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Relationship of perioperative anaphylaxis to neuromuscular blocking agents, obesity, and pholcodine consumption: a case-control study

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Abstract

Background: The observation that patients presenting for bariatric surgery had a high incidence of neuromuscular blocking agent (NMBA) anaphylaxis prompted this restricted case-control study to test the hypothesis that obesity is a risk factor for NMBA anaphylaxis, independent of differences in pholcodine consumption.
Methods: We compared 145 patients diagnosed with intraoperative NMBA anaphylaxis in Western Australia between 2012 and 2020 with 61 patients with cefazolin anaphylaxis with respect to BMI grade, history of pholcodine consumption, sex, age, comorbid disease, and NMBA type and dose. Confounding was assessed by stratification and binomial logistic regression.
Results: Obesity (odds ratio [OR]=2.96, χ^2=11.7, P=0.001), 'definite' pholcodine consumption (OR=14.0, χ^2=2.6, P<0.001), and female sex (OR=2.70, χ^2=9.61, P=0.002) were statistically significant risk factors for NMBA anaphylaxis on univariate analysis. The risk of NMBA anaphylaxis increased with BMI grade. Confounding analysis indicated that both obesity and pholcodine consumption remained important risk factors after correction for confounding, but that sex did not. The relative rate of rocuronium anaphylaxis was estimated to be 3.0 times that of vecuronium using controls as an estimate of market share, and the risk of NMBA anaphylaxis in patients presenting for bariatric surgery was 8.8 times the expected rate (74.9 *vs* 8.5 per 100 000 anaesthetic procedures).
Conclusions: Obesity is a risk factor for NMBA anaphylaxis, the risk increasing with BMI grade. Pholcodine consumption is also a risk factor, and this is consistent with the pholcodine hypothesis. Rocuronium use is associated with an increased risk of anaphylaxis compared with vecuronium in this population.

Keywords: anaphylaxis; hypersensitivity; neuromuscular blocking agent; obesity; pholcodine; rocuronium

Editor's key points

- This restricted case-control study tested the hypothesis that obesity is a risk factor for anaphylaxis to neuromuscular blocking agents (NMBAs) independent of differences in pholcodine consumption.
- The risk of NMBA anaphylaxis increased with obesity and pholcodine consumption, with rocuronium use showing a greater risk than vecuronium.
- Obese patients are more likely to suffer NMBA anaphylaxis than non-obese patients, and greater risk exists with increasing BMI.

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An excessive number of patients who suffer neuromuscular blocking agent (NMBA) anaphylaxis after anaesthetic induction before bariatric surgery in Western Australia cannot be explained by previously hypothesised risk factors including pholcodine consumption and sex.[1–4] This led us to hypothesise the existence of a novel common risk factor, obesity. A challenge was designing a study free from selection bias. In 2012, the European Medicines Agency recommended a restricted case-control study to investigate risk factors for NMBA anaphylaxis using a control group consisting of patients administered an NMBA who did not experience anaphylaxis.[5] Significant limitations in this design were avoided by using a control group that ensured that all enrolled patients had an indication for an NMBA, suffered anaphylaxis, and that the identity of the agent causing anaphylaxis (cases, NMBA *vs* controls, cephazolin) was unknown at the time exposures were determined.

Methods

We tested the hypothesis that obesity is a risk factor for NMBA anaphylaxis. Potential confounding factors, including pholcodine consumption, age, sex, NMBA identity, and dose, were measured. We also sought to estimate the risk of NMBA anaphylaxis in patients presenting for bariatric surgery in Western Australia compared with the risk in the overall surgical population, and the relative risk of rocuronium anaphylaxis compared with vecuronium anaphylaxis using controls as an approximation of market share. All patients provided informed consent for the prospective collection of data. Ethical approval for this study was granted by the WNHS Human Research Ethics Committee (approval reference Q15703), O Block, KEMH, Subiaco, Western Australia (Chairperson Jeffrey Keelan), on May 4, 2017. The trial was registered with the Australia and New Zealand Clinical Trials Group (Universal Trial Number U1111-1237-5570, ACTRN12619001104145).

Study protocol

We used a blinded case-control design with a restricted control group consisting of patients who suffered anaphylaxis to cephazolin after also being exposed to an NMBA. This has the advantage of blinding (for concurrently recruited cases and controls) with respect to the measured variables (obesity and pholcodine consumption).

In Western Australia, NMBAs and cephazolin are the most common causes of intraoperative anaphylaxis, and the pre-skin-test probability for each agent in a patient who has received both before the anaphylactic episode is approximately equal.[6] The source population was patients referred to the Western Australian Anaesthetic Allergy Clinic (WAAAC) between 2012 and 2020 for investigation of suspected intraoperative anaphylaxis. The WAAAC is the sole referral centre for intraoperative anaphylaxis in Western Australia. Patients were included for analysis if surgery or anaesthesia required administration of an NMBA and subsequent skin testing diagnosed NMBA or cephazolin anaphylaxis. Written informed consent was obtained from all participants. Historical cases and controls were collected from 2012 and 2016, and concurrent cases and controls from 2016 to 2020.

