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Clinical Investigation

CLINICAL INVESTIGATION

Pholcodine exposure increases the risk of perioperative anaphylaxis to neuromuscular blocking agents: the ALPHO case-control study

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Abstract

Background: Neuromuscular blocking agents (NMBAs) are among the leading cause of perioperative anaphylaxis, and most of these reactions are IgE mediated. Allergic sensitisation induced by environmental exposure to other quaternary ammonium-containing compounds, such as pholcodine, has been suggested. The aim of this study was to assess the relationship between pholcodine exposure and NMBA-related anaphylaxis.

Methods: ALPHO was a multicentre case-control study, comparing pholcodine exposure within a year before anaesthesia between patients with NMBA-related perioperative anaphylaxis (cases) and control patients with uneventful anaesthesia in France. Each case was matched to two controls by age, sex, type of NMBA, geographic area, and season. Pholcodine exposure was assessed by a self-administered questionnaire and pharmaceutical history retrieved from pharmacy records. The diagnostic values of anti-pholcodine and anti-quaternary ammonium specific IgE (sIgE) were also evaluated.

Results: Overall, 167 cases were matched with 334 controls. NMBA-related anaphylaxis was significantly associated with pholcodine consumption (odds ratio 4.2; 95% confidence interval 2.3–7.0) and occupational exposure to quaternary ammonium compounds (odds ratio 6.1; 95% confidence interval 2.7–13.6), suggesting that apart from pholcodine, other environmental factors can also lead to sensitisation to NMBAs. Pholcodine and quaternary ammonium sIgEs had a high negative predictive value (99.9%) but a very low positive predictive value (<3%) for identifying NMBA-related reactions.

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Conclusions: Patients exposed to pholcodine 12 months before NMBA exposure have a significantly higher risk of an NMBA-related anaphylaxis. The low positive predictive values of pholcodine and quaternary ammonium sIgEs precludes their use to identify a population with a high risk of NMBA-related anaphylaxis.
Clinical trial registration: NCT02250729.

Keywords: anaesthesia; anaphylaxis; neuromuscular blocking agents; pholcodine; quaternary ammonium compounds

Editor's key points

- Neuromuscular blocking agents (NMBAs) are a leading cause of perioperative anaphylaxis. Allergic sensitisation by environmental exposure to quaternary ammonium-containing compounds such as pholcodine has been implicated.
- This multicentre French national study retrospectively assessed the relationship between pholcodine exposure and NMBA-related anaphylaxis.
- In this case-control study, NMBA-related anaphylaxis was associated with pholcodine exposure and occupational exposure to quaternary ammonium compounds.
- Pholcodine and quaternary ammonium specific IgEs had high negative predictive value but a low positive predictive value, limiting their use for identifying risk for NMBA-related reactions.

Neuromuscular blocking agents (NMBAs) represent one of the leading causes of perioperative anaphylaxis.[1–5] Although rare, with an estimated frequency of 184 reactions per million anaesthesia procedures in France, NMBA-related anaphylaxes are largely unpredictable, potentially catastrophic, and remain a major concern for anaesthesia providers.[1,3,6] The main mechanism involves the interaction between specific IgE (sIgE) and an epitope present in the structure of NMBAs resulting in massive activation of mast cells and basophils.[7] Quaternary ammonium (QA) groups, essential for the relaxant properties of any NMBA, are considered the main allergenic structures recognised by sIgE antibodies detected in the sera of most patients who experience NMBA-related anaphylaxis.

Classically, anaphylaxis requires prior exposure to the antigen to induce sensitisation.

However, many subjects who react to an NMBA have never been exposed to one of these drugs, challenging the immunological dogma of the necessity of a previous exposure to elicit the production of sIgEs.[8] This led to the speculation that the origin of allergic sensitisation could be induced by environmental exposure to other compounds containing a substituted ammonium ion. In 2005, Florvaag and Johansson proposed pholcodine, an opiate that contains an ammonium group, as an important risk factor for NMBA sensitisation, and have gradually strengthened this hypothesis until 2011.[9–13] Pholcodine-containing drugs were withdrawn from the Norwegian market in March 2007, and a reduction in the prevalence of specific antibodies recognising pholcodine, but also the NMBA suxamethonium, was observed in the general population over the subsequent 2 yr.[9]

As a result, in 2011, the European Medicines Agency (EMA) launched a referral procedure for re-evaluation of the benefit:risk ratio of pholcodine. The EMA decided to keep pholcodine on the European market but to request a case-control study to further investigate a possible increased risk of NMBA-related anaphylaxis associated with pholcodine exposure. The objective of the ALPHO study was to investigate the relationship between exposure to pholcodine during the year preceding the index general anaesthesia procedure including NMBA injection and the onset of an NMBA-related reaction. The secondary objective focused on the diagnostic value of QA and pholcodine sIgEs for the prediction of perioperative anaphylaxis.

