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Generalized allergic reactions during anesthesia

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Twenty-eight adults with a history of a generalized allergic reaction during anesthesia were investigated. The reactions were systemic in 23 adults, urticaria/angioedema in four, and bronchial obstruction in one adult. The study population and an additional 35 subjects with a history of use of thiopental during anesthesia but without reactions were investigated by methods including thiopental skin test, succinylcholine skin test, and IgE RAST for antibodies to thiopental, succinylcholine, or latex. Among the 28 patients with reactions, 17 had positive thiopental skin tests; 14/28 reactors and 1/35 of the control group had an IgE thiopental RAST value >2 SD above the mean for control sera from ragweed-allergic subjects. The one control subject with a positive thiopental RAST also was the only control subject with a positive thiopental skin test. IgE succinylcholine RAST was negative in all 23 reactor sera tested. The IgE latex RAST was strongly positive in one reactor. In conclusion, evidence of allergy, particularly allergy to thiopental as a possible basis for the reactions, was obtained in >50% of the patients who were investigated. No allergy to succinylcholine was found. (J ALLERGY CLIN IMMUNOL 1992;89:768-74.)

Key words: Anesthesia, anaphylaxis, thiopental, succinylcholine, latex skin tests, RAST

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Generalized reactions during anesthesia present a number of diagnostic problems. Characteristic clinical features may be overlooked in the operating theater in which surgical drapes may obscure cutaneous findings. Hypotension may be attributed to blood loss or pharmacologic myocardial depression; bronchospasm may be considered a reflex response to endotracheal intubation. Moreover, many commonly used anesthetic agents can stimulate mast cell mediator release on a nonimmunologic basis. The clinical features produced by mast cell release are similar regardless of the triggering mechanism, and yet definition of this mechanism is necessary for predicting the risk of future reactions. An agent that stimulates mast cell mediator release on a nonimmunologic basis may not be absolutely contraindicated for future use, insofar as HR is dependent on drug dose and the rate of administration, and these conditions can be suitably adjusted.^{1,2} Drugs that have caused anaphylaxis (generally IgE dependent) are clearly contraindicated.

During general anesthesia, multiple agents are generally administered, and many can elicit reactions on an immunologic or nonimmunologic basis. None of the agents cause a uniquely identifiable reaction.³ The effects of any of these agents can be delayed, causing misleading temporal relationships between drugs administered later and the clinical reaction.³

Successful management of these patients includes stabilization during the acute reaction and avoidance of future reactions. The latter is based on the identification, when this is possible, and the avoidance of the causal agent and potentially cross-reacting compounds. At the same time, it is in the best interests of the patient to eliminate access to as few drugs as is necessary to allow maximal flexibility in the subsequent choice of anesthetic agents.

Substances to which there is exposure during anesthesia, for which sensitization can be demonstrated, include thiopental, succinylcholine, and latex, as well as blood products, antibiotics, protamine, and plasma expanders. Thiopental can stimulate an anaphylactic reaction or nonimmunologic HR.⁴⁻⁶ Reported incidence of thiopental-induced anaphylaxis ranges from 1/14,000⁷ to 1/30,000.⁸ Muscle relaxants are also known to cause generalized reactions. Succinylcholine has been identified as a frequent cause of such reactions, particularly in France.^{9,10}

Anaphylaxis to latex has been recognized only in recent years, and the subject has recently been reviewed.¹¹

An evaluation of patients with a history of an allergic-like reaction during general anesthesia is presented in this article. Skin tests and serology, consisting of thiopental, succinylcholine, and latex IgE

Abbreviations used

HR: Histamine release

RT: Room temperature

RAST, were performed in an attempt to identify a sensitizing substance.