Cases were defined as patients with anaphylaxis induced by an NMBA. Controls were defined as patients with cephazolin-induced anaphylaxis who also received an NMBA before the anaphylactic event. Intraoperative anaphylaxis was defined as a perioperative hypersensitivity reaction that was potentially life-threatening, occurring temporally to drug administration, with that drug testing positive (8 mm wheal with a flare) on intradermal testing with all other potential triggers testing negative. Intradermal testing was in accordance with guidelines published by the Australian and New Zealand College of Anaesthetists (rocuronium 0.01 mg ml^{-1}, vecuronium 0.04 mg ml^{-1}, mivacurium 0.002 mg ml^{-1}, cisatracurium 0.02 mg ml^{-1}, atracurium 0.01 mg ml^{-1}, pancuronium 0.02 mg ml^{-1}, suxamethonium 0.1 mg ml^{-1}, cephazolin 1 mg ml^{-1}). These concentrations are consistent with those recommended by the European Network for Drug Allergy/European Academy of Allergy and Clinical Immunology (ENDA/EAACI) with the exception of rocuronium (20% of the ENDA/EACCI concentration) and cephazolin (50%). 0.02–0.03 mL was injected with a 30-gauge hypodermic needle, and the skin test read with reference to positive and negative controls at 15 min.[7]

The patient anaesthetic record, allergy clinic referral letter, standardised assessment notes, skin testing results and investigations, and allergist reply correspondence were reviewed for all cases. For historical cases and controls, if pholcodine consumption was not explicitly recorded in the clinic assessment notes, patients were contacted and re-interviewed. All concurrent cases had pholcodine consumption determined before skin testing (blinded). Severity of anaphylaxis was estimated according to the four-level scale introduced by Mertes and colleagues.[8] Obesity was defined using four grades according to the four-level scale defined by the WHO (grade 1 – normal BMI <29.9 kg m^{-2}, grade 2 – Obese class 1 BMI 30–34.9 kg m^{-2}, grade 3 – Obese class 2 BMI 35–39.9 kg m^{-2}, grade 4 – Obese class 3 BMI ≥40 kg m^{-2}).[9]

Patient risk factors considered were age, sex, comorbid disease (ASA physical status classification), BMI, history of pholcodine consumption (12 months before anaphylaxis), and NMBA dose. Characteristics of the anaphylactic reaction included anaphylaxis severity grade, acute mast cell tryptase level, whether surgery was abandoned, and whether the patient required admission to intensive care after the event. Weight and height were determined from the anaesthetic record or consultation notes in historical cases, and immediately before skin testing in concurrent cases. Pholcodine consumption was classified as 'definite', 'uncertain', or 'absent', and determined by seeking a history of cough suppressant use, and then determining if the consumed suppressant contained pholcodine. 'Definite' pholcodine consumption required patient confirmation using a picture of the pharmaceutical packaging for the consumed preparation. 'Absent' consumption was defined as no history of use of cough medicines or consumption of a cough medicine that was identified as not containing pholcodine, and 'uncertain' consumption was defined as possible or certain consumption of a cough suppressant but which could not be identified sufficiently to determine whether or not it contained pholcodine.

BMI was collected as continuous data, but analysed as both a dichotomous variable (BMI greater or less than 30 kg m^{-2}) to answer the question of whether obesity is associated with NMBA anaphylaxis, and as a grouped ordinal variable to assess 'dose–response' and allow estimation of risk for different degrees of obesity in a clinically useful form (the clinically relevant WHO grades of obesity). Assessment of confounding by stratification using the Mantel–Haenszen test required obesity to be entered as a dichotomous variable (BMI greater or

less than 30 kg m^{-2}). For simultaneous assessment of exposure variables for confounding by binomial logistic regression analysis, grades of obesity were modelled as a continuous variable and the assumption of linearity confirmed using the Box–Tidwell test.

NMBA dose before the anaphylactic reaction was recorded, and reported as percentage of recommended induction dose. The exposure variable of interest was whether a dose in excess of the recommended induction dose was administered ('excessive dose'). A dichotomous scale was created with 'excessive' defined as the administration of greater than twice the ED_{95} for a non-depolarising NMBA (ED_{95} of atracurium 0.23 mg kg^{-1}, cisatracurium 0.05 mg kg^{-1}, pancuronium 0.07 mg kg^{-1}, vecuronium 0.05 mg kg^{-1}, mivacurium 0.08 mg kg^{-1}, and rocuronium 0.3 mg kg^{-1}), or greater than three times the ED_{95} (i.e. 1 mg kg^{-1} dose) for suxamethonium.[10,11]

Study size

Sample size calculation was based on the rates of pholcodine consumption for cases of anaphylaxis occurring between 2012 and 2016. The rate of pholcodine consumption in cases was 33% and in controls was 14%. Cases and controls were expected to be enrolled in a 3:2 ratio. A total sample size for an unmatched case-control study was estimated to be 158 patients and was calculated using OpenEpi, version 3, open source calculator (openepi.com) using the approximation by Fleiss and colleagues.[12] This sample size would be adequate to power the study to detect a difference in mean BMI between groups of 3 kg m^{-2} or greater (assuming beta=0.8, s^2=36), and allow the development of a prediction model using binomial logistic regression to assess confounding for four variables (using the conservative criterion of 20 events per number of degrees of freedom required to represent all variables in the model).[13]