Methods

Study design

The ALPHO study NCT02250729 was a multicentre case-control study, supported by the EMA and funded by the pharmaceutical companies marketing pholcodine-containing antitussive drugs. This study was conducted between 2014 and 2020 in 24 academic French anaesthesia departments and allergology units constituting the GERAP network (Groupe d'Etude des Réactions Anaphylactiques Peropératoires).[1,14–16]

Patient screening and enrolment

Patients who experienced perioperative anaphylaxis involving an NMBA (cases) were identified by French anaesthetists and referred to one of the participating centres. Each reaction was reported to the ALPHO investigators and triggered a search for two matched controls who had been anaesthetised with the same NMBA but had not experienced a reaction. The matching criteria were: i) age (more than and under 65 yr); ii) sex; iii) type of NMBA (suxamethonium; steroidal NMBA (rocuronium or vecuronium); benzylisoquinoline (atracurium, cisatracurium, or mivacurium); iv) geographic area (northern or southern France); and v) anaesthesia period corresponding to the date of reaction plus or minus 90 days.

Each case underwent NMBA allergy skin tests (prick tests and intradermal skin tests) according to French and European Academy of Allergy and Clinical Immunology (EAACI) guidelines.[17,18] A centralised retrospective confirmation of NMBA-related cases was performed by two specialists blinded for pholcodine exposure. Cases were excluded if they did not have at least one positive skin test for one of the injected NMBAs, or if their skin tests were not performed according to EAACI guidelines.[18]

Controls were included according to matching criteria by an anaesthetist investigator of the ALPHO study during their hospital stay. They were required to complete the medication self-administered questionnaire. A history of perioperative

anaphylaxis during anaesthesia and pregnancy at the time of screening were exclusion criteria.

Data collected included medical history, drugs administered during anaesthesia, characteristics and management of the reaction, and occupation/profession. Patients reporting current or past cleaning profession or hairdressers were considered professionally exposed to QAs.[19,20] Blood tryptase and histamine measurements were performed according to French guidelines: at T0 (30 min after the reaction), T1 (1–2 h after the reaction), and T2 (at least 24 h after the reaction).[17]

Assessment and definition of pholcodine exposure

Exposure to pholcodine over the last 12 months before the anaesthesia event was assessed in cases and controls from two separate sources: 1) a self-administered questionnaire collecting the names and package visuals of all currently available pholcodine-containing drugs in France since 2014, and other marketed cough suppressants and non-pholcodine analgesics to serve as decoys. This questionnaire was completed during the allergy consultation for cases or during hospitalisation for controls; 2) the patient's pharmaceutical history retrieved from their community pharmacy records. Patients were considered as exposed to pholcodine over the 12 months before anaesthesia if they reported taking at least one pholcodine-containing medication in the self-administered questionnaire, if the medication history reported dispensing at least one pholcodine-containing medication, or both.

Pholcodine sensitisation

Specific IgE-antibodies to pholcodine and QA (sIgE-PHO, sIgE-QA) were measured by two techniques: 1) ImmunoCAP® (Phadia AB/Thermo Fisher Scientific, Uppsala, Sweden) allergens c261 (pholcodine, PHO-c261) and c260 (QA-c260), and 2) Sepharose ammonium quaternary-fluorescence immunoassay (SAQ-FIA). SAQ-FIA uses a choline analogue coupled to Sepharose. After incubation with serum, the solid phase was washed with buffer to retain the sIgE, and subsequently incubated with labelled anti-IgE (first step A). Results of sIgE to QA (QA-SAQ sIgE) were expressed as the percent binding labelled anti-IgE to the solid phase. Secondly, for sIgE to pholcodine (PHO-SAQ-sIgE), inhibition tests were done by incubating the serum with pholcodine (step B). Percent inhibition (I) was estimated from the signals in the second step (B) and first step (A), using the formula: $I=A-B/A\times100$.[21]

