

In Vitro Diagnosis of Immediate Drug Hypersensitivity During Anesthesia: A Review of the Literature



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Quantification of specific IgE (sIgE) antibodies constitutes an important measure to document anesthesia-related immediate hypersensitivity reactions (IHRs). However, only a few drug-specific assays are available and their predictive value is not known. In cases of non-IgE mediated IHRs, diagnosis might benefit from cellular tests such as basophil mediator release tests and basophil activation tests (BATs). To review the potential and limitations of quantification of sIgE, mediator release, and BAT in anesthesia-related IHRs, a literature search was conducted using the key words allergy, basophil activation, CD63, CD203c, diagnosis, drugs, hypersensitivity, flow cytometry, MRGPRX2, specific IgE antibodies, leukotrienes, histamine, and tryptase; this was complemented by the authors' experience. The drugs and compounds that have predominantly been studied are neuromuscular blocking agents (NMBAs), β -lactams, latex, and chlorhexidine. For sIgE NMBA, sensitivity and specificity varies between 38.5% to 92% and 92% to 100%, respectively. For sIgE β -lactams, sensitivity varies between 0% to 85% and specificity between 52% to 100%. sIgE to morphine should not be used in isolation to diagnose IHRs to NMBAs or opiates. sIgE for latex, and, in difficult cases, molecular diagnosis with quantification of sIgE to *Hevea* components constitute reliable diagnostics. For drugs, the sensitivity of BAT varies between 50% and 60% and specificity reaches 80% to 90%. Basophil mediator release tests seem to be abandoned and supplanted by BATs. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1176-84)

Key words: Allergy; Anesthesia; Basophil activation; Drugs; Flow cytometry; Immediate drug hypersensitivity reaction (IDHR); Specific IgE (sIgE); Beta-lactam; Penicillin; MRGPRX2; Neuromuscular blocking agents (NMBA); Opiates; Tryptase

INTRODUCTION

The gold standard to ascertain correct diagnosis of immediate hypersensitivity reactions (IHRs) to drugs is a controlled drug provocation test (DPT) with the culprit compound(s). However, DPTs entail a risk of severe, life-threatening complications and can be contraindicated (eg, patients having suffered from life-threatening reactions) or impossible (eg, full-dose DPT in hypersensitivity to curarizing neuromuscular blocking agents [NMBAs]). Moreover, the predictive value of DPTs is not known and DPTs might yield false-negative results.¹ Therefore, the diagnostic approach of anesthesia-related IgE-mediated IHR generally starts with history taking, thorough review of anesthetic/surgical notes, complemented with skin testing and/or *in vitro* quantification of specific IgE (sIgE) antibodies. However, only a few drug sIgE assays are available, and most of them have not been clinically validated. Furthermore, IHRs might not *per se* involve IgE/high-affinity receptor for IgE (Fc ϵ RI)-cross-linking, but may also result from alternative pathways such as an off-target occupation of the Mas-related G-protein receptor MRGPRX2^{2,3} that cannot be detected by an sIgE antibody assay. The development and validation of cellular tests such as basophil activation tests (BATs) would, to some extent, be promising in such cases.

The objective of this article was to review the literature on the value of serum tryptase, histamine, commercially available drug sIgE assays, and BATs such as mediator release tests in the diagnosis of anesthesia-related IHRs. Emphasis is put on some misconceptions, shortcomings, and unmet needs. As with any subject still beset by many questions, alternative interpretations, hypotheses, or explanations expressed here may not find universal acceptance.

QUANTIFICATION OF SERUM TRYPTASE

Although quantification of peak and baseline serum tryptase does not contribute to the identification of the culprit, serum tryptase has proven to be extremely valuable in diagnosing anesthesia-related IHRs, mainly to confirm mast cell degranulation and/or to rule out or confirm (clonal) mast cell disorders⁴ and mast cell activation syndromes.⁵ Currently, in the