MATERIAL AND METHODS

Patients and anesthetic reactions

Twenty-eight patients with a history of a generalized allergic reaction during anesthesia were studied during a 7-year period. Patients' characteristics are summarized in Table I. Ages ranged from 12 to 59 years. There was a preponderance (24/28) of female patients, and 11 patients were atopic and 12 were not. The atopic status was not known in five patients. Characterization of the type of reaction was done retrospectively from patients' records, and specific details were not available in all cases. The term "anaphylaxis" was often used in describing the type of reaction and reflected the clinical impression of attending physicians. Clinical manifestations included combinations of hypotension, rash, and bronchospasm. We have classified these reactions as "systemic" so as not to imply an IgE-mediated mechanism. Elsewhere, "anaphylaxis" implies an immunologically mediated event. Systemic reactions included multisystem reactions or hypotension (21 patients), generalized urticaria/angioedema (four patients), and isolated severe bronchial obstruction (one patient). All patients received thiopental, but there was considerable variation in the additional, often multiple, anesthetic reagents administered (data not presented). In some cases, no information regarding the identity of agents other than thiopental was available. The previous anesthetic history was available in 17 cases. All patients had previously undergone general anesthesia at least once, and several of these patients had undergone general anesthesia many times (data not presented). It was not possible to document fully the previous use of thiopental.

Thiopental-exposed control subjects

Thirty-five control subjects with a history of previous anesthesia that included thiopental without clinical reactions were recruited from among hospital personnel. The age range was 29 to 65 years, thirty of whom were female.

Ragweed-allergic control sera

Sera from 29 ragweed-allergic patients with wide-ranging, usually high IgE content (mean [IgE], 221 IU/ml; range, 46 to 660 IU/ml), were used as controls in the thiopental RAST.

Succinylcholine RAST-positive control serum

A serum specimen known to yield a positive IgE succinylcholine RAST and succinylcholine-coated disks were provided by Dr. J. Watkins.

TABLE I. Characteristics of patients with generalized allergic reactions with anesthesia

Pt	Age (yr)	Sex	Previous anesthetic	Atopic history	Anesthetic reaction	Skin tests		RAST (% uptake)		
						Thiopental	Succinylcholine	Thiopental	Latex	Succinylcholine
1	17	F	+	+	S	—	ND	1.2	4.6	0.9
2	30	F	+	—	U	+	ND	4.3	6.4	2.5
3	37	F	+	+	U	+	—	27.2	5.0	2.8
4	33	F	+	+	S	+	—	16.9	7.9	3.5
5	30	F	+	N/A	S	ND	ND	3.1	7.8	1.2
6	31	F	N/A	N/A	S	+	—	15.0	8.4	3.3
7	39	F	N/A	+	S	—	—	2.2	2.8	1.9
8	59	F	+	+	S	+	—	10.0	3.2	1.8
9	29	F	N/A	—	U	+	ND	2.2	3.5	0.7
10	48	F	+	+	S	+	ND	6.2	ND	ND
11	28	F	+	—	S	+	—	10.4	4.1	2.5
12	19	M	N/A	—	S	—	ND	1.4	2.6	0.7
13	22	F	+	—	S	+	ND	3.7	3.1	0.6
14	32	F	N/A	—	S	+	ND	1.5	ND	0.6
15	32	F	N/A	—	S	+	ND	6.0	5.4	ND
16	33	F	N/A	N/A	S	+	ND	5.6	16.9	6.4
17	43	F	N/A	—	S	—	—	3.1	2.7	0.8
18	55	F	N/A	N/A	S	—	—	1.4	1.3	0.7
19	12	F	N/A	+	S	+	—	2.4	2.2	0.7
20	29	F	N/A	N/A	S	+	ND	5.7	6.5	ND
21	52	M	+	+	S	+	—	29.0	43.0	1.7
22	16	M	+	+	S	+	—	2.1	49.0	1.2
23	43	F	+	—	U	—	—	1.8	2.6	0.6
24	35	F	+	—	S	—	—	2.0	1.0	2.4
25	30	F	+	—	S	—	—	2.9	0.9	1.0
26	35	F	+	+	S	—	ND	3.2	1.5	1.2
27	43	F	+	+	B	—	—	5.8	1.9	ND
28	43	M	+	—	S	+	ND	4.5	ND	ND

S, Systemic reaction; U, urticaria/angioedema; B, bronchial obstruction; N/A, not available; ND, not done.

