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British Journal of Anaesthesia, 125 (6): 856–859 (2020)
doi: 10.1016/j.bja.2020.08.044
Advance Access Publication Date: 26 September 2020

Mast cell activation tests: a new tool in the investigation of suspected perioperative allergic reactions?

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This editorial accompanies: Mast cell activation test in chlorhexidine allergy: a proof of concept by Elst et al., *Br J Anaesth* 2020:125: 970–975, doi: 10.1016/j.bja.2020.06.024

Keywords: diagnostic tests; drug hypersensitivity; immediate hypersensitivity; immunoglobulin E; mast cells; perioperative; sensitivity; specificity

With deaths attributable to anaesthesia estimated to range from 1:125 000 to 1:180 000 anaesthetics,[1–3] there has been focus on the development of safety management systems to prevent avoidable deaths.[4,5] If we want to continue to improve anaesthesia outcomes and safety, then we must also focus on the diagnosis and treatment of rare, but potentially life-threatening perioperative events that account for an increasing proportion of adverse outcomes.[6] In this regard, immediate hypersensitivity reactions remain a major concern for anaesthesiologists with a mortality of ~4%.[7,8] In this issue of the *British Journal of Anaesthesia*, Elst and

DOI of original article: 10.1016/j.bja.2020.06.024.

colleagues[9] provide proof of concept for the application of mast cell activation tests in drug allergy testing. To appreciate the relevance of this interesting development, it is important to understand the limitations of currently available tests for drug allergy, especially in the context of suspected perioperative drug allergy.

The gold standard test for diagnosis of drug allergy is a double-blind placebo-controlled drug provocation test, in which increasing doses of drug or placebo are administered. Although identification of the culprit drug in an immediate perioperative hypersensitivity reaction is essential to avoid a potentially life-threatening re-exposure to the responsible drug, provocation tests have mostly not been recommended in the investigation of perioperative allergy, mainly because of the resources required to manage the pharmacological effects of drugs, such as induction agents and neuromuscular blocking agents.[10] In addition, provocation tests are not devoid of risk because of their potential for inducing a severe systemic reaction. Even if they are regarded as a gold standard, their predictive value is not absolute.[11] At present, their use appears limited to some experienced centres with doses limited to subtherapeutic levels[10]: the impact on the sensitivity of the challenge test of not progressing to the full therapeutic dose remains to be defined. Therefore, immunoglobulin E (IgE)-mediated hypersensitivity reactions are usually diagnosed using skin tests or detection of allergen-specific IgE to the incriminated drug.[12]

Although a positive skin test may reveal a sensitisation, it does not always correlate with clinical reactivity.[13] Skin test concentrations are usually defined based on an expert consensus,[12] rather than on systematic investigation of skin reactivity to increasing concentrations of a drug in healthy subjects.[14] They are not always possible in case of irritant drugs or abnormal skin reactivity of the patient, and false-positive or negative results can occur.[15] *In vitro* detection of allergen-specific IgE may be of diagnostic value for a limited number of drugs.[16,17] The diagnostic value is influenced by the prevalence of sensitisation in the population studied,[18,19] and may decrease with time depending on the specific drug.[20,21]

The necessity to avoid potentially life-threatening re-exposure and unnecessary exclusion of a drug explains the increasing interest in the development of more accurate tests to diagnose drug allergy and in particular assays of effector cells. This interest originally focused on the histamine release assay performed on whole blood.[22] To overcome technical difficulties and to improve the diagnostic accuracy of cellular tests, alternative strategies using a sulfidoleukotriene release assay on leucocytes (CAST® ELISA)[23] and basophil activation tests (BATs) using flow cytometry have been developed.[24,25]

The BAT is a functional assay that measures the ability to induce activation of basophils in the presence of a suspected allergen by detecting expression of CD203c or CD63.[26] The BAT is gaining in popularity for diagnosis of drug allergy with improved flow-cytometry data analysis and development of commercially available kits. However, 5–10% of individuals have non-responding basophils, in which no upregulation of CD203c or CD63 expression occurs in response to IgE-mediated allergen stimulation.[26]

Hypersensitivity reactions can also result from a non-IgE-mediated mechanism.[27] It is estimated that ~15% of drug-induced hypersensitivity reactions[28] and ~40% of reactions occurring in the operating theatre are not related to an IgE mechanism.[29] Allergen-specific IgG antibodies have been proposed to contribute when the allergen is an abundant circulating large molecule (e.g. therapeutic antibodies or dextran). There is evidence that a similar mechanism might be involved through an IgG–neutrophil pathway with small molecules, such as neuromuscular blocking agents.[30] Non-allergic or pseudo-allergic reactions may also occur. This has led to the recent discovery of the involvement of the MRGPRX2 receptor, found on the surface of mast cells, in drug-induced non-IgE-mediated reactions.[31]

The mechanism of hypersensitivity reactions to drugs, particularly during the perioperative period, but also the mechanism of sensitisation to small molecules remain debated. If peptidergic antigen processing seems well established, this is not the case concerning drug sensitisation. Several mechanisms, including the hapten model, the p-i concept (direct pharmacological interaction of drugs with immune receptors), the altered peptide repertoire model, and the altered T-cell receptor repertoire model have been proposed to explain drug interactions between antigen-presenting cells and T cells.[32,33] This emphasises that new tools are required to investigate the mechanisms and nature of sensitisation and of hypersensitivity reactions, which can differ between proteins and small molecules.

