

Intraoperative vecuronium anaphylaxis compounded by latex hypersensitivity

Daniel R McCormack, DO; Anna I Heisser, MD; and Laurie J Smith, MD

Background: Anaphylaxis to latex or muscle relaxant drugs has been demonstrated in the perioperative period but there are no reports of a patient with anaphylaxis to both of these substances.

Methods: We report a patient with meningocele who was initially thought to have anaphylaxis to latex during induction of anesthesia. After recurrence of anaphylaxis following removal of latex as the suspected agent, the muscle relaxant vecuronium was found to be the actual etiology.

Results: Skin testing to several muscle relaxants and other anesthetic medications confirmed a hypersensitivity to vecuronium. Skin testing and subsequent physical contact with latex also established a hypersensitivity to this substance.

Conclusions: This report demonstrates the need to scrutinize closely every notation in the anesthesia record when evaluating perioperative anaphylaxis and to consider that hypersensitivity to more than one substance may be present.

INTRODUCTION

Intraoperative anaphylaxis is a problem of increasing importance with an incidence that has been steadily rising over the past two decades.¹ Although a readily apparent cause is often found with good time-symptom correlation and positive skin tests to a suspected agent, it may also be difficult to unmask the etiology despite concerted efforts. Repeat perioperative anaphylaxis after a perceived agent has been removed and treated can be especially perplexing.

Latex is now one of the well recognized causes of perioperative anaphylaxis, having received considerable attention since Nutter first reported it in 1979.² This is espe-

cially true in patients with congenital spinal cord defects who have a much higher prevalence of latex hypersensitivity than the general population.³ Systemic muscle relaxants are also responsible for many of these cases of anaphylaxis⁴⁻⁶ as well as over half of the adverse reactions⁷ encountered during general anesthesia.

We report a case of intraoperative anaphylaxis in a patient with meningocele initially thought to be caused by latex that was subsequently discovered to be the result of hypersensitivity to the muscle relaxant vecuronium.

CASE REPORT

A 5 1/2-year-old girl with a meningocele, hydrocephalus, syringomyelia and Arnold Chiari malformation was admitted for decompression of the Chiari malformation and shunting of the syrinx. During anesthetic induction there was a precipitous drop in oxygen saturation followed by a drop in pulse rate and blood pressure. Lung compliance decreased and manual ventilation

became difficult. General anesthesia was reversed and she was given epinephrine and several doses of phenylephrine hydrochloride with return of her oxygen saturation and vital signs to normal. Perioperative medications given to the patient prior to the event included ketamine, halothane, and midazolam but the changes in vital signs seemed to coincide with placement of a latex tourniquet on the patient's right arm. Subsequent skin testing verified a sensitivity to latex and the patient also developed an urticarial rash at the site of a latex-containing nasal oxygen tubing used later in her hospital course.

Two days later, after pretreatment with H₁ and H₂ blockers and prednisone, the patient was taken back to a now "latex free" operating room. Shortly after commencing induction the patient again developed bradycardia and hypotension. She also developed wheezing and an irregular, raised, red rash on her right arm. The anesthesia was reversed and she was given intravenous epinephrine, diphenhydramine, and methylprednisolone with gradual stabilization of her vital signs and resolution of the symptoms. Her record revealed that in addition to propofol and thiopental, vecuronium had been given immediately before the patient developed anaphylaxis and coincided most closely with the onset of her symptoms. Three days later the patient was found to be skin test positive to vecuronium. She was tested to a number of other anesthetic agents as well (Table 1) with positive skin tests to atracurium and pancuronium and negative skin tests to succinylcholine, thiopental, and propofol.