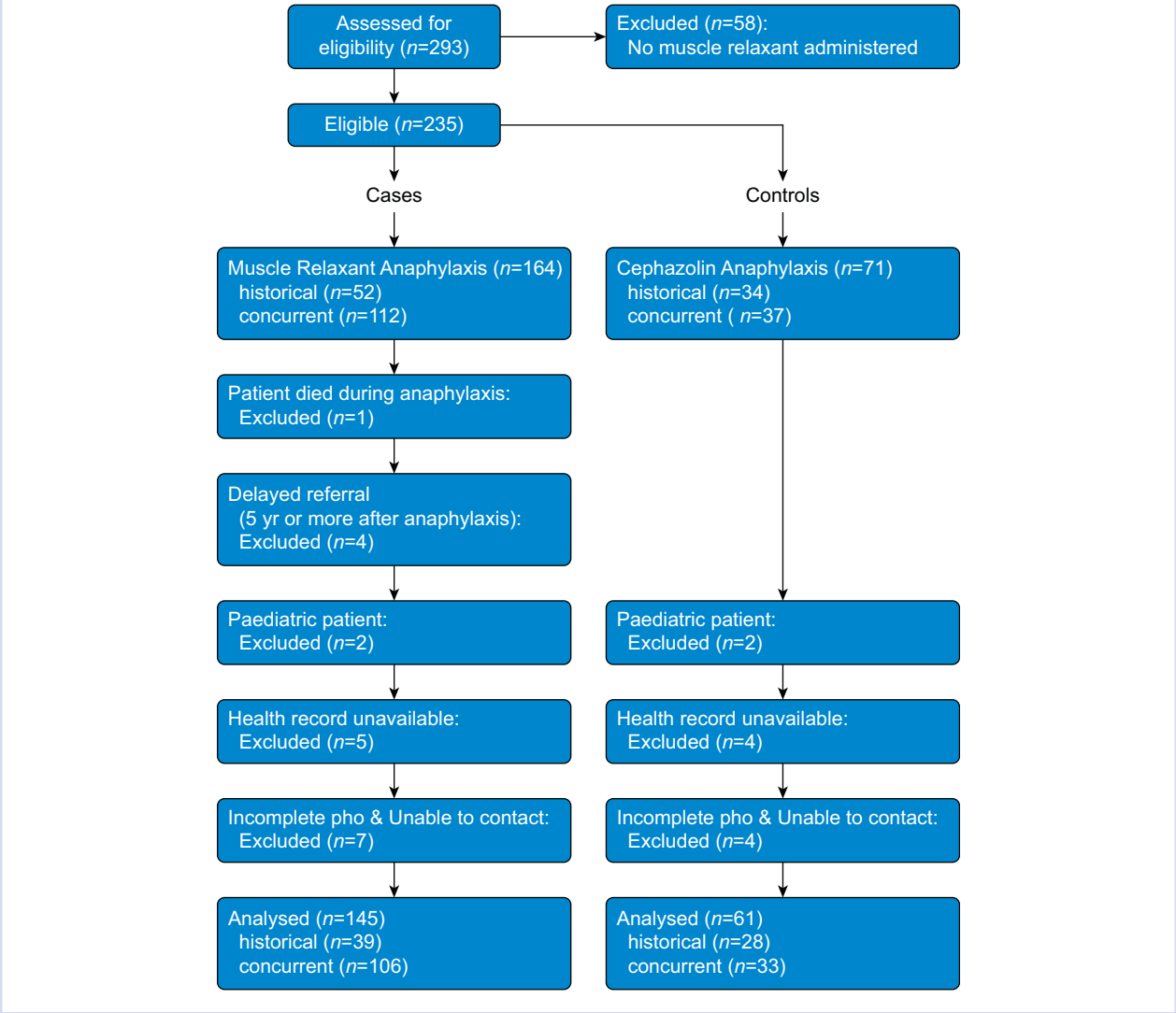

Fig 1. Participant flow chart.

Statistical methods

Categorical variables were recorded as counts with the corresponding proportions. Heterogeneity between groups was tested for categorical variables with the Pearson χ^2 test, and for continuous variables with an independent samples *t* test. Assessment of confounding was initially by stratification analysis using the Mantel–Haenszel test for correlated exposure variables. Confounding was identified by a difference in the stratified and unstratified odds ratio (OR) of >10%, ensuring that there was no evidence of interaction (substantially dissimilar ORs across strata).[14]

Simultaneous controlling for confounding was by binomial logistic regression analysis of identified exposure and confounding variables to develop a predictive model for cases. Proper specification of the model was as described.[15] Variables were included if they had a plausible association with anaphylaxis. Covariates were then removed from the model if they were non-significant (defined at the 0.1 alpha level) and not a confounder (identified by change in parameter estimate of greater than 20%). The assumption of linearity between the independents and the log odds of the dependent was tested using Box–Tidwell test. OR estimates were presented for covariates in the final model. The potential for bias arising from missing data was assessed according to the classification of Rubin, with testing of data missing completely at random (MCAR) by Little's MCAR test.[16] Subjects with data MCAR were analysed by pairwise deletion.

Statistical significance was set *a priori* at $P<0.05$ (two-sided). All analyses were conducted using the Statistical Package for Social Sciences (SPSS) for Mac, Version 21.0 (IBM Corp; Armonk, NY, USA).