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Abbreviations used

BAT- Basophil activation test
DPT- Drug provocation test
FcεRI- High-affinity receptor for IgE
IDHR- Immediate drug hypersensitivity reaction
IHR- Immediate hypersensitivity reaction
NMBA- Neuromuscular blocking agent
sIgE- Specific IgE

commercially available assay, total tryptase is quantified as the sum of continuously secreted baseline tryptase and β -tryptase released from degranulating mast cells (ImmunoCAP Thermo-fisher, Uppsala, Sweden). Because relevant increases have been observed way below the traditional decision threshold of 11.4 $\mu\text{g/L}$, it has been suggested to abandon this cutoff.⁶⁻⁸ For example, an incremental threshold of 20% was shown to identify potential mast cell mediator release in an additional 14% of cases with peak tryptase between 5 and 14 $\mu\text{g/L}$ and a further 15% with peak tryptase below 5 $\mu\text{g/L}$. Others have proposed that an increase in tryptase over baseline (24 hours after the acute event) levels is clinically relevant when it exceeds $2 + (1.2 \times \text{baseline})$.^{9,10} Although in the study by Sprung et al, quantification of peak tryptase was performed between 30 minutes and 4 hours from the event, it is recommend to take the peak sample as close to 60 minutes after the reaction as possible, and if not possible later samples should still be taken and compared with a baseline taken at a later date.¹¹ Alternatively, by comparing the 2 measurements, anaphylaxis could be ruled out even for acute tryptase values of more than 11.4 $\mu\text{g/L}$ in cases of baseline hyper-tryptasemia.⁹ Quantifying baseline tryptase has another additional purpose, because elevated baseline levels might be indicative for underlying (clonal) mast cell disorders⁴ that might underlie severe IHRs, particularly in men who do not demonstrate urticaria/angioedema.¹² β -Tryptase levels of more than 1 $\mu\text{g/L}$ indicate mast cell degranulation. However, this test is not commercially available. Quantification of plasma histamine, although highly sensitive, was inferior to quantification of serum tryptase for discrimination between IgE-dependent and IgE-independent anesthesia-related IHRs.¹³ Resuscitation maneuvers by themselves appear not to modify mediator concentrations.¹⁴ Alternatively, it is important to stress that an elevated peak tryptase measurement does not necessarily indicate mast cell activation.^{9,15} In chronic renal failure, elevated "peak" serum tryptase¹⁵ might result from mast cell hyperplasia due to slow elimination of stem cell factor.¹⁶ Note that tryptase is not cleared by the kidneys.¹⁷ Tryptase can also be elevated in critically ill patients without anaphylaxis¹⁸ and victims of trauma.¹⁹ False-negative results mainly result from incorrect sampling time (ideally 60-90 minutes after onset of symptoms).

PRINCIPLES OF QUANTIFICATION OF DRUG sIgE ANTIBODIES AND BAT

Like tissue-resident mast cells, basophils can be triggered in IgE-dependent and various IgE-independent ways. Cross-linking of the surface-bound FcεRI generally occurs through (glyco) proteins, chemical allergens, or autoantibodies directed against FcεRI or membrane-bound sIgE antibodies. Quantification of sIgE antibodies predominantly relies on quantification of a drug-(hapten)-carrier antibody complex in which the secondary

antihuman IgE is conjugated to an enzyme with colorimetric reading in the ELISA or with a fluorescence reading in the fluorescent enzyme immunoassay.²⁰ However, only a limited number of drug sIgE immunoassays are available and most of these assays have not been thoroughly validated, mainly as a result of the unavailability of sufficient numbers of patients and exposed or challenged control individuals.

An IgE-independent activation will mainly result from coupling of surface receptors with endogenous (eg, cytokines, anaphylatoxins, chemokines, IgG, and neuropeptides) or exogenous (eg, pathogen-associated molecular patterns) elements. Among these receptors is the Mas-related G-protein receptor MRGPRX2 that can lead to a quick but rather transient mast cell degranulation²¹ and appears to be involved in different mast cell-associated conditions including nonimmune immediate drug hypersensitivity reactions (IDHRs).^{22,23} Recently, McNeil et al² described the potential of MRGPRX2-related mast cell activation by various drugs containing a tetrahydroisoquinoline motif such as some fluoroquinolones and various NMBAs. The MRGPRX2 receptor has subsequently also been incriminated in reactions toward opioids²⁴ and vancomycin.²⁵ Alternatively, other largely unknown pathways might also induce degranulation.

