

Intraoperative anaphylaxis: An association with latex sensitivity

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Latex products have recently been identified as the cause of severe intraoperative anaphylactic reactions. We have identified a group of pediatric patients who appear to be at increased risk for such reactions. Fifteen patients with either spina bifida or congenital urologic abnormalities experienced 19 intraoperative anaphylactic reactions. All patients had frequent previous exposures to rubber materials since infancy as part of their management and/or investigative procedures. Seven of 15 patients had a previous history of local skin reactions to rubber. Only four patients were atopic. All patients had undergone multiple (two to 26) operative procedures before their reactions, the onset of which ranged from 40 to 290 minutes after induction of anesthesia. The reactions varied in intensity from urticaria to severe cardiorespiratory collapse. All these patients subsequently had positive allergy skin tests and positive RAST to latex antigen. We conclude that this group is at risk when they are exposed to latex intraoperatively as a result of frequent past exposure to these materials. Allergic evaluation for latex allergy may assist in the preoperative evaluation of similar patients. In sensitized patients, appropriate prophylactic measures, particularly the avoidance of latex, is required. (J ALLERGY CLIN IMMUNOL 1991;87:662-6.)

Several case reports of IgE-dependent allergic reactions to latex products have described a spectrum of responses that include rhinitis,¹ urticaria,¹⁻⁵ asthma,⁶ angioedema,⁷ and anaphylaxis.⁷⁻¹⁰ Recently, several authors have reported intraoperative anaphylaxis in both children and adults in which latex surgical gloves were identified as the etiologic agent.¹¹⁻¹⁴

We report a unique series of 19 intraoperative allergic reactions that occurred in a group of 15 pediatric patients with spina bifida and/or congenital urologic abnormalities. We believe that these patients represent

Abbreviation used

SPT: Skin prick test

a population at increased risk for allergic reactions as a consequence of their repeated daily exposure to latex products.

In this study we evaluated these patients to determine (1) a possible role of latex sensitivity as an etiologic mechanism of their reactions, (2) the relationship of atopy and the likelihood of latex sensitivity, and (3) the spectrum of allergic reactions occurring in this group of individuals.

PATIENTS AND METHODS

Patients

All patients who experienced intraoperative allergic reactions, as identified by the anesthesia staff at The Hospital for Sick Children during the period July 1987 to September 1989 were evaluated. Eighteen incidents of allergic reactions that occurred in 14 pediatric patients were assessed. Each patient had either spina bifida or a congenital urologic abnormality.

The medical and atopic histories of each patient were reviewed as well as their history of sensitivity to various materials, including latex. Atopy is defined as a history of

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one or more of the following: asthma, rhinitis, or eczema, with or without positive skin tests to common environmental allergens. Serologic tests were performed at the time of the reaction. Six weeks later, all patients were skin tested, as described below.

As a consequence of our investigations of these allergic reactions, the hospital records of patients who had experienced intraoperative anaphylaxis from July 1985 to July 1987 were reviewed. We identified only one additional patient with spina bifida who had experienced intraoperative anaphylaxis in November 1985. Investigations for that patient at that time were negative for allergy to anesthetic agents. Allergy tests to common allergens and latex antigen were done in August 1989.

Control subjects

Twelve healthy nonatopic adults, including five parents of the study patients and 12 atopic, otherwise healthy pediatric patients, served as a control group for the SPT to latex antigen.

Material

Raw natural latex in undiluted form (Smith and Nephew, Inc., Ajax, Ontario) was used as latex antigen in the allergy skin test.

