

Hypersensitivity Reactions to Neuromuscular Blocking Agents

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Abstract: Neuromuscular blocking agents are the leading drugs responsible for immediate hypersensitivity reactions during anaesthesia. Most hypersensitivity reactions represent IgE-mediated allergic reactions. Their incidence is estimated to be between 1 in 3 000 to 1 in 110 000 general anaesthetics. However striking variations have been reported among countries.

The mechanism of sensitisation seems to implicate the presence of a substituted ammonium ion in the molecule. Due to lack of exposure prior to the reaction in a large number of reactors, it has been hypothesised that sensitisation may involve other, as yet undefined, substituted (quaternary and tertiary) ammonium ion containing compounds such as pholcodine, present in the environment of the patient. This hypothesis is still under investigation. The mechanism of non-IgE mediated hypersensitivity reactions is less well known. Identified mechanisms correspond to direct histamine release or interactions with muscarinic and nicotinic receptors.

Allergic reactions cannot be clinically distinguished from non-IgE-mediated reactions. Therefore, any suspected hypersensitivity reaction must be investigated using combined pre and postoperative testing. Because of the frequent but not systematic cross-reactivity observed with muscle relaxants, every available neuromuscular blocking agent should be tested, using intradermal tests to confirm the responsibility of the suspected drug which should be definitely excluded. Cross-sensitivity investigation will also try to identify the safety of drugs that can be potentially used in future anaesthesia. The determination of basophil activation investigations using direct leukocyte histamine release test or flow cytometry would be of particular interest to investigate cross sensitisation in complement to skin tests.

There is no demonstrated evidence supporting systematic pre-operative screening in the general population at this time. However, since no specific treatment has been shown to reliably prevent anaphylaxis, allergy assessment must be performed in all high-risk patients.

In view of the relative complexity of allergy investigation, and of the differences between countries, an active policy to identify patients at risk and to provide any necessary support from expert advice to anaesthetists and allergologists through the constitution of allergeo-anaesthesia centres in every country should be promoted.

Key Words: Neuromuscular blocking agents, anaesthesia, anaphylaxis, allergy, IgE, skin test, flow cytometry.

I. INTRODUCTION

Anaesthesia is usually considered to be merely pharmacologically induced unconsciousness but is in fact that medical speciality which ensures optimum operative conditions for both the patient and for the surgeon. In this regard the survey and prevention of adverse drug reactions occurring during the preoperative is regarded by anaesthesiologists as critical to reduce overall mortality and morbidity related to anaesthesia. Anaesthesia is composed of the triad of hypnosis, analgesia and muscle relaxation. The first anaesthetic was administered in 1846 and for most of the following century anaesthesia was provided by the administration of sufficiently large doses of a single agent to provide acceptable

operating conditions. This original anaesthetic monotherapy has been replaced in the last 70 years by balanced anaesthesia, an anaesthetic provided by means of multiple pharmacological agents to achieve the desired phenomena of unconsciousness, of analgesia and the obtundation of autonomic reflexes and of muscle relaxation.

Adequate muscle relaxation is a *sine qua non* of many surgical procedures; to prevent patient movement and injury, to permit surgical access to body cavities, to prevent shivering and decrease oxygen consumption. It is a vital component of anaesthetic technique *per se* facilitating endotracheal intubation, mechanical ventilation of the lungs and of the treatment of laryngeal spasm. It is also an important adjuvant in intensive care medicine. The profound muscle relaxation afforded by muscle relaxants does not just facilitate modern surgery and anaesthesia but indeed often makes them possible. In this regard, allergologists must be well aware of the

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consequences of the diagnosis of sensitisation to a NMBA, of the importance of avoiding false positive or negative results during the allergy work-up, and of the necessity to identify possible safe agents for future procedures.

This overview of the literature will consider hypersensitivity reactions related to suxamethonium and the currently available and most recent non-depolarising NMBAs with a special emphasis on immunoglobulin E (IgE) mediated hypersensitivity reactions to NMBAs.

II. PHYSIOLOGY OF NEUROMUSCULAR TRANSMISSION AND BLOCKADE

A complete description of the physiology of neuromuscular transmission and blockade is outside the scope of this review and this section will be limited to a brief *aide mémoire* of mechanisms of neuromuscular transmission and blockade and of the various drugs commonly used. Profound muscle relaxation is provided by means of the administration of neuromuscular blocking agents (NMBAs) which impede impulse transmission at the neuromuscular junction (NMJ). The neuromuscular junction is composed of the end of the α motor neuron, the motor end plate which is a region of the

cell membrane of the skeletal muscle fibre lying opposite and the synaptic cleft between them. Under physiological conditions when a nerve impulse reaches the terminal of the nerve acetylcholine (ACh) is released in a calcium dependant manner from synaptic vesicles within the nerve ending into the synaptic cleft across which it diffuses towards the motor end plate, which has a high concentration of nicotinic ACh receptors. This receptor is a negatively charged ion channel composed of 5 subunits, 2α , β , γ/ϵ and δ . ACh binds to the α subunits, opening the channel which causes an ion flux, reducing the transmembrane potential of the end plate, which potential is then propagated over the membrane of the muscle fibre initiating the process of muscle contraction. ACh is then rapidly hydrolysed by acetylcholinesterase, present in high concentrations at the NMJ, causing the ACh receptor ion channel to revert to its resting closed state. There is a high degree of redundancy of ACh receptors at the NMJ, there is no diminution of the muscle response to a stimulus until over 70 % of ACh receptors are occupied by a NMBA.

NMBAs are divalent ammonium compounds which bind to the α subunit of the ACh receptor. There are two classes of NMBAs which disrupt the process of neuromuscular transmission in two different manners (Fig. 1) [1, 2].