The foundations of current flow-assisted BAT were laid 25 years ago²⁶ and in the meantime the technique has largely supplanted older mediator release assays that rely on difficult quantification of mediators released in the supernatant. Actually, the last reviews on mediator release tests date back to 2003.^{27,28} To our knowledge, since then no large case-control studies including more than 15 patients and significant numbers of (exposed) control individuals on the application of the various mediator release tests have been published, except a report including patients who suffered from perioperative hypersensitivity reactions resulting from various causes.²⁹

Traditional BAT relies on a flow cytometric analysis of various activation and degranulation markers on the surface membrane. These changes can be detected and quantified on a single-cell level using specific mAbs conjugated with different LASER-excitable fluorochromes. The technical principles and requirements of BAT have been detailed elsewhere.³⁰ Basophils are traditionally identified by markers such as CCR3 (CD193)/CD3, CD123/HLA-DR, or IgE/CD203c. Of these markers, only CD203c is lineage specific. After activation, the appearance and/or upregulation of surface activation and/or degranulation markers such as CD203c and/or CD63 is quantified. For a review on the applications and limitations of the BAT in drug IHRs, see Mangoldt et al.³¹ Histamine release can also be quantified by flow cytometry³² and the technique is applicable in IHRs to drugs.³³

β-LACTAMS

The most studied sIgE assays are those for β -lactams, especially amoxicillin and benzyl penicilloyl. Although several cases of positive sIgE results in IHRs with negative skin test results have been described,³⁴⁻³⁸ sIgE assays for β -lactams, as listed in Table I, generally exhibit a poor sensitivity that decreases over time.⁴⁵ Besides these disappointing sensitivity data, there is increasing evidence supporting low specificity of the tests.^{35,37,42,43,46,47} In some studies, false positivity could have resulted from nonspecific binding in the solid-phase assay as a result of elevated total IgE titers.^{42,43,47,48} An alternative

TABLE I. sIgE to β -lactams

Compound	Reference test	Assay	Sensitivity	Specificity	N	Reference
Various β -lactams	H + ST	CAP-FEIA	BPO + AXO + peni G + AMP: 31.8%	BPO + AXO + peni G + AMP: 88.6%	58	39
Various β -lactams	H $\pm$ ST $\pm$ DPT	CAP-FEIA	BPO: 32% AXO: 43% BPO + AXO: 50%	BPO: 98% AXO: 98% BPO + AXO: 96%	129	40
Various β -lactams	H $\pm$ ST $\pm$ DPT	CAP-FEIA	BPO: 10%-68% AXO: 41%-53%	BPO: 98% AXO: 95%	410	38
Various β -lactams	H	CAP-FEIA	37.9%	86.7%	58	41
Various β -lactams*	H $\pm$ ST $\pm$ DPT	CAP-FEIA RAST†	0%-25%† 42.9%-75%†	83.3%-100%† 66.7%-83.3%†	45	34
Various β -lactams	H $\pm$ ST	CAP-FEIA	85%‡	54%‡	176	42
		CAP-FEIA	44%§	80%§		
Various β -lactams	H $\pm$ ST	CAP-FEIA	66%	52%	293	43
Amoxicillin	H + ST + DPT	CAP-FEIA	19%	NA	57	44

AMP, Ampicillin; AXO, amoxicillin; BPO, benzyl penicilloyl; CAP-FEIA, fluorescence enzyme immunoassay available from Phadia Thermofisher; H, history; Peni G, penicillin G; RAST, radio allerge sorbent test; ST, skin test.

Note that there is no IgE for clavulanic acid available.

*Homemade assay.

†Sensitivity and specificity vary according to clinical manifestations.

‡For a threshold of 0.10 kU/L.

