

ORIGINAL ARTICLE

Anaphylaxis

Neuromuscular blocking agents induced anaphylaxis: Results and trends of a French pharmacovigilance survey from 2000 to 2012

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Abstract

Background: Perioperative anaphylaxis mainly involves neuromuscular blocking agents (NMBAs) with an IgE-mediated mechanism. In France, this life-threatening condition is reported by anesthetists and allergologists, and two safety alerts concerning suxamethonium were raised in 2011 and 2012. This led to start a national survey over the 2000-2012 period which objectives were to provide a descriptive analysis, to estimate incidence rates, and to analyze the trends over this period.

Methods: The French pharmacovigilance database was retrospectively queried for all the available NMBAs. Anaphylaxis cases with elevated tryptase and positive skin tests were qualified as “confirmed cases.” Subgroup analysis compared atracurium and cisatracurium vs suxamethonium and rocuronium.

Results: A total of 680 confirmed cases and 944 nonconfirmed cases were identified. Suxamethonium was the most implied NMBA (64%). Incidence rates (according to sales data) of suxamethonium and rocuronium were, respectively, 10- and 13-folds higher than those of the others NMBAs, regardless the confirmed/nonconfirmed status. Cisatracurium incidence rates remained stable over the period, while suxamethonium and atracurium increased and rocuronium first decreased but re-increased after 2006. Male patients were more frequent in the subgroup “atracurium-cisatracurium” ($P = .019$), whereas obesity and emergency setting were more frequent in the subgroup “rocuronium-suxamethonium.” Shared characteristics were the poorly documented previous exposure to NMBA(s) and an insufficient adherence of patients to perform skin tests, showing the need to improve this procedure.

Conclusion: Suxamethonium and rocuronium are markedly more involved in perioperative anaphylaxis than the other available NMBAs. Patients should be more informed about their perioperative anaphylaxis and its consequences.

KEYWORDS

anaphylaxis, Incidence, neuromuscular blocking agents, rocuronium, suxamethonium

1 | INTRODUCTION

Perioperative anaphylaxis is a real concern for anesthetists and mainly involves neuromuscular blocking agents (NMBAs) with an IgE-mediated mechanism.¹⁻³ Despite epinephrine and aggressive fluid therapy for the management of severe anaphylactic reactions, about 4% of cases of NMBA anaphylaxis have a fatal outcome.⁴ NMBAs belong to a variety of chemical families, all of them displaying two ammonium groups, which are either two quaternary ammonium ions (QAI) or one QAI and a tertiary protonated amine, accounting both for the ability to induce neuromuscular blockade and for NMBA binding to IgE.¹ One depolarizing NMBA (suxamethonium or succinylcholine [SUX]) and six nondepolarizing NMBAs are currently available worldwide. Among nondepolarizing NMBAs, three have a substituted tetrahydroisoquinoline chemical structure, *that is*, atracurium (ATRA), cisatracurium (CIS), and mivacurium (MIV), and three have a steroidal structure, *that is* pancuronium (PAN), rocuronium (ROC), and vecuronium (VEC).

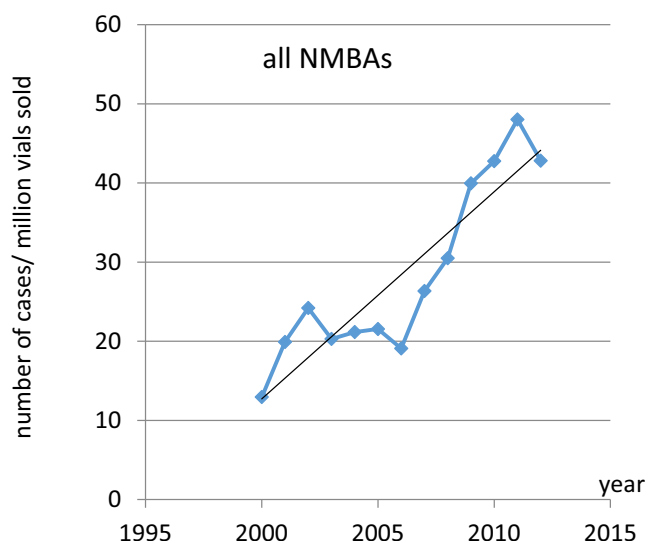
IgE-mediated reactions are diagnosed by the combination of a typical clinical anaphylaxis picture,⁵ elevated serum tryptase at the time of the reaction and, around 6 weeks later, positive skin testing (skin prick test [SPT] and intradermal test [IDT]) and/or in vitro tests.⁶⁻⁸ Skin testing involves the incriminated NMBA but also the other available NMBAs in order to detect cross-reactivity and to provide recommendations on the safe use of other NMBA(s) for future anesthesia.⁹ In vitro tests remain discussed, as specific IgE (sIgE) to morphine (c260 ImmunoCAP®-Phadia) or to SUX (c202 ImmunoCAP(R)-Phadia) lack specificity, whereas basophil activation tests lack of sensitivity and validated decision thresholds.¹⁰ However, in cases with fatal outcome with a typical clinical presentation and increased tryptase, positive sIgE are sometimes the only test to give a trend to the diagnosis.