Allergy skin tests

Thiopental skin tests, up to a maximal concentration of 0.25 mg/ml intradermally, were performed on 27/28 of the patients and on all thiopental-exposed control subjects. Succinylcholine skin tests (up to 0.1 mg/ml intradermally) were performed on 15 patients and on all the control subjects.

Preparation of thiopental-sepharose complex

Thiopental (80 mg) was dissolved in distilled water (12 ml) and added to washed Epoxy-activated Sepharose 6B (500 mg).⁴ The pH was adjusted to 12 with 2.5 N of NaOH, and the mixture was gently shaken overnight at RT to allow covalent coupling. The gel was then washed with water, 0.1 mol/L of borate buffer, pH 8, and 0.1 mol/L of acetate buffer, pH 4, before remaining free-activated groups were blocked by incubation with 1 mol/L of ethanolamine, pH 9, at RT for 3½ hours. The washing steps were repeated as above, and the gel was resuspended in distilled water (50 ml) and stored at 4° C.

Thiopental RAST

Serum (50 µl) was added to thiopental-Sepharose complex (5 mg of solid phase) in duplicate and incubated at RT for 3 hours. Tubes were washed and centrifuged three times with saline containing Tween 20. ¹²⁵I-labeled antihuman IgE (approximately 10,000 cpm per tube) was added, followed by overnight incubation at RT and three more washings with Tween-saline before counting in an LKB (Turku, Finland) gamma spectrometer. The percent radioactive uptake of ¹²⁵I-labeled antihuman IgE was calculated.

Preparation of latex disks

Latex was added to 0.1 mol/L of NaHCO₃, pH 9, to a final concentration of 10 µg/ml. Approximately 100 CNBr-activated disks were added to 10 ml of the latex solution and gently shaken overnight at 4° C. The antigen solution was aspirated, and the disks were washed three times by adding 0.1 mol/L of NaHCO₃ at RT for 10 minutes, followed by aspiration. Available sites were blocked by incubation with ethanolamine (30 µl/10 ml of 0.1 N of NaHCO₃) at

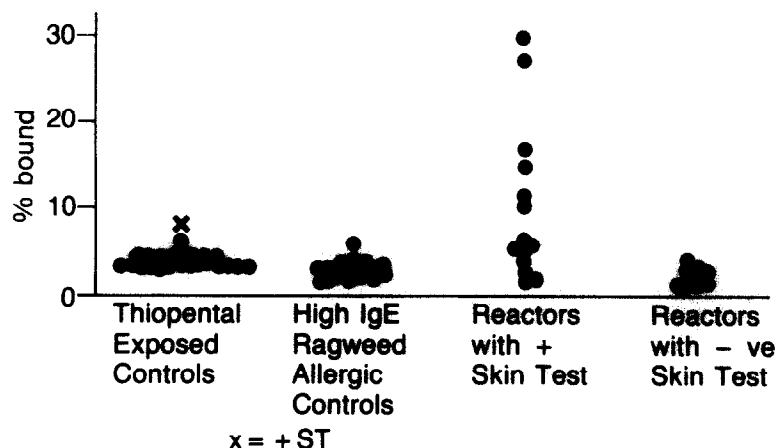


FIG. 1. Thiopental RAST results. Reactors are patients who had a reaction during anesthesia. The X indicates result with serum of one control subject who had a positive thiopental skin test.

RT for 3½ hours. The ethanolamine solution was aspirated, and the disks were washed twice with 0.5 mol/L of NaHCO₃, followed by a 10-minute incubation with 0.1 mol/L of Na acetate buffer, pH 4, and then a second 30-minute incubation with acetate buffer. After two washes with incubation buffer, the disks were suspended in a small volume of incubation buffer and stored at 4° C.

