from the parents revealed that the pa-
tient had developed lip edema while blowing up a balloon prior to this
admission. Further detailed history specific to latex products revealed
that she had developed significant periorbital edema, ocular pruritus,
and a papular pruritic rash near the affected eye within 0.5 h of de-
parture from her dentist. This had occurred over the previous 4 or 5
yr, when the dentist wore gloves, but was temporally related to blowing
up the latex balloons she would receive at the completion of the dental
procedure. Despite the absence of latex gloves during subsequent
dental procedures, the reactions continued to occur until exposure to
the balloons was also discontinued. The parents attempted premedica-
tion with diphenhydramine (Benadryl)9 prior to dental visits; this
resulted in diminution but not prevention of these symptoms. At no
point did she experience any other systemic signs or symptoms.

Given this new history and the recent appreciation that latex products
may precipitate IgE-mediated anaphylactic reactions, the patients was
skin-tested with a latex extract (provided courtesy of J. Dolovich, M.D.,
Canada). Skin prick testing revealed a 4+ positive reaction to liquid
latex suspension at a 1:100 dilution. Histamine phosphate was used as
the positive control, and normal saline without preservatives was used
as the negative control. Four normal subjects were tested with this
latex extract and were nonreactive to similar and higher concentrations
of the latex extract. Subsequent RAST testing for latex was performed
in two separate laboratories. In one, specific IgE binding was 18.3% (me-
near control of 2.5%; Johns Hopkins University, Reference Labo-
ratory for Dermatology, Allergy, and Clinical Immunology). In the
other, binding was 15.3% (mean control 0.4%; 95% confidence inter-
val 0.17–0.95%). Although RAST inhibition was not performed with this
patient's serum, the latter laboratory has verified antigen-specific in-
hibition with soluble latex antigen.5

β-Lactam antibiotic skin testing was also performed to assess all po-
tential drug hypersensitivity. The β-lactam penicillin skin-testing was
performed using native penicillin G, the major determinant benzyl-
penicilloyl poly-L-lysine, and a minor determinant mixture (minor de-
terminant mixture was specially prepared in the Massachusetts General
Hospital pharmacy) and contained the following: penicillin G, benzyl-
penicillin G, benzyl penicillolate, and benzylpenicillolate. It was stored at
−70°C, transported on dry ice, and diluted at the time of use. Skin
tests were considered positive if the wheel diameter of the agent was
50% larger than the wheel of the negative control and associated with
significant surrounding erythema. The β-lactam antibiotic skin testing
revealed positive intradermal reactions to all three of the reagents
tested, with appropriately reactive controls. The patient's IgE serum
level was 1,850 IU/ml (normal 0–200), and separate testing for air-
borne seasonal and perennial allergens revealed no antibodies. There
was no evidence of dermatographism during the skin-testing.

A bladder-neck fascial sling for urinary incontinence was performed
in May, 1991. Preoperative medications included only co-trimoxazole
(Bactrim™), oxybutynin chloride ( Ditropan™), and pseudoephedrine.
With parental informed consent obtained, no preoperative medication
prophylaxis was used. The duration of the procedure was approximately
5 h and 15 min. Anesthetic management included nitrous oxide, hal-
othane, sodium thiopental (repeated doses), vecuronium (repeated doses),
morphine (multiple doses), gentamicin, and vancomycin. The trachea
was extubated at the end of the procedure. Meticulous attention was
directed to avoid all pre-, intra-, and postoperative exposure to latex
products and to any hospital material that may have contained latex
components. This included all rubber products used in the anesthetic
machine, circuit, mask, blood-pressure cuffs, gloves, syringes (glass sy-
ringes were required), and intravenous infusion tubing, as well as mul-
itidose medication vials.

Postoperatively, the patients received bupivacaine (Marcaine™) local
anesthetic infusion for 24 h via a subcutaneous catheter placed around
the surgical wound. She received a single intravenous dose of morphine,
multiple doses of intravenous methadone, and then oral methadone for
successful postoperative pain control. Postoperatively, she continued
to receive gentamicin and vancomycin; all β-lactam antibiotics were
avoided. The procedure was conducted without any adverse sequelae
or reactions. No evidence for any IgE-mediated reactions was noted
during this procedure.

DISCUSSION

In a previous report, two patients with repeated epis-
isodes of intraoperative anaphylaxis were eventually found
to be allergic to latex.10 Our patient was tested and indeed
found to be allergic to multiple substances in common use
during her serial anesthetics. The first anaphylactic event, if latex-related, may have occurred after bladder
catheterization and as a result of sensitization developed
during the nine prior uncomplicated surgical procedures.
This episode developed prior to the surgical incision and
administration of the cefazolin sodium but immediately
after administration of fentanyl. The second, milder ana-
Phylactic reaction was suspected to be due to pancuronium. A positive response to skin-testing to succinylcholine (administered twice previously) suggested the possibility of an IgE-mediated hypersensitivity to the intravenous muscle relaxants. If pancuronium was the responsible agent, the hypersensitivity must have resulted from cross-reactivity between these agents, perhaps because of the quaternary ammonium moieties in the muscle relaxant group.\textsuperscript{2,11,12} At ages 4 and 7 yr, the patient underwent similar surgical procedures, was exposed to latex gloves, and received identical anesthetic management and antibiotics, but anaphylaxis occurred only as part of the latter operation. It is conceivable that prior to age 4, allergic reactions during general anesthesia were due to a hypersensitivity other than latex. After age 4, the allergic reactions may have been due to latex, as suggested from the history of cutaneous hypersensitivity to latex objects at age 5. Allergy skin-testing at age 7 confirmed the presence of latex-specific IgE and all determinants of the \( \beta \)-lactam antibiotic moiety.