Results

We assessed 293 patients for eligibility (Fig. 1); 58 patients with cephazolin anaphylaxis were ineligible (no NMBA administered before anaphylaxis) in the process of creating a restricted control group. A similar proportion of eligible patients in the groups of cases or controls were excluded because of missing documentation of pholcodine consumption and inability to contact the patient to verify status (4.6% *vs* 5.6%) or unavailability of the medical record (3.3% *vs* 5.6%).

The analysed dataset was complete with the exception of peak mast cell tryptase and determination of excessive dose of NMBA administered. Peak mast cell tryptase was missing (not tested at the time of anaphylaxis) in 10% of cases and 15% of controls, and the dose of NMBA administered was not recorded or illegible on the anaesthetic chart in 10% of cases and 8% of controls. Missing data satisfied requirements for MCAR classification ($P=0.701$).

Characteristics of cases and controls are presented in Table 1. There were 206 patients included in the analysis, 67 historical and 139 concurrent. The mean age was 47.5 yr, and comorbid disease (ASA physical status 2–4) was present in 75.2%. Anaphylaxis was severe (grade 3 or 4) in 85.4%, and postoperative ICU admission was required in 74.1% of participants.

The mean BMI of controls (cephazolin anaphylaxis with co-administered NMBA) was similar to that of ineligible patients excluded from enrolment (cephazolin anaphylaxis with no administered NMBA) at 27.7 *vs* 26.0 kg m^{-2}. The control group also had a similar BMI to the Western Australia population mean (27.8 kg m^{-1}, 2012–2018 census), although the proportion of females was greater (55.7% *vs* 50.2%).[17] Definite pholcodine consumption was reported in 4.9% of the control group. Rocuronium was administered to 73.3% of controls, and was

Table 1 Characteristics of participants and univariate analysis of exposure variables. NMBA, neuromuscular blocking agent.

Exposure variables	All	Cases (NMBA)	Controls	*P* value
n	206	145	61	
Age, yr (range)	47.5 (16–89)	48.1 (16–89)	45.8 (16–77)	0.392
Female	146 (70.9%)	112 (77.2%)	34 (55.7%)	0.002*
ASA physical status 1	59 (28.6%)	34 (23.4%)	25 (421.0%)	0.011*
ASA physical status 2	96 (46.6%)	76 (52.4%)	20 (32.8%)	0.010*
ASA physical status 3	45 (21.8%)	33 (22.8%)	12 (19.7%)	0.625
ASA physical status 4	5 (2.4%)	1 (0.7%)	4 (6.6%)	0.012*
BMI (kg m^{-2})	30.9 (29.8–32.0)	32.2 (30.8–33.6)	27.7 (26.1–29.3)	<0.001*
BMI ≤29.9 kg m^{-2}	104 (50.5%)	62 (42.8%)	42 (68.9%)	<0.001*
BMI 30–34.9 kg m^{-2}	52 (25.2%)	39 (26.9%)	13 (21.3%)	0.400
BMI 35–39.9 kg m^{-2}	27 (13.1%)	23 (15.9%)	4 (6.6%)	0.071
BMI ≥40 kg m^{-2}	23 (11.2%)	21 (14.5%)	2 (3.3%)	0.020*
No pholcodine consumption	87 (42.6%)	54 (37.8%)	33 (54.1%)	0.031*
Uncertain pholcodine consumption	53 (26.0%)	28 (19.6%)	25 (41.0%)	<0.001*
Definite pholcodine consumption	64 (31.4%)	61 (42.7%)	3 (4.9%)	<0.001*
Rocuronium	151 (73.7%)	107 (73.8%)	44 (73.3%)	1.000
Percentage of recommended NMBA	109% (104–114%)	108% (101–114%)	111% (102–120%)	0.531
Excessive dose NMBA	105 (56.8%)	68 (52.7%)	37 (66.1%)	0.107
Outcome	All	Cases (NMBA)	Controls	P value
Anaphylaxis severity grade 1	4 (1.9%)	2 (1.4%)	2 (3.3%)	0.367
Anaphylaxis severity grade 2	26 (12.6%)	16 (11.0%)	10 (16.4%)	0.217
Anaphylaxis severity grade 3	136 (66.0%)	93 (64.1%)	43 (70.5%)	0.379
Anaphylaxis severity grade 4	40 (19.4%)	33 (23.4%)	6 (9.8%)	0.024*
Mast cell tryptase peak (μg L^{-1})	38.6 (32.0–45.2)	41.6 (33.1–50.0)	31.1 (22.1–40.1)	0.154
Surgery abandoned	129 (62.6%)	94 (64.8%)	35 (57.4%)	0.207
Postoperative ICU admission	152 (74.1%)	109 (75.2%)	43 (71.7%)	0.603