Latex RAST

Latex RAST was performed in duplicate. In each tube a single disk, coated with latex, was covered with 50 µl of patient serum and incubated for 3 hours at RT. Test sera were compared with sera from ragweed-allergic control subjects in the same procedure. The disks were washed three times with a 10-minute incubation at RT with 2 ml of 0.9% saline with 0.05% Tween. ¹²⁵I-labeled antihuman IgE (50 µl) was added to each tube (approximately 20,000 cpm per tube) and incubated overnight at RT. The disks were then washed three times as above and counted in an LKB gamma spectrometer. The percent uptake of ¹²⁵I-labeled antihuman IgE was then calculated.

Succinylcholine RAST

Succinylcholine RAST was performed as single tests with sera of 23 patients studied for general anesthetic reactions as well as with a positive reference serum. The procedure was the same as for the latex RAST.

Determination of total serum IgE

Total serum IgE was determined by the PRIST method (Pharmacia Diagnostics, Inc., Montreal, Canada).

Statistical analysis

The mean and standard deviation of the RAST results of the control subjects and control sera of ragweed-sensitive subjects were calculated according to standard definitions.

A positive RAST was defined as >2 SD above the mean of the control groups. The mean IgE levels of the reactors and the thiopental-exposed control subjects were compared with the Student's *t* test at the 95% confidence level.

RESULTS

Skin tests

In the patients with a history of a generalized allergic reaction during anesthesia, 17/27 thiopental skin tests were positive (Table I). Fifteen patients had succinylcholine skin tests, and all were negative (Table I). One of the 35 control subjects had a positive skin test to thiopental; the tests of the other control subjects were negative (data not presented). In the control subjects, succinylcholine skin tests were all negative.

Thiopental RAST

Thiopental RAST results on the sera of the patients are compared with results on the sera of the thiopental-exposed and the ragweed-allergic control subjects in Fig. 1. The RAST mean and standard deviation for the thiopental-exposed control group were 3.567 and 0.87; 11/28 of the patients with a history of a reaction had a thiopental RAST result >2 SD above the mean (5.32) of the thiopental-exposed group with no history of a reaction. The mean RAST value for the ragweed-allergic control group was 2.50 with an SD of 0.51; 14/28 of the patients who reacted thus had a RAST >2 SD above the mean of the ragweed-allergic control group (i.e., >3.52). The one thiopental-exposed control subject with a positive RAST (value, 6.8) was the only control subject having a positive thiopental skin test.

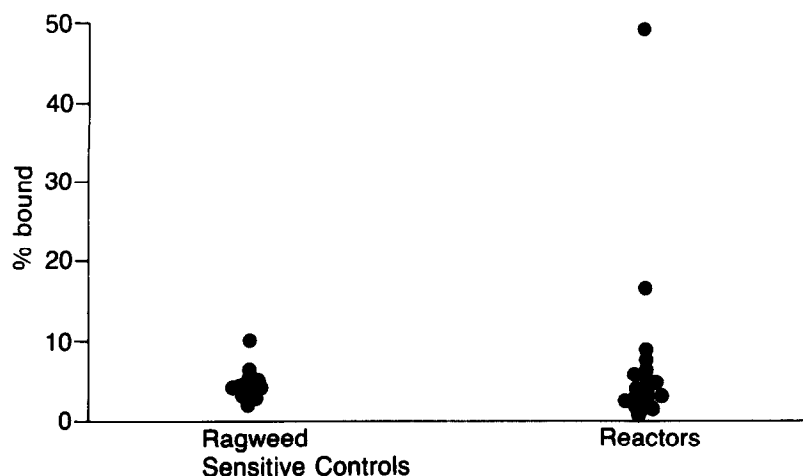


FIG. 2. Two positive tests among reactor sera.

Succinylcholine RAST

Sera from 23 patients with a history of a reaction to anesthetics were tested in the succinylcholine IgE RAST; none were positive (data not presented).

