

Hypersensitivity reactions during anesthesia. Results from the ninth French survey (2005-2007)

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ABSTRACT

Background. Hypersensitivity reactions occurring during anesthesia remain a major cause of concern for anesthesiologists. We report the results of the ninth consecutive survey of hypersensitivity reactions observed during anesthesia in France. This report will be used as an epidemiologic reference prior to this intervention.

Methods. Between January 1, 2005 to December 31, 2007, 1253 patients who experienced an immune-mediated (IgE-mediated) or non-immune-mediated (non-IgE-mediated) hypersensitivity reaction were referred to one of the 40 participating centers. Diagnosis was established on the basis of clinical history, skin tests and/or specific IgE assay.

Results. An IgE-mediated or non-IgE-mediated reaction was diagnosed in 786 cases (63%) and 467 cases (37%), respectively. The most common causes of anaphylaxis were neuromuscular blocking agents (NMBA) (N.=373, 47.4%), latex (N.=158, 20%), and antibiotics (N.=141, 18.1%). Succinylcholine (N.=226, 60.6%) was the most frequently incriminated NMBA, whereas the low frequency of reactions involving cis-atracurium was confirmed (N.=22, 5.9%) when market shares of each NMBA were taken into account. An increased number of reactions involving vital dyes was recorded (N.=34, 4.4%).

Conclusion. These changes in the epidemiology of allergic reactions confirm the need for regular epidemiologic surveys of anaphylaxis in the perioperative period. (*Minerva Anestesiologica* 2012;78:868-78)

Key words: Anesthesia, general - Anaphylaxis - Pholcodine - Anti-bacterial agents.

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Hypersensitivity reactions occurring during anaesthesia remain a major cause of concern for anesthesiologists. Their incidence and associated morbidity and mortality remain poorly defined. Several reports indicate that the relative risk of allergic reactions may vary with time, depending on changes in clinical practice,^{1,2} but also on changes in several environmental factors.^{3,4}

A controversy still persists concerning possible differences regarding the relative risk of allergic reactions among neuromuscular blocking agents (NMBAs).^{2,5} The recent introduction of sugammadex, a chemically modified γ -cyclodextrin designed to allow for rapid reversal of rocuronium-induced neuromuscular block, may significantly change the respective market-shares of the different neuromuscular blocking agents (NMBAs) used in common clinical practice. Therefore, rocuronium has been proposed to replace succinylcholine for rapid sequence induction.⁶ In the same time, it has been suggested that sugammadex might offer the possibility to alleviate the severity of hypersensitivity reaction by removing the responsible allergen in case of rocuronium induced hypersensitivity reaction.⁷

Recently, a reduction of the prevalence of sensitization to NMBAs by reducing population exposure to pholcodine, a potential cross-sensitizing agent has been advocated.^{3,8} This has raised question concerning a possible retrieval of pholcodine from the market in France and in the European community, this question being currently under investigation. As a conservative measure, waiting for further evidence supporting the link between pholcodine consumption and the prevalence of hypersensitivity reactions, sales conditions for pholcodine have been changed from over the counter sales to prescription only delivery, a measure which is expected to reduce of the proportion of the population exposed.

All these proposals or changes in clinical practice and their consequences, particularly in terms of morbidity should be evaluated. This clearly reinforces the need for a close and continuous monitoring of the epidemiology of anaesthesia-related hypersensitivity reactions.

This paper reports the results of a three-year survey of immediate IgE and non-IgE-mediated

hypersensitivity reactions observed during anesthesia in France (2005-2007).