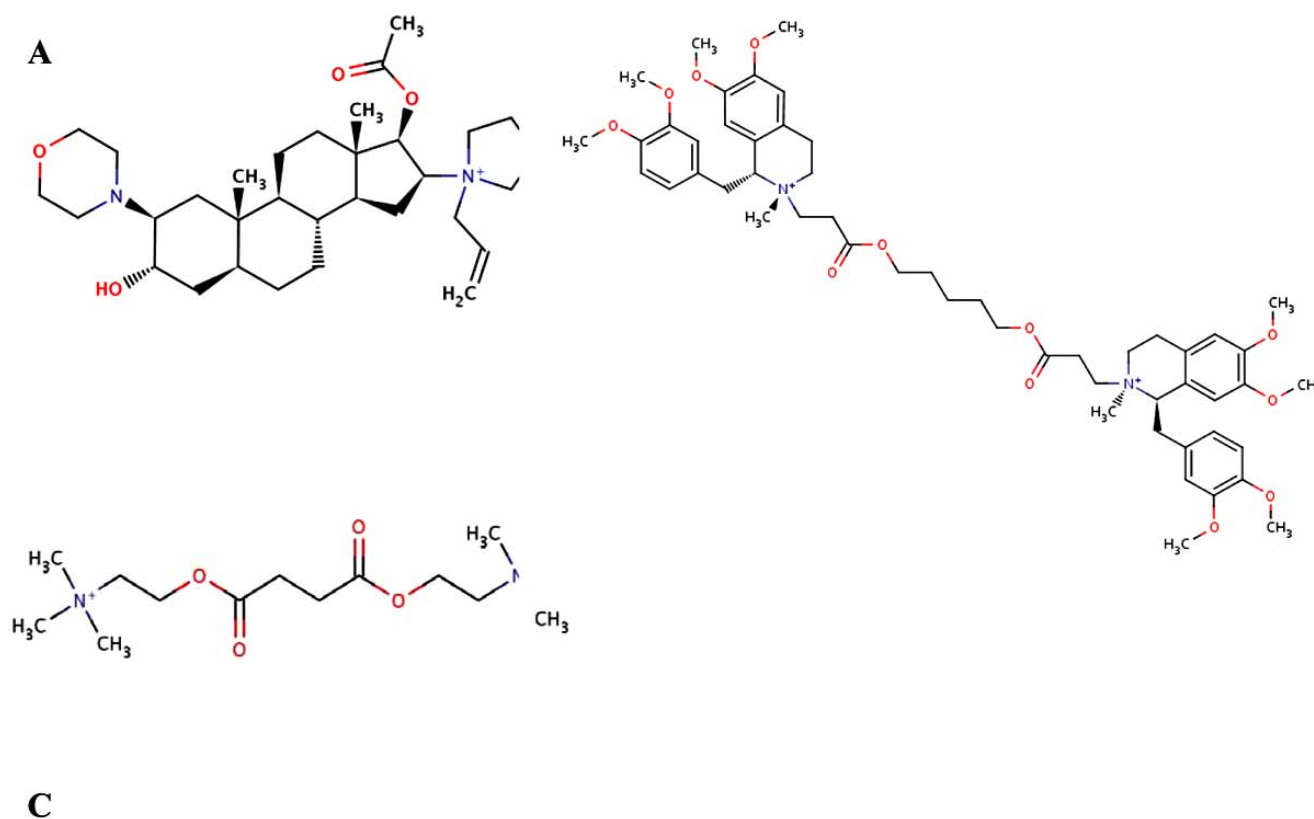


Fig. (1). Chemical structure of the main neuromuscular blocking agents used in clinical practice. Panel A: rocuronium (non-depolarising steroidal relaxants), Panel B: cis-atracurium (non-depolarising benzyloquinolinium relaxant), Panel C: suxamethonium (depolarising relaxant).

Depolarising (non-competitive) NMBAs bind to the α subunit of the ACh receptor thus initiating depolarisation of the membrane and muscle contraction, however they are not rapidly hydrolysed by acetylcholinesterase but leaving the ion channel in a depolarised state render it refractory to further ACh i.e. a depolarising or non-competitive block. There are no antagonists to depolarising NMBAs.

Non-depolarising (competitive) NMBAs effect neuromuscular blockade by binding to the α subunits of the ACh receptor without inducing opening of the ion channel, blocking the binding of ACh, that is to say they act as classic competitive antagonists of ACh. Non depolarising blockade can be antagonised by the administration of anticholinesterases, which by increasing the concentration of ACh at the neuromuscular junction overcome the competitive block, in an analogous manner to their mechanism in the treatment of myasthenia gravis, however there must be significant pre-existing recovery of neuromuscular transmission prior to the administration of an anticholinesterase to ensure adequate reversal of the blockade.

Depolarising NMBAs

Suxamethonium and decamethonium are depolarising NMBAs. Suxamethonium, a dimer of ACh, is the only depolariser in common clinical use. It has a very fast onset of action and short duration of action, the combination of which make it an indispensable tool in the management of anaesthetic emergency situations where rapid control of the airway is required (e.g. "crash" induction, laryngospasm). However it has a very poor adverse effect profile, so much so that finding a replacement for suxamethonium has been almost a "holy grail" of anaesthetic research.

Non-Depolarising NMBAs

Non-depolarising NMBAs are either curare alkaloids, benzyliisoquinolinium or aminosteroid compounds. In clinical practice the choice of non-depolariser is based on side effects, route of elimination and most importantly duration of action. The naturally occurring prototype of this class was d-tubocurarine, originally used as arrow poison in South America, which was first used to produce surgical muscle relaxation in the 1940s. It has numerous side effects, particularly cardiovascular and histamine release, and a great deal of the subsequent history of muscle relaxants has been a quest for "cleaner" synthetic replacements.

Pancuronium, a synthetic aminosteroid does not cause histamine release nor ganglionic blockade, it does cause a vagolytic tachycardia. It also is long acting and is excreted renally. Vecuronium an intermediate acting aminosteroid causes neither ganglionic blockade, histamine release nor tachycardia and is metabolised in the liver. Rocuronium is similar but causes a slight tachycardia. It has been used in high doses to provide a very rapid onset but has an intermediate duration of action. Atracurium is a benzyliisoquinolinium intermediate acting NMBA, it causes some histamine release and hypotension which is offset by a compensatory increase in heart rate and is broken down by non-organ non-enzyme Hoffman degradation. Its isomer cis-atracurium is devoid of histamine release. Mivacurium, a benzyliisoquinolinium is the shortest acting non-depolariser currently avail-

able though not so short acting as to replace suxamethonium, it causes some histamine release and although a non-depolariser is metabolised by plasma cholinesterase. Rapacuronium a rapid onset, short acting aminosteroid NMBA was heralded as the first drug with the potential to replace suxamethonium, however reports of severe bronchospasm including possible deaths led to its withdrawal from the market soon after its introduction.

III. EPIDEMIOLOGY OF HYPERSENSITIVITY REACTIONS TO NMBAs

General anaesthesia is a unique situation which can be described as a reversible state of unconsciousness, amnesia, analgesia and immobility resulting from the administration of a combination of several drugs in a very short period of time [3]. Many of these drugs can elicit adverse reactions which can be either related to their pharmacological properties of the drugs and usually dose-dependent, or unrelated to them and less dose-dependent. This phenomenon came under particular attention in the late 1970s with the observation of possible non-specific histamine release triggered by compounds of simple chemical structure [4]. This led to intense debate concerning the nature of adverse reactions occurring during anaesthesia, which were initially termed *anaphylactoid phenomena* [5]. However, several clinical reports of allergic reactions to neuromuscular blocking agents [6-9] rapidly established the importance of immune mediation in anaesthetic drug induced adverse reactions. In an attempt to counteract unclear and heterogeneous usage of terms, the nomenclature task force of the European Academy of Allergy and Immunology, followed by the World Allergy Organisation, have proposed that anaphylactic-type reactions should be reclassified into *allergic anaphylaxis* and *non-allergic anaphylaxis*, allergic reaction being further divided in *IgE-mediated* and *non-IgE-mediated reactions* [10, 11]. However, most reports published in the literature do not clearly distinguish between severe life-threatening reactions (anaphylaxis) and less severe reactions. Therefore we will mainly use the term *hypersensitivity* to avoid any consideration regarding the severity of the reactions in this manuscript.

Neuromuscular blocking agents induced allergic reactions are almost exclusively IgE-mediated. Delayed allergic reactions have been rarely described and were limited to suxamethonium induced reactions [12, 13].

Immediate hypersensitivity reactions to anaesthetic and associated agents used during the perioperative period seem to have had an increasing frequency since the 1970s, but with respect to reported reactions to specific families of compounds some frequencies have increased, some remained stable while others declined [14]. Nevertheless, the true incidence of anaphylactic reactions and their associated morbidity and mortality remain poorly defined. This is due to uncertainties over reporting accuracy and exhaustiveness. Indeed, the clinical reaction must be recognised, and it should be emphasised that patients experiencing a hypersensitivity reaction during anaesthesia present with a variety of signs and that these may not all appear simultaneously. The quality of information obtained from multiple cases under such circumstances will necessarily be variable regarding complete-

ness and precision, and a detailed case history usually represents an important part of the diagnosis. Another uncertainty is the magnitude of under-reporting of reactions particularly in the case of mild reactions or when recently introduced drugs, as compared with older drugs, are involved [15]. Other possible biases may include differences in anaesthetic practices between centres or countries. In addition, the surveillance and analysis of adverse drug reactions represent a statistical challenge, because these reactions are rare, random, and mostly independent of repeated exposure of patients to a low risk intervention [16].

Finally, there are often difficulties in obtaining valid data on the number of patients exposed to the risk in the population in which reactions are reported. Because of all the aforementioned possible biases and of under-reporting, spontaneous reporting systems are usually considered inappropriate for the assessment of adverse drug reaction rates [17], or differences in incidence rates [18, 19].