In France, perioperative anaphylactic reactions are commonly reported by anesthetists to the network of Regional Pharmacovigilance Centres (RPvC) and by allergologists to the Groupe d'Etudes des Réactions Anaphylactiques Peranesthésiques (GERAP).^{2,3,11-13} The GERAP closely collaborates with the RPvCs network, so that finally the French National Pharmacovigilance Database (FPvD) implemented by RPvCs becomes a high quality source to study perioperative anaphylaxis.

In 2011 and 2012, two safety alerts concerning a possible increase in SUX-induced anaphylaxis were raised by RPvCs and led the French Medicine Agency (Agence Nationale de Sécurité du Médicament et des produits de santé, ANSM) to start in February 2012 a global survey on NMBA anaphylaxis covering the 2000-2012 period.

During this period, the "NMBA landscape" underwent some changes, with the availability of generics for ATRA, CIS, and SUX, the commercialization of sugammadex, a cyclodextrin which reverses neuromuscular blockade with the aminosteroid nondepolarizing muscle relaxants ROC and VEC,¹⁴ and the discontinuation of the marketing of PAN.

The first objective of this work was to provide a descriptive analysis of NMBA-induced anaphylactic reactions recorded in the FPvD



GRAPHICAL ABSTRACT

Perioperative anaphylaxis mainly involves neuromuscular blocking agents (NMBAs), and over the 2000-2012 period, suxamethonium and rocuronium each had anaphylaxis incidence rates more than ten-fold higher than atracurium and cisatracurium. Over this 13-year period, the incidence rate of NMBA anaphylaxis showed a significant increase for suxamethonium and atracurium, whereas it remained stable for cisatracurium. Rocuronium displayed a 2-period curve with a significant increase from 2005. Patients need to be more aware about the importance of allergological skin tests for ensuring safe further anesthetic procedures.

over the 2000-2012 survey period and to estimate incidence and severity rates, with a separate analysis of the group of confirmed IgE-mediated anaphylactic reactions. The second objective was to analyze the evolution of the main characteristics over the study period.

2 | METHODS

The FPvD was queried in June 2014 for all adverse effects, with onset between 01/01/2000 and 31/12/2012, relating to any of the 7 NMBAs available in France during this period, *that is*, ATRA, CIS, MIV, ROC, SUX, VEC, and PAN, irrespective of the originator or generic status.

2.1 | Case definition of NMBA related IgE-mediated anaphylaxis

Cases of NMBA anaphylaxis had to display (1) typical features of NMBA anaphylaxis (ie, close relation between drug injection and clinical anaphylaxis symptoms, no other causes for the hypersensitivity reaction or shock); (2) no other drug or substance (eg, antibiotic, dye, hydroxyethyl starch, and latex) with higher causality assessment¹⁵ than the NMBA; (3) at least one of these parameters:

elevated serum tryptase or serum histamine within the 2 hours of the anaphylactic reaction; positive results of quaternary ammonium or NMBA-specific IgE test; and positive skin tests (SPT and/or IDT). Elevated basal tryptase was taken into account when it was available to exclude cases of mastocytosis.

Cases with both elevated tryptase and positive skin tests were qualified as "NMBA confirmed IgE anaphylaxis," named "confirmed cases" in the study. The other cases were considered as nonfully confirmed IgE anaphylaxis in the study and therefore qualified as "nonconfirmed IgE anaphylaxis."

2.2 | Data collection

Patient's characteristics were collected including sex, age, and body mass index (BMI); previous exposure to a NMBA; medical condition (ie, hypertension, other cardiovascular disease, and diabetes); and drug allergies (NMBA or others). Past exposure to NMBA was approached through previous surgical history, prior history of anaphylaxis during anesthesia, and previous bariatric surgery which is a condition of certain NMBA exposure. Patients were considered obese if BMI was ≥ 30 or if the narrative clearly stated that the patient was obese and not just overweight.

Characteristics and setting of the anaphylactic reaction were assessed through type of NMBA; type of surgery (categorized in cardiovascular; cutaneous (including abscess and wound repair); ear-nose-throat (ENT), including dental; endoscopic procedures; urinary and reproductive organs; neurological (including ophthalmological); orthopedic; visceral (digestive, thyroid, and chest surgery); and emergency intubation); emergency setting (clearly specified or peritonitis, intestinal perforation, testis strangulation, and intubation in intensive care unit (ICU)); outcome of the anaphylactic reaction (fatal or not); and the severity of the reaction according to a scale adapted from Ring

and Messmer.⁵ Grades 3 and 4 reactions were considered as severe reactions, and grade 1 and grade 2 reactions were considered as non-severe. Results of allergy skin tests (SPT, IDT) were recorded and, when available, cross-reactivity to other NMBAs was also collected.