Materials and methods

This was a retrospective study involving patients having experienced an adverse immediate hypersensitivity reaction, suspected of being allergic, during anesthesia between January 1, 2005 and December 31, 2007. In all cases the mechanism of the reaction was assessed on the basis of a standardized diagnostic protocol performed in an allergo-anesthesia outpatient clinic, as described elsewhere (Figure 1).⁹

The protocol included a questionnaire concerning age at the time of reaction, sex, number of previous anesthetic procedures, history of allergy, and drugs used before the reaction. Details were obtained regarding the degree of reaction graded from I to IV depending on increasing severity (grade I=presence of cutaneous signs; grade II=presence of measurable but not life-threatening symptoms, including cutaneous effects, arterial hypotension (defined as a decrease of more than 30% in blood pressure associated with unexplained tachycardia), cough or difficulty in mechanical ventilation; grade III=presence of life-threatening reactions: cardiovascular collapse, tachycardia or bradycardia, arrhythmias, severe bronchospasm; grade IV=circulatory failure, cardiac and/or respiratory arrest).

Data concerning allergy investigations were recorded: type of skin tests performed (*i.e.*, skin prick-test and/or intradermal test), cross-reactivity between neuromuscular blocking agents (NMBAs) in cases of adverse reaction to a NMBA, results of plasma histamine and serum tryptase monitoring during the adverse reaction, and of IgE-specific assays testing responses to quaternary ammonium or latex when available. To refine the study of cross-reactivity between the different NMBAs classes, results obtained in the present survey were pooled with results from our two last consecutive surveys to conduct a larger database analysis.^{10,11}

Allergic or IgE-mediated anaphylaxis was diagnosed on the basis of skin test and/or IgE assay results consistent with the clinical history and the anesthetic protocol. Otherwise, the di-

