

Adverse Reactions to Neuromuscular Blocking Agents

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Neuromuscular blocking agents (NMBAs) play a predominant role in the incidence of severe adverse reactions occurring during anesthesia. Most hypersensitivity reactions are of immunologic origin (IgE-mediated) or are related to direct stimulation of histamine release. The incidence of IgE-mediated hypersensitivity or anaphylaxis is estimated between 1 in 10,000 and 1 in 20,000 anesthetics, and NMBAs represent the most frequently involved substances, with a range of 50% to 70%. Any suspected anaphylactic reaction must be extensively investigated using combined perioperative and postoperative testing. Because of the frequent cross-reactivity observed with muscle relaxants, every available NMBA should be tested. This should help provide documented advice for future administration of anesthesia. There is no demonstrated evidence for systematic preoperative screening in the general population at this time. Other well-known adverse effects have been described, such as the succinylcholine-triggered cytotoxic effects on muscle cells, but these are responsible for characteristic clinical symptoms, which are usually easy to distinguish from anaphylactic reactions

Introduction

Historically, neuromuscular blocking agents (NMBAs) were mainly considered to be substances that are more toxic than drugs. However, with the development of mechanical ventilation, the introduction of NMBAs, by Griffith and Johnson in 1942, marked a new era in the practice of anesthesia and surgery. NMBAs are quaternary ammonium compounds structurally related to acetylcholine. There are structural differences between depolarizing muscle relaxants (leptocurares) such as succinylcholine, which are thin, flexible molecules, and nondepolarizing muscle relaxants (pachycurares), which are large, rigid ring systems into which the quaternary groups are incorporated. Available nondepolarizing relaxants include a variety of agents that can be classified according to chemical class: the steroidal compounds (pancuronium, vecuronium, rocuronium) and the benzylisoquinolinium substances (atra-

curium, cisatracurium, mivacurium), or they can be classified according to duration of action. NMBAs are used to facilitate intubations; to ensure good skeletal muscle relaxation to provide the surgeon with optimal operating conditions; to facilitate mechanical ventilation; or to reduce oxygen consumption. They are adjuvants, not substitutes, for anesthesia and/or sedation and analgesia. Therefore, investigations of adverse reactions and their mechanisms are difficult to design because of the need for mechanical ventilation, and, consequently, concomitant administration of anesthetic drugs, which might influence the study results.

However, anesthesia represents a pharmacologically unique practice of medicine, during which most drugs administered intravenously or by inhalation have a narrow toxic-to-therapeutic ratio and have the potential to produce a variety of predictable and unpredictable adverse reactions. Since the first reports describing anaphylactic reactions to succinylcholine, increasing interest has been focused on hypersensitivity reactions to NMBAs. In light of the increasing number of anesthetic drugs, the need for confirmation and quantitative risk assessment of suspected rare, serious, adverse reactions, requiring precise epidemiologic studies has continually been reinforced. In addition, awareness of the constant changes in anesthetic practice has led to elaboration of a growing number of practice guidelines concerning diagnosis, high-risk group identification, and management of anaphylaxis [1,2•]. In this overview of the literature, we consider the various adverse reactions related to succinylcholine and the currently available and most recent nondepolarizing NMBAs, with a special emphasis on immune- (anaphylactic) and non-immune-mediated (anaphylactoid) hypersensitivity reactions to NMBAs. Other adverse reactions, such as effects on muscle cells, are briefly reviewed, but a complete description of these specific effects is outside the scope of this article.

Hypersensitivity to Neuromuscular Blocking Agents

Epidemiology

Hypersensitivity reactions to anesthetic and associated agents used during the perioperative period have been reported with increasing frequency in most developed countries. Most reports on the incidence of these adverse reactions originate in France, Australia, the United Kingdom, and New Zealand [3,4]. They reflect an active policy of systematic clinical and/or laboratory investigation of hypersensitivity reactions sus-

Table 1. Substances responsible for anaphylaxis during anesthesia in France*

	1984–1989 <i>n</i> = 821 %	1990–1991 <i>n</i> = 813 %	1992–June 1994 <i>n</i> = 1030 %	July 1994–1996 <i>n</i> = 734 %	1997–1998 <i>n</i> = 486 %	1999–2000 <i>n</i> = 518 %
NMBAs	81	70.2	59.2	61.6	69.2	58.2
Latex	0.5	12.5	19	16.6	12.1	16.7
Hypnotics	11	5.6	8	5.1	3.7	3.4
Opioids	3	1.7	3.5	2.7	1.4	1.3
Colloids	0.5	4.6	5	3.1	2.7	4
Antibiotics	2	2.6	3.1	8.3	8	15.1
Others	2	2.8	2.2	2.6	2.9	1.3
	100%	100%	100%	100%	100%	100%

*Results from six consecutive surveys. *n*—number of substances responsible; NMBA—neuromuscular blocking agent.