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Table 1. Results of Skin Testing with Anesthetic Agents

Drug	Prick, wt/vol 1/10*	Intradermal, wt/vol		
		1/10,000*	1/1,000*	1/100*
Atracurium	0/0	0/0	0/0	6 x 6/15 x 16
Pancuronium	0/0	5 x 5/25 x 33	8 x 9/22 x 22	
Vecuronium	0/0	0/0	7 x 10/15 x 18	
Succinylcholine	0/0	0/0	0/0	0/0
Thiopental	0/0	0/0	0/0	0/0
Propofol	0/0	0/0	0/0	0/0
Histamine	9 x 9/34 x 35			
Saline control	0/0	0/0	0/0	0/0

* Wheal & flare, mm.

Review of the anesthesia record from her first procedure showed that vecuronium was administered just prior to development of that episode of anaphylaxis. This was inadvertently overlooked in the initial assessment of the patient as the anesthesia record had only a small notation in the upper left corner, "vec", an abbreviation for vecuronium. This was not recognized as an indication that this drug was given. One week later the patient underwent an uneventful shunting procedure using halothane, succinylcholine, and propofol.

DISCUSSION

Muscle relaxants are used extensively during general anesthesia and are a common cause of anaphylaxis during operative procedures.^{4-6, 8} They have been identified as the greatest of the identifiable causes of intraoperative anaphylaxis by Moscicki et al.⁸ and responsible for the majority of adverse reactions by Boileau et al.⁷ Their major action is the interruption of transmission of the nerve impulse at the skeletal neuromuscular junction and/or autonomic ganglia.⁹ Many of these agents have histamine releasing properties as well that can result in hypotension, tachycardia, and other symptoms.¹⁰⁻¹⁴ although it has been shown that a physiologic response may not occur despite increased serum histamine levels.¹⁵ These increases in serum histamine compound the issue when considering muscle relaxants as a cause of ana-

phylaxis. These drugs also have a different side effect profile in children compared with adults. The majority of reactions in children have been observed locally along the tract of the injected blood vessel^{16, 17} with hypotension unusual and generalized skin rashes infrequent in those younger than 10 years of age.¹⁵ These findings could be due to less histamine being released or the child's end organs may simply be less responsive.

The muscle relaxant causing anaphylaxis in our case has been shown to be a strong inhibitor of histamine N-methyl-transferase.¹⁸ Histamine N-methyl-transferase belongs to one of two enzymatic pathways, methylation and oxidation, responsible for histamine metabolism and is the one present in the greatest amount in humans.^{19, 20} This inhibition by vecuronium is noncompetitive with respect to histamine in vitro meaning that high histamine levels, such as those occurring during an anaphylactic reaction, will not overcome the inhibition.¹⁸ The extent to which vecuronium will inhibit histamine N-methyl-transferase activity and reduce histamine metabolism in vivo has not yet been established and the importance of this potential additive effect in causing symptoms in patients such as ours who also exhibit IgE-mediated reactions to this drug is unknown.

It has been firmly established that skin testing is a valid, reproducible method for establishing sensitivity

to these drugs²⁰⁻²⁷ and that muscle relaxants, including vecuronium, can be responsible for classic type I IgE-mediated hypersensitivity reactions.^{8, 28} Serum-specific IgE against muscle relaxants has also been found.²⁹⁻³¹ The antigenic portion rests in the quarternary or tertiary ammonium group³² which is the part of the molecule responsible for most of the neuromuscular-blocking properties of these agents.⁹ The N⁺ of the ammonium ions included in the ring structure and the presence of a choline-like side chain impart the apparent cross-reactivity seen with skin testing between muscle relaxant drugs. In vivo, this cross-reactivity appears only to be of consequence between drugs containing the N⁺ incorporated ring.²¹ This correlation was seen in our patient who had positive skin tests to vecuronium, atracurium, and pancuronium, all of which have the N⁺ of the ammonium ions included in a ring, and negative in the other drugs tested.

