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doi: 10.1016/j.bja.2020.08.035
Advance Access Publication Date: 1 October 2020

Measurement of pholcodine-specific IgE in addition to morphine-specific IgE improves investigation of neuromuscular blocking agent anaphylaxis

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Keywords: allergy; anaphylaxis; hypersensitivity; morphine; neuromuscular blocking agent; perioperative; pholcodine; specific IgE

Editor—Neuromuscular blocking agents (NMBAs) are one of the leading causes of perioperative hypersensitivity reactions.[1,2] Investigation of these reactions typically includes skin testing and measurement of specific immunoglobulin E (sIgE) where available. Different patterns of NMBA cross-reactivity between patients appear to indicate variability in the IgE binding epitopes recognised.[3] Specific IgE to NMBAs is frequently examined using morphine as a marker for the substituted ammonium groups considered to be the main allergenic epitopes of NMBAs.[4] Pholcodine is a morphine derivative that has also been suggested as an effective marker for detection of sIgE to substituted ammonium epitopes.[5] However, considerable variation can be seen between sIgE concentrations to morphine or pholcodine in NMBA-allergic patients. The analysis reported here was undertaken to investigate these variations and the value of the pholcodine-sIgE assay in the assessment of NMBA-allergic patients.

A retrospective study was carried out for all patients investigated at the Royal North Shore Hospital Anaesthetic Allergy Clinic (Sydney, Australia) from June 2009 to September 2019. Standardised skin testing was performed according to protocols outlined by the Australian and New Zealand Anaesthetic Allergy Group[6] with a panel of NMBAs including rocuronium, vecuronium, pancuronium, succinylcholine, and cisatracurium. Measurement of pholcodine and morphine sIgE

was performed for all patients via the Phadia ImmunoCAP system (Thermo Fisher Scientific, Uppsala, Sweden). The study was approved by the Northern Sydney Local Health District Human Research Ethics Committee (LNR/14/HAWKE/315).

A total of 801 consecutive patients were examined. Of these, 255 exhibited positive skin test results for NMBAs (187 female, 68 male, median age 52 yr). Results for patients reactive to the benzylisoquinoline group of NMBAs only (15 patients), without cross-reactivity to aminosteroidal NMBAs or to succinylcholine, were not included in further analysis because of the fact that morphine and pholcodine-sIgE determination has previously been shown not to be useful in this group.[7]

Optimal cut-off thresholds of 0.22 kUA L^{-1} (pholcodine-sIgE) and 0.19 kUA L^{-1} (morphine-sIgE) were determined by receiver operating characteristic curve analysis. These values represent sIgE concentrations above which optimal test sensitivity and specificity are achieved relative to skin testing. At these thresholds, the combined testing protocol of both pholcodine-sIgE and morphine-sIgE allowed detection of additional NMBA-allergic patients compared with using each test alone. Of the skin test-positive patients, six were detected by pholcodine-sIgE only and two by morphine-sIgE only.

Pholcodine-sIgE concentrations were quantitatively higher than morphine-sIgE concentrations in 56% of skin test-positive patients with morphine-sIgE concentrations higher than pholcodine-sIgE in 24%. Where patients had pholcodine-sIgE concentrations two or more times the concentration of morphine-sIgE, a significantly increased proportion had skin sensitisation to succinylcholine as compared with where concentrations were equivalent for both substrates or where pholcodine-sIgE concentrations were reduced with respect to morphine-sIgE (Table 1). This difference was not seen where initiating or cross-reactive NMBAs did not include succinylcholine.

These results indicate that measurement of sIgE to both pholcodine and morphine is useful in the assessment of allergy to NMBAs to maximise detection of susceptible patients. This combined testing protocol provides additional diagnostic support, which is valuable when considering the potentially life-threatening nature of perioperative allergic reactions and that no currently utilised test has absolute sensitivity and specificity for confirmation of NMBA allergy. For this reason, the use of multiple testing modalities is advised.[8]

Comparison of variation in the concentrations of sIgE between the pholcodine and morphine substrates may also provide increased information regarding which NMBAs could present a risk for future procedures. Results from the current analysis indicate that this may be of use in the assessment of risk associated with subsequent succinylcholine exposure.

The differences observed in sIgE concentrations to each of the pholcodine and morphine substrates in NMBA allergic patients could indicate the presence of antibody binding sites on the pholcodine molecule in addition to the substituted ammonium group shared in common with morphine. The presence of such additional binding sites, cross-reactive with allergenic epitopes on NMBAs, appears particularly likely in the case of succinylcholine. This corresponds with previous reports that have linked detection of sIgE to both pholcodine and succinylcholine[9,10] in association with NMBA anaphylaxis, though whether this reflects sensitisation to the substituted ammonium group alone or to additional epitopes remains to be determined. Further studies examining these differences in sIgE concentrations with respect to NMBA sensitivities and further elucidation of potential allergenic epitopes may prove beneficial in the accurate assessment of NMBA allergic patients.