Latex RAST

Results are illustrated in Fig. 2. One of 25 of the patients who reacted had a strongly positive IgE latex RAST (value, 49.0) and a second patient had a mildly positive test.

Total serum IgE levels

Patients' mean serum IgE levels were 401 IU/ml; Sx, 1061 (range, <5 to 5500) (Table I). The mean total serum IgE in the thiopental-exposed control group was 83; Sx, 184 (range, <5 to 1018). This difference was not statistically significant at the 95% confidence level.

DISCUSSION

In this study, allergy skin tests and IgE RAST were used to identify possible sensitization to thiopental, succinylcholine, and latex in a group of patients with a history of generalized reactions during anesthesia. Skin tests included a negative (saline) control and a positive (histamine) control. A control population with known previous exposure to thiopental without clinical reaction was studied. The negative thiopental and succinylcholine skin tests and the negative IgE thiopental RAST in the control group are evidence that nonspecific results are unlikely. There was one subject in the control group with a positive skin test to thiopental; she was the only control subject with a positive thiopental RAST and was told to avoid thiopental.

Test sera were compared in the thiopental RAST with control sera from ragweed-allergic subjects preselected for high IgE concentration. The thiopental RAST values of these sera with high IgE were not significantly different from values of the thiopental-exposed control subjects; moreover, there was no correlation between total serum IgE and thiopental RAST values (data not presented). These results minimize the possibility that the serum IgE concentration had a nonspecific influence on the RAST result. Despite numerous attempts, we were unable to obtain reproducible specific RAST-inhibition studies. The reasons remain unclear.

Our single patient with a strongly positive latex RAST experienced anaphylaxis while he was undergoing an ileostomy revision after multiple previous procedures requiring general anesthesia. Interestingly, he had a history of immediate contact urticaria on exposure to latex-containing materials, as reported for other latex-allergic patients.

In 11/28 patients, no sensitization was identified. Reactions in these patients might have been due to nonimmunologic HR induced by one or more of the anesthetic agents or the presence of IgE antibody to an agent for which no test was done.

Our skin testing was initially limited to thiopental, with which we had clinical experience and a population of negative control subjects. Succinylcholine and latex testing was undertaken at a later date, and we were not able to recall all patients for skin testing to these agents. Skin testing to other agents was not undertaken since testing standards were not standardized and since we were concerned that nonimmunologic HR by these agents might prevent meaningful interpretation of results. Because RASTs for most of

these agents did not exist, we would have been unable to give any evidence supporting an underlying IgE mechanism.

On the basis of both skin testing and RAST, it can be considered that, potentially, 17/28 of the generalized reactions were due to thiopental allergy, 1/28 to both thiopental and latex allergy, 1/28 to latex allergy alone, and none to succinylcholine. Our results may overestimate the true relative frequency of thiopental allergy because of a possible bias in patient selection; many patients were referred because it was known that we had an interest and the ability to perform an *in vitro* test for thiopental allergy.

The positive skin tests and positive thiopental and latex IgE RAST results suggest an IgE basis for these reactions. Previous studies have documented the presence of IgE antibody to thiopental⁴; other studies⁶ have suggested that relatively few reactions are antibody mediated. Anaphylaxis during anesthesia as a result of IgE-dependent sensitization to latex is being increasingly recognized,^{11, 21} but the incidence is not known. We did not rechallenge our patients with the suspected agent and, to our knowledge, none of our patients have subsequently been reexposed to general anesthesia. As a result, we are unable to calculate the sensitivity, specificity, or the predictive values of the skin tests or RAST. We are following our patients to evaluate the role of the value of testing in the management of future anesthesia in our patients. However, in view of negative skin tests and RAST results in the control population, a positive skin test or RAST to thiopental or latex can be considered to indicate sensitization and a probable increased risk of a generalized reaction on reexposure to the same agent. In subjects with a history of a reaction to penicillin or stinging-insect venom and a positive skin test, rechallenge elicits a generalized allergic reaction in about 50% of cases.^{9, 12, 13}

Succinylcholine skin tests were negative in 15 patients; RASTs were negative in 23 patients. The positive RAST result with a positive reference serum from a patient in England, obtained from Dr. J. Watkins, indicates that the test is valid. The absence of succinylcholine allergy in these cases appears to contrast with experience in France,^{10, 14} Australia,¹⁵ and the United States²⁰ in which succinylcholine is reported to induce more frequently allergic reactions during anesthesia. Not all our patients were tested for this agent, which may have led us to underestimate the frequency of sensitization to the drug.