The limitations of BATs and the search for a better understanding of the mechanisms of hypersensitivity reactions have led to development of new cellular assays based on mast cell activation. This idea was initially successfully applied to the study of sensitisation to peptidergic allergens.[34] Elst and colleagues[9] now show that this approach can also be applied to the study of immediate hypersensitivity reactions to small molecules (i.e. haptens). The choice of chlorhexidine as allergen in this proof-of-concept study is highly relevant to perioperative reactions.[35,36] Although Elst and colleagues focused on IgE-mediated allergic reactions using a form of passive sensitisation of mastocytes derived from *in vitro* culture of CD34+ circulating progenitor cells from patients suspected to be allergic to chlorhexidine, the technique could have broader applications, such as identifying the drugs responsible for direct activation of mast cells, especially in the case of direct activation of the MRGPRX2 receptor, for example.

However, there is far to go from this proof-of-concept to routine clinical use. One of the problems in the field is attempted validation of tests by comparing results with other imperfect tests, and we have described problems with each of the existing tests. The approach used by Elst and colleagues[9] was to select positive control patients on the basis that they had positive results in two different tests for chlorhexidine sensitivity. This will improve accuracy of diagnosis if erroneous test results are random errors of mechanistically independent tests, but not if some patients are biologically susceptible to systematic errors in tests that are mechanistically related. Comparison of the proposed mast cell activation test with results of other tests is not such an issue in the proof-of-concept stage, but it will become relevant in further evaluation of the test accuracy. Therefore, this test and current tests need to be evaluated independently of other test results, for example, by using cases where the clinical features meet consensus criteria for an 'almost certain' diagnosis of hypersensitivity to chlorhexidine.[37] Another consideration is the source of mast cells. The technique proposed by Elst and colleagues requires production of mast cells derived from progenitors collected from the patient. Such cultures cannot be maintained over time, with new samples required for each assay. This makes the technique time consuming and expensive, and makes it difficult to standardise a test for

clinical use. The use of an immortalised mast cell line expressing a fully functional IgE receptor could possibly provide an alternative approach.[38]

There is no ideal diagnostic test for patients with a suspected perioperative allergic reaction, and much remains to be done before diagnostic testing is optimised. This includes improved standardisation and estimates of the accuracy of current tests, which will require multicentre collaboration. An improved understanding of the mechanisms underlying immediate hypersensitivity reactions to small molecules may lead to tests that supersede those currently available. The work of Elst and colleagues[9] is potentially an important step forward in the exploration of these reactions in a clinical research setting, and may indeed ultimately translate into a clinically valuable diagnostic test.

Authors' contributions

Both authors conceived, drafted, reviewed, and revised drafts of the paper and approved the final version.

Declarations of interest

PMH is a member of the editorial board of the *British Journal of Anaesthesia*. P-MM is the scientific advisor for the Allergy to Neuromuscular Blocking Agents and Pholcodine Exposure study (NCT02250729), funded by a consortium of pharmaceutical companies: Zambon, Urgo, Pierre Fabre, Boots, Hepatoum, Biocodex, Sanofi, LBR, GSK, APL, Bell's Healthcare, Pinewood, T & R, and Ernest Jackson.

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British Journal of Anaesthesia, 125 (6): 859–862 (2020)
doi: 10.1016/j.bja.2020.08.046
Advance Access Publication Date: 18 September 2020

Perioperative genetic screening: entering a new era

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This editorial accompanies: Genetic mutations associated with susceptibility to perioperative complications in a longitudinal biorepository with integrated genomic and electronic health records by Douville et al., *Br J Anaesth* 2020:125: 986–994, doi: 10.1016/j.bja.2020.08.009

Keywords: butyrylcholinesterase; Factor V Leiden; malignant hyperthermia; perioperative genetic screening; personalised medicine; pharmacogenomics

Malignant hyperthermia (MH) and butyrylcholinesterase (BCHE, pseudocholinesterase) deficiency are historically among the first reported pharmacogenetic diseases, defined as inherited conditions that are characterised by an absence of phenotypic changes as long as the triggering agent is absent.[1,2] Only personal or familial history of adverse reactions and molecular genetic investigations are able to preemptively identify such susceptibility. Although traditional molecular genetic analysis is slow and laborious, more advanced, chip-based methods have been developed in order to sequence the loci of BCHE and MH.[3] This editorial accompanies the paper in the *British Journal of Anaesthesia* by Douville and colleagues[4] presenting a novel approach that consists in combining available high-throughput genotyping data for BCHE deficiency, MH susceptibility, and Factor V Leiden thrombophilia with information from an electronic healthcare record (EHR) system. The study used various genotyping platforms to achieve full coverage of the genetic loci under investigation. Three of the known BCHE variants with the largest effect on enzyme activity and the Factor V Leiden mutation were covered using a customised dense genotyping chip, or genome wide association (GWA) data. Screening for pathogenic MH variants was performed with sequence analysis of the *RYR1* and *CACNA1S* genes using whole exome sequencing (WES) and single molecule molecular inversion probes.[4]

The study used the Michigan Genomics Initiative (MGI)[5] biorepository that collects blood samples for genetic analysis from tens of thousands of perioperative patients. Genomic

DOI of original article: 10.1016/j.bja.2020.08.009.