Statistical analysis

Analyses were performed in SAS v9.4 (SAS Institute, Cary, NC, USA). Categorical variables were expressed as numbers and percentages, and continuous variables as median and interquartile range. Comparison tests of proportions and means were performed using χ^2 test, Fisher's exact test, and Student's *t*-test or Mann–Whitney test. For multivariate conditional logistic regression models, a bivariate analysis was performed to select the adjustment variables and only variables with a *P*-value $\leq$0.2 were candidates for multivariate conditional logistic regression models. The strength of association was estimated by adjusted odds ratios (ORs) with their 95% confidence intervals (CI; 5% level of statistical significance of the two-tailed tests). Two multivariate models were compared: 1) multivariate logistic regression model including all selected candidate variables; 2) stepwise candidate variable selection procedure (entry threshold at *P*=0.2 and model exit threshold at 0.05). The model with the lowest Akaike information criterion (AIC) was retained for the results. Concordance analysis was based on Cohen's Kappa coefficient.

Results

Selection process

A total of 937 patients were screened for eligibility between July 21, 2014 and July 20, 2020 (Fig 1). Of these, 282 experienced perioperative anaphylaxis possibly related to an NMBA, and 655 had uneventful anaesthesia. After centralised review blinded for pholcodine use, 78 patients with pholcodine and five without pholcodine were excluded. NMBA-related cases and controls were strictly comparable with respect to matching variables (Supplementary Table S1). There were 37 cases that could not be matched with controls. Finally, 167 NMBA-related anaphylaxis cases were matched with 334 patients with uneventful anaesthesia.

Patient characteristics

The characteristics of the cases and controls are shown in Table 1. Patients were predominantly female (cases 92 [55%] *vs* controls 184 [55%]), and BMI was significantly higher in cases than in controls. No significant differences were observed regarding medical history or chronic medication. Cases reported significantly more atopy than controls. Supplementary Table S2 shows the associated surgical procedures.

Pholcodine consumption

The self-questionnaire was completed in 163 (98%) of cases and 333 (99%) of controls. Pharmacist-reported medication history was available in 121 (72%) cases and 172 (51%) controls. According to the self-questionnaire, 71 (43%) cases and 63 (19%) controls reported the use of pholcodine in the past year. When considering only the pharmacist reported medication history, 26 (22%) cases and seven (4%) controls ascertained the use of pholcodine. Eighteen (13%) cases and three (1%) controls indicated use of pholcodine in both sources. Overall, 79 (47%) cases and 67 (20%) controls reported use of pholcodine in the year preceding the anaesthesia index ($P<0.001$).

Neuromuscular blocking agent-related perioperative hypersensitivity reactions

An NMBA-related anaphylaxis occurred during an emergent surgery in 42 (25%) cases. In 20 (12%) cases, the patient was in the operating theatre for bariatric surgery. Suxamethonium was used in 105 (63%) cases, rocuronium in 21 (13%) cases, atracurium in 53 (32%) cases, cisatracurium in 21 (13%) cases, and mivacurium in three (2%) cases (Supplementary Table S3); some patients received more than one NMBA.

Most of the reactions were severe with 14 (9%), 140 (84%), 13 (7%) reactions of anaphylaxis grade II, III, and IV, respectively. The main clinical sign observed was cardiovascular collapse (*n*=134; 80%) (Supplementary Table S3). Epinephrine was used in 145 (87%) cases to treat the reaction. Median tryptase level was 53 (18–113) $\mu g\ L^{-1}$ at T0 (*n*=129; 77%), 33 (15–69) $\mu g\ L^{-1}$ at T1 (*n*=114; 68%) and 5 (3–8) $\mu g\ L^{-1}$ at the basal state (*n*=83; 50%). The distribution of tryptase according to pholcodine consumption showed no significant difference (Fig 2).