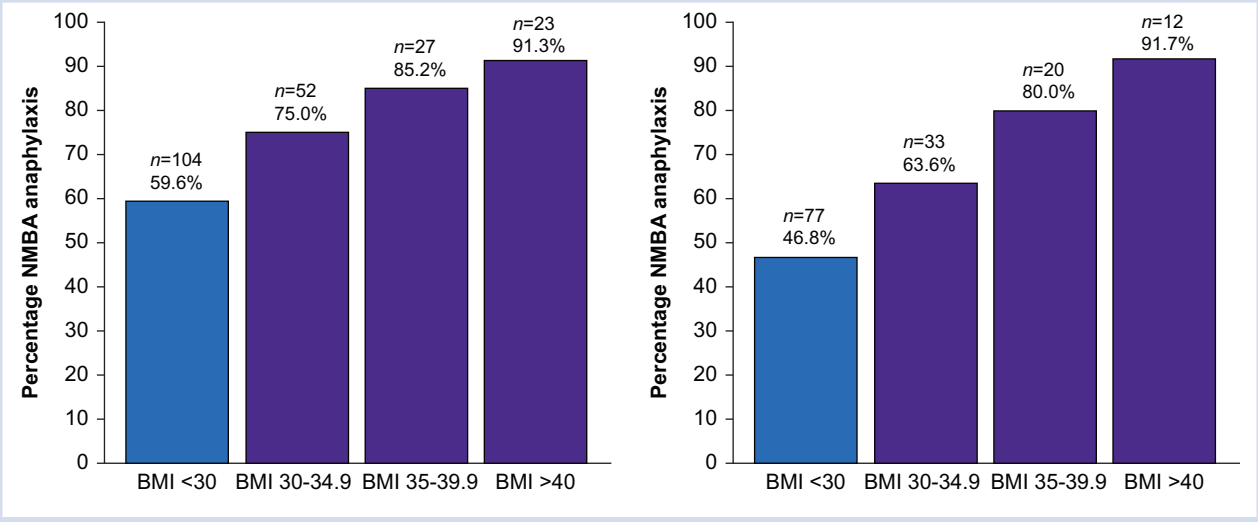

Fig 2. Percentage of subjects in each BMI grade with neuromuscular blocking agent (NMBA) anaphylaxis. Left panel: all subjects; right panel: subjects without a history of 'definite' pholcodine exposure.

the responsible trigger in 73.8% of cases of NMBA anaphylaxis. In comparison, vecuronium was administered to 14.8% of controls, and was the responsible trigger in only 4.9% of cases of NMBA anaphylaxis.

Outcomes

A BMI >29.9 kg m^{-2} (OR=2.96, 95% CI 1.57–5.58, χ^2=11.7, P=0.001), definite pholcodine consumption (OR=14.0, 95% CI 4.2–46.9, χ^2=27.7, P<0.001), and female sex (OR=2.70, 95% CI 1.42–5.10, χ^2=9.62, P=0.002) were significantly associated risk factors for NMBA anaphylaxis on univariate analysis.

Compared with patients with a normal BMI, grade 1 obesity (BMI 30–34.9 kg m^{-2}), grade 2 obesity (BMI 35–39.9 kg m^{-2}), and grade 3 obesity (BMI ≥40 kg m^{-2}) had increasing proportions of patients with NMBA anaphylaxis (59.6%, 75.0%, 85.2%, and 91.3%, respectively; χ^2=14.0, P=0.03). This 'dose–response' relationship persisted in patients who did not have a history of 'definite' pholcodine exposure (Fig. 2). 'Definite' pholcodine consumption in the 12 months before anaphylaxis was reported in 31.1% of study participants. Obese patients had a higher, but not statistically significant, percentage with 'definite' consumption than non-obese patients (36.3% *vs* 26.0%, OR=1.62, 95% CI 0.895–2.946, χ^2=2.557, P=0.11). The rate was higher in concurrent compared with historical cases (34.5 *vs* 23.9%, χ^2=2.39, P=0.122), and the difference in reported rates was also higher in this subgroup (45.3% in cases *vs* 0.0% in controls; χ^2=22.8, P<0.001) compared with historical subjects (33.3% in cases *vs* 10.7% in controls; OR=4.17, 95% CI 1.06–16.4, χ^2=4.59, P=0.032). Overall, 'definite' pholcodine consumption' dramatically increased the odds of NMBA anaphylaxis compared with 'no pholcodine consumption' (OR=12.4, 95% CI 3.61–42.9, P=0.0001). There was no significant difference between 'uncertain' pholcodine consumption and 'no' pholcodine consumption in the odds of NMBA anaphylaxis (OR=0.684, 95% 0.34–1.37, P=0.28; Fig. 3).

Cases and controls were of comparable ages, with a similar NMBA dose administered (as a percentage of recommended induction dose; cases 108% *vs* controls 111%, P=0.520). Comorbid disease (ASA physical status 2–4) was similar in cases compared with controls (75.9% *vs* 73.8%, χ^2=0.101, P=0.751) as was severity of anaphylaxis when assessed by peak mast cell tryptase, proportion of surgical procedures abandoned, and postoperative intensive care admissions. However, more cases than controls suffered grade 4 anaphylaxis (23.4% *vs* 9.8%, χ^2=5.08, P=0.024). Obesity was associated with severe anaphylaxis (grade 3 or 4 91.2% *vs* 79.8%; OR=2.61 [95% CI 1.13–6.03], χ^2=5.35, P=0.021).