2.3 | Sales data

Sales data between 2000 and 2012 were obtained from the marketing authorization holders for ROC, MIV, VEC, ATRA, and PAN, and from the ANSM for SUX and CIS.

2.4 | Statistical analysis

Demographic, clinical, anesthetic, and perioperative reaction data were expressed as means $\pm$ SD (quantitative variables) and percentages (qualitative variables). Variables describing cases of anaphylactic reactions were compared by bivariate analysis (chi-square test for categorical variables and Student's *t* test for continuous variables). Comparisons between confirmed cases and nonconfirmed cases, and between NMBAs were made by the Student's *t* test. Incidence trends were assessed by linear regression, and the significance of the slope was tested with Student's *t* test at 11 degrees of freedom and a 0.1% alpha risk. We used SAS software, version 9.3 (SAS Institute, Cary, NC).

3 | RESULTS

Over the 12-year study period, the query retrieved 1624 cases of NMBA anaphylaxis among which 680 were confirmed IgE-dependent anaphylaxis (confirmed cases), and 944 cases were non-IgE-dependent confirmed anaphylaxis (nonconfirmed cases) (Figure 1).

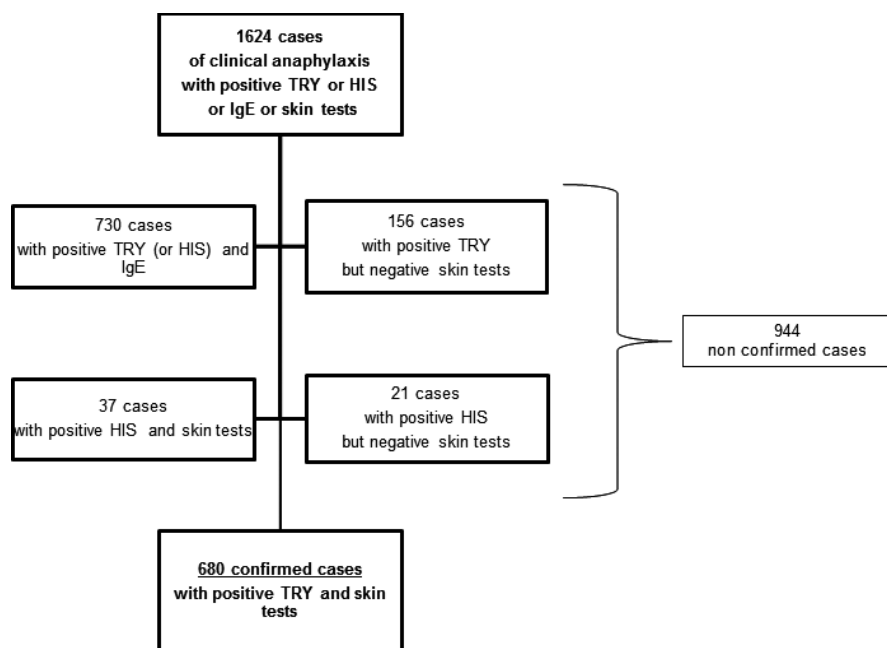


FIGURE 1 Results of the query and distribution according to results of tryptase (TRY), histamine (HIS), specific IgE, and skin tests

TABLE 1 Numbers of cases and incidence rates (per million of sold vials) for each NMBA between 2000 and 2012 in France

	All cases				Confirmed cases				Nonconfirmed cases			
	n	%	Incidence rate	95% CI	n	%	Incidence rate	95% CI	n	%	Incidence rate	95% CI
ATRA	258	15.9	11.2	9.9-12.7	84	12.4	3.6	2.9-4.5	174	18.4	8	6.5-8.8
CIS	107	6.6	6.3	5.2-7.6	33	4.9	1.9	1.3-2.7	74	7.8	4	3.5-5.5
ROC	156	9.6	117.6	99.9-137.6	55	8.1	41.5	31.2-54.0	101	10.7	76	62.0-92.5
SUX	1039	64	147.6	138.8-156.9	494	72.6	70.2	64.4-77.0	545	57.7	77	70.8-83.9
MIV	15	0.9	9.5	5.3-15.7	3	0.4	1.9	0.4-5.6	12	1.3	8	3.9-13.3
VEC	34	2.1	12.4	8.6-17.3	7	1	2.5	1.0-5.2	27	2.9	10	6.5-14.3
PAN	15	0.9	6.3	3.6-10.5	4	0.6	1.7	0.5-4.3	11	1.2	5	2.3-8.3
All NMBA	1624	100	29.5	20.8-30.9	680	100	12.3	11.4-13.3	944	100	17.1	16.0-18.3

ATRA, atracurium; CIS, cisatracurium; MIV, mivacurium; PAN, pancuronium; ROC, rocuronium; SUX, suxamethonium; VEC, vecuronium.

