

Diagnosis and pathogenesis of the anaphylactic and anaphylactoid reactions to anaesthetics

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Summary

Immediate adverse reactions to anaesthetics have an immune mechanism in more than 50% of the cases. They are mainly due to muscle relaxant drugs. A prospective evaluation of tryptase, histamine and serotonin for diagnosing anaphylaxis to anaesthetics was performed over 2 years. The sensitivity of each marker was at 60–70% and it reached 80% when combining tryptase and histamine. Specific IgE have been already observed in serum from patients allergic to muscle relaxant, thiopentone, morphine, phenoperidine, propofol and radio-contrast media. However, the recent progress in the identification of drug epitopes by Sepharose-solid drug phase IgE radioimmunoassay has to be reconsidered as non-specific binding of hydrophobic drugs such as propofol to hydrophobic serum IgE has been observed recently in patients with drug allergy. In addition, association of drugs such as propofol and muscle relaxant may potentiate the mediator release by a non-elucidated mechanism.

Keywords: anaesthetics, drug allergy, anaphylaxis, IgE, histamine, tryptase

Introduction

Most of the allergic adverse reactions to anaesthetic drugs are immediate type reactions. They have been described for the first time with cremophor-based drugs, such as alfathesin and propanilid, in the early 1970s [1]. The subsequent development of biological tests for determining the release of cell mediators in blood and for identifying specific anti-drug IgE in serum helped to diagnose and to estimate the frequency and the pathogenesis of these reactions more accurately [2]. Various mechanisms of cell-mediator release, either IgE-mediated or non-immunological, have been described. The latter include the osmotic release of histamine, the activation of the complement and/or the kinin-kallikrein system and the direct membrane effect of the drug [3]. Two types of reactions have therefore been defined. An anaphylactic reaction occurs after previous sensitization to the drug or to a related agent and is the result of the drug-bridging-specific antibodies bound to target cells, such as basophils and mast

cells. The non-immune anaphylactoid reaction does not involve specific antibodies and a previous exposure is not necessary. Laboratory tests are therefore crucial to distinguish both types of reaction [2].

Epidemiology

The incidence of life-threatening allergic reactions to anaesthetic drugs is unknown. The largest studies have been published in France where incidences of 1:6000 and of 1:3500 were estimated, respectively for true anaphylaxis and for all types of immediate reactions (anaphylactoid and anaphylactic) [4]. Two surveys have been published in France in 1990 and 1993, corresponding to 1240 and 1585 patients, respectively [4,5]. More recently, a survey included 1750 patients tested in 27 diagnostic centres, between January 1992 and June 1994 [6]. In this study, the sex ratio (F/M) was 2:4. The immune origin of the shock, attested by radioimmunoassay (RIA) in sera, was found in 57.8% of the patients and was due to muscle relaxants in 59.2%. The incidence of reactions to the different muscle relaxants was correlated with the clinical use of muscle relaxants, except for suxamethonium

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which was responsible for 39% of the reactions due to muscle relaxants and represented only 5% of muscle relaxants sold in France. Suxamethonium appeared also to carry a greater risk in the Australian population [7]. In Australia, 59% of the 821 reactions to anaesthetics recorded between 1974 and 1992 were due to muscle relaxants. In Great Britain, a 529 patient series was reported, studied by biological tests only, which showed also the predominancy of muscle relaxants [8]. Smaller series that included both biology and cutaneous testing showed that anaphylaxis to muscle relaxants was not only an Australian and French disease, but also that it occurred in about 50% of the anaphylactic shocks due to anaesthetics in Great Britain, USA and Canada [9–11]. Hypnotics and morphinics were the second drugs which were implicated in the 1990 French series but the last survey (1996) showed a dramatic increase of the shocks due to latex [4–6].

