



Review

Serum specific IgE antibodies in immediate drug hypersensitivity

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ABSTRACT

Immediate drug hypersensitivity reactions (IDHRs) constitute a significant health problem that may be compounded by consequences of diagnostic error. In daily practice, IDHR diagnostic work up starts with drug-specific skin testing and/or quantification of specific IgE (sIgE) antibodies in serum. Here we critically review the performance, i.e. potential and limitations of sIgE to β -lactam antibiotics (β -LABs), curarizing neuromuscular blocking agents (NMBAs), opiates and (semi)synthetic opioids, fluoroquinolones (FQs), poppy seed (*papaver somniferum*), chlorhexidine and finally Hevea latex. Quintessence of these studies is clear. Quantification of these drug-specific sIgE should not be used in isolation to document or exclude diagnosis of an IDHR. False negative results entail the risk for subsequent potentially life-threatening anaphylaxis upon re-exposure. False positive results lead to erroneous avoidance and unnecessary substitutions and fails to identify the true etiology.

1. Introduction

Immediate drug hypersensitivity reactions (IDHRs) constitute a significant health problem. IDHRs can mechanistically be subdivided as immune (allergic), antibody mediated (mainly IgE) and nonimmune (nonallergic) when other mechanisms of mast cell and basophil activation are involved [1]. The gold standard to ascertain correct diagnosis of an IDHR is a controlled drug challenge test (DCT) with the culprit compound(s). However, DCTs entail a risk of severe, life-threatening complications and can be contraindicated (e.g., patients having suffered from life-threatening reactions) or impossible (e.g., full-dose DPT in hypersensitivity to curarizing neuromuscular blocking agents (NMBAs)). Therefore, in clinical practice diagnostic work-up of an IDHR generally starts with skin testing and/or quantification of drug-specific IgE (sIgE) antibodies. Detection of serum sIgE is traditionally performed using a solid-phase assay. However, only a limited number of drug-specific assays are available and many uncertainties remain about their diagnostic utility and performance. Hence, this review that will focus on sIgE for β -lactam antibiotics (β -LABs), substituted ammonium structures and NMBAs, opiates and (semi)synthetic opioids, fluoroquinolones (FQs) and poppy seed (*papaver somniferum*). Because many of these drugs are used in the perioperative period, at the

end of this review, the potential and limitations of sIgE to chlorhexidine, *Hevea* latex and its components are outlined.

2. β -lactam antibiotics (β -LABs)

As shown in Fig. 1, β -lactam antibiotics comprise penicillins (PCNs), cephalosporins (CPNs), monobactams and carbapenems. Common to all β -LABs, as indicated by the name, is the core four-membered β -lactam ring. The β -lactam ring in PCNs is connected to a five-membered thiazolidine ring, or penam, and the side chain, R, which differentiates the different PCNs. In CPNs, the β -lactam ring is bound to a six-membered dihydrothiazine ring, or cepham. Both PCNs and CPNs are distinct from the other β -LABs, carbapenems and monobactams. As shown in Table 1, sensitivity and specificity of sIgE assays for β -LAB vary significantly, between 0 and 85% and 52–100%, respectively. As the performance of a test might differ considerably from one β -LAB to another β -LAB, and because of different inclusion criteria, correct interpretation of sensitivity and specificity data from these studies is not always straightforward. Although, several cases of positive sIgE results in IDHRs with negative skin tests have been described [2–6], sIgE assays for β -LABs generally exhibit a (too) poor sensitivity that decreases over time [7,8]. Besides these disappointing sensitivity data, there is

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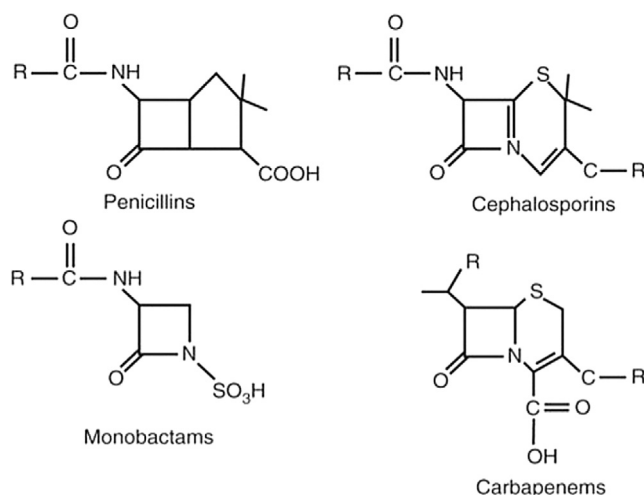


