Morphine-specific IgE testing in the assessment of neuromuscular blocking agent allergy : comment on Br J Anaesth 2024; 132: 193–5

# Correspondence to Chow et al (Br J Anaesth. 2023)

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To the Editor,

We have read the correspondence by Chow *et al* (1) with great interest. However, we would like to bring to the attention some studies that already provided important information regarding the potential and limitations of the ImmunoCAP s(pecific)IgE morphine as a diagnostic for neuromuscular blocking agent (NMBA) allergy. Shortly after its introduction, the diagnostic utility of this assay was explored in 2007 by our group (2). From this study it emerged that the traditionally recommended threshold of 0.35 $kUA.L^{-1}$ is appropriate and that the application of a lower allergen-specific threshold did not benefit its performance. An observation that was later confirmed by Laroche *et al* (3), but not by Anderson *et al* (4) who reported on an optimal cut-off of 0.19 $kUA.L^{-1}$. However, it has been consistently demonstrated that the morphine-based assay exhibits several limitations that seem to prevent an eventual standalone use for documenting an IgE-mediated allergy to NMBAs. First of all, contrary to our initial observation (2) and the authors' findings, specificity of the test might pose a problem, as IgE reactivity to morphine has been found positive in up to 5-10% of patients without NMBA allergy (3, 5-7). The reason(s) for this apparently clinically irrelevant results remain(s) elusive but could geographically differ and to some extent result from interference of elevated total IgE (2, 3), whether or not provoked by consumption of pholcodine (6). Unfortunately, in the absence of individual total IgE titers in the study by Chow *et a*l (1), we cannot comment on this phenomenon as a possible explanation of (at least some) of the 16 positive sIgE morphine results observed in their 70 (23%) so-called undetermined cases displaying incongruent negative skin tests. Noticeably, Laroche *et al* (3), also found an incongruent positive sIgE morphine result in 14/57 (24.6%) cases with negative skin tests. Mean total IgE in these patients was about 350 $kU.L^{-1}$. Another concern relates to the correct interpretation of incongruent positive sIgE and negative skin test results and the final recommendation for the individual patient. In the absence of data from complementary diagnostics or re-exposure, it is impossible to determine the clinical significance of incongruent outcomes; likely relevant for one patient and not at all for another. Based on our experience with basophil and mast cell activation tests (8) as well as our re-exposure data (9), it seems justified to assume that a positive sIgE morphine result in isolation is most likely clinically irrelevant. And, therefore, should not preclude the further use of the NMBAs that test negative in skin tests (and basophil activation tests) (9). Finally, as acknowledged by the

authors, the morphine sIgE test might be unreliable to detect an allergy to benzylisoquinolines (10, 11).

In conclusion, although, readily commercially available and easily executable, sIgE morphine leaves us with some weaknesses that should not be ignored. A positive sIgE result should not necessarily preclude further use of NMBA that test negative in skin tests and BAT. In undetermined cases with unreliable skin tests, a positive sIgE result should encourage close collaboration between anaesthetists and immunologist/allergologist to determine the best individual approach and utility of additional testing such as BAT and provocation tests. Conversely, a negative sIgE morphine result does not rule out an NMBA allergy, particularly an allergy to benzylisoquinolines.

**Author contributions**

All authors have equally contributed to the manuscript.

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