Cell mediator release

Histamine from mast cells and basophils and tryptase from mast cells are the two mediators that have been extensively evaluated in anaphylactic and anaphylactoid reactions to anaesthetics [12]. The determination of plasma histamine assists the aetiological diagnosis, but it does not correlate with the clinical features [2]. In addition, histamine-releasing potency is unrelated to the incidence of severe reactions. For example, morphine is a much more potent releaser than muscle relaxant, while *in vivo* reactions to morphine are rare [13,14]. Direct histamine release, e.g. non-immunological release by a direct cell membrane activation of the drug, is **usually unlikely to be a major cause of strong reactions**. One of the reasons could be that, *in vitro*, immunological histamine release is associated with the release of other mediators of target cells, while direct release is not [15].

To validate this hypothesis *in vivo*, we have compared prospectively blood levels of histamine, tryptase and serotonin in patients who had an adverse reaction to anaesthetics, in a 2 year-period, in two French regions, Normandy (in the west) and Lorraine (in the east) [16,17]. The selection criterion was the presence of clinical signs of anaphylaxis after blood injection of anaesthetic drugs. Blood was withdrawn in the few minutes following the shock reaction and also after delays of 30 min, 120 min, and 24 h. In addition, patients were examined in the allergology department 1 or 2 months after the shock event. Skin testing and specific IgE RIAs to drugs were then performed. A total of 41 patients who had an adverse reaction during anaesthesia were registered in eastern France during the 2-year-period. Drug allergy with anaphylaxis was established in 23 cases (56.1%). Bronchospasm, cardiovascular and cutaneous symptoms were recorded in 43.5%, 82.6% and 82.6% of the patients with proven allergy, respectively and in 28.5%, 78.6% and 57.1% of the other patients, respectively.

Tryptase, histamine and methylhistamine were increased respectively in 68.1%, 56.2% and 47.3% of patients with proven allergy. The sensitivity reached 81% when the three mediators were cumulated. Muscle relaxants were implicated in the shock in as many as 18 (75%) of the cases with proven allergy. Patients allergic to muscle relaxants were also allergic to another drug in 12 cases. This involved phenoperidin, propofol and thiopental in four, six and two cases, respectively.

A total of 49 patients with an adverse reaction to anaesthesia were registered in western France during the same period. They were classified as allergic in 21 cases, non-allergic in 15 cases. The diagnosis of allergy was probable but could not be established in 13 cases who did not attend the allergology consultation. Cardiovascular and cutaneous symptoms were recorded with a frequency similar to that registered in the series from eastern France. The level of tryptase was increased in the blood collected just after the shock event in 65%, 41.1% and 14.3% of the patients with proven allergy, suspicion of allergy, and absence of drug allergy, respectively. Tryptase seemed therefore to be relatively specific for anaphylaxis. These frequencies were not modified in samples collected either 30 min or 120 min after shock event. By comparison, histamine levels were increased by 61.9%, 46.1% and 21.4%, respectively in the same group of patients; serotonin blood levels were increased in 61.9%, 46.1% and 66.6%, respectively (Fig. 1). We have previously shown *in vitro* release of serotonin from platelets in patients allergic to muscle relaxant drugs [18]. The fact that an increased blood level of serotonin was also observed in non-allergic patients **with the same frequency** than in allergic patients suggests that this mediator may be released by either an IgE-dependent or an IgE-independent mechanism. No specific relationship was found between clinical symptoms and any of the three mediators investigated.

The increase of plasma histamine is usually transient, in allergic as well as in non-allergic patients, suggesting that clinical symptoms depend on other mediators. In addition, the 'releasability' of mediator from mast cells varies in function of their tissue distribution [19]. Finally, although tryptase and histamine blood levels from our series were elevated in a majority of allergic patients undergoing shock, their sensitivity and specificity was not sufficient for confirming the diagnosis of anaphylaxis. The sensitivity reached 80% when considering both markers. It seems therefore more advisable to measure both histamine and tryptase than a single mediator in patients suspected to have an allergic reaction during anaesthesia.