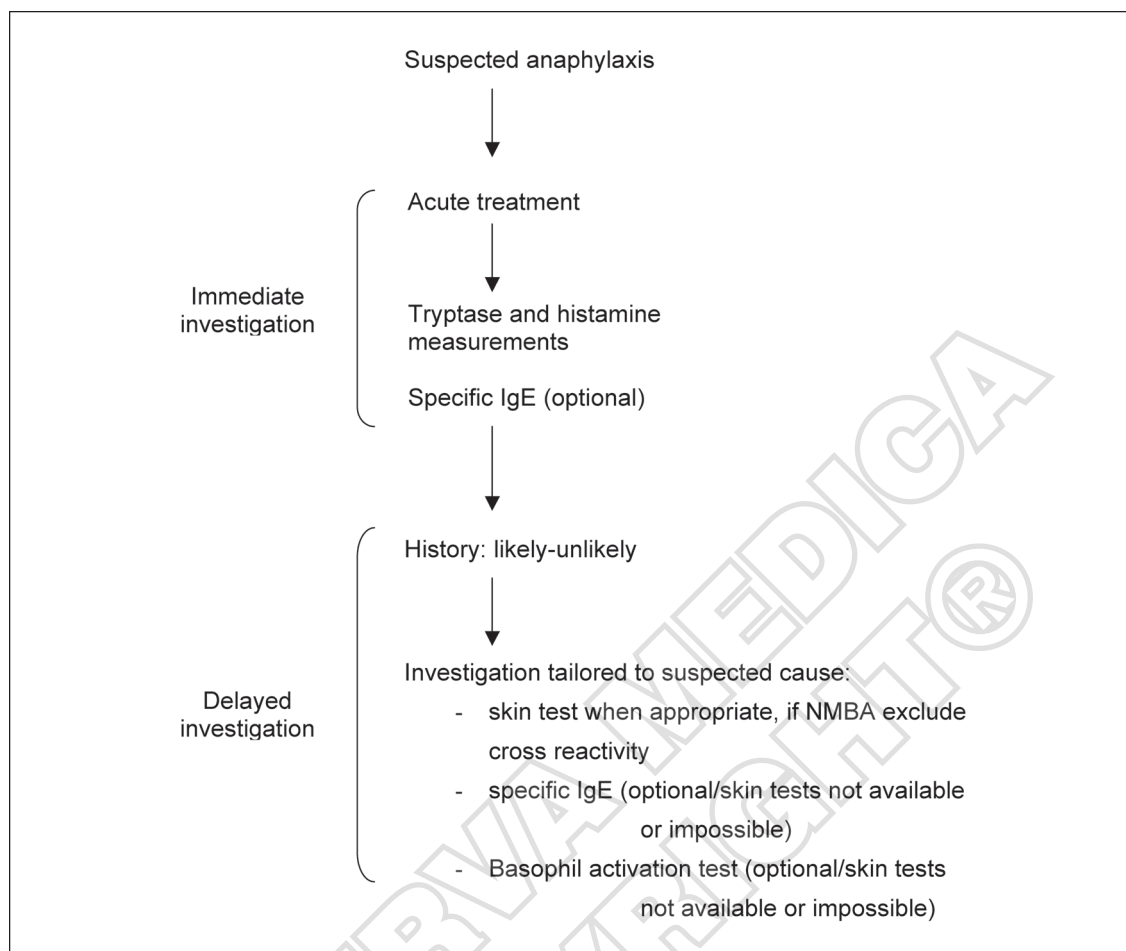


Figure 1.—Algorithm for the diagnosis of immediate hypersensitivity reaction to anesthetic drugs.

agnosis of non-IgE-mediated anaphylaxis was retained.

To compare the incidence of anaphylaxis to available neuromuscular blocking agents, the number of vials of each agent sold in France during the entire study period and the number of vials effectively used in anesthesia was then estimated on the basis of data obtained from a market survey in France.¹²

Statistical analysis

Statistical analysis was performed using the SAS 8.02 software (SAS institute INC, Carg, NC, USA). Results are expressed as mean $\pm$ SEM. Comparisons were performed using Pearson Chi-square test. A P value ≤ 0.05 was considered statistically significant.

Results

Patients

One thousand two hundred fifty-three patients who experienced a clinical adverse reaction suspected to be allergic were included. At the end of the allergy work-up, a diagnosis of IgE-mediated immediate hypersensitivity reaction was established in 786 cases (63%), whereas the remaining 467 cases (37%) were considered as non-immune-mediated.

A significant female predominance was observed in both groups (IgE-mediated reactions: female, N.=551 [70.2%]; male, N.=234 [29.8%]; non-IgE-mediated reactions: female, N.=306 [65.5%]; male, N.=161 [34.5%]). This

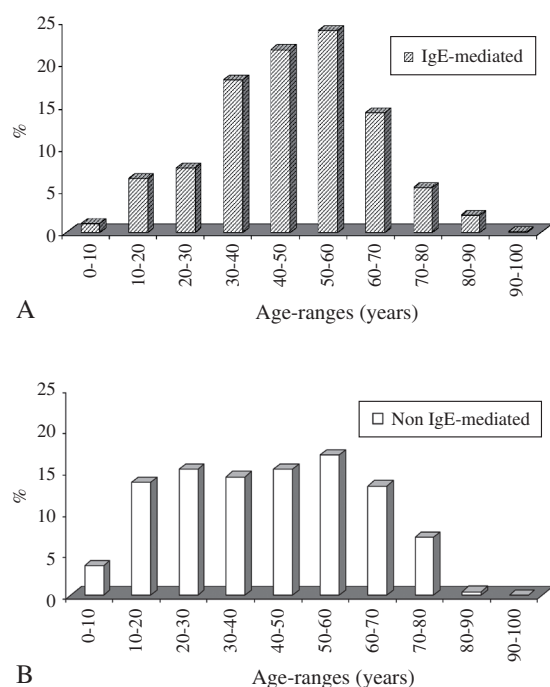


Figure 2.—Distribution of IgE-mediated and non-IgE-mediated hypersensitivity reactions according to age-ranges (10 years).

predominance was observed irrespective of the causal agent.

The distribution of IgE-mediated and non-IgE mediated reactions according to age is shown in Figure 2.