Hypersensitivity to \( \beta \)-lactam antibiotics was considered but not initially tested for because these antibiotics, both cephalosporins and semisynthetic penicillins, were given multiple times previously without adverse sequelae. In addition, the urticaria and flushing during the procedure at age 3 were not associated with the administration of \( \beta \)-lactam antibiotics.

The most recent surgical procedure was conducted without prophylaxis against anaphylaxis and without exposure to latex allergens or to \( \beta \)-lactam antibiotics. The procedure lasted 5.5 h without any evidence of an IgE-mediated reaction. Of note, sodium thiopental, vecuronium, morphine, and local anesthetics were used in this last, uneventful procedure eliminating these drugs as suspected causative agents in the prior procedures. The patient’s clinical history suggests that latex is the more likely causative agent than cefazolin because it was used during previous procedures without sequelae, and other cephalosporins and penicillins had been used with impunity.

As the use of latex rubber products proliferates with the adoption of universal precautions, the incidence of latex hypersensitivity is likely to increase. Contact dermatitis representing a type IV delayed-type hypersensitivity to rubber-based chemical additives and stabilizers has long been identified, and recently IgE-mediated anaphylaxis to latex has been recognized.\textsuperscript{4,15–20} There is little information on the incidence of IgE-mediated immediate hypersensitivity to latex, but the overall incidence of hypersensitivity to surgical latex gloves among physicians is reported to be 7.5%, among nurses 5.6%, among hospital employees 1.3% and among nonmedical occupation controls 0.8%.\textsuperscript{18} A recent preliminary prospective study suggested that approximately 34% of patients with spina bifida have IgE antibodies specific for rubber proteins.\textsuperscript{21} In patients with myelodysplasia the incidence has been estimated from 18–28% by informal questionnaire.\textsuperscript{22} A retrospective review suggested a high frequency of intraoperative anaphylaxis in children with myelodysplasia, probably as a result of latex hypersensitivity.\textsuperscript{23} Histories of these children revealed contact urticaria to balloons, shortness of breath upon contact with a rubber dam used during a dental procedure, and tinnitus, pruritus, and dyspnea during urethral catheterization, possibly due to latex glove contact. Preliminary prick or scratch skin testing to latex is positive in most of these patients, with RAST testing corroborating the presence of latex-specific antibodies.

Although one clinical study reported the presence of immediate and delayed hypersensitivity in three atopic children, atopy is not consistently associated with latex allergy in children.\textsuperscript{18,19} A recent report identified hypersensitivity to ethylene oxide and latex in three children with spina bifida. Repeated exposure to gloves and medical materials sterilized with ethylene oxide was suggested as the etiology of the sensitization.\textsuperscript{24} Patients who have had repeated exposures to latex products for medical reasons (e.g., catheterization in spina bifida patients) and who have undergone multiple surgical procedures may develop hypersensitivity to latex products.

Avoidance of exposure to latex in the perioperative period, including the use of nonlatex surgical gloves for medical personnel, is feasible. There may be certain patient populations, including those with a history of prior allergic reactions under general anesthesia, multiple surgical procedures, chronic latex exposure through repeat catheterization, or clinical outpatient reactions upon latex contact who are at higher risk for IgE-mediated hypersensitivity. Consideration should be given to pharmaceuticals and nonpharmaceuticals as potentially causative agents, including the now well-recognized latex allergen. Alternatives to standard instruments and medical products include silicone urinary catheters, nonlatex surgical gloves (Neolon\textsuperscript{25} Becton Dickinson AcuteCare Division, Franklin Lakes, NJ, or Elastyn\textsuperscript{26} Allermed Labs., Mill Valley, CA), avoidance of multidose medication vials, avoidance of contact with latex-containing drains, and the use of non–rubber-based (polyvinylchloride) blood pressure cuffs. All patients proven to have true IgE-mediated hypersensitivity to latex should wear a proper allergy identification bracelet. These patients should also carry autoinjectable epinephrine should a severe systemic or anaphylactic event develop as a result of accidental latex exposure.

Intraoperative latex anaphylaxis, with its potential for life-threatening consequences, merits more attention by anesthesiologists and surgeons, particularly in patients with chronic disease.
REFERENCES


Pulmonary Hypertension Associated with Liver Disease
Is Not Reversible after Liver Transplantation

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Pulmonary hypertension is an unusual but well-known complication of liver disease.1 Patients with pulmonary hypertension are usually considered unacceptable candidates for liver transplantation because intraoperative morbidity and mortality is assumed to be high. The role of liver transplantation in reversing this form of pulmonary vascular disease is not known. We present a patient with severe pulmonary hypertension who underwent orthotopic liver transplantation.

CASE REPORT

A 23-yr-old woman with chronic active hepatitis was admitted for pre-liver transplant evaluation. The diagnosis of chronic active hepatitis was established by biopsy 12 yr prior to admission. Symptoms related