Most of the patients from our prospective study had a reaction against muscle relaxants in association with other anaesthetics, such as propofol and phenoperidin, with positive IgE-RIA and skin tests for both drugs, as described previously [20]. In addition, we have shown that the association

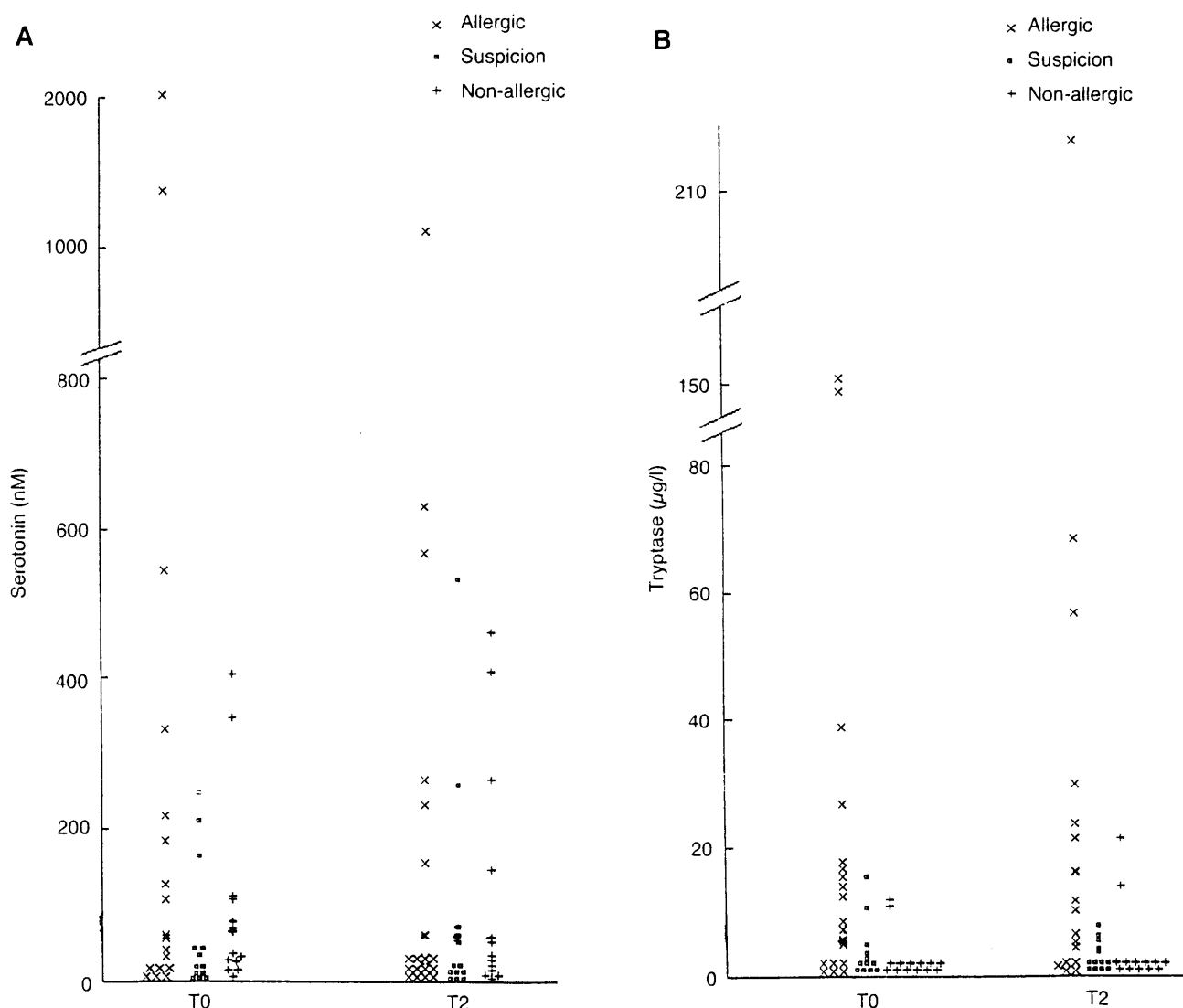


Fig. 1. Blood level of tryptase (A) and serotonin (B) in 49 patients who had an adverse reaction during anaesthesia. These patients were classified in three groups: proven allergy ($n=21$), suspicion of allergy ($n=13$), and absence of allergy ($n=15$). Blood was collected just after the shock (T0) and 120 min later (T2).

