

Biological Tests for Diagnosing the IgE-Mediated Allergy to Anesthetic Drugs

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The allergic adverse reactions to anesthetics are mostly immediate reactions. Two terms are currently used in the literature to define them: anaphylactoid and anaphylactic. The term anaphylactoid should be used when no direct evidence exists for the involvement of an immune mechanism. In fact, several anaphylactoid reactions have become true anaphylactic reactions when the development of solid-drug phase radioimmunoassays (RIA) allowed detection of specific IgE in the serum of the patients. Anaphylactic reactions to anesthetics are rare according to French and English data; they are respectively in the order of 1/9,000 and 1/4,500-20,000 in these countries [1-3]. In Australia, such reactions occur once every 5-25,000 anesthetics, with a 3.4% mortality [4]. In the French experience, about 80% of anaphylactic reactions in anesthesiology are due to muscle relaxant drugs. The biological tests are efficient for studying the cellular release of mediators in vitro (leukocyte histamine release) or in vivo (histamine, methylhistamine, tryptase, eosinophil cationic protein) and for detecting serum specific antidrug IgE (RAST, Sepharose-drug RIA and QAS-RIA). There is some controversy about the strategy for using these biological tests. Are they useful for preventive screening and for diagnosis? What is their value for eliciting a harmful drug in sensitized patients? In this review, we will first consider the pathomechanisms of anaphylactoid and anaphylactic reactions before describing the biological data in several examples of allergy to anesthetic drugs and proposing a strategy for the use of the biological tests in this type of allergy.

*Pathomechanism of Anaphylactoid and Anaphylactic Reactions**Anaphylaxis*

The anaphylactic reaction is mediated by IgE antibodies bound to the surface of either mast cells and basophils via high affinity specific receptors FcεRI or of lymphocytes, eosinophils and platelets via low affinity receptors FcεRII [5]. Activation of mast cell and basophil FcεRI is obtained via the bridging between adjacent IgE molecules by the antigen. This bridging requires at least the presence of two epitopes in the drug antigen or in the whole hapten (drug complexed to a carrier protein). Allergy to muscle relaxants is the most documented model of drug anaphylaxis in anesthesiology [2]. The activation of FcεRI is the mechanism by which the majority of adverse reactions to muscle relaxants occur. Baldo and Fisher [6, 7] performed a RIA for detecting antimuscle relaxant IgE in sera of sensitized patients using a solid-drug phase prepared by covalent coupling of muscle relaxants to epoxy-Sepharose. By inhibition of the IgE-RIA in presence of structural analogs, they demonstrated that the common epitope involved a substituted ammonium ion. Most of the muscle relaxant drugs share two substituted ammonium ions and are therefore divalent in regard to their ability to bind specific IgE. Didier et al. [8] showed that the optimal length between two epitopes had to be higher than 6 Å in order to bind two adjacent IgEs on the target cell. Flexibility of the molecule can also improve its reactivity. After bridging of the FcεRI-IgE complex by multivalent antigens, the final pathway is the release of mediators from mast cells and basophils. This requires the opening of calcium channels as an intermediate step. Preformed substances which are stored in granules include histamine, eosinophil and neutrophil chemostatic factors. In vitro leukocyte histamine release (LHL) is the usual test to study the basophil degranulation in presence of allergens. The release of tryptase is specific to mast cells and its measurement in plasma is a good parameter for investigating an IgE-dependent activation of tissue mast cells [9]. Membrane-derived mediators can also be released by FcεRI activation; these include prostaglandin D₂, leukotriene C₄ and platelet-activating factor [10]. Substances which act on calcium channel opening can modulate in this way the process of degranulation. This is the case of adrenergic and cholinergic chemical factors.

Activation of FcεRII by drug-IgE bridging can also theoretically lead the blood platelets and eosinophils to a release of mediators. We have recently studied the platelet serotonin release by incubating in vitro blood of sensitized patients with increasing concentrations of muscle relaxant. Platelet

serotonin release (PSR) was positive in 6 out of 10 patients allergic to muscle relaxants [11]. Eosinophil cationic protein is another substance which could be measured in the blood to study the degranulation of eosinophils.