Causal agents

IgE-MEDIATED REACTIONS

The most common causes of allergic reactions were NMBAs (N.=373, 47.4%), followed by latex (N.=158, 20%) and antibiotics (N.=141, 18.1%) (Table I). Opioids were involved in 17 cases (2.2%), hypnotics in eight cases (1.1%), colloids in 18 cases (2.3%), and other substances in 69 cases (8.9%), with an unexpected high number of reactions involving dyes. These results can be compared with our previous data obtained during our eight previous surveys (Table II).^{1, 2, 10, 11, 13-16}

In 14 cases, patients were found to be sensitized to two different agents: an NMBA and la-

tex in five cases, latex and morphine in two cases, latex and nefopam in two cases, latex and gelatine in two cases, latex and a cephalosporin in one case, latex and a non-steroidal anti-inflammatory drug in one case, and patent blue and cephalosporin in one case.

The respective contribution of each NMBA is shown in Table III. Succinylcholine (N.=226) was the most frequently incriminated NMBA, followed by atracurium (N.=73), vecuronium (N.=17) and rocuronium (N.=16).

However, these results should be examined in light of the actual clinical use of the different NMBAs which could be estimated on the basis of the results of the NMBA market share survey in anesthesia and of their respective use in anesthesia over the same time period in France (Table III).

Cross-sensitivity between NMBAs was analysed in a series of 738 cases corresponding to the current study and to additional cases extracted from our database. Only 12 patients were found to be sensitised to all NMBAs. Single agent sensitisation was frequent in cases of allergy to succinylcholine (N.=279, single agent sensitization 56%), whereas it was less common with steroidal (N.=280, 21%) or benzylisoquinoline (N.=179, 35%) compounds. Cross-reactivity limited to compounds from the same sub-class was observed in 31% of cases with steroidal, and 18% of cases with benzylisoquinoline compounds.

NON-IGE-MEDIATED REACTIONS

A precise identification of the drug responsible for the adverse reaction is more difficult to establish in case of non IgE-mediated reactions, because the adverse reactions could result from additive side effects of different drugs injected simultaneously. However, when the anesthetic protocols used in the case of IgE-mediated *versus* non-IgE-mediated reactions were compared, some minor differences were observed. The use of succinylcholine was more frequent at anesthesia induction in case of allergic reactions than in case of non-IgE-mediated reactions (IgE-mediated reactions: N.=235 [30%], non-IgE-mediated reactions: 79 [17%]; $P<0.0001$). No differences were observed regarding the use of other NM-

TABLE I.—*Agents involved in IgE-mediated anaphylactic reactions during anesthesia (N.=786) between January 1, 2005 and December 31, 2007 in France.*

Causal agent			Number of patients
Neuromuscular blocking agent (N.=373, 47.4%)	Succinylcholine	(60.6%)	226
	Atracurium	(19.6%)	73
	Cisatracurium	(5.9%)	22
	Vecuronium	(4.6%)	17
	Rocuronium	(4.3%)	16
	Pancuronium	(2.7%)	10
	Mivacurium	(1.9%)	7
Latex (N.=158, 20%)	Alloferine		2
			88
Antibiotics (N.=141, 18.1%)	Cephalosporin		62
	Penicillin		50
	Vancomycin		22
Hypnotics (N.=8, 1.1%)	Others		7
	Propofol		3
	Midazolam		2
Opioids (N.=17, 2.2%)	Ketamine		2
	Thiopentone		1
	Morphine		13
Colloids (N.=18, 2.3%)	Sulfentanyl		3
	Remifentanyl		1
	Gelatine		17
Local anesthetics (N.=5, 0.6%)	Hetastarch		1
			5
Other agents (N.=69, 8.9%)	Patent blue		33
	Methylene blue		1
	Nefopam		12
	contrast media		8
	gadolinium		1
	Protamine		5
	Povidone		3
	NSAID		1
	Steroids		2
	acetaminophen		1
	n-acetylcysteine		1

TABLE II.—*Substances responsible for anaphylaxis during anesthesia in France. Results from nine consecutive surveys.*