Fig. 1. Structure of β-lactam antibiotics.

increasing evidence supporting low specificity of the tests [3,5,9–12]. In some studies false positivity could have resulted from nonspecific binding in the solid phase assay as a result of elevated total IgE titres [10–13]. An alternative explanation for false-positive sIgE penicillin seems to be sIgE antibodies to phenylethylamine that test negative in a basophil activation test (BAT) [13]. The overall conclusion is inevitable, quantification of serum sIgE to β-LAB does not merit the status of primary diagnostic but should, like BATs, be considered as adjuncts to more performant skin testing. As a matter of fact, as recently proposed in an EAACI position paper [14], both *in vitro* tests, are mainly indicated in difficult cases with negative and/or equivocal skin testing in order to reduce the need for DCT. Whether the introduction of specific IgE over total IgE ratio's (sIgE/tIgE) - by reducing the number of clinically irrelevant results - benefits serological diagnosis of IgE-mediated β-LAB allergy in patients with elevated tIgE titres, remains to be established [8,11]. Alternatively, it should be kept in mind that sensitivity of confirmatory diagnostics for β-LAB allergy fade over time and might even become entirely negative [7,8].

3. Neuromuscular blocking agents (NMBAs)

In many countries, NMBAs are a predominant cause of anaesthesia-related anaphylaxis [15,16]. As indicated in recent guidelines and position papers [17,18], skin tests are the primary instrument to establish or discard diagnosis of NMBA hypersensitivity. However, the predictive value of skin testing is not absolute thereby leaving room for additional *in vitro* tests [19,20]. In the absence of commercially available assays, for over 2 decades, different groups have developed various home-made NMBA-sIgE assays to document sensitization to NMBAs. However, none of these techniques have entered the market. Today, sensitization to NMBAs is serologically assessed indirectly through quantification of IgE reactivity to tertiary and quaternary substituted ammonium structures that are known to be the major epitopes of NMBA [21,22]. As shown in Table 2, most frequently applied methods are a choline chloride, a p-aminophenyl phosphoryl choline (PAPPC) and/or morphine-based assays (only a morphine sIgE assay is currently commercially available). With respect to the ImmunoCAP FEIA for suxamethonium, rocuronium, atracurium and morphine the sensitivity and specificity for the individual NMBA-specific varies between 38.5–92% and 85.7–100%, respectively. Furthermore, it has been demonstrated that commercially available morphine assay reliably depicts suxamethonium and rocuronium-reactive antibodies but fails to detect atracurium-reactive antibodies [23,24]. Alternatively, quantifying IgE reactivity to substituted ammonium structures to identify patients at risk or to document NMBA hypersensitivity is not recommended [25,26] because of the large

numbers of clinically uncertain positive results found in the general population [24,27,28]. For example, Leysen *et al.* [26], showed that a positive sIgE to morphine is not a formal contraindication for subsequent administration of atracurium and cisatracurium in patients displaying negative skin test responses to these benzyliisoquinolines. Explanations for these false-positive sIgE results are elevated tIgE titres [24] and intake of the opiate antitussive pholcodine [29]. Unlike sIgE to β-LABs [7,8], sIgE antibodies to substituted ammonium epitopes generally remain positive for several years after the index reaction [25,30]. Whether, as recently anticipated by Spoerl *et al.* [31], anaphylaxis to NMBA such as rocuronium might occur independently from IgE but relate to off-target occupancy of the MRGPRX2 receptor expressed by mast cells [32] and, therefore, go undetected in sIgE assays remains unclear. Taken together, and as recommended in recent guidelines and position papers [17,18], the current policy is to offer sIgE (and BATs) to patients with negative or equivocal skin tests who suffered from severe perioperative anaphylaxis and in whom no alternative cause was demonstrable. Finally, it is of note that although sIgE to NMBA and substituted ammonium structures can be positive in patients who suffered from anaphylaxis to the sugammadex-rocuronium host-guest inclusion complex (S-R-Cx), these results cannot be diagnostic. As a matter of fact, it appears IgE recognition in such patients to involve structural changes at the primary rim of the reversal drug. Changes that occur independent from the guest [33].