The initial identification of latex as the etiology of the hemodynamic problems in our patient reflected the heightened awareness of latex as a cause of anaphylaxis in patients with congenital spinal cord anomalies. This was particularly so because of the time course of the change in vital signs in relation to placement of the latex tourniquet reflecting an apparent cause and effect relationship. This is supported by one report in the literature of intraoperative latex anaphylaxis and muscle relaxant sensitivity.³³ In this report, the patient displayed self-limited hypotension following the initial and each incremental dose of atracurium with no other adverse findings until anaphylaxis developed after the onset of the intraabdominal part of the procedure. The patient was resuscitated and the procedure completed without further difficulty after the surgical team switched to vinyl gloves. Subsequent testing showed positive skin tests to both latex and atracurium. After the sec-

and episode of anaphylaxis in our patient, a more detailed inspection of the first anesthesia record showed a more probable etiology of the anaphylaxis with a solid cause and effect relationship between the administration of vecuronium and onset of symptoms. Clinical hypersensitivity to latex was also demonstrated by the later development of urticaria at the site of contact of a latex containing nasal oxygen cannula.

CONCLUSIONS

The recognition of the specific cause of anaphylaxis rests on observations of clinical and pathologic features associated with exposure to a foreign substance and demonstration of specific IgE against that agent.³⁴ Our case shows the importance of this temporal relationship. Specific IgE-mediated sensitivity by itself is not sufficient evidence to implicate a substance as being causative. Reliance on the known high prevalence of latex allergy in patients with spinal cord anomalies plus a positive skin test is shortsighted and could result in a tragic outcome for patients. All medications administered during the perioperative period must be considered as potential causes of anaphylaxis. Anesthesia records must be closely inspected and every notation explored and investigated to prevent future episodes of anaphylaxis.

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Request for reprints should be addressed to:
Daniel R. McCormack, DO
Allergy & Immunology
WOMAC Army Medical Center
Ft. Bragg, NC 28307-5000

TRANSIENT HYPOGAMMAGLOBULINEMIA OF INFANCY

The incidence of transient hypogammaglobulinemia of infancy over a 10-year period in Victoria, Australia was 23 per million births; that of proved and probable transient hypogammaglobulinemia of infancy was 61 per million. After exclusion of identifiable causes of hypogammaglobulinemia and children in whom the low concentrations were associated with severe illness there were 15 patients less than 2 years of age with initial serum IgG concentrations less than the fifth centile followed by second measurements within the normal range. The fifth centile for IgG concentrations was 2.90 (0.1 years), 1.45 (0.2-0.6 years), 2.02 (0.6-0.8 years), 2.10 (0.8-1.0 years), and 2.82 g/L (1-2 years). Another 24 patients with single low IgG concentrations were classified as having possible transient hypogammaglobulinemia of infancy.

Of the 15 with proved transient hypogammaglobulinemia of infancy, 12 had symptoms of atopy or food allergy or intolerance including cow milk intolerance in 4, asthma in 3, asthma and eczema in 2 and asthma and immediate food hypersensitivity in one, atopic dermatitis and allergic enteropathy due to cow milk in one, and erythroderma with greatly elevated serum IgE in one. The three other patients had gastrointestinal symptoms without evidence of atopy.

Twelve of these 15 patients with transient hypogammaglobulinemia of infancy also had serum IgA concentrations that were also less than the fifth centile; in four of these and one other IgA concentrations were less than the fifth centile when IgG concentrations became normal. One IgM concentration was less than the fifth centile both initially and when the IgG concentration became normal, and eight others had IgM concentrations initially less than the 20th centile.

The authors have not found any association between transient hypogammaglobulinemia of infancy and recurrent infections. The transient hypogammaglobulinemia resolved within less than 24 months in all but one patient.

Three infants not judged to have hypogammaglobulinemia of infancy had brief periods of hypogammaglobulinemia of less than 6 weeks associated with severe illness.

The association with atopy and food intolerance suggests allergen-induced gastrointestinal inflammation may cause loss of IgG or transient hypogammaglobulinemia of infancy may cause allergy or food intolerance in some patients.

—RMS

Walker AM, Kemp AS, Hill DJ, Shelton MJ. Features of transient hypogammaglobulinemia in infants screened for immunological abnormalities. *Arch Dis Child* 1994;70:183-6.