3.1 | Type of NMBA, incidence rates

3.1.1 | Global assessment (Table 1)

SUX was the most implied NMBA, with 1039 cases including 494 confirmed cases and 545 nonconfirmed cases, followed in order by ATRA, ROC, CIS, VEC, PAN, and MIV. When taking in account sales data, the global "all NMBA" anaphylaxis incidence was 29.5 cases per million vials (1624 cases/55 126 323 vials; 95% CI 28.0-30.9)), and SUX and ROC, respectively, had an incidence rate 10- and 13-folds higher than ATRA, CIS, MIV, VEC, or PAN.

In the group of confirmed cases, the "all NMBA" incidence was 12.3 cases per million vial (95% CI 11.4-13.3). The incidence rate of SUX anaphylaxis was twice higher than ROC, 19-fold higher than ATRA, and 22-fold higher than CIS. ROC had an incidence rate 11-fold higher than ATRA and 37-fold higher than CIS. In the group of nonconfirmed cases, the incidence rate was the same for ROC and SUX, being 10-fold higher than ATRA, and 19-fold higher than CIS.

3.1.2 | Changes over the 2000-2012 period

The evolution of annual incidence rates, expressed in number of cases per million vials sold, showed stability for CIS an increasing trend for SUX and a "2-period" curve for ROC with a decrease up to 2006 and a re-increase from 2007 (Figure 2A-B), regardless the confirmed (or nonconfirmed) status. ATRA also showed an increasing trend, significant only for confirmed cases (alpha risk 0.1%).

3.2 | Patients' and anaphylaxis characteristics

3.2.1 | Global assessment

Patients were mainly women (62.5%) with an overall mean age of 51.7 ± 15.0 years. Most of cases were severe (56.2% grade 3 reactions and 13.1% grade 4), and 3.8% had fatal outcome. Patients with

fatal outcome were mainly males (62.2%). Visceral surgical setting was the most frequent (33.2%), followed by orthopedics (11.5%), gynecological/urological (10.5%), dental/ENT (4.7%), endoscopy (4.3%), cardiovascular (3.8%), skin/abscess (2.0%), neurological/ophthalmological (1.9%), and intubation (0.7%). The type of surgery was not documented in 32.0%.

Characteristics of the confirmed and the nonconfirmed groups are detailed in Table 2. In the group of confirmed cases, patients were significantly older, grade 3 reactions were more frequent, and fatal outcome was expectedly less frequent, since confirmation requires the patient to be alive. However, two patients with fatal outcome had positive skin tests: The first patient experienced a fatal relapse during skin tests, and the second patient died 8 days after the initial shock, following a nonanaphylactic surgical complication. Meanwhile, his skin tests had been found positive for SUX. The number of pediatric cases was 31, with 11 in the group of confirmed cases.

Previous exposure to NMBA could be fully excluded in 24 cases (1.5%), whereas it was certain in only 55 patients (3.4%), 22 of them having a history of perioperative anaphylactic reaction. In 506 patients (31.1%), previous exposure was considered as possible because of previous surgery, but finally, this characteristic remained not assessable in most of cases (64%). Basal tryptase was available in only one-fifth of the confirmed cases.

Overall, severe reactions (grades 3 and 4) occurred in 75.8%, 68.6%, 57.9%, and 50.8% of cases of anaphylaxis triggered by SUX, ROC, CIS, and ATRA respectively. And among the 680 confirmed cases, these proportions were higher, respectively, 81.7%, 78.2%, 81.8%, and 65.5%. The proportion of confirmed cases was the highest in the category of grade 3 reactions.

3.2.2 | Changes over the 2000-2012 period

The age of patients and the proportion of males showed nonsignificant increasing trends (same results in the group of the 680 confirmed cases, data not shown). The severity of reactions (all NMBA) also showed an increasing trend with notification rates of severe