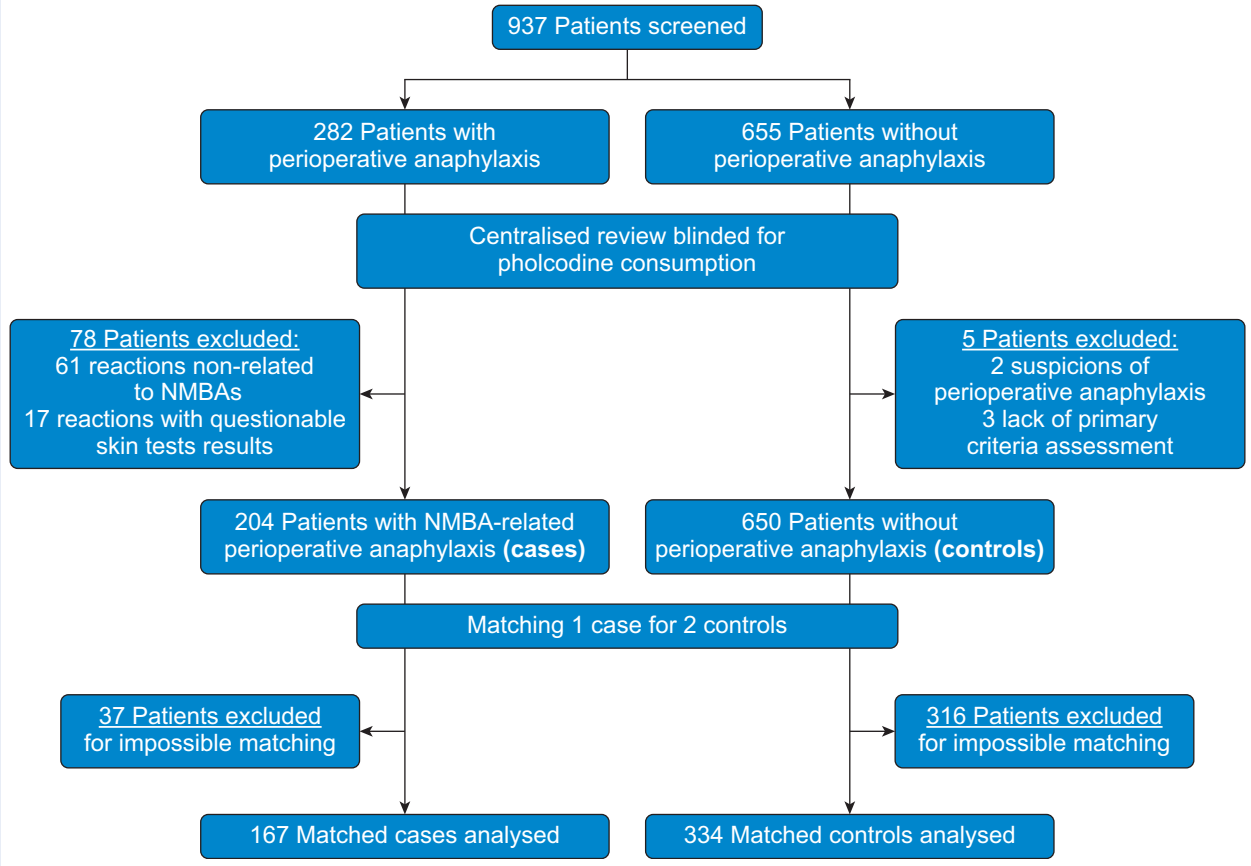

Fig 1. Flow chart of the ALPHO study. NMBA: neuromuscular blocking agent.

Allergy workup

The allergy workup was performed within a median period of 9 (7–11) weeks after the reaction. All patients had positive skin tests to at least one injected NMBA. At the end of the allergic workup, suxamethonium was incriminated in 101 (60%) cases, rocuronium in 21 (13%) cases, atracurium in 35 (21%) cases, cisatracurium in 11 (7%) cases, and mivacurium in two (1%) cases. Three (2%) patients were sensitised to two NMBAs injected during the surgery (suxamethonium and atracurium).

Multivariate analysis

The multivariable analysis showed that pholcodine consumption was associated with NMBA-related anaphylaxis with an OR of 4.2 (95% CI 2.5–7.0) (Table 2). Occupational exposure to QA and hepato-gastrointestinal history were also associated with NMBA-related anaphylaxis with an OR of 6.1 (95% CI 2.7–13.6) and 2.1 (95% CI 1.3–3.3), respectively.

When considering only the self-questionnaire as the source of the pholcodine exposure, pholcodine consumption remained associated with NMBA-related anaphylaxis with OR 4.1 (95% CI 2.4–6.8), as occupational exposure to QA (OR 6.3 [95% CI 2.8–14.4]) and hepato-gastrointestinal history (OR 4.1 [95% CI 2.4–6.8]). When considering only the pharmacist-reported medication history, only pholcodine exposure (OR 4.8 [95% CI 1.6–14.7]) and occupational exposure to QA (OR 2.9 [95% CI 1.1–7.6]) remained significantly associated with NMBA-related anaphylaxis. When considering pholcodine exposure only if both sources were positive, pholcodine exposure (OR 11.0 [95% CI 3.1–39.4]), occupational exposure to QA (OR 5.5 [95% CI 2.3–13.2]), hepato-gastrointestinal history (OR 1.7 [95% CI 1.0–3.0]), and atopy (OR 2.1 [95% CI 1.1–3.9]) were significantly associated with NMBA-related anaphylaxis (data not shown).