Anesthetic agents were prepared in varying dilutions on the day of testing in the pharmacy of The Hospital for Sick Children. These agents included induction agents (sodium thiopentone and ketamine), muscle relaxants (succinylcholine, d-tubocurarine, pancuronium, vecuronium, and atracurium), narcotics (morphine sulfate, meperidine, and fentanyl citrate), and droperidol. These drugs were tested undiluted and in dilutions of 1:100 to 1:100,000, as outlined by Fisher.¹⁵ Penicillin skin tests were performed with potassium benzylpenicillin (10^4 U/ml; Eli Lilly Canada, Inc., Scarborough, Ontario), Pre-Pen (penicilloyl polylysine major determinant) (6×10^{-5} mol/L; Kremers-Urban [Canada], Brampton, Ontario), and minor determinant mixture (penicilloate/penilloate, 10 mmol/L) (University of Connecticut Health Center, Farmington, Conn.) by previously reported methods.^{16, 17} SPTs to determine atopy were performed with 10% products of 18 common allergens (Bencard Laboratories, Mississauga, Ontario).

Skin tests

Six weeks after the intraoperative reactions, each patient received skin tests to identify possible allergy. Both SPTs and intradermal tests were used for the anesthetic agents and penicillin reagents as indicated. Tests with latex and common allergens were by the SPT method. Tests were performed on the back or volar aspect of the forearm by the modified skin prick technique¹⁸ with a Microlance lancet (Becton Dickinson Canada, Mississauga, Ontario). Normal saline and histamine phosphate (1:200) (Bencard Laboratories) were used as negative and positive controls, respectively. Intradermal tests were performed with a 27-gauge needle with injection of 0.02 ml of the test solution into the

volar aspect of the forearm. Normal saline was the negative control for intradermal tests. The prick and intradermal tests were examined at 20 minutes, and the resulting wheal was measured. A test was considered positive if the wheal was 3 mm or larger in diameter than the negative control wheal.¹⁹ All skin tests were performed by a single investigator (M. G.).

RAST

RAST was performed on sera of all patients with natural latex as the antigen, as previously described.⁹ The sera of 12 ragweed-allergic patients were used as controls. Student's unpaired *t* test was used to compare RAST results of patients and the control group with *p* < 0.05 considered as statistically significant.

RESULTS

Patients

All patients had either spina bifida or multiple congenital urologic abnormalities. There were six female and nine male patients ranging in age from 2 to 15 years; each patient had a prolonged history of frequent bladder and/or bowel catheterization and multiple surgical procedures. Seven patients (47%) had a previous history of local reactions to latex. These reactions included eczematous rashes, urticarial lesions, or angioedema from contact with rubber gloves and/or rubber toy balloons. Two patients were known to be sensitive to latex before their intraoperative reactions; the other five patients had a similar history of sensitivity that was elicited only after their intraoperative reactions. None of these patients were aware of reactions during catheterization. Only four of the 15 patients (27%) were atopic, as evidenced by a history of eczema, rhinitis, or asthma (Table I).

The types of surgery during which these patients experienced their first adverse reactions included urologic, orthopedic, gastrointestinal, and plastic procedures. They had undergone from two to 26 previous operative procedures that were all uneventful. Reactions occurred between 40 and 290 minutes after induction of anesthesia.

The severity of the allergic reactions ranged from mild to life-threatening. Eleven of the 19 reactions included severe cardiovascular and respiratory manifestations with or without cutaneous changes. Patient 6 had only mild urticaria and erythema. In the remaining seven reactions, there were no cardiovascular changes or minor hypotension. Patient 3 experienced two reactions during two separate procedures, which required continuous therapy during the surgery. Two patients, 3 and 7, experienced more severe reactions during subsequent surgical procedures despite prophylactic measures, which included prednisone, diphenhydramine, and ephedrine.

TABLE I. Clinical profile of patients with intraoperative anaphylaxis to latex

Patient No.	Atopy		History of rubber sensitivity	Clinical reactions	
	History*	Total IgE†		Onset of reaction (min)	Type of reaction
1		686	+	60	S, R, C
2 a		1742	+	60	S, R, C
b				90	S, R
3 a		228	+	110	S, R, C
b				105/205	R
c				140/300	R, C
4		120	+	45	R, C
5		132	+	105	R
6		180		140	C
7 a	+	384		225	S, R
b				290	S, R, C
8	+	1267	+	105	S, C
9	+	2400		90	R, C
10		600	+	45	S, R, C
11		672		75	S, H
12		72		150	S, R, C
13		19		120	H
14	+	96		40	H
15		9787		60	H

S, Skin (urticaria/erythema); R, respiratory (bronchospasm); H, hypotension; C, cardiovascular collapse.