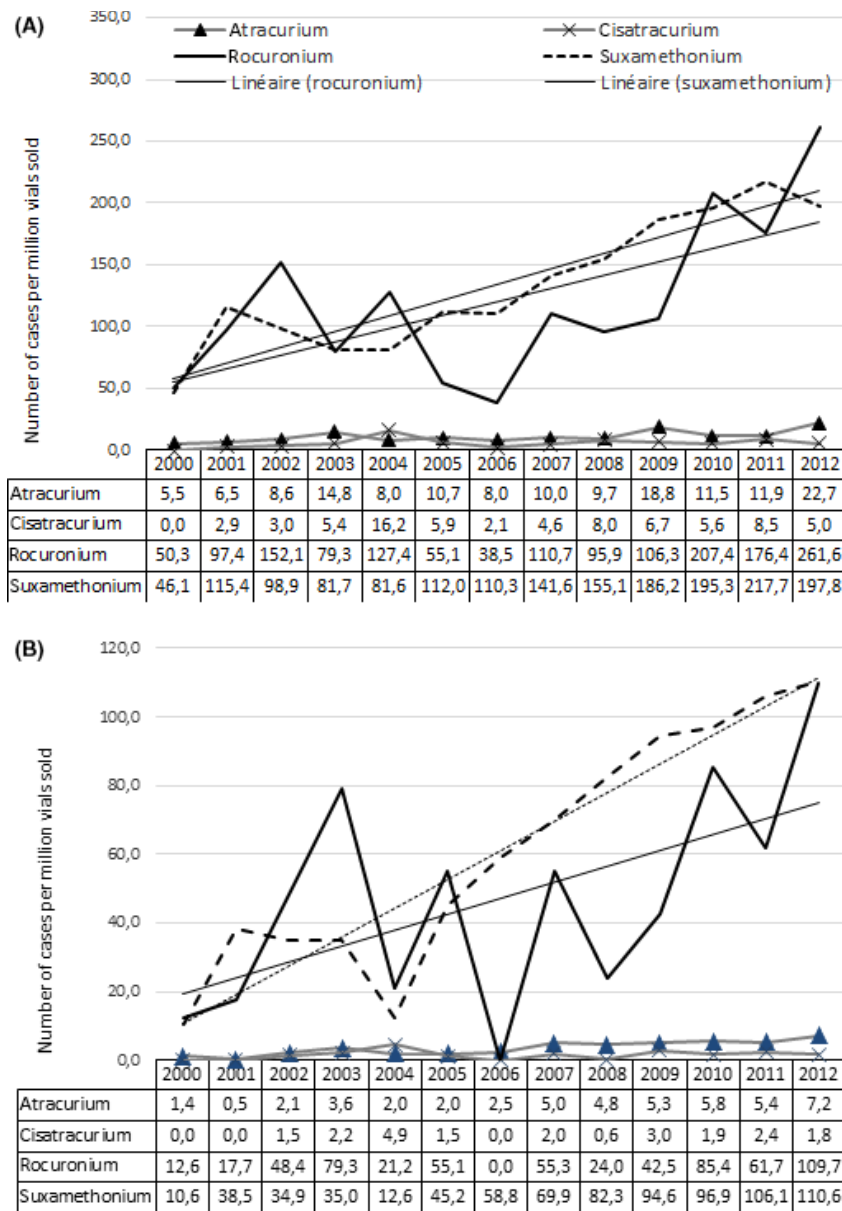


FIGURE 2 (A) Evolution over the 2000–2012 period of anaphylactic reactions incidence rates (number of cases per million vials sold) for atracurium (gray line triangle mark), cisatracurium (gray line cross mark), rocuronium (plain black line), and suxamethonium (black dotted line) in the whole group of 1624 cases, and (B) in the group of the 680 confirmed cases. Trends linear curves (suxamethonium dotted line, rocuronium plain line) [Colour figure can be viewed at wileyonlinelibrary.com]

(grades 3 and 4) reactions that increased more markedly after year 2006 than rates of nonsevere (grades 1 and 2) reactions (Figure 3). Severe reactions' incidence rates markedly increased for ROC and SUX, but an increase was also noted for ATRA and in a smaller extent with CIS.

3.3 | Comparison of ATRA or CIS vs SUX or ROC

Among the group of confirmed cases, the subgroup of ATRA and CIS (ATRA-CIS, $n = 117$) was compared with the subgroup of ROC and SUX (subgroup ROC-SUX, $n = 549$) (Table 3). Male patients were more frequent in the subgroup ATRA-CIS ($P = .019$), whereas obesity and emergency setting were expectedly more frequent in the subgroup ROC-SUX (respectively, $P = .007$ and $P < .0001$). Age of patients, severity of the anaphylactic reaction, and fatal outcome did not differ significantly. Surgical setting was significantly different

($P = .018$), with more visceral and skin/abscess surgery, and endoscopic procedures in the ROC-SUX subgroup.

3.4 | Skin cross-reactivity among NMBA

Among the group of confirmed cases, complete data of cross-reactivity skin tests with other NMBA(s) were available for 473 patients (Table 4). Of them, 225 (47.6%) were found with no cross-reactions, whereas 248 (52.4%) had at least one positive skin test with another NMBA (only 1 in 49.2%, 2 in 30.2%, and more than 3 in 20.5%). Patients with ROC anaphylaxis were frequently found with cross-reactivity (81.6%), mostly with VEC or SUX. The proportion of patients with SUX anaphylaxis with cross-reactions was lower (44.4%). Patients with ATRA anaphylaxis had an expected cross-reactivity with CIS and *vice versa*. A phenomenon of cosensitisation cannot be ruled out with these two molecules.