§For a threshold of 0.35 kU/L.

explanation for false-positive sIgE penicillin seems to be sIgE antibodies to phenylethylamine that test negative in a BAT.⁴⁸ In summary, sIgE antibodies to β -lactams seem of restricted value and should ideally not be used in isolation to exclude or confirm IHRs to these antibiotics. To avoid misdiagnosis, these assays should be complemented with BAT, skin testing, and where appropriate a DPT.^{49,50} Table II summarizes the data of BAT in IHRs to β -lactams. Up to now, 10 studies have investigated the BAT as a diagnostic tool in IHRs to β -lactams, mainly to amoxicillin. Compared with the quantification of sIgE antibodies, BAT shows a higher sensitivity (about 50%) and specificity ($\sim$ 90%). As for sIgE, sensitivity of BAT to β -lactams is rather low and decreases over time but both test results can remain positive for years.^{45,59} Therefore, we cannot adhere to the recommendation by the ENDA/EAACI drug allergy interest group not to perform drug sIgE tests after 3 years,⁶⁰ particularly because skin test responsiveness also decreases over time.^{45,61} Finally, it should be kept in mind that sensitization to amoxicillin/clavulanate can also result from sensitization to clavulanic acid,⁶² which needs specific testing.⁴⁴ For a diagnostic algorithm for IHRs to β -lactam antibiotic, the reader is referred elsewhere.⁶³

NEUROMUSCULAR BLOCKING AGENTS

In many countries, curarizing NMBA represent a significant cause of anesthesia-related anaphylaxis.⁶⁴⁻⁶⁸ As indicated in our diagnostic algorithm for NMBA (Figure 1), skin tests are the primary instrument to confirm IHRs to NMBA and cannot be substituted by BAT or quantification of sIgE.⁷¹ However, the predictive value of skin testing is not absolute, thereby leaving room for additional *in vitro* tests. In the absence of readily available assays, for about 2 decades, several groups have tried to define the accuracy of various homemade NMBA-sIgE assays (Table III).^{72,73,78,79} At present, IHRs to NMBA are serologically assessed indirectly through assays measuring IgE reactivity to tertiary and quaternary substituted ammonium structures that

have been shown to be the major epitopes of NMBA.^{80,81} Most frequently applied methods are a choline chloride assay,^{72,73,82-87} a p-aminophenyl phosphoryl choline assay,^{72,82,83,88} and/or morphine-based assays.^{70,72-78,88} With respect to the ImmunoCAP FEIA for suxamethonium, rocuronium, atracurium, and morphine, the sensitivity and specificity for the individual NMBA sIgE tests varies between 38.5% and 92% and 85.7% and 100%, respectively. Furthermore, it has been demonstrated that a morphine-based immunoassay is a valuable test to detect suxamethonium and rocuronium-reactive antibodies but not to depict atracurium-reactive antibodies.^{70,74} Quantifying IgE reactivity to tertiary and quaternary substituted ammonium structures to identify patients at risk or to document NMBA hypersensitivity^{69,89} might cause a large number of false-positive results because they are prevalent in the general population.^{70,75,76} Therefore, these assays cannot be recommended as a screening tool to identify patients at risk or to document NMBA hypersensitivity.^{69,89} For example, Leysen et al⁸⁹ showed that a positive sIgE to morphine is not a contraindication for the administration of atracurium and cisatracurium in patients with negative skin test results to these benzyloisoquinolines. Explanations for these false-positive sIgE results are an elevated total IgE⁷⁰ and intake of the opiate antitussive pholcodine.⁹⁰ sIgE antibodies to tertiary and quaternary substituted ammonium epitopes can remain positive for several years after the acute reaction.^{69,91} Alternatively, as recently stressed by Spoerl et al,³ IHRs to NMBA such as rocuronium might occur independently from IgE/Fc ϵ RI cross-linking and relate to MRGPRX2-mediated activation of mast cells² and, therefore, not be detected by sIgE assays.

