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The basophil activation tests in drug allergy

Le test d'activation de basophiles dans l'allergie médicamenteuse

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Abstract

This review intends to summarize the application of the basophil activation test (BAT) in the diagnostic management of drug allergy. The BAT relies upon flow cytometric quantification of alterations of particular basophilic activation markers. In the context of drug allergy the BAT has been proven reliable to diagnose allergy from neuromuscular blocking agents, β -lactam antibiotics, 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. © 2011 Elsevier Masson SAS. All rights reserved.

Keywords: Drug; CD63; CD203c; Allergy; Flow cytometry; Basophil activation test (BAT)

Résumé

Le but de cet article est de faire le point sur l'utilisation du test d'activation de basophiles (TAB) par cytométrie en flux dans l'allergie médicamenteuse. Cette étude a été centrée sur les curarisants, les antibiotiques (en particulier, les pénicillines), 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. © 2011 Elsevier Masson SAS. Tous droits réservés.

Mots clés : Médicament ; CD63 ; CD203c ; Allergie ; Cytométrie en flux ; Test d'activation de basophiles (TAB)

1. Introduction

Although the drug provocation tests (DPT) are regarded as “the gold standard” to establish or exclude the presence of hypersensitivity to a certain drug, DPT are hampered by obvious ethical and practical issues and are therefore not suitable for routine clinical practice. By consequence, physicians generally rely upon skin tests, quantification of specific IgE antibodies (sIgE) and basophil release tests to confirm their clinical suspicion. However, neither skin tests nor quantification of sIgE (if available) demonstrate an absolute predictive value and there is certainly room for novel diagnostic instruments. Flow cytometry is a useful tool for the analysis of different cellular types and can be used to identify different cell populations, even basophils, who present less than 0.5% of the total number of leukocytes in the peripheral blood. The

basophil activation test (BAT) relies on flow cytometric identification and quantification of alterations of specific activation markers on the surface-membrane or inside the basophils. These changes can be detected and quantified on a single-cell basis using specific monoclonal antibodies coupled to particular fluorochromes. Practically, basophils are identified by specific markers such as CCR3 $\pm$ /CD3 $\pm$, CD123 $\pm$ /HLA-DR $\pm$, IgE $\pm$ /CD203c $\pm$. Of these markers only CD203c is lineage specific. In a second step, the up-regulation of specific activation markers such as CD63 and CD203c is quantified. Activation of basophils can also be measured by means of phosphorylation of intracellular molecules (e.g. mitogen-activated-protein-kinase [p38MAPK]).

2. Applications

At this moment, the BAT proved reliable for the diagnosis of IgE-mediated allergies including aeroallergens, food, hymenoptera venom and Hevea latex. In the context of diagnosis of

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drug allergy, BAT has been validated for neuromuscular blocking agents (NMBAs), β -lactam antibiotics and clavulanic acid as β -lactamase inhibitor, iodinated contrast media, the antiseptic chlorhexidine, gelatine-based plasma expanders and the infusion-excipient carboxymethylcellulose. An important observation from these studies is the fact that chemicals, such as drugs, elicit less-pronounced in vitro basophil activation, compared to protein allergens such as inhalant- and food allergens.

2.1. NMBA

NMBA remain the most common cause of adverse reactions during general anaesthesia. Most of these reactions are immediate type reactions and are induced by an IgE-mediated allergic response or a nonspecific histamine release. Although skin tests represent a primary tool for diagnosing these reactions, the BAT has proved to be particularly relevant in cases where skin tests yield equivocal or negative results. It appears that the BAT NMBA is highly specific but not very sensitive. However, the low sensitivity could relate to the arbitrarily chosen decision thresholds. Variations in sensitivity can also reflect differences in timing between the reaction and the performance of diagnostic test, difference in applied drug concentrations and in selection of patients/controls.

Alternatively, the basophil activation test is useful in the identification of cross-reactivity, which occurs more frequently in the aminosteroid-derived than in the benzylisoquinolone-derived NMBA. Moreover, the BAT is complementary to skin tests in detecting cross-reactivity between NMBA.

Recently we applied BAT to demonstrate that sugammadex, a compound that selectively encapsulates the NMBA rocuronium, does probably not mitigate rocuronium-induced anaphylaxis.

2.2. β -lactam antibiotics

Diagnosis of allergy to β -lactam antibiotics generally relies upon skin testing and quantification of sIgE antibodies. However, in particular cases novel instruments such as the BAT are gaining importance. There are currently five studies

that have evaluated the BAT in the diagnosis of β -lactam allergy. As for NMBA the BAT appears to be highly specific but not very sensitive.

2.3. Aspirin and NSAID

Hypersensitivity reactions to NSAIDs are very common. The majority of these reactions are not IgE-mediated but result from inhibition of COX-1, which leads to a depletion of prostaglandin E2 with unstrained synthesis of cysteinyl leukotrienes and mediator release from basophils, mast cells and eosinophils. Patients suffering from this type of reaction are clinically presenting with respiratory and cutaneous reactions and react to different NSAID. By consequence, in most patients BAT will not be useful to document "hypersensitivity" to NSAID.

3. Conclusion

It is obvious that the BAT provides the physician with a new instrument to diagnose drug allergy, particularly IgE-mediated reactions. However, additional comprehensive studies are mandatory before the BAT can enter mainstream use. In these studies it will be imperative to include well-characterised patients and (exposed) control individuals and abandon arbitrarily set decision thresholds. Moreover, it is anticipated that the optimal stimulation conditions will vary from drug to drug. Whether the BAT might further improve from application of novel (or combinations of) identification and activation markers remains to be established.

Conflict of interest statement

The author has not declared any conflict of interest.

Further reading

Ebo DG, Hagendorens MM, Bridts CH, De Clerck LS, Stevens WJ. The basophil activation test in immediate drug allergy. *Acta Clin Belg*– 2009;64(2):129-35. PubMed PMID: 19432025.