of Diprivan® (propofol in lecithin emulsion) and muscle relaxant can potentiate the *in vitro* release of histamine from basophiles of five patients who underwent a shock after injection of both drugs [16]. Such a potentiating effect shows the necessity to perform skin tests and biological tests for each drug but also for the association of them. It shows also that the association of propofol with muscle relaxants should be avoided, when possible [16].

IgE recognition of anaesthetic drugs

Baldo and Fischer were the first to demonstrate the presence of anaesthetic-specific IgE in serum [21] using muscle

relaxant coupled to epoxy-Sepharose. Specific IgE adsorbed to the solid phase was detected using a radiolabelled anti-IgE antibody. Inhibition of IgE binding was obtained by preincubation of the sera with either soluble muscle relaxants or structurally related compounds. They concluded that quaternary and tertiary ammonium ions were involved in the allergenic site. This explained the crossreactivity between the different muscle relaxants observed by skin testing, *in vitro* leucocyte histamine release and serum IgE-RIA, including muscle relaxants recently commercialized, such as rocuronium [22]. Our group has improved the sensitivity of detection of specific IgE in serum up to 90% by coupling an analogue of choline

to Sepharose via an ether linkage (QAS-RIA) [23,24]. Muscle relaxant-specific IgE antibodies can be measured with the same diagnostic value at the time of the reaction and after 2 months [25].

We have estimated the affinity of muscle relaxants for IgE by determining their inhibition constant (K_i) for IgE binding to QAS. Inhibition constant values ranged between 1.5 nM and 2.5 mM. In most of the 12 patients studied, the K_i was the lowest for the muscle relaxant responsible for the allergic reaction [24]. It is therefore likely that anti-muscle relaxant IgE do not recognize a single epitope as they have a wide affinity range for the drug. This suggests also that quaternary ammonium is not the only part of the molecule that is implicated in the IgE-binding. A hydrophobic environment seems to be necessarily close to the quaternary ammonium ion as we have observed negative IgE-RIA with tetraethylammoniummethyl-trihydroxymethyl-sepharose (TEAE)-THM in 21 sera with a positive QAS-RIA.

Specific IgE against thiopentone, morphine, phenoperidine and propofol have been also detected in serum of sensitized patients, using IgE-RIA [25–27]. Two different allergenic determinants have been identified on opposite sides of the thiopentone molecule. One of these determinants involves the ring nitrogens in the pyrimidin nucleus and can be responsible for *in vitro* crossreactions with sera from patients allergic to muscle relaxants [26,28].

More recently, we have investigated 21 cases of immediate adverse reactions to radio-contrast media, which were studied by skin testing, determination of blood level of cell mediators and detection of IgE by RIA. Tryptase and histamine were increased in 16 and 15 patients, respectively while only three had IgE detected by RIA, using ioxitalamate and ioxaglate covalently coupled to Sepharose as a solid reactive phase. Three patients also had positive skin

Table 1. Anaesthetic drugs responsible for anaphylactic shock during 1992–1994 in France [from reference 6]