Specific IgEs

QA-SAQ sIgE was assayed in 160 (96%) cases and 334 (100%) controls, and QA-c260 in 162 (97%) cases and 333 controls. Pholcodine-SAQ sIgE was assayed in 160 (96%) cases and 334 (100%) controls and PHO-c261 in 162 (97%) cases and 333 controls. Table 3 shows the results of sIgE assays in cases and controls. Supplementary Figure S1 shows the receiver operating characteristic (ROC) curves for sIgEs. There was no difference for sIgE values between patients who reported using pholcodine in the previous year and those who did not, with the exception of PHO-c261 in controls (Fig 3). Both SAQ-FIA and ImmunoCAP® methods were well correlated: Pearson coefficient (QA-SAQ/PHO-SAQ) 0.86, $P<0.001$; Pearson coefficient (QA-c260/PHO-c261) 0.85, $P<0.001$.

SIgEs had a high negative predictive value of 99.9% but a very low positive predictive value of 2.8, 0.3, 5.3, and 0.4% for

Table 1 Characteristics of control and case and control cohorts. ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; NMBAs, neuromuscular blocking agents; PHO, pholcodine.

	Controls n=334	Cases n=167	P
Patient characteristics			
Age (yr)	56 (43–67)	57 (49–66)	0.10
BMI (kg m^{-2})	25.8 (22.6–30.1)	27.5 (24.2–34.9)	<0.01
Occupational exposure to quaternary ammoniums			
Hairdresser	6 (2)	5 (3)	0.52
Cleaner	12 (4)	28 (17)	<0.01
Medical history			
Cardiovascular	151 (45)	88 (53)	0.11
Respiratory	75 (23)	46 (28)	0.21
Metabolic	80 (24)	52 (31)	0.09
Gastrointestinal	74 (22)	50 (30)	0.06
Surgical history			
Number of previous surgeries	2 (1–3)	2 (1–3)	0.63
Allergic history			
Atopy	49 (15)	42 (25)	<0.01
Drug allergy	62 (19)	35 (21)	0.46
Food allergy	26 (8)	11 (7)	0.63
Chronic medications			
ß-Blockers	61 (19)	31 (20)	0.81
ARBs	34 (11)	26 (17)	0.05
ACE inhibitors	40 (13)	25 (17)	0.23
Antihistamines	16 (5)	8 (5)	0.97
PHO Pholcodine exposure	67 (20)	79 (47)	<0.01

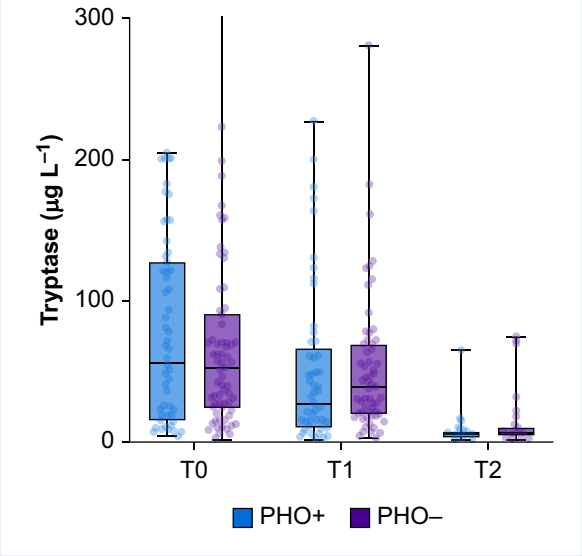

Fig 2. Serum tryptase level at T0 (<30 min), T1 (1–2 h), and T2 (>24 h) after a neuromuscular blocking agent-related perioperative anaphylactic reaction, according to the consumption of pholcodine in the past year. Dots represent individual values; boxes represent the inter-quartile range with the median line. Bars are from minimum to maximum values. PHO+, patients exposed to pholcodine; PHO–, patients not exposed to pholcodine.