Within these limits in mind, the estimated incidence of all immune and non-immune-mediated immediate hypersensitivity reactions was 1 in 5 000 to 1 in 13 000 anaesthetics in Australia, 1 in 5 000 in Thailand, 1 in 4 600 in France, 1 in 1 250 to 1 in 5 000 in New Zealand, 1 in 3 500 in England [20-23]. The estimated incidence of anaphylaxis was 1 in 10 000 to 1 in 20 000 in Australia in 1993 [24], 1 in 13 000 in France in 1996 [25] and 1 in 1 700 to 1 in 20 000 in Norway in 2005 [26].

In most reports, NMBAs represent the most frequently involved substances, ranging from 50 to 70 % [14, 27-29]. However, striking differences can be observed between countries. In France, the incidence of IgE-mediated hypersensitivity reactions to NMBAs in 1996 was estimated at 1 in 6 500 anaesthetics involving a muscle relaxant [25] representing around 60 % of IgE-mediated reactions. It was estimated at 1 per 3 000 to 1 per 110 000 exposures in Norway, representing 93.2 % of IgE-mediated reactions [26]. However, IgE mediated reactions involving NMBAs appear to be far less frequent in Denmark and Sweden [30-32]. Allergic reactions to NMBAs have also been reported for smaller series in the United States [33].

Although rare, IgE-mediated hypersensitivity reactions may lead to death, even when appropriately treated, with a mortality ranging from 3.5 % in Australia [34], 4.7 % in Japan [35] to 10 % in the United Kingdom [36]. A recent report based on data from the voluntary Yellow Card Scheme, the main reporting system for adverse drug reactions, analysed adverse drug reactions to seven neuromuscular blocking drugs over a 30-year period of time (1963-2002) [15]. Only tubocurarine, suxamethonium, alcuronium, atracurium, pancuronium, vecuronium and mivacurium were included in the study. Rocuronium and cis-atracurium were excluded because an insufficient time had passed since their introduction. Of 950 adverse drug reactions reported, 9 % had a fatal outcome. In this series, allergic reports occurred most commonly ($n = 499$), but many reports were of other types of adverse events, possibly with an allergic component but not identified as such. In France, in a study of the mortality rate due to anaesthesia based on the analysis of the death certificates from the national mortality database, only 3 deaths related to an allergic reaction were identified [37].

Anaphylactic reactions have been reported for all NMBAs, even with recently introduced substances [14]. In most reports, suxamethonium appears to be more frequently involved, with some differences reflecting variations in anaesthetic practices between one country to another [14, 15, 26, 28, 38]. In contrast pancuronium and cis-atracurium are the NMBAs associated with the lowest incidence of anaesthetic anaphylaxis in large series [14, 28, 29, 38, 39]. Some controversy has arisen concerning a potential increased prevalence of immediate hypersensitivity reactions to rocuronium. A trend concerning an increased frequency of allergic reactions to rocuronium was initially reported in Norway and France [40-42], but not in Australia [43], the United Kingdom [44] and USA [33]. Because of statistical limitations, analysis of epidemiologic data from Norway was unable to confirm whether or not rocuronium represented an increased risk [16, 26]. In the same time, surveys conducted in France by the GERAP (*Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques*), a network of 40 French allergeo-anaesthesia outpatient clinics organised in 1985 whose aim is to promote the survey of allergic and non-immune-mediated reactions occurring during anaesthesia, still seem to indicate a trend towards an increased risk when the respective market shares of the different NMBAs were taken into account [14, 29, 38]. Nevertheless, multiple clinical, methodological and statistical issues might have contributed to the apparent increased potential of anaphylaxis to suxamethonium and rocuronium, as well as to the apparent low potential of reactions to pancuronium or cis-atracurium [16, 45]. Further large epidemiologic studies will be necessary to elucidate this problem.

The prevalence of muscle relaxant sensitivity, based on skin test positivity and/or detection of specific IgE to substituted (tertiary or quaternary) ammonium ions in the overall population, shows wide variation not only between but also within countries. In France, a positive reaction in 9.3 % of the general population has been reported [46], with extremes ranging from 1.6 % in patients with no history of atopy and/or drug allergy to 16 % in patients with these risk factors [47]. This contrasts with the incidence of anaphylaxis to neuromuscular blocking agents, which has been estimated to be only 1 in 6 500 anaesthetics [25]. However, similar results have been reported in Norway, a country where the rate of IgE-mediated reactions to NMBAs is high, with 3.7 % and 10 % of atopic subjects were IgE-sensitised to suxamethonium and morphine, respectively, whereas no positive sera was found in patients originating from Sweden, a country where the rate of allergic reactions to NMBAs is low [30].

IV. MECHANISMS

IgE-Mediated Hypersensitivity Reactions

Most hypersensitivity reactions to NMBAs are acute type I allergic reactions resulting primarily from the rapid antigen-induced, usually IgE-dependent release of potent, pharmacologically active preformed mediators such as histamine and tryptase from mast cells and basophiles. Platelets are also potential target cells, whose low affinity IgE receptors mediate an IgE-dependant release of serotonin *in vitro*, in blood samples from allergic patients [48]. Neuromuscular blocking agents are low molecular weight molecules and have been usually considered as haptens incapable of induc-

ing the production of drug-specific antibodies by themselves. Consequently, prior conjugation of the drug or of one of its degradation products with a protein carrier and processing by professional antigen-presenting cells before presentation of peptides on the cell surface in close association with a class I or II histocompatibility molecule is usually regarded as the initial step of sensitisation. Direct interaction with proteins present on the surface of antigen presenting cells, as reported for sensitising metal and some antibiotics, and class II histocompatibility molecular interactions, should also be given consideration [49]. In this regard the capacity of Dendritic cells, which are considered to be the most powerful antigen-presenting cells, to present NMBA related epitopes that are recognised by T cells has been recently demonstrated *in vitro* [50].

The elicitation of an IgE-mediated reaction is influenced by different immunochemical requirements. In anaphylaxis, mast cells and basophils are activated by cross-linking of Fc ϵ RI molecules. This is thought to occur by binding of multivalent antigens to the attached molecules. In 1983, Baldo and Fisher demonstrated the role played by alcuronium reactive antibodies in some life-threatening reactions elicited by this neuromuscular blocking agent [51]. These antibodies were found to cross-react with other muscle relaxants and with a variety of apparently structurally unrelated drugs. Structure-activity studies designed to explore the molecular basis of the antibody binding have established that quaternary and tertiary ammonium ions were the main component of the allergenic sites on the reactive drugs [51, 52]. Since the structure of neuromuscular blocking agents includes two substituted ammonium ions per molecule, this explains the cross-reactivity between the different muscle relaxants observed with IgE antibodies in most patients, and evidenced by skin testing [42, 51-58]. This has also been proposed as a possible explanation for the increased number of anaphylactic reactions to neuromuscular blocking agents, in comparison to other drugs used during anaesthesia. However the IgE recognition site of the molecule depends also from the molecular environment of the ammonium ion, in function of the hydrophobicity and distance with polar groups such as hydroxyls [59, 60]. This may explain the heterogeneity of the cross-reactivity among patients. The IgE binding has been characterized by measuring the inhibition constant (K_i) by dixon plot, in anti-NMBA IgE-RIA. This constant is an inverse value of affinity constant (k_{ass}): the highest it is, the lowest is the affinity of Drug/IgE binding. A hydrophobic environment seemed to be necessary, close to the quaternary ion, to allow IgE binding to the muscle relaxant. Indeed, in tiemonium, a widely used and safe drug with ammonium ions (with no reported allergic reaction), a hydroxyl group present at a distance of about 3 Å from the quaternary ion explained why this molecule had a high K_i (microM), e.g. a very low affinity for the anti-quaternary IgE from patients allergic against NMBA [60].