4. Opiates and (semi-)synthetic opioids

Despite their widespread use, IgE-mediated allergies to opiates (morphine, codeine) and semi-synthetic opioid pholcodine remain rare [34]. Besides, correct diagnosis is not straightforward, mainly because of uncertainties associated with the results of drug-specific IgE antibodies and skin testing [35–37]. Recently, it has been proposed the sIgE assays for a *Papaver somniferum* (poppy seed) extract and morphine can benefit the diagnosis of IgE-mediated opiate allergy [38,39]. However, using graded DCT we were unable to confirm this enthusiasm, mainly because of the high prevalence of sIgE antibodies to poppy seed, morphine and pholcodine in an allergic population [24,37]. In other words, the sIgE assays poppy seed, morphine and pholcodine should not be used in isolation to diagnose IgE-mediated opiate hypersensitivity. Alternatively, opiates and the semisynthetic opioid pholcodine are well-known potent nonspecific histamine releasers [35,36], probably via binding of the MRGPRX2 receptor that is present on cutaneous mast cells [40]. These limitations of opiate sIgE assays and skin tests cannot be overemphasized. Actually, erroneous opiate allergy diagnosis not only entails unnecessary avoidance measures but, most importantly, ultimately might put patients at risk by nonidentification of the true culprit. For the time being it seems the BAT to be the sole reliable diagnostic for opiate allergy [37,41]. Therefore, for opiates and semi-synthetic opioids we recommend to start confirmatory diagnosis with BAT, and, if negative, and necessary, to perform a DCT. In contrast, for synthetic opioids such as fentanyl, sufentanyl and remifentanyl diagnosis can start with skin testing eventually complemented with BAT and/or DCT for difficult cases [17,18,34,35]. For a recent comprehensive review on DCT the reader is referred elsewhere [42].

5. Fluoroquinolones (FQ)

Quinolones are synthetic antibiotics based on the 4-quinolone and 1,8-naphthyridine nuclei. They can cause severe hypersensitivity reactions, even after first exposure, with moxifloxacin being an important culprit [43]. Immediate drug hypersensitivity reactions to FQ constitute a difficult pathomechanistic conundrum and pose a significant diagnostic challenge [44]. As a matter of fact, evidence has emerged a large majority, if not almost all, FQ IDHR to be independent of IgE but rather to result from off-target occupation of the MRGPRX2 receptor [32,45,46]. This alternative pathomechanism does not only explain the

Table 1
Specific IgE to β -lactam antibiotics (β -LABs) (actualised from [77]).

Compound(s)	Reference test	Assay	Sensitivity	Specificity	N°	Reference
Various β -LABs	H + ST	CAP-FEIA	BPO + AXO + peni G + AMP: 31.8%	BPO + AXO + peni G + AMP: 88.6%	58	[78]
Various β -LABs	H $\pm$ ST $\pm$ DCT	CAP-FEIA	BPO: 32% AXO: 43% BPO + AXO: 50%	BPO: 98% AXO: 98% BPO + AXO: 96%	129	[79]
Various β -LABs	H $\pm$ ST $\pm$ DCT	CAP-FEIA	BPO: 10–68% AXO: 41–53%	BPO: 98% AXO: 95%	410	[6]
Various β -LABs	H	CAP-FEIA	37.9%	86.7%	58	[80]
Various β -LABs ¹	H $\pm$ ST $\pm$ DCT	CAP-FEIA	0–25% ²	83.3–100% ²	45	[2]
		RAST ²	42.9–75% ²	66.7–83.3% ²		
Various β -LABs	H $\pm$ ST	CAP-FEIA	85% ³	54% ³	176	[11]
		CAP-FEIA	44% ⁴	80% ⁴		
Various β -LABs	H $\pm$ ST	CAP-FEIA	66%	52%	293	[12]
Amoxicillin	H + ST + DCT	CAP-FEIA	19%	NA	57	[81]
Cefazolin	H + ST $\pm$ DCT	CAP-FEIA	49% ⁵	94% ⁵	80	[8]

H: history, ST: skin test, DCT: drug challenge test, N°: number.