Table 1 Comparison of pholcodine/morphine specific immunoglobulin E ratios with respect to neuromuscular blocking agent sensitivity.

Sensitizing NMBA	Proportion of patients with positive skin test (%)		P-value
	Pholcodine/morphine sIgE ratio ≥2.0 (*n*=43)	Pholcodine/morphine sIgE ratio ≤1.0 (*n*=62)	
Succinylcholine	69.7	48.4	0.044
Rocuronium	81.4	82.2	1.000
Vecuronium	60.5	66.1	0.680
Pancuronium	34.9	37.1	0.839
Cisatracurium + other*	4.7	3.2	1.000

NMBA, neuromuscular blocking agent; sIgE, specific immunoglobulin E.
* Results included only where patients exhibited sensitivity to cisatracurium with cross-reactivity to an aminosteroidal NMBA or succinylcholine. Pholcodine and morphine-sIgE concentrations have been shown not to be of use where patients are sensitised to benzylisoquinoline NMBAs such as cisatracurium alone. Comparison of groups was performed by Fisher's exact test.

Declarations of interest

The authors declare that they have no conflicts of interest.

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doi: 10.1016/j.bja.2020.05.049
Advance Access Publication Date: 27 June 2020

Choice of hypnotic drug for obstetric and non-obstetric general anaesthesia. Comment on *Br J Anaesth* 2020; 125: e81–7

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Keywords: airway management; general anaesthesia; medication safety; propofol; thiopental; tracheal intubation; training

Editor—Difficult airway management is one of the leading causes of severe maternal complications and death related to obstetric general anaesthesia.[1] Airway management conditions depend on maternal airway anatomy that should be assessed before any obstetric anaesthesia; they also depend on the skill of the operator, the anaesthetic drugs administered, and the sequence of induction of anaesthesia. Induction of anaesthesia should take into account the pharmacokinetic and pharmacodynamic parameters of the drugs used. In particular, administration of neuromuscular blocking agents provides the best intubating conditions, regardless of the co-administered hypnotic drug.[2]

In a prospective multicentre study assessing the risk factors for maternal hypoxaemia, which included as secondary outcomes risk factors for difficult intubation during induction of general anaesthesia for non-elective Caesarean section, Bonnet and colleagues[3] reported that use of propofol at induction of anaesthesia was protective for difficult or failed tracheal intubation in comparison with other hypnotic drugs. In other words, their results suggest that intubating conditions are better when co-administering propofol with succinylcholine than when co-administering thiopental with succinylcholine.

This result may have significant implications for clinical practice and provides support for arguments for replacing thiopental with propofol in obstetric general anaesthesia.[4] In particular, a crucial point to consider is the definition of what a 'difficult intubation' is. Number of intubation attempts was used to define difficult intubation in the study by Bonnet and colleagues,[3] a criterion that is dependent in part on the skill of the operator and the anatomy of the patient. The use of a standardised qualitative scoring system, such as that proposed by the consensus conference of good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents, would have been more appropriate to assess intubating conditions as the criteria used in this scale are independent of the morphological characteristics of patients and allow reliable comparison of intubating conditions provided by various general anaesthesia induction regimens.[2,5,6] Other points to consider are co-administration of opioids and doses and timing of administration of the hypnotic and neuromuscular blocking drugs, which can also affect intubating conditions. Beyond these methodological issues that prevent any definitive conclusion regarding intubating conditions when using propofol *vs* thiopental co-administered with succinylcholine, the underlying question of the place of thiopental in both obstetric and non-obstetric anaesthesia remains.

Although thiopental was used in almost three quarters of the cases in the study by Bonnet and colleagues,[3] its use in obstetric anaesthesia has been decreasing for 20 yr in the UK,[7] creating a vicious cycle whereby decreased use leads to decreased experience of trainees and junior anaesthetists with thiopental, which in turn results in decreased use. Previous reports of thiopental over- or under-dosage and of more frequent accidental awareness when using thiopental compared with other drugs illustrate the unfamiliarity of anaesthetists with this drug, begging the question of whether we should teach our trainees better or give up the use of thiopental in anaesthesia.[4]

The current coronavirus disease 2019 pandemic has led to worldwide drug shortages, particularly of propofol and neuromuscular blocking agents. This has required defining strategies to spare propofol,[8] including prioritising regional anaesthesia whenever possible or use of other hypnotic drugs. We decided to use thiopental as a first-line hypnotic in our unit for induction of obstetric general anaesthesia and emergency non-obstetric general anaesthesia, and for elective non-obstetrical surgery of more than 60 min requiring general

DOI of original article: 10.1016/j.bja.2020.03.010.