

Scientific Summary

Potential drug allergic reactions are frequently encountered by healthcare professionals. Confirming drug hypersensitivity can be difficult. Clinical history over-estimates the diagnosis and skin testing has low sensitivity, this leaves drug provocation tests as the gold standard; however, re-exposing patients is not without risk. Issues relating to incorrect patient reporting and loss of sensitivity over-time can lead to the unnecessary avoidance of certain drugs and sub-optimal treatment. There is a general consensus on the need for biological tests to establish the nature of culprit agents and to predict immunogenicity.

The immune responses involved in drug allergy are now better understood. As a result there are a growing number of laboratory tests that are capable of evaluating the response to a drug from the blood of an individual thus avoiding the risk of re-exposing them. Most of these tests are performed at a time of clinical stability after the reaction; however, some can be performed at the time of the reaction to confirm that an allergic process is taking place.

In this review we evaluate the evidence for these traditional investigations. In addition we explore modern techniques and the role they may play in future clinical care. This includes discussions about newer drug classes, for example biological agents.

In vitro diagnostic tests can be useful for the evaluation of mediators released during the acute phase of the reaction and for identification of the culprit drug after resolution. The in vitro test used for the diagnosis will depend on the mechanism involved (allergic reactions or non-allergic reactions) and reaction kinetics (immediate or IgE-mediated reactions and non-immediate or T-cells mediated) and the drug involved in the reaction.

For immediate reactions, specific IgE determination has variable sensitivity depending on the responsible drug and is only available for a limited number of drugs. Newer functional assays measuring basophil activation, either through measurement of mediator release (histamine/CysLT) or by phenotypic changes (CD63/CD203c), show promise but require further standardisation and validation.

Non-immediate reactions are more heterogeneous with different cellular and immunological mediator involved. Nowadays, there are no commercial
assays for these T cell mediated reactions. The lymphocyte transformation test (LTT) has a higher sensitivity than skin testing in evaluating some drugs but it is difficult to perform with wide variations between centres. As well as new approaches to improve the LTT, other assays measuring cell activation, such as ELISpot, cell activation markers (CD69), and cytokine release, are currently being evaluated.

Non-allergic hypersensitivity, especially to NSAID, has been evaluated with different cellular tests with heterogeneous results highlighting the need of further studies focusing on the better understanding of the pathogenesis of cross-reactive hypersensitivity to NSAIDs. Different drugs bring different challenges and how we apply these assays to individual drug classes continue to be studied. In the near future it is hoped that certain assays, or perhaps combinations of assays, will be validated in large populations in well characterised populations and will provide a basis to accurately characterise hypersensitive individuals without the need for re-exposure to the drug and hopefully lead to commercial systems that are standardised across countries.

Drug hypersensitivity reactions (DHR) are an increasing public health problem in developed countries, with a substantial proportion of the population labelled as being drug allergic but with no confirmation. This diagnosis results in the use of different therapeutic alternatives that are not the first-choice option, with a higher proportion of adverse effects, more expensive treatment and which, in the case of antibiotics, increase bacterial resistance. Thus, a correct diagnosis is critical given that fewer than 30% of those initially considered allergic are in fact really allergic.

DHR can be immune mediated (drug allergy), either IgE mediated or T-cell dependent, or non-immune mediated, with each type requiring different diagnostic approaches. The diagnosis of DHR has not been appropriately addressed, resulting in potentially serious consequences of diagnostic error. The correct diagnosis is made difficult for many reasons: different drugs can elicit various DHR with a distinct pathophysiology; the lack of knowledge of the exact epitope causing the DHR; the imputability is difficult to assess when several drugs are administered simultaneously; skin tests have low sensitivity with many drugs; the drug provocation test (DPT), considered the gold standard for diagnosis, is time consuming and hampered by ethical and practical limitations, especially in patients with severe clinical symptoms; and, finally, as new drugs such as biologicals appear novel patterns of DHR might be observed and further hamper the diagnostic
process. There is therefore an increasing demand for validated in vitro diagnostic tests. These tests have the advantages of being less time consuming for the patient, they can be done in high risk cases and in those with cutaneous diseases, and they do not interfere with different treatments. However, important confusion exists regarding the validation of the methods and there is a lack of guidelines and recommendations.

The in vitro tests currently available for diagnosis (fluoroenzymeimmunoassay and basophil activation tests) are mainly directed to immediate reactions; however, their sensitivity is low and there is no great consensus about their use. It has not been established when to use these tests or even if they can substitute the skin test or DPT. Regarding delayed reactions, the panorama is even more confused and there is no validated in vitro test, with the lymphocyte transformation test being the most used. The aim of the task force is to review the literature and data on the state of the art for all available in vitro tests, data from the experience of the participant groups, evaluate the grade of evidence to support the proposed methods, and publish the results.

The main goal was to collect data from the literature and group’s own experience about in vitro diagnostic tests for immediate and delayed DHR.

The outcomes and benefits for EAACI are:
1. Rostrum paper addressing the state of the art of in vitro diagnostic methods in DHR, supported by the literature or the group’s own experience.
2. Position paper with guidelines about the best validated methods employed in DHR according to the literature and standardized in the multicenter study.