	1984-1989 N.=821 %	1990-1991 N.=813 %	1992-1994 N.=1030 %	1994-1996 N.=734 %	1997-1998 N.=486 %	1999-2000 N.=518 %	2001-2002 N.=502 %	2003-2004 N.=406 %	2005-2007 N.=786 %
NMBAs	81.0	70.2	59.2	61.6	69.2	58.2	54	49.6	47.4
Latex	0.5	12.5	19.0	16.6	12.1	16.7	22.3	26.4	20.0
Hypnotics	11.0	5.6	8.0	5.1	3.7	3.4	0.8	1.4	1.1
Opioids	3.0	1.7	3.5	2.7	1.4	1.3	2.4	1.4	2.2
Colloids	0.5	4.6	5.0	3.1	2.7	4.0	2.8	4.6	2.3
Antibiotics	2.0	2.6	3.1	8.3	8.0	15.1	14.7	12.2	18.1
Others	2.0	2.8	2.2	2.6	2.9	1.3	3.0	4.4	8.9
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%

N.=number of IgE-mediated reactions. NMBAs: neuromuscular blocking agents.

TABLE III.—*Market share of NMBA's and number of IgE-mediator reactions observed between January 1, 2005 and December 31, 2007 in France (N.=373).*

		Market share in anesthesia (vials %)	Anaphylactic shocks 2005-2007 Number (%)
Succinylcholine	100 mg/10 mL	12.2	226 60.6
Atracurium	50 mg/5 mL	45.2	73 19.6
Cis-atracurium	20 mg/10 mL		
Cis-atracurium	5 mg/2.5 mL	29.6	2 5.9
Cis-atracurium	10 mg/5 mL		
Vecuronium	4 mg/1 mL	4.8	17 4.6
Vecuronium	10 mg/1 mL		
Rocuronium	50 mg/5 mL	1.1	16 4.3
Pancuronium	4 mg/2 mL	4.1	10 2.7
Mivacurium	10 mg/5 mL	2.7	7 1.5
Mivacurium	20 mg/10 mL		

BA's, hypnotics, opioids, or the administration of antibiotics.

Risk factors

No difference was observed between IgE and non-IgE-mediated reactions when the incidences of atopy (IgE: 23.6, non-IgE 25.4%, $P=ns$), asthma (IgE: 9.0%, non-IgE: 14%, $P=ns$), food intolerance (IgE: 6.6%, non-IgE: 5.1%, $P=ns$) or drug intolerance (IgE: 16.9%, non-IgE: 15.2%, $P=ns$) were compared (Table IV).

In 37 out of 188 patients (24%) having experienced an anaphylactic reaction to latex, careful

retrospective assessment of their medical history revealed the presence of symptoms suggestive of latex sensitization such as fruit allergy or intolerance to materials containing rubber latex prior to the reaction.

Clinical features

IgE and non-IgE-mediated reactions cannot be distinguished on the basis of clinical symptoms alone. However, when a classification based on symptom severity was applied, clinical manifestations appeared to be more severe in patients with documented IgE-mediated allergic

TABLE IV.—*Clinical symptoms, tryptase levels and history of allergies in IgE and non IgE-mediated reactions during anaesthesia in France between January 1, 2005 and December 31, 2007.*

Clinical symptoms	IgE-mediated N.=786		Non-IgE-mediated N.=467	
	(Number of patients)	%	(Number of patients)	%
Cardiovascular symptom	(599)	76.2	(174)	37.5
Arterial hypotension	(268)	34.1	(87)	18.7
Cardiovascular collapse	(309)	40	(51)	11.0
Cardiac arrest	(46)	5.8	(2)	-
Bronchospasm	(280)	40.0	(103)	22.0
Cutaneous symptoms	(551)	71.0	(438)	94.0
Median tryptase $\mu\text{g/L}^{-1}$	33		5	
(median [range])	(1-1260)		(1-182)	
History of allergy				
Atopy		23.6		25.4
Asthma		8.3		14.1
Drug intolerance		16.9		15.2
Food intolerance		6.6		5.1

reactions than in patients presenting with non-IgE-mediated reactions ($P < 0.001$). Most allergic reactions were Grade III (57.2%), whereas non-IgE-mediated reactions were mainly Grade I (43%).