CAP-FEIA: fluorescence enzyme immunoassay available from Phadia Thermofisher. RAST: radio allerge sorbent test.

Peni G: penicillin G, AMP: ampicillin, BPO: benzyl penicilloyl, AXO: amoxicillin.

Note that there is no IgE for clavulanic acid available

¹ Home-made assay.

² Sensitivity and specificity vary according to clinical manifestations.

³ For a threshold of 0.10 kUA/L.

⁴ For a threshold of 0.35 kUA/L.

⁵ According to a sIgE/tIgE ratio of 1.42×10^{-3} (see text).

almost uselessness of FQ skin testing [47] (as seen with opiates that also act via this receptor) but also the poor sensitivity of BATs (for review: [48]) and home-made sIgE assays [49] for FQs. Accordingly, the European Network on Drug Allergy and European Academy of Allergy and Clinical Immunology Drug Allergy Interest Group has made no drug specific recommendations about skin testing with FQs [50] and use of the BAT in FQ hypersensitivity remains a controversial area [51].

6. 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 [52], IDHRs (including life-threatening anaphylaxis) [53–57] and even a combination of both, contact dermatitis and IDHR [58]. For a traditional arbitrarily chosen decision threshold of 0.35 kUA/L, the sensitivity of sIgE

Table 2
Specific IgE to NMBAs and substituted ammonium structures (adapted from [77]).

Compound	Reference test	Assay	Sensitivity	Specificity	N°	Reference
Various NMBAs	H $\pm$ ST	RIA	PAPPC: 97%	PAPPC: 97%	75	[82]
		RIA	MOR: 83%	NA		
		RIA	QAS: 86%	NA		
Various NMBAs	H + ST	RIA	QAS: 87.9%	NA	83	[83]
		RAST	SUC: 66.7%			
		RAST	Alcuronium: 40.7%			
Various NMBAs	H + ST	RIA	MOR: 85%	98%	118	[23]
		RIA	NMBA-specific: 52%			
Various NMBAs	H + ST	CAP-FEIA	SUXA: 38.5%	SUX: 96.3–99.6%	866	[28]
		CAP-FEIA	MOR: 67.7%			
Rocuronium ¹	H + ST	CAP-FEIA	SUXA: 72% ² SUXA: 60% ³ ROCU: 92% ² ROCU: 68% ³ MOR: 88% PHOL: 86%	MOR: 90–95% SUXA: 100% ² SUXA: 100% ³ ROCU: 93% ² ROCU: 93% ³ MOR: 100% PHOL: 100%	82	[24]
Rocuronium	H + 2 tests*	CAP-FEIA	ROCU: 83%	ROCU: 72%	66	[25]
Various NMBAs ¹	H + ST	CAP-FEIA	QAM ⁴ : 87.7%	QAM ⁴ : 90.7%	168	[27]
Atracurium ¹	H + ST	CAP-FEIA	SUXA: 28.6% ATRA: 57.1% MOR: 14.2%	SUXA: 85.7% ATRA: 100% MOR: 85.7%	78	[84]

H: history, ST: skin tests, RIA: radio immunoassay, RAST: radio allerge sorbent test, CAP-FEIA: fluorescence enzyme immunoassay available from Phadia Thermofisher (Uppsala, Sweden), PAPPC: p-aminophenyl phosphoryl choline, MOR: morphine, QAS: quaternary substituted ammonium structure, SUC: succinyl choline, SUX: suxamethonium, ROCU: rocuronium, QAM: quaternary ammonium morphine, ATRA: atracurium. N°: number. NA: not available.

* For validation purposes, diagnosis of rocuronium allergy was considered definite when at least 2 out of 3 tests (skin test, BAT, sIgE) were positive, as a rocuronium challenges at full dose is not possible for obvious ethical reasons.