Differences regarding the relative risk of allergic reactions between NMBA have been recognised in large epidemiologic surveys [25-28, 38, 61, 62]. In this regard, it has been suggested that the flexibility of the chain between the ammonium ions as well as the distance between the substituted ammonium ions might be of importance during the elicitation phase of IgE-mediated reactions [63, 64]. Flexible

molecules, such as suxamethonium, were considered more potent in stimulating sensitised cells than rigid molecules like pancuronium. This hypothesis would be contradicted if a higher risk of sensitisation associated with rocuronium were to be confirmed.

In the past, as for rocuronium, alcuronium has been claimed to be a high risk for anaphylaxis. If this is further confirmed by epidemiologic surveys, propenyl ammonium groups present in both NMBA may be involved in this apparent increased allergenicity.

Cross-sensitisation among the different agents has been reported to be frequent, varying between 60 and 70 % of patients allergic to neuromuscular blocking agents, but it is not constant [14, 25, 29, 61]. Indeed, the patterns of cross-reactivity vary considerably between patients. Cross-reactivity to all NMBA is relatively unusual, but seems to be more frequent with aminosteroid neuromuscular blocking agents than with benzyloquinoline-derived neuromuscular blocking agents [14, 38, 42, 54-56]. In addition to the above-mentioned steric considerations, which could explain why two muscle relaxants do not necessarily behave similarly, further hypotheses have been proposed. In some cases, the antigenic determinant may either correspond to the tertiary or quaternary ammonium epitope or extend to the adjacent part of the molecule. Another possibility might be that IgE antibodies could be complementary to structures other than the ammonium group [52, 65]. The relative affinities of the various muscle relaxants to their corresponding IgEs may also play a role [42, 54, 60, 66]. Indeed, the K_i of six different muscle relaxants was determined in patients who experienced an anaphylactic reaction to muscle relaxants. The values ranged between 1.5 nM and 2.5 microM. The K_i value of the incriminated drug was the lowest (affinity, the highest) in most of the patients [60]. These considerations represent an important issue in the design of an ideal neuromuscular blocking agent with a reduced risk of allergic reactions.

In 15 to 50 % of cases, IgE-mediated anaphylaxis to a neuromuscular blocking agent has been reported at the first known contact with a neuromuscular blocking agent [14, 22, 27, 28, 39, 61, 67]. This suggests a possible cross-reaction with IgE antibodies generated by previous contact with apparently unrelated chemicals as initially hypothesised by structure-activity studies which established that quaternary and tertiary ammonium ions were the complementary allergenic sites on the reactive drugs. This is a particularly attractive hypothesis in cases where patients react to relatively small and ubiquitous epitopes such as a substituted ammonium groups. Indeed, these structures occur widely in many drugs but also in foods, cosmetics, disinfectants and industrial materials. Hence, there would seem to be ample opportunity for sensitive individuals to come into contact with and synthesise IgE antibodies to these unusual, and previously unsuspected, antigenic determinants. Although controversial, such a hypothesis has been proposed concerning adverse reactions to neuromuscular blockers and IgE antibodies generated towards acetylcholine, different membrane phospholipids or food lecithins from soy or egg [62]. However, there is no evidence to support the suggestion that allergy to cosmetics sharing structural similarities predisposes to reactions to NMBA [30, 39, 68].

Nevertheless, recently, Florvaag *et al.*, hypothesised 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 sensitisation. They demonstrated a higher prevalence of IgE antibodies to quaternary and/or tertiary ammonium ion among blood donors and atopic patients from Norway when compared to Sweden [30]. This study also pointed out that amongst common environmental household chemicals substituted ammonium ion antibody binding activities, the only difference between Norway and Sweden was cough mixtures containing pholcodine. The later demonstration that pholcodine exposure in sensitised individuals [69], particularly in patients having experienced an allergic reaction to a NMBA [70] was responsible for a significant increase in specific IgEs to NMBAs led to the hypothesis that pholcodine exposure could lead to IgE-sensitisation to pholcodine and other quaternary ammonium ions and thereby increases the risk of allergic reaction to NMBAs. Interestingly, an increase in total IgE was also reported in this study, in favour of at least a component of non-allergen-specific stimulation by pholcodine. This also raises the problem of a possible interference by total IgE as recently demonstrated in subjects with total IgE concentrations exceeding 1,500 kU/l [71]. Nevertheless, the “pholcodine” hypothesis is under further investigation in a collaborative study involving several countries across Europe and the USA trying to establish a possible relation between the prevalence of IgE against substituted (quaternary or tertiary) ammonium ions (pholcodine, morphine, suxamethonium) and pholcodine consumption, a parameter which varies considerably between countries.

Similarly, the hypothesis of a possible relationship between the risk of quaternary ammonium ion induced occupational asthma and the risk of sensitisation against NMBAs is under investigation in an ongoing study in France [72, 73].

Delayed Immune-Mediated Hypersensitivity Reactions

Only a few reports concern delayed allergic reactions to NMBAs [12, 13, 74, 75]. T cell-mediated immune responses play an important role in both immediate and delayed types of adverse drug reactions [76, 77]. Recently, a delayed hypersensitivity to suxamethonium, driven by an oligoclonal T helper cell 1-skewed CD4⁺ memory T cell population, expressing the skin homing receptors CLA and CCR4 has been described [12]. This represents the first report describing a muscle relaxant specific TCL [49].

Non-Immune Mediated Hypersensitivity Reactions

The rate of non IgE-mediated immediate hypersensitivity reactions usually varies between 20 % and one third of the reported cases in most large series [14, 26, 29, 38, 61]. In a recent report based on spontaneous reporting to the Yellow Card Scheme, the main reporting system for adverse drug reactions in the United Kingdom, non allergic suspected reactions to NMBAs occurred with almost the same frequency as did those with an allergic component [15].

Although the precise mechanisms of these reactions remain difficult to establish, they usually result from direct non specific mast cell and basophil activation. Direct histamine

release is usually regarded as responsible for the non-IgE-mediated reactions observed [78]. There is a not always clear correlation between circulating histamine levels and the resulting symptoms, particularly as regarding bronchospasm [79, 80]. Histamine may produce adverse effects during anaesthesia, which can be prevented by H1 and H2 blockers [79, 81]. Reactions resulting from direct histamine release are usually less severe than IgE-mediated reactions [14, 29], with the exception of a subset of patients who have been considered as “super-responders” to the histamine releasing effect of neuromuscular blocking agents [61]. Histamine release is predominantly found with the use of the benzylisoquinolines d-tubocurarine, atracurium and mivacurium, and the aminosteroid rapacurium [82]. These differences could be related to different mechanism of mast cell activation, as recently suggested by dermal microdialysis experiments conducted in human volunteers [83].

Neuromuscular blocking drugs may also cross-react with nicotinic and muscarinic receptors responsible for actions at extra-neuromuscular 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 : suxamethonium, non-depolarizing agents : benzylisoquinolines or aminosteroid compounds), although it varies considerably among them and may not be seen at clinical doses [84]. Neuromuscular blocking drugs 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 noradrenaline and its reuptake at sympathetic nerve endings [85].

Recently, severe bronchospasm resulting from the administration of rapacurium was reported in children [86]. Increased airway resistance related to rapacurium administration have been reported in children and adults [87, 88]. It has been suggested that the higher affinity of rapacurium for M2 versus M3 muscarinic receptors could account for the high incidence of bronchospasm observed in clinical practice [89-91]. As a result of these adverse reactions, rapacurium has been withdrawn from the market in the USA.

V. CLINICAL FEATURES

It is worthwhile mentioning that the signs of anaphylaxis that occur during anaesthesia, differ to some extent from signs and symptoms that occur during anaphylaxis not associated with anaesthesia. All early symptoms usually observed in the awake patient such as malaise, pruritus, dizziness and dyspnoea are absent in the anaesthetised patient. In addition, cutaneous signs may be difficult to notice in a completely draped patient, also many signs such as an increase in heart rate, a decrease in blood pressure or an increase in airway resistance may be initially misinterpreted as a result of an interaction between the clinical status of the patient and the drugs administered during the procedure, dose-related site effect of the drugs, or excessively light anaesthesia. Therefore, vigilance is essential, as reactions may be well established before they are noticed.