*Clinical history of atopy is defined as one or more of the following: asthma, eczema, or allergic rhinitis.

†Normal range, 70 to 266 ng/ml.

Test results

SPTs to latex antigen were positive in all 15 patients, that is, >3 mm in mean diameter larger than control site, and were negative in all 24 control subjects (Table II). All patients had negative skin tests to anesthetic agents, and all patients skin tested to penicillin were nonreactive. Skin tests were positive to three or more common environmental allergens in three of the four atopic patients.

In the IgE latex RAST, there was significantly higher binding ($p < 0.00001$) by the patients' sera (range, 9% to 59%; mean, 29.9%; $\pm$ SD, 14.5) than by the control sera (range, 3% to 11%; mean, 5.8%; $\pm$ SD, 2.4) (Table II). All test sera were in a range higher than the mean $\pm$ 1 SD (8.2) for the control sera.

Three atopic patients, Nos. 7, 8, and 9, had elevated total serum IgE concentration, as expected. However, five nonatopic patients, Nos. 1, 2, 10, 11, and 15, also had elevated serum IgE concentration (Table I).

DISCUSSION

We have studied a group of 15 patients who experienced allergic reactions during surgery. RAST and

allergy skin test results suggested a possible role for latex as the etiologic agent. Latex is the natural milky sap obtained from the rubber tree (*Hevea brasiliensis*) and is used in the manufacture of natural rubber products. Not unexpectedly, it contains proteins that have been found to be the allergens.⁹

All our patients had either spina bifida or congenital urologic abnormalities and were exposed to latex products, such as catheters and gloves on an intermittent basis, as part of their routine care. In addition, all our patients had multiple surgical procedures. Patients with these factors in common therefore represent a population at risk for anaphylaxis during surgery.

Fourteen of our 15 patients were identified by the anesthesia staff between 1987 and 1989. The paucity of patients identified by chart review between 1985 and 1987 may be due to a combination of a lack of awareness of the problem, attributing the situation to other clinical entities and inadequate coding of clinical information.

The mechanism of sensitization, however, is not clear. Two recent case reports described patients with spina bifida who experienced intraoperative anaphylaxis to latex after multiple (eight to 29) surgical pro-

cedures. The authors postulated that latex allergy was acquired as a result of exposure to these materials during surgery.^{12, 13} However, six patients in our study had fewer (two to eight) procedures before their reactions. Sensitization to rubber could have occurred from its intermittent use in diagnosis and treatment. Anaphylaxis has been reported to occur after use of balloon-tipped catheters for barium enemas, thus providing evidence for systemic absorption of antigenic material.²⁰ Microscopic tears in the rectal or urethral mucosa commonly occur with repeated catheterizations in our patient population. Thus, exposure of such large mucosal surfaces to latex would appear likely to favor sensitization and subsequent anaphylactic reaction under anesthesia.

The incidence of atopy in the general population is 15% to 20%.²¹ Atopic disorders, such as eczema, rhinitis, or asthma, were not a significant characteristic of our patient population. Elevated total IgE levels found in five nonatopic individuals may reflect a specific IgE antibody to latex. This discordance has been observed with allergic reactions to other agents, such as anesthetic drugs,²² penicillin,²³ and bee stings.²⁴ Therefore, it is important to elicit information of reactions to materials that are used by individuals on a regular basis, whether they are atopic or not.