pected to be mediated by an immune mechanism (*ie*, anaphylaxis). Anaphylactic reactions have also been reported for smaller series in the United States. Nevertheless, the true incidence of anaphylactic reactions and their associated morbidity-mortality remain poorly defined. This is due to uncertainties in reporting accuracy and exhaustion, as evidenced by the differences observed in reports from various developed countries. First of all, the clinical reaction must be recognized, and it should be emphasized that patients experiencing anaphylaxis during anesthesia present with a variety of signs. These might not appear all at once. In addition, some debate remains regarding interpretation and significance of the skin and laboratory tests usually required to distinguish between anaphylaxis and non-immune-mediated hypersensitivity. Finally, there are often difficulties in obtaining valid data on the number of patients exposed to the risk in the population from which reactions are reported. With these limits in mind, the estimated incidence of all immune and non-immune-mediated hypersensitivity reactions was 1 in 5000 to 1 in 13,000 anesthesia in Australia in 1980; 1 in 4600 in France; 1 in 1250 to 1 in 5000 in New Zealand; and 1 in 3500 in England [3,4]. The estimated incidence of anaphylaxis was 1 in 10,000 to 1 in 20,000 in Australia in 1993 [5] and 1 in 13,000 in France in 1996 [6]. Although rare, these reactions can lead to death, even when appropriately treated, with a mortality rate ranging from 3.5% [7] to 4.7% [8].

The overall distribution of the various causal agents incriminated in anaphylaxis during anesthesia is very similar in most reported series (Table 1). NMBAs represent the most frequently involved substances, with a range of 50% to 70% anesthesia, followed by latex (12% to 16.7%), and, in recent reports, antibiotics (Fig. 1).

In France, the incidence of NMBA anaphylaxis in 1996 was estimated at 1 in 6500 anesthetics involving a muscle relaxant [6]. Anaphylactic reactions have been reported for all NMBAs, even with recently commercialized substances [9•].

It should also be noted that in 15% to 50% of cases, anaphylaxis to an NMBA is reported in absence of any previous exposure to an NMBA [4].

In most reports, succinylcholine seems to be more frequently involved, with some differences reflecting variations

in anesthesiology practices from one country to another [3,9•,10]. However, some possible modifications in the epidemiology of anaphylaxis to NMBAs have been highlighted in the last two recent surveys conducted in France by the Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques (GERAP), a network of 40 French allergeo-anesthesia outpatient clinics organized in 1985, whose aim is to promote the survey of allergic and non-immune-mediated reactions occurring during anesthesia. In these two largest surveys ever conducted (between January 1, 1997 and December 31 1998, and between January 1, 1999 to December 31, 2000, respectively), rocuronium seems to be the most frequently involved agent, whereas the number of cases involving succinylcholine remains relatively stable [9•,11]. 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. When combined, succinylcholine and rocuronium represent more than 65% of the reactions but less than 16% of the market share in France. However, the results are based on an estimation of the number of patients exposed and should, therefore, be considered with circumspection.

In these studies, diagnosis was mainly based on history and skin test results, which have been extensively used for the diagnosis of anaphylaxis during anesthesia. However, in the absence of a diagnostic gold standard, skin test sensitivity and specificity remain difficult to establish. In addition, anesthesiologists might have paid more attention to the effects of more recently available drugs, especially in cases of mild reactions. Therefore, the controversy concerning adverse reactions to rocuronium remains a matter of debate. Some reports suggest an increased frequency of anaphylaxis to rocuronium, [9•,11,12] whereas others consider that the incidence of reactions involving rocuronium reflect market use [13,14].

Cross-sensitization among the different agents is observed in 70% of patients presenting with anaphylaxis to muscle relaxants [6]. It seems to be more frequent with aminosteroid NMBAs than with benzylisoquinoline-derived NMBAs [9•,11,15,16].

The prevalence of muscle-relaxant sensitivity, based on skin test positivity and/or detection of specific IgE to quater-