The various clinical features observed during IgE and non-IgE-mediated reactions are summarized in Table IV. Cutaneous symptoms were more frequent in non-IgE-mediated reactions (94% *vs.* 71%, $P < 0.0001$), whereas cardiovascular collapse (40% *vs.* 11%, $P < 0.0001$) and bronchospasm (35.7% *vs.* 22%, $P < 0.0001$) were more frequent in case of allergic reactions.

Diagnostic tests

TRYPTASE AND HISTAMINE

Histamine and tryptase plasma levels were determined at the time of the adverse reaction in 48% ($N = 599$) cases.

Histamine levels were significantly elevated ($> 9 \text{ nmol l}^{-1}$) in 78.2% of IgE-mediated reactions (mean: 215 ± 27 , median: 65.5, range: 0.2-7160) and in 42% of non-IgE-mediated reactions (mean: 83.5 ± 30 , median: 6, range: 0.3-3970).

Similarly, tryptase levels were significantly elevated ($> 25 \mu\text{g l}^{-1}$) in 60.5% of IgE-mediated reactions (mean: 56.7 ± 4.3 , median: 32.15, range: 1-1260), and in 10.6% of non-IgE-mediated reactions (mean: 13.3 ± 1.9 , median: 5, range: 0.6-182).

SPECIFIC IgE ASSAYS

Specific IgE assay was performed in 303 patients having experienced NMBA anaphylaxis. Results were positive in 251 cases (82.8%). In 12 patients, IgE assay was positive with negative skin tests.

Specific latex IgE assay was performed in 114 patients having experienced an anaphylactic reaction to latex confirmed by prick test positivity. It was positive in 95 cases (83.3%).

Discussion

This study is the ninth survey concerning the epidemiology of anaphylactic reactions occur-

ring during anesthesia conducted in France by the GERAP since 1989. Although some trends regarding the relative contribution of the various substances incriminated are confirmed, changes in the relative contribution of the various NM-BAs commercially available and the increasing number of blue dye-related reactions should be noted.

NMBAs still remain the most frequently incriminated drugs, but they account now for less than half of the cases recorded (Table II). However, their absolute number remains stable. This contrasts with the apparent decrease in the number of reactions related to NMBAs recently reported in Norway following the recent withdrawal from the market of the cough suppressant pholcodine.³ Indeed, 15% to 50% of allergic reactions to NMBAs are reported at the first known contact with a NMBA.¹⁷ Substituted ammonium ions have long been considered as the most likely epitope for the specific binding of IgE to NMBAs.¹⁸ Since these structures occur widely in many drugs but also in foods, cosmetics, disinfectants and industrial materials, a possible cross-reaction with IgE antibodies generated by previous contact with apparently unrelated chemicals has been hypothesized. Recently, Florvaag *et al.* suggested that the striking difference in the rate of allergic reactions to neuromuscular blocking agents which is more than six times as common in Norway as in Sweden, could be due to differences in preoperative sensitization in relation to pholcodine consumption.¹⁹ They later demonstrated that pholcodine exposure in patients having experienced an allergic reaction to a NMBA was responsible for a significant increase in specific IgEs to NMBAs in patients having experienced an allergic reaction to one of these drugs.²⁰ This led to the hypothesis that pholcodine exposure could either lead to IgE-sensitization to pholcodine and other quaternary ammonium ions or increase the titre of specific IgEs to quaternary ammonium ions and thereby could increase the risk of allergic reaction to NMBAs. This hypothesis was further supported by the results of an international prevalence study, showing a statistically significant association between pholcodine consumption and prevalence of

IgE-sensitization to pholcodine and succinylcholine.²¹

Taken together, these results led the French authorities, as a conservative measure, to change sales conditions for pholcodine from over the counter sales to prescription only delivery, a measure which is expected to lead to a reduction of the proportion of the population exposed. The present study represents the first step of an epidemiologic survey, providing a detailed picture of immediate hypersensitivity reactions occurring during anesthesia, with special emphasis on allergic reactions to NMBAs, prior to any reduction in pholcodine consumption.