Direct Degranulation

This degranulation is directly dependent on drug concentration. In vitro, LHL is positive with a typical dose-dependent curve, as observed by several authors in LHL performed with muscle relaxants, propofol and barbiturates [12-14]. In our experience, LHL induced by hypnotic drugs is greater in atopic than in nonallergic subjects [13]. In vivo, the histamine release will depend on the cellular reactivity and on the dose and rate of injection of the drug [13]. Every new anesthetic should be tested in vitro and in vivo for mediator release not only from mast cells and basophils, but also from platelets and eosinophils. Parameters should include histamine, tryptase, eosinophil cationic protein and serotonin in order to investigate the release of markers from at least one of these target cells. Reactivity of basophils and mast cells is different. For instance, this has been shown by Stellato et al. [12] by comparing in vitro histamine release provoked by muscle relaxants from blood basophils and isolated mast cells. In this study, basophils from nonallergic subjects did not release histamine significantly when they were incubated with either succinylcholine, *d*-tubocurarine, vecuronium or atracurium. By contrast, there was a significant heterogeneity of mast cells in regard to their response: atracurium was more effective than vecuronium, and vecuronium more effective than *d*-tubocurarine and succinylcholine [13]. In addition, there were also functional differences depending on the tissue origin of mast cells. However, no definitive conclusion can be drawn from this type of experiment since contradictory findings have been published. For example, North et al. [15] observed that in vitro histamine release from human neonatal foreskin was dose-dependent in presence of *d*-tubocurarine and atracurium and absent in presence of vecuronium.

Complement System Activation

The complement system can be activated by the drug via two major mechanisms (fig. 1). The classical pathway corresponds to the activation of component C1 by immune complexes [16]. The antibody is usually of the IgM class and sometimes of the IgG class. The alternative pathway activation involves directly component C3. Aggregated IgG, IgA or IgE can provoke the activation, but activation occurs usually without antibody. Anaphylatoxins (C3a and C5a) are the breakdown products of complement system activa-

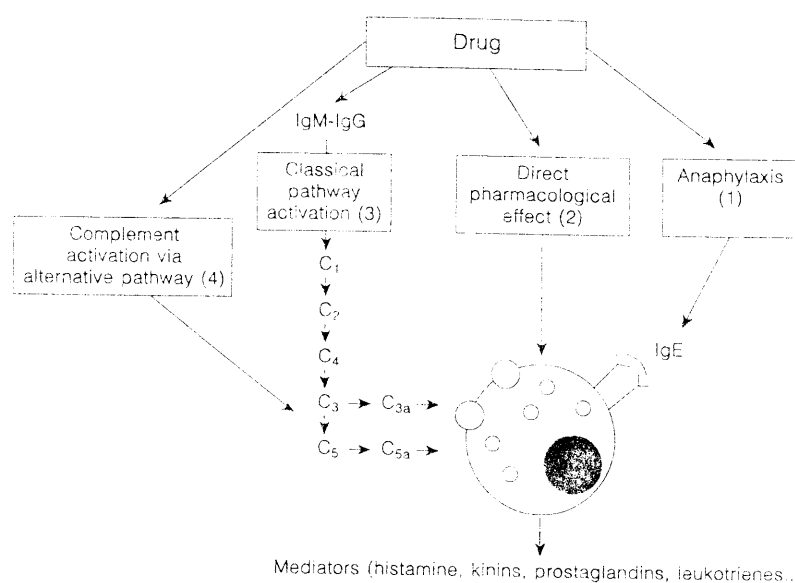


Fig. 1. Mechanisms of mast cell degranulation: anaphylaxis (1–3) and anaphylactoid/nonimmune (2–4) mechanisms.

tion. They can be responsible for release of mast-cell mediators. The anaphylactic reaction can thus be a combination of an IgE-mediated release of mediators and of a complement activation by the classical pathway. In fact, complement has rarely been found to be involved in adverse reactions to anesthetics, except for adverse reactions to Althesin [17].