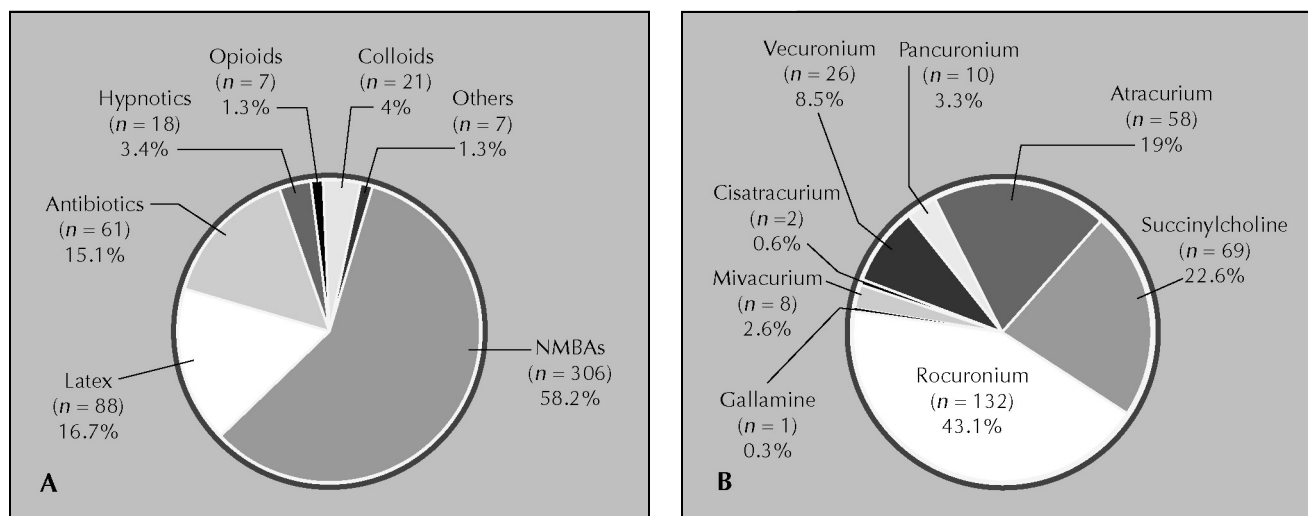


Figure 1. **A**, Agents involved in anaphylaxis occurring during anesthesia in France from January 1999 to December 2000. **B**, Neuromuscular blocking agents responsible for anaphylaxis within the same time period as that in **A**.

nary ammonium ions in the overall population, shows wide variation. A positive reaction in 9.3% of the general population has been reported [17], with extremes ranging from 1.6% in patients with no history of atopy and/or drug allergy to 16% in patients presenting with these risk factors [18]. This contrasts with the incidence of anaphylaxis to NMBAs, which has been estimated to be only 1 for 6500 anesthetics [6].

Mechanisms

Anaphylaxis

Anaphylaxis is an acute type I allergic reaction resulting primarily from the rapid antigen-induced, usually IgE-dependent, release of potent, pharmacologically active mediators from mast cells and basophils. NMBAs are low molecular-weight molecules and considered to be haptens. As such, they are incapable of inducing the production of drug-specific antibodies by themselves. Consequently, the initial step of sensitization is usually considered to be previous conjugation of the native drug or one of its degradation products with protein carrier and processing by professional antigen-presenting cells (APCs) before presentation of peptides on the cell surface that are in close association with a class I or II histocompatibility molecule. Direct interaction with proteins present on the surface of APCs, as reported for sensitizing metal and some antibiotics, and class II histocompatibility molecular interactions, should also be given consideration [19]. Therefore, the capacity of dendritic cells, which are considered to be the most powerful APCs, to present NMBA-related epitopes that are recognized by T cells has been recently demonstrated *in vitro* [20].

The elicitation of an immediate IgE-mediated reaction to the same drug is influenced by different immunochemical requirements. In anaphylaxis, mast cells and basophils are activated by cross-linking of Fcε receptor 1 (FcεRI) molecules. This is thought to occur by binding of multivalent antigens to

the attached molecules. This could be a possible explanation for the increased number of anaphylactic reactions to NMBAs, in comparison with other drugs used during anesthesia. With respect to muscle relaxants, the main antigenic determinants involved in the generation of specific IgE antibodies are substituted ammonium ions. This was initially demonstrated by Baldo and Fisher [21]. As a result, it has been hypothesized that most NMBAs, which bear two similar quaternary ammonium ions per molecule, are capable of bridging IgE antibodies and eliciting anaphylaxis. Therefore, the flexibility of the chain between the ammonium ions as well as the distance between the quaternary ammonium ions might be important during the elicitation phase of the anaphylaxis [22]. Flexible molecules, such as succinylcholine, can stimulate sensitized cells more strongly than rigid molecules (*eg*, pancuronium). The relative affinities of the various muscle relaxants to their corresponding IgEs might also play a role. This also explains the cross-reactivity between the different muscle relaxants observed with IgE antibodies of most patients, and initially evidenced by skin testing. In addition to the above-mentioned steric considerations, which could explain why two muscle relaxants do not necessarily behave similarly, other hypotheses have been proposed. In some cases, the antigenic determinant might either correspond to the quaternary ammonium epitope or extend to an adjacent part of the molecule. Another possibility might be that IgE antibodies could be complementary to structures other than the ammonium group [23].

In some instances, IgE-mediated anaphylactic reactions have been reported at the first known contact with an NMBA. This suggests a possible cross-reaction with IgE antibodies generated by previous contact with apparently unrelated chemicals. This is a particularly attractive hypothesis in cases in which patients react to relatively small and ubiquitous epitopes, such as a quaternary ammonium group. Although controversial, such a hypothesis has been proposed concern-

ing adverse reactions to NMBAs and IgE antibodies generated toward acetylcholine, different membrane phospholipids, or food lecithins from soy or egg [24].

