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The basophil activation test in the diagnosis of anaesthesia-related allergy

Tests d'activation des basophiles dans l'allergie peranesthésique

D.G. Ebo

*Department immunology, allergology, rheumatology, university hospital Antwerp, university Antwerp, Campus Drie Eiken,
Universiteitsplein 1, 2610 Antwerp, Belgium*

Abstract

This review intends to summarise on the application of the basophil activation test (BAT) in the diagnostic management of anaesthesia-related allergy. The BAT relies upon flow cytometric quantification of alterations of particular basophilic activation markers. In the context of anaesthesia-related allergy the technique has been applied and proven reliable to diagnose IgE-mediated allergy from drugs (e.g., neuromuscular blocking agents, β -lactam antibiotics), natural rubber latex, chlorhexidine, plasma expanders and dyes. Moreover, the technique has proven to be complementary to skin tests in the assessment of cross-reactivity and tailoring safe alternative regimens for future anaesthesia.

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Résumé

Le but de cet article est de faire le point sur l'utilisation du test d'activation des basophiles (TAB) par cytométrie en flux dans l'allergie en période péri-anesthésique. Cette analyse a été centrée sur les curarisants, les antibiotiques (en particulier, les pénicillines), le latex naturel, la chlorhexidine et les colloïdes. Ces études ont mis en évidence que le TAB est non seulement un instrument complémentaire et fiable pour confirmer le diagnostic, mais peut aussi contribuer à l'évaluation de la réactivité croisée et à l'identification d'alternatives sûres pour une anesthésie ultérieure.

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1. Introduction

Correct management of anaphylaxis during anaesthesia requires a multidisciplinary approach with prompt recognition and treatment of the acute event by the attending anaesthesiologist and subsequent determination of the responsible agent(s) with strict avoidance of subsequent administration of all incriminated and/or cross-reacting compounds [1–3]. Unfortunately, for several reasons, correct identification of the causative compound(s) and safe alternatives is not always straightforward. It can be hampered as a broad spectrum of different drugs that can elicit heterogeneous allergic and nonallergic reactions with distinct and sometimes unclear pathological mechanisms. Problems are certainly compounded as multiple drugs need to be administered (simultaneously)

during anaesthesia. Finally, none of the traditionally available tests, such as quantification of specific IgE (sIgE) and skin tests demonstrates absolute diagnostic accuracy. Consequently, novel reliable diagnostic tests would be more than welcome.

In recent years, the advent of specific monoclonal antibodies against different basophil activation markers and high-performant multicolour flow cytometers has resulted in the development of novel techniques to analyse and quantify in vitro allergen-specific activation of peripheral blood basophils. In this review the technique (basophil activation test: BAT) will be briefly discussed and its application in anaesthesia-related allergy summarised.

2. Principals of the basophil activation test

Upon encounter of specific allergens that crosslink membrane-bound IgE molecules, basophils not only secrete

E-mail address: immuno@ua.ac.be.

and generate a variety of quantifiable bioactive mediators, but also up-regulate the expression of different activation markers, such as CD63 and CD203c. These changes in phenotype can be detected on a single-cell basis by multicolour flow cytometry using specific monoclonal antibodies.

Currently, the technique proved reliable for the diagnosis of different IgE-mediated allergies including classical inhalant allergens (pollen, house dust mite), primary and secondary food allergies, hymenoptera venom allergy, drug allergies and *Hevea* latex allergy (for review: [4,5]).

3. Applications of the basophil activation test in anaesthesia-related allergy

3.1. Neuromuscular blocking agents

Currently, five studies have assessed the BAT test in allergy from neuromuscular blocking agents (NMBA) (Table 1, [6–10]). From these studies it appears the BAT to be a highly specific (over 90%) but less sensitive (36–92%) tool to diagnose allergy from NMBA. However, the lower sensitivity observed in different of these publications merits consideration. First of all, anaphylaxis from NMBA can be life-threatening. Therefore, it is critical to establish the most sensitive decision threshold. In our study we had the opportunity to enroll sufficient numbers of well-characterised rocuronium allergic and tolerant individuals, enabling precise calculation of the optimal discriminative cut-off value. In contrast, in the other publications, decision thresholds were set arbitrarily relative to spontaneous CD63 expression by nonactivated (resting) basophils. Second, optimal stimulation conditions might differ considerably from NMBA to NMBA [6], rendering the proposal to adopt a universal decision threshold for all NMBA difficult to justify and probably obsolete. Thirdly, it has been demonstrated sensitivity of the BAT to decrease dramatically over time elapsed from the acute event [9]. Alternatively, false-negative results might also be explained by recent exposure to the allergen with transient refractoriness of the cells and/or temporarily reduced levels of allergen-specific circulating and membrane-bound IgEs. Therefore, ideally testing should be carried out between six weeks and 12 months after the acute event.