Anesthetic Drugs Responsible for Anaphylactoid and Anaphylactic Reactions

Table 1 indicates the drugs responsible for anaphylaxis at the University Hospital Center of Nancy (France) since 1984. Muscle relaxant drugs were implicated in about 184 cases. Thiopentone was the second cause with only 8 cases. For most of the drugs, specific IgE have been identified in patients' sera by RIA.

Muscle Relaxant Drugs

In a recent French report of 668 cases of anaphylaxis to muscle relaxants, the drugs responsible for the reaction were suxamethonium, vecuronium,

Table 1. Anesthetic drugs responsible for causing anaphylaxis in 204 patients tested in Nancy (since 1984)

Drugs	Interactions	
	n	%
Muscle relaxants	184	90.2
Thiopentone	8	7.4
Propofol	3	
Diazepam	2	
Midazolam	2	
Fentanyl	3	2.4
Alfentanil	1	
Dextromoramide	1	

gallamine, alcuronium and pancuronium in respectively 54.3, 15.3, 11, 10.5 and 8.7% of the total. This can be explained by the relative frequency of use but also by the specific reactivity of each drug. Didier et al. [8] have shown that flexible molecules such as suxamethonium were much more effective for IgE-dependent leukocyte histamine release than were rigid molecules such as pancuronium. In addition, several muscle relaxants such as atracurium and *d*-tubocurarine can be responsible for a direct degranulation of basophils.

Results of skin test, passive transfer testing and leukocyte histamine release suggested that immunoglobulins were involved in most of the adverse reactions [18–22]. In 1983, Baldo and Fisher [6, 7] were the first to demonstrate the presence of drug-reactive IgE in the serum of sensitized patients. They incubated the sera of patients with the muscle relaxant coupled to epoxy-Sepharose and detected the serum-reactive IgE adsorbed to the solid-drug phase using a radiolabeled anti-IgE antibody. Inhibition of IgE binding to the solid-drug phase was tested by preincubation of the serum with either soluble muscle relaxant or structurally related compounds [6, 7]. They concluded that quaternary and tertiary ammonium ions were involved in the allergenic site [6]. Opportunity for sensitive individuals to come into contact with ammonium ion compounds contained in food, cosmetics and industrial material could explain the finding that a number of sensitized patients have never been in contact with any muscle relaxant before having an adverse reaction to such drugs [6].

A cross-sensitivity between the different muscle relaxants has been observed by skin testing, LHL and solid-drug phase RIA [6, 7, 22-25]. The cross-sensitivity can easily be studied by the inhibitory effect of the different muscle relaxants in the solid-drug phase RIA [6, 7, 26]. It can also be observed with other drugs which contain substituted ammonium ions, such as neostigmine, promethazine, trimetaphan, tiemonium, dicynone and morphine. The choice of the drug for preparing a solid-drug phase has a direct influence on the sensitivity of the RIA for detecting the antimuscle relaxant IgE. For example, in our experience, sensitivity of choline-Sepharose, alcuronium-Sepharose, choline-paper disc (RAST Pharmacia) and alcuronium-paper disc (RAST Pharmacia) was respectively in the order of 75, 37, 67 and 41% in a series of 27 patients allergic to either alcuronium, vecuronium or pancuronium [26]. This lack of sensitivity is observed even for sera of patients which are tested with the drug-phase corresponding to the drug implicated in the adverse reaction. Didier et al. [8] have detected specific IgE with Sepharose-choline RIA in only 5 of 19 patients allergic to suxamethonium. Recently, Assem [27] published an evaluation of the IgE-RAST with choline-paper disc and alcuronium-paper disc. He observed a positive result in 32 out of 35 patients with positive LHL and in 1 out of 8 patients with negative LHL. Patients with positive LHL represent about 70% of the allergic patients, in our experience [25]. RAST to choline-paper disc and to alcuronium-paper disc has also been used to detect specific IgG in sera of patients allergic to muscle relaxant drugs [27]. Specific IgA could also be present in sera of sensitized patients. We have studied the adsorption of serum IgA to QAS in 13 patients and in 8 control subjects (fig. 2). The uptake of anti-IgA IgG was higher than the upper normal value in 8 patients' sera. The presence of specific IgA in sensitized patients is not surprising if one considers that food contains quaternary ammonium compounds such as lecithins. The significance of these findings and the implication of specific IgG and specific IgA in modulating the allergic reaction remain to be determined.