Non-immune-mediated hypersensitivity

Immune-mediated and non-immune-mediated hypersensitivity reactions to NMBAs cannot be distinguished on the basis of clinical symptoms alone. In the last epidemiologic survey of hypersensitivity reactions during anesthesia conducted in France between January 1, 1999 and December 31, 2000 [9•], 33% of the reported cases were not IgE-mediated. Although the precise mechanisms of these reactions remain difficult to establish, they were probably more related to other, specific side effects of NMBAs, such as direct histamine release or cross-reactivity with nicotinic and muscarinic receptors responsible for actions at extraneuromuscular junction cholinergic receptors, causing peripheral autonomic and ganglionic effects. The potential to cause these effects is found with all of the available agents (depolarizing agent—succinylcholine; non-depolarizing agents—benzylisoquinolines or aminosteroid compounds), although it varies considerably among them and might not be seen at clinical doses.

Direct histamine release is usually regarded as the most frequent cause of non-IgE-mediated (anaphylactoid) reactions. Histamine release is predominantly found with the use of succinylcholine, the benzylisoquinolines atracurium and mivacurium, and the aminosteroid rapacuronium [25]. These differences could be related to different mechanisms of mast cell activation, as recently suggested by dermal microdialysis experiments conducted in human volunteers [26].

Neuromuscular blocking drugs also have the potential to produce adverse cardiovascular effects at muscarinic and nicotinic receptors, resulting in an increase (vagolytic) or decrease (vagal) in heart rate. They can also, as with pancuronium, block the release of norepinephrine and its reuptake at sympathetic nerve endings [27].

Recently, it has been suggested that the higher affinity of rapacuronium for M2 versus M3 muscarinic receptors could account for the high incidence of bronchospasms observed in clinical practice [28]. As a result of these adverse reactions, the sale of rapacuronium has been suspended in the United States.

Clinical Features

The difference between immune or non-immune-mediated hypersensitivity reactions cannot be made on clinical grounds alone, because clinical symptoms can be very similar. The intensity of reactions shows striking variation from one patient to another. Manifestations can range from mild non-life-threatening reactions to severe shock and death.

Factors that influence allergic reaction symptom severity in the sensitized individual include the distribution and reactivity of sensitized mast cells and basophils, individual organ susceptibility, released mediators, and the endogenous response they elicit [29]. Anaphylaxis commonly involves the

skin and the cardiovascular and respiratory systems, but can involve virtually any system, including the gastrointestinal, central nervous, and genitourinary systems.

In our most recent study, when a classification based on symptom severity was applied, clinical manifestations were more severe in patients with documented anaphylaxis, when compared with non-IgE-mediated reactions. In most cases, anaphylactic reactions were severe (88.1% of cases, grade II or more) and often life-threatening (65.1%, grades III and IV). This is in contrast with reactions of a nonimmune type, which were grade I 55.3% of the time. Nevertheless, some cases corresponding to true IgE-mediated anaphylactic reactions were classified as grade I or II. In this series, for unexplained reason, anaphylaxis against NMBAs appears to be more severe than anaphylactic reactions to latex [9•].

Alertness is essential, because reactions can be well established before they are noticed. Therefore, information concerning the various clinical features encountered is essential. The most commonly reported initial features are pulselessness, difficulty in lung inflation, and desaturation [5]. In our experience, a decreased end-tidal CO₂ expiration value is also of valuable diagnostic interest. In our last series, cutaneous symptoms were more frequent in non-IgE-mediated reactions (93.7% vs 71.9%, $P < 0.0001$), whereas cardiovascular collapse (50.8% vs 11.1%, $P < 0.0001$) and bronchospasm (39.8% vs 19.2%, $P < 0.0001$) were more frequent in cases of anaphylaxis [9•]. Therefore, the absence of cutaneous symptoms does not preclude the diagnosis of anaphylaxis. In addition, clinical features might occur as isolated conditions (Table 2). These results concur with previously published data [5,6,10]. As a result, an anaphylactic reaction restricted to a single clinical symptom (eg, bronchospasm, tachycardia with hypotension) can easily be misdiagnosed because many other pathologic conditions might present identical clinical manifestations. In mild cases restricted to a single symptom, spontaneous recovery might be observed even in the absence of any specific treatment. It should be kept in mind, however, that, under such circumstances, the lack of a proper diagnosis and appropriate allergy assessment could lead to fatal re-exposure.

In most cases, after adequate treatment, clinical signs regress within an hour without sequelae. However, in some cases, bronchospasm can be particularly severe and resistant to treatment, with a risk of cerebral anoxia or death. Prolonged inotropic support might also be required in some patients. Moreover, previous treatment by β -blockers is a potential risk factor explaining a lack of tachycardia, as well as resistance of arterial hypotension to adrenaline [30].