The difference between IgE and non-IgE-mediated anaphylactic reactions cannot be made on clinical grounds alone, since clinical symptoms and signs can be very similar.

Therefore every hypersensitivity reactions occurring during the perioperative period should be investigated to identify the mechanism of the reaction as well as the responsible substance [22, 32, 92]. The intensity of reactions shows striking variation between patients. Manifestations may range from mild non life-threatening reactions to severe shock and death [22]. However, IgE-mediated reactions are usually more severe than non-IgE-mediated reactions, and this is particularly true in case of anaphylaxis to NMBAs (Fig. 2) [14, 29, 61]. In addition, for at yet unexplained reason, IgE-mediated reactions to NMBAs have been shown to be more severe than reactions to other substances like latex in some series [14, 29, 38].

Anaphylactic reactions may occur at any time during the perioperative period, but, in the case of hypersensitivity to neuromuscular blocking agents, they are observed early after induction of anaesthesia, within minutes or seconds after injection of the responsible drug [22, 32, 67]. Factors, which influence allergic reaction symptom severity in the sensitised individual, include the distribution and reactivity of sensitised mast cells and basophils, individual organ susceptibility, released mediators and the endogenous response they elicit [93]. Anaphylaxis commonly involves the skin, cardiovascular and respiratory systems, but virtually any system, including the gastrointestinal, central nervous and genitourinary systems can be involved. The most commonly reported initial features are pulselessness, difficulty in ventilation and desaturation [24]. In our experience, a decreased end-tidal CO₂ is also of diagnostic value. In our most recent series, cutaneous symptoms were observed in only 66 to 70 % of patients in case of IgE-mediated reactions whereas they were present in more than 90 % in non-IgE mediated reactions [14, 29]. On the contrary cardiovascular collapse and bronchospasm were present in more than 50 % and 39 % of IgE-mediated reactions but only in 11 % and 19 % of non IgE-mediated reactions respectively [14, 29]. Thus the absence of cutaneous symptoms does not exclude the diagnosis

of anaphylaxis. Bradycardia occurs more often with peri-anaesthetic anaphylaxis as compared with other causes of anaphylaxis [94, 95]. In addition, clinical features may occur in isolation such as a sudden cardiac arrest without any other clinical signs, as it was the case in 29 out of 491 IgE-mediated reactions in our last published survey [29]. A comparison between clinical signs observed in case of IgE-mediated reactions compared with non-IgE mediated reactions, based on results extracted from the French database of the GERAP is detailed on Table 1.

These results concur with previously published data [24, 25, 28]. As a result, an anaphylactic reaction restricted to a single clinical symptom (e.g. bronchospasm, tachycardia with hypotension) can easily be misdiagnosed because many other pathological conditions may have an identical clinical presentation. In mild cases restricted to a single symptom, spontaneous recovery may 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 can 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. Treatment mainly depends on early adrenaline administration and volume expansion. Adrenaline administration should be tailored to the severity of symptoms (Table 2) (i.e. initial dose : 10 to 20 µg in grade II reactions, 100 to 200 in case of grade III reactions, repeated every 1 to 2 minutes as necessary) [96]. Rapid, but goal-oriented, administration of adrenaline is mandatory to ensure treatment efficacy, but also to minimise potential side effects of treatment [29]. Prolonged inotropic support may also be required in some patients. Moreover, prior treatment with β-blockers is a potential risk factor explaining an absence of tachycardia, as well as resistance of arterial hypotension to adrenaline [97]. In cases re-

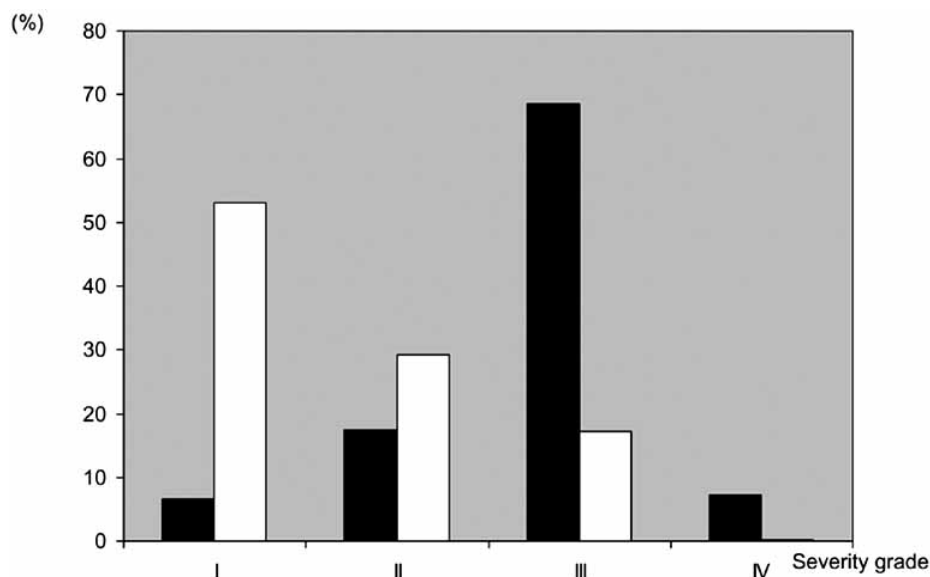


Fig. (2). Severity of IgE-mediated reactions to neuromuscular blocking agents (NMBAs) (filled bar) compared with non-IgE-mediated reactions (open bar) occurring during anaesthesia according to increasing severity grade. A significant higher severity is observed in case of allergic reactions to NMBAs (personal data extracted from the French GERAP database).

Table 1. Clinical Signs Observed in Case of IgE-Mediated Reactions to a Neuromuscular Blocking Agent (NMBA) Compared with Non IgE-Mediated Reactions (Personal Data Extracted from the French GERAP Database)

Clinical Signs	IgE-Mediated Reaction to NMBAs (%)	Non-IgE Mediated Reactions (%)
Cutaneous symptoms	698 (65.4 %)	664 (94.8 %)
Erythema	501	477
Urticaria	150	177
Oedema	80	60
Cardiovascular symptoms	906 (90.7 %)	254 (36,4 %)
Hypotension	186	141
Cardiovascular collapse	703	74
Bradycardia	26	9
Cardiac arrest	76	2
Bronchospasm	463 (43.4 %)	135 (19.3%)

sistant to adrenaline, the use of vasoactive drugs such as noradrenaline, glucagon or even vasopressin or vasopressin analogues has been advocated [96, 98, 99].

Table 2. Grade of Severity for Quantification of Immediate Hypersensitivity Reactions

Grade	Signs
I	Cutaneous signs : generalized erythma, urticaria, angioedema
II	Measurable but not life-threatening symptoms Cutaneous signs, hypotension, tachycardia Respiratory disturbance : cough, difficulty to inflate
III	Life-threatening symptoms : collapse, tachycardia or bradycardia, arrhythmias, bronchospasm
IV	Cardiac and/or respiratory arrest

The differential diagnosis of any adverse reaction during or following anaesthesia should include the possibility of an anaphylaxis [100]. This has been recently emphasised in a prospective study which demonstrated that a systematic follow-up of patients with unexplained reactions during anaesthesia increased the estimated incidence of IgE-mediated hypersensitivity reactions during anaesthesia by 50 % [92]. The differential diagnosis of peri-anaesthetic anaphylaxis includes conditions, which are not specific to allergic reactions to neuromuscular blocking agents (Table 3). It also includes reactions which are more particular to suxamethonium administration, such as malignant hyperthermia [101, 102], myotonias and masseter spasm [103, 104], muscle cell damage [102, 105], or suxamethonium induced hyperkalaemia which can cause fatal cardiac dysrhythmias and cardiac arrest in patients with burns, massive trauma or acute upper or lower motoneuron disease (spinal cord injury, stroke, demyelinating disease...) (for review see [67, 102]).