An 'excessive dose' of NMBA was less common in cases than controls, although this result was not statistically

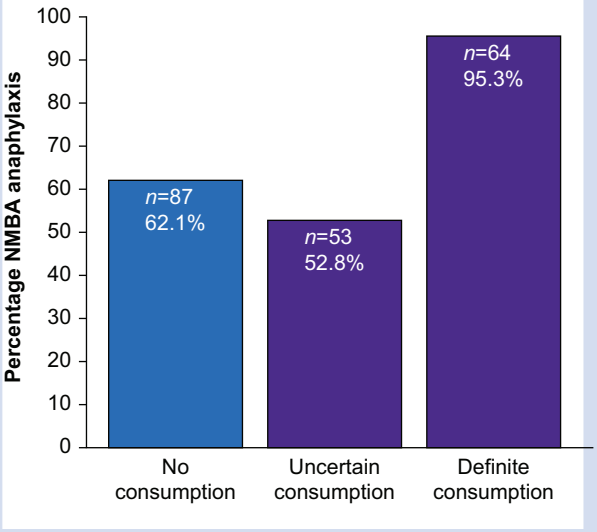

Fig 3. Percentage of subjects with neuromuscular blocking agent (NMBA) anaphylaxis in the categories of 'No', 'Uncertain' and 'Definite' pholcodine consumption (62.1%, 52.8%, and 95.3%, respectively; χ^2=29.6, P<0.001).

Table 2 Stratification tables for the significant exposure variables on univariate analysis. OR, odds ratio; pho, pholcodine.

	Female−	Female+	Breslow–Day	Crude OR	Corrected OR	Mantel–Haenszel
Obese	2.70	2.73	0.983	2.96	2.71	0.002
Definite pho	14.9	12.0	0.893	14.0	13.1	<0.001
	Obese−	**Obese+**	**Breslow–Day**	**Crude OR**	**Corrected OR**	**Mantel–Haenszel**
Female	2.40	2.44	0.983	2.70	2.42	0.013
Definite pho	29.6	6.20	0.211	14.0	12.5	<0.001
	Definite pho−	**Definite pho−**	**Breslow–Day**	**Crude OR**	**Corrected OR**	**Mantel–Haenszel**
Obese	3.22	0.673	0.200	2.96	2.81	0.004
Female	2.44	2.04	0.893	2.70	2.41	0.019

significant (52.7% *vs* 66.1%, χ^2=2.84, OR=0.572, P=0.092). There was no evidence that an excessive dose of NMBA was associated with increased severity of anaphylaxis (grade 3 or 4 anaphylaxis in 83.8% of participants receiving an excessive dose *vs* 91.3% in those who did not, χ^2=2.23, OR=0.496, P=0.136; ICU admission in 72.4% receiving an excessive dose *vs* 77.5%, χ^2=0.628, OR=0.761, P=0.428). When expressed as a percentage of the recommended NMBA induction dose, there was an inverse correlation with participant BMI (Pearson correlation −0.305, P<0.001).

There was no significant difference in the proportion of cases or controls receiving rocuronium (73.8% *vs* 73.3%, χ^2=1.02, P=0.946). There was also no significant difference in the number of obese patients receiving rocuronium compared with the non-obese (75.2% *vs* 72.1%, χ^2=0.259, P=0.611), or for different BMI grades (grade 1 72.1%, grade 2 72.5%, grade 3 77.8%, grade 4 78.3%, χ^2=0.647, P=0.886).

Assessment of confounding by stratification is presented in Table 2. Definite pholcodine consumption was more common in the obese (BMI >29.9 kg m^{-2} in 36.3% *vs* 26.0%, OR=1.62, P=0.11) and females (34.9% *vs* 21.7%, OR=1.94, P=0.062), but neither result was statistically significant. Females were also more likely to be obese than males (54.1% *vs* 38.3%, OR=1.90, P=0.040). These dichotomous exposure variables were stratified according to the other two significant variables. When stratified by sex, the association between obesity and NMBA anaphylaxis was similar, and the stratum-corrected OR (using the Mantel–Haenszel method) varied from the unstratified OR by <10%. However, when stratified by obesity, the association between sex and NMBA anaphylaxis varied by a larger degree, and the stratum-corrected OR varied from the unstratified OR by >10%. There was evidence of interaction between the exposure variable 'definite' pholcodine consumption and the associations of both obesity and sex with NMBA anaphylaxis; however, this analysis relies on a very small number of cases (3) in the control group who did have a history of 'definite' pholcodine exposure.

Relationships amongst the covariates without missing data were considered using binomial logistic regression. The initial model included definite pholcodine consumption (OR=12.7), BMI grade (OR=1.75 per grade), female sex (OR=2.11), and age (OR=1.01 per year), all factors with P <0.25 on univariate analysis. Rocuronium as NMBA drug was added. Comorbid disease (ASA physical status) was not entered owing to the potential for multicollinearity with BMI grade (BMI grade 3 is a criterion for ASA 3). The initial and final models are presented in Table 3. BMI grade was approximated in the model as a scale variable with values of 1 (BMI ≤29.9 kg m^{-2}), 2 (BMI 30–34.9 kg m^{-2}), 3 (BMI 35–39.9 kg m^{-2}), and 4 (BMI ≥40 kg m^{-2}). Linearity of the logit was demonstrated with Box–Tidwell test (P=0.999). In the initial model, history of definite pholcodine consumption, BMI grade, and female sex were significant factors. Non-significant (P>0.10) and non-confounding (change in parameter estimates <20%) covariates were removed sequentially, resulting in a final model that included only pholcodine consumption, BMI grade, and female sex, the

Table 3 Initial and final binomial logistic regression model for NMBA anaphylaxis. CI, confidence interval; NMBA, neuromuscular blocking agent.