TABLE 2 Characteristics of “confirmed” and “nonconfirmed” NMBA anaphylaxis cases

	Confirmed cases		Nonconfirmed cases		P*
	N	%	N	%	
All	680		944		
Age (mean $\pm$ SD)	52.9 $\pm$ 14.7		50.8 $\pm$ 15.2		0.005
Gender					
Male	252	37.1	357	37.8	0.755
Severity					
Grade 1	4	0.6	70	7.4	NS
Grade 2	110	16.2	213	22.6	
Grade 3	455	66.9	458	48.5	
Grade 4	82	12.1	130	13.8	
Not documented	29	4.3	73	7.7	
Fatal outcome	2	0.3	59	6.3	<0.0001
Previous exposure					
Sure	23	3.4	32	3.4	NS
Excluded	12	1.8	12	1.3	
Possible	260	38.2	246	26.1	
Not documented	385	56.6	654	69.3	
Emergency setting	106	15.6	135	14.3	0.47

*P value: alpha risk = 5%.

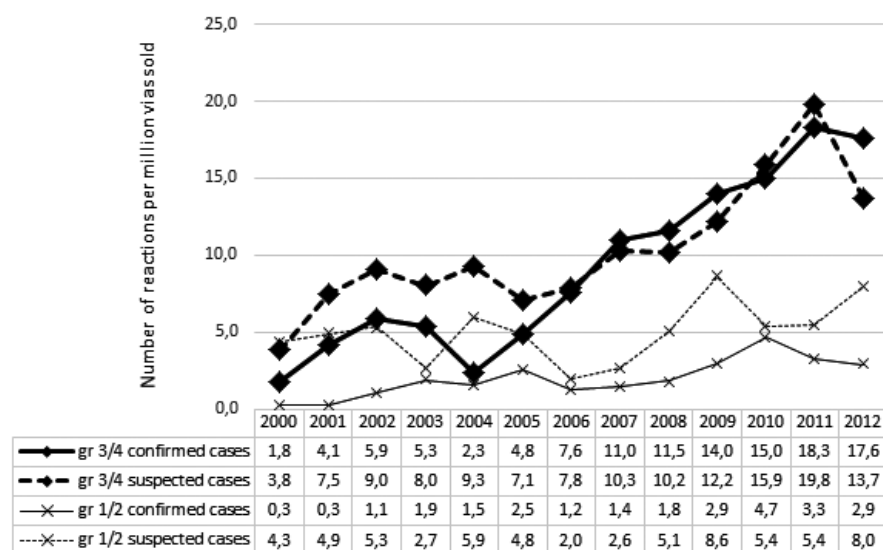
NS: non significant test (after Bonferroni correction).

TABLE 3 Characteristics of the confirmed cases in two subgroups atracurium-cisatracurium (ATRA-CIS) and rocuronium-suxamethonium (ROC-SUX)

Number	ATRA-CIS N = 117	ROC-SUX N = 549	P*
Age (mean $\pm$ SD)	50.7 $\pm$ 16.5	53.3 $\pm$ 14.4	0.085
Gender (%)			
Male	46.2	34.6	0.019
Obesity (%)	4.3	12.9	0.007
Severity (%)			
Grade 1	0.9	0.4	NS
Grade 2	23.1	14.9	
Grade 3	60.7	68.5	
Grade 4	9.4	12.8	
Not documented	6.0	3.5	
Fatal outcome (%)	5.1	9.8	0.106
Previous exposure (%)			
Sure	3.4	3.5	NS
Possible	34.2	38.4	
Excluded	2.6	1.6	
Not documented	59.8	56.5	
Emergency setting (%)	3.4	18.4	<0.0001

*P value: alpha risk = 5%.

NS: non significant test (after Bonferroni correction).

**FIGURE 3** Evolution of severity over the 2000-2012 period (all NMBA) expressed by incidence rates (number of cases per million vials sold) for grade 1 and grade 2 reactions (thin lines cross marks) and grade 3 and 4 reactions (thick lines square marks) according to the confirmed (plain lines) or nonconfirmed (dotted lines) status

4 | DISCUSSION

Our 12-year survey highlighted three main points: (1) The risk of anaphylaxis was tenfold higher for SUX and ROC in comparison with ATRA, CIS, MIV, PAN, and VEC; (2) characteristics of patients did not significantly changed over the study period; and (3) only obesity and an emergency setting were significantly more frequent in patients with ROC or SUX anaphylaxis. These two last criteria are

likely to reflect their frequent use in rapid sequence induction and in bariatric surgery.