VI. RISK FACTORS

Although several risk factors occur more frequently in patients with anaphylaxis during anaesthesia, their preva-

lence in the general population is such that few would benefit in terms of preoperative screening, especially when anaphylactic reactions to neuromuscular blocking agents are concerned.

Table 3. Differential Diagnosis of Anaphylaxis to Neuromuscular Blocking Agents

All NMBAs	Suxamethonium
Overdose of vasoactive substance	Malignant hyperthermia
Asthma	Myotonias and Masseter Spasm
Arrhythmia	Hyperkalaemia
Myocardial infarction	
Pericardial tamponade	
Pulmonary oedema	
Pulmonary embolism	
Tension pneumothorax	
Venous embolism	
Sepsis	
Hereditary angioedema	
Mastocytosis	

In all series of reactions to neuromuscular blocking agents, there is a significant female predominance varying from 2:1 to 4:1, even when possible differences between the number of anaesthetics performed on men and women is taken into account [14, 27, 38, 39]. Age cannot be considered as a true risk factors since reactions to neuromuscular blocking agents have been reported at all ages, including in children as young as one year [14, 106].

A family history of anaphylaxis has been suggested as important in one report of cousins who reacted to neuromuscular blocking agents [107], but no similar cases have been reported in the literature [108].

In many large series of patients sensitised to a neuromuscular blocking agent, a disproportionate number of patients

have histories of atopy, allergy or asthma [27, 109-112]. However, other studies have failed to demonstrate an increased risk of allergy to neuromuscular blocking agents in atopic patients [14, 29, 113]. Similarly, neither a history of allergy to other drugs, chronic fatigue syndrome nor multiple chemical sensitivity predispose to anaphylaxis during anaesthesia [22, 39]. There is no evidence of increased risk of anaphylaxis to neuromuscular blocking agents in patients who have had anaphylaxis to drugs not used in the operating theatre.

Since a first exposure to an antigen is considered as a prerequisite for the development of a sensitisation, it has been suggested that patients who have previously been exposed to a neuromuscular blocking agent may constitute a high-risk group. However, the highest incidence of prior exposure to a muscle relaxant in patients allergic to neuromuscular blocking agents is around 50 % [39]. As mentioned previously, it is apparent that under some circumstances IgE antibodies against tertiary or quaternary ammonium ion are not formed in response to exposure to a muscle relaxant but to an as yet unidentified antigen. Thus in clinical practice, the use of a history of previous exposure to a neuromuscular blocking agent as a potential risk factor may preclude the identification of at least half of potential reactors [39].

Similarly, there is no evidence to support the hypothesis that allergy to quaternary or tertiary ammonium ion containing products or drugs, such as household chemicals or cosmetics, predisposes to anaphylaxis to neuromuscular blocking agents. Nevertheless, as mentioned previously, special attention should be paid to the forthcoming results of the ongoing collaborative study which investigates a possible link between sensitisation to pholcodine and to muscle relaxants [30, 69, 70].

Finally, the only real documented risk factor of allergic reaction to neuromuscular blocking agents is a history of a severe undiagnosed adverse event during previous anaesthesia which should be investigated with preoperative skin-testing before undergoing elective surgery [96, 108].

VII. INVESTIGATION OF A SUSPECTED ALLERGIC REACTION TO A NMBA

Any suspected hypersensitivity reaction during anaesthesia must be extensively investigated using combined preoperative and postoperative testing to confirm the nature of the reaction, to identify the responsible drug, to detect possible cross-reactivity in cases of anaphylaxis to a neuromuscular blocking agent and to provide recommendations for future anaesthetic procedures [96, 114]. Serious attempts have been made to standardise and validate *in vitro* and *in vivo* techniques for the diagnosis of drug allergy [39, 96, 108, 114-117].

However, in the absence of any gold standard such as a challenge test, the performance of the various diagnostic methods used to investigate sensitisation against neuromuscular blocking agents is difficult to ascertain.

The diagnostic strategy is based on a detailed history including concurrent morbidity, previous anaesthetic history and any known allergies, and on a combination of investigations performed both immediately and days to weeks later.

Biological investigations include mediators release assays at the time of the reaction [118], quantification of specific IgE, immediately or 6 weeks later [118-120], skin tests [116] and other biological assays such as histamine release tests or basophil activation assays [117, 120]. Early tests are essentially designed to determine whether or not an immunological mechanism is involved. Delayed testing attempts to identify the responsible drug. Whenever possible, confirmation of the incriminated allergen should be based on immunological assessment using more than one test.

Basophils and Mast Cell Mediators' Quantification

During an IgE-mediated reaction, basophils and mast cells are activated and then degranulate and release mediators in intracellular fluids [121]. These mediators can be measured in the patient's serum and have proved to be useful for the diagnosis of anaphylaxis during anaesthesia [14, 92, 118, 122-124]. Histamine concentrations are maximal almost immediately and decrease thereafter with a half-life of about 20 min [123]. Therefore, circulating levels should be assayed within the first hour of a reaction, and in mild cases, only the early measurements may be increased [122]. 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 due to accelerated histamine degradation. When increased, histamine circulating levels confirm basophil cell activation which can result from direct or IgE-mediated activation. In our most recent study, the sensitivity of this test for the diagnosis of anaphylaxis was estimated at 75 %, the specificity at 51 %, the positive predictive value at 75 % and the negative predictive value at 51 %. Urinary methylhistamine assays is no longer recommended in view of its low sensitivity in comparison with tryptase and histamine assays.

Tryptase reaches a peak in the patient's serum 30 minutes after the first clinical manifestations. Its half-life is 90 minutes, and the levels usually decrease over time but in some cases elevated levels can still be detected for up to 6 h or more after the onset of anaphylaxis [118, 123, 125]. Basophils and mast cells highly differ in the amount of tryptase contained in their granules, as mast cells contain high tryptase levels (12-35 pg/cell) and basophils very low levels (<0.05 pg/cell) [126, 127]. Thus, although elevated tryptase levels can be observed in different situations, an elevated tryptase concentration > 25 $\mu\text{g.L}^{-1}$ is usually regarded as specific for mast cell activation and differentiates between an IgE-mediated and alternative effector cell activation [118, 120], but the absence of increased serum tryptase does not rule out an allergic reaction [120, 125]. In our last series, using tryptase measurements for the diagnosis of anaphylaxis, its sensitivity was estimated at 64 %, specificity at 89.3 %, positive predictive value at 92.6 % and negative predictive value at 54.3 % [14].

Specific IgE Assay

In vitro tests are available to detect the presence of serum specific IgE antibodies. Baldo and Fisher were the first to demonstrate that drug reactive IgE were involved in anaphylactic reactions, using NMBA's coupled to epoxy Sepharose in a radioimmunoassay [128]. The detection of anti-drug specific IgE assays in serum is performed by a sandwich-type

immunoassay in which the serum IgE is first adsorbed to a reactive phase and subsequently quantified via the binding of an anti IgE tracer. The reactive phase is prepared by covalently coupling a drug derivative to a solid phase such as nitrocellulose membrane or a polymer [60].

IgE binding on different NMBA solid phases and competitive inhibition assays with several muscle relaxants and other drugs and chemicals including morphine demonstrated a cross reactivity of specific IgE [51, 58, 128-130]. However, some patients do not react with all NMBA, showing that the substituted ammonium ion is at least not always the only part of the epitope. One of the non specific interactions that may occur between specific IgE and the support is the hydrophobic interaction [59, 60]. In the absence of reliable NMBA-specific IgE assays, various authors have advocated the application of a quaternary or tertiary ammonium assay to diagnose allergy from substituted ammonium determinants of NMBAs. Gueant *et al.* improved a RIA method for detecting NMBA IgE in serum using a quaternary ammonium compound coupled to Sepharose (QAS-RIA) [131, 132]. The sensitivity of this test was estimated at 88 %. An inhibition step in presence of 130 nmol of soluble drug is performed and the highest percentage is observed with the incriminated drug in most of cases (83.3 %). Guilloux *et al.* have developed a RIA test by coupling a p aminophenyl-phosphorylcholine on agarose (PAPPC RIA) [133]. P-aminophenyl phosphoryl choline contains a larger choline derivative (quaternary ammonium ion), including a secondary ammonium group, an aromatic ring and a phosphate group. Both methods were found to have similar sensitivity and specificity [60].