Alternatively, studies of IgE-dependent reactions to succinylcholine, mainly in women, and specifically in subjects with no previous anesthetic use of succinylcholine, may be relevant. These observations sug-

gest that there may be a nonanesthetic sensitization to a cross-reacting substance encountered in Europe but not in Canada. The cross-reactivity would be with a substance with a quaternary ammonium group¹⁴ and could be a cosmetic ingredient.¹⁵

Skin tests are widely available, easy to perform, and inexpensive. Reliability is increased by inclusion of positive and negative control tests and a nonreactive control population, as was done in this study. The latter control is to prevent the use of a substance that is inherently irritating or the use of a concentration of a substance that produces a nonspecific reaction. To eliminate one cause of false negative results, the "refractory phase" when drug-specific IgE had been depleted at the time of a reaction, our patients were tested at least 4 weeks after the reaction. Patients were instructed to stop antihistamine before allergy skin tests, and compliance was assessed by inclusion of the histamine skin test. Avoidance of agents implicated by positive skin tests might prevent reactions during subsequent anesthetics,¹⁶ but this data regarding the validity of positive and negative skin tests are, nevertheless, limited. A major disadvantage of the RAST is that it may be less sensitive than the skin test, as in the case of penicillin and our thiopental-exposed group. In the present series, there were no positive RASTs with a negative skin test to thiopental. Conversely, four patients who reacted had a positive thiopental skin test but negative RAST. This, unfortunately, limits the potential for remote diagnosis. A positive RAST result is probably relevant. A negative RAST result is not definitive since the skin test could, nevertheless, be positive.

Reactions to muscle relaxants,^{10, 15, 17} but not thiopental,¹⁷ occur mainly in women. There was a preponderance of female patients in our study population (24/28; 86%). Among atopic subjects, there is possibly a slight increase in risk of anesthetic reactions.¹⁷

History, regarding the presence or absence of atopy, was available in 23 of our reactors; 11/23 (48%) were atopic, which is higher than 10% to 20% of the general population. Although it appeared that our reactors also had higher IgE levels than the thiopental-exposed control subjects (401 IU/ml versus 83 IU/ml), this difference was not statistically significant.

We found no correlation between the presence of atopy and positive findings on skin testing or RAST; 7/11 known atopic subjects were positive on skin testing compared with 7/12 nonatopic subjects.

Previous exposure is necessary for immunologic sensitization. All patients in this series, in whom a history was available, had previous anesthesia at least once. Repeated and multiple procedures may be associated with an increased risk of reactions.¹ All these

risk factors have a low yield in identifying reactors; only a history of an anesthetic reaction carries a high enough risk to warrant diagnostic tests.¹⁸ Routine pre-operative screening tests are not recommended.^{18, 19}

Management should include an effort to identify the causative agent. Subsequent anesthesia may be safe if the offending drug is avoided.³ When no specific causative agent has been identified, the anesthetic agents administered at the time of reaction and all potentially cross-reacting compounds are best avoided.¹⁶ This, unfortunately, greatly restricts the choice of drugs available for future anesthetics. Premedication with adrenocortical steroid and H₁ and H₂ blockers has been demonstrated to be effective in reducing reactions to radiocontrast material.¹⁹ The efficacy of this premedication in the prevention of anesthetic anaphylactic reactions and deaths is unknown, although recently, a combined approach with premedication and avoidance of agents producing positive skin tests was used successfully in patients undergoing subsequent anesthesia.²⁰

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