Our results are in alignment with Reddy et al who also reported a tenfold higher risk with ROC and SUX in a small series with a “real-life” denominator based on the exact count of anesthesia with NMBA involvement.¹⁶ A denominator is essential to assess the risk because market shares of NMBA considerably vary, and raw numbers of anaphylaxis cases are misleading. The denominator of our

TABLE 4 Skin tests cosensitization among NMBA

NMBA ^a	Non complete skin testing	Complete skin testing		NMBA-positive skin test (cosensitization) N (% ^b)						
		No cross-reaction	Positive cross-reaction(s)	ATRA	CIS	MIV	PAN	ROC	SUX	VEC
ATRA	25	18	40		19 (47.5)	13 (32.5)	4 (10.0)	6 (15.0)	11 (27.5)	6 (15.0)
CIS	12	3	19	14 (73.7)		5 (26.3)		2 (10.5)	3 (15.8)	5 (26.3)
MIV	0	1	2						1	1
PAN	2	1	1	1	1			1		
ROC	16	7	31		1 (3.0)	2 (6.0)	11 (35.5)		15 (48.4)	19 (61.3)
SUX	147	193	154	17 (11.0)	32 (20.8)	26 (16.9)	44 (28.6)	49 (31.8)		94 (61.0)
VEC	5	1	2				2	1	1	

^aNeuromuscular blocking agent incriminated in anaphylaxis.

^bPercentage in relation to the total number of cases with positive cross-reactions for this incriminated NMBA (the total is over 100% because of cases with multiple cross-reactions). Percentages were not calculated for mivacurium (MIV), pancuronium (PAN), and vecuronium (VEC) because of their very low number of cases.

survey was based on sold vials as in many other studies.^{13,17} Even if the amount of sold vials remains imperfect per se, it is still very useful to compare NMBA with each other. We also would like to highlight that we drew the same conclusions about incidence rates regardless the confirmed status of cases by skin tests.

Our survey showed that SUX was implied in more than half of cases, this proportion being even higher among confirmed cases. The high frequency of SUX anaphylaxis is already well documented,^{2,12,13} and we found that its incidence rate clearly increased over the study period, but whether it is a real increase in occurrence or a notification bias remains a challenging issue, as we cannot exclude during this period that allergologists and anesthesiologists transmitted more often their cases to RPPCs. As a matter of fact, we observed simultaneous increase in ATRA, and to a lesser extent, CIS anaphylaxis incidence rates. However, rapid sequence induction is an established method of inducing anesthesia in patients at risk of pulmonary aspiration and allowing rapid intubation of the trachea, and ROC and SUX are recommended in this context, although the choice between the two NMBA remains controversial.¹⁸⁻²⁰

The high incidence of anaphylaxis with ROC is not a new fact. In October 2002, a regulatory information had already been sent to French anesthesiologists to communicate about the results of a survey between 1995 and 2001 revealing a higher frequency of anaphylaxis with ROC than with other NMBA.^{21,22} This temporarily led between 2000 and 2006 to a decreased consumption, but since 2009, ROC became considered as an agent of choice in bariatric surgery because of its fast onset and its rapid reversal by sugammadex.²³ Sugammadex is a modified cyclodextrin specifically designed to reverse neuromuscular blockade by encapsulating ROC and is available since 2008.²⁴ Its affinity is 2.5 times higher for ROC than for VEC, and it has no affinity for SUX.²⁵ Because of this efficient reversal, ROC might be also used for short surgical acts²⁶ or in surgical environments trying to reduce the stay in operating rooms. Sugammadex has sometimes been reported to improve the management of severe ROC anaphylaxis at the beginning of its use,²⁷ but today, this action remains controversial because i) the improvement may be coincidental with the already

instituted therapy with epinephrine and fluid resuscitation, ii) the possibility of encapsulated ROC to be able to interact with IgE cannot be ruled out, and iii) sugammadex has not been shown to interact with mast cell degranulation yet.²⁸⁻³¹ Moreover, the complex of ROC and sugammadex could itself induce hypersensitivity according to a literature review of 14 cases that occurred within 4 minutes after sugammadex injection, 10 of them confirmed by sugammadex-positive skin prick tests.³² The complex of ROC and sugammadex also proved to be sensitizing in a patient recurrent anaphylaxis after sugammadex.³³ And finally, some cases considered as improved by sugammadex revealed to be not related to ROC anaphylaxis, hence wiping an impact of sugammadex in these cases.³⁴

Sadler et al also recently highlighted the renewal of high incidence of ROC-induced anaphylaxis in a 10-year survey performed in a specialized diagnostic center.¹⁷ They found that ROC was responsible for 56% of cases of NMBA anaphylaxis and had a higher rate of IgE-mediated anaphylaxis compared with VEC.