Profound changes are observed concerning the relative contribution of the various NMBAs available when compared with our last reports.^{1, 2, 10} However, based on sales data, the number of patients exposed each year remains relatively stable. The number of anesthesia performed each year in France has been estimated at 8 million, general anesthesia accounting for more than 70% of the procedures, NMBAs being used in half cases.²² As in most series, succinylcholine appears to be more frequently involved,^{15, 23} and this proportion largely exceeds its market share (Table III). On the contrary, rocuronium is no longer the most frequently incriminated drug (Table III), but its market share has rapidly declined with time, representing only 1.14% in France.¹² Following the introduction of rocuronium on the market, a controversy has taken place regarding a possible increased risk of allergic reaction with this drug.^{1, 2, 5, 24, 25} Although the relative contribution of rocuronium to NMBAs-related allergic reactions remains higher than its market share, the number of reactions is now too low to allow for statistical comparisons with the relative frequency of hypersensitivity reactions reported with other NMBAs. However, the market share of rocuronium can be expected to increase in the forthcoming years following the introduction of sugammadex. This has led to the proposal to replace succinylcholine, a drug at high allergy risk, by high doses of rocuronium for rapid sequence induction.⁶ In addition, sugammadex might offer the possibility to alleviate the severity of hypersensitivity reaction by removing the responsible allergen in case of

rocuronium induced hypersensitivity reaction.⁷ Therefore, it will be of particular interest to compare the results obtained in the present survey with those that will be collected in the future to provide a definite evaluation of the relative risk of allergic reactions with rocuronium compared to other NMBAs, and to re-evaluate its benefit/risk ratio.

In the same way, our new report confirms the excellent safety profile of cis-atracurium regarding the relative allergic risk when compared with other NMBAs. Cis-atracurium represents now around one third of the NMBAs used in the operating room in France, but account for only 5.9% of the allergic reactions reported. This clearly confirms our initial hypothesis of a low-risk of allergic reactions with this drug in our previous studies performed when its market share was low.^{2, 10}

Cross-reactivity studies appear to be of critical importance in cases of allergic reaction to an NMBA. Although mono-sensitisation appears to be relatively frequent in cases of reactions involving succinylcholine, multiple sensitisations is observed in the majority of patients. However, sensitisation to all NMBAs appears to be really uncommon, therefore it is almost always possible to identify a safe drug for future anesthesia.

Latex sensitization remains the second most common cause of anaphylaxis during anesthesia in the general population. It was involved in 20% of cases. Once again, in one third of our cases, careful assessment of their medical history performed after the reaction revealed the presence of symptoms suggestive of latex sensitization prior to the anaphylactic reaction. The use of specific questionnaire prior to anesthesia to identify patients at risk of sensitization to latex has long been advocated in France. However, despite increasing awareness of the reality of this risk, a recent survey conducted to investigate anesthesiologists adherence to these guidelines revealed that the number of centers where specific questionnaires were in use, was very limited.²⁶ The main reason provided by anesthesiologists was the increased workload and reduced time dedicated to preoperative evaluation of patients. This clearly

highlights the limits of a policy of prevention mainly based on patient-at risk identification during preanesthetic visits. On the contrary, it strongly supports the promotion of primary and secondary prophylaxis based on the use of a latex-safe environment in multioperated children and the generalization of the use of unpowdered latex gloves in operating rooms.^{4, 27}

Allergic reactions to antibiotics continue to increase with time. At present, they account for 18.1% of the anaphylactic reactions diagnosed in our centers (Table II). As for latex, this supports the need for careful at-risk patient identification prior to anesthesia.