Recently, Fisher *et al.* supported the use of a morphine-based immunoassay for the detection of specific IgE to ammonium ions in the sera of sensitised subjects [58]. However, the practice of adopting a morphine based assay to diagnose allergy from NMBAs has been recently called into question by Florvaag *et al.* who demonstrated IgE antibodies against morphine in 5 % and 10 % of Norwegian blood donors and probably allergic individuals, respectively [30]. The most likely explanation for these findings was hypothesised to lie in the high consumption of pholcodine-containing syrups in Norway.

More recently, EBO *et al.* investigated the diagnostic value of quantification of IgE by ImmunoCAP (Phadia AB, Uppsala, Sweden) in the diagnosis of rocuronium allergy [71]. They also studied whether IgE inhibition tests can predict clinical cross-reactivity between neuromuscular blocking agents. They concluded that the rocuronium ImmunoCAP constitutes a reliable technique to diagnose rocuronium allergy, provided an assay-specific decision threshold is applied, because these assays reach a sensitivity of more than 85 % and absolute specificity.

In clinical practice, immunoassays for the detection of drug reactive IgE may provide important information to confirm the responsibility of suspected drug [14, 120]. This test is usually performed several weeks after the reaction but can be carried out at the time of the reaction [96, 118, 119]. Indeed, a common misunderstanding was that IgE antibodies in serum were consumed during an anaphylactic reaction, thus leading to false negative results. At least for NMBAs,

this assumption has been demonstrated to be false [118, 119]. In France, the French Society of Anaesthetists (SFAR, Société Française d'Anesthésie et de Réanimation) guidelines recommend specific IgE assays in the diagnosis of anaphylaxis to neuromuscular blocking agents, thiopentone and latex [96].

Skin Testing

In most reports, skin tests in association with history remain the mainstay of the diagnosis of an IgE-mediated reaction. Intradermal skin- or prick-tests are usually carried out 4 to 6 weeks after a reaction, because prior to 4 weeks the intracellular stocks of histamine and other mediators are still lower than normal [134]. Skin tests to neuromuscular blocking agents may remain positive for years later [135]. Ideally, testing should be carried out by a professional experienced in performing and interpreting tests with anaesthetic agents [96]. Treatments such as antihistamines, or neuroleptics known to decrease cutaneous reactivity, should be interrupted. Pregnancy, youth or treatment with angiotensin-converting enzyme inhibitor or β -blocking agents does not contraindicate skin testing. Although very uncommon, systemic reactions can occur during skin testing, with a higher risk with intradermal tests as compared with prick tests. The prevalence of skin test induced anaphylaxis has been estimated at less than 0.3 % [136]. For this reason some authors suggested interrupting any treatment with a β -blocking agent prior testing to avoid any possible interference with adrenaline administration in the event of a systemic reaction [137].

Prick-tests and intradermal reactions with dilutions of commercially available drug preparations are advised. Although highly reliable, skin tests are not infallible [138]. Standardised procedures and dilutions must be precisely defined for each agent tested in order to avoid false positive results due to any direct histamine releasing properties as is the case for known histamine-releasing compounds such as mivacurium, atracurium and tubocurarine and as such should be tested with more dilute solutions [42, 55, 67, 96, 139, 140]. 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. A certain degree of controversy remains as to the maximal concentrations to be used [141, 142]. Moreover, by observing positive prick test to undiluted rocuronium and vecuronium in healthy volunteers, some authors even called into question whether neuromuscular blocking agents are the principal cause of anaphylaxis during anaesthesia and whether skin tests can be applied to diagnose allergy to muscle relaxants [143]. However several criticisms have been levelled at the results of this study [144] and other authors didn't observe similar false positive results in healthy volunteers [142, 145]. Detailed recommendations for skin and intradermal-test dilutions of anaesthetic drugs including NMBAs have recently been proposed by the SFAR and the French Society of Allergology (SFAIC, Société Française d'Allergologie et d'Immunologie Clinique) (Table 4) [96]. The accuracy of these recommended maximal concentration have been further confirmed in a prospective study conducted in 120 healthy volunteers tested with all neuromuscular blocking agents available at increasing concentration both on the anterior part of the forearm and on the back. Results

Table 4. Concentrations of Anaesthetic Agents Normally Non-Reactive in Practice of Skin Tests

Available Agents		Prick-Tests		Intradermal Tests	
INN	C (mg·mL ⁻¹)	Dilution	MC(mg·mL ⁻¹)	Dilution	MC(µg·mL ⁻¹)
atracurium	10	1/10	1	1/1000	10
cis-atracurium	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
thiopentone	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
remifentanil	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
lignocaine	10	undiluted	10	1/10	1000
mepivacaine	10	undiluted	10	1/10	1000
ropivacaine	2	undiluted	2	1/10	200

INN = International non proprietary name; C = concentration; MC = maximal concentration.

were similar on both injection sites [116]. Skin tests are interpreted after 15 to 20 min. 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 greater 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, all available neuromuscular blocking agents should be tested [28, 39, 67, 96, 97, 120, 135]. This should help avoid future adverse reactions and provide documented advice for the future administration of anaesthesia [28, 96, 115, 120]. However, one should always remember that no diagnostic procedure can be devoid of false positive or negative results. Although rare, some cases of renewed allergic reactions following exposure to a neuromuscular blocking agent considered to be safe have been reported in the literature [138, 146]. Therefore when administering a NMBA to a sensitised patient with a negative skin one should bear in mind the risk-benefit ratio. In addition any new muscle relaxant should be routinely tested in patients known to be allergic to these agents in order to detect possible cross-reactivity [96].

The estimated sensitivity of skin tests for muscle relaxants is approximately 94 to 97 % [54, 147]. There has been

some controversy concerning the advantages of either prick versus intradermal testing. Studies comparing both techniques show little differences between them [139, 140]. The intradermal test is said to be easier to perform for the infrequent user and to have a higher sensitivity while the skin prick test is easier to prepare, causes less trauma and pain to the skin and as such is usually favoured in children [134]. 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 [148]. 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.

Mediator Release Tests

Basophil Activation Assays

Allergen-induced mediator release tests quantify mediators released during effector cell degranulation, mainly peripheral blood basophils, following stimulation with specific antigen [125]. There are two categories of mediator release tests: histamine release tests and sulphidoleukotriene release tests (cellular allergen stimulation test: CAST). MATA *et al.* (1992) have evaluated the *in vitro* leukocyte histamine release (LHR) tests for the diagnosis of allergy to muscle re-

laxant drugs in 40 patients and a control group of 44 subjects with negative leukocyte histamine release [149]. Leukocyte histamine release tests were positive in 65 % of the allergic patients, for a threshold corresponding to a specificity at 100%. The concordance between LHR test and QAS-RIA was 64 % [65, 149]. Despite a very good specificity, their diagnostic application remains limited because of the heavy experimental conditions and unsufficient sensitivity [125]. Therefore they are not used as routine diagnostic tests [96]. They could be useful when cross-reactivity among muscle relaxants is investigated with a view to future anaesthesia in sensitised patients. Similarly, reports concerning the monitoring of serotonin [48], eosinophil cationic protein [150] or LTC4 [151] release have also been published, however, these assays cannot be recommended in routine clinical practice at the present time.