QA-SAQ, QA-c260, PHO-SAQ, and PHO-c261, respectively (Table 3). In the subgroup of cases and controls who reported previous-year pholcodine use, the presence of PHO-c261 sIgE in patients was the only factor significantly associated with NMBA-related anaphylaxis with OR 60.7 (95% CI 25.6–143.8) (Table S4).

Discussion

Patients exposed to pholcodine 12 months before an anaesthesia procedure have a significantly higher risk of an NMBA-related anaphylaxis, which confirms a link between pholcodine exposure and NMBA-related anaphylaxis. The strong association between occupational exposure and occurrence of NMBA-related reaction suggests that other environmental factors might also lead to sensitisation to NMBAs. QA-sIgE and PHO-sIgE have excellent performance in discriminating cases from controls. Their negative predictive value is very high, indicating a low risk of NMBA-related anaphylaxis if they are undetectable. However, the low positive predictive values of QA-sIgE and PHO-sIgE precludes their use to identify a population with a high risk of NMBA-related anaphylaxis.

The hypothesis of the role of pholcodine raised in 2005 by Florvaag and collegues,[9–13] was based mainly on sIgE tests without information on the confirmation of anaphylactic reactions to NMBAs by skin tests. In 2017, 6 yr after the withdrawal of pholcodine in Norway, this team confirmed a decrease in sensitisation to NMBAs in the general Norwegian population, especially in women 15–41 yr old.[22,23] At the same time, an Australian observational study comparing pholcodine exposure in patients with perioperative anaphylaxis related to NMBA *vs* patients who had perioperative anaphylaxis related to cefazolin showed that pholcodine consumption was associated with a significant increased risk of NMBA-related anaphylaxis (OR=14.0, P<0.001).[24] However, pholcodine exposure was estimated on the basis of information collected several years later by patient interview in only one-third of the patients included.

Table 2 Risk factors for neuromuscular blocking agent-related perioperative anaphylaxis. Results of odds ratio (OR) are expressed as OR (95% confidence interval), BMI, body mass index.

	Bivariate analysis		Multivariate analysis	
	OR	P	OR	P
Pholcodine exposure	4.5 (2.8–7.3)	<0.01	4.2 (2.5–7.0)	<0.01
Occupational exposure to quaternary ammoniums	6.0 (2.9–12.8)	<0.01	6.1 (2.7–13.6)	<0.01
Atopy	1.8 (1.1–2.8)	0.02	–	–
BMI (kg m^{-2})		0.08		
BMI 25–30 kg m^{-2}	1.1 (0.7–1.8)	0.45		
BMI ≥30 kg m^{-2}	1.7 (1.0–2.6)	0.03	–	–
Cardiovascular history	1.4 (0.9–2.2)	0.09	–	–
Metabolic history	1.5 (1.0–2.4)	0.07	–	–
Endocrine history	1.8 (0.9–3.5)	0.10	–	–
Hepato-gastrointestinal history	1.5 (1.0–2.3)	0.06	2.1 (1.3–3.3)	<0.01

Table 3 Specific IgE levels in case and control cohorts from the ALPHO study and their respective diagnostic values. AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value. *Based on an estimated incidence of 184/1 000 000 anaesthesia procedures.[1]. QA-SAQ and PHO-SAQ: sIgE-QA and sIgE-PHO measured by Sepharose ammonium quaternary-fluorescence immunoassay (SAQ-FIA), QA-SAQ expressed as fixation rate (%), PHO-SAQ expressed as inhibition rate (%); QA-c260, PHO-c261: sIgE-QA and sIgE-PHO measured by ImmunoCAP® (Phadia AB/Thermo Fisher Scientific, Uppsala, Sweden).

	Controls	Cases	P	AUC	Optimal threshold	Sensitivity (%)	Specificity (%)	PPV*	NPV*
QA-SAQ (%)	1.0 (0.9–1.0)	3.5 (2.8–5.5)	<0.001	0.98	1.8	94 (92–96)	99 (99–100)	2.8	99.9
QA-c260 (kUa L^{-1})	0.0 (0.0–0.0)	1.5 (0.3–5.6)	<0.001	0.95	0.04	87 (84–90)	94 (92–96)	0.3	99.9
PHO-SAQ (%)	0.0 (0.0–0.0)	40.0 (23.0–45.0)	<0.001	0.96	10.0	92 (89–94)	100 (99–100)	5.3	99.9
PHO-c261 (kUa L^{-1})	0.0 (0.0–0.0)	2.2 (0.4–6.5)	<0.001	0.95	0.05	88 (88–94)	96 (94–98)	0.4	99.9

Our study is the first fully case-control study comparing pholcodine exposure of patients with confirmed anaphylaxis to NMBA with controls anaesthetised under the same conditions without perioperative anaphylaxis. It clearly demonstrates that patients exposed to pholcodine 12 months before exposure to an NMBA have a significantly higher risk of NMBA-related anaphylaxis. This strong association is observed regardless of the source used to estimate pholcodine exposure, either by self-questionnaire, the patient's pharmaceutical history from his/her community pharmacist, or a combination of both, including when exposure was corroborated by the two sources.