One reason for explaining the lack of sensitivity of RAST-paper disc and of Sepharose-drug RIA could be that the epitopes are less accessible for binding to IgE antibodies, after chemical coupling. To overcome this problem, we have proposed using quaternary ammonium compounds other than muscle relaxant drugs for preparing the solid phase. A new reactive phase named QAS (quaternary ammonium Sepharose) was prepared by ether linkage of choline to Sepharose [26, 28]. The sensitivity of the QAS-RIA was estimated to be 88% in 83 sensitized patients. Inhibition of the QAS-RIA

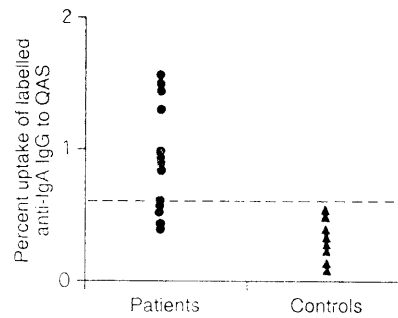


Fig. 2. Percentage of uptake of anti-IgA onto QAS after incubation with sera of 13 patients allergic to muscle relaxant drugs (●) and with 4 atopic and 4 nonallergic controls (▲). The results in 8 of the 13 patients were higher than the upper limit for controls.

with soluble muscle relaxants was performed with each muscle relaxant and compared to clinical data and skin tests. The highest inhibition percentage was observed with the incriminated drug (determined from skin tests, LHL, and clinical report) in 83% of the cases [26]. However, a significant inhibition was also observed with the other muscle relaxant in most of the cases [26]. Harle et al. [29] have also prepared a reactive solid phase by coupling to Sepharose reactive compounds other than muscle relaxants, such as triethylamine and morphine. Using this system, they increased the sensitivity of the IgE-RIA up to 88–100%.

Recently, we have studied the isoprotein pattern of serum IgE of patients allergic to muscle relaxants [unpubl. data]. The main isoelectric point of total IgE ranged from 5.6 to 6.3 in 6 patients' sera. By comparison, the IgE isoprotein pattern from 6 nonallergic patients was similar, with isoelectric points ranging from 5.4 to 6.2. A single isoprotein was detected by QAS-RIA in the 6 sera of allergic patients, with an isoelectric point ranging from 5.0 to 5.3. This isoprotein was not observed in the control sera (fig. 3). This means that the IgE fraction corresponding to antimuscle relaxant-specific IgE is more acidic, and therefore more anionic at neutral pH, than total serum IgE. This increase of the negative net charge could explain in part the binding of this anionic immunoglobulin to a cationic drug. However, the affinity of the specific IgE for QAS was not dependent on the ionic strength of the incubation medium of IgE-RIA. The binding of IgE to the allergenic determinant is thus immunospecific, and not only the result of a nonspecific ionic interaction. Further studies are needed to see if this acidic IgE corresponds

