

ALLERGY PRACTICE FORUM

Allergen extracts. Standardization of preparations for bronchial provocation tests. A position paper

L. FRØLUND, S. BONINI, G. COCCO, R. J. DAVIES, J. G. R. DE MONCHY, G. MELILLO and R. PAUWELS (EAACI Sub-committee on Bronchial Provocation Tests)

Pulmonary Department Y, KAS Gentofte, Hellerup, Denmark

Summary

Standardization of allergen provocation tests of the airways requires standardization of each of the steps involved, including standardization of the extracts used. The value of international standards is emphasized and so is the determination of a clinically relevant potency. The allergen extracts used for bronchial provocation tests must be compared with qualitatively and quantitatively clinically relevant standards using complementary immunochemical and biological methods. Ideally the same extracts should be used for diagnosis (skin test, specific IgE determinations, provocations) and treatment (immunotherapy). The importance of the biological compared with the non-biological methods is that the biological methods are established in allergenic patients in order to select a clinically relevant potency of the allergen in question, and this potency ought to be confirmed in clinical trials. Once established the biological potency of an in-house preparation can be reproduced by supplementary *in vitro* methods. Very few commercial allergen preparations are available which fulfil the above-mentioned criteria.

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Introduction

Standardization of allergenic extracts has been required from clinical allergists in order to improve the precision of results as well as the safety of the diagnostic procedures. This monograph is addressed to physicians dealing with provocation tests of the airways with allergens, and calls attention to the *in vitro* and *in vivo* techniques commonly used to characterize and standardize allergenic extracts as recent advances have been achieved in this respect and international standards have been introduced. At present no consensus recommendations on the subject exist.

Since 1873 bronchial allergen provocation has been used to evaluate the relevance of a specific allergen in patients suspected of suffering from extrinsic asthma, although the test in itself does not diagnose asthma. In recent years, the provocation tests have been employed in the investigation of the pathogenesis of allergic asthma and the protective effect of various medications [1]. Despite their widespread use, only during the last 10 years

have the procedures been standardized and the reproducibility determined [2], just as well-characterized and standardized allergen extracts have become available.

Allergy results from immunological reactions and the active moieties have to be identified amongst immunogenic molecules which are mainly proteins. Only those compounds which are extractable under natural conditions when meeting the host's mucosa will act as potential sensitizers. Allergens, causing Type I allergy, are defined as molecules which specifically bind IgE in at least one serum from a group of humans with clinical symptoms of allergy towards the specific allergen source. All antigenic components may be regarded as potential allergens.

In general the search for potential allergens can be reduced to the proteins extracted by aqueous solution, simulating physiological conditions of ionic strength and pH [3]. Allergenic extracts derived under such conditions are a complicated mixture of antigenic components, and the number of detectable antigens varies and may be underestimated due to the limited sensitivity of the analysis performed [3,4]. All potential allergenic sources

Correspondence: Dr L. Frølund, Pulmonary Department Y, KAS Gentofte, Niels Andersenvej 65, DK 2900 Hellerup, Denmark.

standardization of procedures is essential and, as several factors influence the response and thereby the interpretation, each factor must be described and controlled. The technical and methodological factors include preparation and storage of test solutions, aerosol generation and inhalation, measurement of response and expression of the results. The non-technical factors include patient characteristics such as baseline airway caliber, bronchial hyperresponsiveness to non-specific agents (histamine, methacholine), reaction to skin-prick test with allergens, medication, environment factors and medical diseases.

The allergen extracts used for diagnostic tests, as well as in treatment, must be compared with qualitatively and quantitatively clinically relevant standards, using a combination of complementary immunochemical and biological methods. Clinical accuracy and reliability depend on the quality of standardization procedures, i.e. the combination and number of tests applied and the quality of every single test performed. Clinical safety and efficacy depend not only on the quality of standardization but also on the applied potencies. Standardization using biological methods is established in allergic patients in order to select a clinically relevant potency of the allergen in question and this potency is confirmed in clinical trials later on. The AU and BU are biological units, although not directly comparable, reflecting a biological equilibration of reference preparations on selected patient material. The advantages of extracts labelled in standardized units are that they are generally very consistent from batch to batch. Very few commercial allergen preparations are available which fulfil the above-mentioned criteria.

Standardization is a pre-requisite for the improvement of allergy diagnosis and treatment, but standardization must be followed by clinical documentation in order to establish the optimal dose and regimens for both diagnostic and therapeutic purposes.

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