Investigating Allergic Reactions to Neuromuscular Blocking Agents

Every patient who experiences a hypersensitivity reaction during anesthesia should benefit from immediate and delayed investigations to confirm an eventual IgE-mediated allergic reaction, to identify the responsible drug, and to

Table 2. Clinical features of anaphylactic and anaphylactoid reactions during anesthesia in France between January 1, 1999 and December 31, 2000

Clinical symptoms	Anaphylaxis <i>n</i> = 518			Anaphylactoid reactions <i>n</i> = 518		
	Patients, <i>n</i> (%)		Sole feature	Patients, <i>n</i> (%)		Sole feature
Cardiovascular symptom	387	(74.7)		92	(33.9)	
Arterial hypotension	90	(17.3)	2	50	(18.4)	1
Cardiovascular collapse	264	(50.8)	32	30	(11.1)	2
Bradycardia	7	(1.3)	0	2	(0.7)	0
Cardiac arrest	31	(5.9)	10	—	—	0
Bronchospasm	207	(39.8)	7	52	(19.2)	2
Cutaneous symptoms	374	(71.9)	50	254	(93.7)	136
Angioedema	64	(12.3)	—	21	(7.7)	—

detect possible cross-reactivity in cases of anaphylaxis to an NMBA [2•]. The anesthetist administering the drugs associated with the suspected anaphylactic reaction must be responsible for ensuring that these tests are performed and interpreted adequately. The investigation should be conducted in concert with an allergologist or a clinical immunologist. However, the anesthetist remains responsible for providing further advice to the patient, informing the patient's primary care physician and recording all pertinent data in the patient's medical record.

The diagnostic strategy for a suspected anaphylactic reaction is based on a detailed history, including concurrent morbidity, previous anesthetic history, and any known allergies, as determined by laboratory tests performed on samples taken during and shortly after the reaction and tests conducted days to weeks later. Early tests are essentially designed to determine whether or not an immunologic mechanism is involved. Delayed testing is conducted to identify the responsible drug. Whenever possible, confirmation of the incriminated allergen should be based on immunologic assessment using more than one test.

Tryptase and histamine

Although elevated tryptase levels can be observed in different situations, an elevated serum tryptase concentration greater than 25 µg L⁻¹ is strongly in favor of an anaphylactic mechanism [2•]. However, a negative test does not completely rule out anaphylaxis. Tryptase concentration should be determined approximately an hour after the start of the reaction, but, in some cases, can still be detected for 1 to 6 hours or more after the onset of anaphylaxis [31]. In our last series, when tryptase measurements were aimed at the diagnosis of anaphylaxis, sensitivity was estimated at 64%, specificity at 89.3%, positive predictive value at 92.6%, and negative predictive value at 54.3% [9•].

Histamine should be assayed within the first hour of a suspected anaphylactic reaction, and in mild cases, only early measurements should be increased [32]. Histamine assay should be avoided during pregnancy (particularly near term) and in patients receiving high doses of heparin, because of a high rate of false negativity. In our most recent study, the

sensitivity of this test for the diagnosis of anaphylaxis could be estimated at 75%, the specificity at 51%, the positive predictive value at 75%, and the negative predictive value at 51%. Urinary methylhistamine assay is no longer recommended, in view of its low sensitivity in comparison with tryptase and histamine assay.

Specific IgE assay

Baldo and Fisher [21] initially demonstrated the presence of NMBA-specific IgE in serums using muscle relaxant coupled to Epoxy-Sepharose (Pharmacia, Piscataway, NJ). Specific IgE adsorbed to the solid phase was detected using radiolabeled anti-IgE. Inhibition of IgE binding was obtained by preincubation of the sera with either soluble muscle relaxants or structurally related compounds. They concluded that the quaternary and tertiary ammonium ions were involved in the allergenic site. This explained the cross-reactivity between different muscle relaxants observed by skin testing, in vitro leukocyte histamine release, and serum IgE radioimmunoassay (RIA). The value of radioallergosorbent tests (RAST) for IgE antibodies to muscle relaxants is well-established [33]. Although the sensitivity of the CAP-RAST assay (Pharmacia [Upjohn], Piscataway, NJ) is limited (succinylcholine: 66%; alcuronium: 40%), several teams have improved the sensitivity of specific serum IgE detection up to 90% to 97% by coupling an analogue of choline to Sepharose (SAQ) [34], or p-aminophenylphosphoryl-choline on agarose beads (PAPPC) [35]. Recently, specific IgE detection based on morphine in solid-phase form has been proposed [36]. Inhibition of specific IgE binding can be controlled by placing the tested serum in the presence of the offending molecule in soluble form.