Table IV presents the data about BAT in IHRs to NMBA. In general, sensitivity of the assay varies between 36% and 92%, whereas specificity reaches 95%. Importantly, BAT not only enables identification of the culprit drug but also provides the opportunity to study cross-reactivity and identify safe alternatives for future anesthesia use.^{96,99} Alternatively, because resting basophils barely express MRGPRX2, it is unlikely that traditional

TABLE II. BAT in immediate β -lactam hypersensitivity

Stimulus	Reference test	Activation marker	Sensitivity (%)	Specificity (%)	Number of patients and controls	Reference
β -Lactam	H	CD63	50	93	88	41
β -Lactam	H + DPT	CD63	39	93	53	51
β -Lactam	H $\pm$ ST $\pm$ IgE $\pm$ DPT	CD63	49	91	110	52
Amoxicillin	H $\pm$ ST	CD203c CD63	52 22	100 79	41	53
β -Lactam	H	CD63	50	89-97	262	54
β -Lactam	H $\pm$ ST $\pm$ IgE	CD63-CCR3 CD63-IgE	55 53	100	39	55
Amoxicillin	H	CD63	29	NA	14 patients, no controls	56
Amoxicillin	H $\pm$ ST $\pm$ DPT	CD63	50	NA	61 patients, number of controls not mentioned	57
Amoxicillin	H $\pm$ ST	CD63	50	NA	30 patients	58
Amoxicillin	H $\pm$ ST $\pm$ DPT	CD63	47	93	57	44
Clavulanic acid			62	89	58	
Cefazolin	H + ST	CD63 CD203c	33 67	94 94	16 patients, 17 controls	59

H, History; NA, not available; ST, skin test.

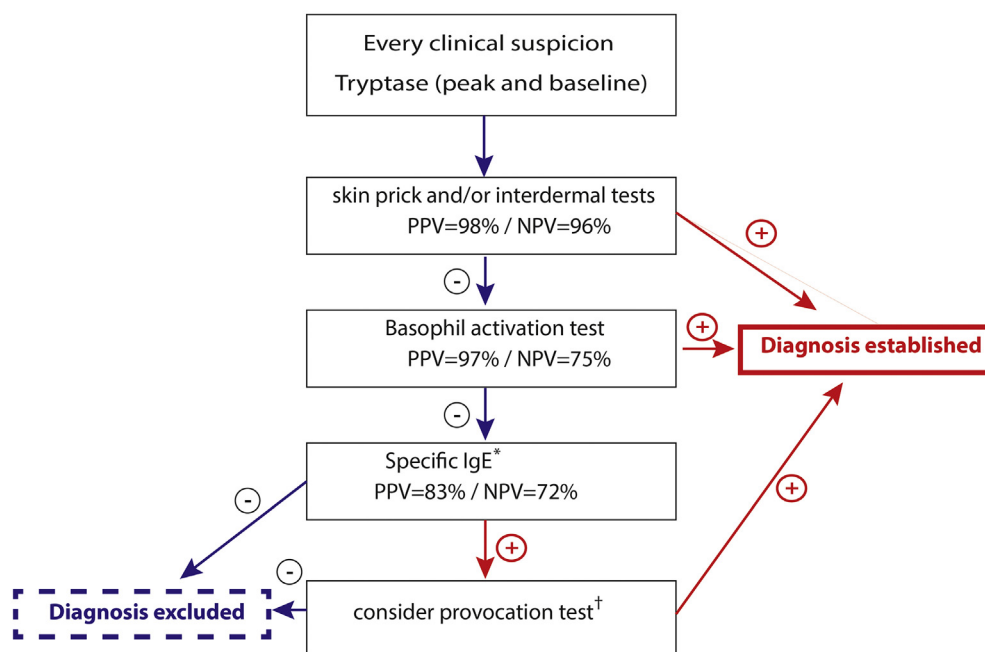


FIGURE 1. Diagnostic algorithm NMBA. NPV, Negative predictive value; PPV, positive predictive value; ROC, receiver-operating characteristic. Values are provided for rocuronium⁶⁹ using an ROC-calculated drug-specific decision threshold of 0.13 kUA/L.⁷⁰ *Drug sIgE available for suxamethonium, rocuronium, and atracurium and should use drug-specific thresholds. sIgE morphine is applied as a biomarker for sensitization to aminosteroids and suxamethonium (not useful for benzylisoquinolines). †Challenging at maximum 1/10th of therapeutic dose.

BAT using cells in steady state be of value in reactions occurring from off-target occupation of this receptor.¹⁰⁰ Our current policy is to offer BAT and sIgE to patients with negative or equivocal skin test results who suffered from severe anaphylaxis and in whom no alternative cause was demonstrable.