¹ applying ROC-generated drug-specific thresholds,

² for a ROC-generated threshold of 0.11 kUA/L for suxamethonium and 0.13 kUA/L for rocuronium,

³ for a traditional threshold of 0.35 kUA/L.

⁴ “optimized” morphine-based assay

chlorhexidine varied between 84.2 and 91.6% and specificity between 93.7 and 100%. For a ROC-generated threshold of 0.20 kUA/L sensitivity was 94.1% and specificity 90.7% [55,56]. As for β -LABs [11–13] and NMBAs [24], elevated tIgE levels were shown to negatively affect specificity of chlorhexidine sIgE measurement [56]. Recently, it was demonstrated the optimal sampling time for sIgE chlorhexidine was between 1 and 4 months [59], but chlorhexidine sIgE might persist for years [60].

7. *Hevea latex*

Correct diagnosis of IgE-mediated *Hevea* latex allergy via quantification of latex-sIgE can pose significant difficulties. Results of latex-sIgE can be false-negative [61–63] or, much more frequently, false-positive, that is, clinically irrelevant [61–66]. The consequences of false-negative results are obvious, as these entail a risk for life-threatening anaphylaxis upon subsequent exposure. However, over-diagnosis by false-positive results can also have dramatic consequences. For example, during diagnostic work-up of perioperative anaphylaxis, clinical irrelevant results could erroneously lead to the diagnosis of IgE-mediated latex allergy and premature stopping of further testing for the true culprit. Besides, identification of clinically irrelevant latex-sensitization should prevent unnecessary and generally expensive latex avoidance measures. Therefore, because of the deceptive nature of anti-latex sIgE antibodies, latex-sIgE should not be used in isolation to diagnose IgE-mediated latex allergy. Today 15 components of latex from *Hevea brasiliensis* (Hev b) have been identified and successfully cloned (see: <http://www.allergen.org/search.php?allergen=latex>). Some of them have become available for single or multiplex molecular diagnosis of IgE-mediated latex allergy. As a matter of fact, the commercially available component-specific IgE assays for natural latex are non-glycosylated recombinant (r) Hev b 1, 3, 5, 6.01, 6.02, 8, 9 and 11. Particularly, rHev b 5 and 6 and in a lesser extent also rHev b 1 and 3 (both rubber particle-associated proteins) have been shown to be the most important biomarkers to diagnose genuine IgE-mediated latex allergy [67–71]. Sensitization to Hev b 5 and 6 is primarily found in adult health care workers (HCW) and to a lesser extent also in children suffering from spina bifida (SB) and meningomyelocele. In contrast, sensitization to *Hevea* profilin Hev b 8 (latex profilin) generally, but certainly not always, points to a clinical irrelevant cross-reactivity [66,72–76].

8. Discussion

From this review it emerges that correct interpretation of drug-specific IgE antibody results is not always straight forward. Although sIgE antibody testing can provide useful information, the technique can rarely be applied as a solitary diagnostic to document or exclude sensitization, mainly as they lack absolute predictive values. For β -LABs the main issue is poor sensitivity, which cannot be increased without significant loss of specificity. Alternatively, calculation of a sIgE/tIgE results might benefit specificity of the tests. For NMBAs (suxamethonium, rocuronium and atracurium), sIgE tests attain acceptable sensitivity and specificity, provided the application of drug-specific cut-offs. Quantification of sIgE to morphine appears to be a reliable biomarker to depict sensitization to rocuronium and suxamethonium but not for benzylisoquinolines such as atracurium and cisatracurium. IgE reactivity to morphine in general and allergic population is as high as 5–10%. Therefore, the test should not be applied in isolation to diagnose IDHR to NMBAs or opiates. Similarly, prudence is required when interpreting positive sIgE results for chlorhexidine and *Hevea* latex.

In conclusion, drugs and chlorhexidine sIgE assays do generally not merit the status of primary diagnostic, mainly because of low specificity. However, they can be used as an adjunct to confirm or discard diagnosis, especially when skin testing yield negative or unequivocal results. For *Hevea* latex, sIgE, together with skin testing, can be used as a first diagnostics approach but difficult cases might require additional

component resolved diagnosis to establish correct diagnosis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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