From some of these studies [6,8,10] it also emerges that the BAT constitutes an additional tool that allows simultaneous

testing of different potential cross-reactive drugs and to tailor safe alternative regimens. In this context, it has demonstrated the BAT to be complementary to skin tests to identify cross-reactivity between the rocuronium and vecuronium [10], whereas IgE-inhibition is of limited value [11].

3.2. β -lactam antibiotics

The diagnostic approach for immediate allergic reactions to β -lactam antibiotics has recently been standardized under the aegis of the European Network for Drug Allergy and the European Academy of Allergy and Clinical Immunology interest group on drug hypersensitivity [12]. From this position paper it emerges that a considerable number of patients need drug provocation tests as quantification of sIgE and skin test yield equivocal, contradictory or negative results. At present, two studies have addressed the utility of the BAT in allergy from β -lactam antibiotics. In a comparative analysis between quantification of sIgE and basophilic CD63 expression, in 58 patients suffering from skin test proven β -lactam allergy and 30 healthy control individuals, sensitivity and specificity of the assays approximated 38% and 87% for sIgE and 50% and 94% for the BAT [13]. Almost similar sensitivity (49%) and specificity (91%) data were found in the study by Torres et al. [14].

3.3. *Hevea latex*

Application of the BAT in the diagnosis of *Hevea* latex allergy was first described by our group. In this study the BAT demonstrated a sensitivity of 93% and specificity of 92%, respectively [15]. Since several independent groups have confirmed the BAT to be highly reliable to diagnose IgE-mediated *Hevea* latex allergy with a sensitivity and specificity readily exceeding 90% [16–18]. In addition, it has been demonstrated that the BAT might be helpful in the discrimination between clinical relevant and irrelevant latex sIgE antibodies [15].

3.4. Miscellaneous

In isolated cases, the BAT helped to identify the plasma expander hydroxyl ethyl starch [19], cremophor (the emulsifier

Table 1
Basophil activation tests in allergy from NMBA

Stimulus	Reference test	Patients	Controls	Cut-off	Sensitivity (%)	Specificity (%)	Reference
NMBA ^a	H + IDT	21	14	15 (Arb)	64	93	[6]
NMBA ^a	H + IDT	39	10	10 (Arb)	54	100	[7]
NMBA ^a	H	14	10	10 (Arb)	79	100	[8]
					36 ^c	100 ^c	
NMBA ^a	H + IDT	47	45	15 (Arb)	36	93	[9]
					86		
Rocuronium	H + SPT/IDT	14	13 ^b	4 (ROC)	91.7	100	[10]

NMBA: neuromuscular blocking agents.

^a Heterogeneous composition of the patients with respect to offending NMBA.

^b Eight of the 13 control individuals had an uneventful exposure to rocuronium.

^c According to a CD203c-based assay. Arb: arbitrarily set threshold; ROC: Receiver operating curve analysis.

of the intravenous cyclosporine formulation [20]), the anti-septic chlorhexidine [21], the dye patent blue [22], the topical applied antibiotic rifamycin SV [23] and the plasma expander gelatin [24] as offending agent in patients with sometimes life-threatening allergic reactions. Moreover, in some of these patients the BAT allowed to identify potential cross-reactive compounds and contributed to establish the individual therapeutic alternative.

4. Conclusion and perspectives

It is clear that the BAT provides the physician with a novel diagnostic instrument in the diagnosis of anaesthesia-related allergy that generally results from drugs or related compounds, particularly in those cases where traditional tests are unavailable or yield equivocal and/or negative results. However, additional comprehensive studies are mandatory to further validate the technique and allow entrance of the BAT in mainstream diagnostic use. As emerges from the studies on NMBA, a critical issue will be the accurate inclusion of well-identified patient and relevant control groups in order to establish optimal drug-specific decision thresholds and abandon predefined and rather arbitrarily chosen cut-offs for determination of sensitivity, specificity and predictive values.

Finally, it is appreciated that the BAT can also constitute a complementary tool to identify potential cross-reactive compounds and to tailor the individual therapeutic safe alternatives.

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