OPIATES AND (SEMI-)SYNTHETIC OPIOIDS

Genuine IgE-mediated allergies to opiates (morphine, codeine) and semi-synthetic opioid pholcodine remain rare

notwithstanding their frequent and universal use. In addition, correct diagnosis is not straightforward, mainly because of uncertainties associated with the measurement of drug sIgE antibodies and skin testing.¹⁰¹ Recently, it has been suggested that the 2 commercially available sIgE assays for a *Papaver somniferum* (poppy seed) extract and morphine can add to the diagnosis of IgE-mediated opiate allergy.^{102,103} However, using DPT we were unable to confirm these data,¹⁰⁴ mainly because of the high prevalence of sIgE antibodies to these compounds in an allergic population. This observation is highly relevant when facing

TABLE III. sIgE to NMBAs and substituted ammonium structures

Compound	Reference test	Assay	Sensitivity	Specificity	N	Reference
Various NMBAs	H ± ST	RIA	PAPPC: 97%	PAPPC: 97%	75	⁷²
		RIA	MOR: 83%	NA		
		RIA	QAS: 86%	NA		
Various NMBAs	H + ST	RIA	QAS: 87.9%	NA	83	⁷³
		RAST	SUC: 66.7%			
		RAST	Alcuronium: 40.7%			
Various NMBAs	H + ST	RIA	MOR: 85%	98%	118	⁷⁴
		RIA	NMBA-specific: 52%			
Various NMBAs	H + ST	CAP-FEIA	SUXA: 38.5%	SUX: 96.3%-99.6%	866	⁷⁵
		CAP-FEIA	MOR: 67.7%	MOR: 90%-95%		
Rocuronium*	H + ST	CAP-FEIA	SUXA: 72% [†]	SUXA: 100% [†]	82	⁷⁰
			SUXA: 60% [‡]	SUXA: 100% [‡]		
			ROCU: 92% [†]	ROCU: 93% [†]		
			ROCU: 68% [‡]	ROCU: 93% [‡]		
			MOR: 88%	MOR: 100%		
			PHOL: 86%	PHOL: 100%		
Rocuronium	H + 2 tests [§]	CAP-FEIA	ROCU: 83%	ROCU: 72%	66	⁶⁹
Various NMBA*	H + ST	CAP-FEIA	QAM : 87.7%	QAM : 90.7%	168	⁷⁶
Atracurium*	H + ST	CAP-FEIA	SUXA: 28.6%	SUXA: 85.7%	78	⁷⁷
			ATRA: 57.1%	ATRA: 100%		
			MOR: 14.2%	MOR: 85.7%		

ATRA, Atracurium; CAP-FEIA, fluorescence enzyme immunoassay available from Phadia ThermoFisher; H, history; MOR, morphine; NA, not available; PAPPC, p-aminophenyl phosphoryl choline; QAM, quaternary ammonium morphine; QAS, quaternary ammonium structure; RIA, radio immunoassay; RAST, radio allergosorbent test; ROC, receiver-operating characteristic; ROCU, rocuronium; ST, skin test; SUC, succinyl choline; SUX, suxamethonium.

*Applying ROC-generated drug-specific thresholds.

[†]For an ROC-generated threshold of 0.11 kUA/L for suxamethonium and 0.13 kUA/L for rocuronium.

[‡]For a traditional threshold of 0.35 kUA/L.

[§]For validation purposes, diagnosis of rocuronium allergy was considered definite when at least 2 out of 3 test results (ST, BAT, sIgE) were positive, because rocuronium challenges at full dose are not possible.

||“Optimized” morphine-based assay.

TABLE IV. BAT in immediate NMBA hypersensitivity

Stimulus	Reference test	Activation marker	Sensitivity (%)	Specificity (%)	N	Reference
Various NMBAs	H	CD63	64	81	26	⁹²
		CD45	43	96		
Various NMBAs	H ± ST	CD63	54	100	56	⁹³
Various NMBAs	H	CD63	79	100	31	⁹⁴
		CD203c	36	100		
Various NMBAs	H ± ST	CD63	36-86*	93	92	⁹⁵
Rocuronium	H ± ST	CD63	92 [†]	100	22	⁹⁶
Various NMBAs	H ± ST ± IgE	CD63	60	100	49	⁹⁷
Rocuronium	H + 2 tests [‡]	CD63	80	96	104	⁶⁹
Various NMBAs	H + ST	CD63	68	100	56	⁹⁸
Atracurium	H ± ST	CD63	71 [§]	100	75	⁹⁹

H, History; ST, skin test.