Our results also suggest that, apart from pholcodine, other unidentified compounds containing tertiary or QA groups act as sensitising agents. These agents are widely present in the human environment among drugs, cosmetics, disinfectants, industrial materials, and foods. We observed that professional exposure to QA remained strongly associated with NMBA-related anaphylaxis regardless of the source of information. This possible role of environmental factors has been suspected based on inhibition experiments of the binding of sIgE antibodies detected in patients suffering from perioperative anaphylaxis to other compounds containing substituted ammonium ion epitopes.[8,25,26] This hypothesis has gained some support with the report of a high prevalence of sensitisation to QA ions in several countries where pholcodine was not available,[10] and with evidence that professional exposure to QA-containing compounds among hairdresser students increases IgE-sensitisation to NMBAs.[19]

In our series, a history of hepato-gastrointestinal disease was identified as an additional possible risk factor. This could be related to a higher probability of taking cough syrups (presence of cough in case of gastro-oesophageal reflux/hiatal hernia).

The results of QA-sIgE and PHO-sIgE showed an excellent performance in discriminating anaphylaxis cases from controls, with a significant correlation between results obtained with these different assays. This supports the recognition of common epitopes between the QA and PHO-sIgE tests. However, these tests have a very low positive predictive value and cannot be used to identify patients at risk for NMBA anaphylaxis. In our study, QA-sIgE and PHO-sIgE had an excellent negative predictive value supporting a low risk of NMBA-related anaphylaxis when their serum levels are undetectable. This could theoretically help to rule out the risk of NMBA-related anaphylaxis in patients reporting recent exposure to pholcodine within 12 months. This situation might be overwhelming given the common use of pholcodine-containing cough syrups. The value of this strategy would warrant a medico-economic study. In addition, NMBA-related anaphylaxis has a low prevalence in the general population, estimated at 184 reactions for 1 000 000 anaesthetic procedures.[1] Thus, considering the poor positive predictive value of QA-sIgE and PHO-sIgE, the risk of excessively ruling out NMBAs in patients exposed to pholcodine in the past with positive QA-sIgE or PHO-sIgE could exceed the benefits in terms of allergic risk. Therefore, this strategy should not be recommended based only on the ALPHO study results.