Allergic reactions to local anesthetics remain very uncommon despite their frequent use. Our results are in agreement with the literature, which suggests that most of adverse reactions to local anesthetics are related to inadvertent intravascular injection leading to excessive blood concentrations of the local anesthetic, or systemic absorption of epinephrine that was combined with the local anesthetic. This supports the recent proposal from the French Society of Anesthesiology and the French Society of Allergology to perform epidural labour anesthesia following a negative test dose in case of alleged allergy to local anesthetics when the clinical history is not suggestive of a severe reaction and skin tests to local anesthetics have not been performed.²⁸ However, the scheduling of a skin test by an allergist is a priority and remains recommended in pregnant women.²⁸

Our results also highlight the large diversity of the substances that might be involved as well as the rapid increase in the number of allergic reactions involving dyes (Table I). Vital dyes are used for many years in a variety of clinical situations. With their increased use for lymphatic mapping or in the preparation of labile blood products, reports of anaphylactic reactions have become more frequent.^{29, 30} Clinicians must be aware of this specific risk and of the clinical characteristics of these reactions. Indeed, the clinical diagnosis of anaphylaxis is, in fact, presumptive, based on a close temporal relation with the administration of the implicated substance. This is clearly not the case for hypersensitivity reactions elicited by dyes which are usually delayed and sustained,

occurring between thirty to sixty minutes following injections,²⁹ because of the kinetics of re-sorption from the subcutaneous tissue at the site of dye injection. Recommendations concerning skin tests to vital dyes have been recently issued in France.²⁸

At the end of the allergy work-up, 63% of the hypersensitivity reactions we reported were IgE-mediated. However, in a third of our cases, the precise mechanisms of reactions remain unclear. Consequently, further efforts must be made to determine the possible mechanisms.

In our series, a significant female predominance was observed. The hypothesis of a possible cross-sensitization with quaternary ammonium ion-containing compounds such as cosmetics has long been proposed to explain the increased incidence of immediate hypersensitivity reactions observed in women. However, this hypothesis remains to be confirmed. On the contrary, the role played by sex hormones in this increased risk has recently been demonstrated by our group, showing the absence of female predominance before puberty.¹¹

This epidemiological survey suffers several limitations inherent to any spontaneous adverse drug reaction reporting. Indeed, the surveillance and analysis of adverse drug reactions represent a statistical challenge, because these reactions are rare, random, and mostly independent from the successive exposure of patients to a low-risk intervention. Although possible biases and under-reporting do exist, we believe that the large number of reactions investigated in our centers provide a representative picture of the situation. In addition, patients exposure to the various NMBA's available was estimated on the basis of sales data and not on anesthetic protocol.

Conclusions

In conclusion, immediate hypersensitivity reactions remain a significant adverse event during anesthesia. In a large number of cases, the precise mechanisms of reactions remain unclear, and further efforts must be made for their identification. In view of the constantly evolving anesthesiology practices, specific epidemiological

surveys represent an efficient tool to identify new substances at-risk and to evaluate the respective risk of different drugs.

Key messages

— Immediate hypersensitivity reactions remain a major cause of morbidity and mortality in the perioperative period.

— The diagnosis of allergic reactions during anesthesia relies on clinical symptoms. Cutaneous signs may be absent in severe reactions.

— Tryptase levels should be investigated during immediate hypersensitivity reactions to document mast cell activation.

— History, tryptase measurements at the time of the reaction and delayed skin tests are the cornerstone of the diagnosis of IgE-mediated hypersensitivity reactions.

— The epidemiology of allergic reactions is modified by changes in clinical practice.

— Neuromuscular blocking agents remain the main cause of allergic reactions during anesthesia. Cross-reactivity investigation between neuromuscular blocking agents is mandatory.

— Allergic reactions to antibiotics and dyes have rapidly increased.

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