We observed that characteristics of patients with NMBA anaphylaxis did not significantly change over the 2000-2012 study period, with only nonsignificant trends of increasing age and increasing male proportion, which could be interesting to follow-up in the future. One constant characteristic over the whole survey period was, however, the poorly documented previous exposure to NMBA (s). This lack of information definitely compromised our assessment of NMBA previous exposure, with only a tiny proportion of our cases being warranted with no previous NMBA exposure, whereas it ranges from 11% to 75% in the literature.^{12,35} Previous NMBA exposure remains difficult to collect, because anesthetic substances are rarely tracked in medical correspondences. This is unfortunate because the absence of previous NMBA exposure supports the possibility of cross-reactivity between NMBA and other substances, which perhaps could be avoidable. For instance, pholcodine, an opiate cough suppressant substance, with two quaternary ammonium groups like NMBA, is highly suspected to provide IgE cross-reactivity, and its withdrawal in Sweden, and later in Norway, led to a decrease in SUX anaphylaxis in these countries.³⁶⁻⁴⁰

Another important point of our survey concerned missing information about basal tryptase and confirmation skin tests. Although they are definitely vital for the patient and essential for the anesthesiologist to perform a safe anesthesia after anaphylaxis,^{13,41,42} they were impossible to collect in many cases, meaning that they were sometimes not performed at all, thus placing the patient in potential danger of recurrence, or in a situation where NMBA were inappropriately avoided. The reasons are multiple, including the possibility that patients might have omitted to remember their appointment for skin tests if they were not enough aware about what happened during anesthesia particularly in nonsevere cases, or not enough informed about the consequences of a reoccurrence. We effectively found a higher (although nonsignificant) proportion of nonsevere reactions in nonconfirmed cases. The recommended delay between anaphylactic reaction and skin tests is around 6 weeks,⁴³ and some authors proposing to reduce it if the patient needs to be re-operated quickly after the anaphylactic shock. In this particular eventuality, only positive tests would be interpretable, as negative tests might be flawed by the decreased degranulation capacities of the patient close to the anaphylactic shock,⁴⁴ but in normal time, patients have to remember to return to hospital for the skin tests, and this is why we point out the necessity to better inform them about the importance of these tests. One proposal is to give them a card at discharge, clearly stipulating they experienced perioperative anaphylaxis, naming the anesthetic substances, and the date of the scheduled allergy tests. This measure could thus inform the anesthesiologist in case of emergency and could also help the patient to recall him to honor in time his scheduled appointment at the allergologist, instead of requiring an urgent appointment many years later, which happens unfortunately quite often.

Skin tests allow to find cross-reactivity between NMBA and to counsel the anesthesiologist for future anesthetic procedures.⁴² In our series, patients with ROC anaphylaxis were more frequently found with cross-reactivity than patients with SUX anaphylaxis, these latter displaying the lowest proportion of cross-reactions (55.6%). The last GERAP survey over the 2011-2012 period showed that 62% of the SUX anaphylactic patients were not found with other NMBA cross-reactivity.¹³ Regarding cross-reactions between ATRA and CIS, it is expected in view of their similarity and the fact that CIS is an isomer present in ATRA,⁴⁵ but we found that it was not systematic. In the same vein, the absence of cross-reactivity with ATRA does not preclude sensitivity to CIS and vice versa. This is a strong argument to support skin testing after any suspicion of NMBA anaphylaxis, even with CIS which appears less involved in perioperative anaphylaxis.

Finally, the strength of our survey is its powerful national coverage, with medically confirmed data mostly due to the collaboration between GERAP allergologists and practitioners of the French RPPCs network. Although it would have been informative, the two databases (GERAP and FPvD) were not matched to quantify the proportion of duplicates. The main limits of our survey come from the retrospective nature of the data with some missing information, especially about surgical context and previous NMBA exposure.

5 | CONCLUSION

Our survey demonstrates that SUX and ROC are at least 10-fold more frequently involved in perioperative anaphylaxis than other NMBA, and that a global increase in NMBA anaphylaxis incidence is observed over the 2000-2012 period, possibly explained by improvements in reporting by physicians and in collecting the cases by RPPCs. We highlight the re-emerging worrisome high risk of ROC anaphylaxis and the fact that NMBA administrations were not sufficiently documented in medical files, compromising the exclusion of previous exposure(s) before a surgery, and a fortiori before anaphylaxis, to correctly identify other potential cross reacting substances, such as pholcodine. Finally, we suggest that patients should be better informed about their perioperative anaphylaxis to improve adherence to their scheduled appointment for allergy skin testing. This measure is essential to reduce the recurrence of NMBA anaphylaxis.

CONFLICT OF INTERESTS

L. Argouillon, K. Masmoudi, S. Fedrizzi, J. Cottin, and C. Latache disclose any conflict of interest in relation to this study. N. Petitpain, PM Mertes and P. Gillet are involved in the coordination team of the academic ALPHO study (Anaphylaxis to neuromuscular blocking agents and PHOLcodine exposure) funded by a consortium of 16 companies selling pholcodine, including MSD.

AUTHOR CONTRIBUTIONS

N. Petitpain involved in study design, data collection, data analysis, writing, and supervision of the manuscript. L. Argouillon performed data collection, data analysis, and writing. K. Masmoudi, S. Fedrizzi, and J. Cottin involved in study design and data collection. C. Latache carried out data analysis and writing. PM Mertes and P. Gillet involved in study design, writing, and supervision of the manuscript.

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APPENDIX 1

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