*Increasing sensitivity when only the reactions that occurred during the 3 y were taken into account.

[†]Taking into account the nonresponders sensitivity is 76%.

[‡]For validation purposes, diagnosis of rocuronium allergy was considered definite when at least 2 out of 3 test results (skin test, BAT, sIgE) were positive, because rocuronium challenges at full dose are not possible.

[§]Taking into account the nonresponders sensitivity is 63%.

patients for whom correct identification of the causative compound(s) is impeded because of simultaneous intake or administration of different agents, for example, during general anesthesia. Erroneous opiate allergy diagnosis might not only entail unnecessary avoidance measures but also, most importantly, ultimately put patients at risk by overlooking alternative diagnoses such as an allergy to rocuronium or suxamethonium. For the time being the sole *in vitro* method to document opiate

allergy is the BAT, because basophils from opiate-tolerant individuals, unlike their cutaneous mast cells, are unresponsive to opiates.^{104,105} Moreover, negative BAT results, along with negative skin test results for different NMBAs and negative provocation test results for the structurally almost similar opiates, suggest that these drugs are probably safe in pholcodine hypersensitivity.¹⁰⁵ Therefore, for opiates and semi-synthetic opioids we recommend to start with BAT, and, if the result is negative, a

DPT. In contrast, for synthetic opioids such as fentanyl, sufentanyl, and remifentanyl, diagnosis can start with skin testing eventually complemented with BAT and/or DPT for difficult cases.^{101,106}

CHLORHEXIDINE

Chlorhexidine, a cationic bisguanide antiseptic and disinfectant, is used as the (di)acetate or (di)glucuronide salt. These chlorhexidine salts can trigger irritant dermatitis, allergic contact dermatitis,¹⁰⁷ IDHR (including life-threatening anaphylaxis),¹⁰⁸⁻¹¹¹ and even a combination of both contact dermatitis and IDHR.¹¹² For a traditional arbitrarily chosen decision threshold of 0.35 kUA/L, the sensitivity of sIgE chlorhexidine varied between 84.2% and 91.6% and specificity between 93.7% and 100%. For a receiver-operating characteristic-generated threshold of 0.20 kUA/L, sensitivity was 94.1% and specificity 90.7%.^{110,111} As for β -lactam^{42,43,48} and NMBA,⁷⁰ raised total IgE levels were shown to have an impact on chlorhexidine sIgE measurement at levels higher than 500 kU/L and more particularly at levels higher than 2000 kU/L.¹¹¹ Recently, it was demonstrated that the optimal sampling time for sIgE chlorhexidine was between 1 and 4 months,¹¹³ but sIgE might persist for years.⁶⁶

LATEX

Another significant cause of anesthesia-related anaphylaxis is *Hevea* latex (*Hevea brasiliensis*). Diagnosis of latex allergy mainly relies on skin testing and/or various *in vitro* tests. However, correct diagnosis of IgE-mediated allergy to natural latex is not always straightforward, mainly because of the false-positive sIgE results,^{114,115} especially in patients suffering from grass and weed pollen allergy who are sensitized to cross-reactive carbohydrate determinants and/or profilin (*H brasiliensis*) 8.¹¹⁶⁻¹²⁰ Therefore, in a significant number of patients additional tests such as skin tests, component-resolved diagnosis,¹¹⁷⁻¹²⁰ and eventually BAT^{115,121-124} might be required to establish correct diagnosis. For a review on component-resolved diagnosis, the reader is referred elsewhere.¹²⁵