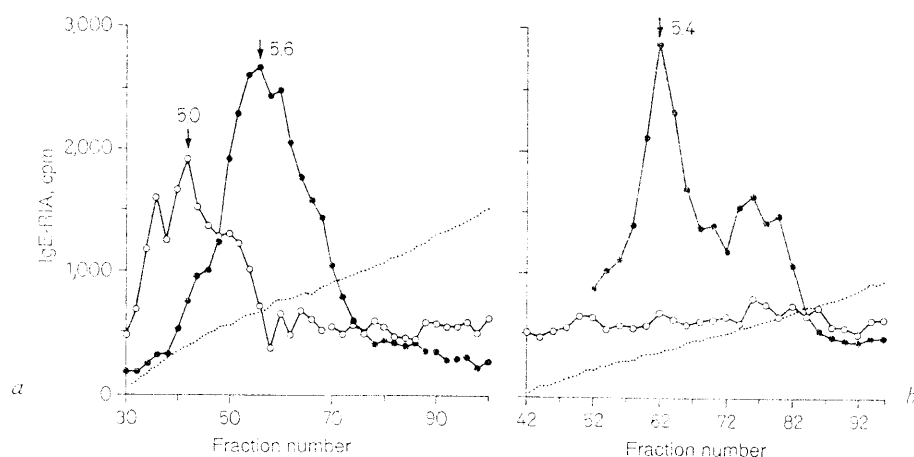


Fig. 3. Isoprotein pattern of serum IgE from a patient allergic to muscle relaxant drugs (a) and from a nonallergic subject (b). Isoelectrofocusing was performed in a 110-ml I KB column using carrier ampholytes in a final concentration of 1% and in a 0-50% sucrose gradient. Total IgE (●) and specific IgE (○) were measured in each fraction by Immunotech-RIA and QAS-RIA, respectively. The dotted line indicates the pH gradient and the arrows the isoelectric points.

corresponds to the specific IgE response to the contact with the allergen or if it is a predisposing risk factor corresponding to a constitutionally abnormal IgE.

LHL is the second biological test which can be performed for the diagnosis of allergy to muscle relaxant drugs [18, 22, 25, 30]. In a recent series of patients allergic to muscle relaxants, the LHL was found positive in about 70%. LHL gave a lower cross-reactivity with nonincriminated muscle relaxants, compared to QAS-RIA [25, 26]. We preferred to perform the LHL test with total blood instead of washed isolated leukocytes. Using such a protocol, a very low spontaneous release of histamine is observed [25]. In addition, incubation of the drug with total blood is a better *in vitro* test than incubation with washed cells since it takes into account the binding of drug compounds to carrier proteins. We measure the released histamine by a RIA which uses a monoclonal antibody specific of acylated histamine (Immunotech, Luminy, France). This method is sensitive and reproducible and should be preferred to the radioenzymatic method since it has been shown that muscle relaxants can act as inhibitors of N-methylhistamine transferase [31]. Using the LHL with total blood, we estimated the upper normal limit of histamine release in control samples to be 5% [25].

LHL seems to be more suitable than QAS-RIA to predict the harmfulness of a muscle relaxant. It could be used with skin tests for assessing this possibility in a further anesthesia, if our preliminary data are confirmed [25, 26, 30].

Thiopentone

The incidence of life-threatening anaphylactic reaction is estimated to be about 1/30,000 for thiopentone. The anaphylactic reaction to thiopentone seems to be IgE-mediated in most of the cases, but it can be associated with an activation of the complement system by classical and alternative pathways, according to Watkins [32]. Nonimmunological activation of mast cells with thiopentone in vivo and in vitro had been substantiated by several groups [33, 34]. In our experience, in vitro histamine release from basophils of atopic patients is greater in these patients than in controls, in the presence of thiopentone [13].

Harle et al. [35, 36] performed a RIA with thiopentone-Sepharose for detecting antidrug IgE in the sera of patients who experienced an anaphylactic reaction to thiopentone. It was established that the secondary pentyl and ethyl groups and the thio region of the molecule were involved in the epitope recognized by IgE of allergic patients [35]. IgE antibodies of sera from some patients allergic to muscle relaxant can show a significant binding to thiopentone-Sepharose [35]. This binding is not inhibited by thiopentone. In fact, the binding of IgE antibodies of sera from patients allergic to thiopentone can be inhibited by muscle relaxant drugs such as alcuronium, *d*-tubocurarine and succinylcholine and also by morphine. False-positive results are observed with Sepharose-thiopentone RIA or with thiopentone-paper RAST, especially for patients with high IgE levels [27, 35]. The diagnosis of anaphylaxis to thiopentone requires performing IgE-RIA with hapten inhibition in order to eliminate these false-positive results. A simultaneous anaphylaxis to thiopentone and to a muscle relaxant (pancuronium or suxamethonium) has recently been reported by our group. The diagnosis was performed by LHL tests and IgE solid-drug phase RIA [37].