Although classically performed several weeks after the reaction, the aforementioned tests can be conducted on blood drawn at the time of the reaction. As a result, the presence of specific IgE against the suspected drug at the time of the reaction can be substantiated. Satisfactory correlation with subsequent immunologic investigation has been reported when NMBAs are incriminated [31]. They can also help to confirm the diagnosis by identifying the responsible drug in patients in whom skin tests could not be performed or were found to be negative. However, a limit to the general-

ized use of these assays for NMBAs is that, due to the preparation of the materials required for the test, they are usually only possible in specialized laboratories.

Skin testing

Intradermal skin or prick tests are usually done 6 weeks after a reaction, but can remain positive for years later. Ideally, testing should be conducted by a professional experienced in performing and interpreting tests with anesthetic agents [1,2•]. Treatments such as antihistamines, known to decrease cutaneous reactivity, should be interrupted. Prick tests and intradermal reactions with dilutions of commercially available drug preparations are advised. Standardized procedures and dilutions must be precisely defined for each agent tested, to avoid false-positive results due to direct histamine-releasing properties. This is the case for known histamine-releasing compounds, such as mivacurium, atracurium, and tubocurarine. As such, these should be tested with more dilute solutions [2•,4,15,16,37]. Control tests using saline (negative control) and codeine (positive control) must accompany skin tests, to determine whether or not the skin is apt to release histamine and react to it. Although a certain degree of controversy remains as to the maximal concentrations to be used [38,39], detailed recommendations for skin and intradermal test dilutions of anesthetic drugs, including NMBAs, have recently been proposed by the French Society of Anesthesia (SFAR [Société Française d'Anesthésie et de Réanimation]) and the French Society of Allergology (SFAIC [Société Française d'Allergologie et d'Immunologie Clinique]) (Table 3) [2•]. Skin tests are interpreted after 15 minutes. A prick test is considered positive when the diameter of the wheal is at least equal to half of that produced by the codeine test and at least 3 mm larger than the negative control. Intradermal tests are considered positive when the diameter of the wheal is twice or more the diameter of the injection wheal.

Because of the frequent but not systematic cross-reactivity observed with muscle relaxants, every available NMBA should be tested. This should help prevent future adverse reactions, and provide documented advice for future administration of anesthesia. Moreover, any new muscle relaxant should be routinely tested in patients known to be allergic to these agents to detect possible cross-reactivity [2•].

The estimated sensitivity of skin tests for muscle relaxants is approximately 94% to 97% [40,41]. There has been some controversy concerning the advantages of either prick or intradermal testing. Studies comparing both techniques show little differences between them [37,42]. However, reliability over time concerning prick testing has not been assessed, and the reliability of prick tests alone in the individual patient has been questioned by some authors [43]. Consequently, prick testing is advised for the diagnosis of the muscle relaxant responsible for an anaphylactic reaction, but intradermal testing should be preferred when investigating cross-reaction.

Other biologic tests

Several other tests have been proposed to allow indirect detection of specific IgE to anesthetic drugs. The leukocyte histamine release test is reliable for muscle relaxants [44]. Its sensitivity is approximately 71% [45]. When combined with the simultaneous use of skin tests, and IgE-RIA, it allows detection in most cases. However, it is very expensive, time consuming, sometimes considered as a research tool, and not recommended in routine practice. Nevertheless, it could be useful when specific IgE assays are not available or when cross-reactivity among muscle relaxants in view of future anesthesia in sensitized patients is investigated.

The study of human basophil activation by detection of altered plasma membrane molecule expression using flow cytometry has also been proposed [46–48]. These tests are based on the changes of membrane molecules, such as CD 63, resulting from basophil activation in the presence of a suspected allergen. Their sensitivity in the diagnosis of muscle relaxant allergy is estimated at 64% and their specificity at 93% [47]. Their potential involvement in the diagnosis of anaphylactic reactions to neuromuscular blockers requires further evaluation.

Reports concerning the monitoring of serotonin [49], eosinophil cationic protein [50], or leukotriene C4 [51] release have also been published; however, currently, these assays cannot be recommended in routine clinical practice.

Investigation strategy prior to anesthesia

The potential severity of anaphylaxis to NMBAs underscores the interest of developing a rational approach to reduce its incidence by identifying potential risk factors before surgery. However, in the absence of established predictive value of tests for the occurrence of anaphylactic reactions, there is no demonstrated evidence for systematic preoperative screening in the general population at this time [2•,4,10]. Similarly, there is no evidence for the need of investigating sensitization against NMBAs (or other anesthetic drugs) in patients who are either atopic or sensitized to substances they would not be exposed to during anesthesia.