OTHER AGENTS

Bovine gelatin constitutes the active component in certain plasma substitutes and hemostatic sponges and can be present in various other drugs such as vaccines. Since the first descriptions of the allergenicity of gelatin,¹²⁶ IgE-mediated IHRs to this compound, including fatal anaphylaxis, have been increasingly reported. Today, 2 distinct types of IgE-mediated bovine gelatin allergy are recognized. First, genuine gelatin allergy that results from sensitization to the protein part of the molecule. Second, gelatin allergy resulting from a sensitization to a glycan moiety of the molecule, that is, galactose- α (1,3)-galactose,¹²⁷⁻¹²⁹ as first described by Chung et al¹³⁰ and Commins et al.¹³¹ To our knowledge, there are no studies that have determined the diagnostic accuracy of sIgE gelatin. However, it is of note that patients with life-threatening anaphylaxis to gelatin as a result of galactose- α (1,3)-galactose sensitization are generally overlooked by traditional gelatin-sIgE assay and need additional testing including quantification of galactose- α (1,3)-galactose sIgE antibodies and gelatin skin testing.¹²⁷⁻¹²⁹

DISCUSSION

Correct management of anaphylaxis during anesthesia requires a multidisciplinary approach with prompt recognition and treatment by the attending anesthesiologist, quantification of peak tryptase, and subsequent determination of the responsible agent(s) with strict avoidance of all incriminated and cross-reactive compounds. From this review it emerges that diagnosis of anaphylaxis during anesthesia is not always straightforward. It can be hindered because a broad spectrum of different drugs can elicit heterogeneous immune and nonimmune hypersensitivity reactions. Problems are certainly compounded as multiple drugs are administered simultaneously and drugs or compounds not related to anesthesia (eg, premedication, disinfection, antibiotic rinsing by surgeon, and lymph node mapping) can also be the cause of an IHR. Nevertheless, diagnostic workup should be offered to all patients with a clinical suspicion of anesthesia-related IHRs, irrespective of the grade of severity. Evaluation should comprise all agents the patient was exposed to and it should be kept in mind that a patient might demonstrate multiple sensitizations. In our own survey of more than 650 patients, double sensitization occurred in approximately 8% of the cases (A. Uyttendaele, PhD, unpublished data, 2017).

From this review it appears that drug chlorhexidine and latex-sIgE antibody testing can provide useful information but can rarely be applied as solitary diagnostic tests to exclude or document IHRs because they lack 100% predictive values. For β -lactam determinants, the main issue is poor sensitivity, which could not be increased without significant loss of specificity.⁴² For NMBA, drug sIgE tests seem to attain acceptable sensitivity and specificity, provided the application of drug-specific cutoffs.^{70,111} Although quantification of sIgE to morphine appears to be a reliable biomarker of sensitization to tertiary and quaternary ammonium structures, IgE reactivity to this compound in general and allergic population is as high as 5% to 10%. Therefore, the test should not be applied in isolation to diagnose IHRs to NMBA or opiates. With respect to the unsatisfactory sensitivity of some tests, it has been argued that this observation relates to the time interval elapsed between the acute reaction and testing. Although we agree that late testing can result in lower sensitivity, we do not adhere to the recommendation of the ENDA/EAACI Drug Allergy Interest Group. Based on a single publication about negatization of sIgE to β -lactams,⁴⁵ further use of drug sIgE is dissuaded when the time interval exceeds 3 years.⁶⁰ However, this is not our experience⁷⁷ and drug sIgE may persist as long as 5 to 30 years.^{61,91} With respect to the low specificity of some tests it is reemphasized that correct interpretation of sIgE results requires taking into account total IgE values.^{42,70,111} Whether the introduction of sIgE/total IgE ratios increases specificity⁴² remains to be confirmed. We currently do not apply these ratios.

Since the earliest days of the BAT it was obvious that this technique would become an asset in the allergological diagnostic instrumentation to document IHRs, particularly when diagnosis cannot be established by other means. Moreover, it is anticipated that BATs using "conditioned" basophils expressing the MRGPRX2 receptor might become an easily accessible instrument to study and diagnose IgE/Fc ϵ RI-independent IDHRs that result from off-target occupation of this receptor. However, additional collaborative large-scale studies are needed to verify whether the BAT fulfils this promise, to optimize and harmonize

the protocols, to avoid instigation of cynicism and scepticism, and to enable and justify its entrance in routine diagnostic application.

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