Morphine

Morphine, like other opioids, is a potent histamine-releasing drug. However, anaphylactoid reactions to this drug are very rare. They can be the result of a direct effect of the drug on degranulation and also of an immune mechanism. Recently, Harle et al. [38] have reported one case of anaphylaxis after injection of papaveretum-hyoscine. IgE of the patient's serum reacted

with Sepharose-morphine and Sepharose-codeine. Nalorphine, meperidine and methadone were effective inhibitors of the solid-drug phase RIA [38]. The authors suggested that the allergenic determinant comprised a cyclohexenyl ring with a hydroxyl group at C-6 and a methyl substituent attached to the N-atom of morphine [38].

Propofol

Propofol in a lipid emulsion (Diprivan[®]) was thought to be a poor histamine releaser. In fact, we have recently observed that LHL in the presence of Diprivan was greater in atopic patients than in controls [13]. In France, very few adverse reactions have been reported since it became available in 1987. We published an article on two cases in 1987, one of which was a true anaphylaxis with a typical bell-shaped LHL curve and the presence of antidrug IgE in serum [39]. We have now reported 14 patients with anaphylactoid or anaphylactic reaction to Diprivan [40]. Detection of IgE was performed by a RIA in which propofol was noncovalently adsorbed to phenyl-Sepharose by hydrophobic binding. In this type of IgE-RIA, identification of the allergenic determinant by hapten inhibition of RIA was not possible. A high binding level of IgE in sera from patients who underwent an adverse reaction to Diprivan was observed with this phenyl-Sepharose-reactive phase. It can be explained either by specific binding of IgE or by nonspecific binding of hydrophobic IgE [40]. The possibility of anaphylactoid reaction mediated by nonspecific hydrophobic interaction of hydrophobic drugs with hydrophobic IgE has therefore to be investigated.

Assessment of Anaphylactic Reaction by Biological Tests

A series of biological tests have to be performed immediately after the reaction (intraoperative testing) to establish the diagnosis of drug anaphylaxis. Some of these tests can be repeated 6–8 weeks later to confirm the diagnosis (postoperative testing) [41].

Intraoperative Testing

This includes the investigation for mediator release and for the presence of antidrug antibodies.

Serum tryptase: The peak concentration appears 1–2 h after the onset of the reaction. The tryptase level returns to baseline after 24 h. An elevated concentration can also be observed in the case of mastocytosis [9].

Urinary methylhistamine: A raised concentration is observed during the first 24 h. Plasma histamine is of limited value because it decreases rapidly after the adverse reaction.

Complement activity: Interpreting the assays is difficult because changes are detectable for a short time after the adverse reaction.

Drug-specific IgE antibodies: IgE are detected in serum by solid-drug phase RIA. Antidrug IgE can be detected just after the adverse reaction as well as 6 weeks later [42]. Interpretation of solid-drug phase RIA requires the performance of a series of controls [6]: (a) serum + Sepharose-ethanolamine; (b) solid-drug Sepharose + cord serum; (c) solid-drug Sepharose + serum from atopic patients (control sera); (d) solid-drug Sepharose + serum from non-allergic patients (control sera), and (e) hapten inhibition.

The limit of positivity of the RIA is estimated from the background radioactivity level (measured with control sera). According to Harle et al. [29, 36], a positive result corresponds to at least three times the background level.

Postoperative Biological Tests Are Performed in Association with Skin Testing

These tests include drug-specific IgE antibodies and LHL. The latter test is performed on total heparinized blood incubated with dilutions of the commercially available drug solution from 10^{-1} to 10^{-5} .

Conclusion

The biological tests currently used for the diagnosis of anaphylaxis to an anesthetic drug are in vitro leukocyte histamine release test and drug-specific IgE-RIA. It has been suggested that IgE-RIA should be used for screening patients preoperatively. In fact, the principal use of these tests is for diagnosis. A clear definition of risk factors has to be established before proposing antidrug IgE-RIA as a preventive test. Preliminary results suggest that the LHL test is complementary to skin testing for investigating the cross-reactivity of muscle relaxants, in order to choose a harmless molecule for a further anesthesia.

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