	P value (Wald)	Adjusted odds ratio	95% CI
Initial model			
Definite pholcodine consumption	<0.001	12.7	3.73–43.3
BMI grade	0.008*	1.75/grade	1.16–2.64/grade
Female	0.050*	2.11	1.00–4.45
Age (yr)	0.317	1.01/yr	0.99–1.03
Rocuronium	0.816	0.913	0.42–1.97
Final model			
Definite pholcodine consumption	<0.001*	12.7	3.75–43.1
BMI grade	0.004*	1.80/grade	1.20–2.70/grade
Female sex	0.085	1.88	0.92–3.84

* p value less than or equal to 0.05

three exposure variables considered in stratification analysis. After simultaneous correction for confounding, definite pholcodine consumption and BMI grade remained the only significant factors.

Exclusion of historical cases and controls did not alter the statistically significant association between either obesity or definite pholcodine consumption with NMBA anaphylaxis in the remaining 139 concurrently enrolled participants. To decrease the likelihood of pholcodine exposure misclassification causing bias, analysis was repeated with pholcodine exposure considered to have occurred in all cases with definite or uncertain consumption as an estimate for the boundary of the minimum effect of pholcodine consumption. Considering only concurrent cases, this definition of pholcodine consumption was associated with 56.6% of cases, but only 36.4% of controls (OR=2.28, χ^2=4.13, P=0.042). Binomial logistic regression indicated that this remained a significant factor after correction for confounding (Table 4).

Discussion

This case-control study identified obesity as a novel risk factor for NMBA anaphylaxis, a plausible explanation for the higher anaphylaxis rate in bariatric surgical patients. The mean BMI of cases was almost 5 kg m^{-2} greater than that of controls, and the OR of NMBA anaphylaxis was 3.8 times greater for obese participants (BMI >29.9 kg m^{-2}). The risk increased with increasing degrees of obesity, such that the OR for participants with super-morbid obesity (BMI ≥40 kg m^{-2}) was 7.0 times that of non-obese participants.

Obesity was associated with NMBA anaphylaxis independently of pholcodine consumption. This is the first time pholcodine consumption has been shown to be a risk factor for NMBA anaphylaxis in a clinical study, which supports the pholcodine hypothesis. Female sex has been identified previously as a risk factor for NMBA anaphylaxis.[4]

The strength of this study is in the restricted selection of controls. Not all patients undergoing anaesthesia require administration of an NMBA, which are reserved for patients with particular characteristics (unfasted, obese, anatomical abnormalities) or having certain surgical procedures (e.g. intra-abdominal or intracranial). If cases (anaphylaxis triggered by an NMBA) were compared with controls that did not receive an NMBA, we might find we are measuring the indications for its administration. For example patients with cephazolin anaphylaxis who did not receive an NMBA (and therefore were ineligible for inclusion) had a lower mean BMI than the control group. Selection of controls was intended to minimise selection bias, as selection by virtue of indication for NMBA was therefore equally distributed between cases and controls. Cases and controls were also comparable with regard to age, ASA physical status, and severity of anaphylactic reaction (anaphylaxis grade, peak tryptase, proportion in whom the surgical procedure was abandoned, and proportion requiring ICU admission).

Alternative explanations for the observed associations include random error or systematic error. Systematic errors were minimised by using a restricted control group that was indistinguishable from the case group at the time of data collection. Selection bias was minimised by choosing a homogeneous group of patients who all received an NMBA and had all suffered perioperative anaphylaxis. Characteristics associated with either NMBA administration or anaphylaxis would therefore be expected to be equally distributed between groups. Previous exposure to an NMBA was not able to be accurately discovered and is a potential confounding factor, but has not been shown to increase the risk of perioperative anaphylaxis.[18,19] Recall bias was minimised by limiting the period of consumption to 12 months before the reaction (IgE antibodies return to pre-exposure levels after 1–2 yr), and by determining history of pholcodine consumption and BMI before skin testing in concurrent cases.[20] Both participants and investigators were blinded to triggering agent or whether participants would be eligible at the time consumption was determined. The association between 'definite' pholcodine consumption and NMBA anaphylaxis was greater when the minority of participants with historically collected exposure and outcome status were excluded from analysis. The association persisted when pholcodine consumption was considered to include both cases with a definite history and uncertain history of consumption.

The rate of pholcodine consumption in patients who were determined to have NMBA anaphylaxis was very high but consistent with previous estimates. Sera collected during 2009–12 were found to contain phocodine-specific IgE antibodies in 10% of Australian patients, 12.5 times the rate in countries where pholcodine is not available.[21] As the rate of sensitisation after consumption is estimated to be 20–25% of individuals, this would be consistent with a prevalence of pholcodine consumption of 40–50%. This is

Table 4 Logistic regression model for concurrent cases with pholcodine exposure as the aggregate of definite and uncertain consumption. CI, confidence interval.