Muscle relaxants <i>n</i> = 610	Suxamethonium	240
	Vecuronium	220
	Atracurium	88
	Pancuronium	29
	Gallamine	19
Hypnotics <i>n</i> = 61	Alcuronium	14
	Thiopental	31
	Propofol	29
Benzodiazepines <i>n</i> = 22	Etodimate	1
	Midazolam	7
	Flunitrazepam	9
Morphinics <i>n</i> = 36	Diazepam	6
	Fentanyl	18
	Dextromoramide	11
	Alfentanil	4
	Pethidine	2
Plasma substitutes <i>n</i> = 51	Naloxone	1
	Gelatine	40
	Dextrans	8
	Albumin	2
Other drugs <i>n</i> = 54	Amidon 200000	1
	Antibiotics	32
	Local anaesthetics	7
	Aprotinine	6
	Ethylene oxide	3
	Formol	1
	Protamine	1
	Oxytocine	1
	Hydroxyzine	1
	Papaine	1
Latex	Radio-contrast media	1
		195

Table 2. Adsorption to hydrophobic solid drug phases of IgE from patients who had an adverse reaction to propofol and a positive propofol-Sepharose IgE-RIA

Patients	Epoxy-Sepharose coupled to			Sepharose coupled to		
	Propofol	Paracetamol	OH-glafenine	Phenyl	Octyl	QAS
DA	9.2 (+)	3.0 (±)	6.6 (–)	27.8 (+)	4.3 (+)	0.5 (–)
HU	9.3 (+)	3.4 (±)	7.6 (–)	23.6 (+)	3.3 (±)	14.8 (+)
BO	7.8 (+)	4.5 (+)	6.2 (–)	—	3.0 (+)	24.4 (+)
SE	22.4 (+)	5.8 (+)	9.0 (±)	16.6 (+)	9.0 (+)	0.9 (–)
HE	5.8 (±)	5.0 (+)	22.0 (+)	34.6 (+)	28.9 (+)	26.5 (+)
DO	7.3 (+)	2.2 (–)	6.9 (–)	23.6 (+)	1.8 (–)	0.4 (–)
BE	3.7 (±)	3.0 (±)	8.6 (–)	20.9 (+)	3.4 (±)	15.9 (+)
PO	5.0 (±)	4.5 (±)	6.2 (–)	26.9 (+)	2.9 (±)	19.2 (+)
Controls	1.7 ± 0.4	1.5 ± 0.4	4.1 ± 1.6	4.6 ± 0.7	1.5 ± 0.2	1.2 ± 0.6

tests. This showed that an immune mechanism can be involved in some, at least severe, immediate reaction to radio-contrast media [29].

We have investigated the presence of hydrophobic IgE in serum of patients allergic to hydrophobic anaesthetic agents, such as propofol. Hydrophobic IgE were detected by radioimmunoassay using either phenyl-Sepharose or octyl-Sepharose as reactive phase [30] in eight patients with an allergic adverse reaction to propofol (Table 2). The phenyl-Sepharose IgE-RIA was positive in all. In addition, IgE-RIA were also positive with paracetamol (Table 2), suggesting that propofol-IgE binding may involve a non-specific recognition of the cyclohexenyl ring. Propofol is included in a lipid emulsion with lecithins. Lecithins share quaternary ammonium ions in the hydrophilic face of the micelles which can react with anti-muscle relaxant IgE. We observed five cases with a positive QAS IgE-RIA in our series of eight patients. The simultaneous presence in serum of hydrophobic IgE and of anti-quaternary ammonium IgE could be a risk factor for an adverse allergic reaction to Diprivan® and may explain the potentiating effect of the association Diprivan-muscle relaxants on the *in vitro* leucocyte histamine release performed in patients who reacted against both drugs [16].

In conclusion, the pathogenesis of immediate allergic reactions to anaesthetics remains unclear, in at least three aspects: the respective role of the main mediators involved in the pathogenesis of the shock; the identification of epitopes from drugs by means of solid-phase IgE-RIA and **inhibition studies has to be reconsidered** as hydrophobic IgE can be responsible for non-specific crossreactions, and association of drugs such as propofol and muscle relaxant may potentiate the mediator release in some cases, by a mechanism that is not elucidated.

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