Consequently, pre-anesthetic assessment of sensitization to NMBAs should be limited to the following high-risk patients :

- Patients presenting a documented allergy to muscle relaxants. In this case, newly commercialized muscle relaxants should be tested before renewed anesthesia.
- Patients having experienced an unexplained reaction during a previous general anesthesia, including severe hypotension, bronchospasm, or edema during recovery. It is conceivable that the reaction might have been related to sensitivity to an anesthetic agent or latex. The list of all injected substances will help guide the allergist through the assessment. If the anesthetic protocol is unavailable, the substances (*ie*,

Table 3. Concentrations of anesthetic agents normally nonreactive in practice of skin tests

Available agents		Prick tests		Intradermal tests	
INN	C, mg x mL ⁻¹	Dilution	MC, mg x mL ⁻¹	Dilution	MC, µg x mL ⁻¹
Atracurium	10	1/10	1	1/1000	10
Cisatracurium	2	Undiluted	2	1/100	20
Mivacurium	2	1/10	0.2	1/1000	2
Pancuronium	2	Undiluted	2	1/10	200
Rocuronium	10	Undiluted	10	1/100	100
Suxamethonium	50	1/5	10	1/500	100
Vecuronium	4	Undiluted	4	1/10	400
Etomidate	2	Undiluted	2	1/10	200
Midazolam	5	Undiluted	5	1/10	500
Propofol	10	Undiluted	10	1/10	1000
Thiopental	25	Undiluted	25	1/10	2500
Alfentanil	0.5	Undiluted	0.5	1/10	50
Fentanyl	0.05	Undiluted	0.05	1/10	5
Morphine	10	1/10	1	1/1000	10
Remifentanyl	0.05	Undiluted	0.05	1/10	5
Sufentanil	0.005	Undiluted	0.005	1/10	0.5
Bupivacaine	2.5	Undiluted	2.5	1/10	250
Lidocaine	10	Undiluted	10	1/10	1000
Mepivacaine	10	Undiluted	10	1/10	1000
Ropivacaine	2	Undiluted	2	1/10	200

C—concentration; INN—International Nonproprietary Name; MC—maximal concentration.

muscle relaxants and latex) that are most often incriminated in epidemiologic studies (skin tests, eventually specific IgE assays) should be tested. One should keep in mind, however, that skin tests performed belatedly after an adverse reaction during anesthesia could be falsely negative. This is due to a possible spontaneous decrease of specific IgE concentration with time. It is always preferable that any investigation be carried out 6 weeks after the adverse reaction.

Prevention

Prevention of anaphylaxis has two major objectives. It should be aimed at preventing sensitization of a patient to a particular allergen, or aimed at preventing the occurrence of an anaphylactic reaction to a re-introduced allergen in a pre-sensitized patient. In this regard, in the wake of the relatively high rate of sensitization in the absence of any prior exposure, optimal prevention of sensitization to NMBAs, even if their administration were to be radically curtailed, is probably unattainable.

Pretreatment with corticosteroids or histamine-receptor antagonists, by either H₁- or H₁- and H₂-receptor antagonists remains controversial. No evidence of beneficial effects of prophylactic administration of corticosteroids in anesthesia has been shown at this time. Pretreatment with H₁- and H₂-receptor antagonists has been found to reduce histamine-mediated adverse effects in various studies. Antihistamine

administration was effective in reducing the adverse effects of nonimmune histamine release following muscle relaxant [52,53]. However, histamine detected during alarming immune-mediated reactions is merely a marker of co-release of more dangerous mediators. In addition, such a prophylactic approach has been found to be ineffective, or, in some cases, deleterious [4]. Many authors consider that pretreatment with corticosteroids, or antihistamines, or both, do not provide reliable prevention of immune-mediated reaction [24,54]. Nevertheless, even in the absence of any well-documented studies concerning anaphylaxis, some authors propose pretreatment with H₁ or H₁ and H₂ antagonists as useful in the management of the patient with a history of anaphylaxis or at risk of nonimmune histamine release [24,43]. In France, the use of these associations remains a matter of controversy. When prescribed, preventive treatment is usually limited to H₁-receptor antagonists. However, proven anaphylactic reactions to NMBAs, even in the wake of preoperative H₁- and H₂-receptor antagonists and steroids, have been documented in epidemiologic surveys [9,11].

The use of monovalent haptens, which can occupy antibody sites without bridging specific IgE fixed on sensitized cells, has also been proposed for muscle relaxants. In this respect, any molecule presenting a quaternary ammonium ion could be considered as a potential monovalent hapten. Choline and tiemonium were initially used; unfortunately clinical tolerance of the highest doses was poor. As a result, the concentrations obtained were too low to be effective [55,56]. Recently, Moneret-Vautrin *et al.* [57] demonstrated

inhibition of skin mast-cell reactivity to muscle relaxants by mixing them with the monovalent haptens cytidylcholine and ethamsylate. Furthermore, they obtained an inhibition of leukocyte histamine release for up to 3 hours following the infusion of these monovalent haptens in patients allergic to muscle relaxants. Morphine, with its high affinity to reactive muscle relaxant antibodies, has also been proposed as a possible preventive hapten [10,43]. However, prevention of muscle-relaxant anaphylaxis by monovalent haptens cannot be recommended in standard clinical practice [2•].