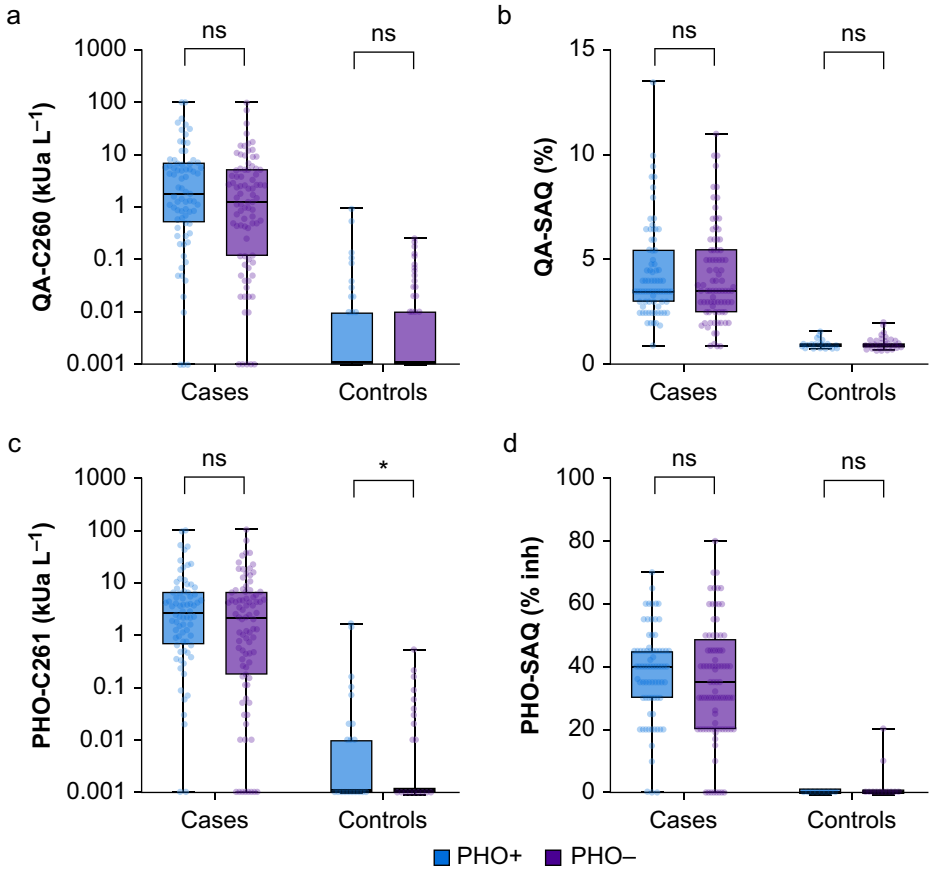

Fig 3. Specific IgE (sIgE) level (in kUa L^{-1}) in cases and controls according to their pholcodine (PHO) consumption in the past year. (a) (c) Quaternary ammonium specific IgE and pholcodine specific IgE measured by ImmunoCAP® (Phadia AB/Thermo Fisher Scientific, Uppsala, Sweden, QA-c260, PHO-c261); (b) (d) quaternary ammonium specific IgE and pholcodine specific IgE measured by Sepharose ammonium quaternary-fluorescence immunoassay (SAQ-FIA), QA-SAQ expressed by fixation rate (%), PHO-SAQ expressed by inhibition rate (%). Dots represent individual values; boxes represent the inter-quartile range with the median line. Bars are from minimum to maximum values. ns, not significant; PHO+, patients exposed to pholcodine; PHO−, patients not exposed to pholcodine. *P<0.05.

Limitations

Our assessment of pholcodine exposure was based on two imperfect but complementary sources. Regarding drug prescription history retrieved from community pharmacists, we observed a higher proportion of missing information in controls. This was possibly related to a weaker motivation of these patients who did not experience NMBA-related anaphylaxis to collect the required information. We also observed a weak agreement between the results of self-administered questionnaires and drug prescription histories, primarily as a result of positive answers in the self-questionnaire not confirmed by the medication history of pharmacists. This can be because patients could report intake of pholcodine syrups available in their 'family medicine cabinet' possibly prescribed or bought for another family member. However, interestingly, pholcodine exposure remained significantly associated with NMBA-related anaphylaxis whatever the combination of sources, thus lowering the impact of this weak agreement.

Conclusions

Our study confirms a significant association between pholcodine consumption in the year preceding NMBA exposure and NMBA-related perioperative anaphylaxis. Other environmental factors, including occupational exposure to quaternary ammonium compounds, should be considered in the risk of NMBA-related anaphylaxis, but they currently remain poorly defined. In this context, pholcodine appears to be a well-identified risk factor that can be addressed. These results supporting the careful re-evaluation of the benefit:risk ratio of pholcodine-containing cough syrups contributed in December 2022 to the EMA recommendation to withdraw pholcodine-containing medicinal products from the European market.[27]

The mechanism for the role of pholcodine remains elusive, but our QA-sIgE and PHO-sIgE investigations support common epitopes between pholcodine and NMBAs. Specific IgE assays for quaternary ammonium compounds and pholcodine have a good negative predictive value but a low positive predictive value. Considering the low prevalence of NMBA-related

perioperative anaphylaxis and the potentially large number of subjects exposed to pholcodine, the value of QA-sIgE or PHO-sIgE in assessing the risk of NMBA-related anaphylaxis resulting from pholcodine exposure cannot be assumed and requires further evaluation.

Authors' contributions

Designed and planned the study: PMM, NP, JLG, CB, PG.
Implemented the study: PMM, NP, DL, JMM, PD.
Accessed and verified the data: CB, MD, PMM, NP, CT.
Analysed and interpreted the trial data: PMM, NP, CT, AG, DLQ, JLG, CB, MD, PG.
Wrote the first draft of the manuscript: PMM, NP, CT.
Read and approved the final version of the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication: all authors.
All members of the ALPHO study group were in charge of inclusion of cases and controls, data collection, and approved the final version of the manuscript.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2023.02.026.

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