Flow Cytometry

The basis of flow-assisted allergy diagnosis relies on quantification of shifts in expression of basophilic activation markers after challenge with a specific allergen using specific antibodies conjugated with a fluorochrome or a dye. Activated basophils not only secrete quantifiable bioactive mediators but also upregulate the expression of different markers which can be detected efficiently by flow cytometry using specific monoclonal antibodies [117, 152-157]. Currently, the most commonly used antibody in allergy diagnosis is anti-CD63 and, to a lesser extent anti-CD203c [158-160].

Flow cytometry can contribute to the diagnosis of hypersensitivity reactions from neuromuscular blocking agents [117], but additional studies on larger samples of cases are needed for its evaluation. Indeed, excepted in one study, the performance of this method is not significantly higher than that of the LHR test. In addition, its interpretation is operator dependent. Abuaf *et al.* showed the sensitivity and specificity of a CD63-based basophil activation assay was 64 % and 93 %, respectively in a series including 21 patients with definite anaphylaxis from these drugs [152]. Monneret *et al.* concluded that their flow cytometry protocol using CCR3 and/or CD203c was a promising tool in allergy diagnosis, even if its sensitivity needed to be improved [161]. Kvedariene *et al.* evaluated flow cytometry performances for the diagnosis of NMBA allergy in 47 patients and found a sensitivity at 36.1% that dramatically improved when considering the tests performed in the last 3 years [162]. The authors therefore advise diagnosing NMBA allergy as rapidly as possible after the reaction. More recently, EBO *et al.* proposed a modified diagnostic threshold for estimating the sensitivity of Basophil Activation Test (BAT) for rocuronium and estimated that BAT constitutes a reliable instrument to confirm rocuronium anaphylaxis [163]. Studies of this test in larger case populations will permit to evaluate its performances.

Although basophil activation monitoring using flow cytometry seems promising, several methodological issues remain to be addressed. These include realisation of the test on whole blood or isolated basophils, the need for preactivation with IL-3, the choice of appropriate dose for different allergens, positive and negative controls, characterisation and activation markers, and finally the appropriate diagnostic

threshold for different allergens [117]. Nevertheless, once fully validated, the basophil activation test using flow cytometry will probably represent an interesting diagnostic tool for NMBA anaphylaxis and for cross sensitisation studies.

Investigation Strategy Prior to Anaesthesia

The potential severity of anaphylaxis to neuromuscular blocking agents 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 values of tests for the occurrence of anaphylactic reactions, there is no demonstrated evidence for systematic pre-operative screening in the general population at this time [22, 28, 39, 96, 97, 108]. Similarly, there is no evidence of a need to investigate sensitisation against NMBAs (or other anaesthetic drugs) in patients who are either atopic or sensitised to substances they would not be exposed to during anaesthesia.

Consequently, pre-anaesthetic assessment of sensitisation against NMBAs should be limited to the following high-risk patients:

- Patients presenting with a documented history of allergy to muscle relaxants. In this case newly available muscle relaxants should be tested prior to anaesthesia.
- Patients having experienced an unexplained reaction during previous general anaesthesia or perioperatively, including severe hypotension, bronchospasm, or oedema. It is conceivable that the reaction might have been related to sensitivity to an anaesthetic agent or latex. The list of all injected substances is helpful in guiding the allergologist through his assessment. If the anaesthetic records are unavailable the substances most often incriminated in epidemiological studies should be tested (i.e. muscle relaxants and latex: skin tests, eventually specific IgE assays). One should keep in mind, however, that skin tests performed belatedly after an adverse reaction during anaesthesia can 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.

VIII. PREVENTION

Prevention of anaphylaxis to NMBAs has two major objectives. It should be aimed at preventing sensitisation 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-sensitised patient. In light of the relatively high rate of sensitisation without prior exposure, optimal prevention of sensitisation to neuromuscular blocking agents, even if their administration were to be radically curtailed, will probably be difficult to achieve. However, restricting the use of high risk drugs such as suxamethonium to clinical situations requiring that particular drug e.g. emergency intubation has been reported to reduce the incidence of reactions to NMBAs in Australia [39].

In another way, because of a possible relation between pholcodine exposure and sensitisation to NMBAs, this drug has been withdrawn from the market in Norway. Further studies will be needed to ascertain whether this measure will

led to a significant reduction of anaphylactic reactions to NMBAs in this country [30, 70]. This could also be cost effective since several studies pointed out that more than 80 % of the real cost per dose of muscle relaxant was for the chance of dying or sustaining adverse reactions including anaphylaxis [164], and that both patients and the society have a specific interest in the reduction of side effects and in cost containment [165, 166].

Pre-treatment with corticosteroids or histamine-receptor antagonists, by either H₁ or H₁ and H₂- receptor antagonists remains controversial. It has been proposed as an efficient way to reduce anaphylaxis due to chymopapaine administration [167]. No evidence of beneficial effects of prophylactic administration of corticosteroids in allergic reactions to NMBAs has been shown at this time. Pre-treatment with H₁- and H₂-receptor antagonists has been found to reduce histamine-mediated adverse effects in various studies [168, 169]. Antihistamine administration was effective in reducing the adverse effects of non-immune histamine release following muscle relaxant [170]. [Hosking, 1988 #86; Doenicke, 1996 #85] 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 even in some cases detrimental [22]. Many authors consider that pre-treatment with corticosteroids, antihistamines or both, does not provide for reliable prevention of immune-mediated reaction [62, 171]. Also allergic reactions to NMBAs even in the wake of preoperative H₁- H₂-receptor antagonists and steroids have been documented in several epidemiological surveys [14, 29, 38].

Since NMBAs produced reactions by cross-linking cell bound IgE antibodies through their divalent substituted ammonium ions, the use of monovalent haptens, which can occupy antibody sites without bridging specific IgE, has been proposed. In this respect, any molecule presenting a substituted tertiary or 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 [172, 173]. Moneret-Vautrin and colleagues demonstrated inhibition of skin mast-cell reactivity to muscle relaxants by mixing them with the monovalent haptens cytidylcholine and ethamsylate [174]. 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 [28, 39, 148]. However, large doses of morphine would be necessary and the use of H₁ and H₂ receptor antagonists will be necessary to counteract the cardiovascular effects of such high doses [39, 175]. This possibility has not yet been evaluated and prevention of muscle relaxant anaphylaxis by monovalent haptens cannot be recommended at present in standard clinical practice [39, 67, 96].

IX. CONCLUSION

Amongst all drugs used for general anaesthesia, neuromuscular blocking agents play a predominant role in the in-

cidence of severe IgE-mediated hypersensitivity reactions. Since their introduction to modern anaesthesia practice, much progress has been made in the identification of adverse reactions and their potential mechanism. Differences in the incidence of IgE-mediated reactions between countries, frequent but variable cross-sensitisation and the absence of previous exposure in a large number of reactors have led to the hypothesis of a possible role of environmental tertiary or quaternary ammonium ion containing compounds in the process of sensitisation. Although at yet no such possible allergen has been identified, the possible role of pholcodine is under investigation.

Because no premedication can effectively prevent an allergic reaction, any suspected hypersensitivity reaction must be extensively investigated using combined pre and postoperative testing. Patients must be fully informed of investigations results, and advised to provide a detailed report prior to future anaesthesia. The wearing of a warning bracelet or possession of a warning card is strongly indicated.

With the exception of high risk patients, systematic preoperative screening for sensitisation against NMBA is not justified at this time. A thorough preanaesthetic history is the most important tool for screening at-risk subjects. Particular attention must be paid to patients who have already experienced such a reaction during anaesthesia, or those alleging an allergy to muscle relaxants. In these cases, the choice of the safest possible anaesthetic agents should be based on the result of a rigorously performed allergologic assessment.

In view of the relative complexity of allergy investigation, an active policy to identify patients at risk and to provide all necessary support from providing expert advice to anaesthetists and allergologists through the constitution of allergeo-anaesthesia centres should be promoted.

ABBREVIATIONS

NMBAs	=	Neuromuscular blocking agents
MMJ	=	Neuromuscular junction
ACh	=	Acetylcholine

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