	P value (Wald)	Adjusted odds ratio	95% CI
Initial model			
Definite pholcodine consumption	0.043*	2.50	1.03–6.09
BMI (kg m^{-2})	0.001*	1.15	1.06–1.25
Female	0.035*	2.70	1.07–6.80
Age (yr)	0.682	0.99	0.97–1.02
Rocuronium	0.585	1.32	0.49–3.54
Final model			
Definite pholcodine consumption	0.047*	2.45	1.01–5.91
BMI (kg m^{-2})	<0.001*	1.15	1.06–1.24
Female sex	0.025*	2.80	1.14–6.91

* p value less than or equal to 0.05

consistent with an estimate that 40% of the population of Norway was exposed to pholcodine before its withdrawal in 2007.[20]

Confounding between exposure variables obesity, pholcodine consumption, and sex was detected. Obese patients were more likely to have a history of pholcodine consumption and were more likely to be female. There was also evidence of interaction between variables, with variation in stratum-specific ORs depending on the presence or absence of pholcodine consumption. Both physiological and behavioural causes of interaction are plausible. Obese patients report a higher frequency of upper and lower respiratory tract infections, and it is possible that the use of antitussives in this group is increased.[22] Pholcodine is highly lipid soluble and able to be detected in the urine of patients at least 7 weeks after a single dose.[23,24] It is possible that obesity increases the efficacy or duration of the sensitising effect of pholcodine as a consequence of long-lived accumulation in adipose tissue. However, the largest difference in risk associated with obesity occurred in the stratum of patients who had no history of pholcodine consumption. A possible explanation is that an unidentified sensitiser other than pholcodine exists in the community, and that obese patients are either more likely to be exposed, or that exposure is more likely to result in sensitisation to NMBAs.[25,26] Obesity, but not sex or pholcodine consumption, was also associated with increased severity of anaphylaxis (grade 3 or 4). It is possible that this is a physiological interaction rather than immunological as comorbid disease was more common in obese participants.

Dose of NMBA administered has been suggested as a factor in antibody-independent activation of anaphylaxis, such as via mas-related G protein-coupled receptors.[27] Although there was no significant difference in dose of NMBA administered when corrected for weight between groups, obese patients receive a larger absolute dose of NMBA. NMBAs are generally given as a rapid injection irrespective of the dose administered, and it is plausible that obese patients are administered the drug at a higher injection rate and achieve higher instantaneous blood concentrations than the non-obese. Nonetheless, we failed to see an association between dose of NMBA and severity of reaction in our population of exclusively IgE-mediation anaphylaxis. This is expected as patients were diagnosed with IgE-dependent anaphylaxis, supporting the evidence that this does not involve mas-related G protein-coupled receptors.

Patients anaesthetised for bariatric surgery appear to have a higher than expected risk of perioperative anaphylaxis in Western Australia. The Poisson estimate for the incidence of perioperative anaphylaxis was 74.9 per 100 000 anaesthetics (95% CI 46.4–128/100 000). The 6th National Audit Project (NAP6) found an overall incidence of perioperative anaphylaxis of 8.5 per 100 000 anaesthetics in the UK in 2016 (95% CI 7.5–9.6 per 100 000 anaesthetics).[28] This statistically significant eight-fold increase in risk in bariatric surgery patients was predominantly the consequence of anaphylaxis to NMBAs, as the rate of cefazolin anaphylaxis in patients presenting for bariatric surgery occurred at an expected incidence of 10.7 per 100 000 anaesthetics.[29]

Rocuronium was the NMBA responsible for the majority of cases of anaphylaxis. It is also the most frequently administered NMBA in Western Australia, favoured because of its rapid onset at high dose, intermediate duration of action, and ability to be antagonised with sugammadex. These characteristics make it particularly useful in the obese; however, we did not observe that it was more commonly used in cases than controls. As rocuronium was the NMBA administered in the majority of both cases and controls, it is possible that the risk factors measured are specific for rocuronium rather that general to all NMBAs. Rocuronium has an increased rate of anaphylaxis compared with vecuronium.[6] If we assume that controls were randomly selected from the population of patients receiving cefazolin by virtue of suffering anaphylaxis, the identity of the NMBA administered to this selected group can be considered a random sample of the population; 72.1% received rocuronium, compared with vecuronium in 14.8%. However, over the same period rocuronium was responsible for 73.8% of cases of NMBA anaphylaxis *vs* 4.8% from vecuronium. This would suggest that, for each dose of rocuronium or vecuronium administered, the rate of anaphylaxis for rocuronium is 3.0 times that of vecuronium. This is remarkably close to the estimate of 2.9 we made in 2011 from a non-overlapping observational series based on NMBA ampoule sales data. Clinicians should consider that rocuronium might not produce the optimal expected utility in obese patients.[30]

Conclusions

Obese patients are more likely to suffer NMBA anaphylaxis than the non-obese, and the association is greater with increasing BMI grade. This relationship is also a feature of the subgroup of patients who did not have a history of pholcodine consumption. The severity of anaphylaxis was also increased in obese patients. Patients presenting for bariatric surgery have a particularly high risk of NMBA anaphylaxis compared with the general surgical population. Pholcodine is an independent risk factor for NMBA anaphylaxis, consistent with the pholcodine hypothesis, and this is the first time this has been shown in a clinical trial. Its role in sensitising patients to NMBAs may have implications for the availability and licensing of this drug.

Authors' contributions

Conception and design of the study: PS, RC, CG, PP
Acquisition of data: RC, CG, PP, CD, AM
Analysis and interpretation of data: WW, CD, PS
Writing of the first draft of the manuscript: PS, WW, CD
All authors made substantial contributions to revising content and approved for the final version to be published. All authors agree to be accountable for all aspects of the work.

Declaration of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.12.018.

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