Other Adverse Reactions to Neuromuscular Blocking Agents

Besides direct histamine release and adverse cardiovascular and respiratory effects, which can sometimes be difficult to distinguish from anaphylactic reactions, other potential adverse reactions have been described. Some of them can be life-threatening, and others are usually not clinically relevant.

Malignant hyperthermia

The prevalence of malignant hyperthermia is 0.002% in adults and 0.006% in children. It is a rare genetic disorder triggered by exposure to depolarizing NMBAs (succinylcholine) and inhalation of halogenated anesthetics, with a spontaneous mortality rate of 80% [58,59]. In 50% of all cases, the mutation is autosomal dominant, with one of eight potential mutations in the ryanodine receptor. Associated hereditary muscle disorders are central core disease and King-Denborough syndrome [60•]. It results in an excessive, uncontrolled release of calcium from the sarcoplasmic reticulum of skeletal muscle, elicited by the offending agent. As a consequence, skeletal muscle acutely and unexpectedly increases its oxygen consumption and lactate production, resulting in greater heat production, respiratory and metabolic acidosis, muscle rigidity, sympathetic stimulation, and increased cellular permeability. Early features of malignant hyperthermia are tachycardia, cyanosis, muscle stiffness, fever, cardiac dysrhythmias, unstable blood pressure, and myoglobinuria. Treatment involves rapid cooling, 100% oxygen administration, acidosis control, and intravenous dantrolene administration.

Patients with progressive muscular dystrophy, such as Duchenne and Becker dystrophies, might present with acute rhabdomyolysis or mimic malignant hyperthermia following the administration of succinylcholine and halogenated anesthetics. The hypersensitivity is considered to be due to an increased resting intracellular concentration of calcium.

Myotonias and masseter spasm

Myotonic reactions following succinylcholine administration have been observed in hereditary disorders of sodium and chloride channels in muscle cells. Tonic reactions ranging from masseter spasm to generalized myotonic reactions with muscle cell breakdown might occur in patients with non-dystrophic myotonias and periodic paralysis [60•,61].

Muscle cell damage

Myoglobinemia and increased serum creatinine kinase have been reported following succinylcholine administration, particularly in children [59,62]. The etiology could be the shearing forces set up by asynchronous contractions of adjacent muscle cells following their activation by succinylcholine. In some cases, this drug-induced rhabdomyolysis might lead to an extremely high release of myoglobin and myoglobinuria with subsequent toxic renal failure.

Other effects

Succinylcholine administration is associated with a release of potassium ions from muscle cells. In certain clinical situations, such as in patients with burns, massive trauma, or acute upper and lower motoneuron disease (*eg*, spinal cord injury, stroke, demyelinating disease), the resulting hyperkalemia can be severe enough to cause fatal cardiac dysrhythmias and cardiac arrest [25,59].

Plasma cholinesterase activity can be reduced by a number of causes, such as pregnancy, liver disease, and uremia. These conditions usually lead to a slight, clinically unimportant, increase in the duration of action of succinylcholine and mivacurium. A small proportion of patients (1:15000 to 1:2000) have a genetically determined inability to metabolize succinylcholine and mivacurium, which can lead, in homozygous patients, to prolonged paralysis after usual doses.

Nondepolarizing NMBAs produce dose-dependent developmental toxicity in rat embryos. However, the concentrations required to obtain these effects are at least 30-fold higher than those achieved in humans under normal clinical circumstances [60•].

Severe burning pain has been associated with the administration of rocuronium and vecuronium bromide [63], and a high incidence of muscle pain has been reported with the use of succinylcholine.

Conclusions

Among all drugs used for general anesthesia, NMBAs seem to play a predominant role in the incidence of severe adverse reactions. Since their introduction in modern anesthesia practice, much progress has been made in the identification of adverse reactions and their potential mechanism. However, despite the introduction of newer drugs in clinical practice, the incidence of serious, immediate hypersensitivity-type reactions has remained virtually unchanged.

Because no premedication can effectively prevent an allergic reaction, any suspected anaphylactic reaction must be extensively investigated using combined perioperative and postoperative testing. Patients must be fully informed of the results of the investigations, and advised to provide a detailed report prior to any future anesthesia. A medical alert bracelet or a warning card is strongly indicated for these patients.

Currently, with the exception of the high-risk patient, a systematic preoperative screening for sensitization against NMBA is not justified. A thorough pre-anesthetic history is

the most important tool for screening subjects who are at risk of having an abnormal reaction during anesthesia. Particular attention must be paid to patients who have already experienced such a reaction during anesthesia, or those alleging an allergy to muscle relaxants. In these cases, the choice of the safest possible anesthetic agents should be based on the result of a rigorously performed allergologic assessment.

In view of the constantly evolving anesthesiologic practices, and of the relative complexity of allergy investigation, an active policy to identify patients at risk and to provide any necessary support from expert advice to anesthesiologists and allergologists through the constitution of allergo-anesthesia centers should be promoted.

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