The allergic response to latex, as with drugs, may be manifested by a spectrum of reactions. However, there was no consistency in the type, severity, or time of onset of the various intraoperative reactions. Although most reactions were life-threatening, less severe reactions did occur. These patients with relatively mild reactions may experience more severe reactions in subsequent surgical procedures, as evidenced by patients Nos. 3 and 7 (Table I). Mild reactions occurring in high-risk patients should therefore alert the physician to the risk of a subsequent anaphylactic reaction.

The identification of the agents responsible for an allergic reaction during surgery can be difficult. One feature that appears to distinguish latex-induced reactions is the delayed onset after the start of the surgical procedure. In this study, the earliest time of onset was 40 minutes after the induction of anesthesia. In contrast, anesthetic agents or other intraoperative medications may cause reactions during or shortly after administration.²⁵ Reactions with delayed onset, also noted in the cases described by Slater¹² and Gerber et al.¹³ may develop into anaphylaxis in these high-risk patients.

Assessment of children with spina bifida and/or congenital urologic abnormalities should include a his-

TABLE II. Evaluation of latex sensitivity

Patient No.	Latex skin testing (mm)*	Latex RAST binding (%)†
1	9	59
2	20	39
3	15	16
4	10	35
5	23	21
6	11	9
7	11	28
8	23	36
9	9	28
10	20	26
11	7	38
12	6	16
13	10	13
14	10	29
15	10	56

*Skin test control: wheal <3 mm (24 patients).

†RAST control subjects (17 patients): mean, 5.8; SD, 2.4; range, 3 to 11.

tory of sensitivity to material products, such as rubber. If these abnormalities are present, appropriate skin testing and, if this is possible, RAST evaluation should be performed. We recognize that false-positive and false-negative results may be found. In our study, all 15 patients who had anaphylactic reactions also had positive skin tests and RAST to latex. We therefore suggest that all children who have a local clinical reaction and positive tests to rubber should avoid these materials. Fortunately, today, fewer rubber catheters are in use and may only be used sporadically. These individuals are, however, still exposed to rubber gloves and rubber-tipped enema bags. Catheters made of silicone rubber or polyvinylchloride are commonly used and are available as substitutes. Gloves made of vinyl or other nonlatex materials with trade names Neolon (Deseret Medical, Inc., Sandy, Utah), Dispos-A-Glove (Surgikos Co., Montreal, Canada), and Elastyren (Hermal Pharmaceutical Laboratories, Inc., Oak Hill, N.Y.) can be used.⁹ This may not always be feasible because of unavailability or the surgeon's preference; however, the requirement to avoid latex intraoperatively is quite clear and should be the first priority in management. Gerber et al.¹³ has indicated that use of nonlatex products for subsequent surgery in a latex-sensitive patient may have successfully prevented additional adverse reactions.

In those patients who have experienced intraoperative anaphylaxis previously, additional measures,

such as prophylactic medications, should be used. Two patients, Nos. 3 and 7, received diphenhydramine, ephedrine, and prednisone preoperatively, as described by DeSwarte²⁶ and yet still had adverse reactions under anesthesia. In contrast, three patients, Nos. 9, 10, and 12, received prophylactic diphenhydramine, ranitidine, and hydrocortisone²⁷ and did not experience any adverse reactions. These regimens are empirical and require additional evaluation as to their efficacy and role.

We suggest that all children with spina bifida and/or congenital urologic abnormalities undergo allergy evaluation for latex before each surgical procedure, since the allergic status may change with continuing exposure. If the results become positive, avoidance of latex is advised.

In conclusion, patients with a history of chronic and/or repeated use of latex products may be at increased risk for serious intraoperative allergic reactions. We emphasize the need to suspect agents other than drugs as the cause of anaphylaxis. The possible presence of latex allergy in such patients needs to be examined. Appropriate preoperative investigations, such as RAST or allergy skin tests, are indicated to establish the existence of latex sensitivity in patients at risk. Substitute materials and prophylactic medications should then be considered. When mild allergic reactions occur intraoperatively in these individuals, they should be regarded as a warning of possible anaphylaxis to latex.

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