Optimizing diagnosis in drug hypersensitivity

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Marie-Line M. van der Poorten, MD, PhD[1,2]

Promotors: Didier G. Ebo, MD, PhD[1], prof. dr. Vito Sabato MD, PhD[1], prof. dr. Margo Hagendorens, MD, PhD[1,2]
Co-promoter: Jessy Elst, PhD[1]

[1] Faculty of Medicine and Health Science, Department of Immunology – Allergology – Rheumatology, Antwerp University Hospital and the Infla-Med Centre of Excellence, University of Antwerp, Antwerp, Belgium.
[2] Faculty of Medicine and Health Science, Department of Paediatrics, University of Antwerp, Antwerp University Hospital, Antwerp, Belgium.

marie-line.vanderpoorten@uantwerpen.be

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Abstract

Drug hypersensitivity reactions constitute an important and increasing health problem with significant morbidity and mortality, associated with both over- and underdiagnosis.

Given the dramatic impact of mislabelling, correct diagnosis is of utmost importance. However, this is not always straightforward, since the available diagnostic tests each carry their own limitations.

Hence this thesis, which aimed to optimize the diagnosis of drug hypersensitivity. In a first objective, the cut-off of specific IgE quantification and potential of a specific-to-total IgE ratio was investigated. Next, we looked at the non-irritant concentrations of skin tests. In the third objective, we objectified the need for drug provocation tests with anaesthetic drugs. Finally, the optimal timing of testing was investigated.

Drug hypersensitivity reactions (DHRs) constitute an important and increasing health problem with significant morbidity and mortality because of misdiagnosis. On the one hand, underdiagnoses carries the risk for re-exposure resulting in life threatening reactions. On the other hand, overdiagnosis, in particular self-reported non-verified allergy comprises severe consequences for the individual patient as well as society. Actually, the false label of a drug allergy is associated with erroneous avoidance and unnecessary substitutions, readmissions, poorer outcomes, prolonged hospitalizations, increased costs and, in case of antibiotic agents, increased rates of antimicrobial resistance. [1-3]

Given the serious, sometimes dramatic impact of mislabelling, it becomes clear that getting the label right is of utmost importance. However, this is not always straightforward.

Diagnosis of immediate drug hypersensitivity generally starts with an in-depth clinical history, followed by skin tests and quantification of specific IgE antibodies. However, no tests are absolutely predictive, each carrying their own limitations.

First, the quantification of specific IgE antibodies displays varying sensitivity and specificity, as shown in our in depth review concerning specific IgEs in the first part of this thesis. [4]

Hence one of the main aims of this thesis was to optimize the performance of these tests.

In the context of rocuronium allergy, we showed that a specific-to-total IgE ratio for rocuronium, pholcodine and morphine did not benefit diagnosis. Whether application of such ratios would benefit diagnosis of other drug allergies, remains an interesting area of research.[5]

In the context of a suspected penicillin allergy, our data show that diagnosis of a non-severe penicillin allergy should not rest upon low specific IgE results between 0.10 and 0.35 kUA/L. We propose an amended algorithm for the diagnosis of beta-lactam hypersensitivity, in which all these patients should be offered a drug provocation tests to confirm or refute diagnosis. [6]

Second, skin testing might be unreliable, such as in patients with cutaneous anergy, dermographism or in patients using antihistamines. Moreover, for many the drugs, the maximal non-irritant concentrations have not been established, entailing a risk for over- and underdiagnosis if set too high or too low respectively.

Hence the second main aim of this thesis: optimizing non-irritant concentrations in drugs in which they have not yet been validated. We chose to do this in populations that relate as closely to clinical practice as possible, that is actual beta-lactam allergic patients instead of healthy controls. Here we show for the non-irritant concentrations for immediate readings for ceftazidime to be a tenfold higher than recommended at the start of this thesis. Moreover, for aztreonam and ceftaroline, we are the first study to propose a non-irritant concentration supported by robust research. We are the first study propose different non-irritant concentrations for immediate and non-immediate hypersensitivity reactions respectively. This shows that non-irritant concentrations should not be generalised and that there is a need to further establish drug-specific non-irritant concentrations in a population representing clinical practise.[7, 8]

A third problem in drug hypersensitivity diagnosis, relates to the absence of a reference test in perioperative hypersensitivity. Indeed, where the drug provocation test is considered the gold standard in allergy diagnosis, it has not been recommended in perioperative hypersensitivity reactions, mainly because of the profound effects of anaesthetic drugs. Hence our objective to explore the need for provocation tests with hypnotics, opioids and neuromuscular blocking agents. By examining re-exposures during subsequent anaesthesia after allergic work-up, we concluded that provocation tests with anaesthetic drugs are not systematically warranted nor absolutely critical for correct diagnosis patients with a suspected perioperative hypersensitivity reaction. [9]

Lastly, we performed research examining the optimal timing of testing for drug hypersensitivity. In this study, which was deemed a practice changer by the American Academy of Allergy, Asthma and Immunology, we challenges the dogma to postpone diagnostic work-up for suspected perioperative hypersensitivity for at least 4-6 weeks. When needed, such as in case of urgent re-intervention, early testing should not be excluded.

Moreover, we refute the too generic recommendation that in vitro testing should never be performed more than 3 years after the index reaction.[10]

In conclusion, this dissertation covers unprecedented research, with each individual study adding to the big picture of drug hypersensitivity diagnosis. Our data have contributed to clinical practice, with value to both the scientific society and the individual patients.

Of course, there is still room for improvement and further efforts are required to optimise the diagnostic approach in drug hypersensitivity.

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